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MODULATORS OF THE INTEGRATED STRESS PATHWAY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 62/580,734, filed
5 November 2, 2017 and U.S. Provisional Application No. 62/643,061, 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
10 of a common effector, the translation initiation factor eIF2 α . This step is carried out by four
eIF2 α 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
15 molecular event. eIF2 α 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).

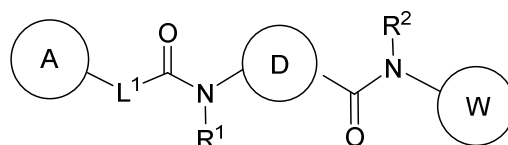
eIF2 (which is comprised of three subunits, α , β and γ) binds GTP and the initiator Met-
tRNA to form the ternary complex (eIF2-GTP-Met-tRNA_i), which, in turn, associates with the
20 40S ribosomal subunit scanning the 5'UTR of mRNAs to select the initiating AUG codon.
Upon phosphorylation of its α -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
25 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
30 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 (B1₂ B2₂ B3₂ B4₂ B5₂) 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 eIF2 α (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

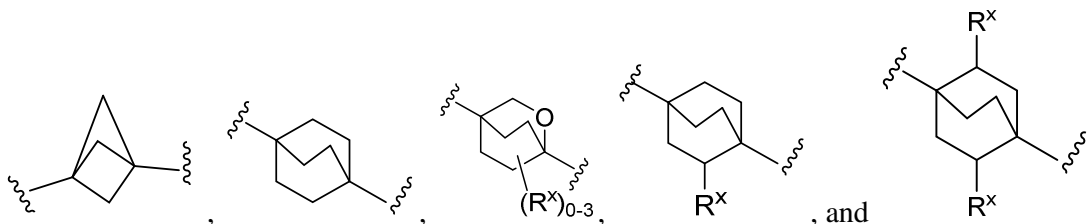
In one aspect of the present disclosure, there is provided a compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of:



L¹ is CH₂O-* or CH₂CH₂O-*, wherein “-*” indicates the attachment point to A;

R^1 and R^2 are each independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy-C₂-C₆ alkyl, hydroxy-C₂-C₆ alkyl, or silyloxy-C₂-C₆ alkyl;

A and W are each independently phenyl or 5-6 membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y ;

each R^X is independently selected from the group consisting of C₁-C₆ alkyl, hydroxy-C₁-C₆ alkyl, halo-C₁-C₆ alkyl, amino-C₁-C₆ alkyl, cyano-C₁-C₆ alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-SR^E$, $-S(O)R^D$, and $-S(O)_2 R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, hydroxy-C₁-C₆ alkyl, C₁-C₆ alkoxy-C₁-C₆ alkyl, halo-C₁-C₆ alkyl, halo-C₁-C₆ alkoxy, amino-C₁-C₆ alkyl, cyano-C₁-C₆ alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2 R^D$, 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 heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X ;

each G^1 is independently C₃-C₆ cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C₃-C₆ cycloalkyl, 4-7-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 C₁-C₆ alkyl, hydroxy-C₁-C₆ alkyl, halo-C₁-C₆ alkyl, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, and $-S(O)_2 R^D$;

R^A is, at each occurrence, independently hydrogen, C₁-C₆ alkyl, halo-C₁-C₆ alkyl, $-C(O)NR^B R^C$, $-C(O)R^D$, or $-C(O)OR^D$;

each of R^B and R^C is independently hydrogen or C₁-C₆ alkyl; or

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

each R^D is independently C₁-C₆ alkyl, or halo-C₁-C₆ alkyl;

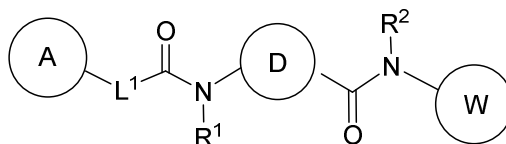
each R^E is independently hydrogen, C₁-C₆ alkyl, or halo-C₁-C₆ alkyl;

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

each of R^{B1} and R^{C1} is independently hydrogen or C_1 - C_6 alkyl; 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 of Formula (II-a):



Formula (II-a)

or a pharmaceutically acceptable salt thereof, wherein:

D is bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or 2-oxabicyclo[2.2.2]octane, each of which is optionally substituted with 1-4 R^X groups;

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

W is phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, isoxazolyl, or pyrazolyl, each of which is optionally substituted on one or more available carbons with 1-5 R^Y groups; and wherein pyrazolyl may be optionally substituted on an available nitrogen with hydrogen or $-CH_3$;

L^1 is CH_2O- or CH_2CH_2O- , wherein “-” indicates the attachment point to A;

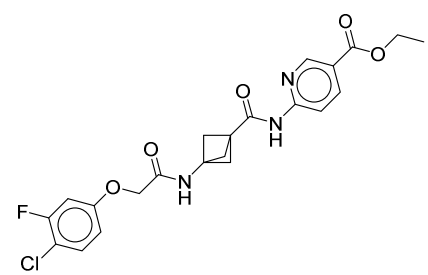
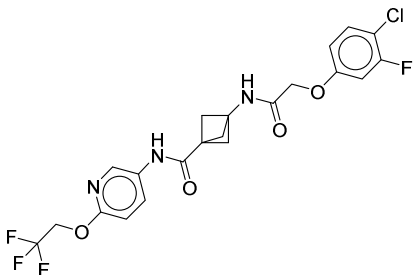
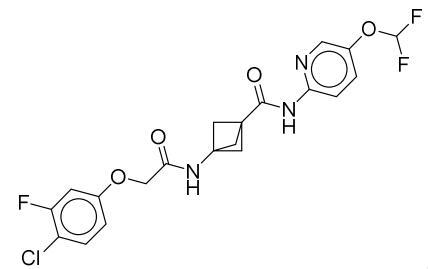
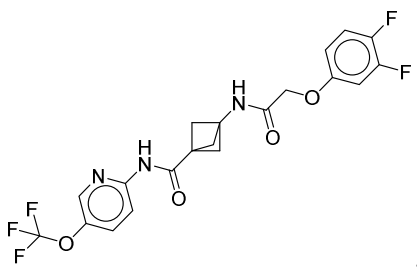
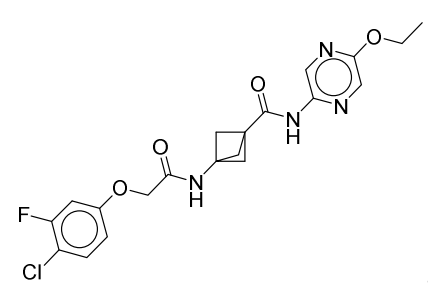
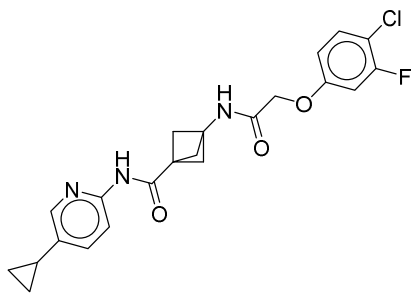
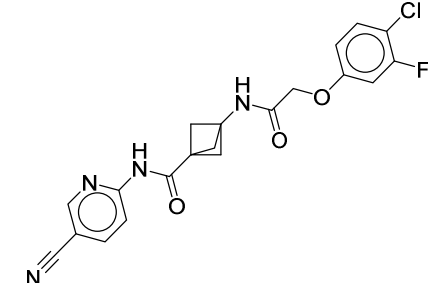
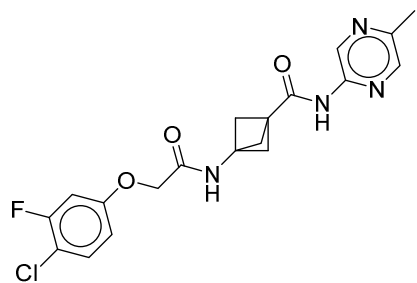
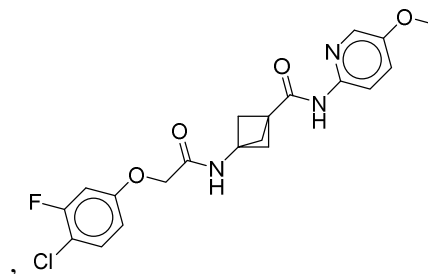
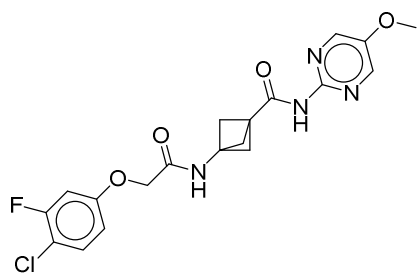
each R^X is independently fluoro, oxo, $-OH$, $-OCH_3$, $-C(O)OH$, or $-C(O)OCH_3$;

each R^Y is independently hydrogen, bromo, chloro, fluoro, iodo, $-CF_3$, $-CHF_2$, $-CH_2CF_3$, $-CH_3$, $-CH_2CH_3$, $-OH$, $-CH_2OH$, $-C(CH_3)_2OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCH_2CF_3$, $-S(O)_2CH_3$, $-S(O)_2CH_2CH_2CH_3$, $-CN$, $-N(CH_3)_2$, $-SF_5$, $-SCH_3$, $-NH_2$, $-C(CH_3)_3$, $-CH(CH_3)_2$, $-CH_2CN$, $-CH_2NH_2$, $-CH(OH)CH_3$, $-C(OH)(CH_3)CF_3$, $-S(O)_2CH_3$, $-C(O)CH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-OCHF_2$ or G^1 ; or

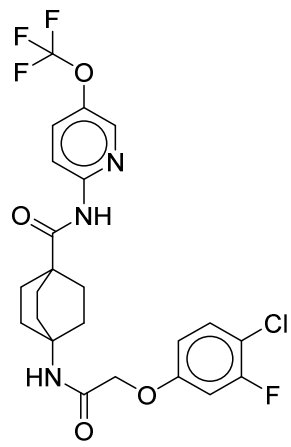
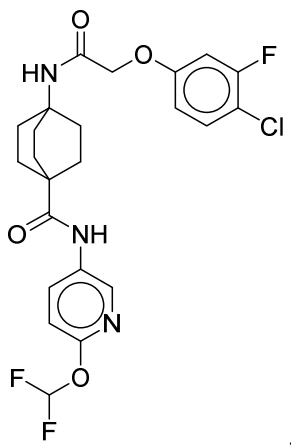
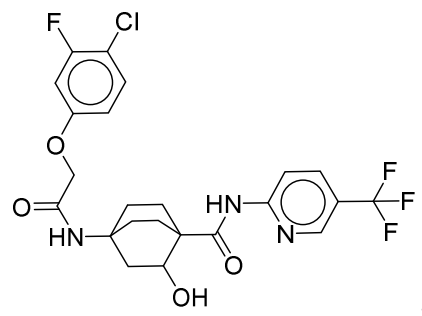
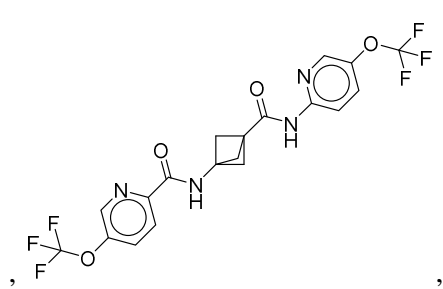
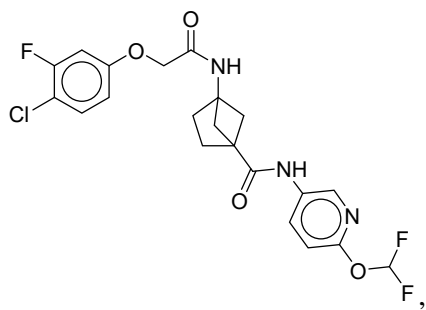
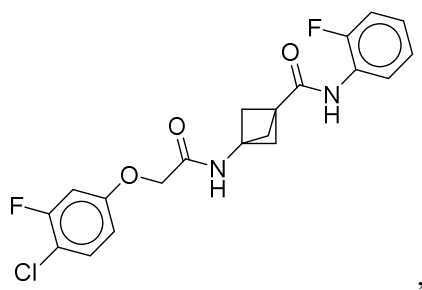
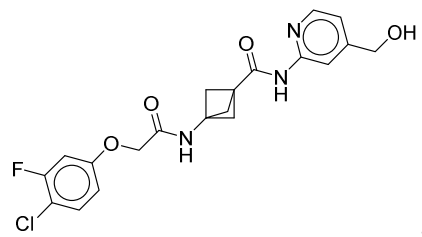
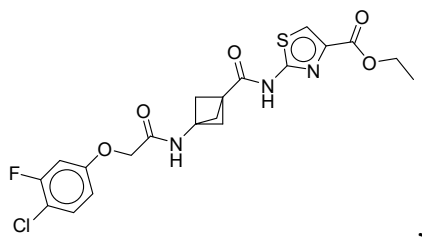
2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a furanyl, pyrrolyl, or dioxolanyl ring, each of which is optionally substituted with 1-2 R^X ; and

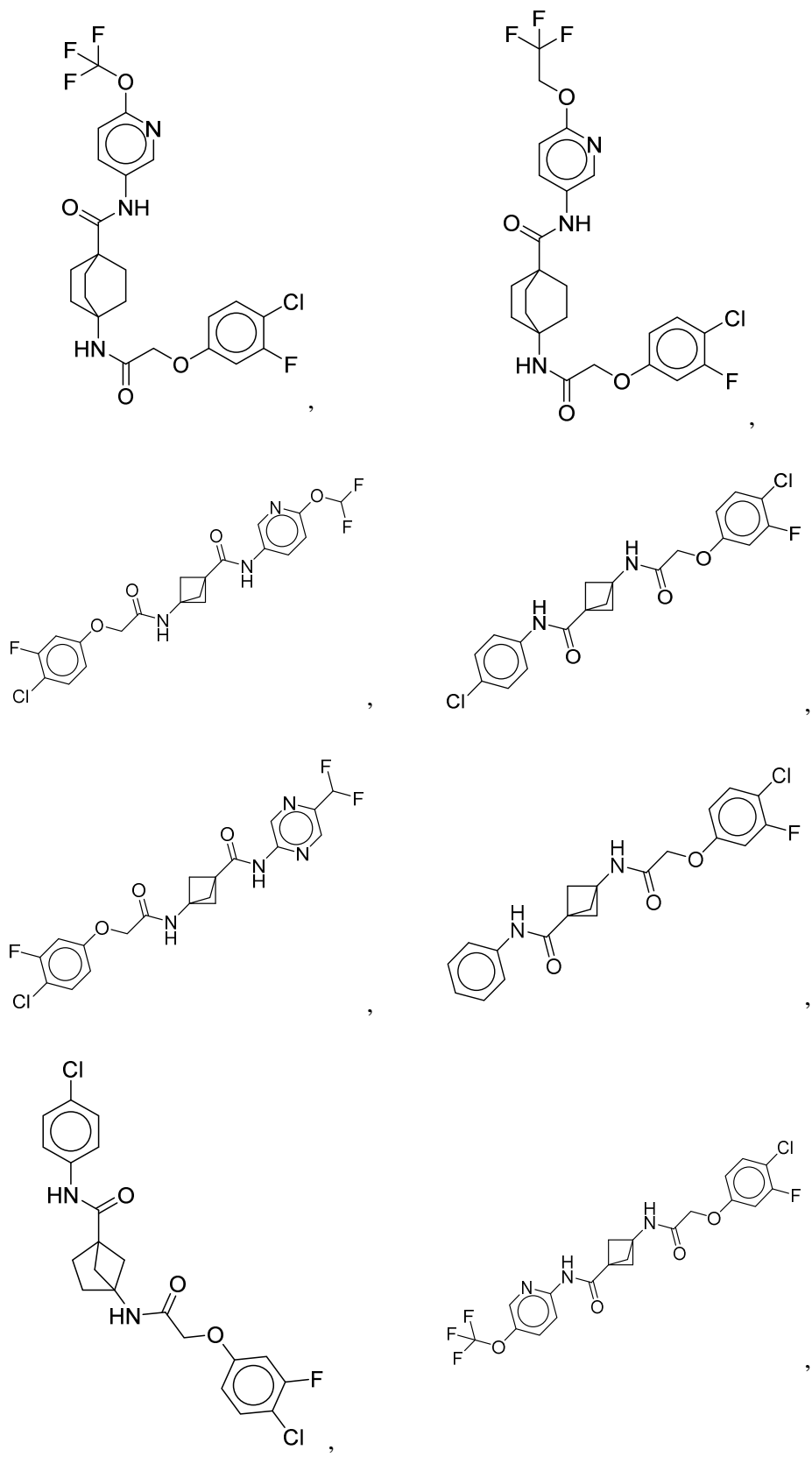
each of R^1 and R^2 is hydrogen or $-CH_3$.

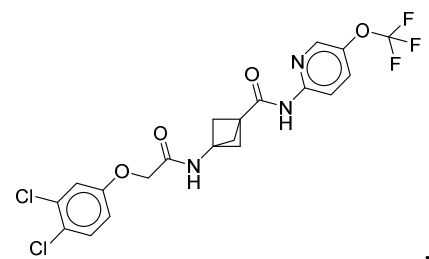
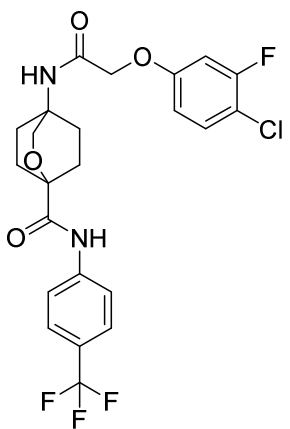
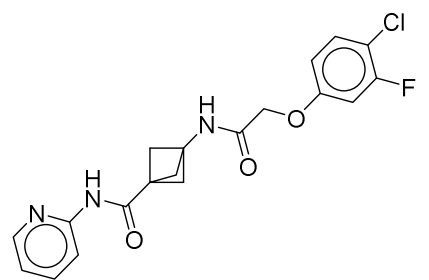
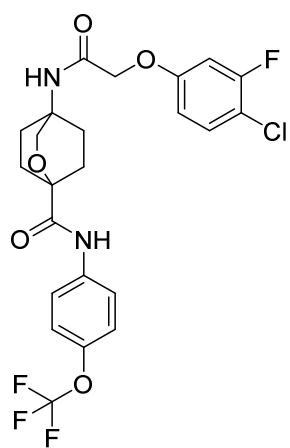
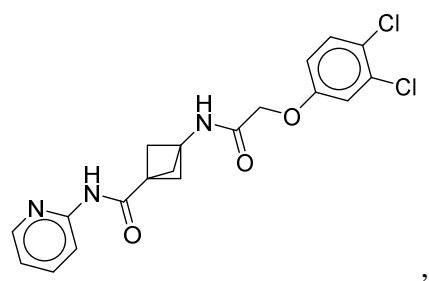
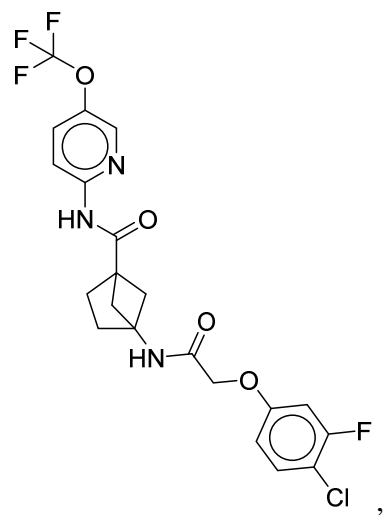
In a further aspect of the present disclosure, there is provided a compound, wherein the compound is selected from the group consisting of:



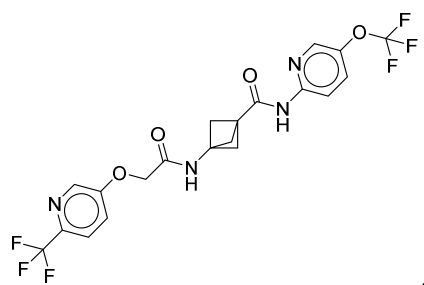
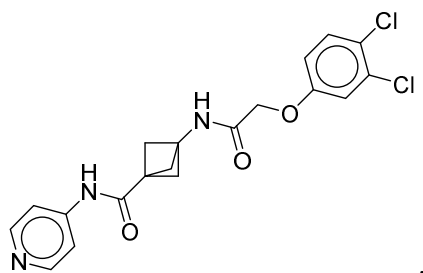
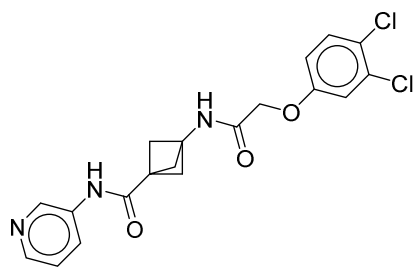
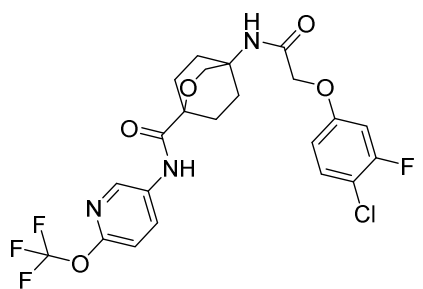
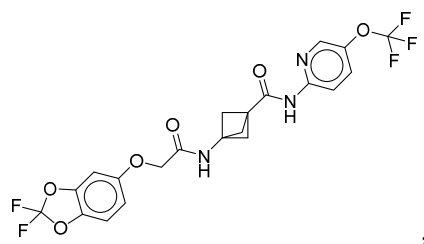
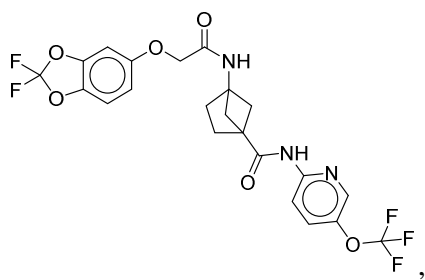
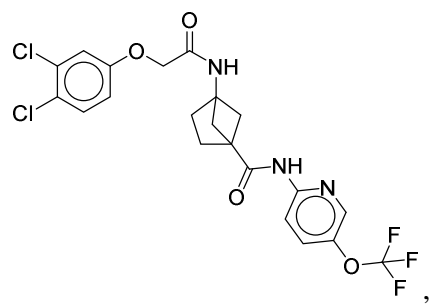
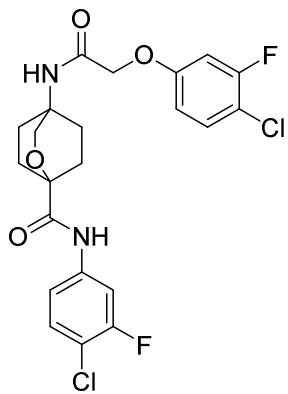
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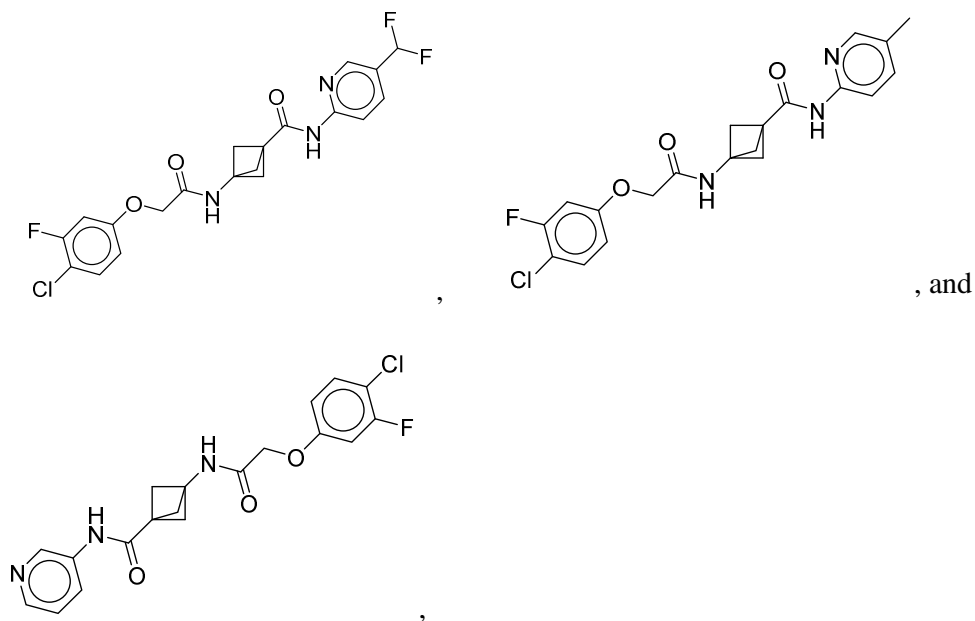






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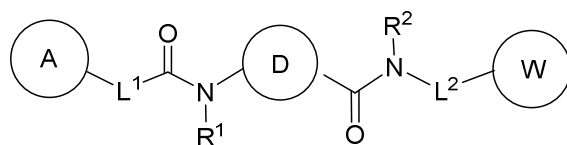




or a pharmaceutically acceptable salt thereof.

The present disclosure features 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, the present disclosure features an eIF2B modulator (e.g., an eIF2B activator) comprising a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In other examples, the present disclosure features methods of using a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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).

In one example, the present disclosure features a compound of Formula (I):



Formula (I)

- 3 -

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 with 1-4 R^X groups; and wherein if the bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen moiety may be optionally substituted by R^{N1} ;

L^1 is C_1 - C_6 alkylene or 2-7-membered heteroalkylene, wherein each C_1 - C_6 alkylene or 2-7-membered heteroalkylene is optionally substituted with 1-5 R^X ;

L^2 is C_1 - C_6 alkylene or 2-7-membered heteroalkylene, wherein each C_1 - C_6 alkylene or 2-7-membered heteroalkylene is optionally substituted with 1-5 R^X ;

R^1 and R^2 are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_2 - C_6 alkyl, hydroxy- C_2 - C_6 alkyl, silyloxy- C_2 - C_6 alkyl, and C_1 - C_6 alkyl- $C(O)NR^B R^C$;

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, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OR^D$, and $-S(O)_2R^D$;

A and W are each independently phenyl or 5-6 membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y ;

each R^X 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, amino- C_1 - C_6 alkyl, cyano- C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-SR^E$, $-S(O)R^D$, 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, C_1 - C_6 alkoxy- 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, HO_2C - C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2R^D$, 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 heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X ;

each G^1 is independently C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl, 4-7-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, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, and $-S(O)_2 R^D$;

R^A is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, $-C(O)NR^B R^C$, $-C(O)R^D$, 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 optionally substituted with 1-3 R^Z ;

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;

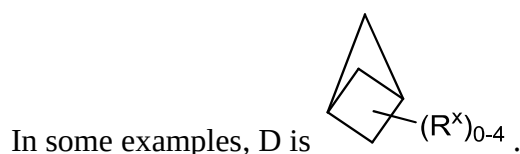
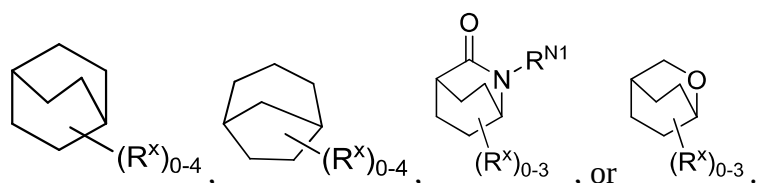
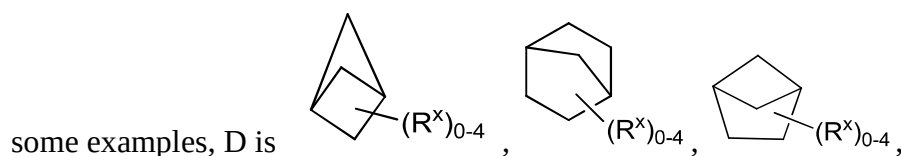
each R^F is independently hydrogen, C_1 - C_6 alkyl, halo, or halo- C_1 - C_6 alkyl;

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.

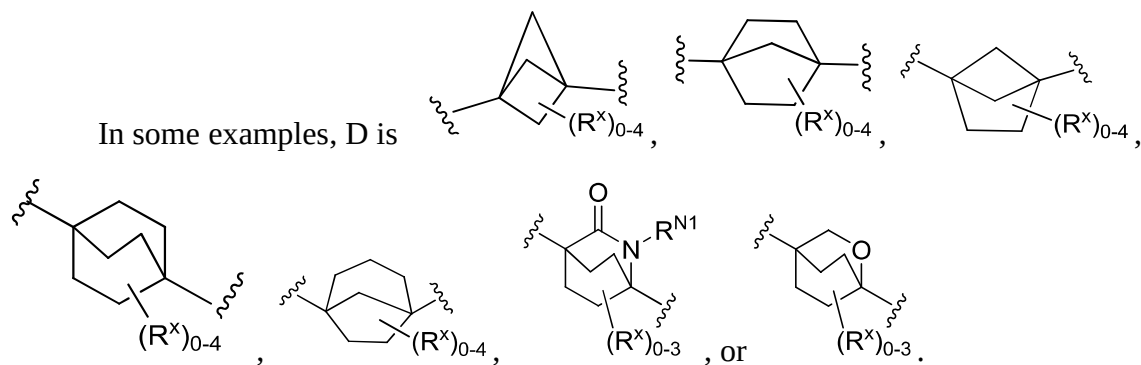
In some examples, D is a bridged bicyclic cycloalkyl or bridged bicyclic heterocyclyl, each of which is optionally substituted with 1-4 R^X .

In some examples, D is a bridged 5-8 membered bicyclic cycloalkyl or heterocyclyl, each of which is optionally substituted with 1-4 R^X . bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane, bicyclo[2.1.1]hexane, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[3.2.1]octane, 2-azabicyclo[2.2.2]octane, or 2-oxabicyclo[2.2.2]octane, each of which is optionally substituted with 1-4 R^X groups.

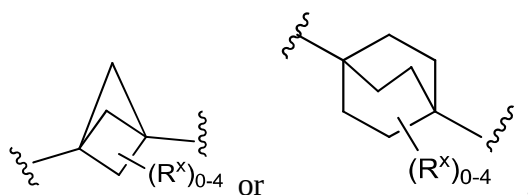
In some examples, D is bicyclo[1.1.1]pentane optionally substituted with 1-4 R^X . In



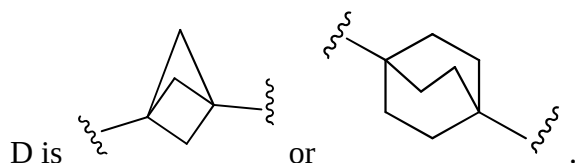
In some examples, D is



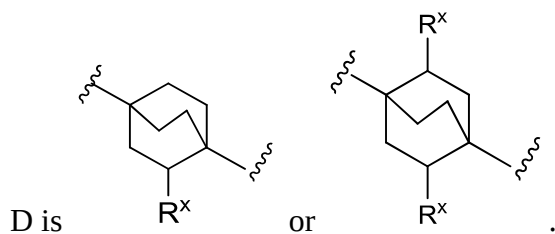
In some examples, D is



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

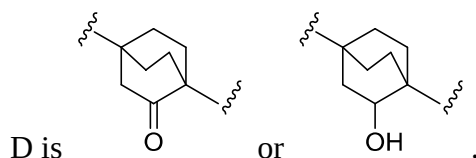


In some examples, D is substituted with 1 or 2 R^X . In some examples,



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, R^X is oxo or $-OR^A$ (e.g., oxo or OH). In some examples,



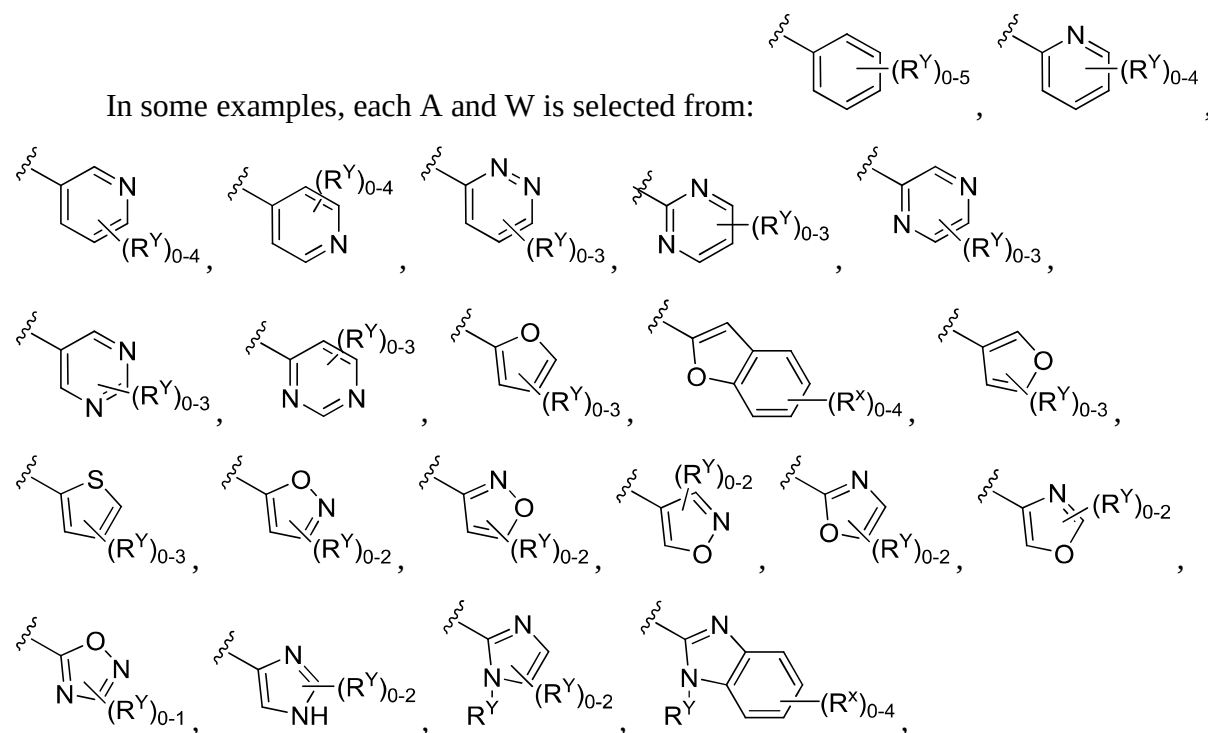
In some examples, L^1 is CH_2O-^* or $CH_2CH_2O-^*$, wherein “ $-^*$ ” indicates the attachment point to A.

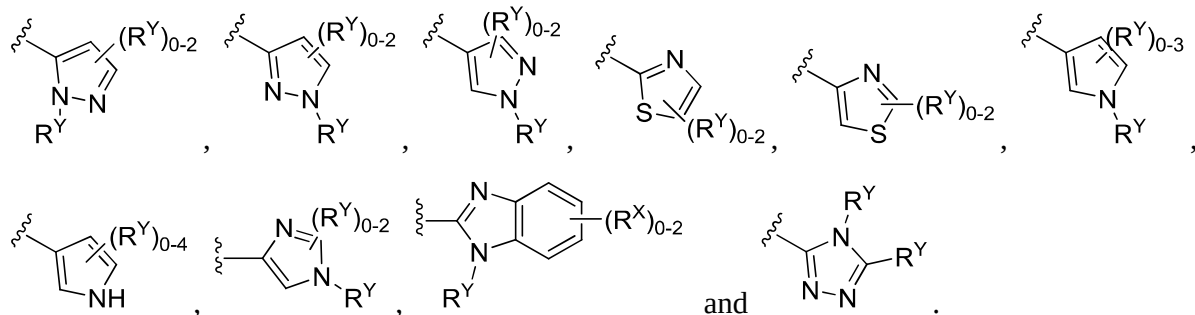
In some examples, L^2 is selected from the group consisting of $-\text{CH}_2^*$, $-\text{CH}_2\text{CH}_2^*$, $\text{CH}_2\text{CH}_2\text{CH}_2^*$, $-\text{CH}(\text{CH}_3)^*$, $-\text{CH}_2(\text{CH}_3)\text{CH}_2^*$, $-\text{CH}_2\text{C}(\text{O})^*$, $-\text{CH}_2\text{O}^*$, $-\text{N}(\text{CH}_2\text{CONH}_2)\text{CH}_2^*$ and $-\text{CH}_2\text{CH}_2\text{O}^*$, wherein “ * ” indicates the attachment point to W.

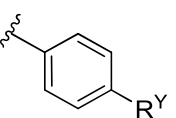
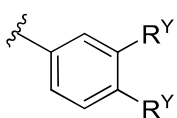
In some examples, R^1 and R^2 are each hydrogen or $\text{C}_1\text{-C}_6$ alkyl. In some examples, R^1 and R^2 are each hydrogen or $-\text{CH}_3$. In some examples, R^1 and R^2 are each hydrogen.

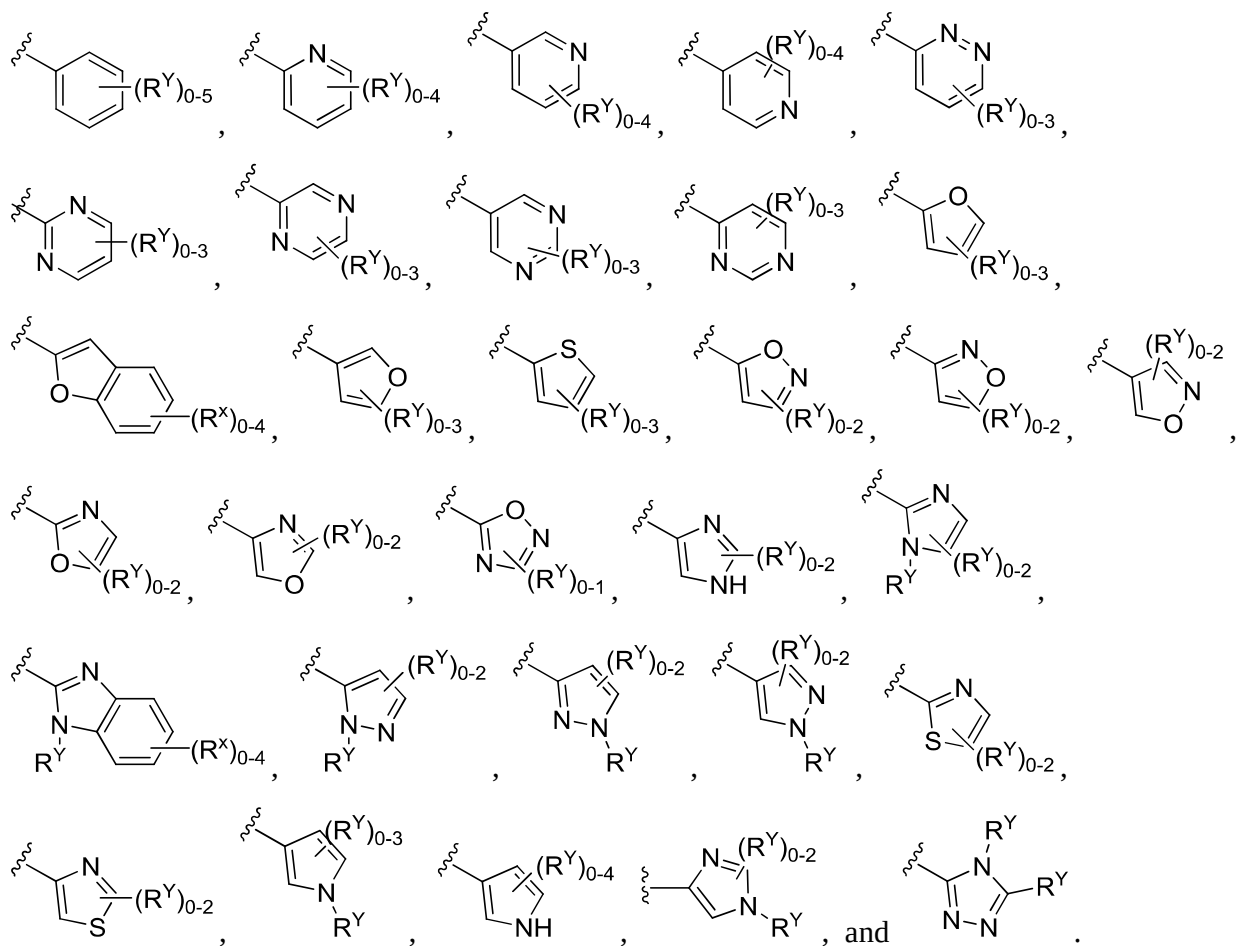
In some examples, A is phenyl and W is independently phenyl or 5-6-membered heteroaryl. In some examples, each A and W is independently phenyl. In some examples, A is phenyl and W is 5-6-membered heteroaryl.

In some examples, W is a monocyclic 5-6-membered heteroaryl. In some examples, 2 R^Y groups on adjacent atoms of W, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl or heterocyclyl optionally substituted with 1-5 R^X forming a bicyclic heteroaryl. In some examples, W is a 10-membered heteroaryl, a 9-membered heteroaryl, a 6-membered heteroaryl, or a 5-membered heteroaryl. In some examples, W is a heteroaryl containing nitrogen, oxygen or sulfur as allowed by valence.





In some examples, A is  or  and W is selected from:



In some examples, each R^Y is independently C_1 - C_6 alkyl, CO_2H - C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo- C_1 - C_6 alkoxy, halo, cyano, $-OR^A$, $-NR^B R^C$, $-C(O)NR^B R^C$, $-S(O)_2 R^D$, $-S(R^F)_m$, or G^1 , or 2 R^Y groups on adjacent atoms, together with the

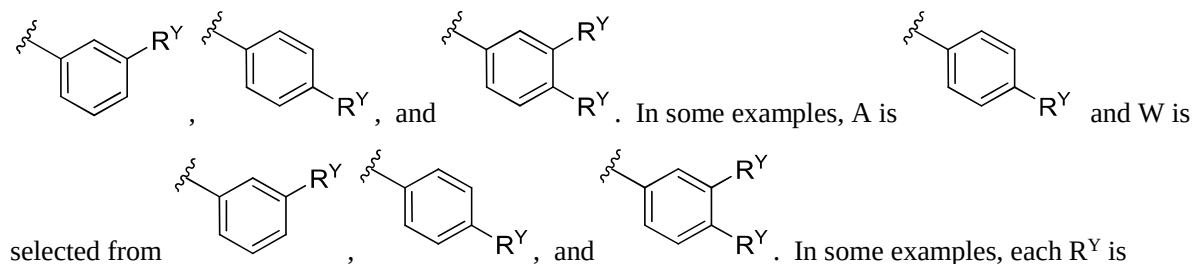
atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7 membered heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X .

In some examples, R^Y is chloro, fluoro, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CF_3$, $-CHF_2$, $-CH_2CO_2H$, $-CH_2OCH_3$, CH_2CO_2H , $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCHF_2$, $-OCF_3$, $-OCH_2CHF_3$, $-C(O)NH_2$, $-N(CH_3)_2$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, or $-SCF_3$.

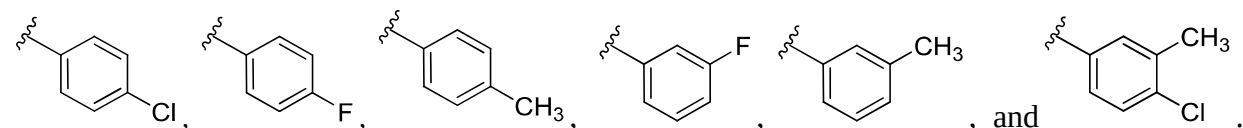
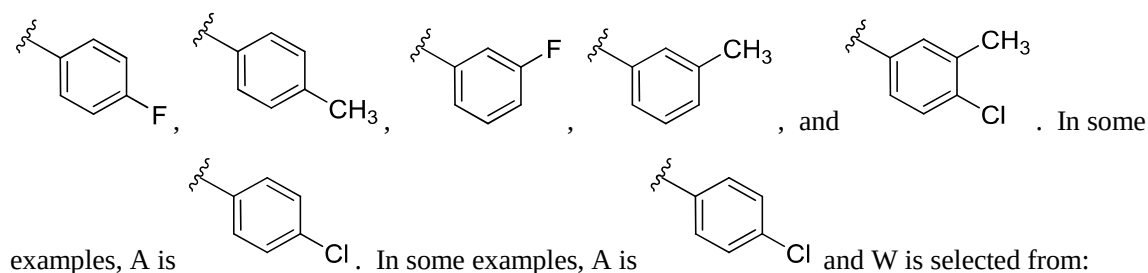
In some examples, each A and W is optionally substituted with 1-5 R^Y . In some examples, R^Y is C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo- C_1 - C_6 alkoxy, halo, cyano, $-OR^A$, $-NR^B R^C$, $-S(O)_2 R^D$, $-S(R^F)_m$, or G^1 . In some examples, R^Y is chloro, fluoro, $-CH_3$, $-CH_2CH_3$, $CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CF_3$, $-CH_2OCH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCHF_2$, $-OCF_3$, $-OCH_2CHF_2$, $N(CH_3)_2$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, or SCF_3 .

In some examples, G^1 is phenyl optionally substituted with 1-3 R^Z . In some examples, each R^Z is C_1 - C_6 alkyl (e.g., CH_3).

In some examples, each A and W is independently a phenyl optionally substituted with 1-5 R^Y , and each R^Y is independently C_1 - C_6 alkyl or halo. In some examples, each of A and W is selected from:

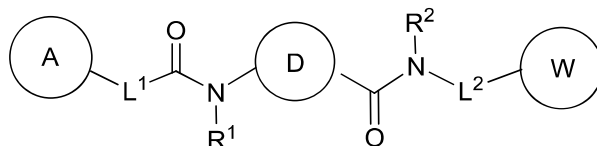


independently chloro, fluoro, or CH_3 . In some examples, each of A and W is selected from



In some examples, G^1 is phenyl optionally substituted with 1-3 R^Z . In some examples, each R^Z is C_1 - C_6 alkyl (e.g., CH_3).

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

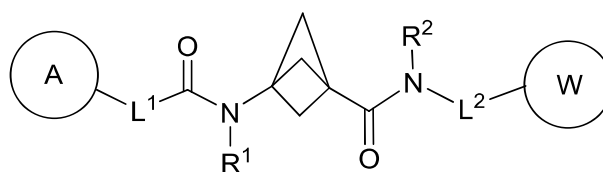


Formula (I-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 with 1-4 R^X ; L^1 and L^2 are each independently C_1 - C_6 alkylene or 2-7-membered heteroalkylene, wherein each C_1 - C_6 alkylene or 2-7-membered heteroalkylene is optionally substituted with 1-5 R^X ; R^1 and R^2 are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_2 - C_6 alkyl, hydroxy- C_2 - C_6 alkyl, silyloxy- C_2 - C_6 alkyl; A and W are each independently phenyl or 5-6-membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y ; each R^X 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, amino- C_1 - C_6 alkyl, cyano- C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-SR^E$, $-S(O)R^D$, and $-S(O)_2 R^D$; 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, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2 R^D$, 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 or heterocyclyl optionally substituted with 1-5 R^X ; each G^1 is independently C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl, 4-7-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, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, and $-S(O)_2 R^D$; R^A is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, 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 optionally

substituted with 1-3 R^Z ; 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, halo- 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, the compound of Formula (I) is a compound of Formula (I-b):



Formula (I-b)

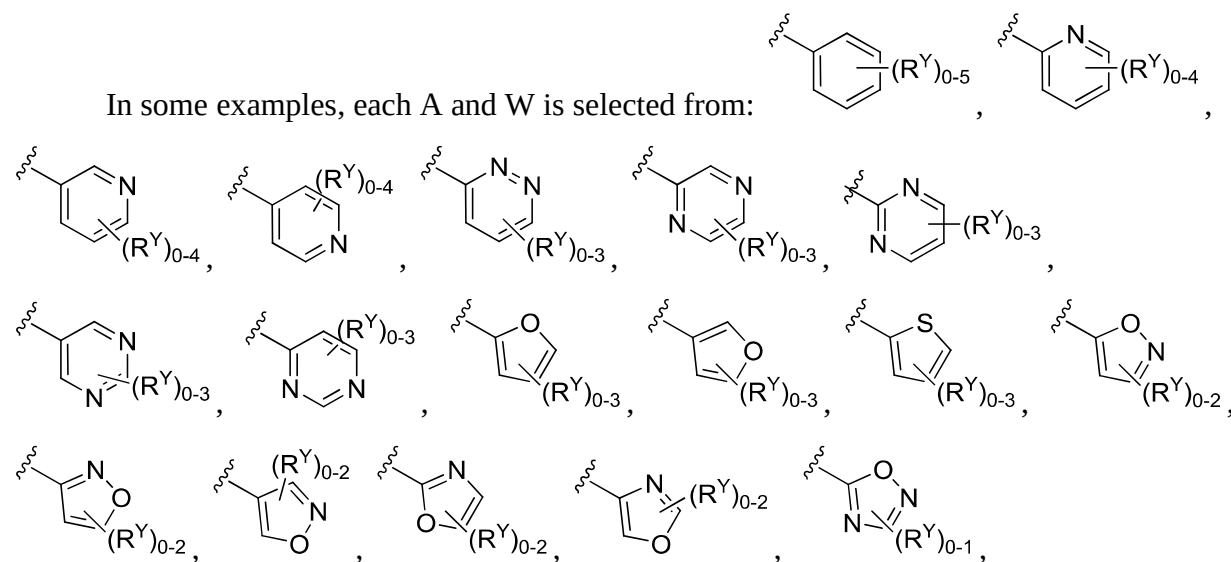
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein at least one of L^1 and L^2 is independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X , wherein “-*” indicates the attachment point to A and W, respectively; R^1 and R^2 are each hydrogen or C_1 - C_6 alkyl; A is phenyl substituted with 1-2 R^Y ; W is phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with 1-5 R^Y ; each R^X is oxo or $-OR^A$; and each R^Y is independently selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo- C_1 - C_6 alkoxy, halo, cyano, $-OR^A$, $-NR^B R^C$, $-C(O)NR^B R^C$, $-S(O)_2 R^D$, $-S(R^F)_m$, or 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 heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X ; G^1 is phenyl optionally substituted with 1-3 R^Z ; each R^Z is independently C_1 - C_6 alkyl; R^A is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, or halo- C_1 - C_6 alkyl; each of R^B and R^C is independently hydrogen or C_1 - C_6 alkyl; each R^D is independently C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, or $-NR^{B1} R^{C1}$; each R^F is independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, or halo; each of R^{B1} and R^{C1} is independently hydrogen or C_1 - C_6 alkyl; 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.

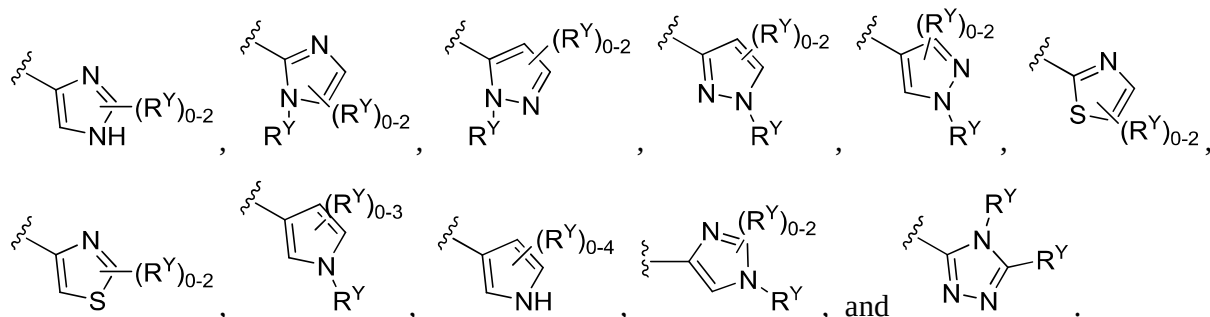
In some examples, at least one of L^1 and L^2 is independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X . In some examples, both of L^1 and L^2 are independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X . In some examples, L^1 is 2-7-membered heteroalkylene and L^2 is independently selected from C_1 - C_6 alkylene or 2-7-membered heteroalkylene, wherein each alkylene and heteroalkylene is optionally substituted by 1-5 R^X . In some examples, both of L^1 and L^2 are independently 2-

7-membered heteroalkylene substituted by 0 R^X . In some examples, L^1 is independently selected from CH_2O^* or $CH_2CH_2O^*$, L^2 is independently selected from $-CH_2^*$, $-CH_2CH_2^*$, $CH_2CH_2CH_2^*$, $-CH_2(CH_3)^*$, $-CH_2(CH_3)CH_2^*$, CH_2O^* or $CH_2CH_2O^*$, and “ $-^*$ ” indicates the attachment point to A and W, respectively. In some examples, each L^1 and L^2 is independently selected from CH_2O^* or $CH_2CH_2O^*$, and “ $-^*$ ” indicates the attachment point to A and W, respectively. In some examples, L^1 is CH_2O^* and L^2 is $CH_2CH_2O^*$, and “ $-^*$ ” indicates the attachment point to A and W, respectively.

In some examples, R^1 and R^2 are each hydrogen or C_1 - C_6 alkyl. In some examples, R^1 and R^2 are each hydrogen or $-CH_3$. In some examples, R^1 and R^2 are each hydrogen.

In some examples, each A and W is independently phenyl or 5-6 membered heteroaryl, optionally substituted with 1-5 R^Y . In some examples, A is phenyl and W is independently phenyl or 5-6 membered heteroaryl. In some examples, each A and W is independently phenyl. In some examples, A is phenyl and W is 5-6 membered heteroaryl. In some examples, W is a monocyclic heteroaryl. In some examples, W is a bicyclic heteroaryl. In some examples, W is a 10-membered heteroaryl, a 9-membered heteroaryl, a 6-membered heteroaryl, or a 5-membered heteroaryl. In some examples, W is a heteroaryl containing nitrogen, oxygen or sulfur as allowed by valence.

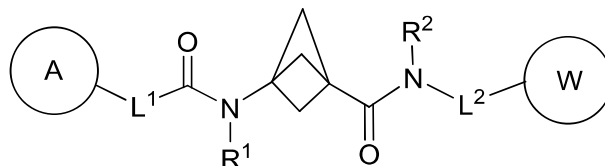




In some examples, each A and W is optionally substituted with 1-5 R^Y . In some examples, R^Y is C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo- C_1 - C_6 alkoxy, halo, cyano, $-OR^A$, $-NR^B R^C$, $-S(O)_2 R^D$, or $-S(R^F)_m$. In some examples, R^Y is chloro, fluoro, $-CH_3$, $-CH_2CH_3$, $CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-CF_3$, $-CH_2OCH_3$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-OCHF_2$, $-OCF_3$, $-OCH_2CHF_2$, $N(CH_3)_2$, $-S(O)_2CH_3$, $-S(O)_2NH_2$, or SCF_3 .

In some examples, G^1 is phenyl optionally substituted with 1-3 R^Z . In some examples, each R^Z is C_1 - C_6 alkyl (e.g., CH_3).

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



Formula (I-c)

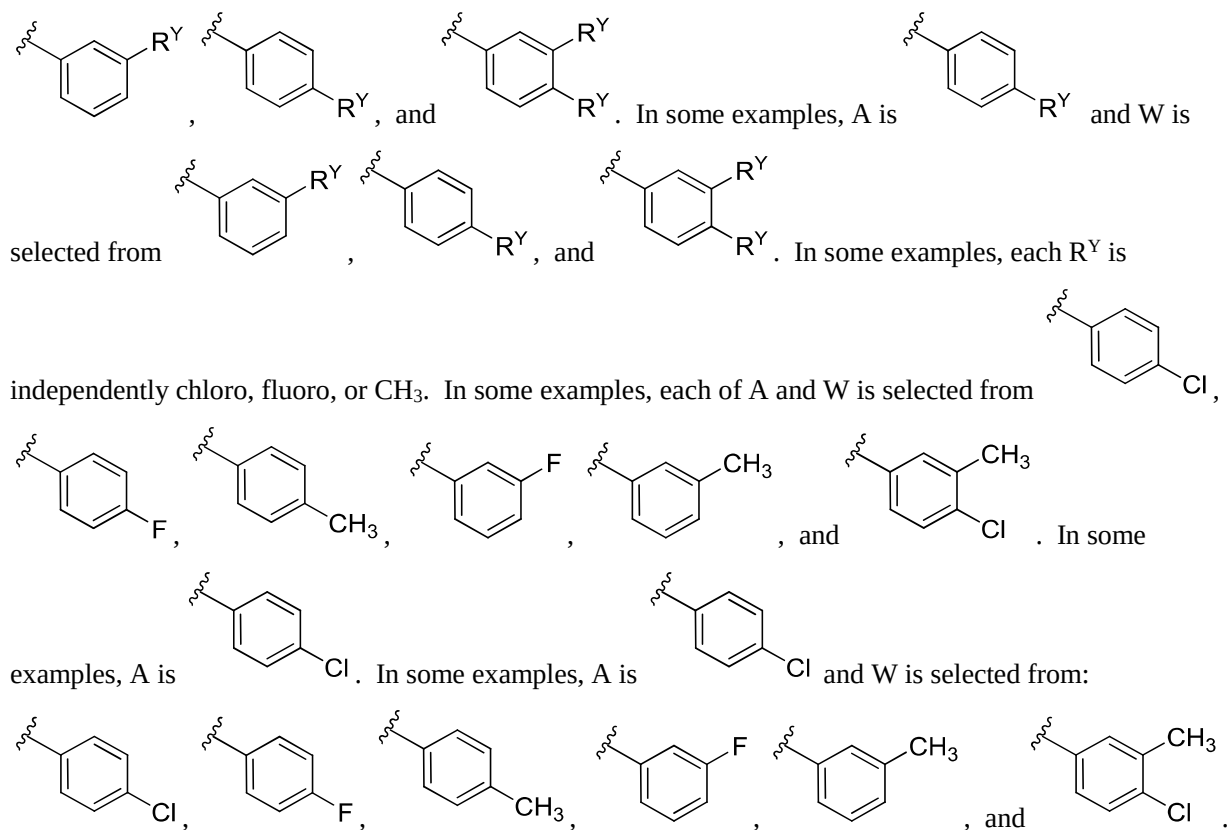
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein L^1 and L^2 are each independently CH_2 -, $-CH_2CH_2$ -, $CH_2CH_2CH_2$ -, $-CH_2(CH_3)$ -, $-CH_2(CH_3)CH_2$ -, CH_2O - or CH_2CH_2O -, wherein “-” indicates the attachment point to A and W, respectively; R^1 and R^2 are each hydrogen; A and W are each independently phenyl substituted with 1-2 R^Y ; and each R^Y is independently selected from the group consisting of chloro, fluoro, and CH_3 .

In some examples, at least one of L^1 and L^2 is independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X . In some examples, both of L^1 and L^2 are independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X . In some examples, both of L^1 and L^2 are independently 2-7-membered heteroalkylene substituted by 0 R^X . In some examples, at least one of L^1 and L^2 is independently C_1 - C_6 alkylene optionally substituted by 1-5 R^X . In some examples, each L^1 and L^2 is independently selected from

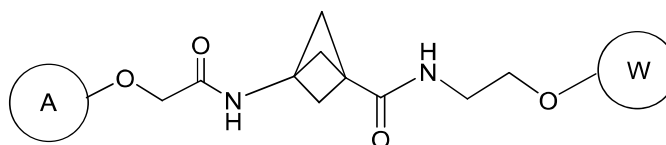
CH₂-, CH(CH₃)-, CH₂CH₂-, CH(CH₃)CH₂-, CH₂CH₂CH₂-, CH₂O- or CH₂CH₂O-, and “-” indicates the attachment point to A and W, respectively. In some examples, each L¹ and L² is independently selected from CH₂O- or CH₂CH₂O-, and “-” indicates the attachment point to A and W, respectively. In some examples, L¹ is CH₂O- and L² is CH₂CH₂O-, and “-” indicates the attachment point to A and W, respectively.

In some examples, R¹ and R² are each hydrogen.

In some examples, each A and W is independently a phenyl optionally substituted with 1-5 R^Y, and each R^Y is independently C₁-C₆ alkyl or halo. In some examples, each of A and W is selected from:



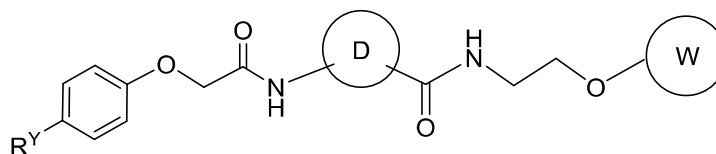
In some examples, the compound of Formula (I) is a compound of Formula (I-d):



Formula (I-d)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of A and W is defined as for Formula (I).

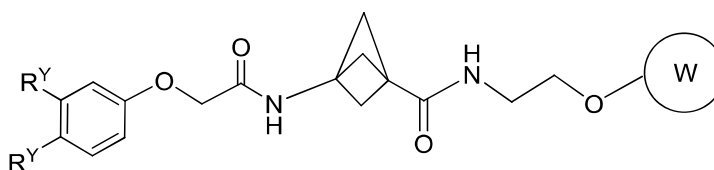
In some examples, the compound of Formula (I) is a compound of Formula (I-e):



Formula (I-e)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of D, W and R^Y is defined as for Formula (I).

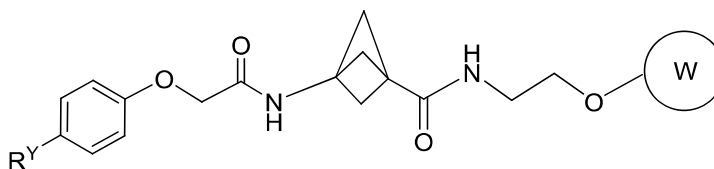
In some examples, the compound of Formula (I) is a compound of Formula (I-f):



Formula (I-f)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of W and R^Y is defined as for Formula (I).

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



Formula (I-g)

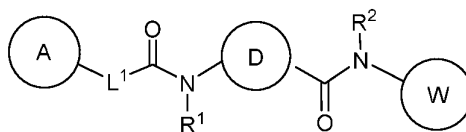
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein each of W and R^Y is defined as for Formula (I).

In some examples, the compound of Formula (I) (e.g., a compound of Formula (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) is selected from a compound set forth in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some examples, the compound of Formula (I) (e.g., a compound of Formula (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt thereof is formulated as a pharmaceutically acceptable composition comprising a disclosed compound and a pharmaceutically acceptable carrier.

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Also disclosed herein is a compound of Formula (II):



Formula (II)

- 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 with 1-4 R^X groups; and wherein if the bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen moiety may be optionally substituted by R^{N1} ;

L^1 is 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^X ;

R^1 and R^2 are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_2 - C_6 alkyl, hydroxy- C_2 - C_6 alkyl, or silyloxy- C_2 - C_6 alkyl;

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, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OR^D$, and $-S(O)_2 R^D$;

A and W are each independently phenyl or 5-6 membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y ;

each R^X 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, amino- C_1 - C_6 alkyl, cyano- C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-SR^E$, $-S(O)R^D$, and $-S(O)_2 R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, hydroxy- C_1 - C_6 alkyl, C_1 - C_6 alkoxy- 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, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2 R^D$, 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 heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X ;

each G^1 is independently C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl, 4-7-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, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, and $-S(O)_2 R^D$;

R^A is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, $-C(O)NR^B R^C$, $-C(O)R^D$, 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 optionally substituted with 1-3 R^Z ;

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

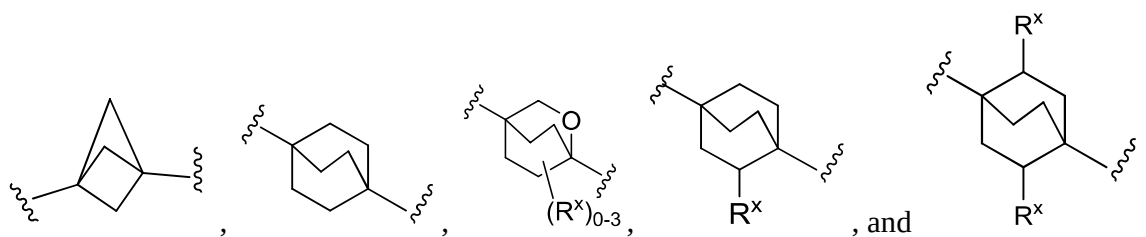
each R^E is independently hydrogen, C_1 - C_6 alkyl, or halo- C_1 - C_6 alkyl;

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

each of R^{B1} and R^{C1} is independently hydrogen or C_1 - C_6 alkyl; 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.

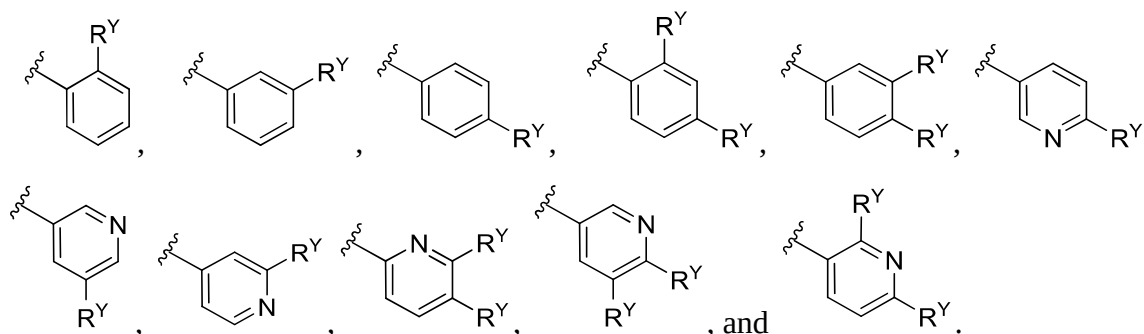
In some examples, D is selected from the group consisting of



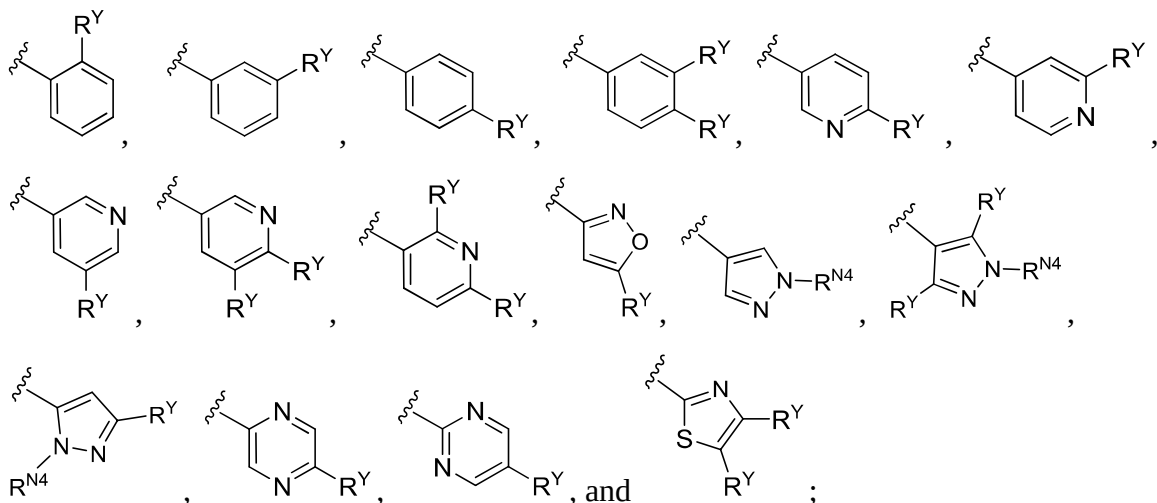
In some examples, each R^X is independently selected from the group consisting of oxo, $-OR^A$ (e.g., OH or OCH_3), $-C(O)OH$, $-C(O)OR^D$ (e.g., $-C(O)OCH_3$), halo, and hydroxy- C_1 - C_6 alkyl. In some examples, each of R^1 and R^2 is hydrogen or CH_3 . each R^X is independently selected from the group consisting of oxo, $-OH$, $-OCH_3$, $-C(O)OH$, $-C(O)OCH_3$, halo, and hydroxy- C_1 - C_6 alkyl.

In some examples, L^1 is CH_2O-* or CH_2CH_2O-* , wherein “-*” indicates the attachment point to A.

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



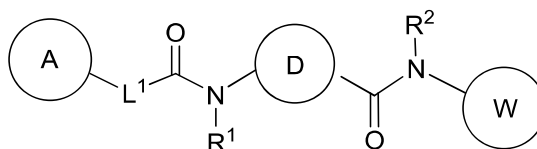
In some examples, W is selected from the group consisting of:



wherein R^{N4} is hydrogen or CH_3 .

In some examples, each R^Y is independently hydrogen, bromo, chloro, fluoro, iodo, CF_3 , CHF_2 , CH_2CF_3 , CH_3 , CH_2CH_3 , OH, CH_2OH , $C(CH_3)_2OH$, OCH_3 , OCH_2CH_3 , OCF_3 , OCH_2CF_3 , $S(O)_2CH_3$, $S(O)_2CH_2CH_2CH_3$, CN, $N(CH_3)_2$, SF_5 , SCH_3 , NH_2 , $C(CH_3)_3$, $CH(CH_3)_2$, CH_2CN , CH_2NH_2 , $CH(OH)CH_3$, $C(OH)(CH_3)CF_3$, $S(O)_2CH_3$, $C(O)CH_3$, $C(O)OCH_3$, $C(O)OH$, $OCHF_2$ or G^1 .

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



Formula (II-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

D is bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or 2-oxabicyclo[2.2.2]octane, each of which is optionally substituted with 1-4 R^X groups;

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

W is phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, isoxazolyl, or pyrazolyl, each of which is optionally substituted on one or more available carbons with 1-5 R^Y groups; and wherein pyrazolyl may be optionally substituted on an available nitrogen with hydrogen or CH₃;

L¹ is CH₂O-* or CH₂CH₂O-*, wherein “-*” indicates the attachment point to A;

each R^X is independently fluoro, oxo, OH, OCH₃, C(O)OH, or C(O)OCH₃;

each R^Y is independently hydrogen, bromo, chloro, fluoro, iodo, CF₃, CHF₂, CH₂CF₃, CH₃, CH₂CH₃, OH, CH₂OH, C(CH₃)₂OH, OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, S(O)₂CH₃, S(O)₂CH₂CH₂CH₃, CN, N(CH₃)₂, SF₅, SCH₃, NH₂, C(CH₃)₃, CH(CH₃)₂, CH₂CN, CH₂NH₂, CH(OH)CH₃, C(OH)(CH₃)CF₃, S(O)₂CH₃, C(O)CH₃, C(O)OCH₃, C(O)OH, OCHF₂ or G¹;

2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a furanyl, pyrrolyl, or dioxolanyl ring, each of which is optionally substituted with 1-2 R^X; and

each of R¹ and R² is hydrogen or CH₃.

In some examples, the compound of Formula (II) (e.g., a compound of Formula (II-a) 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 (II) (e.g., a compound of Formula (II-a) is selected from a compound set forth in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In another example, the present disclosure features a method of treating a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, a metabolic disease, 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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 vanishing white matter disease, childhood ataxia with CNS hypo-myelination, a leukodystrophy, a leukoencephalopathy, hypomyelinating or demyelinating disease, an intellectual disability syndrome, 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, Alzheimer's disease, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, frontotemporal dementia, Gerstmann-Straussler-Scheinker disease, Huntington's disease, dementia (e.g., HIV-associated dementia or Lewy body dementia), kuru, Parkinson's disease, progressive nuclear palsy, a tauopathy, or a prion disease. In some examples, the neurodegenerative disease comprises vanishing white matter disease. In some examples, the neurodegenerative disease comprises a psychiatric disease such as agoraphobia, Alzheimer's disease, anorexia nervosa, amnesia, anxiety 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 examples, the neurodegenerative disease comprises a disease or disorder with symptoms of cognitive impairment or cognitive decline such as Alzheimer's disease, Parkinson's disease, Huntington's disease, schizophrenia, autism, frontotemporal dementia, dementia (e.g., HIV-associated dementia or Lewy body dementia), age related dementia, chronic traumatic encephalopathy, HIV-induced neurocognitive impairment, a HIV-associated neurocognitive disorder, a hypoxic injury (e.g., premature brain injury, chronic perinatal hypoxia), traumatic brain injury, stroke, or postoperative cognitive dysfunction. In some examples, the neurodegenerative disease comprises an intellectual disability syndrome. In some examples, the neurodegenerative disease comprises mild cognitive impairment.

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 cancer in combination with a chemotherapeutic agent for the enhancement of memory (e.g., long term memory).

In some examples, the method comprises the treatment of an inflammatory disease. In some examples, the inflammatory disease comprises postoperative cognitive dysfunction, traumatic brain injury, 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, 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, Freidrich's ataxia, a muscle wasting disorder (e.g., muscle atrophy, sarcopenia, cachexia), inclusion body myopathy, progressive muscular atrophy, motor neuron disease, carpal tunnel syndrome, epicondylitis, tendinitis, back pain, muscle pain, muscle soreness, repetitive strain disorders, 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, 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, e.g., the mitochondrial myopathy, 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 eIF2 α activity or level, modulation (e.g., an increase) in eIF2 α phosphorylation, modulation

(e.g., an increase) of phosphorylated eIF2 α 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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 eIF2 α signaling pathway or ISR pathway).

In another example, the present disclosure features a method of treating a leukodystrophy such as vanishing white matter disease (VWMD) or childhood ataxia with central nervous system hypomyelination. In some examples, the leukodystrophy is characterized by an amino acid mutation (e.g., an amino acid deletion, amino acid addition, or amino acid substitution) in a tRNA synthetase. In some examples, administration of a compound of Formula (I) or Formula (II) enhances eIF2B activity in a subject with a leukodystrophy, such as vanishing white matter disease (VWMD) or childhood ataxia with central nervous system hypomyelination.

In another example, the present disclosure features a method of treating a disease or disorder related to an amino acid mutation (e.g., an amino acid deletion, amino acid addition, or amino acid substitution) in a gene or gene product (e.g., RNA or protein) that modulates (e.g., reduces) protein synthesis. In some examples, administration of a compound of Formula (I) or Formula (II) enhances residual GEF activity of a mutant GEF complex in a subject.

In another example, the present disclosure features a composition for use in treating a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease in a subject, wherein the composition comprises a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

In some examples, the neurodegenerative disease comprises vanishing white matter disease, childhood ataxia with CNS hypo-myelination, a leukodystrophy, a leukoencephalopathy, hypomyelinating or demyelinating disease, an intellectual disability syndrome, 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 leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), DARS2-related spectrum disorders, Alzheimer's disease, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, frontotemporal dementia, Gerstmann-Straussler-Scheinker disease,

Huntington's disease, dementia (e.g., HIV-associated dementia or Lewy body dementia), kuru, Parkinson's disease, progressive nuclear palsy, a tauopathy, or a prion disease. In some examples, the neurodegenerative disease comprises vanishing white matter disease. In some examples, the neurodegenerative disease comprises a psychiatric disease such as agoraphobia, Alzheimer's disease, anorexia nervosa, amnesia, anxiety 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 examples, the neurodegenerative disease comprises a disease or disorder with symptoms of cognitive impairment or cognitive decline such as Alzheimer's disease, Parkinson's disease, Huntington's disease, schizophrenia, autism, frontotemporal dementia, dementia (e.g., HIV-associated dementia or Lewy body dementia), age related dementia, chronic traumatic encephalopathy, HIV-induced neurocognitive impairment, a HIV-associated neurocognitive disorder, a hypoxic injury (e.g., premature brain injury, chronic perinatal hypoxia), traumatic brain injury, stroke, or postoperative cognitive dysfunction. In some examples, the neurodegenerative disease comprises an intellectual disability syndrome. In some examples, the neurodegenerative disease comprises mild cognitive impairment.

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 cancer in combination with a chemotherapeutic agent for the enhancement of memory (e.g., long term memory).

In some examples, the inflammatory disease comprises postoperative cognitive dysfunction, traumatic brain injury, 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, or atopic dermatitis.

In some examples, the musculoskeletal disease comprises muscular dystrophy, multiple sclerosis, Freidrich's ataxia, a muscle wasting disorder (e.g., muscle atrophy, sarcopenia, cachexia), inclusion body myopathy, progressive muscular atrophy, motor neuron disease, carpal tunnel syndrome, epicondylitis, tendinitis, back pain, muscle pain, muscle soreness, repetitive strain disorders, or paralysis.

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, phenylketonuria, proliferative retinopathy, or Kearns-Sayre 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, e.g., the mitochondrial myopathy, 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 composition for use in treating a disease or disorder related to modulation (e.g., a decrease) in eIF2B activity or level, modulation (e.g., a decrease) of eIF2 α activity or level, modulation (e.g., an increase) in eIF2 α phosphorylation, modulation (e.g., an increase) of phosphorylated eIF2 α pathway activity, or modulation (e.g., an increase) of ISR activity in a subject, wherein the composition comprises a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. 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 eIF2 α signaling pathway or ISR pathway).

In another example, the present disclosure features a composition for use in treating a leukodystrophy such as vanishing white matter disease (VWMD) or childhood ataxia with central nervous system hypomyelination. In some examples, the leukodystrophy is

characterized by an amino acid mutation (e.g., an amino acid deletion, amino acid addition, or amino acid substitution) in a tRNA synthetase. In some examples, the composition comprising a compound of Formula (I) or Formula (II) enhances eIF2B activity in a subject with a leukodystrophy, such as vanishing white matter disease (VWMD) or childhood ataxia with central nervous system hypomyelination.

In another example, the present disclosure features a composition for use in treating a disease or disorder related to an amino acid mutation (e.g., an amino acid deletion, amino acid addition, or amino acid substitution) in a gene or gene product (e.g., RNA or protein) that modulates (e.g., reduces) protein synthesis. In some examples, the composition comprising a compound of Formula (I) or Formula (II) enhances residual GEF activity of a mutant GEF complex in a subject.

DETAILED DESCRIPTION OF THE INVENTION

The present invention features compounds, compositions, and methods comprising a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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.

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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.

5 Compound described herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (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.

10 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 “ $\text{C}_1\text{-C}_6$ alkyl” is intended to encompass, C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_5$, $\text{C}_1\text{-C}_4$, $\text{C}_1\text{-C}_3$, $\text{C}_1\text{-C}_2$, $\text{C}_2\text{-C}_6$, $\text{C}_2\text{-C}_5$, $\text{C}_2\text{-C}_4$, $\text{C}_2\text{-C}_3$, $\text{C}_3\text{-C}_6$, $\text{C}_3\text{-C}_5$, $\text{C}_3\text{-C}_4$, $\text{C}_4\text{-C}_6$, $\text{C}_4\text{-C}_5$, and $\text{C}_5\text{-C}_6$ 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 (“ $\text{C}_1\text{-C}_{20}$ alkyl”). In some embodiments, an alkyl group has 1 to 12 carbon atoms (“ $\text{C}_1\text{-C}_{12}$ alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“ $\text{C}_1\text{-C}_8$ alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“ $\text{C}_1\text{-C}_6$ alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“ $\text{C}_1\text{-C}_5$ alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“ $\text{C}_1\text{-C}_4$ alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“ $\text{C}_1\text{-C}_3$ alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“ $\text{C}_1\text{-C}_2$ 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 (“ $\text{C}_2\text{-C}_6$ alkyl”). Examples of $\text{C}_1\text{-C}_6$ 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).
30 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 C₁₋₁₀ alkyl (e.g., -CH₃). In certain embodiments, the alkyl group is substituted C₁₋₆ alkyl. Common alkyl abbreviations include Me (-CH₃), Et (-CH₂CH₃), iPr (-CH(CH₃)₂), nPr (-CH₂CH₂CH₃), n-Bu (-CH₂CH₂CH₂CH₃), or i-Bu (-CH₂CH(CH₃)₂).

5 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, -CH₂CH₂CH₂CH₂-. 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
10 divalent radical derived from an alkene. An alkylene group may be described as, e.g., a C₁-C₆-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 ("C₂-
15 C₂₀ alkenyl"). In some embodiments, an alkenyl group has 2 to 10 carbon atoms ("C₂-C₁₀ alkenyl"). In some embodiments, an alkenyl group has 2 to 8 carbon atoms ("C₂-C₈ alkenyl"). In some embodiments, an alkenyl group has 2 to 6 carbon atoms ("C₂-C₆ alkenyl"). In some embodiments, an alkenyl group has 2 to 5 carbon atoms ("C₂-C₅ alkenyl"). In some
20 embodiments, an alkenyl group has 2 to 4 carbon atoms ("C₂-C₄ alkenyl"). In some embodiments, an alkenyl group has 2 to 3 carbon atoms ("C₂-C₃ alkenyl"). In some embodiments, an alkenyl group has 2 carbon atoms ("C₂ 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 C₂-C₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂-C₆ alkenyl groups
25 include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), and the like. Each instance of an alkenyl group may be independently optionally substituted, *i.e.*, unsubstituted (an "unsubstituted alkenyl") or substituted (a
30 "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 C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is substituted C₂₋₆ alkenyl.

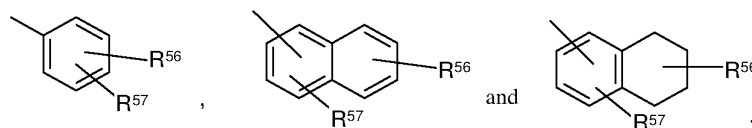
 "Aryl" refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14

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ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C₆-C₁₄ aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). An aryl group may be described as, *e.g.*, a C₆-C₁₀-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 C₆-C₁₄ aryl. In certain embodiments, the aryl group is substituted C₆-C₁₄ aryl.

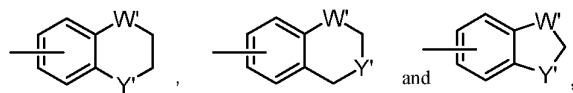
In certain embodiments, an aryl group is substituted with one or more of groups selected from halo, C₁-C₈ alkyl, halo-C₁-C₈ alkyl, haloxy-C₁-C₈ alkyl, cyano, hydroxy, alkoxy C₁-C₈ alkyl, and amino.

Examples of representative substituted aryls include the following



wherein one of R⁵⁶ and R⁵⁷ may be hydrogen and at least one of R⁵⁶ and R⁵⁷ is each independently selected from C₁-C₈ alkyl, halo-C₁-C₈ alkyl, 4-10 membered heterocyclyl, alkanoyl, alkoxy-C₁-C₈ alkyl, heteroaryloxy, alkylamino, arylamino, heteroaryl amino, NR⁵⁸COR⁵⁹, NR⁵⁸SOR⁵⁹, NR⁵⁸SO₂R⁵⁹, C(O)Oalkyl, C(O)Oaryl, CONR⁵⁸R⁵⁹, CONR⁵⁸OR⁵⁹, NR⁵⁸R⁵⁹, SO₂NR⁵⁸R⁵⁹, S-alkyl, S(O)-alkyl, S(O)₂-alkyl, S-aryl, S(O)-aryl, S(O)₂-aryl; or R⁵⁶ and R⁵⁷ 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(R⁶⁶)₂, NR⁶⁶, O, and S; and each Y' is selected from carbonyl, NR⁶⁶, O and S; and R⁶⁶ is independently hydrogen, C₁-C₈ alkyl, C₃-C₁₀ cycloalkyl, 4-10 membered heterocyclyl, C₆-C₁₀ 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, quinoxalinonyl, 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-C₁-C₆ 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: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-, -S(O)₂-, -S(O)-CH₃, -S(O)₂-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃-, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, -O-CH₃, and -O-CH₂-CH₃. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -CH₂O-, -NR^BR^C-, or the like, it will be understood that the terms

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heteroalkyl and $-\text{CH}_2\text{O}$ or $-\text{NR}^{\text{B}}\text{R}^{\text{C}}$ 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 $-\text{CH}_2\text{O}$, $-\text{NR}^{\text{B}}\text{R}^{\text{C}}$, 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, $-\text{CH}_2\text{O}-$ and $-\text{CH}_2\text{CH}_2\text{O}-$. 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 $-\text{C}(\text{O})_2\text{R}'-$ may represent both $-\text{C}(\text{O})_2\text{R}'-$ and $-\text{R}'\text{C}(\text{O})_2-$.

"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

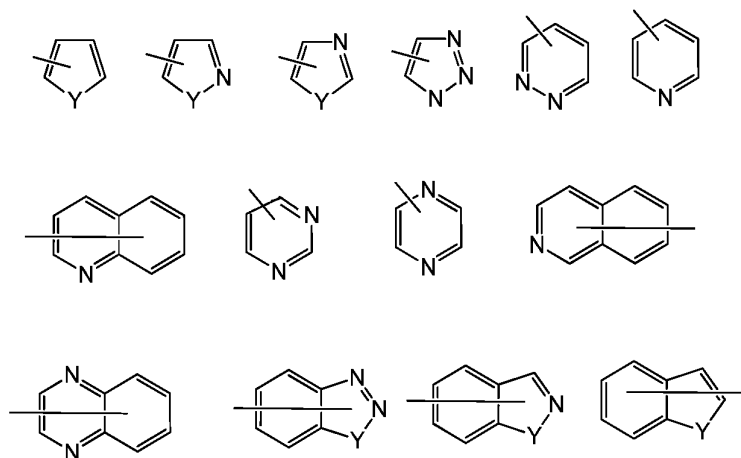
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system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms 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:

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wherein each Y is selected from carbonyl, N, NR⁶⁵, O, and S; and R⁶⁵ is independently hydrogen, C₁–C₈ alkyl, C₃–C₁₀ cycloalkyl, 4–10 membered heterocyclyl, C₆–C₁₀ aryl, and 5–10 membered heteroaryl.

- 5 “Cycloalkyl” refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms (“C₃–C₁₀ cycloalkyl”) and zero heteroatoms in the non–aromatic ring system. In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃–C₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃–C₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃–C₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅–C₁₀ cycloalkyl”). A cycloalkyl group may be described as, e.g., a C₄–C₇–membered cycloalkyl, wherein the term “membered” refers to the non-hydrogen ring atoms within the moiety.
- Exemplary C₃–C₆ cycloalkyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃–C₈ cycloalkyl groups include, without limitation, the aforementioned C₃–C₆ cycloalkyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), cubanyl (C₈), bicyclo[1.1.1]pentanyl (C₅), bicyclo[2.2.2]octanyl (C₈), bicyclo[2.1.1]hexanyl (C₆), bicyclo[3.1.1]heptanyl (C₇), and the like. Exemplary C₃–C₁₀ cycloalkyl groups include, without limitation, the aforementioned C₃–C₈ cycloalkyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl, (C₁₀), cyclodecenyl (C₁₀), octahydro–1*H*–indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), 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 C₃-C₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is a substituted C₃-C₁₀ cycloalkyl.

In some embodiments, “cycloalkyl” is a monocyclic, saturated cycloalkyl group having from 3 to 10 ring carbon atoms (“C₃-C₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃-C₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃-C₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅-C₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅-C₁₀ cycloalkyl”). Examples of C₅-C₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃-C₆ cycloalkyl groups include the aforementioned C₅-C₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃-C₈ cycloalkyl groups include the aforementioned C₃-C₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). 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 C₃-C₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C₃-C₁₀ 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

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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
5 “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
10 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–
15 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
20 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
25 limitation, azirdinyl, oxiranyl, thiorenly. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, 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
30 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

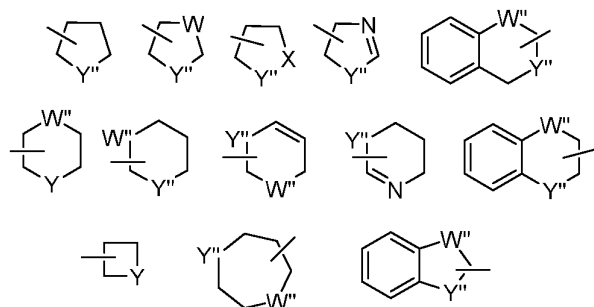
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limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered

5 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 C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl,

10 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:



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wherein each W'' is selected from CR⁶⁷, C(R⁶⁷)₂, NR⁶⁷, O, and S; and each Y'' is selected from NR⁶⁷, O, and S; and R⁶⁷ is independently hydrogen, C₁–C₈ alkyl, C₃–C₁₀ cycloalkyl, 4–10 membered heterocyclyl, C₆–C₁₀ aryl, and 5–10-membered heteroaryl. These heterocyclyl rings may be optionally substituted with one or more groups selected from the group consisting of

20 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.

25 “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-

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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 $\text{-NR}^{70}\text{R}^{71}$, wherein R^{70} and R^{71} are each independently
5 hydrogen, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, 4–10 membered heterocyclyl, $\text{C}_6\text{-C}_{10}$ 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
10 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
15 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
20 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,
25 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
30 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

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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⁻), NO₃⁻, ClO₄⁻, OH⁻, H₂PO₄⁻, HSO₄⁻, sulfonate ions (*e.g.*, methanesulfonate, 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

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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)-

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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)-, 5 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 10 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 15 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, 20 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. 25 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, 30 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

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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, eIF2 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).

5 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.,
10 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, eIF2 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
15 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 eIF2 α phosphorylation or activity of phosphorylated eIF2 α or reduced eIF2 activity or increase in activity of phosphorylated eIF2 α signal transduction or the ISR signalling pathway). As used
20 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 eIF2 α activity or the ISR pathway. For example, a disease associated with
25 phosphorylated eIF2 α may be treated with an agent (e.g., compound as described herein) effective for decreasing the level of activity of phosphorylated eIF2 α or a downstream component or effector of phosphorylated eIF2 α . For example, a disease associated with eIF2 α , 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.

30 "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, eIF2 α , 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, eIF2 α , 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, eIF2 α , or a component of the eIF2 pathway, pathway activated by eIF2 α 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, eIF2 α , 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, eIF2 α , or component of the eIF2 pathway or ISR pathway) that may modulate the level of another protein or increase

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cell survival (e.g., decrease in phosphorylated eIF2 α pathway activity may increase cell survival in cells that may or may not have an increase in phosphorylated eIF2 α pathway activity relative to a non-disease control or decrease in eIF2 α pathway activity may increase cell survival in cells that may or may not have an increase in eIF2 α 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, eIF2 α , 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, eIF2 α , 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, eIF2 α , 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, eIF2 α , 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 eIF2 α activity may increase cell survival in cells that may or may not have a reduction in eIF2 α 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, eIF2 α , 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, eIF2 α , 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, eIF2 α , or a component of the eIF2 pathway or ISR pathway but may benefit from modulation of eIF2B, eIF2 α , or a component of the eIF2 pathway or ISR pathway (e.g., decreasing in level or level of activity of eIF2B, eIF2 α or a component of the eIF2 pathway).

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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, eIF2 α , or component of the eIF2 pathway or ISR pathway is an anti-cancer agent. In embodiments, a modulator of eIF2B, eIF2 α , or component of the eIF2 pathway or ISR pathway is a neuroprotectant. In embodiments, a modulator of eIF2B, eIF2 α , or component of the eIF2 pathway or ISR pathway is a memory enhancing agent. In embodiments, a modulator of eIF2B, eIF2 α , 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, eIF2 α , or component of the eIF2 pathway or ISR pathway is an anti-inflammatory agent.

10 In some embodiments, a modulator of eIF2B, eIF2 α , 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.

15 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

20 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

25 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.

30 “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.,

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through administration of a compound of Formula (I) or Formula (II), 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, hydroxymethylcellulose, polyvinyl pyrrolidone, 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,

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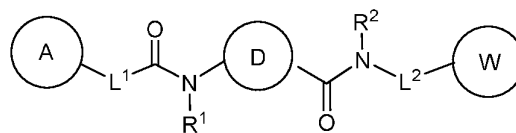
transdermal patches, etc. By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g., anti-cancer agent, chemotherapeutic, or treatment for a neurodegenerative disease). 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 "eIF2 α " are interchangeable and refer to the protein "eukaryotic translation initiation factor 2 alpha subunit eIF2S1". In embodiments, "eIF2alpha", "eIF2a" or "eIF2 α " refer to the human protein. Included in the terms eIF2alpha", "eIF2a" or "eIF2 α " are the wildtype and mutant forms of the protein. In embodiments, "eIF2alpha", "eIF2a" or "eIF2 α " 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

In one aspect, the present invention features a compound of Formula (I):



Formula (I)

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or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 with 1-4 R^X groups; and wherein if the bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen moiety may be optionally substituted by R^{N1} ;

L^1 is C_1 - C_6 alkylene or 2-7-membered heteroalkylene, wherein each C_1 - C_6 alkylene or 2-7-membered heteroalkylene is optionally substituted with 1-5 R^X ;

L^2 is C_1 - C_6 alkylene or 2-7-membered heteroalkylene, wherein each C_1 - C_6 alkylene or 2-7-membered heteroalkylene is optionally substituted with 1-5 R^X ;

R^1 and R^2 are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_2 - C_6 alkyl, hydroxy- C_2 - C_6 alkyl, silyloxy- C_2 - C_6 alkyl, and C_1 - C_6 alkyl- $C(O)NR^B R^C$;

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, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OR^D$, and $-S(O)_2R^D$;

A and W are each independently phenyl or 5-6 membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y ;

each R^X 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, amino- C_1 - C_6 alkyl, cyano- C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-SR^E$, $-S(O)R^D$, 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, C_1 - C_6 alkoxy- 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, HO_2C - C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2R^D$, 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 heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X ;

each G^1 is independently C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally substituted with 1-3 R^Z ;

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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, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, and $-S(O)_2 R^D$;

R^A is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, $-C(O)NR^B R^C$, $-C(O)R^D$, 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 optionally substituted with 1-3 R^Z ;

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;

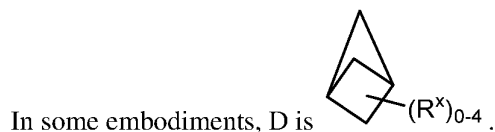
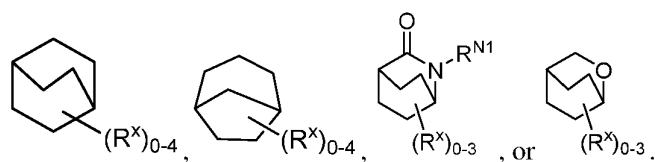
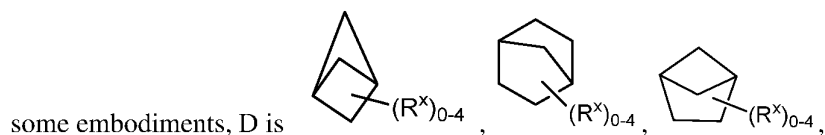
each R^F is independently hydrogen, C_1 - C_6 alkyl, halo, or halo- C_1 - C_6 alkyl;

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.

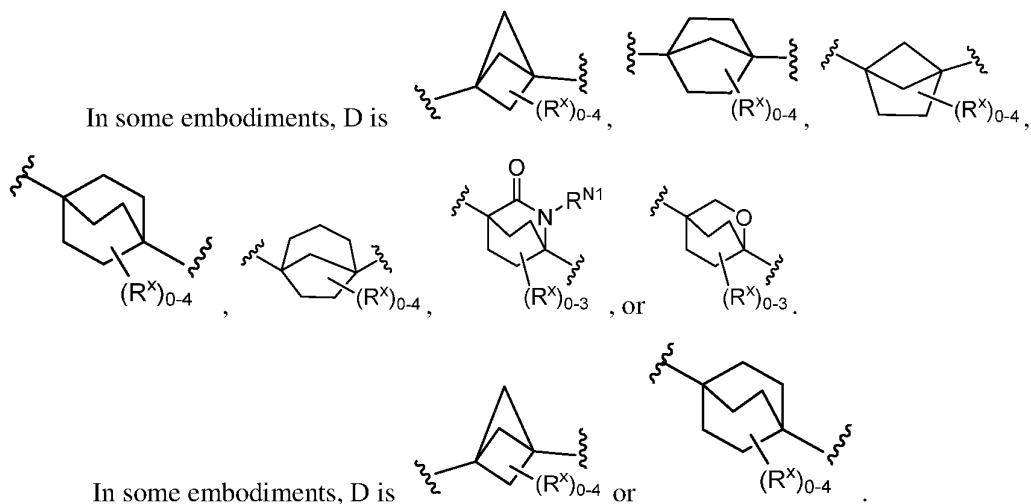
In some embodiments, D is a bridged bicyclic cycloalkyl or bridged bicyclic heterocyclyl, each of which is optionally substituted with 1-4 R^X .

In some embodiments, D is a bridged 5-8 membered bicyclic cycloalkyl or heterocyclyl, each of which is optionally substituted with 1-4 R^X . bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane, bicyclo[2.1.1]hexane, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[3.2.1]octane, 2-azabicyclo[2.2.2]octane, or 2-oxabicyclo[2.2.2]octane, each of which is optionally substituted with 1-4 R^X groups.

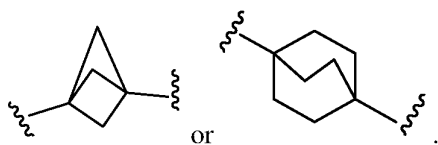
In some embodiments, D is bicyclo[1.1.1]pentane optionally substituted with 1-4 R^X . In



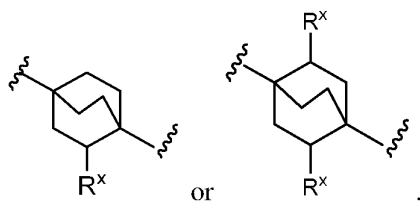
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5 In some embodiments, D is substituted with 0 R^X . In some embodiments, D is

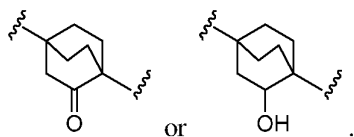


In some embodiments, D is substituted with 1 or 2 R^X . In some embodiments, D is



10 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, R^X is oxo or $-OR^A$ (e.g., oxo or OH). In some embodiments, D is



In some embodiments, L^1 is CH_2O-^* or $CH_2CH_2O-^*$, wherein “ $-^*$ ” indicates the

15 attachment point to A.

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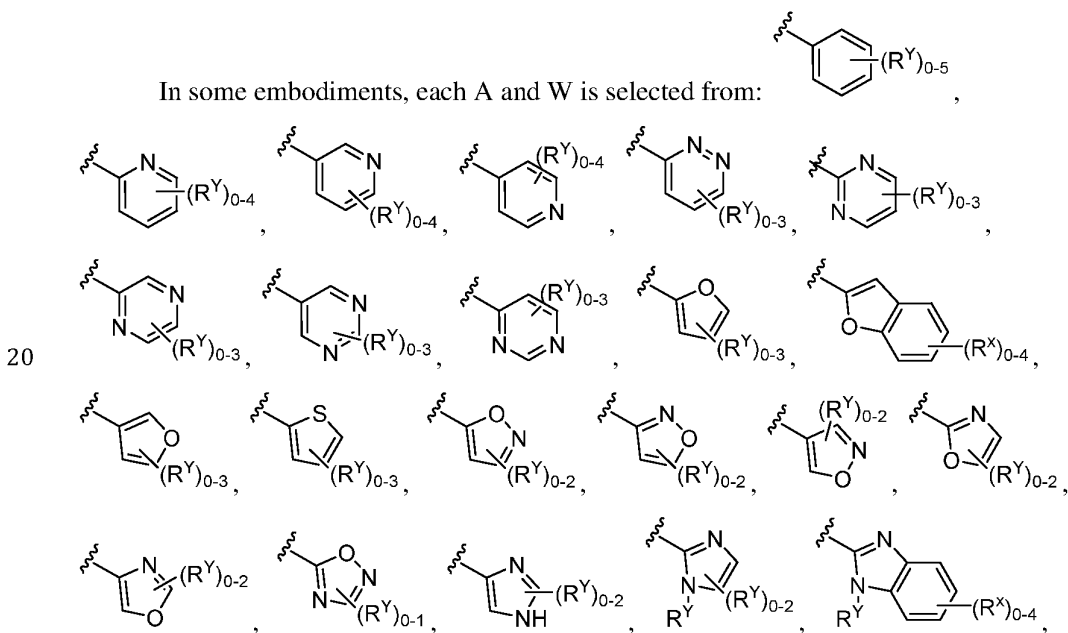
In some embodiments, L^2 is selected from the group consisting of $-\text{CH}_2^*$, $-\text{CH}_2\text{CH}_2^*$, $\text{CH}_2\text{CH}_2\text{CH}_2^*$, $-\text{CH}(\text{CH}_3)^*$, $-\text{CH}_2(\text{CH}_3)\text{CH}_2^*$, $-\text{CH}_2\text{C}(\text{O})^*$, $-\text{CH}_2\text{O}^*$, $-\text{N}(\text{CH}_2\text{CONH}_2)\text{CH}_2^*$ and $-\text{CH}_2\text{CH}_2\text{O}^*$, wherein “-*” indicates the attachment point to W.

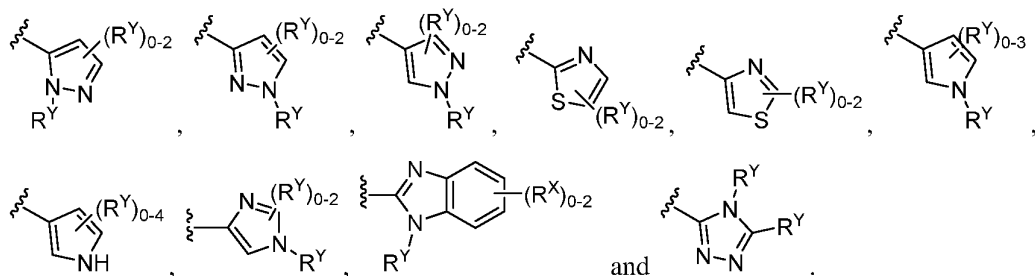
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In some embodiments, R^1 and R^2 are each hydrogen or $\text{C}_1\text{-C}_6$ alkyl. In some embodiments, R^1 and R^2 are each hydrogen or $-\text{CH}_3$. In some embodiments, R^1 and R^2 are each hydrogen.

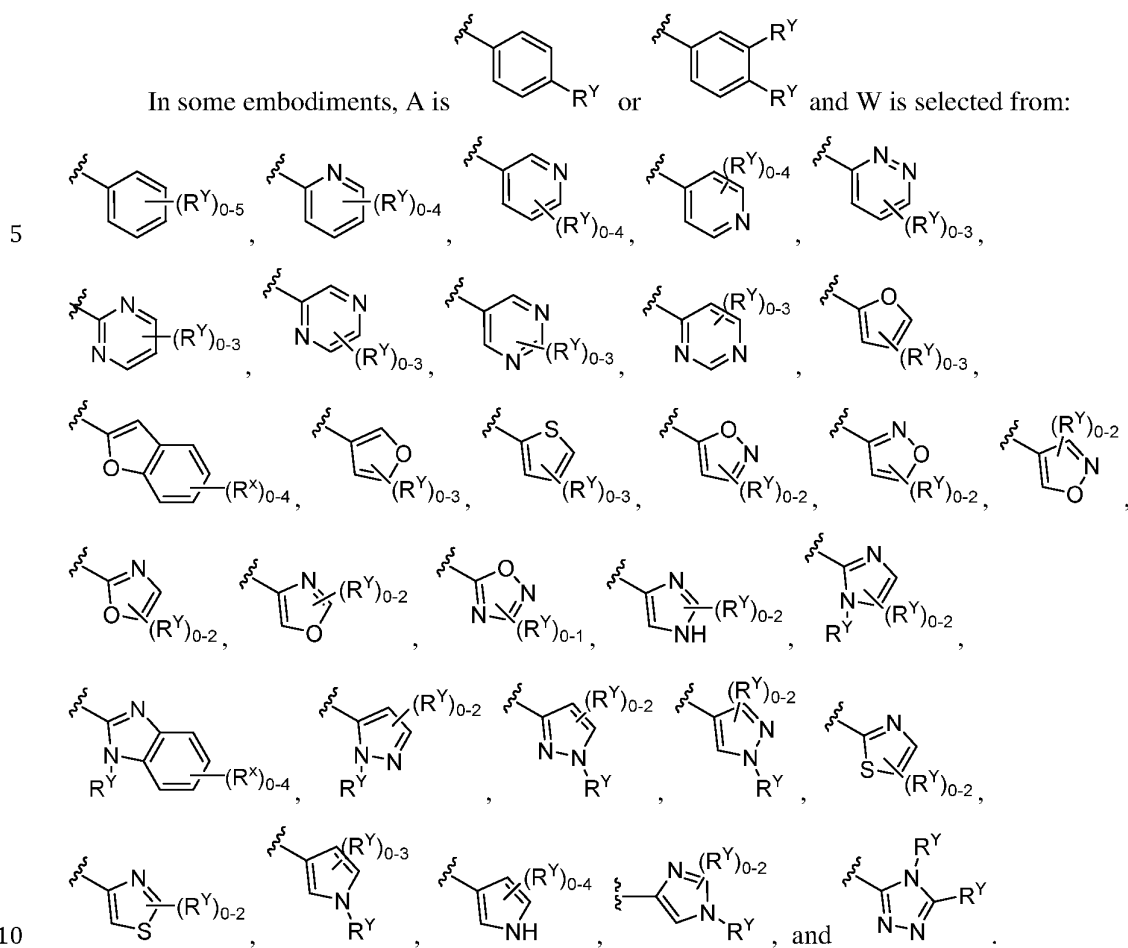
10 In some embodiments, A is phenyl and W is independently phenyl or 5-6-membered heteroaryl. In some embodiments, each A and W is independently phenyl. In some embodiments, A is phenyl and W is 5-6-membered heteroaryl.

In some embodiments, W is a monocyclic 5-6-membered heteroaryl. In some embodiments, 2 R^Y groups on adjacent atoms of W, together with the atoms to which they are attached form a 3-7-membered fused cycloalkyl or heterocyclyl optionally substituted with 1-5 R^X forming a bicyclic heteroaryl. In some embodiments, W is a 10-membered heteroaryl, a 9-membered heteroaryl, a 6-membered heteroaryl, or a 5-membered heteroaryl. In some embodiments, W is a heteroaryl containing nitrogen, oxygen or sulfur as allowed by valence.





In some embodiments, A is or and W is selected from:



In some embodiments, each R^Y is independently C₁-C₆ alkyl, CO₂H-C₁-C₆ alkyl, C₁-C₆ alkoxy-C₁-C₆ alkyl, halo-C₁-C₆ alkyl, halo-C₁-C₆ alkoxy, halo, cyano, -OR^A, -NR^BR^C, -C(O)NR^BR^C, -S(O)₂R^D, -S(R^F)_m, or G¹, or 2 R^Y groups on adjacent atoms, together with the

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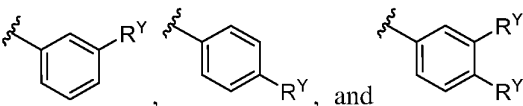
atoms to which they are attached form a 3-7-membered fused cycloalkyl, 3-7 membered heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X .

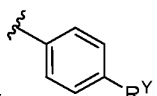
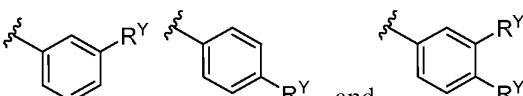
In some embodiments, R^Y is chloro, fluoro, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CO}_2\text{H}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OCHF}_2$, $-\text{OCF}_3$, $-\text{OCH}_2\text{CHF}_3$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_2\text{NH}_2$, or $-\text{SCF}_3$.

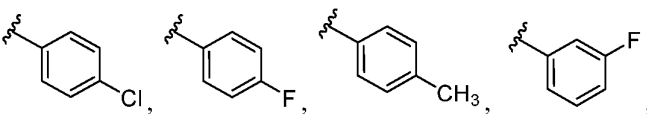
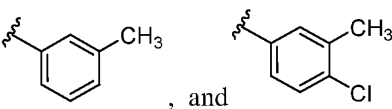
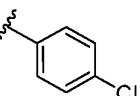
In some embodiments, each A and W is optionally substituted with 1-5 R^Y . In some embodiments, R^Y is C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo- C_1 - C_6 alkoxy, halo, cyano, $-\text{OR}^A$, $-\text{NR}^B\text{R}^C$, $-\text{S}(\text{O})_2\text{R}^D$, $-\text{S}(\text{R}^F)_m$, or G^1 . In some embodiments, R^Y is chloro, fluoro, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CF}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OCHF}_2$, $-\text{OCF}_3$, $-\text{OCH}_2\text{CHF}_2$, $\text{N}(\text{CH}_3)_2$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_2\text{NH}_2$, or SCF_3 .

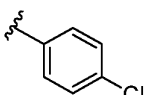
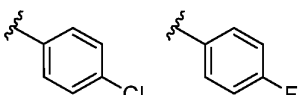
In some embodiments, G^1 is phenyl optionally substituted with 1-3 R^Z . In some embodiments, each R^Z is C_1 - C_6 alkyl (e.g., CH_3).

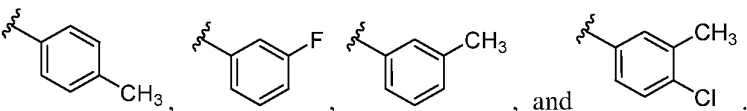
In some embodiments, each A and W is independently a phenyl optionally substituted with 1-5 R^Y , and each R^Y is independently C_1 - C_6 alkyl or halo. In some embodiments, each of A

and W is selected from: . In some embodiments,

A is  and W is selected from . In some embodiments, each R^Y is independently chloro, fluoro, or CH_3 . In some embodiments,

each of A and W is selected from , . In some embodiments, A is . In some

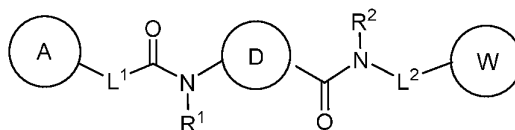
embodiments, A is  and W is selected from: .

.

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In some embodiments, G^1 is phenyl optionally substituted with 1-3 R^Z . In some embodiments, each R^Z is C_1 - C_6 alkyl (e.g., CH_3).

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



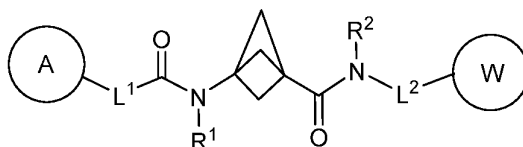
Formula (I-a)

- 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 with 1-4 R^X ; L^1 and L^2 are each independently C_1 - C_6 alkylene or 2-7-membered
- 10 heteroalkylene, wherein each C_1 - C_6 alkylene or 2-7-membered heteroalkylene is optionally substituted with 1-5 R^X ; R^1 and R^2 are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_2 - C_6 alkyl, hydroxy- C_2 - C_6 alkyl, silyloxy- C_2 - C_6 alkyl; A and W are each independently phenyl or 5-6-membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y ; each R^X is independently selected from the group consisting of C_1 - C_6
- 15 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, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-SR^E$, $-S(O)R^D$, and $-S(O)_2 R^D$; 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
- 20 alkyl, cyano- C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2 R^D$, 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 or heterocyclyl optionally substituted with 1-5 R^X ; each G^1 is independently C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl is optionally
- 25 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, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, and $-S(O)_2 R^D$; R^A is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, 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
- 30 with the atom to which they are attached form a 3-7-membered heterocyclyl optionally

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substituted with 1-3 R^Z ; 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, halo- 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.

5 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, or stereoisomer thereof,

10 wherein at least one of L^1 and L^2 is independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X , wherein “-:” indicates the attachment point to A and W, respectively; R^1 and R^2 are each hydrogen or C_1 - C_6 alkyl; A is phenyl substituted with 1-2 R^Y ; W is phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with 1-5 R^Y ; each R^X is oxo or – OR^A ; and each R^Y is independently selected from the group consisting of C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo- C_1 - C_6 alkoxy, halo, cyano, – OR^A , – $NR^B R^C$, – $C(O)NR^B R^C$, – $S(O)_2 R^D$, – $S(R^F)_m$, or 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 heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X ; G^1 is phenyl optionally substituted with 1-3 R^Z ; each R^Z is independently C_1 - C_6 alkyl; R^A is, at each

20 occurrence, independently hydrogen, C_1 - C_6 alkyl, or halo- C_1 - C_6 alkyl; each of R^B and R^C is independently hydrogen or C_1 - C_6 alkyl; each R^D is independently C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, or – $NR^{B1} R^{C1}$; each R^F is independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, or halo; each of R^{B1} and R^{C1} is independently hydrogen or C_1 - C_6 alkyl; 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.

25 In some embodiments, at least one of L^1 and L^2 is independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X . In some embodiments, both of L^1 and L^2 are independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X . In some embodiments, L^1 is 2-7-membered heteroalkylene and L^2 is independently selected from C_1 - C_6 alkylene or 2-7-membered heteroalkylene, wherein each alkylene and heteroalkylene is

30 optionally substituted by 1-5 R^X . In some embodiments, both of L^1 and L^2 are independently 2-

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7-membered heteroalkylene substituted by 0 R^X . In some embodiments, L^1 is independently selected from CH_2O^* or $CH_2CH_2O^*$, L^2 is independently selected from $-CH_2^*$, $-CH_2CH_2^*$, $CH_2CH_2CH_2^*$, $-CH_2(CH_3)^*$, $-CH_2(CH_3)CH_2^*$, CH_2O^* or $CH_2CH_2O^*$, and “-*” indicates the attachment point to A and W, respectively. In some embodiments, each L^1 and L^2 is

5 independently selected from CH_2O^* or $CH_2CH_2O^*$, and “-*” indicates the attachment point to A and W, respectively. In some embodiments, L^1 is CH_2O^* and L^2 is $CH_2CH_2O^*$, and “-*” indicates the attachment point to A and W, respectively.

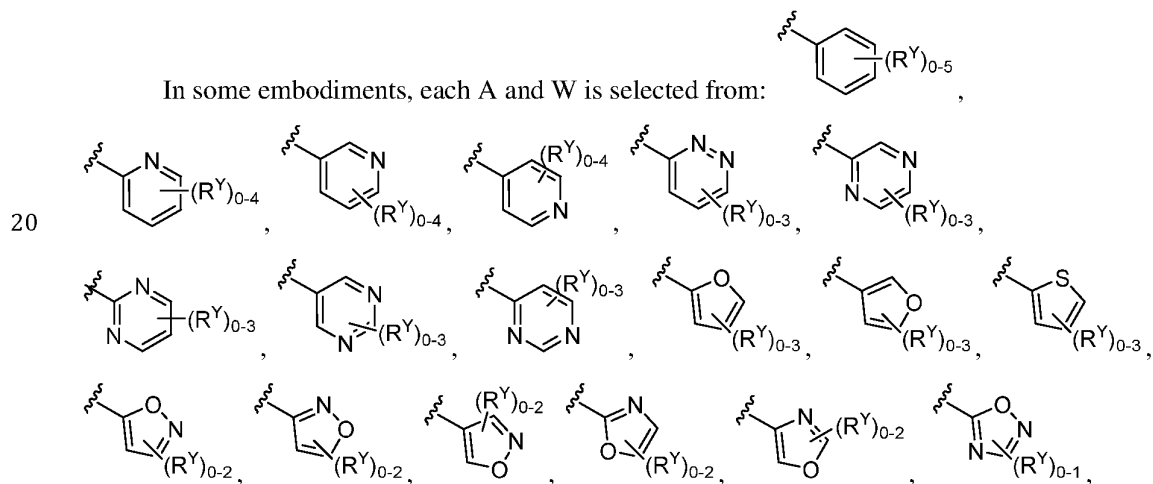
In some embodiments, R^1 and R^2 are each hydrogen or C_1 - C_6 alkyl. In some embodiments, R^1 and R^2 are each hydrogen or $-CH_3$. In some embodiments, R^1 and R^2 are each

10 hydrogen.

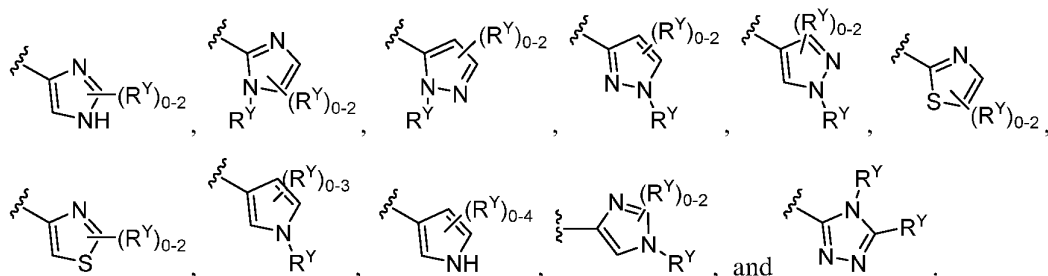
In some embodiments, each A and W is independently phenyl or 5-6 membered heteroaryl, optionally substituted with 1-5 R^Y . In some embodiments, A is phenyl and W is independently phenyl or 5-6 membered heteroaryl. In some embodiments, each A and W is independently phenyl. In some embodiments, A is phenyl and W is 5-6 membered heteroaryl.

15 In some embodiments, W is a monocyclic heteroaryl. In some embodiments, W is a bicyclic heteroaryl. In some embodiments, W is a 10-membered heteroaryl, a 9-membered heteroaryl, a 6-membered heteroaryl, or a 5-membered heteroaryl. In some embodiments, W is a heteroaryl containing nitrogen, oxygen or sulfur as allowed by valence.

In some embodiments, each A and W is selected from:



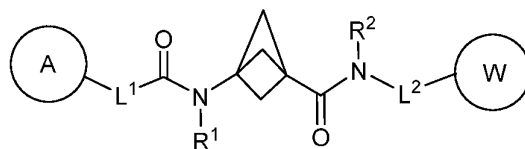
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In some embodiments, each A and W is optionally substituted with 1-5 R^Y. In some embodiments, R^Y is C₁-C₆ alkyl, C₁-C₆ alkoxy-C₁-C₆ alkyl, halo-C₁-C₆ alkyl, halo-C₁-C₆ alkoxy, halo, cyano, -OR^A, -NR^BR^C, -S(O)₂R^D, or -S(R^F)_m. In some embodiments, R^Y is chloro, fluoro, -CH₃, -CH₂CH₃, CH₂CH₂CH₃, -CH₂CH₂CH₂CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -C(CH₃)₃, -CF₃, -CH₂OCH₃, -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -OCHF₂, -OCF₃, -OCH₂CHF₂, N(CH₃)₂, -S(O)₂CH₃, -S(O)₂NH₂, or SCF₃.

In some embodiments, G¹ is phenyl optionally substituted with 1-3 R^Z. In some embodiments, each R^Z is C₁-C₆ alkyl (e.g., CH₃).

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



Formula (I-c)

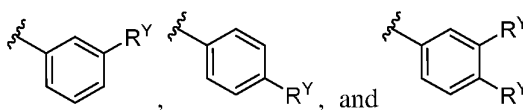
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein L¹ and L² are each independently CH₂-, -CH₂CH₂-, CH₂CH₂CH₂-, -CH₂(CH₃)-, -CH₂(CH₃)CH₂-, CH₂O- or CH₂CH₂O-, wherein “-” indicates the attachment point to A and W, respectively; R¹ and R² are each hydrogen; A and W are each independently phenyl substituted with 1-2 R^Y; and each R^Y is independently selected from the group consisting of chloro, fluoro, and CH₃.

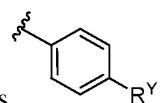
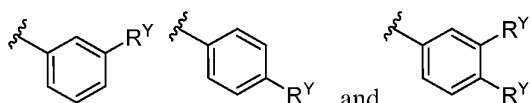
In some embodiments, at least one of L¹ and L² is independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X. In some embodiments, both of L¹ and L² are independently 2-7-membered heteroalkylene optionally substituted by 1-5 R^X. In some embodiments, both of L¹ and L² are independently 2-7-membered heteroalkylene substituted by 0 R^X. In some embodiments, at least one of L¹ and L² is independently C₁-C₆ alkylene optionally substituted by 1-5 R^X. In some embodiments, each L¹ and L² is independently selected from

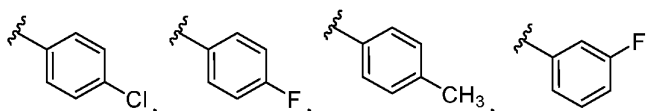
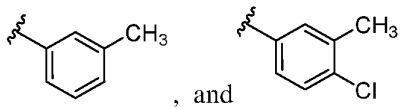
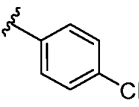
CH₂-, CH(CH₃)-, CH₂CH₂-, CH(CH₃)CH₂-, CH₂CH₂CH₂-, CH₂O- or CH₂CH₂O-, and “-” indicates the attachment point to A and W, respectively. In some embodiments, each L¹ and L² is independently selected from CH₂O- or CH₂CH₂O-, and “-” indicates the attachment point to A and W, respectively. In some embodiments, L¹ is CH₂O- and L² is CH₂CH₂O-, and “-” indicates the attachment point to A and W, respectively.

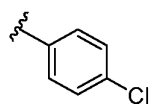
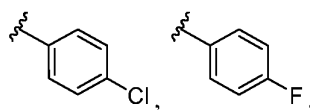
In some embodiments, R¹ and R² are each hydrogen.

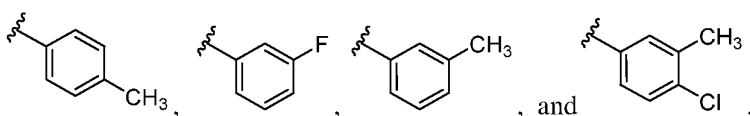
In some embodiments, each A and W is independently a phenyl optionally substituted with 1-5 R^Y, and each R^Y is independently C₁-C₆ alkyl or halo. In some embodiments, each of A

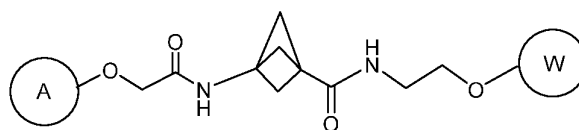
and W is selected from: . In some embodiments,

A is  and W is selected from . In some embodiments, each R^Y is independently chloro, fluoro, or CH₃. In some embodiments,

each of A and W is selected from , . In some embodiments, A is . In some

embodiments, A is  and W is selected from: .

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



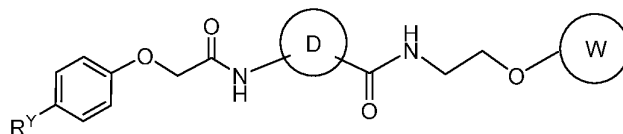
Formula (I-d)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,

wherein each of A and W is defined as for Formula (I).

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

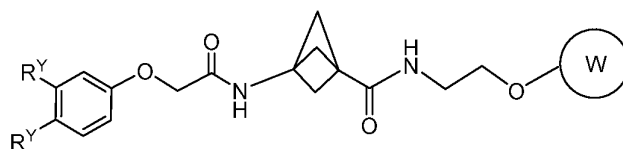
- 58 -



Formula (I-e)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,
wherein each of D, W and R^Y is defined as for Formula (I).

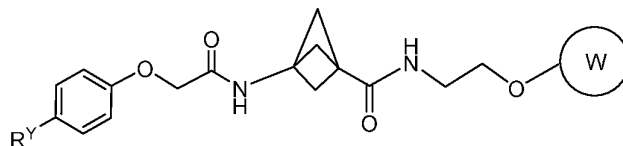
5 In some embodiments, the compound of Formula (I) is a compound of Formula (I-f):



Formula (I-f)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,
wherein each of W and R^Y is defined as for Formula (I).

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



Formula (I-g)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,

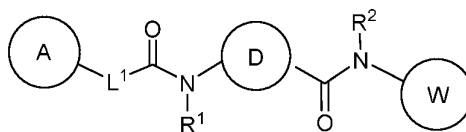
15 wherein each of W and R^Y is defined as for Formula (I).

In some embodiments, the compound of Formula (I) (e.g., a compound of Formula (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) is selected from a compound set forth in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

20 In some embodiments, the compound of Formula (I) (e.g., a compound of Formula (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), or (I-g)) or a pharmaceutically acceptable salt thereof is formulated as a pharmaceutically acceptable composition comprising a disclosed compound and a pharmaceutically acceptable carrier.

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Also disclosed herein is a compound of Formula (II):



Formula (II)

- 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 with 1-4 R^X groups; and wherein if the bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen moiety may be optionally substituted by R^{N1} ;

L^1 is 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^X ;

- R^1 and R^2 are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_2 - C_6 alkyl, hydroxy- C_2 - C_6 alkyl, or silyloxy- C_2 - C_6 alkyl;

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, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OR^D$, and $-S(O)_2 R^D$;

- A and W are each independently phenyl or 5-6 membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y ;

each R^X 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, amino- C_1 - C_6 alkyl, cyano- C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-SR^E$, $-S(O)R^D$, and $-S(O)_2 R^D$;

- each R^Y is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, hydroxy- C_1 - C_6 alkyl, C_1 - C_6 alkoxy- 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, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2 R^D$, and G^1 ; or

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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 heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X ;

each G^1 is independently C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl, 4-7-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, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, and $-S(O)_2 R^D$;

10 R^A is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, $-C(O)NR^B R^C$, $-C(O)R^D$, 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 optionally substituted with 1-3 R^Z ;

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

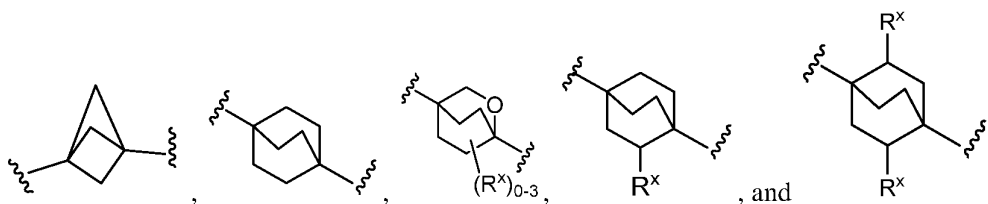
each R^E is independently hydrogen, C_1 - C_6 alkyl, or halo- C_1 - C_6 alkyl;

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

each of R^{B1} and R^{C1} is independently hydrogen or C_1 - C_6 alkyl; 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
20 halo.

In some embodiments, D is selected from the group consisting of

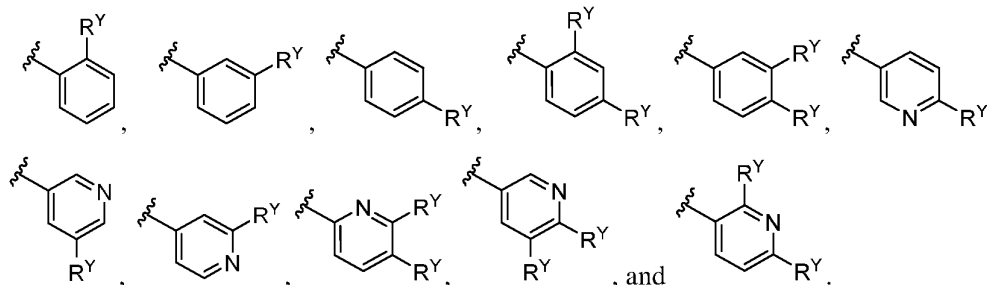


In some embodiments, each R^X is independently selected from the group consisting of oxo, $-OR^A$ (e.g., OH or OCH_3), $-C(O)OH$, $-C(O)OR^D$ (e.g., $-C(O)OCH_3$), halo, and hydroxy-
25 C_1 - C_6 alkyl. In some embodiments, each of R^1 and R^2 is hydrogen or CH_3 , each R^X is independently selected from the group consisting of oxo, $-OH$, $-OCH_3$, $-C(O)OH$, $-C(O)OCH_3$, halo, and hydroxy- C_1 - C_6 alkyl.

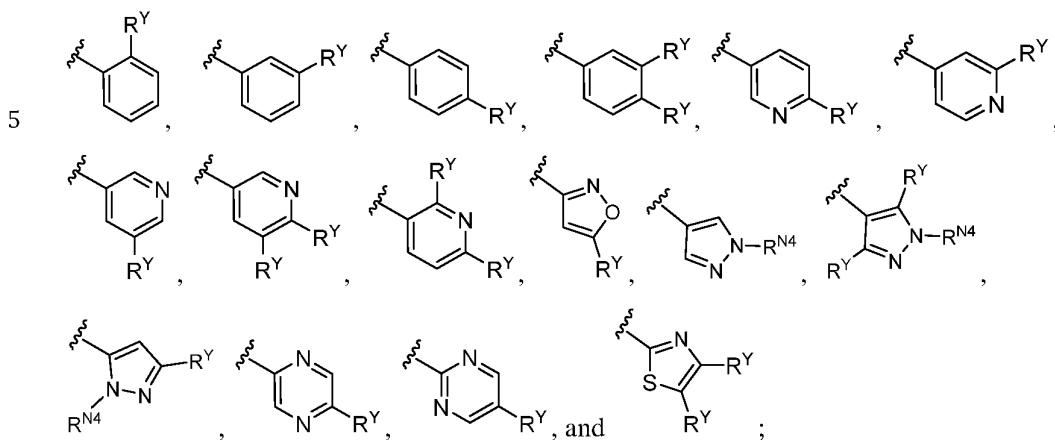
In some embodiments, L^1 is CH_2O^* or $CH_2CH_2O^*$, wherein “ $-^*$ ” indicates the attachment point to A.

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



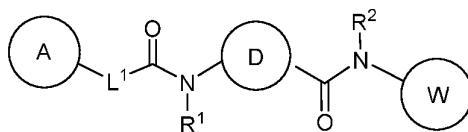
In some embodiments, W is selected from the group consisting of:



wherein R^{N4} is hydrogen or CH_3 .

In some embodiments, each R^Y is independently hydrogen, bromo, chloro, fluoro, iodo, CF_3 , CHF_2 , CH_2CF_3 , CH_3 , CH_2CH_3 , OH , CH_2OH , $C(CH_3)_2OH$, OCH_3 , OCH_2CH_3 , OCF_3 , OCH_2CF_3 , $S(O)_2CH_3$, $S(O)_2CH_2CH_2CH_3$, CN , $N(CH_3)_2$, SF_5 , SCH_3 , NH_2 , $C(CH_3)_3$, $CH(CH_3)_2$, CH_2CN , CH_2NH_2 , $CH(OH)CH_3$, $C(OH)(CH_3)CF_3$, $S(O)_2CH_3$, $C(O)CH_3$, $C(O)OCH_3$, $C(O)OH$, $OCHF_2$ or G^1 .

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



Formula (II-a)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

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D is bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or 2-oxabicyclo[2.2.2]octane, each of which is optionally substituted with 1-4 R^X groups;

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

W is phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, isoxazolyl, or pyrazolyl, each of which is optionally substituted on one or more available carbons with 1-5 R^Y groups; and
 5 wherein pyrazolyl may be optionally substituted on an available nitrogen with hydrogen or CH₃;

L¹ is CH₂O-* or CH₂CH₂O-*, wherein “-*” indicates the attachment point to A;

each R^X is independently fluoro, oxo, OH, OCH₃, C(O)OH, or C(O)OCH₃;

each R^Y is independently hydrogen, bromo, chloro, fluoro, iodo, CF₃, CHF₂, CH₂CF₃,
 10 CH₃, CH₂CH₃, OH, CH₂OH, C(CH₃)₂OH, OCH₃, OCH₂CH₃, OCF₃, OCH₂CF₃, S(O)₂CH₃,
 S(O)₂CH₂CH₂CH₃, CN, N(CH₃)₂, SF₅, SCH₃, NH₂, C(CH₃)₃, CH(CH₃)₂, CH₂CN, CH₂NH₂,
 CH(OH)CH₃, C(OH)(CH₃)CF₃, S(O)₂CH₃, C(O)CH₃, C(O)OCH₃, C(O)OH, OCHF₂ or G¹;

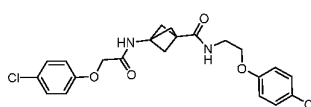
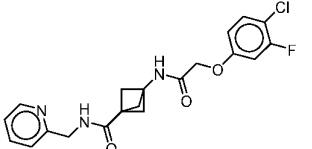
2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a furanyl, pyrrolyl, or dioxolanyl ring, each of which is optionally substituted with 1-2 R^X; and

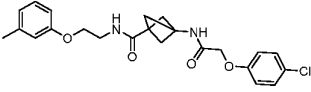
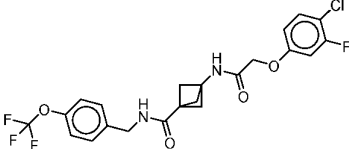
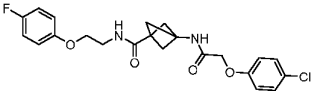
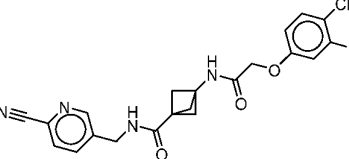
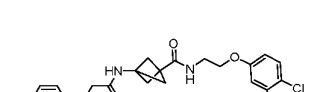
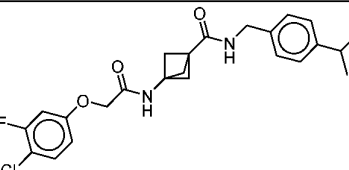
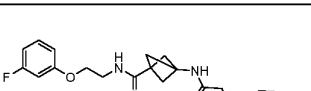
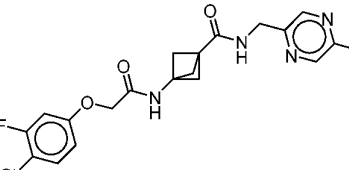
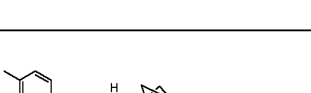
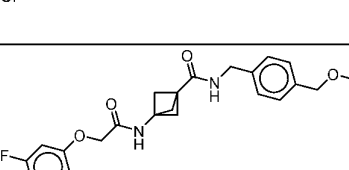
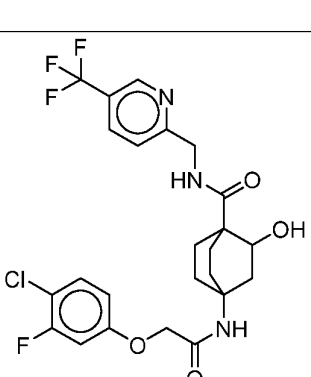
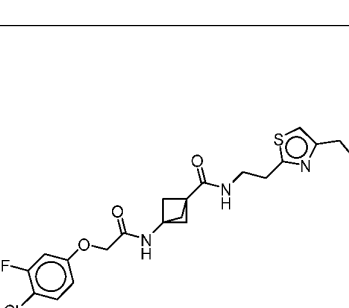
15 each of R¹ and R² is hydrogen or CH₃.

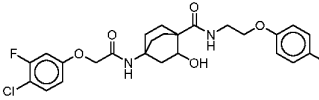
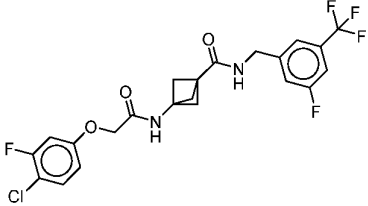
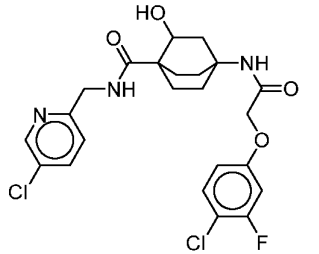
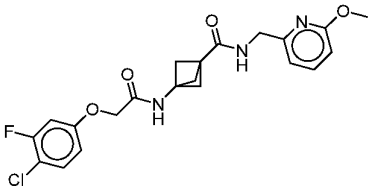
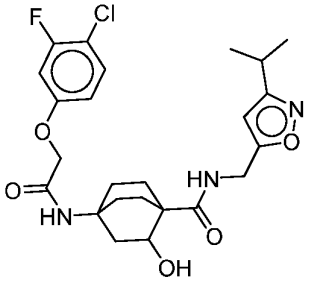
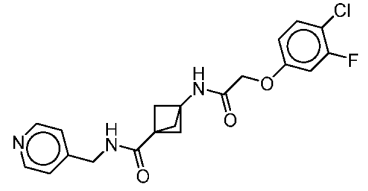
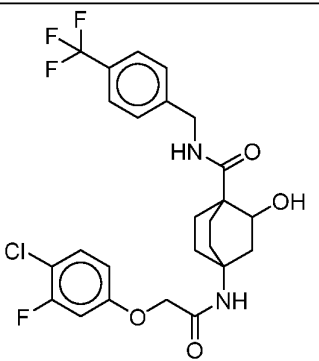
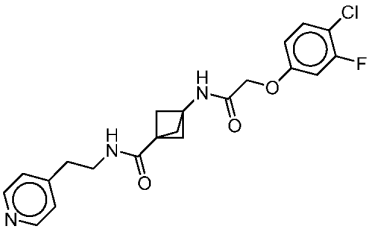
In some embodiments, a compound disclosed herein or a pharmaceutically acceptable salt thereof is formulated as a pharmaceutically acceptable composition comprising a disclosed compound and a pharmaceutically acceptable carrier.

In some embodiments, a compound disclosed herein is selected from a compound set
 20 forth in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

Table 1: Exemplary compounds of the invention

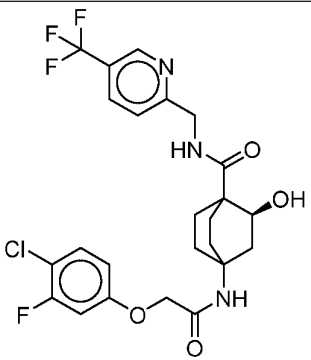
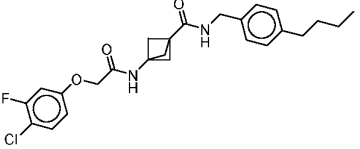
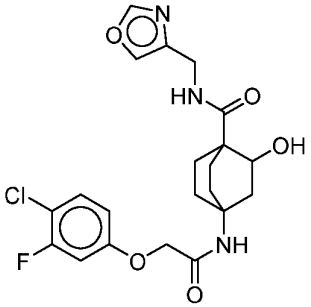
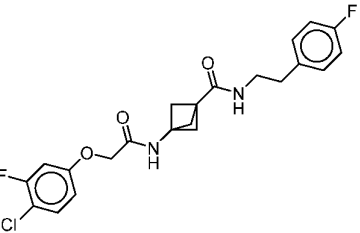
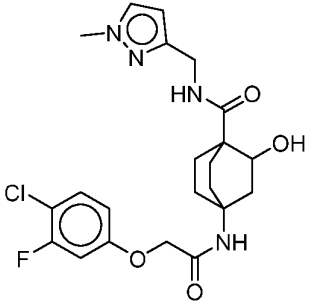
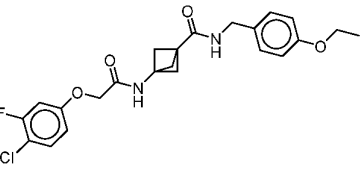
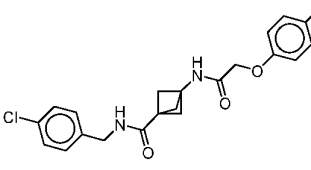
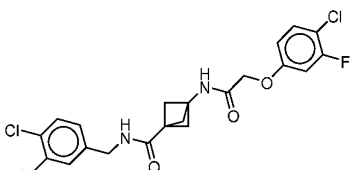
Compound Number	Structure	Compound Number	Structure
100		224	

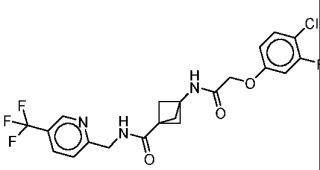
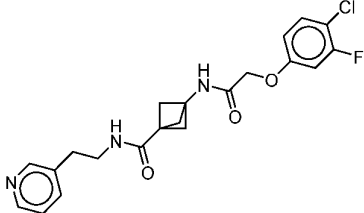
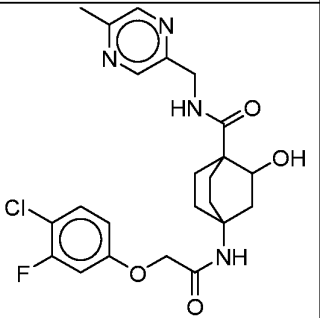
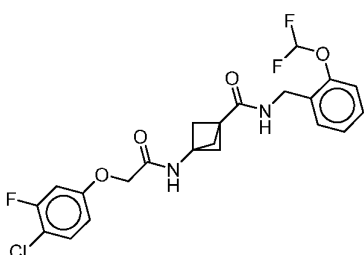
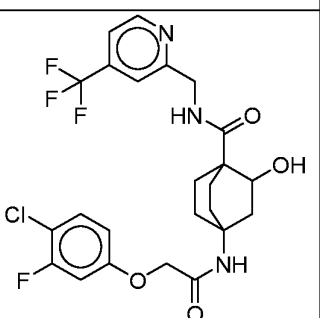
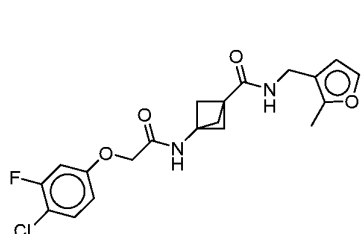
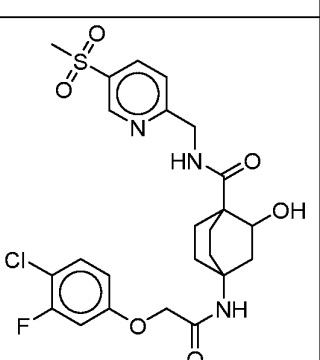
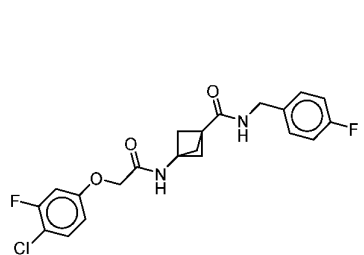
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107		231	
108		232	
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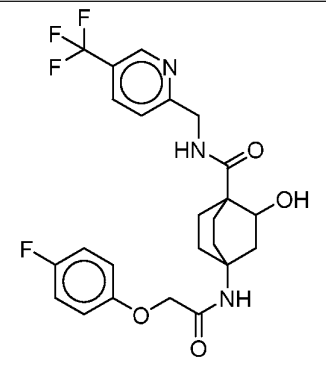
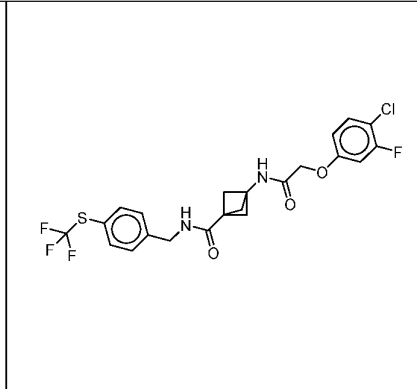
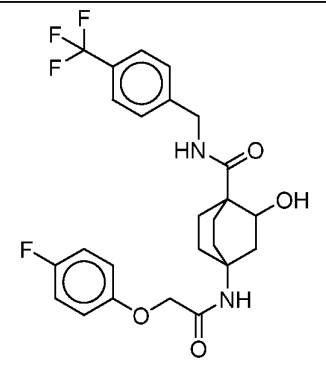
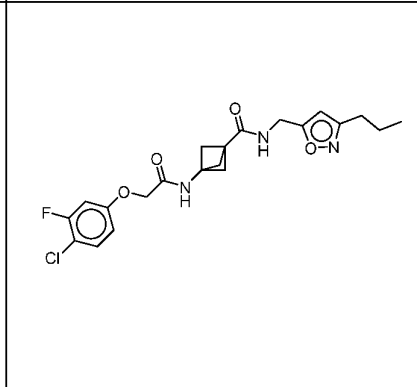
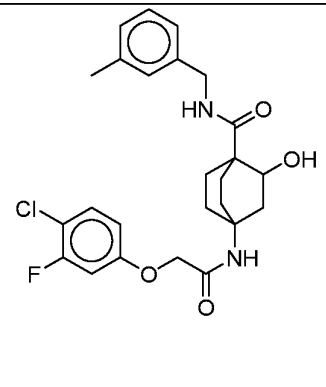
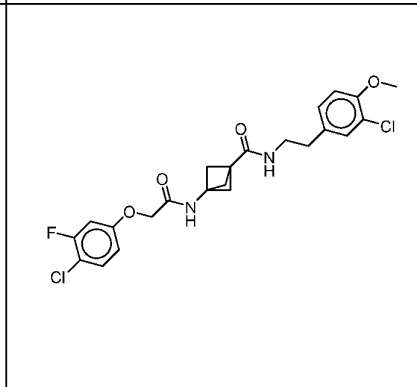
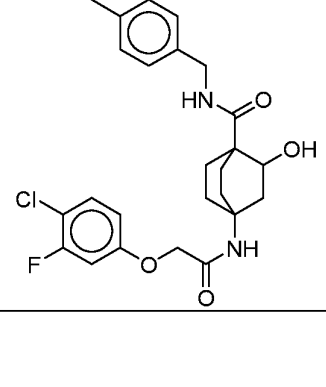
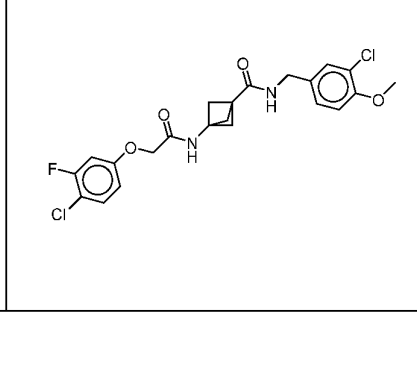
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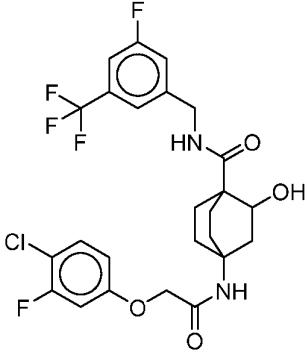
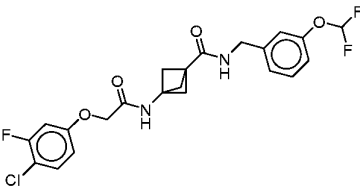
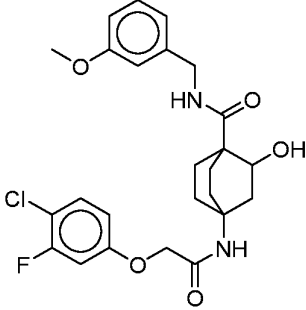
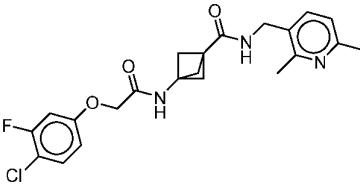
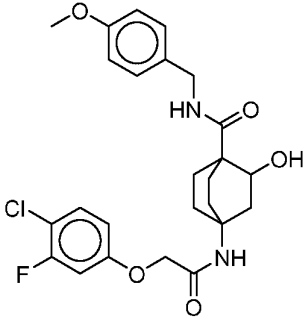
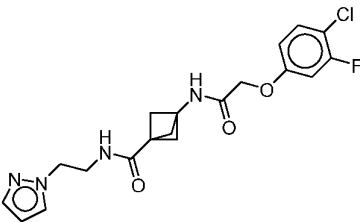
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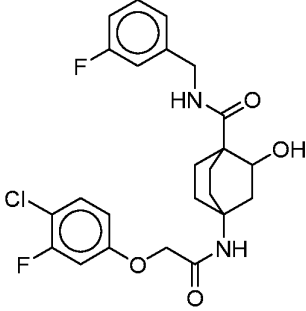
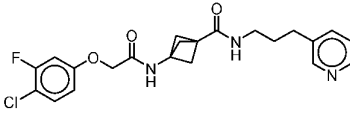
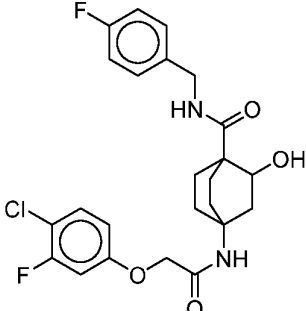
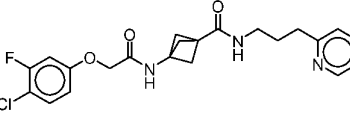
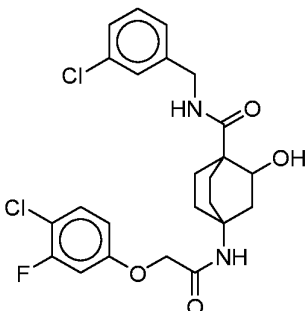
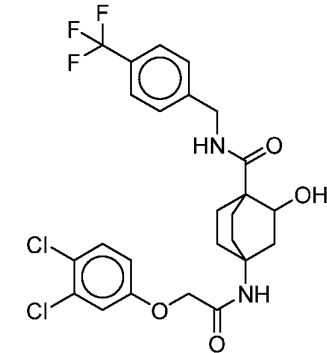
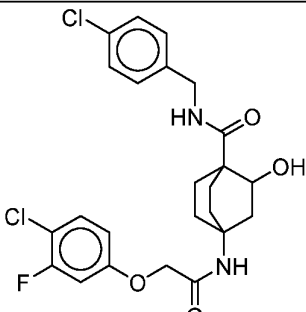
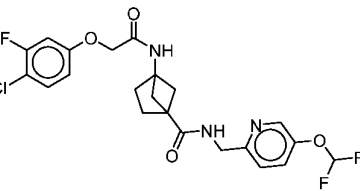
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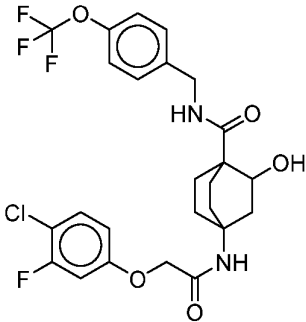
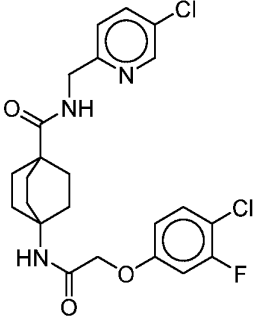
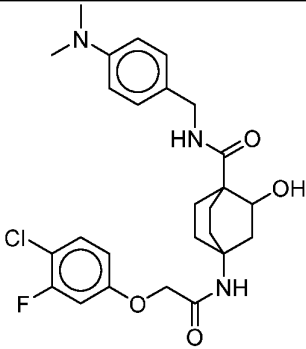
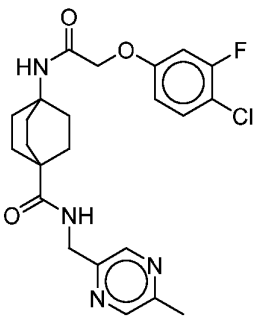
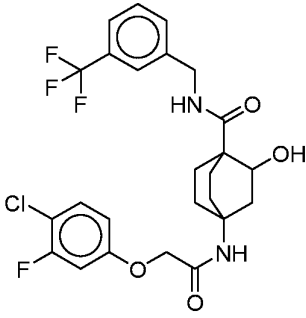
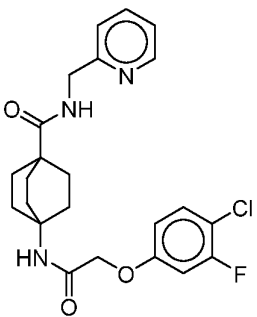
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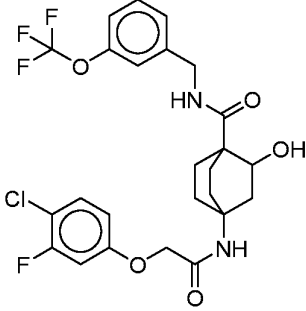
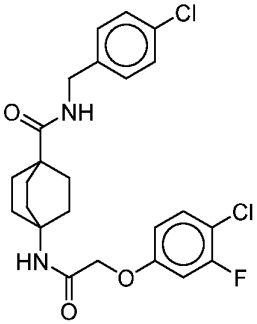
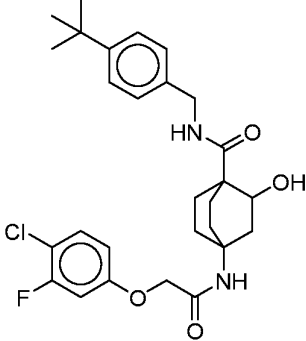
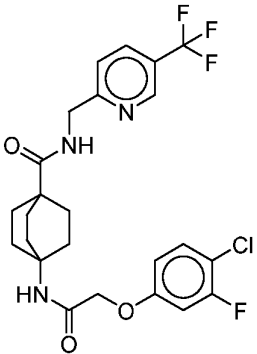
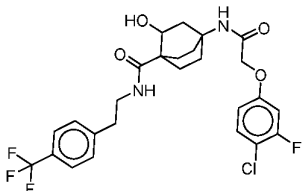
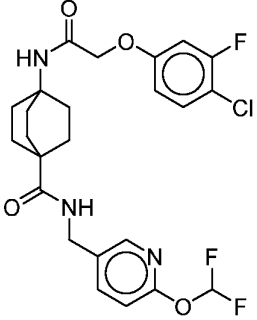
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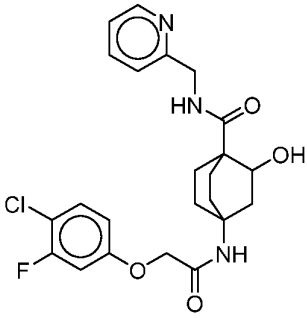
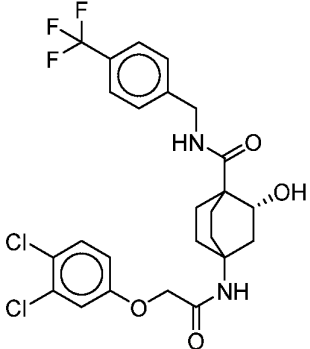
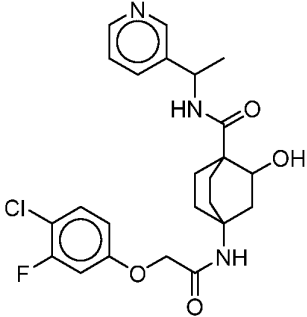
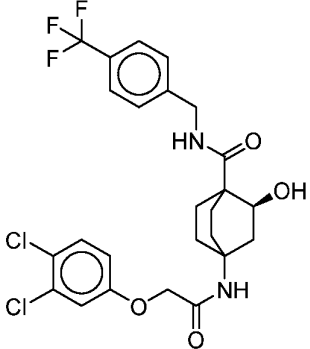
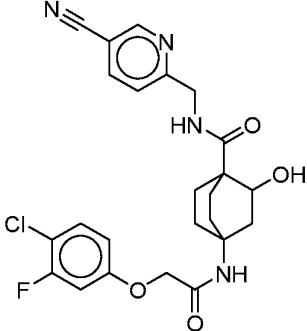
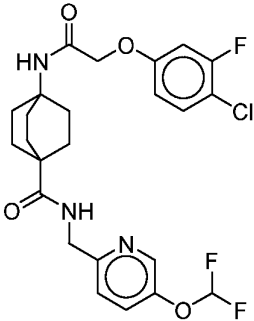
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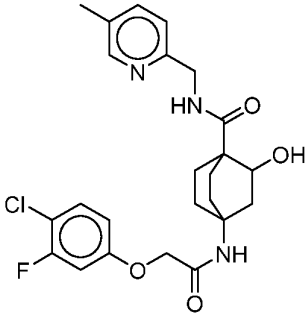
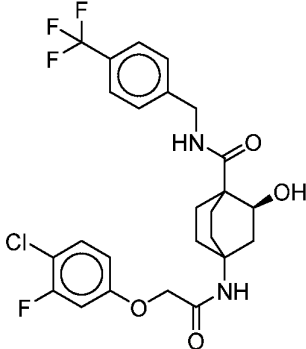
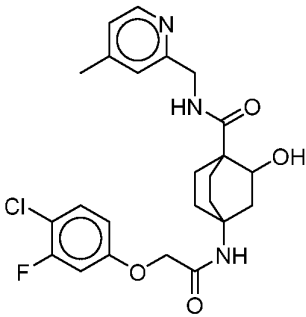
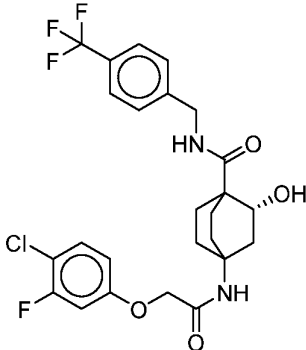
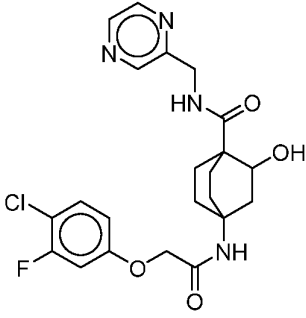
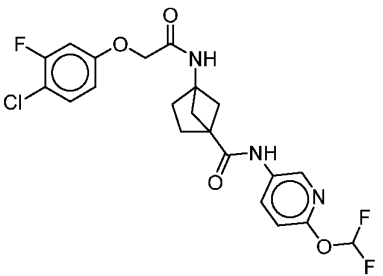
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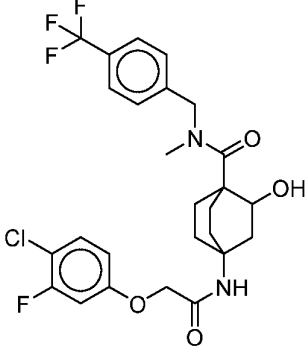
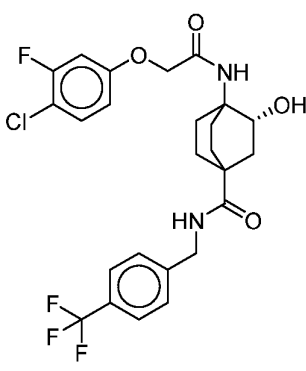
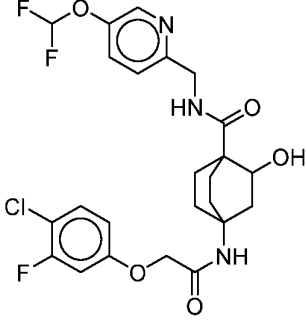
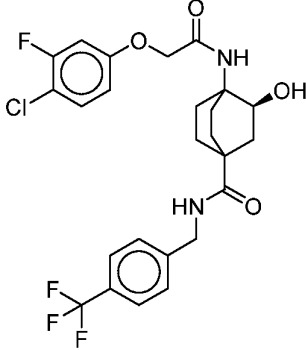
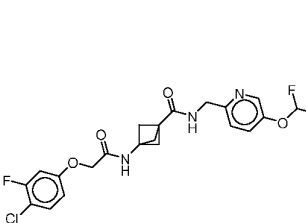
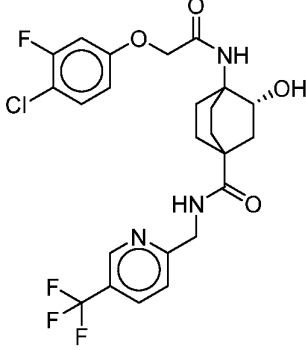
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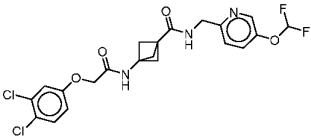
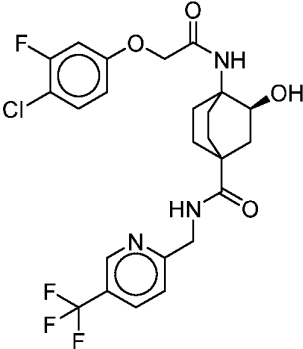
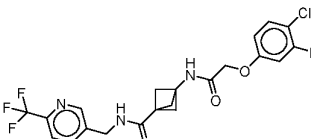
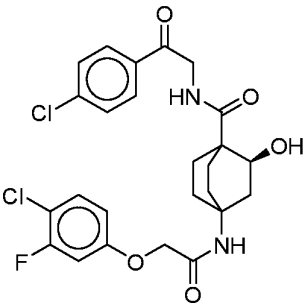
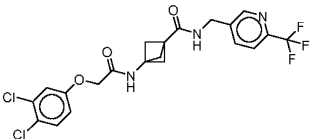
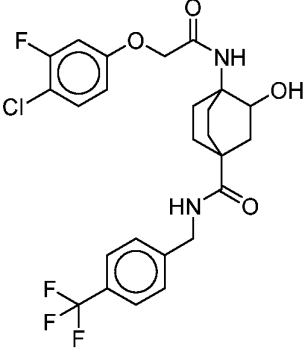
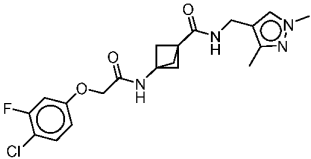
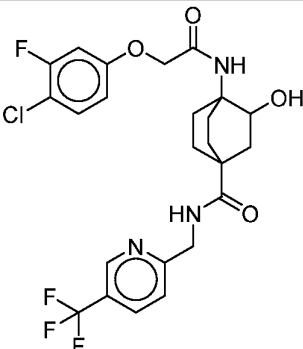
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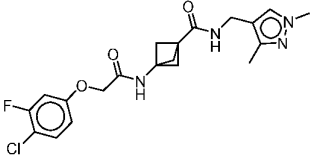
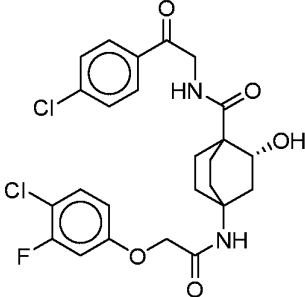
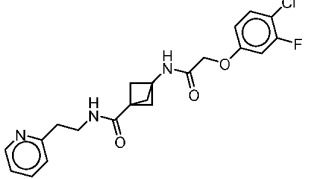
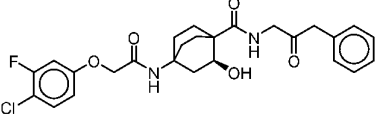
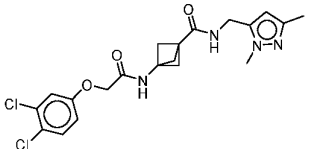
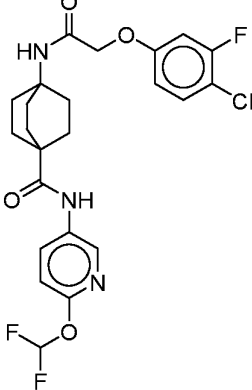
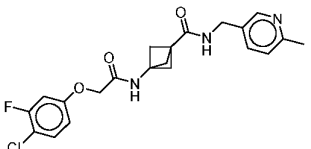
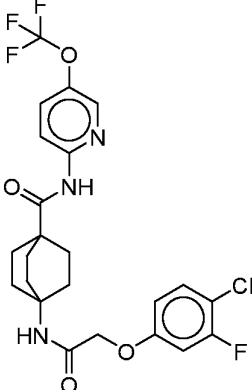
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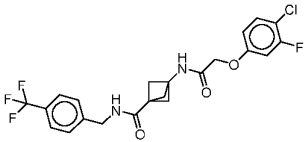
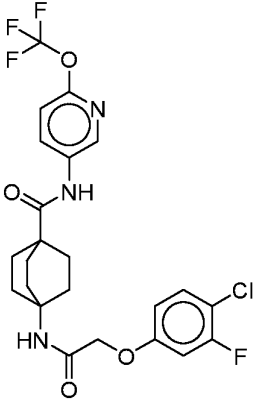
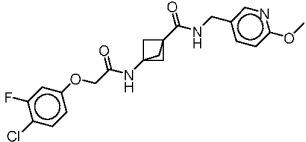
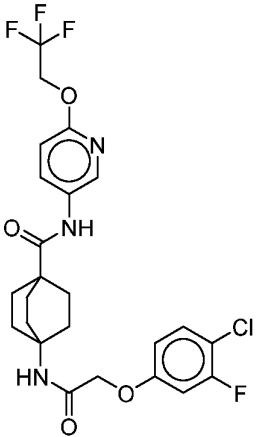
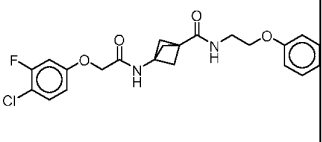
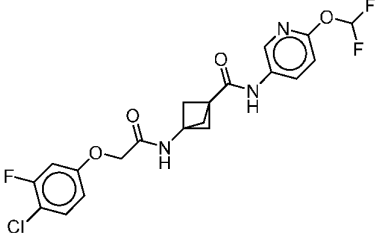
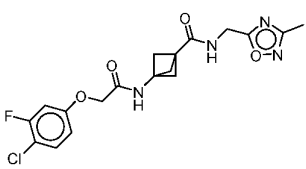
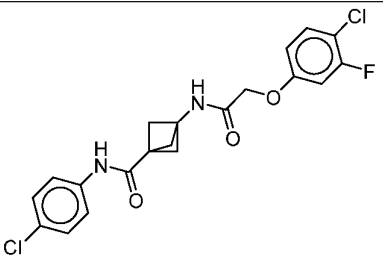
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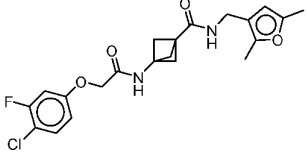
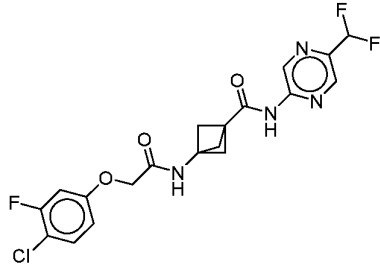
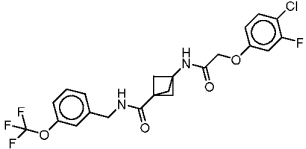
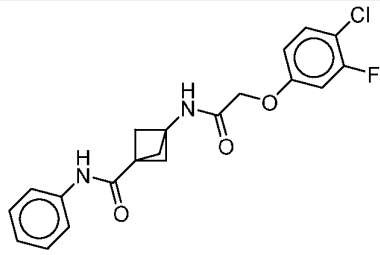
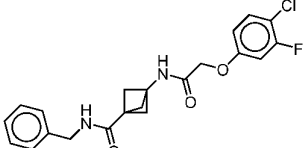
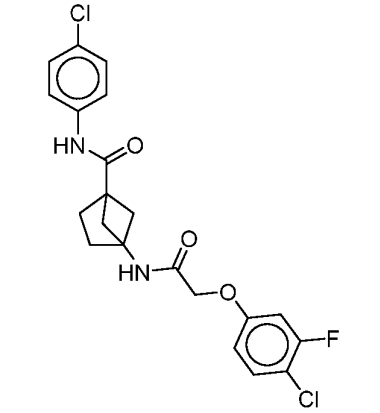
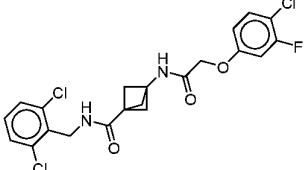
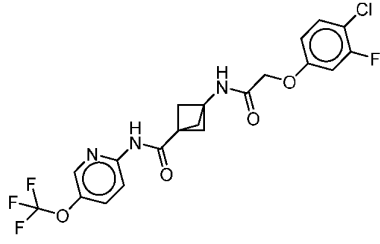
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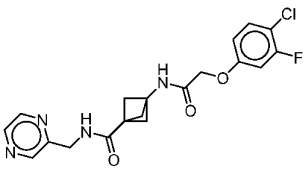
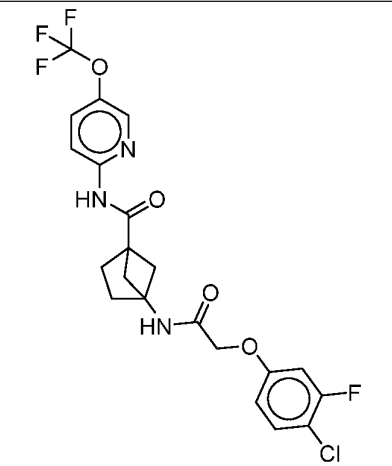
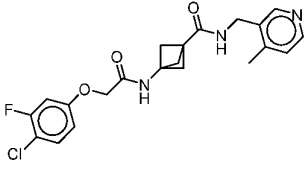
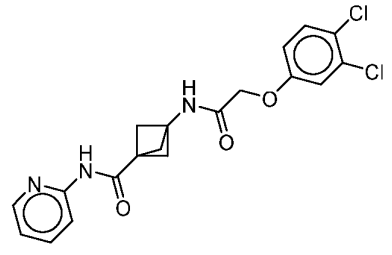
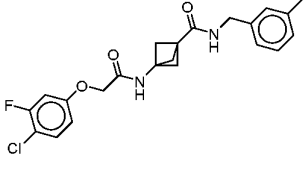
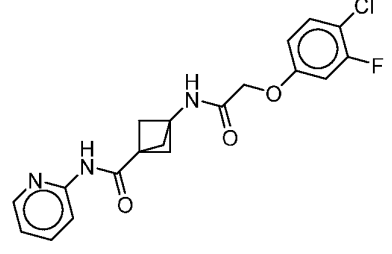
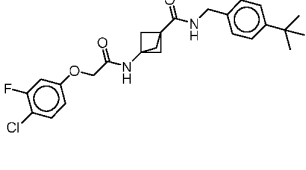
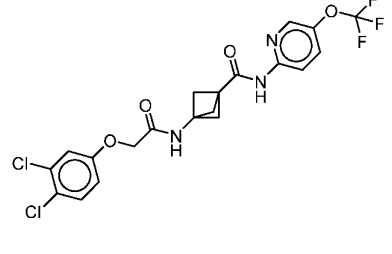
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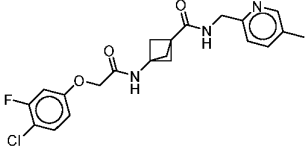
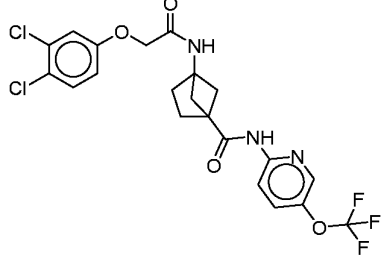
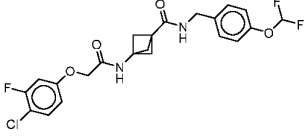
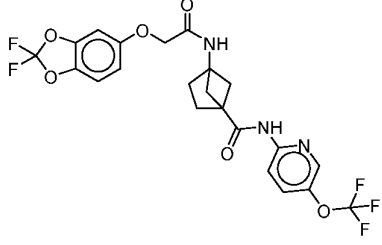
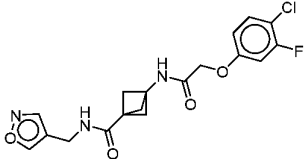
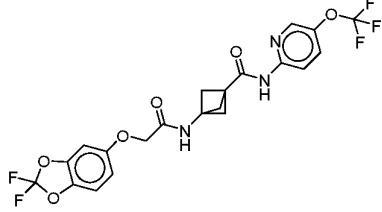
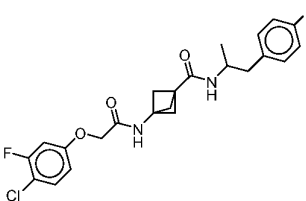
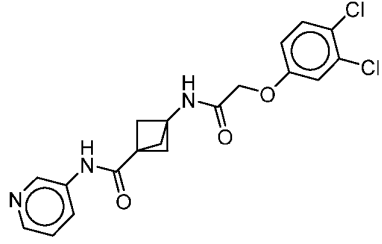
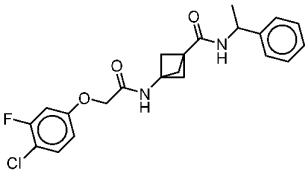
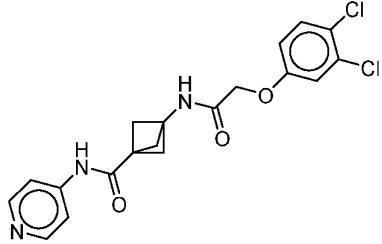
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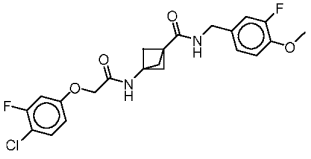
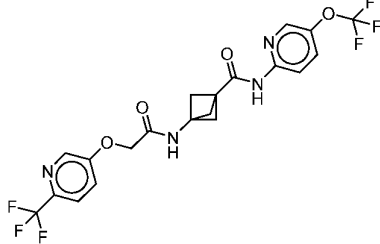
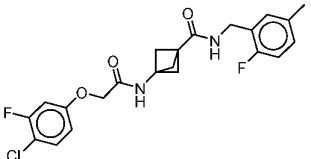
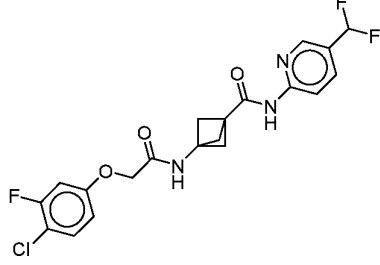
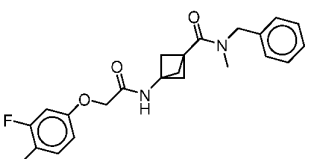
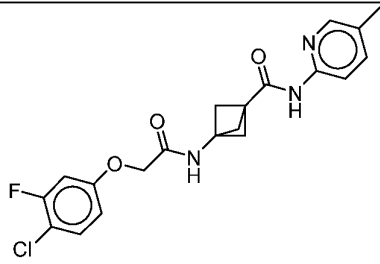
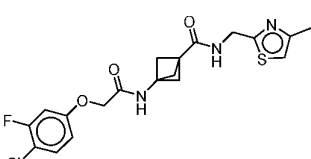
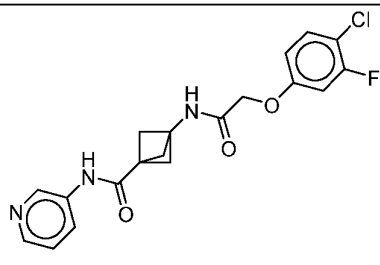
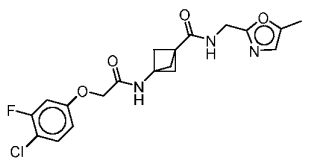
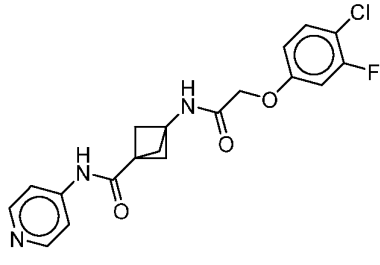
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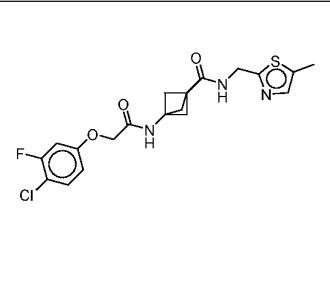
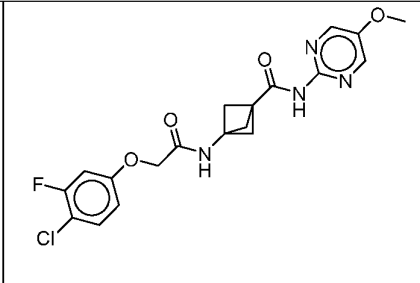
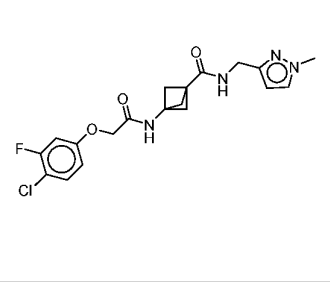
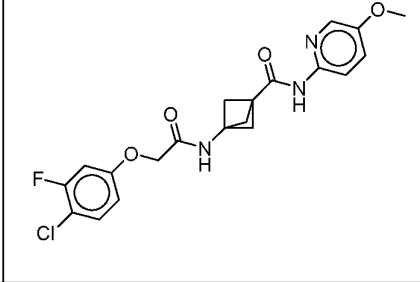
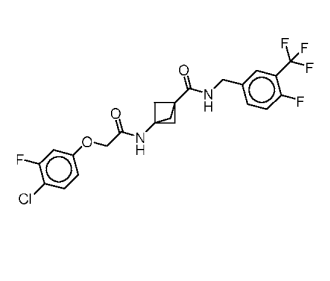
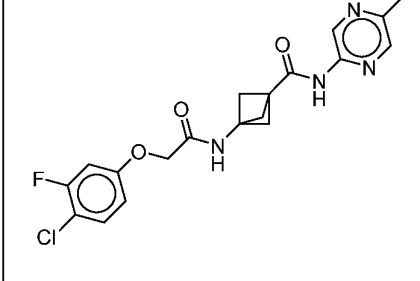
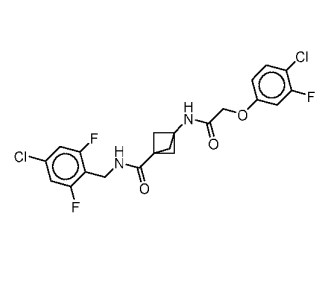
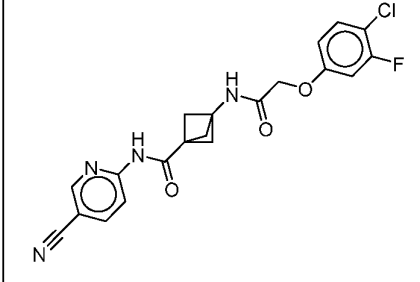
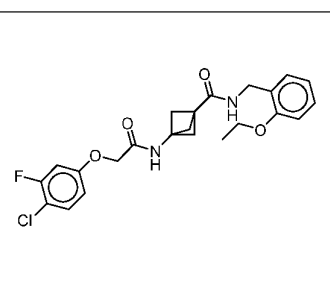
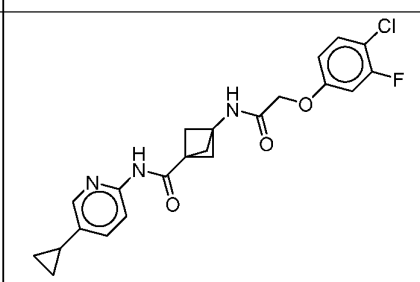
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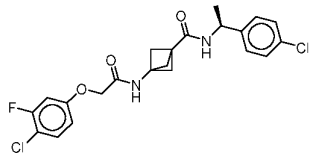
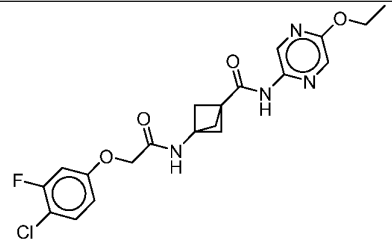
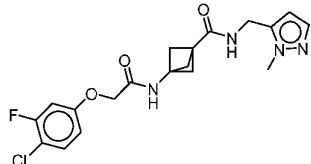
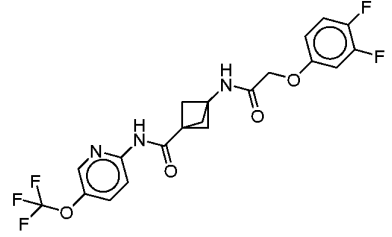
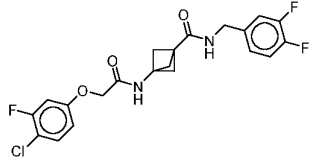
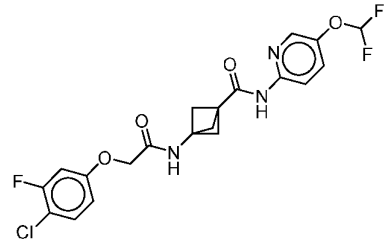
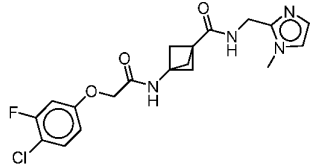
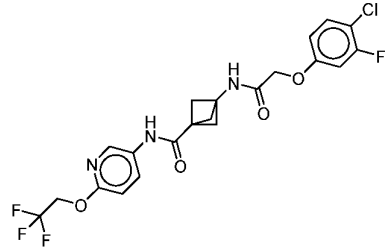
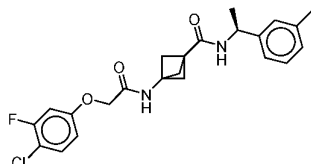
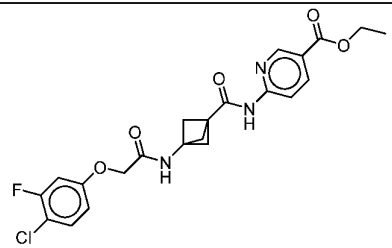
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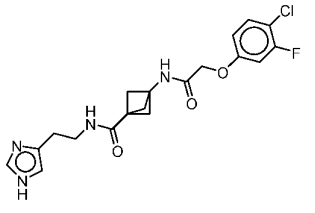
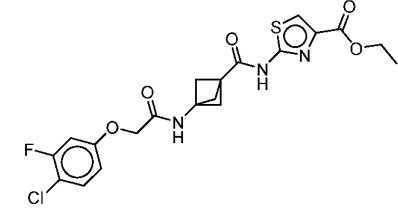
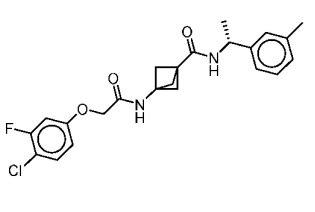
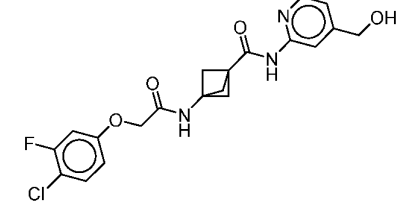
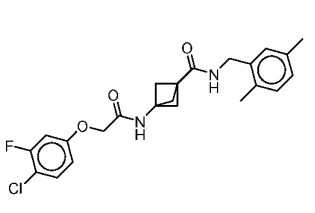
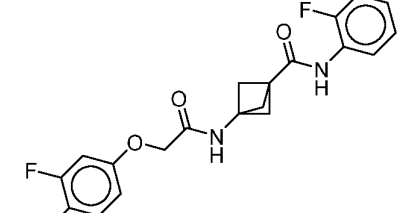
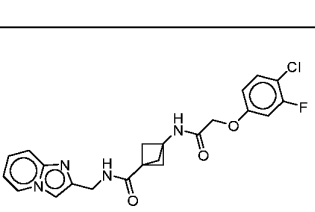
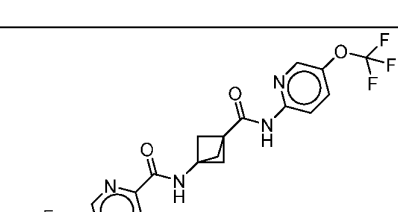
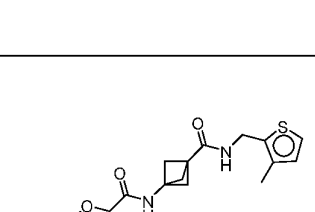
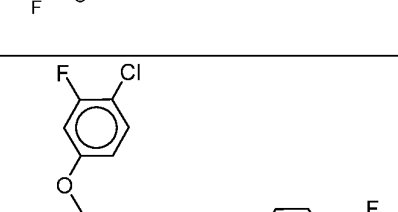
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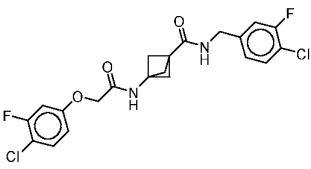
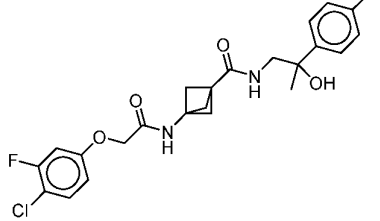
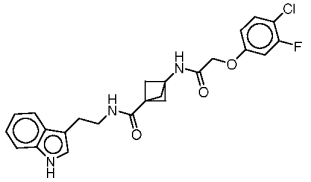
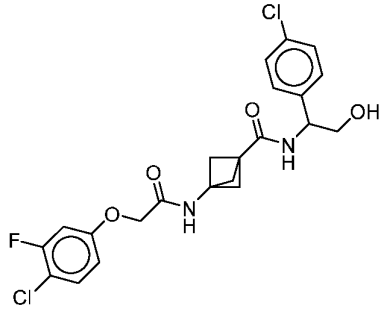
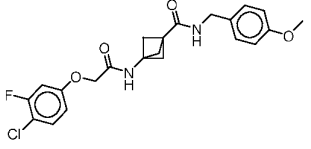
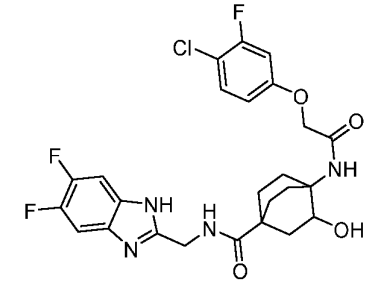
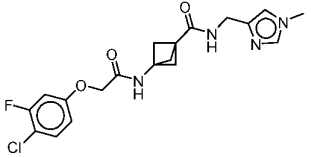
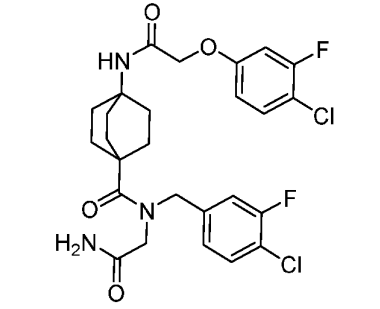
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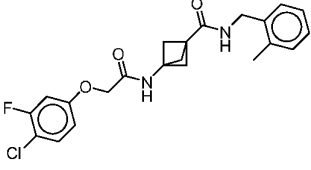
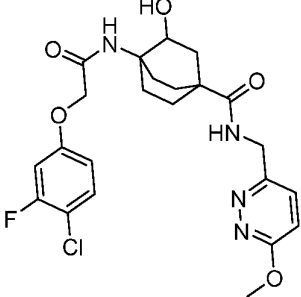
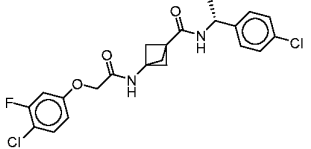
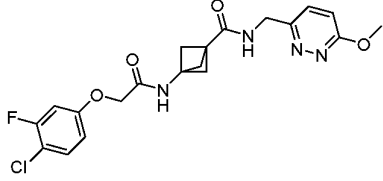
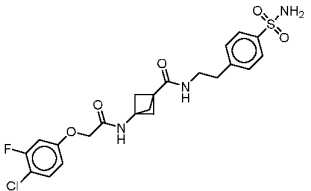
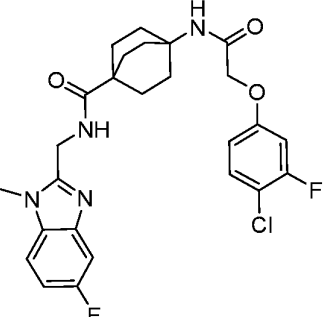
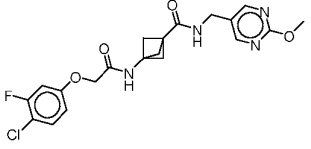
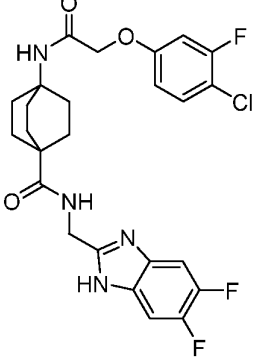
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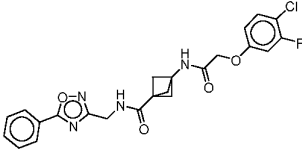
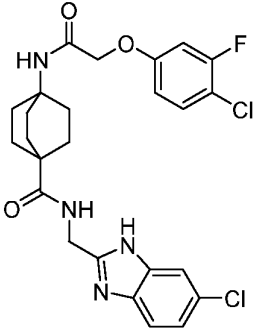
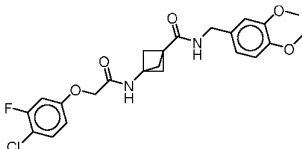
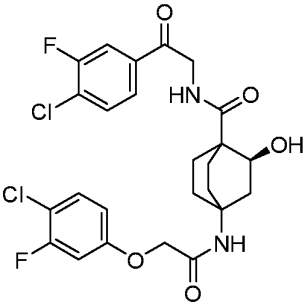
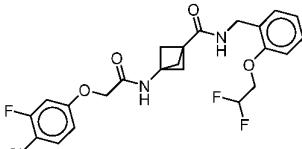
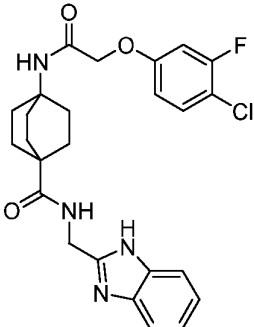
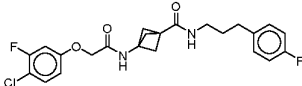
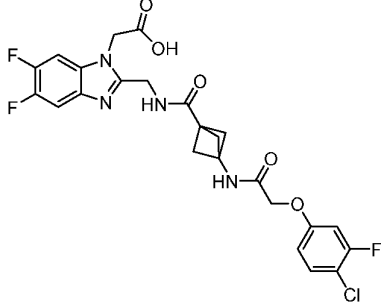
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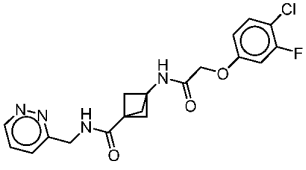
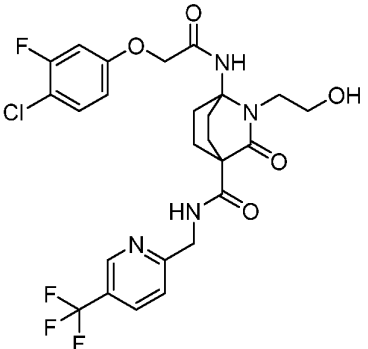
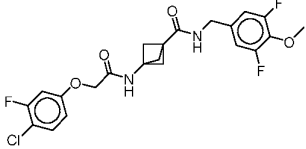
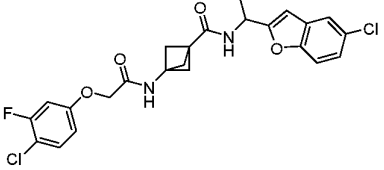
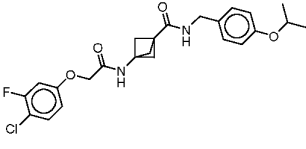
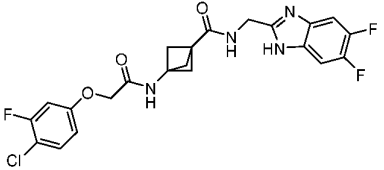
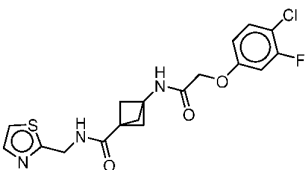
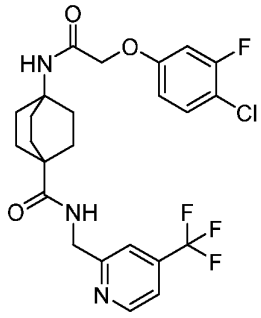
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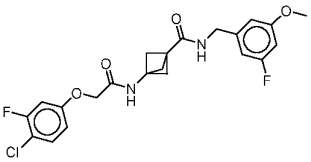
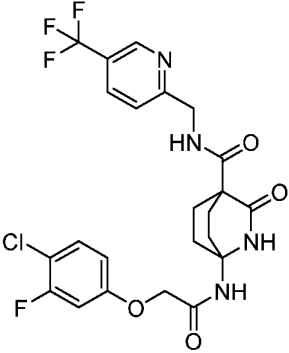
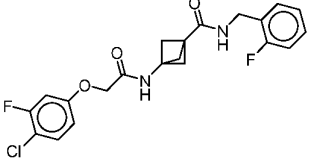
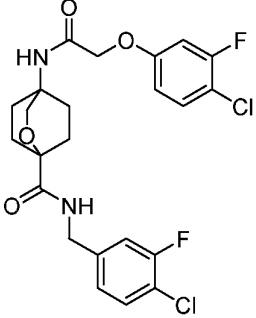
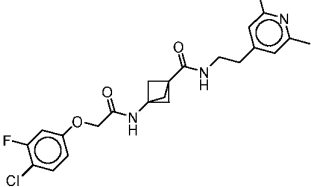
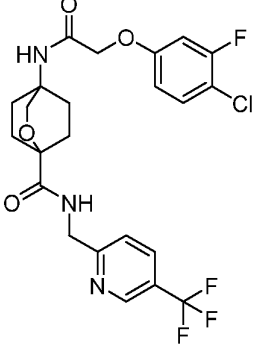
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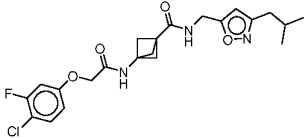
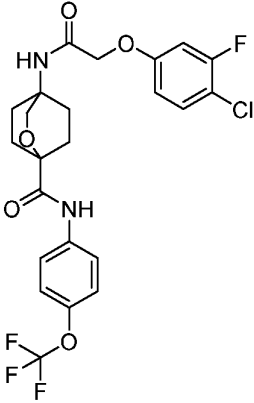
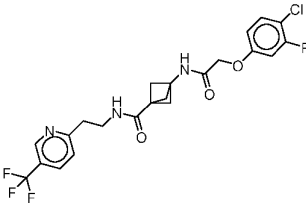
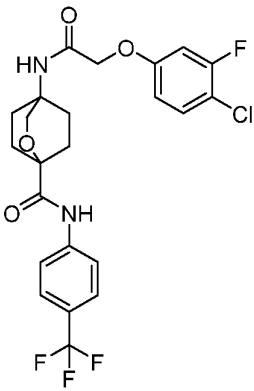
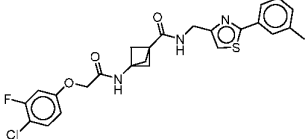
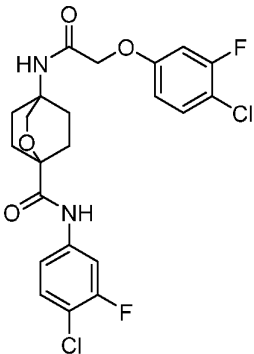
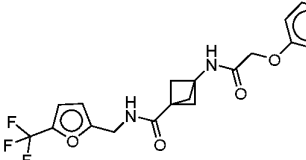
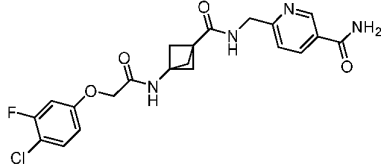
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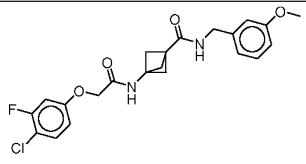
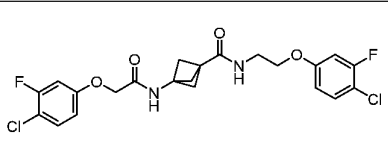
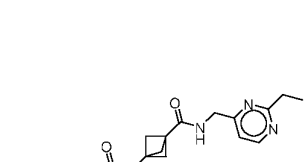
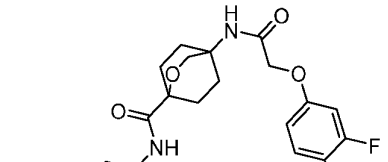
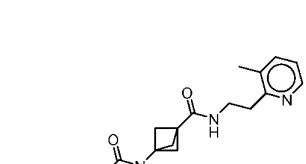
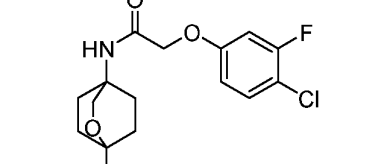
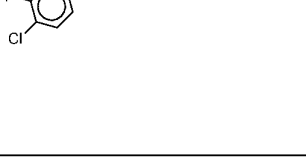
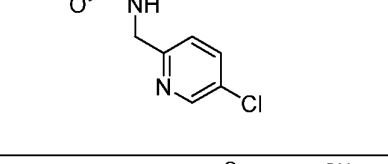
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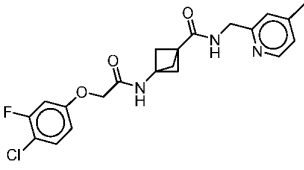
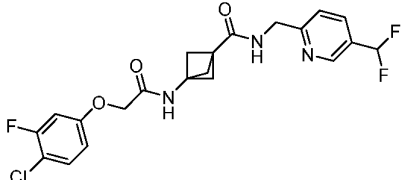
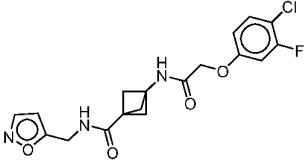
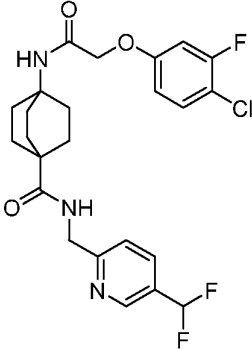
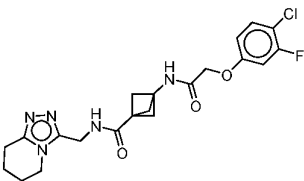
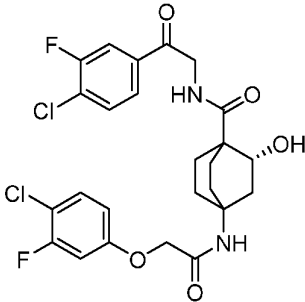
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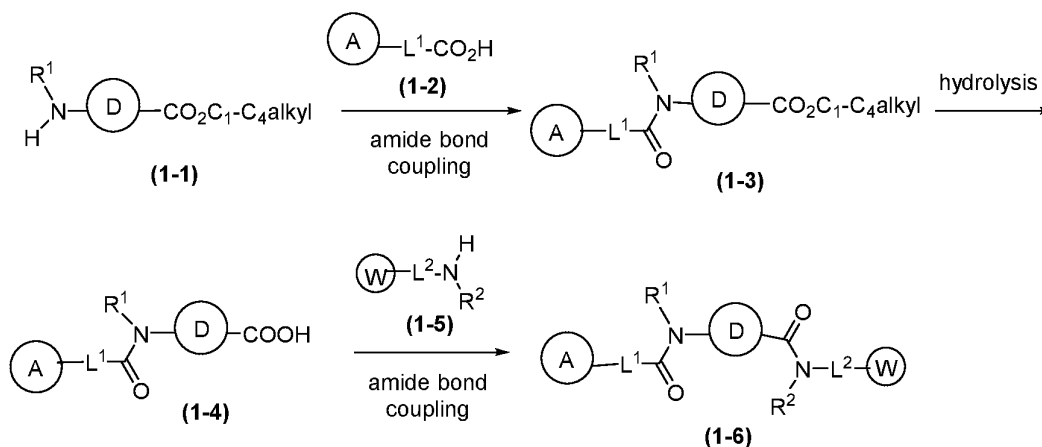
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Methods of Making Exemplary Compounds

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. A representative synthetic procedure is illustrated in, but is not limited to, that shown in Schemes 1-4. The variables A, D, W, L¹, L², R¹, and R² are defined as detailed herein, e.g., in the Summary.

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

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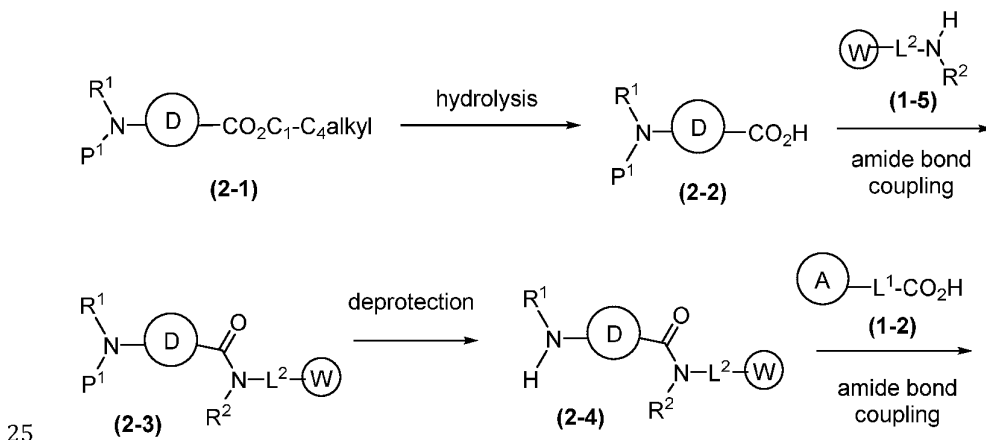
As shown in Scheme 1, compounds of Formula (1-6) can be prepared from compounds of Formula (1-1). Compounds of Formula (1-1) can be coupled with carboxylic acids of Formula (1-2) under amide bond forming conditions to give compounds of Formula (1-3).

- 5 Examples of conditions known to generate amides from a mixture of a carboxylic acid and an amine include but are not limited to adding a coupling reagent such as but not limited to *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
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- 20 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 (dimethylamino)pyridine (DMAP), 1-hydroxy-7-azabenzotriazole (HOAT), and 1-hydroxybenzotriazole (HOBt). The coupling reaction may be carried out optionally in the

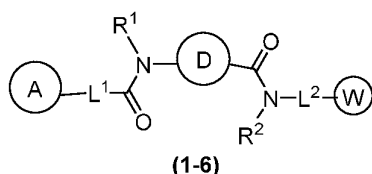
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presence of a base such as triethylamine or diisopropylethylamine. The coupling reaction may be carried out in solvents such as but not limited to tetrahydrofuran, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethyl sulfoxide, dichloromethane, or ethyl acetate. Alternatively, carboxylic acids of Formula (1-2) may be converted to the corresponding acid chlorides by reaction with thionyl chloride, PCl_3 , PCl_5 , cyanuric chloride, 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 can then be reacted with amines of Formula (1-1) optionally in the presence of a base such as a tertiary amine base such as but not limited to 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). Esters of Formula (1-3) can be hydrolyzed to compounds of Formula (1-4). For example, esters of Formula (1-3) can be treated with a base such as lithium hydroxide, sodium hydroxide, or potassium hydroxide in a solvent such as methanol, ethanol, tetrahydrofuran or a mixture of tetrahydrofuran and water at ambient temperature or heated from 0.5 to 8 hours to give compounds of Formula (1-4). Carboxylic acids of Formula (1-4) can be coupled to amines of Formula (1-5) under the amide bond coupling conditions described above to give compounds of Formula (1-6). The carboxylic acids of Formula (1-4) can be converted to the corresponding acid chlorides again as described above. The carboxylic acid chlorides derived from carboxylic acids of Formula (1-4) can be reacted with amines of Formula (1-5) to also give compounds of Formula (1-6). Compounds of Formula (1-6) are representative of compounds of Formula (I).

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



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As shown in Scheme 2, compounds of Formula (1-6) can also be prepared from compounds of Formula (2-1). *N*-Protected amino esters of Formula (2-1), wherein P¹ is an amine protecting group known in the literature or to one of skill in the art, can be hydrolyzed to compounds of Formula (2-2). For example, *N*-protected amino esters of Formula (2-1) can be treated with a base such as lithium hydroxide, sodium hydroxide, or potassium hydroxide in a solvent such as methanol, ethanol, tetrahydrofuran or a mixture of tetrahydrofuran and water at ambient temperature or heated from 0.5 to 8 hours to give compounds of Formula (2-2). Alternatively, when (2-1) is a *tert*-butyl ester, treatment under acidic conditions such as hydrochloric acid in dioxane or trifluoroacetic acid in dichloromethane can provide compounds of formula (2-2). Compounds of Formula (2-2) can be coupled with amines of Formula (1-5) under amide bond forming conditions to give compounds of Formula (2-3). Examples of conditions known to generate amides from a mixture of a carboxylic acid and an amine include but are not limited to adding a coupling reagent such as but not limited to *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-trioxatrimphosphinane 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

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reagents that are often used in the coupling reactions include but are not limited to (dimethylamino)pyridine (DMAP), 1-hydroxy-7-azabenzotriazole (HOAT), and 1-hydroxybenzotriazole (HOBt). The coupling reaction may be carried out optionally in the presence of a base such as triethylamine or diisopropylethylamine. The coupling reaction may

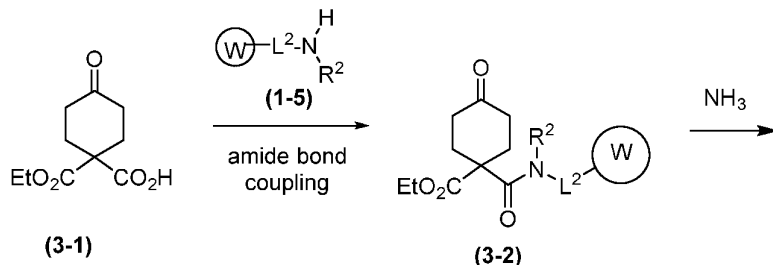
5 be carried out in solvents such as but not limited to tetrahydrofuran, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethyl sulfoxide, dichloromethane, or ethyl acetate. Alternatively, carboxylic acids of Formula (2-2) may be converted to the corresponding acid chlorides by reaction with thionyl chloride, PCl_3 , PCl_5 , cyanuric chloride, or oxalyl chloride. The reactions with thionyl chloride and oxalyl chloride can be catalyzed with *N,N*-dimethylformamide at

10 ambient temperature in a solvent such as dichloromethane. The resultant acid chlorides can then be reacted with amines of Formula (1-5) optionally in the presence of a base such as a tertiary amine base such as but not limited to triethylamine or diisopropylethylamine or an aromatic base such as pyridine, at room temperature in a solvent such as dichloromethane to give amides of Formula (2-3). The amine protecting group, P^1 , of compounds of formula (2-3) can be removed

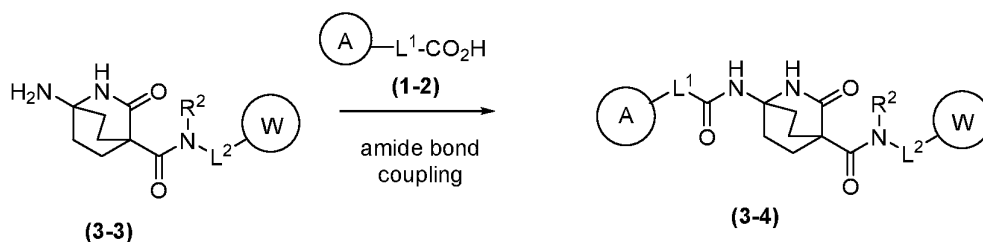
15 under conditions known in the literature or to one of skill to give amines of formula (2-4). Amines of Formula (2-4) can be coupled to carboxylic acids of Formula (1-2) under the amide bond coupling conditions described above to give compounds of Formula (2-3). The carboxylic acids of Formula (1-2) can be converted to the corresponding acid chlorides again as described above. The carboxylic acid chlorides derived from carboxylic acids of Formula (1-2) can be

20 reacted with amines of Formula (2-4) to also give compounds of Formula (1-6). Compounds of Formula (1-6) are representative of compounds of Formula (I).

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



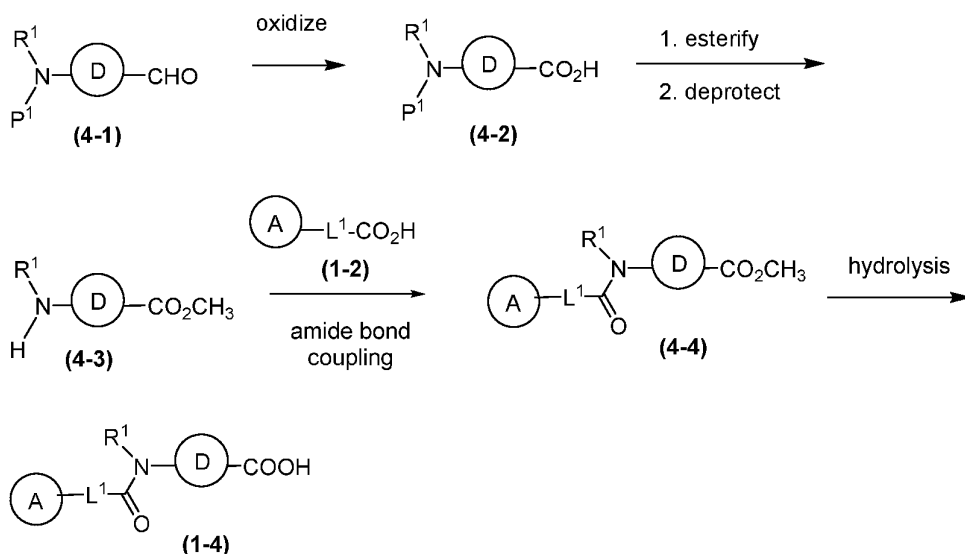
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As shown in Scheme 3, compounds of Formula (3-4) can be prepared from the compound of Formula (3-1). The compound of Formula (3-1) can be coupled with compounds of Formula (1-5) using the amide bond forming conditions described in Schemes 1 and 2 to give compounds of Formula (3-2). Compounds of Formula (3-2) can be reacted with ammonia in a solvent such as but not limited to methanol to give compounds of Formula (3-3). Compounds of Formula (3-3) can be coupled with carboxylic acids of Formula (1-2) under amide bond forming conditions described in Schemes 1 and 2 to give compounds of Formula (3-4). Compounds of Formula (3-4) are representative of compounds of Formula (I).

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



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As shown in Scheme 4, compounds of Formula (1-4) can be prepared from compounds of Formula (4-1). Aldehydes of Formula (4-1), wherein P^1 is an amine protecting group known in the literature or to one of skill in the art, can be oxidized with an oxidant such as but not

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limited to a mixture of sodium chlorite, sodium dihydrogen phosphate, 2-methyl-2-butene in a solvent mixture such as but not limited to *tert*-butanol, tetrahydrofuran and water at or near ambient temperature to give carboxylic acids of Formula (4-2). Compounds of Formula (4-2) can be converted to compounds of Formula (4-3) in a two-step process. In the first step, the
5 carboxylic acid of compounds of Formula (4-2) can be treated with (diazomethyl)trimethylsilane in solvent such as methanol to give the corresponding methyl ester. Subsequently in the next step, the amine protecting group can be removed under conditions known to one of skill in the art and dependent on the particular protecting group. For example, when the amine protecting group is *tert*-butoxycarbonyl, treatment with an acid such as trifluoroacetic acid or hydrogen
10 chloride in a solvent such as dichloromethane or dioxane removes the amine protecting group. Compounds of Formula (4-3) can be coupled with carboxylic acids of Formula (1-2) under amide bond forming conditions described in Schemes 1 and 2 to give compounds of Formula (4-4). Esters of formula (4-4) can be hydrolyzed with a base such as but not limited to lithium hydroxide, sodium hydroxide or potassium hydroxide in an optionally warmed solvent or solvent
15 mixture such as methanol and tetrahydrofuran to give compounds of formula (1-4). Compounds of formula (1-4) can then be taken forward as shown in Scheme 1.

Pharmaceutical Compositions

The present invention features pharmaceutical compositions comprising a compound of
20 Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable excipient. In some embodiments, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, stereoisomer thereof is provided in an effective amount in the pharmaceutical composition. In some
25 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) or Formula (II) (the "active ingredient") into association with a carrier
30 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

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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) or Formula (II), 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) or Formula (II).

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,

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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
5 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
10 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
15 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
20 composition is suitable for buccal or sublingual administration, including tablets, lozenges and pastilles. A compound of Formula (I) or Formula (II) 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,
25 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
30 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

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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

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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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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

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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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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,

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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 eIF2 α signal transduction pathway or component of phosphorylated eIF2 α 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, eIF2 α 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.

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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.

5 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
10 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.
15 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
20 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
25 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
30 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

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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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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, eIF2 α 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

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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, eIF2 α , 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, eIF2 α , 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, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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,

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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).

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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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof and thereby
5 modulate treatment of a particular disease, disorder, or condition, or a symptom thereof.

Neurodegenerative Disease

In some embodiments, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat a neurodegenerative disease. As used herein, the term
10 "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
15 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,
20 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
25 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.

30 In some embodiments, the neurodegenerative disease comprises vanishing white matter disease, childhood ataxia with CNS hypo-myelination, a leukodystrophy, a

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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),
5 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).

10 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
15 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat vanishing white matter disease. Exemplary methods of
20 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 Formula (II), or a
25 pharmaceutically acceptable salt, co-crystal, 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.

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In some embodiments, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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.

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In some embodiments, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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
5 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
10 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
15 inhibitor, a calcium channel inhibitor, or a blood brain barrier inhibitor).

In other embodiments, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 eIF2 α phosphorylation.
20 Regulators of translation, such as compounds disclosed herein (e.g. a compound of Formula (I) or Formula (II)), 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)
25 and prion diseases. In addition, a mutation in eIF2 γ 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
30 term memory, or memory consolidation).

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In still other embodiments, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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
5 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 some embodiments, the patient is a bovine. In some embodiments, the subject is a primate.

Cancer

10 In some embodiments, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, 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,
15 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,
20 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.
25 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,
30 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

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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 insuloma, 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 leukocythemmic 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

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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, subungual 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, cerebriiform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma,

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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, gelatiniformi 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, tuberos carcinoma, verrucous carcinoma, or carcinoma villosum.

In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 Formula (II) or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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) or Formula (II)) and compositions (e.g., compositions comprising a compound

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described herein, *e.g.*, a compound of Formula (I) or Formula (II))) 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
5 compound described herein, *e.g.*, a compound of Formula (I) or Formula (II) 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
10 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.*,
15 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
20 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
25 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
30 therapy.

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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
5 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
10 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
15 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
20 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-
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
30 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

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vedotin, Cetuximab, Gemtuzumab ozogamicin, Ibritumomab tiuxetan, Ipilimumab, Ofatumumab, Panitumumab, Rituximab, Tositumomab, Trastuzumab, Nivolumab, Pembrolizumab, Avelumab, durvalumab and pidilizumab.

Checkpoint blocking antibodies

5 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
10 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
15 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
20 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
25 (*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
30 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
35 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

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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

5 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
10 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
15 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.

20 *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
25 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.

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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.

5

Inflammatory Disease

In some embodiments, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an inflammatory disease. As used herein, the term

10 "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

15 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,

20 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- α (tumor necrosis factor- α), and C-reactive protein (CRP).

25 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,

30 glomerulonephritis, auto-immune thyroiditis, Behcet's disease, Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, ichthyosis, Graves' ophthalmopathy, inflammatory bowel

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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
5 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
10 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 Formula (II), or a
pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
15 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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
20 disease (e.g., an inflammatory disease described herein).

Musculoskeletal Diseases

In some embodiments, the compound of Formula (I) or Formula (II), or a
pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
25 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer,
30 ester, *N*-oxide or stereoisomer thereof include muscular dystrophy (e.g., Duchenne muscular

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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
5 recessive chondrodysplasia punctata, Conradi-Hünemann 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,
10 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
15 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
20 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 Formula (II), or a
25 pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
30 stereoisomer thereof include non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis,

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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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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),

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neuropathy, ataxia, retinitis pigmentosa (NARP), Leber's hereditary optic neuropathy (LHON), and Pearson syndrome.

In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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.

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In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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
5 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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

10 In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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
15 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an ocular disease or condition described herein by
20 decreasing or eliminating a symptom of the disease. In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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
25 described herein.

Kidney Diseases

In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat kidney disease. As used herein, the term "kidney disease"

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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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include Abderhalden–Kaufmann–Lignac syndrome

5 (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

10 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

15 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

20 Nephropathy, C3 Glomerulopathy, C3 Glomerulopathy with Monoclonal Gammopathy, C4 Glomerulopathy, Calcineurin Inhibitor Nephrotoxicity, Callilepsis Laureola Poisoning, Cannabinoid Hyperemesis Acute Renal Failure, Cardiorenal syndrome, Carfilzomib-Induced Renal Injury, CFHR5 nephropathy, Charcot–Marie–Tooth Disease with Glomerulopathy, Chinese Herbal Medicines and Nephrotoxicity, Cherry Concentrate and Acute Kidney Injury,

25 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

30 (Mainzer-Saldino Syndrome or Saldino-Mainzer Disease), Contrast Nephropathy, Copper Sulphate Intoxication, Cortical Necrosis, Crizotinib-related Acute Kidney Injury, Cryocrystalglobulinemia, Cryoglobulinemia, Crystalglobulin-Induced Nephropathy, Crystal-Induced Acute Kidney injury, Crystal-Storing Histiocytosis, Cystic Kidney Disease, Acquired,

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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
 5 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,
 10 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
 15 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
 20 Paroxysmal Nocturnal Hemoglobinuria and Hemolytic Anemia, Hepatic Glomerulopathy, Hepatic Veno-Occlusive Disease, Sinusoidal Obstruction Syndrome, Hepatitis C-Associated Renal Disease, Hepatocyte Nuclear Factor 1 β -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
 25 (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, Hyponatremia, Hyperoxaluria, Hyperphosphatemia, Hypocalcemia, Hypocomplementemic Urticarial Vasculitic Syndrome, Hypokalemia,
 30 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

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- 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
- 5 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 Erythematosus, Lupus Kidney
- 10 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; Ecstasy; 3,4-Methylenedioxymethamphetamine) and Kidney Failure, Meatal
- 15 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
- 20 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,
- 25 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),
- 30 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

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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,

5 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

10 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

15 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

20 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, Tuberos Sclerosis,

25 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,

30 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,

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West Nile Virus and Chronic Kidney Disease, Wunderlich syndrome, Zellweger Syndrome, or Cerebrohepatorenal Syndrome.

In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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.

10 *Skin Diseases*

In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 (verrucae), 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II)

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or a pharmaceutically acceptable salt, co-crystal, 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

5 In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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
10 Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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,
15 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.

20 In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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
25 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or

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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 Formula (II), or a
5 pharmaceutically acceptable salt, co-crystal, 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 -
10 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, $\delta\beta$ -Thalassemia, and $\epsilon\gamma\delta\beta$ -Thalassemia.

In some embodiments, the compound of Formula (I) or Formula (II) or a
15 pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in
20 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is used to treat an autoimmune disease. As used herein, the term
25 "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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof include Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis,
30 Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis,

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- 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),
- 5 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, Cocksackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica),
- 10 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-
- 15 Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammaglobulinemia, 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,
- 20 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
- 25 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
- 30 III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiectomy 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,

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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, 5 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 Formula (II) or a 10 pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in 15 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 Formula (II) or a 20 pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a 25 pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be used as a single agent in a composition or in 30 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof is resistant/recrudescent malaria.

In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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.

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In some embodiments, the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II) or a pharmaceutically acceptable salt, co-crystal, 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, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, thereby modulating the expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof with the cell increases the expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof with the cell decreases the expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof modulates the expression of eIF2B, eIF2 α , a component of the eIF2 pathway, component of the ISR pathway or any combination thereof by the patient's cells,

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thereby treating the condition, disease or disorder. In some embodiments, the condition, disease or disorder is characterized by aberrant expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the expression of eIF2B, eIF2 α , 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, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, thereby modulating the activity of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof with the cell increases the activity of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof with the cell decreases the activity of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the compound of Formula (I) or Formula (II), or a

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pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof modulates the activity of eIF2B, eIF2 α , 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, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the activity of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof, wherein the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof modulates both the expression and the activity of eIF2B, eIF2 α , 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) or Formula (II) 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, eIF2 α , 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) or Formula (II) is metabolized by the patient forming a biologically active compound that modulates the expression and/or activity of eIF2B, eIF2 α , 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).

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In one aspect, disclosed herein is a method of treating a disease related to a modulation of eIF2B activity or levels, eIF2 α 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) or Formula (II). In some
5 embodiments, the modulation comprises an increase in eIF2B activity or levels, increase in eIF2 α 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 eIF2 α signaling pathway).

Methods of Increasing Protein Activity and Production

10 In another aspect, the compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be useful in applications where increasing production output of eIF2B, eIF2 α , 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.

15 In some embodiments, the present invention features a method of increasing expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester,
20 *N*-oxide or stereoisomer thereof. In some embodiments, the method is a method of increasing the expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
25 stereoisomer thereof). In other embodiments, the method is a method of increasing the expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester,
30 *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 Formula (II), or a

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pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases expression of eIF2B, eIF2 α , 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%,
5 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
10 stereoisomer thereof increases expression of eIF2B, eIF2 α , 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,
15 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, eIF2 α , a component of the eIF2 pathway, a component of the ISR pathway
20 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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,
25 eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
30 stereoisomer thereof increases the expression of eIF2B, eIF2 α , 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

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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
5 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases expression of eIF2B, eIF2 α , 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,
10 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 Formula (II), or a pharmaceutically
15 acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be useful in applications where increasing the activity of eIF2B, eIF2 α , 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, eIF2 α , a component of the eIF2 pathway, a component of the ISR pathway or any
20 combination thereof in a cell, the method comprising contacting the cell with an effective amount of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or
25 stereoisomer thereof increases the activity of eIF2B, eIF2 α , 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
30 some embodiments, contacting the cell with an effective amount of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer,

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ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2 α , 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, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof increases the activity of eIF2B, eIF2 α , 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.

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In some embodiments, the compound of Formula (I) or Formula (II) 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, eIF2 α , 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) or Formula (II) is metabolized by the patient forming a biologically active compound that increases the expression and/or activity of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be useful in applications where decreasing production output of eIF2B, eIF2 α , 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, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases expression of eIF2B, eIF2 α , 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, eIF2 α , 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

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the patient an effective amount of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the expression of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof may be useful in applications where decreasing the activity of eIF2B, eIF2 α , 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, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the activity of eIF2B, eIF2 α , 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.

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In some embodiments, the present invention features a method of decreasing the activity of eIF2B, eIF2 α , 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, 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 Formula (II), or a pharmaceutically acceptable salt, co-crystal, solvate, hydrate, tautomer, ester, *N*-oxide or stereoisomer thereof decreases the activity of eIF2B, eIF2 α , 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) or Formula (II) 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, eIF2 α , 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) or Formula (II) is metabolized by the patient forming a biologically active compound that decreases the expression and/or activity of eIF2B, eIF2 α , 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) or Formula (II).

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, 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, or stereoisomer thereof, is co-administered with a second agent (e.g. therapeutic agent). In other embodiments of the method, a

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compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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.

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Combination Therapy

In one aspect, the present invention features a pharmaceutical composition comprising a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, 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, eIF2 α , or a component of the eIF2 pathway or ISR pathway.

15 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, eIF2 α , 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.

20 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, eIF2 α , or a component of the eIF2 pathway or ISR pathway.

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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 eIF2 α phosphorylation. In embodiments, the second agent is an agent for inhibiting a pathway activated by eIF2 α phosphorylation. In embodiments, the second agent is an agent for inhibiting a pathway activated by eIF2 α . 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),

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alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, chlorambucil, melphalan), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomustine, 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), gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatins, 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-I, 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; benzoylstauroporine;

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beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor;
 bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate;
 broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin
 derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole;
 5 CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS);
 castanospermine; cecropin B; cetorelix; 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; cyclopentantraquinones; cycloplatam;
 10 cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine;
 dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil;
 diaziqune; 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;
 15 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;
 20 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;
 25 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
 30 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;

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mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin;
 monophosphoryl lipid A+myobacterium 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;
 5 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
 10 acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan
 polysulfate sodium; pentostatin; pentozole; 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;
 15 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
 20 inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII
 retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; 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;
 25 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;
 30 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

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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; 5 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; aminogluthethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene 10 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; 15 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; 20 fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II (including recombinant interleukin II, or rIL.sub.2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iprop latin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole 25 hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprime; meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; 30 ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprime; rogletimide; safingol; safingol hydrochloride;

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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

5 acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinatate 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

10 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,

15 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.

20 Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. TZZT-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-

25 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,

30 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

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(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, Desaeyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribacoxide, Caribacolin, 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),

10 Dioxostatin, (-)-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,

15 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., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-

20 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 ^{111}In , ^{90}Y , or ^{131}I , etc.), triptolide, homoharringtonine,

25 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 (IressaTM), erlotinib (TarcevaTM), cetuximab (ErbixTM), lapatinib (TykerbTM), panitumumab (VectibixTM),

30 vandetanib (CaprelsaTM), 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,

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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
5 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
10 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 ^{111}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 ,
15 ^{64}Cu , ^{67}Cu , ^{89}Sr , ^{86}Y , ^{87}Y , ^{90}Y , ^{105}Rh , ^mAg , ^mIn , ^{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
20 compound of Formula (I) or Formula (II)) 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 Formula (II)) or composition thereof described herein is an agent approved by the FDA or similar regulatory agency of a
25 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,
30 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,

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- selegiline, rasagiline, entacapone, benztropine, trihexyphenidyl, riluzole, diazepam, chlorodiazepoxide, lorazepam, alprazolam, buspirone, gepirone, isipirone, 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 Formula (II), 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, ginkgo, 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.)

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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; DMSO for dimethyl sulfoxide; HPLC for high performance liquid chromatography; MS for mass spectrum; and NMR for nuclear magnetic resonance.

Example 1: 3-[2-(4-chlorophenoxy)acetamido]-N-[2-(4-chlorophenoxy)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 100)

Example 1A: methyl 3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentane-1-carboxylate

To a solution of 2-(4-chlorophenoxy)acetic acid (10.88 g, 58.5 mmol) in *N,N*-dimethylformamide (150 mL) were added methyl 3-aminobicyclo[1.1.1]pentane-1-carboxylate (Pharmablock, 10.5 g, 53.2 mmol), *N,N*-diisopropylethylamine (27.5 g, 213 mmol) and 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (30.3 g, 80 mmol). The reaction mixture was stirred at ambient temperature for 3 hours, and then partitioned between ethyl acetate (250 mL) and water (250 mL). The aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (5 x 300 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10-20% ethyl acetate/heptane) to provide 15.4 g (94%) of the title compound as light yellow solid. MS (APCI) *m/z* 310 (M+H)⁺.

Example 1B: 3-(2-(4-chlorophenoxy)acetamido)bicyclo[1.1.1]pentane-1-carboxylic acid

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A solution of Example 1A (0.52 g, 0.169 mmol) in tetrahydrofuran (3 mL) was treated with 1 N LiOH solution (3.34 mL) and stirred at ambient temperature for 0.5 hour. The reaction mixture was concentrated and neutralized with 6 N HCl. The resultant precipitate was collected by filtration, washed with water, and dried in a vacuum oven to provide the title compound. MS (APCI) m/z 296 (M+H)⁺.

Example 1C: 3-[2-(4-chlorophenoxy)acetamido]-N-[2-(4-chlorophenoxy)ethyl]bicyclo[1.1.1]-pentane-1-carboxamide (Compound 100)

To a solution of Example 1B (0.025 g, 0.085 mmol) in *N,N*-dimethylformamide (0.5 mL) was added 2-(4-chlorophenoxy)ethan-1-amine (0.015 g, 0.085 mmol), *N,N*-diisopropylethylamine (0.04 mL, 0.212 mmol) and 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (0.035 g, 0.093 mmol) at ambient temperature. The reaction mixture was stirred for 3 hours, and then it was partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (5 x 30 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by HPLC (Phenomenex® Luna® C18(2) 5 µm 100 Å AXIA™ column 250 mm x 21.2 mm, flow rate 25 mL/minute, 10-80% gradient of acetonitrile in buffer (0.1% trifluoroacetic acid in water)) to provide 0.028 g (74%) of the title compound as light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.65 (s, 1H), 7.96 (t, *J* = 5.7 Hz, 1H), 7.40 – 7.25 (m, 4H), 7.05 – 6.90 (m, 4H), 4.38 (s, 2H), 3.95 (t, *J* = 5.9 Hz, 2H), 3.35 (q, *J* = 5.9 Hz, 2H), 2.13 (s, 6H). MS (APCI) m/z 450 (M+H)⁺.

Example 2: 3-[2-(4-chlorophenoxy)acetamido]-N-[2-(3-methylphenoxy)ethyl]bicyclo[1.1.1]-pentane-1-carboxamide (Compound 101)

A solution of Example 1B (25 mg, 0.08 mmol) in *N,N*-dimethylformamide (1.0 mL) was treated with a solution of 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (35 mg, 0.09 mmol) in *N,N*-dimethylformamide (0.5 mL). Then a solution of 2-(*m*-tolylxy)ethanamine (12 mg, 0.08 mmol) in *N,N*-dimethylacetamide (0.15 mL) was added followed by *N,N*-diisopropylethylamine (0.037 mL, 0.21 mmol). The reaction was shaken at ambient temperature overnight and purified by HPLC (2-coupled C8 5 µm 100 Å columns 30 mm x 75 mm each, flow rate of 50 mL/minute, 5-90% gradient of acetonitrile in buffer (0.1% trifluoroacetic acid in water)) to provide the title compound. ¹H NMR (400 MHz, DMSO-*d*₆/D₂O, temperature = 27 °C) δ ppm 8.06 (t, *J* = 5.7 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.01 – 6.93 (m, 2H), 6.77 – 6.68 (m, 3H),

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4.40 (s, 2H), 3.95 (t, $J = 5.9$ Hz, 2H), 3.43 – 3.31 (m, 2H), 2.25 (s, 3H), 2.17 (s, 6H). MS (APCI+) m/z 429.2 (M+H)⁺.

Example 3: 3-[2-(4-chlorophenoxy)acetamido]-N-[2-(4-fluorophenoxy)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 102)

5 The title compound was prepared using the method described in Example 2 by replacing 2-(*m*-tolylloxy)ethanamine with 2-(4-fluorophenoxy)ethanamine (12.4 mg, 0.08 mmol). ¹H NMR (400 MHz, DMSO-*d*₆/D₂O, temperature = 27 °C) δ ppm 8.07 (t, $J = 5.7$ Hz, 1H), 7.38 – 7.32 (m, 2H), 7.15 – 7.06 (m, 2H), 7.02 – 6.90 (m, 4H), 4.40 (s, 2H), 3.95 (t, $J = 5.8$ Hz, 2H), 3.46 – 3.36 (m, 2H), 2.17 (s, 6H). MS (APCI+) m/z 433.2 (M+H)⁺.

10 **Example 4: N-[2-(4-chloro-3-methylphenoxy)ethyl]-3-[2-(4-chlorophenoxy)acetamido]-bicyclo[1.1.1]pentane-1-carboxamide (Compound 103)**

 The title compound was prepared using the method described in Example 2 by replacing 2-(*m*-tolylloxy)ethanamine with 2-(4-chloro-3-methylphenoxy)ethanamine (14.8 mg, 0.08 mmol). ¹H NMR (400 MHz, DMSO-*d*₆/D₂O, temperature = 27 °C) δ ppm 8.07 (t, $J = 5.7$ Hz, 1H), 7.37 – 7.31 (m, 2H), 7.27 (d, $J = 8.7$ Hz, 1H), 7.03 – 6.96 (m, 2H), 6.95 – 6.91 (m, 1H), 6.83 – 6.77 (m, 1H), 4.40 (s, 2H), 3.97 (t, $J = 5.9$ Hz, 2H), 3.45 – 3.35 (m, 2H), 2.27 (s, 3H), 2.17 (s, 6H). MS (APCI+) m/z 463.2 (M+H)⁺.

Example 5: 3-[2-(4-chlorophenoxy)acetamido]-N-[2-(3-fluorophenoxy)ethyl]bicyclo-[1.1.1]pentane-1-carboxamide (Compound 104)

20 The title compound was prepared using the method described in Example 2 by replacing 2-(*m*-tolylloxy)ethanamine with 2-(3-fluorophenoxy)ethanamine (12.4 mg, 0.08 mmol). ¹H NMR (400 MHz, DMSO-*d*₆/D₂O, temperature = 27 °C) δ ppm 8.75 (s, 1H), 8.08 (t, $J = 5.7$ Hz, 1H), 7.36 – 7.28 (m, 3H), 7.03 – 6.93 (m, 2H), 6.82 – 6.74 (m, 3H), 4.40 (s, 2H), 4.00 (t, $J = 5.8$ Hz, 2H), 3.43 – 3.34 (m, 2H), 2.17 (s, 6H). MS (APCI+) m/z 433.2 (M+H)⁺.

25 **Example 6: 3-[2-(4-chlorophenoxy)acetamido]-N-[2-(4-methylphenoxy)ethyl]bicyclo-[1.1.1]pentane-1-carboxamide (Compound 105)**

 The title compound was prepared using the method described in Example 2 by replacing 2-(*m*-tolylloxy)ethanamine with 2-(*p*-tolylloxy)ethanamine (12.4 mg, 0.08 mmol). ¹H NMR (400 MHz, DMSO-*d*₆/D₂O, temperature = 27 °C) δ ppm 8.75 (s, 1H), 8.06 (t, $J = 5.7$ Hz, 1H), 7.39 – 7.31 (m, 2H), 7.12 – 7.05 (m, 2H), 7.01 – 6.94 (m, 2H), 6.86 – 6.78 (m, 2H), 4.40 (s, 2H), 3.93 (t, $J = 6.0$ Hz, 2H), 3.43 – 3.34 (m, 2H), 2.21 (s, 3H), 2.17 (s, 6H). MS (APCI+) m/z 429.2 (M+H)⁺.

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Example 7: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 106)

Example 7A: 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
5 (12.29 mL, 220 mmol), and *p*-toluenesulfonic acid monohydrate (1.397 g, 7.34 mmol) in toluene
(200 mL) was stirred at 120 °C 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 as a clear oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.01 (q, *J* = 7.1 Hz, 2H), 3.81
10 (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 7B: 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
15 cooled to -78 °C under nitrogen, and a solution of Example 7A (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 NH₄Cl solution, and the aqueous phase was extracted with ethyl
20 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 as a clear oil. ¹H 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).

25 *Example 7C: ethyl 1-acetyl-4-oxocyclohexane-1-carboxylate*

A mixture of Example 7B (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
30 to give 5.46 g of the title compound as a clear oil, used without further purification. ¹H 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 7D: ethyl 4-(benzylamino)-2-oxobicyclo[2.2.2]octane-1-carboxylate

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A mixture of Example 7C (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 130 °C 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, air-dried to give 11.3 g of title compound as a 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 as yellow solid. ¹H 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 7E: ethyl 4-amino-2-oxobicyclo[2.2.2]octane-1-carboxylate, hydrochloric acid

To a mixture of Example 7D (11.2 g, 33.2 mmol) in tetrahydrofuran (110 mL) in a 50 mL pressure bottle was added 20% Pd(OH)₂/C, wet (2.2 g, 1.598 mmol), and the reaction was shaken at 50 °C under 50 psi of hydrogen for 22 hours. The reaction mixture was cooled to ambient temperature, and 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 as a light yellow solid. ¹H 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 7F: ethyl 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-oxobicyclo[2.2.2]octane-1-carboxylate

To a suspension of Example 7E (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 as an off-white solid. ¹H 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)⁺.

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Example 7G: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-oxobicyclo[2.2.2]octane-1-carboxylic acid

A suspension of Example 7F (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.

5 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 as a white solid. ¹H 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)[−].

10 *Example 7H: 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid*

A suspension of Example 7G (2.6 g, 7.03 mmol) and sodium borohydride (1.330 g, 35.2 mmol) (8 M solution) in methanol (50.0 mL) was stirred at ambient temperature for 30 minutes. The mixture was concentrated, and the residue was acidified with 1 N HCl. The resultant

15 precipitate was collected by filtration and dried in vacuum oven to give 2.63 g of product as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.93 (s, 1H), 7.50 – 7.39 (m, 2H), 6.98 (dd, *J* = 11.4, 2.8 Hz, 1H), 6.77 (ddd, *J* = 9.0, 2.8, 1.2 Hz, 1H), 4.79 (d, *J* = 4.9 Hz, 1H), 4.40 (s, 2H), 4.02 (dd, *J* = 8.9, 4.1 Hz, 1H), 2.20 (ddd, *J* = 12.7, 9.4, 2.9 Hz, 1H), 2.02 (tdd, *J* = 11.4, 4.4, 2.0 Hz, 1H), 1.85 – 1.44 (m, 8H); MS (ESI⁺) *m/z* 372.0 (M+H)⁺.

20 *Example 7I: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-{{5-(trifluoromethyl)pyridin-2-yl}methyl}bicyclo[2.2.2]octane-1-carboxamide*

A mixture of Example 7G (50 mg, 0.135 mmol), (5-(trifluoromethyl)pyridin-2-yl)methanamine (29.8 mg, 0.169 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.059 mL, 0.338 mmol) in *N,N*-dimethylformamide (1.5 mL) was treated with 2-(3*H*-[1,2,3]triazolo[4,5-
25 *b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (77 mg, 0.203 mmol), and the reaction was stirred at ambient temperature for 16 hours. The mixture was concentrated, and the residue was dissolved in dichloromethane/methanol (1:1 mixture, 2 mL) and treated with sodium borohydride (25.6 mg, 0.676 mmol). The mixture was stirred at ambient temperature for 1 hour. The mixture was concentrated under vacuum, and the crude residue was purified by
30 HPLC (performed on a Phenomenex® Luna® C18(2) 5 μm 100Å AXIA™ column (250 mm × 21.2 mm). A gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) is used, at a flow rate of 25 mL/minute. A linear gradient is used from about 5% of A to about 95% of A over about 10 minutes. Detection method is UV at wave length of 218 nM and 254 nM) to give

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46 mg of product as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.82 (d, J = 2.2 Hz, 1H), 8.17 (t, J = 5.9 Hz, 1H), 8.09 (dd, J = 8.4, 2.4 Hz, 1H), 7.53 – 7.40 (m, 3H), 6.99 (dd, J = 11.4, 2.8 Hz, 1H), 6.78 (dd, J = 8.9, 2.8 Hz, 1H), 4.40 (d, J = 6.0 Hz, 4H), 4.07 (dd, J = 9.4, 2.7 Hz, 1H), 2.23 (ddd, J = 12.6, 9.2, 2.8 Hz, 1H), 2.11 (td, J = 11.9, 3.7 Hz, 1H), 1.86 (tt, J = 15.4, 7.8 Hz, 1H), 1.78 – 1.54 (m, 7H); MS (ESI⁺) *m/z* 530.2 (M+H)⁺.

Example 8: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(4-chlorophenoxy)ethyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 107)

The title compound was prepared using the methodologies described in Example 7 substituting 2-(4-chlorophenoxy)ethanamine for (5-(trifluoromethyl)pyridin-2-yl)methanamine.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.64 (t, J = 5.6 Hz, 1H), 7.50 – 7.39 (m, 2H), 7.28 (d, J = 8.9 Hz, 2H), 7.03 – 6.87 (m, 3H), 6.77 (dd, J = 9.0, 2.9 Hz, 1H), 4.89 (s, 1H), 4.40 (s, 2H), 4.03 – 3.88 (m, 3H), 3.37 (t, J = 5.9 Hz, 2H), 2.18 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H), 1.99 (tt, J = 12.0, 3.3 Hz, 1H), 1.90 – 1.77 (m, 1H), 1.74 – 1.57 (m, 5H), 1.52 (tt, J = 12.2, 5.2 Hz, 2H); MS (ESI⁺) *m/z* 525.1 (M+H)⁺.

Example 9: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5-chloropyridin-2-yl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 108)

The title compound was prepared using the methodologies described in Example 7 substituting (5-chloropyridin-2-yl)methanamine for (5-(trifluoromethyl)pyridin-2-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.47 (d, J = 2.5 Hz, 1H), 8.10 (t, J = 6.0 Hz, 1H), 7.88 – 7.75 (m, 1H), 7.56 – 7.32 (m, 2H), 7.27 (d, J = 8.5 Hz, 1H), 6.99 (dd, J = 11.4, 2.8 Hz, 1H), 6.78 (dd, J = 8.8, 2.7 Hz, 1H), 4.41 (s, 2H), 4.30 (d, J = 5.9 Hz, 2H), 4.06 (dd, J = 9.4, 2.7 Hz, 1H), 2.22 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H), 2.08 (tt, J = 11.7, 3.2 Hz, 1H), 1.85 (ddd, J = 23.0, 14.3, 8.5 Hz, 2H), 1.69 (qt, J = 12.7, 2.7 Hz, 6H), 1.65 – 1.53 (m, 1H); MS (ESI⁺) *m/z* 496.2 (M+H)⁺.

Example 10: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[3-(propan-2-yl)-1,2-oxazol-5-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 109)

The title compound was prepared using the methodologies described in Example 7 substituting 3-isopropyl-isoxazol-5-ylmethylamine hydrochloride for (5-(trifluoromethyl)pyridin-2-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.03 (t, J = 5.9 Hz, 1H), 7.46 (dd, J = 18.3, 9.4 Hz, 2H), 6.99 (dd, J = 11.4, 2.9 Hz, 1H), 6.77 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.13 (s, 1H), 4.96 (s, 1H), 4.40 (s, 2H), 4.28 (d, J = 5.8 Hz, 2H), 4.04 (d, J = 9.1 Hz, 1H), 2.90 (hept, J = 6.9 Hz, 1H), 2.21 (ddd, J = 12.7, 9.2, 2.8 Hz, 1H), 2.10 – 1.99 (m, 1H),

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1.85 (td, J = 11.9, 7.9 Hz, 1H), 1.75 – 1.50 (m, 7H), 1.15 (d, J = 6.9 Hz, 6H); MS (ESI⁺) *m/z* 494.1 (M+H)⁺.

Example 11: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 110)

5 The title compound was prepared using the methodologies described in Example 7 substituting (4-(trifluoromethyl)phenyl)methanamine for (5-(trifluoromethyl)pyridin-2-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.05 (t, J = 6.0 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.49 (s, 1H), 7.49 – 7.37 (m, 3H), 6.99 (dd, J = 11.4, 2.9 Hz, 1H), 6.78 (dt, J = 8.8, 1.8 Hz, 1H), 4.93 (s, 1H), 4.41 (s, 2H), 4.31 (d, J = 5.9 Hz, 2H), 4.06 (dt, J = 9.2, 2.2 Hz, 1H), 2.21
10 (ddd, J = 12.6, 9.2, 2.8 Hz, 1H), 2.14 – 2.02 (m, 1H), 1.86 (tdd, J = 11.4, 5.4, 1.7 Hz, 1H), 1.78 – 1.53 (m, 7H); MS (ESI⁺) *m/z* 529.2 (M+H)⁺.

Example 12: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4,6-dimethylpyridin-3-yl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 111)

A mixture of Example 7H (48 mg, 0.129 mmol), (4,6-dimethylpyridin-3-yl)methanamine
15 (21.98 mg, 0.161 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.056 mL, 0.323 mmol) in *N,N*-dimethylformamide (1.5 mL) was treated with 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (73.6 mg, 0.194 mmol), and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was concentrated, and the crude residue was purified by HPLC (10~100% acetonitrile in 0.1% trifluoroacetic
20 acid/water at 25 mL/minute on a Phenomenex® C18 5μm column (250 mm × 21.2 mm)) to give 69 mg of the title compound as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.22 (t, J = 5.8 Hz, 1H), 7.53 (s, 1H), 7.50 – 7.38 (m, 2H), 7.37 (s, 1H), 6.99 (dd, J = 11.4, 2.8 Hz, 1H), 6.78 (ddd, J = 9.0, 3.0, 1.2 Hz, 1H), 4.48 – 4.37 (m, 4H), 4.06 (dt, J = 8.9, 2.4 Hz, 1H), 2.57 (s, 3H), 2.42 (s, 3H), 2.24 (ddd, J = 12.5, 9.2, 2.9 Hz, 1H), 2.11 (td, J = 11.6, 4.0 Hz, 1H), 1.95 – 1.78 (m,
25 1H), 1.78 – 1.63 (m, 7H); MS (ESI⁺) *m/z* 494.2 (M+H)⁺.

Example 13: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5-fluoropyridin-3-yl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 112)

The title compound was prepared using the methodologies described in Example 12 substituting (5-fluoropyridin-3-yl)methanamine for (4,6-dimethylpyridin-3-yl)methanamine. ¹H
30 NMR (400 MHz, DMSO-*d*₆) δ ppm 8.39 (d, J = 2.9 Hz, 1H), 8.31 (s, 1H), 8.04 (t, J = 6.0 Hz, 1H), 7.56 – 7.37 (m, 3H), 6.99 (dd, J = 11.4, 2.8 Hz, 1H), 6.77 (dd, J = 9.0, 2.7 Hz, 1H), 4.40 (s, 2H), 4.39 – 4.22 (m, 2H), 4.05 (dd, J = 9.9, 2.8 Hz, 1H), 2.21 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H),

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2.07 (td, $J = 11.8, 3.8$ Hz, 1H), 1.91 – 1.75 (m, 1H), 1.76 – 1.51 (m, 7H); MS (ESI⁺) m/z 480.2 (M+H)⁺.

Example 14: (2R)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 113)

5 The title compound was isolated by chiral preparative SFC (Supercritical Fluid Chromatography) of Example 7 as the second eluting peak. Preparative SFC was performed on a THAR/Waters SFC 80 system running under SuperChrom™ software control. The preparative SFC system was equipped with an 8-way preparative column switcher, CO₂ pump, modifier pump, automated back pressure regulator (ABPR), UV detector, and 6-position fraction collector. The mobile phase was comprised of supercritical CO₂ supplied by a Dewar of bone-dry non-certified CO₂ pressurized to 350 psi with a modifier of methanol at a flow rate of 70 g/minute. The column was at ambient temperature and the backpressure regulator was set to maintain 100 bar. The sample was dissolved in a mixture of methanol and dichloromethane (1:1) at a concentration of 14 mg/mL. The sample was loaded into the modifier stream in 1 mL (10 mg) injections. The mobile phase was held isocratically at 30% methanol:CO₂. Fraction collection was time triggered. The instrument was fitted with a Chiralpak® AD-H column with dimensions 21 mm i.d. × 250 mm length with 5 μm particles. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.82 (dt, $J = 2.2, 0.9$ Hz, 1H), 8.17 (t, $J = 5.9$ Hz, 1H), 8.09 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.53 – 7.40 (m, 3H), 6.99 (dd, $J = 11.4, 2.9$ Hz, 1H), 6.78 (ddd, $J = 9.0, 2.9, 1.2$ Hz, 1H), 5.01 (d, $J =$ 4.2 Hz, 1H), 4.40 (d, $J = 6.3$ Hz, 4H), 2.23 (ddd, $J = 12.5, 9.2, 2.9$ Hz, 1H), 2.16 – 2.06 (m, 1H), 1.87 (td, $J = 11.7, 4.9$ Hz, 1H), 1.78 – 1.55 (m, 7H); MS (ESI⁺) m/z 530.1 (M+H)⁺.

Example 15: (2S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 114)

25 The title compound was isolated by chiral preparative SFC of Example 7 as the first peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.82 (dt, $J = 1.8, 0.9$ Hz, 1H), 8.17 (t, $J = 5.9$ Hz, 1H), 8.09 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.53 – 7.39 (m, 3H), 6.99 (dd, $J = 11.4, 2.9$ Hz, 1H), 6.78 (ddd, $J = 8.9, 2.9, 1.2$ Hz, 1H), 5.01 (d, $J = 4.2$ Hz, 1H), 4.40 (d, $J = 6.5$ Hz, 4H), 4.08 (dq, $J = 8.6, 3.4, 2.8$ Hz, 1H), 2.23 (ddd, $J = 12.6, 9.1, 2.9$ Hz, 1H), 2.16 – 2.01 (m, 1H), 1.87 (td, $J = 11.3, 4.7$ Hz, 1H), 1.78 – 1.62 (m, 6H), 1.61 (td, $J = 11.5, 4.2$ Hz, 1H); MS (ESI⁺) m/z 530.2 (M+H)⁺.

Example 16: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(1,3-oxazol-4-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 115)

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The title compound was prepared using the methodologies described in Example 12 substituting 4-oxazolemethanamine hydrochloride for (4,6-dimethylpyridin-3-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.87 (t, J = 5.8 Hz, 1H), 7.75 (s, 1H), 7.52 – 7.39 (m, 2H), 6.98 (dd, J = 11.4, 2.9 Hz, 1H), 6.77 (dd, J = 9.1, 2.8 Hz, 1H), 4.39 (s, 2H), 4.11 (d, J = 5.6 Hz, 2H), 4.06 – 3.98 (m, 1H), 2.20 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H), 2.02 (tt, J = 11.8, 3.3 Hz, 1H), 1.84 (td, J = 11.6, 5.1 Hz, 1H), 1.68 (ddd, J = 12.4, 8.2, 4.7 Hz, 5H), 1.64 – 1.48 (m, 2H); MS (ESI⁺) *m/z* 452.2 (M+H)⁺.

Example 17: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(1-methyl-1H-pyrazol-3-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 116)

The title compound was prepared using the methodologies described in Example 12 substituting (1-methyl-1H-pyrazol-3-yl)methanamine dihydrochloride for (4,6-dimethylpyridin-3-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.81 (t, J = 5.8 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.43 (t, J = 8.9 Hz, 1H), 6.98 (dd, J = 11.4, 2.9 Hz, 1H), 6.77 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.00 (d, J = 2.3 Hz, 1H), 4.47 (s, 1H), 4.39 (s, 2H), 4.14 (d, J = 5.7 Hz, 2H), 4.02 (dt, J = 8.9, 2.1 Hz, 1H), 3.71 (s, 3H), 2.19 (ddd, J = 12.5, 9.2, 2.9 Hz, 1H), 2.01 (tt, J = 11.8, 3.4 Hz, 1H), 1.83 (ddd, J = 12.9, 10.9, 4.7 Hz, 1H), 1.76 – 1.48 (m, 7H); MS (ESI⁺) *m/z* 465.2 (M+H)⁺.

Example 18: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-chlorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 117)

Example 18A: 3-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[1.1.1]pentane-1-carboxylic acid

The reaction and purification conditions described in Example 1A and Example 1B, substituting 2-(4-chloro-3-fluorophenoxy)acetic acid (Aldlab) for 2-(4-chlorophenoxy)acetic acid gave the title compound. MS (APCI⁺) *m/z* 314 (M+H)⁺.

Example 18B: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-chlorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide

The product of Example 18A (52 mg, 0.166 mmol) was suspended in dichloromethane (2 mL) and 1 drop of *N,N*-dimethylformamide was added followed by the addition of oxalyl chloride (2.0 M solution in dichloromethane, 0.124 mL) in one portion. After stirring at ambient temperature for 10 minutes, the reaction mixture was concentrated under reduced pressure. The residue was taken up in dichloromethane (1 mL), and the mixture was transferred to a pyridine (2 mL) solution of 4-chlorobenzylamine (Aldrich, 23.5 mg, 0.166 mmol). The resulting solution was stirred at ambient temperature for 20 minutes and concentrated under reduced pressure. The residue was taken up in *N,N*-dimethylformamide (3 mL), filtered through a glass microfiber frit,

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and purified by preparative HPLC [YMC TriArt™ C18 Hybrid 20 µm column, 25 × 150 mm, flow rate 80 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 (41 mg, 0.094 mmol, 57% yield). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.74 (s, 1H), 8.39 (t, J = 6.1 Hz, 1H), 7.48 (t, J = 8.9 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.26 – 7.20 (m, 2H), 7.06 (dd, J = 11.4, 2.8 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.46 (s, 2H), 4.22 (d, J = 6.1 Hz, 2H), 2.20 (s, 6H); MS (ESI⁺) *m/z* 437 (M+H)⁺.

Example 19: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 118)

A mixture of the product of Example 18A (70 mg, 0.223 mmol), (5-(trifluoromethyl)pyridin-2-yl)methanamine (47.2 mg, 0.27 mmol), *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-yl)methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU, 102 mg, 0.27 mmol), and triethylamine (0.062 mL, 0.45 mmol) in tetrahydrofuran (3 mL) was stirred for 16 hours. The reaction mixture was treated with water and brine and extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure, and the residue was purified by reverse-phase HPLC performed on a Phenomenex® 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 (38.0 mg, 0.081 mmol, 36% yield). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.89 (dt, J = 1.9, 1.0 Hz, 1H), 8.73 (s, 1H), 8.52 (t, J = 6.0 Hz, 1H), 8.23 – 8.11 (m, 1H), 7.57 – 7.39 (m, 2H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (s, 2H), 4.43 (d, J = 6.0 Hz, 2H), 2.24 (s, 6H); MS (ESI⁺) *m/z* 472.1 (M+H)⁺.

Example 20: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(5-methylpyrazin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 119)

The title compound was prepared using the methodologies described in Example 12 substituting (5-methylpyrazin-2-yl)methanamine for (4,6-dimethylpyridin-3-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.43 – 8.36 (m, 2H), 8.12 (t, J = 5.9 Hz, 1H), 7.47 (dd, J = 17.3, 8.5 Hz, 2H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.79 (ddd, J = 8.9, 2.8, 1.2 Hz, 1H), 4.42 (s, 2H), 4.34 (d, J = 5.8 Hz, 2H), 4.07 (dt, J = 9.0, 2.2 Hz, 1H), 2.43 (s, 3H), 2.23 (ddd, J = 12.7, 9.3, 2.9 Hz, 1H), 2.10 (tt, J = 11.6, 3.3 Hz, 1H), 1.88 (td, J = 11.0, 10.6, 4.6 Hz, 1H), 1.78 – 1.54 (m, 7H); MS (ESI⁺) *m/z* 477.2 (M+H)⁺.

Example 21: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[4-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 120)

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The title compound was prepared using the methodologies described in Example 12 substituting (4-(trifluoromethyl)pyridin-2-yl)methanamine hydrochloride for (4,6-dimethylpyridin-3-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.74 (d, J = 5.2 Hz, 1H), 8.18 (t, J = 5.9 Hz, 1H), 7.59 (d, J = 4.5 Hz, 2H), 7.52 (s, 1H), 7.46 (t, J = 8.9 Hz, 1H), 7.01 (dd, J = 11.4, 2.8 Hz, 1H), 6.80 (dd, J = 8.9, 2.6 Hz, 1H), 4.50 – 4.37 (m, 2H), 4.43 (s, 2H), 4.12 – 4.06 (m, 1H), 2.25 (ddd, J = 12.7, 9.3, 3.0 Hz, 1H), 2.12 (td, J = 12.0, 4.1 Hz, 1H), 1.89 (td, J = 11.7, 5.0 Hz, 1H), 1.79 – 1.57 (m, 7H); MS (ESI⁺) *m/z* 530.2 (M+H)⁺.

Example 22: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[5-(methanesulfonyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 121)

The title compound was prepared using the methodologies described in Example 12 substituting (5-(methylsulfonyl)pyridin-2-yl)methanamine for (4,6-dimethylpyridin-3-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.92 (d, J = 2.3 Hz, 1H), 8.23 – 8.15 (m, 2H), 7.53 – 7.39 (m, 3H), 6.99 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 – 6.73 (m, 1H), 4.98 (s, 1H), 4.41 (d, J = 6.3 Hz, 1H), 4.41 (s, 2H), 4.12 – 4.04 (m, 1H), 3.26 (s, 3H), 2.23 (ddd, J = 12.7, 9.3, 2.9 Hz, 1H), 2.12 (tt, J = 12.2, 6.2 Hz, 1H), 1.86 (tt, J = 14.6, 7.3 Hz, 1H), 1.73 – 1.50 (m, 7H); MS (ESI⁺) *m/z* 540.2 (M+H)⁺.

Example 23: 4-[2-(4-fluorophenoxy)acetamido]-2-hydroxy-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 122)

Example 23A: 4-(2-(4-fluorophenoxy)acetamido)-2-oxobicyclo[2.2.2]octane-1-carboxylic acid

The title compound was prepared using the methodologies described in Examples 7F-7G substituting 2-(4-fluorophenoxy)acetic acid for 2-(4-chloro-3-fluorophenoxy)acetic acid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.81 (s, 1H), 7.16 – 7.04 (m, 2H), 6.97 – 6.87 (m, 2H), 4.39 (s, 2H), 2.73 (s, 2H), 2.10 – 1.83 (m, 7H); MS (ESI⁺) *m/z* 336.0 (M+H)⁺.

Example 23B: 4-[2-(4-fluorophenoxy)acetamido]-2-hydroxy-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide

The title compound was prepared using the methodologies described in Examples 7H-7I substituting Example 23A for Example 7G. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.82 (d, J = 2.2 Hz, 1H), 8.18 (t, J = 5.9 Hz, 1H), 8.09 (dd, J = 8.3, 2.4 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.14 – 7.03 (m, 2H), 6.95 – 6.84 (m, 2H), 4.43 – 4.29 (m, 4H), 4.07 (dd, J = 9.2, 2.7 Hz, 1H), 2.23 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H), 2.10 (td, J = 12.2, 3.4 Hz, 1H), 1.87 (td, J = 11.7, 5.0 Hz, 1H), 1.78 – 1.54 (m, 7H); MS (ESI⁺) *m/z* 496.2 (M+H)⁺.

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Example 24: 4-[2-(4-fluorophenoxy)acetamido]-2-hydroxy-N-[(4-(trifluoromethyl)phenyl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 123)

The title compound was prepared using the methodologies described in Example 23 substituting (4-(trifluoromethyl)phenyl)methanamine for (5-(trifluoromethyl)pyridin-2-

5 yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.05 (t, J = 6.0 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.44 – 7.37 (m, 3H), 7.14 – 7.03 (m, 2H), 6.95 – 6.84 (m, 2H), 4.37 – 4.27 (m, 4H), 4.06 (dd, J = 9.4, 2.6 Hz, 1H), 2.22 (ddd, J = 12.7, 9.2, 2.9 Hz, 1H), 2.07 (tt, J = 11.7, 3.1 Hz, 1H), 1.86 (td, J = 12.1, 11.4, 5.0 Hz, 1H), 1.77 – 1.53 (m, 7H); MS (ESI⁺) *m/z* 496.2 (M+H)⁺.

Example 25: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(3-methylphenyl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 124)

The product of Example 7H (37 mg, 0.10 mmol) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 57 mg, 0.15 mmol) were mixed in *N,N*-dimethylacetamide (1.0 mL). *m*-Tolylmethanamine (15 mg, 0.12 mmol) and *N,N*-diisopropylethylamine (43 μ L, 0.25 mmol) were added. The reaction mixture was stirred at

15 room temperature for 16 hours before being purified by reverse phase chromatography: A Phenomenex® Luna® C8(2) 5 μ m 100Å AXIA™ column (50 mm $\times$ 30 mm) with a gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in H₂O (B) was used at a flow rate of 40 mL/minute (0-0.5 minute 5% A, 0.5-6.5 minutes linear gradient 5-100% A, 6.5-8.5 minutes 100% A, 8.5-9.0 minutes linear gradient 100-5% A, 9.0-10.0 minutes 5% A) to yield the title
20 compound (33 mg, 69%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.18 (t, J = 7.9 Hz, 1H), 7.08 – 6.95 (m, 4H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 4.23 (s, 2H), 4.10 (dt, J = 8.9, 2.0 Hz, 1H), 2.27 (m, 4H), 2.08 (dd, J = 12.9, 9.6 Hz, 1H), 1.90 (td, J = 11.3, 10.6, 4.8 Hz, 1H), 1.80 – 1.54 (m, 7H); MS (ESI⁺) *m/z* 475 (M+H)⁺.

Example 26: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(4-methylphenyl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 125)

The title compound was prepared using the methodologies described in Example 25 substituting *p*-tolylmethanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.11 (s, 4H), 7.01 (dd, J = 11.3, 2.9 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 4.22 (s, 2H), 4.08 (dt, J = 8.8, 2.1 Hz, 1H), 2.26 (s, 4H), 2.07 (dd, J =
30 13.4, 10.1 Hz, 1H), 1.89 (td, J = 11.5, 5.2 Hz, 1H), 1.80 – 1.52 (m, 6H); MS (ESI⁺) *m/z* 475 (M+H)⁺.

Example 27: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(3-fluoro-5-(trifluoromethyl)phenyl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 126)

The title compound was prepared using the methodologies described in Example 25 substituting (3-fluoro-5-(trifluoromethyl)phenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.52 – 7.44 (m, 3H), 7.38 (d, J = 9.5 Hz, 1H), 7.01 (dt, J = 11.4, 3.1 Hz, 1H), 6.82 (ddt, J = 9.1, 3.4, 1.7 Hz, 1H), 4.43 (s, 2H), 4.36 (t, J = 5.1 Hz, 2H), 4.16 – 4.02 (m, 1H), 2.28 (td, J = 9.6, 4.8 Hz, 1H), 2.11 (t, J = 12.2 Hz, 1H), 1.90 (td, J = 11.8, 4.9 Hz, 1H), 1.85 – 1.52 (m, 7H); MS (ESI⁺) *m/z* 547 (M+H)⁺.

Example 28: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(3-methoxyphenyl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 127)

The title compound was prepared using the methodologies described in Example 25 substituting (3-methoxyphenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.25 – 7.15 (m, 1H), 7.01 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 – 6.73 (m, 4H), 4.44 (s, 2H), 4.25 (s, 2H), 4.10 (dt, J = 8.9, 2.2 Hz, 1H), 3.72 (s, 3H), 2.27 (ddd, J = 12.5, 9.2, 2.9 Hz, 1H), 2.15 – 2.03 (m, 1H), 1.90 (td, J = 11.5, 11.0, 5.1 Hz, 1H), 1.82 – 1.56 (m, 7H); MS (ESI⁺) *m/z* 491 (M+H)⁺.

Example 29: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(4-methoxyphenyl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 128)

The title compound was prepared using the methodologies described in Example 25 substituting (4-methoxyphenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.47 (t, J = 8.9 Hz, 1H), 7.20 – 7.10 (m, 2H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.89 – 6.76 (m, 3H), 4.43 (s, 2H), 4.20 (s, 2H), 4.08 (dt, J = 9.0, 2.1 Hz, 1H), 3.72 (s, 3H), 2.26 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H), 2.12 – 1.99 (m, 1H), 1.89 (td, J = 11.5, 11.1, 5.2 Hz, 1H), 1.80 – 1.53 (m, 7H); MS (ESI⁺) *m/z* 491 (M+H)⁺.

Example 30: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(3-fluorophenyl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 129)

The title compound was prepared using the methodologies described in Example 25 substituting (3-fluorophenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.38 – 7.24 (m, 1H), 7.13 – 6.91 (m, 4H), 6.83 (ddd, J = 9.2, 2.8, 1.2 Hz, 1H), 4.44 (s, 2H), 4.29 (d, J = 4.7 Hz, 2H), 4.10 (dt, J = 9.1, 2.3 Hz, 1H), 2.28 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H), 2.10 (t, J = 11.6 Hz, 1H), 1.90 (td, J = 11.5, 5.1 Hz, 1H), 1.81 – 1.52 (m, 7H); MS (ESI⁺) *m/z* 479 (M+H)⁺.

Example 31: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-fluorophenyl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 130)

The title compound was prepared using the methodologies described in Example 25 substituting (4-fluorophenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.31 – 7.20 (m, 2H), 7.15 – 7.07 (m, 2H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 9.1, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 4.25 (s, 2H), 4.09 (dt, J = 9.0, 2.1 Hz, 1H), 2.27 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H), 2.15 – 2.02 (m, 1H), 1.90 (td, J = 11.6, 5.2 Hz, 1H), 1.68 (dddd, J = 33.6, 17.3, 12.2, 6.7 Hz, 7H); MS (ESI⁺) *m/z* 479 (M+H)⁺.

Example 32: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(3-chlorophenyl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 131)

The title compound was prepared using the methodologies described in Example 25 substituting (3-chlorophenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.33 (dd, J = 8.7, 7.4 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.19 (dt, J = 7.5, 1.4 Hz, 1H), 7.01 (dd, J = 11.4, 2.8 Hz, 1H), 6.82 (ddd, J = 8.8, 2.9, 1.1 Hz, 1H), 4.44 (s, 2H), 4.27 (d, J = 4.9 Hz, 2H), 4.10 (dt, J = 9.0, 2.4 Hz, 1H), 2.28 (ddd, J = 12.6, 9.3, 2.8 Hz, 1H), 2.10 (t, J = 11.6 Hz, 1H), 1.90 (td, J = 11.6, 5.1 Hz, 1H), 1.71 (qt, J = 15.5, 6.8 Hz, 7H); MS (ESI⁺) *m/z* 495 (M+H)⁺.

Example 33: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-chlorophenyl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 132)

The title compound was prepared using the methodologies described in Example 25 substituting (4-chlorophenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.28 – 7.18 (m, 2H), 7.01 (dd, J = 11.4, 2.8 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 4.30 – 4.20 (m, 2H), 4.09 (dt, J = 9.0, 2.1 Hz, 1H), 2.27 (ddd, J = 12.7, 9.3, 2.9 Hz, 1H), 2.09 (t, J = 11.8 Hz, 1H), 1.90 (td, J = 11.5, 5.1 Hz, 1H), 1.68 (dddd, J = 29.0, 18.0, 8.8, 4.6 Hz, 7H); MS (ESI⁺) *m/z* 495 (M+H)⁺.

Example 34: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[4-(trifluoromethoxy)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 133)

The title compound was prepared using the methodologies described in Example 25 substituting (4-(trifluoromethoxy)phenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.27 (dd, J = 8.6, 1.1 Hz, 2H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 4.34 – 4.23 (m, 2H), 4.16 – 4.01 (m, 1H), 2.27 (ddd, J = 12.5, 9.2, 2.8 Hz, 1H), 2.10 (t, J = 11.7 Hz, 1H), 1.90 (td, J = 11.5, 5.1 Hz, 1H), 1.79 – 1.56 (m, 7H); MS (ESI⁺) *m/z* 545 (M+H)⁺.

Example 35: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[[4-(dimethylamino)phenyl]methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 134)

The title compound was prepared using the methodologies described in Example 25 substituting (4-(dimethylamino)phenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.36 – 7.23 (m, 4H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.26 (s, 2H), 4.09 (dt, J = 9.0, 2.2 Hz, 1H), 3.07 (s, 6H), 2.27 (ddd, J = 12.7, 9.1, 2.8 Hz, 1H), 2.08 (t, J = 11.6 Hz, 1H), 1.90 (td, J = 11.5, 5.1 Hz, 1H), 1.84 – 1.50 (m, 7H); MS (ESI⁺) *m/z* 504 (M+H)⁺.

Example 36: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[3-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 135)

The title compound was prepared using the methodologies described in Example 25 substituting (3-(trifluoromethyl)phenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.58 – 7.52 (m, 4H), 7.48 (t, J = 8.9 Hz, 1H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.38 – 4.27 (m, 2H), 4.14 – 4.03 (m, 1H), 2.28 (ddd, J = 12.5, 9.2, 2.8 Hz, 1H), 2.11 (t, J = 11.6 Hz, 1H), 1.90 (td, J = 11.5, 5.0 Hz, 1H), 1.82 – 1.56 (m, 7H); MS (ESI⁺) *m/z* 529 (M+H)⁺.

Example 37: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[3-(trifluoromethoxy)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 136)

The title compound was prepared using the methodologies described in Example 25 substituting (3-(trifluoromethoxy)phenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.51 – 7.38 (m, 2H), 7.26 (dt, J = 7.7, 1.2 Hz, 1H), 7.20 (d, J = 6.7 Hz, 2H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.34 – 4.24 (m, 2H), 4.10 (d, J = 8.7 Hz, 1H), 2.28 (ddd, J = 12.5, 9.2, 2.8 Hz, 1H), 2.10 (t, J = 11.5 Hz, 1H), 1.90 (td, J = 11.5, 5.1 Hz, 1H), 1.82 – 1.50 (m, 7H); MS (ESI⁺) *m/z* 545 (M+H)⁺.

Example 38: N-[(4-*tert*-butylphenyl)methyl]-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 137)

The title compound was prepared using the methodologies described in Example 25 substituting (4-*tert*-butylphenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.37 – 7.26 (m, 2H), 7.19 – 7.08 (m, 2H), 7.01 (dd, J = 11.4, 2.8 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 4.23 (s, 2H), 4.12 – 4.00 (m, 1H), 2.27 (ddd, J = 12.4, 9.1, 2.8 Hz, 1H), 2.08 (t, J = 11.7 Hz, 1H), 1.90 (td, J = 11.4, 5.0 Hz, 1H), 1.81 – 1.52 (m, 7H), 1.26 (s, 9H); MS (ESI⁺) *m/z* 517 (M+H)⁺.

Example 39: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-{2-[4-(trifluoromethyl)phenyl]ethyl}bicyclo[2.2.2]octane-1-carboxamide (Compound 138)

The title compound was prepared using the methodologies described in Example 25 substituting (4-(trifluoromethyl)phenyl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.64 (d, J = 8.0 Hz, 2H), 7.51 – 7.34 (m, 3H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 4.08 – 3.92 (m, 1H), 3.30 (t, J = 7.1 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H), 2.23 (ddd, J = 12.7, 9.2, 2.9 Hz, 1H), 1.99 (dd, J = 13.5, 10.0 Hz, 1H), 1.87 (td, J = 11.8, 11.4, 5.2 Hz, 1H), 1.80 – 1.38 (m, 7H); MS (ESI⁺) *m/z* 543 (M+H)⁺.

Example 40: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(pyridin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 139)

The title compound was prepared using the methodologies described in Example 25 substituting pyridine-2-ylmethanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.74 – 8.64 (m, 1H), 8.32 (td, J = 7.9, 1.6 Hz, 1H), 7.79 – 7.67 (m, 2H), 7.48 (t, J = 8.9 Hz, 1H), 7.01 (dd, J = 11.3, 2.8 Hz, 1H), 6.82 (ddt, J = 9.1, 3.2, 1.6 Hz, 1H), 4.53 (s, 2H), 4.44 (s, 2H), 4.10 (dt, J = 9.1, 2.4 Hz, 1H), 2.29 (ddd, J = 12.6, 9.1, 2.8 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.93 (qd, J = 11.3, 10.5, 5.0 Hz, 1H), 1.81 – 1.59 (m, 7H); MS (ESI⁺) *m/z* 462 (M+H)⁺.

Example 41: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[1-(pyridin-3-yl)ethyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 140)

The title compound was prepared using the methodologies described in Example 25 substituting 1-(pyridin-3-yl)ethanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.84 – 8.64 (m, 2H), 8.45 (ddt, J = 8.1, 4.1, 1.7 Hz, 1H), 8.01 – 7.90 (m, 1H), 7.48 (t, J = 8.9 Hz, 1H), 7.01 (dd, J = 11.4, 2.8 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.05 (p, J = 7.1 Hz, 1H), 4.44 (s, 2H), 4.20 – 4.03 (m, 1H), 2.33 – 2.20 (m, 1H), 2.18 – 1.98 (m, 1H), 1.98 – 1.81 (m, 1H), 1.80 – 1.56 (m, 7H), 1.45 (d, J = 7.2 Hz, 3H); MS (ESI⁺) *m/z* 476 (M+H)⁺.

Example 42: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5-cyanopyridin-2-yl)methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 141)

The title compound was prepared using the methodologies described in Example 25 substituting (5-cyanopyridin-2-yl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.90 (dd, J = 2.1, 0.8 Hz, 1H), 8.21 (dd, J = 8.2, 2.2 Hz, 1H), 7.52 – 7.39 (m, 2H), 7.02 (dd, J = 11.4, 2.8 Hz, 1H), 6.83 (ddd, J = 9.1, 2.9, 1.2 Hz, 1H), 4.44 (d, J = 4.1 Hz, 4H), 4.11 (dt, J = 8.9, 2.2 Hz, 1H), 2.29 (ddd, J = 12.6, 9.3, 2.9 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.92 (td, J = 11.5, 4.9 Hz, 1H), 1.82 – 1.54 (m, 7H); MS (ESI⁺) *m/z* 487 (M+H)⁺.

Example 43: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(5-methylpyridin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 142)

The title compound was prepared using the methodologies described in Example 25 substituting (5-methylpyridin-2-yl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.56 (t, J = 5.9 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.54 – 7.35 (m, 1H), 7.01 (dd, J = 11.4, 2.8 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.51 (d, J = 5.9 Hz, 2H), 4.45 (d, J = 5.5 Hz, 3H), 4.17 – 4.03 (m, 1H), 2.40 – 2.24 (m, 1H), 2.20 – 2.06 (m, 1H), 2.00 – 1.84 (m, 2H), 1.81 – 1.57 (m, 8H); MS (ESI⁺) *m/z* 476 (M+H)⁺.

Example 44: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(4-methylpyridin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 143)

The title compound was prepared using the methodologies described in Example 25 substituting (4-methylpyridin-2-yl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.65 – 8.51 (m, 1H), 8.24 (dd, J = 8.4, 2.0 Hz, 1H), 7.68 (d, J = 8.2 Hz, 1H), 7.48 (t, J = 8.9 Hz, 1H), 7.01 (dd, J = 11.4, 2.9 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.50 (s, 2H), 4.44 (s, 2H), 4.14 – 4.03 (m, 1H), 2.43 (s, 3H), 2.29 (ddd, J = 12.7, 9.3, 2.9 Hz, 1H), 2.12 (dt, J = 11.9, 6.1 Hz, 1H), 1.92 (td, J = 11.6, 4.7 Hz, 1H), 1.84 – 1.55 (m, 6H); MS (ESI⁺) *m/z* 476 (M+H)⁺.

Example 45: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[(pyrazin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 144)

The title compound was prepared using the methodologies described in Example 25 substituting (pyrazin-2-yl)methanamine for *m*-tolylmethanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.57 – 8.40 (m, 3H), 7.48 (t, J = 8.9 Hz, 1H), 7.02 (dd, J = 11.4, 2.9 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.52 – 4.36 (m, 4H), 4.11 (dt, J = 9.0, 2.4 Hz, 1H), 2.28 (ddd, J = 12.5, 9.3, 2.8 Hz, 1H), 2.17 – 2.06 (m, 1H), 1.91 (td, J = 11.5, 4.9 Hz, 1H), 1.85 – 1.55 (m, 7H); MS (ESI⁺) *m/z* 463 (M+H)⁺.

Example 46: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-methyl-N-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 145)

The title compound was prepared using the methodologies described in Example 12 substituting *N*-methyl-1-(4-(trifluoromethyl)phenyl)methanamine for (4,6-dimethylpyridin-3-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.66 (d, J = 8.1 Hz, 2H), 7.52 (s, 1H), 7.46 (t, J = 8.9 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.00 (dd, J = 11.4, 2.8 Hz, 1H), 6.83 – 6.76 (m, 1H), 4.64 (q, J = 16.0 Hz, 2H), 4.42 (s, 2H), 4.36 (ddd, J = 9.4, 3.9, 1.6 Hz, 1H), 2.99 (s, 3H),

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2.26 (ddd, J = 12.5, 9.3, 2.9 Hz, 1H), 2.15 (tdt, J = 11.2, 6.2, 2.4 Hz, 1H), 1.94 – 1.69 (m, 7H), 1.65 (ddd, J = 12.8, 3.9, 2.1 Hz, 1H); MS (ESI⁺) *m/z* 543.2 (M+H)⁺.

Example 47: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[[5-(difluoromethoxy)pyridin-2-yl]methyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 146)

5 The title compound was prepared using the methodologies described in Example 12 substituting (5-(difluoromethoxy)pyridin-2-yl)methanamine for (4,6-dimethylpyridin-3-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.34 (d, J = 2.8 Hz, 1H), 8.10 (t, J = 5.9 Hz, 1H), 7.58 (dd, J = 8.6, 2.9 Hz, 1H), 7.53 – 7.40 (m, 2H), 7.31 (d, J = 8.6 Hz, 1H), 7.08 – 6.95 (m, 1H), 6.78 (dd, J = 9.0, 2.8 Hz, 1H), 4.41 (s, 2H), 4.32 (d, J = 5.8 Hz, 2H), 4.06 (dd, J = 9.5, 2.8 Hz, 1H), 2.22 (ddd, J = 12.7, 9.2, 2.9 Hz, 1H), 2.09 (tt, J = 11.5, 3.2 Hz, 1H), 1.86 (td, J = 11.6, 5.1 Hz, 1H), 1.71 (q, J = 3.9 Hz, 2H), 1.72 – 1.53 (m, 5H); MS (ESI⁺) *m/z* 528.2 (M+H)⁺.

Example 48: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[[5-(difluoromethoxy)pyridin-2-yl]methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 147)

N,N-Dimethylformamide (2 mL), triethylamine (0.079 mL, 0.57 mmol) and 1-
15 [bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (79 mg, 0.208 mmol, HATU) were added to a mixture of the product of Example 18A (59.4 mg, 0.189 mmol) and (5-(difluoromethoxy)pyridin-2-yl)methanamine (Enamine, 33 mg, 0.189 mmol) in sequential order. The reaction mixture was then stirred at ambient temperature for 30 minutes. The resulting solution was filtered through a glass microfiber frit and purified by
20 preparative HPLC [YMC TriArt™ C18 Hybrid 5 μ m column, 50 $\times$ 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 compound (56 mg, 0.119 mmol, 63% yield). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.73 (s, 1H), 8.44 (t, J = 6.1 Hz, 1H), 8.40 (d, J = 2.8 Hz, 1H), 7.64 (dd, J = 8.6, 2.9 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.29 (dd, J = 8.6, 0.7
25 Hz, 1H), 7.27 (t, J = 73.5 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 6.86 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.47 (s, 2H), 4.33 (d, J = 6.1 Hz, 2H), 2.22 (s, 6H); MS (ESI⁺) *m/z* 470 (M+H)⁺.

Example 49: 3-[2-(3,4-dichlorophenoxy)acetamido]-N-[[5-(difluoromethoxy)pyridin-2-yl]methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 148)

Example 49A: 3-(2-(3,4-dichlorophenoxy)acetamido)bicyclo[1.1.1]pentane-1-carboxylic acid

30 The reaction and purification conditions described in Example 1A and Example 1B, substituting 2-(3,4-dichlorophenoxy)acetic acid (Aldrich) for 2-(4-chlorophenoxy)acetic acid gave the title compound. MS (APCI⁺) *m/z* 330 (M+H)⁺.

Example 49B: 3-[2-(3,4-dichlorophenoxy)acetamido]-N-[[5-(difluoromethoxy)pyridin-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide

The reaction and purification conditions described in Example 48 substituting the product of Example 49A for the product of Example 18A gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.73 (s, 1H), 8.45 (t, J = 6.1 Hz, 1H), 8.40 (d, J = 2.7 Hz, 1H), 7.64 (dd, J = 8.6, 2.9 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.27 (t, J = 73.5 Hz, 1H), 7.27 (d, J = 2.9 Hz, 1H), 6.99 (dd, J = 8.9, 2.9 Hz, 1H), 4.49 (s, 2H), 4.33 (d, J = 6.1 Hz, 2H), 2.22 (s, 6H); MS (ESI⁺) *m/z* 486 (M+H)⁺.

Example 50: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[[6-(trifluoromethyl)pyridin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 149)

The reaction and purification conditions described in Example 48 substituting 3-(aminomethyl)-6-(trifluoromethyl)pyridine (Matrix) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.73 (s, 1H), 8.64 (d, J = 1.9 Hz, 1H), 8.49 (t, J = 6.0 Hz, 1H), 7.93 – 7.84 (m, 2H), 7.49 (t, J = 8.8 Hz, 1H), 7.07 (dd, J = 11.4, 2.8 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.47 (s, 2H), 4.37 (d, J = 6.0 Hz, 2H), 2.22 (s, 6H); MS (ESI⁺) *m/z* 472 [M+H]⁺.

Example 51: 3-[2-(3,4-dichlorophenoxy)acetamido]-N-[[6-(trifluoromethyl)pyridin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 150)

The reaction and purification conditions described in Example 48 substituting the product of Example 49A for the product of Example 18A, and 3-(aminomethyl)-6-(trifluoromethyl)pyridine (Matrix) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.73 (s, 1H), 8.65 – 8.63 (m, 1H), 8.49 (t, J = 6.0 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.55 (d, J = 8.9 Hz, 1H), 7.26 (d, J = 2.9 Hz, 1H), 6.99 (dd, J = 9.0, 2.9 Hz, 1H), 4.48 (s, 2H), 4.37 (d, J = 6.0 Hz, 2H), 2.22 (s, 6H); MS (ESI⁺) *m/z* 488 (M+H)⁺.

Example 52: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 151)

The reaction and purification conditions described in Example 19 substituting (1,3-dimethyl-1H-pyrazol-5-yl)methanamine for (5-(trifluoromethyl)pyridin-2-yl)methanamine gave the titled compound (56 mg, 0.105 mmol, 82% yield). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.71 (s, 1H), 8.25 (t, J = 5 Hz, 1H), 7.49 (t, J = 8 Hz, 1H), 7.05 (dd, J = 9, 3 Hz, 1H), 6.83 (br d, J = 8 Hz, 1H), 5.86 (s, 1H), 4.46 (s, 2H), 4.21 (d, J = 5 Hz, 2H), 3.65 (s, 3H), 2.20 (s, 6H), 2.06 (s, 3H); MS (ESI⁺) *m/z* 421 (M+H)⁺.

Example 53: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(1,3-dimethyl-1H-pyrazol-4-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 152)

The reaction and purification conditions described in Example 19 substituting (1,3-dimethyl-1H-pyrazol-4-yl)methanamine for (5-(trifluoromethyl)pyridin-2-yl)methanamine gave the titled compound (47 mg, 0.088 mmol, 69% yield). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.68 (s, 1H), 7.98 (t, J = 5 Hz, 1H), 7.48 (t, J = 8 Hz, 1H), 7.40 (s, 1H), 7.05 (dd, J = 9, 3 Hz, 1H), 6.83 (br d, J = 8 Hz, 1H), 4.44 (s, 2H), 4.00 (d, J = 5 Hz, 2H), 3.69 (s, 3H), 2.15 (s, 6H), 2.05 (s, 3H); MS (ESI⁺) *m/z* 421 (M+H)⁺.

Example 54: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(pyridin-2-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 153)

The reaction and purification conditions described in Example 19 substituting 2-(pyridin-2-yl)ethanamine for (5-(trifluoromethyl)pyridin-2-yl)methanamine gave the titled compound (40 mg, 0.075 mmol, 59% yield). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.70 (s, 1H), 8.68 (s, 1H), 8.18 (br t, J = 8 Hz, 1H), 7.90 (br t, J = 8 Hz, 1H), 7.63 (m, 2H), 7.50 (t, J = 8 Hz, 1H), 7.06 (dd, J = 9, 3 Hz, 1H), 6.84 (br d, J = 8 Hz, 1H), 4.46 (s, 2H), 3.44 (m, 2H), 3.03 (t, J = 7 Hz, 2H), 2.13 (s, 6H); MS (ESI⁺) *m/z* 418 (M+H)⁺.

Example 55: 3-[2-(3,4-dichlorophenoxy)acetamido]-N-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 154)

The reaction and purification conditions described in Example 49B substituting (1,3-dimethyl-1H-pyrazol-5-yl)methanamine for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the titled compound (48 mg, 0.087 mmol, 68%). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.73 (s, 1H), 8.28 (t, J = 5 Hz, 1H), 7.54 (d, J = 9 Hz, 1H), 7.26 (d, J = 3 Hz, 1H), 6.98 (dd, J = 9, 3 Hz, 1H), 5.87 (s, 1H), 4.48 (s, 2H), 4.22 (d, J = 5 Hz, 2H), 3.65 (s, 3H), 2.20 (s, 6H), 2.08 (s, 3H); MS (ESI⁺) *m/z* 437 (M+H)⁺.

The compounds in the following table were prepared using the methodologies described above.

Example	Name (Compound Number)	NMR	MS
Example 56	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- N-[(6-methylpyridin-3-yl)methyl]bicyclo[1.1.1]pen		MS (APCI ⁺) <i>m/z</i> 418

	tane-1-carboxamide (Compound 155)		(M+H) ⁺
Example 57	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- N-{[4-(trifluoromethyl)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 156)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 7.67 (d, J = 8.1 Hz, 2H), 7.48 (t, J = 8.9 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.05 (dd, J = 11.3, 2.8 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.46 (s, 2H), 4.32 (s, 2H), 2.23 (s, 6H)	MS (APCI ⁺) <i>m/z</i> 471 (M+H) ⁺
Example 58	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- N-[(6-methoxypyridin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 157)		MS (APCI ⁺) <i>m/z</i> 434 (M+H) ⁺
Example 59	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- N-[2-(3,4-dimethylphenoxy)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 158)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 7.47 (t, J = 8.9 Hz, 1H), 7.04 (dd, J = 11.3, 2.8 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.71 (d, J = 2.7 Hz, 1H), 6.63 (dd, J = 8.2, 2.7 Hz, 1H), 4.45 (s, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.37 (t, J = 6.0 Hz, 2H), 2.18 (s, 6H), 2.16 (s, 3H), 2.12 (s, 3H)	MS (APCI ⁺) <i>m/z</i> 461 (M+H) ⁺
Example 60	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- N-[(3-methyl-1,2,4-		MS (APCI ⁺) <i>m/z</i> 409

	oxadiazol-5-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 159)		(M+H) ⁺
Example 61	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2,5-dimethylfuran-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 160)		MS (APCI ⁺) <i>m/z</i> 421 (M+H) ⁺
Example 62	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[3-(trifluoromethoxy)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 161)		MS (APCI ⁺) <i>m/z</i> 487 (M+H) ⁺
Example 63	<i>N</i> -benzyl-3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carboxamide (Compound 162)		MS (APCI ⁺) <i>m/z</i> 403 (M+H) ⁺
Example 64	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2,6-dichlorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 163)		MS (APCI ⁺) <i>m/z</i> 470/473 (M+H) ⁺

Example 65	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(pyrazin-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 164)	¹ H NMR (501 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 8.58 (dd, <i>J</i> = 2.6, 1.5 Hz, 1H), 8.54 – 8.51 (m, 2H), 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.06 (dd, <i>J</i> = 11.3, 2.9 Hz, 1H), 6.90 – 6.83 (m, 1H), 4.47 (s, 2H), 4.40 (s, 2H), 2.25 (s, 6H)	
Example 66	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(4-methylpyridin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 165)		MS (APCI ⁺) <i>m/z</i> 418 (<i>M</i> +H) ⁺
Example 67	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3-methylphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 166)		MS (APCI ⁺) <i>m/z</i> 417 (<i>M</i> +H) ⁺
Example 68	<i>N</i> -[(4- <i>tert</i> -butylphenyl)methyl]-3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carboxamide (Compound 167)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.18 – 7.13 (m, 2H), 7.06 (dd, <i>J</i> = 11.3, 2.9 Hz, 1H), 6.86 (ddd, <i>J</i> = 9.1, 2.9, 1.2 Hz, 1H), 4.46 (s, 2H), 4.21 (s, 2H), 2.22 (s, 6H), 1.26 (s, 9H)	
Example 69	3-[2-(4-chloro-3-	¹ H NMR (400 MHz, DMSO-	MS

	fluorophenoxy)acetamido]- <i>N</i> -[(5-methylpyridin-2- yl)methyl]bicyclo[1.1.1]pen- tane-1-carboxamide (Compound 168)	d_6 -D ₂ O) δ ppm 8.55 (n, J = 2.0, 0.8 Hz, 1H), 8.18 (dd, J = 8.3, 2.0 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.48 (t, J = 8.9 Hz, 1H), 7.05 (dd, J = 11.3, 2.8 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.47 (s, 2H), 4.46 (s, 2H), 2.41 (s, 3H), 2.24 (s, 6H)	(APCI ⁺) <i>m/z</i> 418 (M+H) ⁺
Example 70	3-[2-(4-chloro-3- fluorophenoxy)acetamido]- <i>N</i> -{[4- (difluoromethoxy)phenyl]m- ethyl}bicyclo[1.1.1]pentane -1-carboxamide (Compound 169)	¹ H NMR (400 MHz, DMSO- d_6 -D ₂ O) δ ppm 7.47 (t, J = 8.9 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.16 – 7.08 (m, 2H), 7.12 (t, J = 74.2 Hz, 1H), 7.05 (dd, J = 11.3, 2.9 Hz, 1H), 6.85 (ddd, J = 8.9, 2.9, 1.1 Hz, 1H), 4.45 (s, 2H), 4.22 (s, 2H), 2.21 (s, 6H)	MS (APCI ⁺) <i>m/z</i> 469 (M+H) ⁺
Example 71	3-[2-(4-chloro-3- fluorophenoxy)acetamido]- <i>N</i> -[(1,2-oxazol-4- yl)methyl]bicyclo[1.1.1]pen- tane-1-carboxamide (Compound 170)		MS (APCI ⁺) <i>m/z</i> 394 (M+H) ⁺
Example 72	3-[2-(4-chloro-3- fluorophenoxy)acetamido]- <i>N</i> -[1-(4- fluorophenyl)propan-2- yl]bicyclo[1.1.1]pentane-1- carboxamide (Compound 171)	¹ H NMR (400 MHz, DMSO- d_6 -D ₂ O) δ ppm 7.48 (t, J = 8.9 Hz, 1H), 7.22 – 7.14 (m, 2H), 7.09 – 7.01 (m, 3H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 3.92 (h, J = 6.7 Hz, 1H), 2.71 – 2.60 (m, 2H), 2.11 (s, 6H), 1.03 (d, J = 6.7 Hz,	MS (APCI ⁺) <i>m/z</i> 449 (M+H) ⁺

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		3H)	
Example 73	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -(1-phenylethyl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 172)		MS (APCI ⁺) <i>m/z</i> 417 (M+H) ⁺
Example 74	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3-fluoro-4-methoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 173)		MS (APCI ⁺) <i>m/z</i> 451 (M+H) ⁺
Example 75	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2-fluoro-5-methylphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 174)		MS (APCI ⁺) <i>m/z</i> 435 (M+H) ⁺
Example 76	<i>N</i> -benzyl-3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -methylbicyclo[1.1.1]pentane-1-carboxamide (Compound 175)		MS (APCI ⁺) <i>m/z</i> 417 (M+H) ⁺
Example 77	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(4-methyl-1,3-thiazol-2-		MS (APCI ⁺) <i>m/z</i> 424

	yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 176)		(M+H) ⁺
Example 78	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(5-methyl-1,3-oxazol-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 177)		MS (APCI ⁺) <i>m/z</i> 408 (M+H) ⁺
Example 79	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(5-methyl-1,3-thiazol-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 178)		MS (APCI ⁺) <i>m/z</i> 424 (M+H) ⁺
Example 80	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1-methyl-1 <i>H</i> -pyrazol-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 179)		MS (APCI ⁺) <i>m/z</i> 407 (M+H) ⁺
Example 81	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 180)		MS (APCI ⁺) <i>m/z</i> 489 (M+H) ⁺
Example 82	<i>N</i> -[(4-chloro-2,6-difluorophenyl)methyl]-3-		MS (APCI ⁺)

	[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carboxamide (Compound 181)		m/z 473 (M+H) ⁺
Example 83	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2-ethoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 182)		MS (APCI ⁺) m/z 447 (M+H) ⁺
Example 84	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1 <i>S</i>)-1-(4-chlorophenyl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 183)		MS (APCI ⁺) m/z 451 (M+H) ⁺
Example 85	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1-methyl-1 <i>H</i> -pyrazol-5-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 184)		MS (APCI ⁺) m/z 407 (M+H) ⁺
Example 86	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3,4-difluorophenyl)methyl]bicyclo[1.1.1]pentane-1-		MS (APCI ⁺) m/z 439 (M+H) ⁺

	carboxamide (Compound 185)		
Example 87	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1-methyl-1 <i>H</i> -imidazol-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 186)		MS (APCI ⁺) <i>m/z</i> 407 (M+H) ⁺
Example 88	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1 <i>S</i>)-1-(3-methylphenyl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 187)		MS (APCI ⁺) <i>m/z</i> 431 (M+H) ⁺
Example 89	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(1 <i>H</i> -imidazol-4-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 188)		MS (APCI ⁺) <i>m/z</i> 407 (M+H) ⁺
Example 90	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1 <i>R</i>)-1-(3-methylphenyl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 189)		MS (APCI ⁺) <i>m/z</i> 431 (M+H) ⁺

Example 91	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2,5-dimethylphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 190)		MS (APCI ⁺) <i>m/z</i> 431 (M+H) ⁺
Example 92	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(imidazo[1,2- <i>a</i>]pyridin-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 191)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 8.81 – 8.73 (m, 1H), 8.08 (s, 1H), 7.88 – 7.83 (m, 2H), 7.48 (t, J = 8.9 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.05 (dd, J = 11.3, 2.9 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (br s, 2H), 4.46 (s, 2H), 2.25 (s, 6H)	MS (APCI ⁺) <i>m/z</i> 443 (M+H) ⁺
Example 93	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3-methylthiophen-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 192)		MS (APCI ⁺) <i>m/z</i> 423 (M+H) ⁺
Example 94	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(4-chloro-3-fluorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 193)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 7.51 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.9 Hz, 1H), 7.21 (dd, J = 10.4, 2.0 Hz, 1H), 7.12 – 7.07 (m, 1H), 7.05 (dd, J = 11.3, 2.8 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.45 (s, 2H), 4.23 (s, 2H), 2.22	MS (APCI ⁺) <i>m/z</i> 455 (M+H) ⁺

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		(s, 6H)	
Example 95	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(1 <i>H</i> -indol-3-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 194)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 7.98 (t, <i>J</i> = 5.8 Hz, 1H), 7.54 (dt, <i>J</i> = 7.9, 1.0 Hz, 1H), 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.35 (dt, <i>J</i> = 8.2, 0.9 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.11 – 7.04 (m, 2H), 6.99 (ddd, <i>J</i> = 8.0, 7.0, 1.1 Hz, 1H), 6.87 (ddd, <i>J</i> = 9.0, 2.9, 1.2 Hz, 1H), 4.47 (s, 2H), 3.36 – 3.26 (m, 2H), 2.83 (t, <i>J</i> = 7.4 Hz, 2H), 2.18 (s, 6H)	MS (APCI ⁺) <i>m/z</i> 456 (<i>M</i> +H) ⁺
Example 96	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(4-methoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 195)		MS (APCI ⁺) <i>m/z</i> 433 (<i>M</i> +H) ⁺
Example 97	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1-methyl-1 <i>H</i> -imidazol-4-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 196)		MS (APCI ⁺) <i>m/z</i> 407 (<i>M</i> +H) ⁺
Example 98	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2-		MS (APCI ⁺) <i>m/z</i> 417

	methylphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 197)		(M+H) ⁺
Example 99	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1 <i>R</i>)-1-(4-chlorophenyl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 198)		MS (APCI ⁺) <i>m/z</i> 451 (M+H) ⁺
Example 100	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(4-sulfamoylphenyl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 199)		MS (APCI ⁺) <i>m/z</i> 496 (M+H) ⁺
Example 101	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2-methoxypyrimidin-5-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 200)		MS (APCI ⁺) <i>m/z</i> 435 (M+H) ⁺
Example 102	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(5-phenyl-1,2,4-oxadiazol-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 8.12 – 8.06 (m, 2H), 7.74 – 7.68 (m, 1H), 7.67 – 7.61 (m, 2H), 7.48 (t, <i>J</i> = 8.9 Hz, 1H), 7.05 (dd, <i>J</i> = 11.3, 2.9 Hz, 1H), 6.85 (ddd, <i>J</i> = 9.0,	MS (APCI ⁺) <i>m/z</i> 471 (M+H) ⁺

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	(Compound 201)	2.8, 1.2 Hz, 1H), 4.50 – 4.41 (m, 4H), 2.23 (s, 6H)	
Example 103	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3,4-dimethoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 202)		MS (APCI ⁺) <i>m/z</i> 463 (M+H) ⁺
Example 104	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[2-(2,2-difluoroethoxy)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 203)		MS (APCI ⁺) <i>m/z</i> 483 (M+H) ⁺
Example 105	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[3-(4-fluorophenyl)propyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 204)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ , D ₂ O) δ ppm 7.47 (t, <i>J</i> = 8.8 Hz, 1H), 7.25 – 7.17 (m, 2H), 7.11 – 7.02 (m, 3H), 6.85 (ddd, <i>J</i> = 9.0, 2.9, 1.2 Hz, 1H), 4.45 (s, 2H), 3.03 (t, <i>J</i> = 7.1 Hz, 2H), 2.56 – 2.50 (m, 2H), 2.17 (s, 6H), 1.75 – 1.60 (m, 2H)	MS (APCI ⁺) <i>m/z</i> 449 (M+H) ⁺
Example 106	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(pyridazin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 205)		MS (APCI ⁺) <i>m/z</i> 405 (M+H) ⁺

Example 107	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3,5-difluoro-4-methoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 206)		MS (APCI ⁺) <i>m/z</i> 469 (M+H) ⁺
Example 108	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -({4-[(propan-2-yl)oxy]phenyl)methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 207)		MS (APCI ⁺) <i>m/z</i> 461 (M+H) ⁺
Example 109	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1,3-thiazol-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 208)		MS (APCI ⁺) <i>m/z</i> 410 (M+H) ⁺
Example 110	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3-fluoro-5-methoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 209)		MS (APCI ⁺) <i>m/z</i> 451 (M+H) ⁺
Example 111	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2-		MS (APCI ⁺) <i>m/z</i> 421

	fluorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 210)		(M+H) ⁺
Example 112	3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(2,6-dimethylpyridin-4-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 211)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 7.52 (s, 2H), 7.48 (t, J = 8.9 Hz, 1H), 7.04 (dd, J = 11.3, 2.8 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.45 (s, 2H), 3.37 (t, J = 6.8 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H), 2.62 (s, 6H), 2.15 (s, 6H)	MS (APCI ⁺) <i>m/z</i> 446 (M+H) ⁺
Example 113	3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-{[3-(2-methylpropyl)-1,2-oxazol-5-yl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 212)		MS (APCI ⁺) <i>m/z</i> 450 (M+H) ⁺
Example 114	3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-{2-[5-(trifluoromethyl)pyridin-2-yl]ethyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 213)		MS (APCI ⁺) <i>m/z</i> 486 (M+H) ⁺
Example 115	3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-{[2-(3-methylphenyl)-1,3-thiazol-4-		MS (APCI ⁺) <i>m/z</i> 500 (M+H) ⁺

	yl)methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 214)		
Example 116	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[5-(trifluoromethyl)furan-2-yl)methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 215)		MS (APCI ⁺) <i>m/z</i> 461 (M+H) ⁺
Example 117	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3-methoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 216)		MS (APCI ⁺) <i>m/z</i> 433 (M+H) ⁺
Example 118	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2-ethylpyrimidin-4-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 217)		MS (APCI ⁺) <i>m/z</i> 433 (M+H) ⁺
Example 119	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(3-methylpyridin-2-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 218)		MS (APCI ⁺) <i>m/z</i> 432 (M+H) ⁺

Example 120	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3-chlorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 219)		MS (APCI ⁺) <i>m/z</i> 437 (M+H) ⁺
Example 121	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[3-(3,5-dimethyl-1,2-oxazol-4-yl)propyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 220)		MS (APCI ⁺) <i>m/z</i> 450 (M+H) ⁺
Example 122	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(4-methylpyridin-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 221)		MS (APCI ⁺) <i>m/z</i> 418 (M+H) ⁺
Example 123	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1,2-oxazol-5-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 222)		MS (APCI ⁺) <i>m/z</i> 394 (M+H) ⁺
Example 124	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(5,6,7,8-tetrahydro[1,2,4]triazolo[4,3		MS (APCI ⁺) <i>m/z</i> 448 (M+H) ⁺

	-a]pyridin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 223)		
Example 125	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(pyridin-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 224)		MS (APCI ⁺) <i>m/z</i> 404 (M+H) ⁺
Example 126	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[4-(trifluoromethoxy)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 225)		MS (APCI ⁺) <i>m/z</i> 487 (M+H) ⁺
Example 127	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(6-cyanopyridin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 226)		MS (APCI ⁺) <i>m/z</i> 429 (M+H) ⁺
Example 128	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[4-(propan-2-yl)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 227)		MS (APCI ⁺) <i>m/z</i> 445 (M+H) ⁺

Example 129	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(5-methylpyrazin-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 228)		MS (APCI ⁺) <i>m/z</i> 419 (M+H) ⁺
Example 130	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[4-(methoxymethyl)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 229)		MS (APCI ⁺) <i>m/z</i> 447 (M+H) ⁺
Example 131	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(4-ethyl-1,3-thiazol-2-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 230)		MS (APCI ⁺) <i>m/z</i> 452 (M+H) ⁺
Example 132	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[3-fluoro-5-(trifluoromethyl)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 231)		MS (APCI ⁺) <i>m/z</i> 489 (M+H) ⁺
Example 133	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(6-methoxypyridin-2-yl)methyl]bicyclo[1.1.1]pen		MS (APCI ⁺) <i>m/z</i> 434 (M+H) ⁺

	tane-1-carboxamide (Compound 232)		
Example 134	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(pyridin-4-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 233)		MS (APCI ⁺) <i>m/z</i> 404 (M+H) ⁺
Example 135	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(pyridin-4-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 234)		MS (APCI ⁺) <i>m/z</i> 418 (M+H) ⁺
Example 136	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(1,2-oxazol-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 235)		MS (APCI ⁺) <i>m/z</i> 460 (M+H) ⁺
Example 137	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2,5-dimethoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 236)		MS (APCI ⁺) <i>m/z</i> 463 (M+H) ⁺
Example 138	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3-		MS (APCI ⁺) <i>m/z</i> 421

	fluorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 237)		(M+H) ⁺
Example 139	<i>N</i> -[(4-butylphenyl)methyl]-3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carboxamide (Compound 238)		MS (APCI ⁺) <i>m/z</i> 459 (M+H) ⁺
Example 140	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(4-fluorophenyl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 239)		MS (APCI ⁺) <i>m/z</i> 435 (M+H) ⁺
Example 141	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(4-ethoxyphenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 240)		MS (APCI ⁺) <i>m/z</i> 447 (M+H) ⁺
Example 142	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(3,4-dichlorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound		MS (APCI ⁺) <i>m/z</i> 471/473 (M+H) ⁺

	241)		
Example 143	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(pyridin-3-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 242)		MS (APCI ⁺) <i>m/z</i> 418 (M+H) ⁺
Example 144	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -{[2-(difluoromethoxy)phenyl]methyl}bicyclo[1.1.1]pentane-1-carboxamide (Compound 243)		MS (APCI ⁺) <i>m/z</i> 469 (M+H) ⁺
Example 145	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2-methylfuran-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 244)		MS (APCI ⁺) <i>m/z</i> 407 (M+H) ⁺
Example 146	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(4-fluorophenyl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 245)		MS (APCI ⁺) <i>m/z</i> 421 (M+H) ⁺
Example 147	3-[2-(4-chloro-3-		MS

	fluorophenoxy)acetamido]- <i>N</i> -({4- [(trifluoromethyl)sulfanyl]p henyl)methyl)bicyclo[1.1.1] pentane-1-carboxamide (Compound 246)		(APCI ⁺) <i>m/z</i> 503 (M+H) ⁺
Example 148	3-[2-(4-chloro-3- fluorophenoxy)acetamido]- <i>N</i> -[(3-propyl-1,2-oxazol-5- yl)methyl)bicyclo[1.1.1]pen tane-1-carboxamide (Compound 247)		MS (APCI ⁺) <i>m/z</i> 436 (M+H) ⁺
Example 149	3-[2-(4-chloro-3- fluorophenoxy)acetamido]- <i>N</i> -[2-(3-chloro-4- methoxyphenyl)ethyl]bicycl o[1.1.1]pentane-1- carboxamide (Compound 248)		MS (APCI ⁺) <i>m/z</i> 481 (M+H) ⁺
Example 150	3-[2-(4-chloro-3- fluorophenoxy)acetamido]- <i>N</i> -[(3-chloro-4- methoxyphenyl)methyl]bicy clo[1.1.1]pentane-1- carboxamide (Compound 249)		MS (APCI ⁺) <i>m/z</i> 467 (M+H) ⁺
Example 151	3-[2-(4-chloro-3- fluorophenoxy)acetamido]- <i>N</i> -{[3- (difluoromethoxy)phenyl]m		MS (APCI ⁺) <i>m/z</i> 469 (M+H) ⁺

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	ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 250)		
Example 152	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[(2,6-dimethylpyridin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 251)		MS (APCI ⁺) <i>m/z</i> 432 (M+H) ⁺
Example 153	3-[2-(4-chloro-3-fluorophenoxy)acetamido]- <i>N</i> -[2-(1 <i>H</i> -pyrazol-1-yl)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 252)	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆ -D ₂ O) δ ppm 7.62 (dd, <i>J</i> = 2.3, 0.7 Hz, 1H), 7.49 (t, <i>J</i> = 8.9 Hz, 1H), 7.45 (dd, <i>J</i> = 1.8, 0.7 Hz, 1H), 7.06 (dd, <i>J</i> = 11.3, 2.8 Hz, 1H), 6.86 (ddd, <i>J</i> = 9.0, 2.9, 1.2 Hz, 1H), 6.24 (t, <i>J</i> = 2.1 Hz, 1H), 4.46 (s, 2H), 4.17 (t, <i>J</i> = 6.4 Hz, 2H), 3.41 (t, <i>J</i> = 6.4 Hz, 2H), 2.16 (s, 6H)	MS (APCI ⁺) <i>m/z</i> 407 (M+H) ⁺

Example 154: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(pyridin-3-yl)propyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 253)

The reaction and purification conditions described in Example 48 substituting 3-(pyridin-3-yl)propan-1-amine, hydrochloric acid (AniChem) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.70 (s, 1H), 8.43 (dd, *J* = 2.3, 0.8 Hz, 1H), 8.39 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.77 (t, *J* = 5.7 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.49 (t, *J* = 8.9 Hz, 1H), 7.30 (ddd, *J* = 7.8, 4.8, 0.9 Hz, 1H), 7.07 (dd, *J* = 11.4, 2.9 Hz, 1H), 6.85 (ddd, *J* = 8.9, 2.8, 1.2 Hz, 1H), 4.47 (s, 2H), 3.05 (td, *J* = 7.1, 5.9 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.16 (s, 6H), 1.72 (p, *J* = 7.4 Hz, 2H); MS (ESI⁺) *m/z* 432 (M+H)⁺.

Example 155: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[3-(pyridin-2-yl)propyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 254)

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The reaction and purification conditions described in Example 48 substituting 3-(pyridin-2-yl)propan-1-amine (ChemBridge) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.69 (s, 1H), 8.46 (ddd, J = 4.8, 1.9, 0.9 Hz, 1H), 7.79 (t, J = 5.7 Hz, 1H), 7.68 (td, J = 7.6, 1.9 Hz, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.24 (dt, J = 7.8, 1.1 Hz, 1H), 7.19 (ddd, J = 7.5, 4.9, 1.2 Hz, 1H), 7.07 (dd, J = 11.3, 2.9 Hz, 1H), 6.85 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.46 (s, 2H), 3.07 (td, J = 7.3, 5.9 Hz, 2H), 2.74 – 2.66 (m, 2H), 2.16 (s, 6H), 1.87 – 1.74 (m, 2H); MS (ESI⁺) *m/z* 432 (M+H)⁺.

Example 156: 4-[2-(3,4-dichlorophenoxy)acetamido]-2-hydroxy-N-[[4-

(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 255)

10 *Example 156A: 4-(benzylamino)-2-oxobicyclo[2.2.2]octane-1-carboxylic acid*

A mixture of Example 7D (20.7 g, 61.3 mmol) and sodium hydroxide (49.0 mL, 306 mmol) in methanol/water (1:1, 200 mL) was stirred for 24 hours at ambient temperature. The reaction 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 the title compound. ¹H
15 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 156B: 4-(benzylamino)-2-oxo-N-(4-(trifluoromethyl)benzyl)bicyclo[2.2.2]octane-1-carboxamide

To a mixture of Example 156A (1100 mg, 4.02 mmol), (4-
20 (trifluoromethyl)phenyl)methanamine, hydrochloric acid (1065 mg, 5.03 mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (2.460 mL, 14.09 mmol) in *N,N*-dimethylformamide (25 mL), was added 2-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (2295 mg, 6.04 mmol), and the reaction mixture was stirred at ambient temperature overnight. Water was added, and the mixture was extracted with dichloromethane.
25 The organic layer was concentrated, and the residue was purified on silica gel (30-100% ethyl acetate in heptane) to give the title compound. MS (ESI⁺) *m/z* 431.3 (M+H)⁺.

Example 156C: 4-amino-2-oxo-N-(4-(trifluoromethyl)benzyl)bicyclo[2.2.2]octane-1-carboxamide

A mixture of Example 156B (1.29 g, 2.55 mmol) and 20% Pd(OH)₂/C, wet (0.24 g, 0.872
30 mmol) in tetrahydrofuran (14 mL) in a 20 mL stainless steel pressure vessel was stirred under 50 psi hydrogen at ambient temperature overnight. The suspension was filtered, and the filtrate was concentrated. The residue was purified by reverse phase preparative HPLC (30-100% acetonitrile in 0.1% trifluoroacetic acid/water at 50 mL/minute on Phenomenex® C18 10 μ m 250

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mm × 50 mm column) to give 380 mg of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.25 (m, 4H), 7.67 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 4.40 (d, J = 5.8 Hz, 2H), 2.59 (s, 2H), 2.20 (td, J = 11.2, 9.6, 2.4 Hz, 2H), 2.05 1.87 (m, 4H), 1.82 (td, J = 10.9, 10.2, 3.5 Hz, 2H).

5 *Example 156D: 4-[2-(3,4-dichlorophenoxy)acetamido]-2-hydroxy-N-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide*

To a mixture of Example 156C (185 mg, 0.407 mmol), 2-(3,4-dichlorophenoxy)acetic acid (112 mg, 0.509 mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (0.249 mL, 1.425 mmol) in *N,N*-dimethylformamide (5.0 mL), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (232 mg, 0.611 mmol) was added. The solution
10 was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated, and the residue was purified by reverse phase HPLC (30-100% acetonitrile in 0.1% trifluoroacetic acid/water at 50 mL/minute on Phenomenex® C18 10 μm 250 mm × 50 mm column) to give 220 mg of 4-[2-(3,4-dichlorophenoxy)acetamido]-2-oxo-*N*-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide with about 85% purity.
15 This 4-[2-(3,4-dichlorophenoxy)acetamido]-2-oxo-*N*-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide was dissolved in a mixture of dichloromethane/methanol (5 mL, 1:1) and treated sodium tetrahydroborate (30.8 mg, 0.814 mmol). The mixture was stirred at ambient temperature for 2 hours. The reaction mixture was
20 concentrated, and the residue was purified by preparative reverse phase HPLC (30-100% acetonitrile in 0.1% trifluoroacetic acid/water at 50 mL/minute on Phenomenex® C18 10 μm 250 mm × 50 mm column) to give 114 mg of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.04 (t, J = 6.1 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.53 7.46 (m, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 2.9 Hz, 1H), 6.91 (dd, J = 9.0, 2.9 Hz, 1H), 4.94 (d, J = 4.2 Hz, 1H), 4.42
25 (s, 2H), 4.31 (d, J = 5.9 Hz, 2H), 4.10 4.02 (m, 1H), 2.21 (ddd, J = 12.5, 9.1, 2.8 Hz, 1H), 2.08 (t, J = 11.4 Hz, 1H), 1.86 (td, J = 11.4, 5.0 Hz, 1H), 1.77 1.64 (m, 5H), 1.61 (dtd, J = 17.2, 11.8, 10.7, 6.0 Hz, 2H); MS (ESI⁺) *m/z* 545.1 (M+H)⁺.

Example 157

4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[[5-(difluoromethoxy)pyridin-2-yl]methyl]bicyclo[2.1.1]hexane-1-carboxamide (Compound 256)

30 *Example 157A: methyl 4-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[2.1.1]hexane-1-carboxylate*

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The reaction and purification conditions described in Example 48 substituting 2-(4-chloro-3-fluorophenoxy)acetic acid (Aldlab) for the product of Example 18A, and methyl 4-aminobicyclo[2.1.1]hexane-1-carboxylate, hydrochloric acid (Pharmablock) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. MS (ESI⁺) *m/z* 342 (M+H)⁺.

Example 157B: sodium 4-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[2.1.1]hexane-1-carboxylate, 2 sodium hydroxide

The product of Example 157A (0.4 g, 1.17 mmol) was dissolved in methanol (10 mL) and stirred at ambient temperature. An aqueous NaOH solution (2.5 M, 1.4 mL) was added.

After stirring at 40 °C for 1 hour, the reaction mixture was concentrated under reduced pressure to give the title compound (0.5 g, 1.12 mmol, 95% yield). MS (ESI⁺) *m/z* 328 (M+H)⁺.

Example 157C: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-{[5-(difluoromethoxy)pyridin-2-yl]methyl}bicyclo[2.1.1]hexane-1-carboxamide

The product of Example 157B (60 mg, 0.134 mmol) was combined with trifluoroacetic acid (0.062 mL, 0.80 mmol) and methanol (1 mL), and concentrated under reduced pressure. To the resulting residue was added [5-(difluoromethoxy)pyridin-2-yl]methanamine (27 mg, 0.15 mmol, Enamine), triethylamine (0.075 mL, 0.54 mmol), *N,N*-dimethylformamide (2 mL), and (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (HATU, 56.1 mg, 0.15 mmol) sequentially. After stirring at ambient temperature for 30 minutes, the reaction mixture was filtered through a glass microfiber frit and purified by preparative HPLC [YMC TriArtTM C18 Hybrid 5 µm column, 50 × 100 mm, flow rate 70 mL/minute, 5-100% gradient of acetonitrile in buffer (0.1% TFA)] to give the title compound (41 mg, 0.085 mmol, 63% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.53 (s, 1H), 8.39 (d, *J* = 2.8 Hz, 1H), 8.29 (t, *J* = 6.0 Hz, 1H), 7.64 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.49 (t, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.27 (t, *J* = 73.5 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.85 (ddd, *J* = 9.0, 2.8, 1.2 Hz, 1H), 4.49 (s, 2H), 4.35 (d, *J* = 6.1 Hz, 2H), 2.09 – 2.00 (m, 2H), 1.89 – 1.76 (m, 4H), 1.74 – 1.67 (m, 2H); MS (ESI⁺) *m/z* 484 (M+H)⁺.

Example 158: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(5-chloropyridin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 257)

Example 158A: methyl 4-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[2.2.2]octane-1-carboxylate

The reaction and purification conditions described in Example 48 substituting 2-(4-chloro-3-fluorophenoxy)acetic acid (Advanced Chemblocks) for the product of Example 18A,

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methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate hydrochloride (ArkPharm) for (5-(difluoromethoxy)pyridin-2-yl)methanamine, and (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) for (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (HATU) gave the title compound. MS (APCI⁺) *m/z* 370 (M+H)⁺.

Example 158B: 4-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[2.2.2]octane-1-carboxylic acid, 4 sodium chloride

The product of Example 158A (0.78 g, 2.11 mmol) was dissolved in methanol (6 mL) and stirred at ambient temperature. An aqueous NaOH solution (2.5 M, 3.37 mL) was added. After stirring at 40 °C for 1 hour, the reaction mixture was left stirring at ambient temperature for 72 hours. Aqueous HCl (6.0 M, 2.11 mL) was added, and the resulting solution was concentrated under reduced pressure to give the title compound (1.22 g, 2.07 mmol, 98% yield). MS (ESI⁺) *m/z* 356 (M+H)⁺.

Example 158C: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5-chloropyridin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and (5-chloropyridin-2-yl)methanamine hydrochloride (Frontier) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.52 (dd, *J* = 2.6, 0.7 Hz, 1H), 8.09 (t, *J* = 6.0 Hz, 1H), 7.86 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.19 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.03 (dd, *J* = 11.4, 2.9 Hz, 1H), 6.81 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.30 (d, *J* = 5.9 Hz, 2H), 1.89 – 1.76 (m, 12H); MS (ESI⁺) *m/z* 480 (M+H)⁺.

Example 159: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5-methylpyrazin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 258)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and (5-methylpyrazin-2-yl)methanamine (Aldrich) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.44 – 8.42 (m, 1H), 8.31 (d, *J* = 1.5 Hz, 1H), 8.09 (t, *J* = 5.9 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.03 (dd, *J* = 11.4, 2.9 Hz, 1H), 6.81 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.32 (d, *J* = 5.8 Hz, 2H), 2.46 (s, 3H), 1.88 – 1.74 (m, 12H); MS (ESI⁺) *m/z* 461 (M+H)⁺.

Example 160: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(pyridin-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 259)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and pyridin-2-ylmethanamine (Aldrich) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.47 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.03 (t, J = 6.0 Hz, 1H), 7.73 (td, J = 7.7, 1.8 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.23 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H), 7.17 – 7.13 (m, 1H), 7.03 (dd, J = 11.4, 2.8 Hz, 1H), 6.81 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.32 (d, J = 6.0 Hz, 2H), 1.90 – 1.77 (m, 12H); MS (ESI⁺) *m/z* 446 (M+H)⁺.

Example 161: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(4-chlorophenyl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 260)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and (4-chlorophenyl)methanamine for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.00 (t, J = 6.1 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.37 – 7.33 (m, 2H), 7.22 – 7.18 (m, 2H), 7.03 (dd, J = 11.4, 2.8 Hz, 1H), 6.81 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.21 (d, J = 6.0 Hz, 2H), 1.89 – 1.72 (m, 12H); MS (ESI⁺) *m/z* 479 (M+H)⁺.

Example 162: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[5-(trifluoromethyl)pyridin-2-yl]methyl}bicyclo[2.2.2]octane-1-carboxamide (Compound 261)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and (5-(trifluoromethyl)pyridin-2-yl)methanamine hydrochloride (PharmaBlock) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.89 – 8.85 (m, 1H), 8.21 – 8.13 (m, 2H), 7.51 – 7.46 (m, 2H), 7.39 – 7.36 (m, 1H), 7.03 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.45 (s, 2H), 4.41 (d, J = 5.9 Hz, 2H), 1.92 – 1.74 (m, 12H); MS (APCI⁺) *m/z* 514 (M+H)⁺.

Example 163: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[6-(difluoromethoxy)pyridin-3-yl]methyl}bicyclo[2.2.2]octane-1-carboxamide (Compound 262)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and (6-(difluoromethoxy)pyridin-3-yl)methanamine (ArkPharm) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.09 – 8.06 (m, 1H), 8.04 (t, J = 6.0 Hz, 1H), 7.72 (dd, J = 8.4, 2.5 Hz, 1H), 7.67 (t, J = 73.0 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.06 – 6.98 (m, 2H), 6.81 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.43 (s, 2H), 4.22 (d, J = 5.9 Hz, 2H), 1.87 – 1.69 (m, 12H); MS (ESI⁺) *m/z* 512 (M+H)⁺.

Example 164: (2*R*)-4-[2-(3,4-dichlorophenoxy)acetamido]-2-hydroxy-*N*-{[4-(trifluoromethyl)phenyl]methyl}bicyclo[2.2.2]octane-1-carboxamide (Compound 263)

The title compound was isolated by chiral preparative SFC of Example 156D as the second peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.09 (t, *J* = 6.0 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.57 - 7.50 (m, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 2.9 Hz, 1H), 6.95 (dd, *J* = 9.0, 2.9 Hz, 1H), 5.00 (s, 1H), 4.46 (s, 2H), 4.35 (d, *J* = 5.9 Hz, 2H), 4.10 (dt, *J* = 9.0, 2.2 Hz, 1H), 2.25 (ddd, *J* = 12.7, 9.2, 3.0 Hz, 1H), 2.12 (tt, *J* = 11.8, 3.3 Hz, 1H), 1.90 (tdd, *J* = 11.5, 5.6, 2.0 Hz, 1H), 1.80 - 1.58 (m, 7H); MS (ESI⁺) *m/z* 545.1 (M+H)⁺. Stereochemistry of this compound was arbitrarily assigned.

Example 165: (2*S*)-4-[2-(3,4-dichlorophenoxy)acetamido]-2-hydroxy-*N*-{[4-(trifluoromethyl)phenyl]methyl}bicyclo[2.2.2]octane-1-carboxamide (Compound 264)

The title compound was isolated by chiral preparative SFC of Example 156D as the first peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.09 (t, *J* = 6.0 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 9.2 Hz, 2H), 7.47 - 7.42 (m, 2H), 7.21 (d, *J* = 2.9 Hz, 1H), 6.95 (dd, *J* = 9.0, 2.9 Hz, 1H), 4.99 (s, 1H), 4.46 (s, 2H), 4.34 (d, *J* = 6.0 Hz, 2H), 4.10 (d, *J* = 9.0 Hz, 1H), 2.30 - 2.20 (m, 1H), 2.11 (td, *J* = 11.9, 5.9 Hz, 1H), 1.95 - 1.85 (m, 1H), 1.80 - 1.58 (m, 7H); MS (ESI⁺) *m/z* 545.2 (M+H)⁺. Stereochemistry of this compound was arbitrarily assigned.

Example 166: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-{[5-(difluoromethoxy)pyridin-2-yl]methyl}bicyclo[2.2.2]octane-1-carboxamide (Compound 265)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and (5-(difluoromethoxy)pyridin-2-yl)methanamine (Enamine) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.38 (d, *J* = 2.8 Hz, 1H), 8.08 (t, *J* = 6.0 Hz, 1H), 7.62 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.49 (br s, 1H), 7.48 (t, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 73.5 Hz, 1H), 7.22 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.03 (dd, *J* = 11.4, 2.8 Hz, 1H), 6.81 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.31 (d, *J* = 5.9 Hz, 2H), 1.91 - 1.73 (m, 12H); MS (APCI⁺) *m/z* 512 (M+H)⁺.

Example 167: (2*S*)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-*N*-{[4-(trifluoromethyl)phenyl]methyl}bicyclo[2.2.2]octane-1-carboxamide (Compound 266)

The title compound was isolated by chiral preparative SFC of Example 11 as the first peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.08 (t, *J* = 6.1 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.54 - 7.41 (m, 4H),

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7.03 (dd, J = 11.4, 2.8 Hz, 1H), 6.81 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.98 (s, 1H), 4.44 (s, 2H), 4.34 (d, J = 5.9 Hz, 2H), 4.10 (d, J = 9.0 Hz, 1H), 2.25 (ddd, J = 12.6, 9.2, 2.9 Hz, 1H), 2.11 (ddd, J = 13.9, 8.8, 3.0 Hz, 1H), 1.89 (ddd, J = 12.6, 8.8, 3.4 Hz, 1H), 1.80 - 1.57 (m, 7H); MS (ESI⁺) *m/z* 529.1 (M+H)⁺. Stereochemistry of this compound was arbitrarily assigned.

5 **Example 168: (2R)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 267)**

The title compound was isolated by chiral preparative SFC of Example 11 as the second peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.08 (t, J = 6.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 2H), 7.55 - 7.41 (m, 4H),
10 7.03 (dd, J = 11.5, 2.9 Hz, 1H), 6.81 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.98 (s, 1H), 4.44 (s, 2H), 4.34 (d, J = 5.9 Hz, 2H), 4.10 (d, J = 9.3 Hz, 1H), 2.25 (ddd, J = 12.6, 9.2, 2.8 Hz, 1H), 2.12 (td, J = 11.5, 11.0, 5.8 Hz, 1H), 1.90 (td, J = 11.4, 4.9 Hz, 1H), 1.80 - 1.57 (m, 7H); MS (ESI⁺) *m/z* 529.2 (M+H)⁺. Stereochemistry of this compound was arbitrarily assigned.

15 **Example 169: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(difluoromethoxy)pyridin-3-yl]bicyclo[2.1.1]hexane-1-carboxamide (Compound 268)**

The reaction and purification conditions described in Example 157C substituting 6-(difluoromethoxy)pyridin-3-amine (Enamine) for [5-(difluoromethoxy)pyridin-2-yl]methanamine, and (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) for (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (HATU) gave the title compound. ¹H
20 NMR (400 MHz, DMSO-*d*₆) δ ppm 9.66 (s, 1H), 8.58 (s, 1H), 8.52 (dd, J = 2.7, 0.6 Hz, 1H), 8.14 (dd, J = 8.9, 2.7 Hz, 1H), 7.63 (t, J = 73.2 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.11 - 7.03 (m, 2H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.50 (s, 2H), 2.18 - 2.10 (m, 2H), 1.97 - 1.86 (m, 4H), 1.85 - 1.78 (m, 2H); MS (APCI⁺) *m/z* 471 (M+H)⁺.

25 **Example 170: (3R)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxy-N-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 269)**

The title compound was isolated by chiral preparative SFC of Example 175 as the second peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.11 (t, J = 6.0 Hz, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.49 (t, J = 8.9 Hz,
30 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.31 (s, 1H), 7.06 (dd, J = 11.4, 2.9 Hz, 1H), 6.84 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.12 (s, 1H), 4.48 (s, 2H), 4.30 (d, J = 5.9 Hz, 2H), 4.03 (d, J = 9.1 Hz, 1H), 2.15 (ddd, J = 13.5, 9.3, 2.2 Hz, 1H), 2.03 (ddd, J = 12.7, 10.9, 4.6 Hz, 1H), 1.88 (tt, J = 9.2, 4.3

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Hz, 1H), 1.86 1.77 (m, 1H), 1.82 1.70 (m, 4H), 1.74 1.61 (m, 1H), 1.58 (dt, J = 13.5, 3.0 Hz, 1H); MS (ESI⁺) *m/z* 529.2 (M+H)⁺. Stereochemistry of this compound was arbitrarily assigned.

Example 171: (3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxy-N-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 270)

5 The title compound was isolated by chiral preparative SFC of Example 175 as the first peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.11 (t, J = 6.0 Hz, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.31 (s, 1H), 7.06 (dd, J = 11.4, 2.9 Hz, 1H), 6.84 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.12 (s, 1H), 4.48 (s, 2H), 4.30 (d, J = 5.9 Hz, 2H), 4.03 (d, J = 9.1 Hz, 1H),
10 2.15 (ddd, J = 13.5, 9.3, 2.2 Hz, 1H), 2.03 (ddd, J = 12.7, 10.9, 4.6 Hz, 1H), 1.88 (tt, J = 9.2, 4.3 Hz, 1H), 1.86 - 1.77 (m, 1H), 1.82 - 1.70 (m, 4H), 1.74 - 1.61 (m, 1H), 1.58 (dt, J = 13.5, 3.0 Hz, 1H); MS (ESI⁺) *m/z* 529.1 (M+H)⁺. Stereochemistry of this compound was arbitrarily assigned.

Example 172: (3R)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxy-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 271)

15 The title compound was isolated by chiral preparative SFC of Example 176 as the second peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.87 (dt, J = 1.9, 0.9 Hz, 1H), 8.23 8.12 (m, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.31 (s, 1H), 7.06 (dd, J = 11.4, 2.9 Hz, 1H), 6.84 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.12 (d, J = 4.3 Hz, 1H), 4.48 (s, 2H), 4.40 (d, J = 5.8 Hz, 2H), 4.05 (dt, J = 8.6,
20 3.5 Hz, 1H), 2.18 (ddd, J = 13.6, 9.4, 2.1 Hz, 1H), 2.04 (ddd, J = 12.5, 10.8, 4.6 Hz, 1H), 1.96 1.64 (m, 7H), 1.60 (dt, J = 13.5, 3.0 Hz, 1H); MS (ESI⁺) *m/z* 530.1 (M+H)⁺. Stereochemistry of this compound was arbitrarily assigned.

Example 173: (3S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxy-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 272)

25 The title compound was isolated by chiral preparative SFC of Example 176 as the first peak eluted off the column using the methodologies described in Example 14. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.87 (dt, J = 2.0, 1.0 Hz, 1H), 8.23 8.12 (m, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.31 (s, 1H), 7.06 (dd, J = 11.4, 2.9 Hz, 1H), 6.84 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.11 (d, J = 4.3 Hz, 1H), 4.48 (s, 2H), 4.40 (d, J = 5.8 Hz, 2H), 4.05 (dt, J = 8.4,
30 3.6 Hz, 1H), 2.18 (ddd, J = 13.6, 9.3, 2.0 Hz, 1H), 2.04 (ddd, J = 12.5, 10.8, 4.5 Hz, 1H), 1.95 1.82 (m, 1H), 1.87 1.72 (m, 5H), 1.77 1.65 (m, 1H), 1.60 (dt, J = 13.4, 3.0 Hz, 1H); MS (ESI⁺) *m/z* 530.2 (M+H)⁺. Stereochemistry of this compound was arbitrarily assigned.

Example 174: (2S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(4-chlorophenyl)-2-oxoethyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 273)

Example 174A: 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
5 (12.29 mL, 220 mmol), and *p*-toluenesulfonic acid monohydrate (1.397 g, 7.34 mmol) in toluene
(200 mL) was stirred at 120 °C 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 by silica gel column chromatography (0-30% ethyl acetate in heptane) to
give 12.77 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.01 (q, *J* = 7.1 Hz,
10 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 174B: 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
15 cooled to -78 °C under nitrogen, and a solution of Example 174A (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 NH₄Cl solution, and the aqueous phase was extracted with ethyl
20 acetate. The organic layer was washed with brine, dried over magnesium sulfate and filtered.
The filtrate was concentrated, and the residue was purified chromatographically on silica gel (0-
70% ethyl acetate in heptane) to give 6.78 g of the title compound. ¹H 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).

25 *Example 174C: ethyl 1-acetyl-4-oxocyclohexane-1-carboxylate*

A mixture of Example 174B (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
30 concentrated to give 5.46 g of the title compound which was used without further purification.
¹H 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).

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Example 174D: ethyl 4-(benzylamino)-2-oxobicyclo[2.2.2]octane-1-carboxylate, hydrochloric acid

A mixture of Example 174C (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 130 °C 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. ¹H 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 174E: ethyl 4-amino-2-oxobicyclo[2.2.2]octane-1-carboxylate, hydrochloric acid

To a mixture of Example 174D (11.2 g of HCl salt, 33.2 mmol) in tetrahydrofuran (110 mL) in a 50 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. ¹H 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 174F: ethyl 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-oxobicyclo[2.2.2]octane-1-carboxylate

To a suspension of Example 174E (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 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. ¹H 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

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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 174G: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-oxobicyclo[2.2.2]octane-1-carboxylic acid

5 A suspension of Example 174F (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. ¹H 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, $J =$
10 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 174H: (S)-4-(2-(4-chloro-3-fluorophenoxy)acetamido)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid

To a solution of Example 174G (10 g, 25.7 mmol) in methanol (200 mL) was added
15 NaBH₄ (1.069 g, 28.3 mmol) at -20°C, and the reaction mixture was stirred for 2 hours at the same temperature. Solvent was removed under reduced pressure, and the residue was quenched with aqueous HCl (1.5 M) to pH=1. Water (50 mL) was added, and the resulting mixture was filtered. The collected solid was washed with water (100 mL) and ethyl acetate (100 mL), and dried under high vacuum to give 8.7 g of the racemic title compound. This intermediate was
20 then subjected to preparative chiral SFC purification to give Example 174H as the first peak eluted off the column. The method of separation by chiral SFC (Instrument: Thar SFC80 preparative SFC; Column: Chiralpak AD-H 250×30mm i.d. 5 μ m; Mobile phase: A for CO₂ and B for CH₃OH (0.1% NH₃•H₂O) Eluent B 35% isocratic for 4 minute runtime; Flow rate: 70 g/minute; Wavelength = 220 nm; Column temperature: 40 °C; System back pressure: 100 bar;
25 Cycle time: 4 minutes; Injection amount: 25 mg per injection. Work up: the resulting solution was concentrated under reduced pressure at 40 °C, and the residue was diluted with water (150 mL), adjusted to pH = 1 with aqueous HCl (1.5 M) to pH=1. The resulting mixture was filtered, and the cake was washed with water (100 mL) and ethyl acetate (100 mL), and dried under high vacuum to give the title compound. MS (ESI⁺) m/z 372.0 (M+H)⁺.

30 *Example 174I: (2S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(4-chlorophenyl)-2-oxoethyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide*

A mixture of 2-amino-1-(4-chlorophenyl)ethanone hydrochloride (133 mg, 0.646 mmol), (S)-4-(2-(4-chloro-3-fluorophenoxy)acetamido)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic

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acid (200 mg, 0.538 mmol, Example 174H), *N*-ethyl-*N*-isopropylpropan-2-amine (0.282 mL, 1.614 mmol) in *N,N*-dimethylformamide (DMF) (2 mL) was treated with 2-(3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (307 mg, 0.807 mmol), and the reaction mixture was stirred at ambient temperature for 12 hours. The reaction mixture was diluted with methanol (2 mL) and then purified by preparative reverse phase 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 30 minutes, at a flow rate of 50 mL/minute) to give the title compound (250 mg, 89% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.98 - 7.83 (m, 2H), 7.57 - 7.40 (m, 2H), 7.32 (t, J = 8.6 Hz, 1H), 7.00 (t, J = 4.5 Hz, 1H), 6.74 (dd, J = 10.3, 2.9 Hz, 1H), 6.66 (ddd, J = 8.9, 2.9, 1.3 Hz, 1H), 6.16 (s, 1H), 4.70 (qd, J = 19.7, 4.5 Hz, 2H), 4.35 (s, 2H), 4.27 (dt, J = 9.1, 2.2 Hz, 1H), 2.50 (ddd, J = 13.4, 9.3, 3.0 Hz, 1H), 2.43 - 2.31 (m, 1H), 2.30 - 1.86 (m, 5H), 1.86 - 1.45 (m, 3H); MS(APCI) *m/z* 523.2 (M+H)⁺.

Example 175: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxy-*N*-{[4-(trifluoromethyl)phenyl]methyl}bicyclo[2.2.2]octane-1-carboxamide (Compound 274)

Example 175A: dimethyl 2-oxobicyclo[2.2.2]octane-1,4-dicarboxylate:

To a mixture of dimethyl bicyclo[2.2.2]octane-1,4-dicarboxylate (3.89 g, 17.19 mmol) in acetic acid (40 mL) was added chromium trioxide (3.44 g, 34.4 mmol) at 20 °C, then the mixture was stirred at 90 °C for 18 hours. The reaction mixture was diluted with ethyl acetate (200 mL), poured into water (100 mL) and adjusted to pH = 9 with solid NaHCO₃. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic phase was washed with brine (300 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: ethyl acetate = 20:1-10:1) to give crude title compound which was treated with petroleum ether (50 mL). The solid was collected by filtration and dried under high vacuum to give 0.8 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.68-2.16 (m, 8H), 2.25-2.35 (m, 2H), 2.58 (s, 2H), 3.64 (s, 1H), 3.70 (s, 3H), 3.74 (s, 3H).

Example 175B: 4-(methoxycarbonyl)-2-oxobicyclo[2.2.2]octane-1-carboxylic acid

To a solution of Example 175A (8.4 g, 33.2 mmol) in tetrahydrofuran (80 mL) and methanol (20 mL) was added a solution of lithium hydroxide monohydrate (1.116 g, 26.6 mmol) in water (20 mL) at 0 °C, and the resulting mixture was stirred for 48 hours at 25 °C. The mixture was concentrated under reduced pressure at 25°C, and the residue was diluted with water (40 mL) and extracted with 2-methoxy-2-methylpropane (2 × 80 mL). The aqueous layer was

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adjusted to pH =2 with aqueous 0.5 N HCl, and the precipitate was collected by filtration and dried under high vacuum to give the title compound (4 g, yield 50.6%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.88-2.12 (m, 7H), 2.27-2.39 (m, 2H), 2.60 (s, 2H), 3.72 (s, 1H), 3.75 (s, 3H).

Example 175C: 4-tert-butyl 1-methyl 2-oxobicyclo[2.2.2]octane-1,4-dicarboxylate

- 5 To a solution of Example 175B (4 g, 16.80 mmol) in *t*-butanol (60 mL) was added pyridine (9.57 g, 121 mmol) and *N,N*-dimethylpyridin-4-amine (2.052 g, 16.80 mmol). Then di-*tert*-butyl dicarbonate (18.33 g, 84 mmol) was added slowly at 20 °C, and the mixture was stirred at 35 °C for 24 hours. The resulting solution was concentrated under reduced pressure, and the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The
- 10 organic phase was washed with water (2 × 100 mL), dried with Na₂SO₄ and concentrated under reduced pressure to give the title compound (5.5 g) which was used in the subsequent step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.37 (s, 9H), 1.79 (br d, *J*=12.35 Hz, 2H), 1.83-2.00 (m, 4H), 2.21 (br d, *J*=13.33 Hz, 2H), 2.46 (s, 2H), 3.68 (s, 3H).

Example 175D: 4-(tert-butoxycarbonyl)-2-oxobicyclo[2.2.2]octane-1-carboxylic acid

- 15 To a solution of Example 175C (5.5 g, 19.48 mmol) in tetrahydrofuran (80 mL) and methanol (20 mL) was added a solution of NaOH (0.779 g, 19.48 mmol) in water (20 mL) at 0 °C, and the mixture was stirred at 0 °C to 25 °C for 12 hours. The mixture was concentrated under reduced pressure at 25 °C. The residue was diluted with water (30 mL) and washed with 2-methoxy-2-methylpropane (2 × 50 mL). The aqueous layer was acidified to pH =1 with
- 20 aqueous 1 N HCl, and the precipitate was collected by filtration and dried under high vacuum to give the title compound (2.4 g, yield 41%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.22 (s, 1H), 1.41-1.53 (m, 9H), 1.78-1.98 (m, 2H), 2.03-2.27 (m, 6H), 2.57-2.69 (m, 2H).

Example 175E: tert-butyl 4-(((benzyloxy)carbonyl)amino)-3-oxobicyclo[2.2.2]octane-1-carboxylate

- 25 To a solution of Example 175D (1 g, 3.73 mmol) in toluene (100 mL) was added triethylamine (1.558 mL, 11.18 mmol) and diphenyl phosphorazidate (2.051 g, 7.45 mmol) sequentially at 20 °C, and the mixture was stirred for 2 hours at 120 °C under N₂. Then benzyl alcohol (1.163 mL, 11.18 mmol) was added at 120 °C, and the mixture was stirred at 120 °C for 12 hours. The reaction mixture was cooled to 25 °C and concentrated under reduced pressure.
- 30 The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The organic phase was dried with Na₂SO₄ and concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel eluted with petroleum ether and ethyl acetate (100:1 to 30:1 to 10:1) to give the title compound (0.95 g, yield 62.5%). ¹H NMR (400

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MHz, CDCl₃) δ ppm 1.37 (s, 9H), 1.50-1.56 (m, 2H), 1.70-1.88 (m, 3H), 1.97-2.12 (m, 3H), 2.55 (s, 2H), 2.72-2.90 (m, 2H), 4.99 (s, 2H), 5.92 (br s, 1H), 7.25-7.31 (m, 5H).

Example 175F: tert-butyl 4-amino-3-oxobicyclo[2.2.2]octane-1-carboxylate

To a mixture of Pd(OH)₂ (600 mg, 4.27 mmol) in tetrahydrofuran (60 mL) was added a
5 solution of Example 175E (2 g, 4.82 mmol) in tetrahydrofuran (60 mL) at 20 °C under argon,
and the resulting mixture was stirred for 2 hours under H₂ at 15 psi. The resulting mixture was
filtered through a pad of diatomaceous earth, and the cake was washed with ethyl acetate (30
mL). Water (20 mL) was added, and the resulting mixture was adjusted to pH = 1 with aqueous
1.2 M HCl. The two phases were cut, and the aqueous layer was washed with ethyl acetate (2 ×
10 20 mL). The aqueous layer was lyophilized to give the title compound (1.2 g, yield 88%). ¹H
NMR (400 MHz, CD₃OD) δ ppm 1.46-1.49 (m, 9H), 1.94-2.07 (m, 4H), 2.13-2.25 (m, 4H), 2.74
(s, 2H).

Example 175G: tert-butyl 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-3-oxobicyclo[2.2.2]octane-1-carboxylate

15 A mixture of Example 175F (0.51 g, 1.849 mmol), 2-(4-chloro-3-fluorophenoxy)acetic
acid (0.435 g, 2.127 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.969 mL, 5.55 mmol) in
N,N-dimethylformamide (10.0 mL) was treated with 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-
1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.703 g, 1.849 mmol), and the reaction
mixture was stirred at ambient temperature overnight. Water (100 mL) was added dropwise, and
20 stirring was continued for 15 minutes. The precipitate was collected by filtration, washed with
water and heptane, and dried under vacuum to give 0.74 g of the title compound. ¹H NMR (400
MHz, DMSO-*d*₆) δ ppm 7.67 (s, 1H), 7.45 (t, *J* = 8.9 Hz, 1H), 7.04 (dd, *J* = 11.3, 2.9 Hz, 1H),
6.81 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.52 (s, 2H), 2.53 (d, *J* = 1.3 Hz, 2H), 2.46-2.29 (m, 2H),
1.94 (t, *J* = 9.9 Hz, 2H), 1.87-1.79 (m, 1H), 1.78 (d, *J* = 10.5 Hz, 3H), 1.36 (s, 9H); MS (ESI⁺)
25 *m/z* 426.1 (M+H)⁺.

Example 175H: 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-3-oxobicyclo[2.2.2]octane-1-carboxylic acid

To a solution of *tert*-butyl 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-3-oxobicyclo[2.2.2]octane-1-carboxylate (0.73 g, 1.714 mmol, Example 175G) in dichloromethane
30 (10.0 mL) was added 2,2,2-trifluoroacetic acid (1.321 mL, 17.14 mmol), and the reaction
mixture was stirred at ambient temperature for 2 hours and 50 °C for 1 hour. Volatiles were
removed under high vacuum. The residue was triturated with dichloromethane/heptane to give
0.63 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.53 (s, 1H), 7.71 (s, 1H),

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7.49 (t, J = 8.8 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 6.85 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.57 (s, 2H), 2.59 (d, J = 1.3 Hz, 2H), 2.42 (dd, J = 11.5, 8.5 Hz, 2H), 2.09 1.93 (m, 2H), 1.84 (d, J = 8.3 Hz, 4H); MS (ESI⁺) *m/z* 370.2 (M+H)⁺.

Example 175I: 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-3-hydroxybicyclo[2.2.2]octane-1-carboxylic acid

To a mixture of 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-3-oxobicyclo[2.2.2]octane-1-carboxylic acid (0.25 g, 0.676 mmol, Example 175H) in dichloromethane (2.5 mL) and methanol (2.5 mL), sodium tetrahydroborate (0.064 g, 1.690 mmol) was added, and the mixture was stirred at ambient temperature for 2 days. The reaction mixture was concentrated, and the residue was purified by reverse phase preparative HPLC (30-100% acetonitrile in 0.1% trifluoroacetic acid/water over 25 minutes at 50 mL/minute on a Phenomenex® C18 10 µm 250 mm x 50 mm column) to give 154 mg of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.08 (s, 1H), 7.48 (t, J = 8.9 Hz, 1H), 7.29 (s, 1H), 7.05 (dd, J = 11.4, 2.9 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.07 (d, J = 4.2 Hz, 1H), 4.47 (s, 2H), 4.06 - 3.97 (m, 1H), 2.12 (ddd, J = 13.6, 9.3, 2.4 Hz, 1H), 2.01 (ddd, J = 12.8, 10.9, 4.7 Hz, 1H), 1.94 - 1.59 (m, 7H), 1.55 (dt, J = 13.6, 3.0 Hz, 1H); MS (ESI⁺) *m/z* 372.3 (M+H)⁺.

Example 175J: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxy-N-[[4-(trifluoromethyl)phenyl]methyl]bicyclo[2.2.2]octane-1-carboxamide

To a mixture of 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-3-hydroxybicyclo[2.2.2]octane-1-carboxylic acid (75 mg, 0.202 mmol, Example 175I), 4-(trifluoromethyl)benzylamine (44.2 mg, 0.252 mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (0.141 mL, 0.807 mmol) in *N,N*-dimethylformamide (1.5 mL) was added 2-(3-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (115 mg, 0.303 mmol) followed by stirring at ambient temperature for 60 minutes. The reaction mixture was concentrated, and the residue was purified by preparative reverse phase HPLC (Phenomenex® Luna® C18(2) 10 µm 100Å AXIA™ column (250 mm x 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 90 mg of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.11 (t, J = 6.0 Hz, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.30 (s, 1H), 7.06 (dd, J = 11.4, 2.8 Hz, 1H), 6.84 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 5.11 (s, 1H), 4.48 (s, 2H), 4.30 (d, J = 5.9 Hz, 2H), 4.04 (dd, J = 9.5, 3.0 Hz, 1H), 2.16 (ddd, J = 13.4, 9.3, 2.2 Hz, 1H), 2.03 (ddd, J = 12.6, 10.8, 4.6 Hz, 1H), 1.96 1.62 (m, 7H), 1.58 (dt, J = 13.5, 3.0 Hz, 1H); MS (ESI⁺) *m/z* 529.2 (M+H)⁺.

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Example 176: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxy-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 275)

The title compound was prepared by using the methodologies described in Example 175J substituting (5-(trifluoromethyl)pyridin-2-yl)methanamine, hydrochloric acid for 4-

5 (trifluoromethyl)benzylamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.87 (d, J = 2.3 Hz, 1H), 8.23 - 8.12 (m, 2H), 7.49 (t, J = 8.8 Hz, 1H), 7.38 (d, J = 8.3 Hz, 1H), 7.31 (s, 1H), 7.06 (dd, J = 11.4, 2.9 Hz, 1H), 6.84 (dd, J = 9.1, 2.5 Hz, 1H), 4.48 (s, 2H), 4.40 (d, J = 5.8 Hz, 2H), 4.05 (dd, J = 9.4, 3.0 Hz, 1H), 2.18 (ddd, J = 13.6, 9.3, 2.1 Hz, 1H), 2.04 (ddd, J = 12.6, 10.9, 4.6 Hz, 1H), 1.96 - 1.56 (m, 8H); MS (ESI⁺) *m/z* 530.3 (M+H)⁺.

10 **Example 177: (2R)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(4-chlorophenyl)-2-oxoethyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 276)**

Example 177A: (R)-4-(2-(4-chloro-3-fluorophenoxy)acetamido)-2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid

The title compound was prepared using the procedures described in Examples 174A-
15 174H and was isolated from the chiral SFC purification method described in Example 174H as the second peak eluted off column. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.54-1.77 (m, 7H), 1.84 (td, J=11.55, 4.89 Hz, 1H), 1.96-2.13 (m, 1H), 2.18-2.30 (m, 1H), 2.31-2.45 (m, 1H), 2.53-2.58 (m, 1H), 4.06 (br d, J=7.83 Hz, 1H), 4.44 (s, 2H), 4.49 (s, 1H), 4.84 (br s, 1H), 6.81 (dt, J=8.93, 1.41 Hz, 1H), 7.03 (dd, J=11.49, 2.81 Hz, 1H), 7.43-7.56 (m, 2H), 11.84-12.12 (m, 1H);
20 MS (+ESI) *m/z* = 372.0 (M+H)

Example 177B: (2R)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(4-chlorophenyl)-2-oxoethyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide

The title compound was prepared using the procedure described in Example 174I substituting Example 177A for Example 174H. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.06 - 7.79
25 (m, 2H), 7.58 - 7.42 (m, 2H), 7.32 (t, J = 8.6 Hz, 1H), 6.99 (t, J = 4.4 Hz, 1H), 6.74 (dd, J = 10.3, 2.8 Hz, 1H), 6.66 (ddd, J = 8.9, 2.9, 1.3 Hz, 1H), 6.15 (s, 1H), 4.70 (qd, J = 19.7, 4.5 Hz, 2H), 4.35 (s, 2H), 4.26 (dq, J = 9.2, 2.2 Hz, 1H), 3.71 (d, J = 2.2 Hz, 1H), 2.50 (ddd, J = 13.3, 9.3, 3.0 Hz, 1H), 2.38 (ddt, J = 13.2, 10.8, 3.8 Hz, 1H), 2.17 - 1.89 (m, 5H), 1.90 - 1.67 (m, 3H); MS (APCI) *m/z* 523.2 (M+H)⁺.

30 **Example 178: (2S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-N-(2-oxo-3-phenylpropyl)bicyclo[2.2.2]octane-1-carboxamide (Compound 277)**

The title compound was prepared using the procedure described in Example 174 and substituting 1-amino-3-phenylpropan-2-one hydrochloride for 2-amino-1-(4-

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chlorophenyl)ethanone hydrochloride. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.39 - 7.27 (m, 4H), 7.24 - 7.15 (m, 2H), 6.73 (dd, J = 10.3, 2.9 Hz, 2H), 6.65 (ddd, J = 8.9, 2.9, 1.3 Hz, 1H), 6.16 (s, 1H), 4.34 (s, 2H), 4.26 - 4.16 (m, 2H), 4.15 - 4.05 (m, 1H), 3.75 (s, 2H), 2.45 (ddd, J = 13.4, 9.3, 3.1 Hz, 1H), 2.29 (ddt, J = 12.8, 11.1, 3.6 Hz, 1H), 2.07 - 1.85 (m, 6H), 1.82 - 1.73 (m, 1H), 1.73 - 1.62 (m, 1H); MS(APCI) *m/z* 503.2 (M+H)⁺.

Example 179: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(difluoromethoxy)pyridin-3-yl]bicyclo[2.2.2]octane-1-carboxamide (Compound 278)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, 6-(difluoromethoxy)pyridin-3-amine (Enamine) for (5-(difluoromethoxy)pyridin-2-yl)methanamine, and (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) for (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (HATU) gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.41 (s, 1H), 8.47 (dd, J = 2.7, 0.6 Hz, 1H), 8.11 (dd, J = 8.9, 2.7 Hz, 1H), 7.62 (t, J = 73.2 Hz, 1H), 7.53 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.08 - 7.00 (m, 2H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.45 (s, 2H), 1.89 (s, 12H); MS (APCI⁺) *m/z* 498 (M+H)⁺.

Example 180: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[2.2.2]octane-1-carboxamide (Compound 279)

The product of Example 158B (62 mg, 0.11 mmol) and bis(tetramethylene)fluoroformamidinium hexafluorophosphate (50 mg, 0.16 mmol, Alfa) were charged to a sealed tube, and a solvent mixture of dichloromethane (0.26 mL) and *N,N*-diisopropylethylamine (0.083 mL, 0.47 mmol) was added in one portion. The resulting mixture was stirred at ambient temperature for 30 minutes and 5-(trifluoromethoxy)pyridin-2-amine (22.5 mg, 0.13 mmol, Astatech) was added. The tube was sealed and stirred at 75 °C for 18 hours. The reaction mixture was cooled to ambient temperature and concentrated under reduced pressure. The resulting residue was dissolved in *N,N*-dimethylformamide (3 mL), 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, 0.023 mmol, 22% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.95 (s, 1H), 8.39 - 8.36 (m, 1H), 8.11 (dd, J = 9.2, 0.6 Hz, 1H), 7.83 (ddd, J = 9.2, 3.0, 1.0 Hz, 1H), 7.48 - 7.41 (m, 2H), 7.00 (dd, J = 11.4, 2.8 Hz, 1H), 6.78 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.42 (s, 2H), 1.92 - 1.78 (m, 12H). MS (APCI⁺) *m/z* 516 (M+H)⁺.

Example 181: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(trifluoromethoxy)pyridin-3-yl]bicyclo[2.2.2]octane-1-carboxamide (Compound 280)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, 6-(trifluoromethoxy)pyridin-3-amine (BePharm) for (5-(difluoromethoxy)pyridin-2-yl)methanamine, and (7-azabenzotriazol-1-yl)oxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP) for (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (HATU) gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.57 (s, 1H), 8.57 (d, *J* = 2.7 Hz, 1H), 8.23 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.55 (s, 1H), 7.49 (t, *J* = 8.9 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.04 (dd, *J* = 11.4, 2.9 Hz, 1H), 6.83 (ddd, *J* = 9.0, 3.0, 1.2 Hz, 1H), 4.45 (s, 2H), 1.89 (s, 12H); MS (APCI⁺) *m/z* 516 (M+H)⁺.

Example 182: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]bicyclo[2.2.2]octane-1-carboxamide (Compound 281)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and 6-(2,2,2-trifluoroethoxy)pyridin-3-amine (Enamine) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.30 (s, 1H), 8.40 (dd, *J* = 2.7, 0.7 Hz, 1H), 7.98 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.53 (s, 1H), 7.49 (t, *J* = 8.9 Hz, 1H), 7.04 (dd, *J* = 11.4, 2.9 Hz, 1H), 6.93 (dd, *J* = 8.9, 0.6 Hz, 1H), 6.82 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.93 (q, *J* = 9.1 Hz, 2H), 4.45 (s, 2H), 1.88 (br s, 12H); MS (ESI⁺) *m/z* 530 (M+H)⁺.

Example 183: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(difluoromethoxy)pyridin-3-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 282)

The reaction and purification conditions described in Example 48 substituting (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) for (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (HATU), and 6-(difluoromethoxy)pyridin-3-amine (Enamine) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.87 (s, 1H), 8.81 (s, 1H), 8.50 (dd, *J* = 2.7, 0.7 Hz, 1H), 8.12 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.83 – 7.47 (m, 2H), 7.11 – 7.05 (m, 2H), 6.87 (ddd, *J* = 8.9, 2.8, 1.2 Hz, 1H), 4.50 (s, 2H), 2.34 (s, 6H); MS (ESI⁺) *m/z* 456 (M+H)⁺.

Example 184: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(4-chlorophenyl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 283)

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To a dichloromethane (2.0 mL) solution of the product of Example 18A (52 mg, 0.17 mmol) was added one drop of *N,N*-dimethylformamide followed by oxalyl chloride (2.0 M solution in dichloromethane, 0.124 mL). After stirring at ambient temperature for 10 minutes, the reaction mixture was concentrated under reduced pressure and taken up in dichloromethane (1.0 mL). The resulting solution was transferred to a pyridine (2 mL) solution of 4-chloroaniline (21.2 mg, 0.17 mmol). After stirring at ambient temperature for 30 minutes, the reaction mixture was concentrated under reduced pressure. The resulting residue was taken up in *N,N*-dimethylformamide (3 mL), filtered through a glass microfiber frit and purified by preparative HPLC [YMC TriArt™ C18 Hybrid 20 µm column, 25 × 150 mm, flow rate 80 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 (25 mg, 0.06 mmol, 36% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.70 (s, 1H), 8.78 (s, 1H), 7.72 – 7.63 (m, 2H), 7.50 (t, J = 8.9 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.87 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.49 (s, 2H), 2.32 (s, 6H); MS (ESI⁺) *m/z* 421 (M-H)⁺.

Example 185: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[5-(difluoromethyl)pyrazin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 284)

The reaction and purification conditions described in Example 184 substituting 5-(difluoromethyl)pyrazin-2-amine (Aldrich) for 4-chloroaniline gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 11.01 (s, 1H), 9.37 (d, J = 1.5 Hz, 1H), 8.78 (s, 1H), 8.73 – 8.71 (m, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 7.07 (t, J = 54.4 Hz, 1H), 6.87 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.49 (s, 2H), 2.39 (s, 6H); MS (ESI⁺) *m/z* 441 (M+H)⁺.

Example 186: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-phenylbicyclo[1.1.1]pentane-1-carboxamide (Compound 285)

The reaction and purification conditions described in Example 48 substituting aniline for 5-(difluoromethoxy)pyridin-2-ylmethanamine gave the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.56 (s, 1H), 8.78 (s, 1H), 7.65 – 7.61 (m, 2H), 7.50 (t, J = 8.9 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.09 (dd, J = 11.4, 2.9 Hz, 1H), 7.05 (tt, J = 7.4, 1.2 Hz, 1H), 6.87 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.49 (s, 2H), 2.32 (s, 6H); MS (ESI⁺) *m/z* 389 (M+H)⁺.

Example 187: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(4-chlorophenyl)bicyclo[2.1.1]hexane-1-carboxamide (Compound 286)

Example 187A: tert-butyl (4-((4-chlorophenyl)carbamoyl)bicyclo[2.1.1]hexan-1-yl)carbamate

The reaction and purification conditions described in Example 48 substituting 4-chloroaniline for 5-(difluoromethoxy)pyridin-2-ylmethanamine, and 4-((*tert*-

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butoxycarbonyl)amino)bicyclo[2.1.1]hexane-1-carboxylic acid (Enamine) for the product of Example 18A gave the title compound. MS (ESI⁻) *m/z* 349 (M-H)⁻.

Example 187B: 4-amino-N-(4-chlorophenyl)bicyclo[2.1.1]hexane-1-carboxamide

The product of Example 187A (0.1 g, 0.29 mmol) was stirred in dichloromethane (1 mL) at 0 °C. Trifluoroacetic acid (1 mL, 12.98 mmol) was added in one portion. The reaction mixture was allowed to warm up to ambient temperature over 30 minutes and continued to stir for 1 hour. The resulting mixture was concentrated under reduced pressure, and the resulting residue was purified by preparative HPLC [YMC TriArt™ C18 Hybrid 20 µm column, 25 × 150 mm, flow rate 80 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 (0.06 g, 0.24 mmol, 84% yield). MS (ESI⁺) *m/z* 251 (M+H)⁺.

Example 187C: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(4-chlorophenyl)bicyclo[2.1.1]hexane-1-carboxamide

The reaction and purification conditions described in Example 48 substituting the product of Example 187B for (5-(difluoromethoxy)pyridin-2-yl)methanamine, and 2-(4-chloro-3-fluorophenoxy)acetic acid for the product of Example 18A gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.48 (s, 1H), 8.54 (s, 1H), 7.69 – 7.62 (m, 2H), 7.46 (t, J = 8.9 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.04 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.46 (s, 2H), 2.10 – 2.03 (m, 2H), 1.91 – 1.82 (m, 4H), 1.80 – 1.75 (m, 2H); MS (ESI⁺) *m/z* 437 (M+H)⁺.

Example 188: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 287)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 10.57 (s, 1H), 8.76 (s, 1H), 8.42 (d, J = 3.0 Hz, 1H), 8.16 (dd, J = 9.2, 0.6 Hz, 1H), 7.90 (ddd, J = 9.2, 3.0, 1.1 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (s, 2H), 2.36 (s, 6H); MS (ESI⁺) *m/z* 474 (M+H)⁺.

Example 189: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[2.1.1]hexane-1-carboxamide (Compound 288)

Example 189A: tert-butyl (4-((5-(trifluoromethoxy)pyridin-2-yl)carbamoyl)bicyclo[2.1.1]hexan-1-yl)carbamate

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The reaction and purification conditions described in Example 180 substituting 4-((*tert*-butoxycarbonyl)amino)bicyclo[2.1.1]hexane-1-carboxylic acid (Enamine) for the product of Example 158B gave the title compound. MS (ESI⁺) *m/z* 402 (M+H)⁺.

Example 189B: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[2.1.1]hexane-1-carboxamide

Trifluoroacetic acid (0.25 mL, 3.24 mmol) was added to the product of Example 189A (30 mg, 0.075 mmol), and the mixture was stirred at ambient temperature. After 30 minutes, dichloromethane (2 mL) was added followed by dropwise addition of aqueous sodium carbonate (1.0 M, 10 mL) over a period of 2 minutes. In a separate vial, 2-(4-chloro-3-fluorophenoxy)acetic acid (18.4 mg, 0.09 mmol, Aldlab) was suspended in dichloromethane (2 mL) and 1 drop of *N,N*-dimethylformamide was added followed by oxalyl chloride (2 M solution in dichloromethane, 0.075 mL). After stirring for 10 minutes at ambient temperature, the resulting clear solution was added in one portion to the fast stirring suspension from the previous step and was kept stirring for 20 minutes. The layers were separated, and the organic phase was dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was taken up in *N,N*-dimethylformamide (2mL), filtered through a glass microfiber frit, and purified by preparative HPLC [YMC TriArt™ C18 Hybrid 20 μm column, 25 × 250 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 crude product which was further purified by preparative HPLC [Waters XBridge™ C18 5 μm OBD column, 30 × 100 mm, flow rate 40 mL/minute, 5-100% gradient of MeOH in buffer (0.025 M aqueous ammonium bicarbonate, adjusted to pH 10 with ammonium hydroxide)] to give the title compound (15 mg, 0.03 mmol, 41% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.28 (s, 1H), 8.42 (d, J = 2.9 Hz, 1H), 8.19 (d, J = 9.2 Hz, 1H), 7.89 (dd, J = 8.9, 2.4 Hz, 1H), 7.34 (s, 1H), 2.11 – 1.98 (m, 2H), 1.95 – 1.86 (m, 2H), 1.82 – 1.67 (m, 4H), 1.39 (s, 9H); MS (ESI⁺) *m/z* 402 (M+H)⁺.

Example 190: 3-[2-(3,4-dichlorophenoxy)acetamido]-*N*-(pyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 289)

The reaction and purification conditions described in Example 180 substituting the product of Example 49A for the product of Example 158B, and 2-aminopyridine for (5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.24 (s, 1H), 8.75 (s, 1H), 8.33 (ddd, J = 4.9, 2.0, 0.9 Hz, 1H), 8.04 (dt, J = 8.4, 1.0 Hz, 1H), 7.78 (ddd, J = 8.9, 7.3, 1.9 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H), 7.27 (d, J = 2.9 Hz, 1H), 7.11

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(ddd, J = 7.3, 4.9, 1.0 Hz, 1H), 7.00 (dd, J = 8.9, 2.9 Hz, 1H), 4.49 (s, 2H), 2.35 (br s, 5H); MS (ESI⁺) *m/z* 406 (M+H)⁺.

Example 191: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(pyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 290)

5 The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 2-aminopyridine for (5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.24 (s, 1H), 8.75 (s, 1H), 8.33 (ddd, J = 4.9, 2.0, 0.9 Hz, 1H), 8.04 (dt, J = 8.5, 1.0 Hz, 1H), 7.78 (ddd, J = 8.8, 7.4, 1.9 Hz, 1H), 7.50 (t, J = 8.8 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.86 (ddd, 10 J = 9.0, 2.8, 1.2 Hz, 1H), 4.48 (s, 2H), 2.35 (s, 6H); MS (ESI⁺) *m/z* 390 (M+H)⁺.

Example 192: 3-[2-(3,4-dichlorophenoxy)acetamido]-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 291)

 The reaction and purification conditions described in Example 180 substituting the product of Example 49A for the product of Example 158B gave the title compound. ¹H NMR 15 (400 MHz, DMSO-*d*₆) δ ppm 10.59 (s, 1H), 8.76 (s, 1H), 8.44 – 8.42 (m, 1H), 8.17 (dd, J = 9.2, 0.6 Hz, 1H), 7.90 (ddd, J = 9.2, 3.2, 1.1 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H), 7.27 (d, J = 2.9 Hz, 1H), 7.00 (dd, J = 9.0, 2.9 Hz, 1H), 4.50 (s, 2H), 2.36 (s, 6H); MS (ESI⁺) *m/z* 490 (M+H)⁺.

Example 193: 4-[2-(3,4-dichlorophenoxy)acetamido]-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[2.1.1]hexane-1-carboxamide (Compound 292)

20 *Example 193A: 4-amino-N-(5-(trifluoromethoxy)pyridin-2-yl)bicyclo[2.1.1]hexane-1-carboxamide, trifluoroacetic acid*

 The product of Example 189A (60 mg, 0.15 mmol) was dissolved in dichloromethane (0.5 mL) and trifluoroacetic acid (0.5 mL, 6.49 mmol) was added. After stirring at ambient temperature for 15 minutes, the resulting solution was concentrated under reduced pressure to 25 give the title compound. MS (ESI⁺) *m/z* 302 (M+H)⁺.

Example 193B: 4-[2-(3,4-dichlorophenoxy)acetamido]-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[2.1.1]hexane-1-carboxamide

 The reaction and purification conditions described in Example 48 substituting 2-(3,4-dichlorophenoxy)acetic acid (Aldrich) for the product of Example 18A, and the product of 30 Example 193A for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.59 (s, 1H), 8.76 (s, 1H), 8.44 – 8.42 (m, 1H), 8.17 (dd, J = 9.2, 0.6 Hz, 1H), 7.90 (ddd, J = 9.2, 3.2, 1.1 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H), 7.27 (d, J = 2.9 Hz, 1H), 7.00 (dd, J = 9.0, 2.9 Hz, 1H), 4.50 (s, 2H), 2.36 (s, 6H); MS (ESI⁺) *m/z* 490 (M+H)⁺.

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Example 194: 4-{2-[(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)oxy]acetamido}-*N*-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[2.1.1]hexane-1-carboxamide (Compound 293)

Example 194A: 2,2-difluorobenzo[d][1,3]dioxol-5-ol

To a cold solution of 5-bromo-2,2-difluorobenzo[d][1,3]dioxole (5.75 mL, 42.2 mmol) in tetrahydrofuran (80 mL) was added a 2.0 M solution of isopropylmagnesium chloride in tetrahydrofuran (28.1 mL, 56.1 mmol) within 5-10 minutes while maintaining the temperature in the range of 10-20 °C. The reaction mixture was stirred at the same temperature for another 15 minutes and then allowed to attain room temperature with continued overnight stirring. The reaction mixture was cooled with an ice bath, triisopropyl borate (12.74 mL, 54.9 mmol) was added dropwise over 2 minutes, and stirring at room temperature was continued for 30 minutes. The reaction mixture was cooled to 10 °C and 10% H₂SO₄ solution (50 mL) was added slowly which resulted in a slight exotherm to 20 °C. After stirring for 15 minutes, the mixture was partitioned between water and ethyl acetate, and the combined organic extracts were washed with saturated NaHCO₃ solution. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated. The residue was dissolved in 100 mL of *tert*-butyl methyl ether and cooled to 0 °C. 30% Hydrogen peroxide solution in water (5.39 mL, 52.7 mmol) was added slowly followed by water (60 mL), and the mixture was stirred overnight while warming up to ambient temperature. The reaction mixture was diluted with ethyl acetate and washed twice with sodium thiosulfate solution and brine. The organic layer was dried with magnesium sulfate and filtered. The filtrate was concentrated, and the residue was purified on silica gel (0~50% ethyl acetate in heptane) to give 6.43 g of the title compound as an amber oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.75 (s, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 8.7, 2.5 Hz, 1H); MS (ESI-) *m/z* 173.1 (M-H)⁻.

Example 194B: 2-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)oxy)acetic acid

To a solution of Example 194A (3.0 g, 17.23 mmol) in *N,N*-dimethylformamide (30 mL) at ambient temperature was added potassium carbonate (4.76 g, 34.5 mmol) and *tert*-butyl bromoacetate (2.91 mL, 19.82 mmol). This mixture was warmed to 65 °C and was allowed to stir for 1.5 hours. The mixture was allowed to cool to ambient temperature and was then partitioned between ethyl acetate (50 mL) and H₂O (50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give 5.5 g of *tert*-butyl 2-((2,2-difluorobenzo[d][1,3]dioxol-5-yl)oxy)acetate, which was used without further purification. To a mixture of *tert*-butyl 2-((2,2-difluorobenzo[d][1,3]dioxol-5-

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yl)oxy)acetate (5.0 g, 17.35 mmol) in methanol (60 mL) and water (20.00 mL) was added NaOH (17.35 mL, 87 mmol, 5 M aqueous solution). This mixture was allowed to stir at ambient temperature for 2 hours, and then it was concentrated under reduced pressure. The residue was dissolved in water, and the pH was adjusted to ~1 with 1 N HCl. The resulting solid was collected by filtration to give the title compound (3.28 g, 14.13 mmol, 81% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.10 (s, 1H), 7.30 (d, *J* = 8.9 Hz, 1H), 7.13 (d, *J* = 2.6 Hz, 1H), 6.73 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.69 (s, 2H).

Example 194C: 4-{2-[(2,2-difluoro-2H-1,3-benzodioxol-5-yl)oxy]acetamido}-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[2.1.1]hexane-1-carboxamide

The reaction and purification conditions described in Example 48 substituting the product of Example 194B for the product of Example 18A, and the product of Example 193A for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.35 (s, 1H), 8.52 (s, 1H), 8.42 (dt, *J* = 2.9, 0.8 Hz, 1H), 8.20 (dd, *J* = 9.2, 0.6 Hz, 1H), 7.90 (ddd, *J* = 9.2, 3.0, 1.0 Hz, 1H), 7.33 (d, *J* = 8.9 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 6.78 (dd, *J* = 8.9, 2.6 Hz, 1H), 4.45 (s, 2H), 2.12 – 2.04 (m, 2H), 2.01 – 1.84 (m, 6H); MS (ESI⁺) *m/z* 516 (M+H)⁺.

Example 195: 3-{2-[(2,2-difluoro-2H-1,3-benzodioxol-5-yl)oxy]acetamido}-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 294)

Example 195A: tert-butyl (3-((5-(trifluoromethoxy)pyridin-2-yl)carbamoyl)bicyclo[1.1.1]pentan-1-yl)carbamate

The reaction and purification conditions described in Example 180 substituting 3-((tert-butoxycarbonyl)amino)bicyclo[1.1.1]pentane-1-carboxylic acid (Enamine) for the product of Example 158B gave the title compound. MS (ESI⁺) *m/z* 388 (M+H)⁺.

Example 195B: 3-amino-N-(5-(trifluoromethoxy)pyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide bistrifluoroacetate

The reaction and purification conditions described in Example 193A substituting the product of Example 195A for the product of Example 189A gave the title compound. MS (ESI⁺) *m/z* 288 (M+H)⁺.

Example 195C: 3-{2-[(2,2-difluoro-2H-1,3-benzodioxol-5-yl)oxy]acetamido}-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide

The reaction and purification conditions described in Example 48 substituting the product of Example 194B for the product of Example 18A, and the product of Example 195B for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz,

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DMSO-*d*₆) δ ppm 10.58 (s, 1H), 8.74 (s, 1H), 8.43 (dt, J = 3.0, 0.8 Hz, 1H), 8.17 (dd, J = 9.2, 0.6 Hz, 1H), 7.90 (ddd, J = 9.1, 3.0, 1.1 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 6.78 (dd, J = 8.9, 2.6 Hz, 1H), 4.45 (s, 2H), 2.36 (s, 6H); MS (ESI⁺) *m/z* 502 (M+H)⁺.

Example 196: 3-[2-(3,4-dichlorophenoxy)acetamido]-N-(pyridin-3-

5 **yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 295)**

The reaction and purification conditions described in Example 180 substituting the product of Example 49A for the product of Example 158B, and 3-aminopyridine for (5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.82 (s, 1H), 8.82 – 8.79 (m, 2H), 8.26 (dd, J = 4.7, 1.5 Hz, 1H), 8.05 (ddd, J = 8.4, 2.6, 1.5 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.34 (ddd, J = 8.3, 4.7, 0.8 Hz, 1H), 7.28 (d, J = 2.9 Hz, 1H), 7.00 (dd, J = 8.9, 2.9 Hz, 1H), 4.51 (s, 2H), 2.34 (s, 6H); MS (ESI⁺) *m/z* 406 (M+H)⁺.

Example 197: 3-[2-(3,4-dichlorophenoxy)acetamido]-N-(pyridin-4-

15 **yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 296)**

The reaction and purification conditions described in Example 180 substituting the product of Example 49A for the product of Example 158B, and 4-aminopyridine for (5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.94 (s, 1H), 8.80 (s, 1H), 8.45 – 8.39 (m, 2H), 7.66 – 7.61 (m, 2H), 7.56 (d, J = 8.9 Hz, 1H), 7.28 (d, J = 2.9 Hz, 1H), 7.00 (dd, J = 8.9, 2.9 Hz, 1H), 4.51 (s, 2H), 2.35 (s, 6H); MS (ESI⁺) *m/z* 406 (M+H)⁺.

20 **Example 198: N-[5-(trifluoromethoxy)pyridin-2-yl]-3-(2-[[6-(trifluoromethyl)pyridin-3-yl]oxy]acetamido)bicyclo[1.1.1]pentane-1-carboxamide (Compound 297)**

Example 198A: 2-((6-(trifluoromethyl)pyridin-3-yl)oxy)acetic acid

The reaction and purification conditions described in Example 194B substituting 6-(trifluoromethyl)pyridin-3-ol (Combi-Blocks) for the product of Example 194A gave the title compound. MS (DCI⁺) *m/z* 296 (M+NH₄)⁺.

Example 198B: N-[5-(trifluoromethoxy)pyridin-2-yl]-3-(2-[[6-(trifluoromethyl)pyridin-3-yl]oxy]acetamido)bicyclo[1.1.1]pentane-1-carboxamide

The reaction and purification conditions described in Example 48 substituting the product of Example 195B for (5-(difluoromethoxy)pyridin-2-yl)methanamine, and the product of Example 198A for the product of Example 18A gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.58 (s, 1H), 8.85 (s, 1H), 8.47 (d, J = 2.9 Hz, 1H), 8.43 (dt, J = 2.9, 0.8 Hz, 1H), 8.16 (dd, J = 9.1, 0.6 Hz, 1H), 7.92 – 7.88 (m, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.60 – 7.56 (m, 1H), 4.67 (s, 2H), 2.36 (s, 6H); MS (ESI⁺) *m/z* 490 (M+H)⁺.

Example 199: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[5-(difluoromethyl)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 298)*Example 199A: 5-(difluoromethyl)pyridin-2-amine*

To a solution of 6-aminonicotinaldehyde (0.2 g, 1.64 mmol) in CH₂Cl₂ (7.5 mL) at 0 °C
5 was added bis(2-methoxyethyl)aminosulfur trifluoride (0.91 mL, 4.9 mmol) in CH₂Cl₂ (5 mL)
dropwise via syringe pump over 10 minutes. The mixture was allowed to stir at 0 °C for 20
minutes, then the ice-bath was removed, and the mixture was allowed to warm to ambient
temperature. The mixture was then allowed to stir for an additional 90 minutes and was
quenched by slow addition of saturated, aqueous NaHCO₃ (25 mL) added via addition funnel
10 over 1 hour. The mixture was diluted with CH₂Cl₂ (15 mL), and the layers were separated. The
aqueous layer was extracted with CH₂Cl₂ (3 × 7 mL). The combined organic fractions were
dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue
was purified via column chromatography (SiO₂, 50% ethyl acetate/heptanes) to give the title
compound (0.06 g, 0.42 mmol, 25% yield). MS (ESI⁺) *m/z* 145.1 (M+H)⁺.

15 *Example 199B: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[5-(difluoromethyl)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide*

To the product of Example 18A (0.06 g, 0.19 mmol) and 1-(fluoro(pyrrolidin-1-yl)methylene)pyrrolidin-1-ium hexafluorophosphate(V) (HATU, 0.091 g, 0.29 mmol) was added
a mixture of CH₂Cl₂ (0.3 mL) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.15 mL, 0.86 mmol).
20 This mixture was allowed to stir at ambient temperature for 30 minutes, and then the product of
Example 199A (0.050 g, 0.344 mmol) in CH₂Cl₂ (0.5 mL) was added. The vial was sealed and
the mixture was warmed to 78 °C and was allowed to stir for 16 hours. The mixture was
allowed to cool to ambient temperature, then was dissolved in ethyl acetate, and filtered through
silica gel with ethyl acetate. The filtrate was concentrated under reduced pressure and was
25 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 compound (0.04 g,
0.091 mmol, 48% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.55 (s, 1H), 8.74 (s, 1H),
8.50 (d, J = 2.2 Hz, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.02 7.91 (m, 1H), 7.46 (t, J = 8.9 Hz, 1H),
30 7.25 6.89 (m, 2H), 6.83 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.45 (s, 2H), 2.34 (s, 6H); MS (ESI⁺) *m/z*
440.1 (M+H)⁺.

Example 200: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(5-methylpyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 299)

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To the product of Example 18A (0.06 g, 0.19 mmol) and 1-(fluoro(pyrrolidin-1-yl)methylene)pyrrolidin-1-ium hexafluorophosphate(V) (HATU, 0.091 g, 0.29 mmol) was added a mixture of CH₂Cl₂ (0.5 mL) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.15 mL, 0.86 mmol). This mixture was allowed to stir at ambient temperature for 30 minutes, and then 2-amino-5-methylpyridine (0.041 g, 0.38 mmol) was added. The vial was sealed, and the mixture was warmed to 78 °C and was allowed to stir for 16 hours. The mixture was allowed to cool to ambient temperature, then was dissolved in ethyl acetate, and filtered through silica gel with ethyl acetate. The filtrate was concentrated under reduced pressure and was 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 compound (0.035 g, 0.087 mmol, 45% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.10 (s, 1H), 8.71 (s, 1H), 8.12 (d, J = 2.2 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.56 (dd, J = 8.6, 2.4 Hz, 1H), 7.47 (t, J = 8.9 Hz, 1H), 7.05 (dd, J = 11.4, 2.8 Hz, 1H), 6.83 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 2.30 (s, 6H), 2.21 (s, 3H); MS (ESI⁺) *m/z* 404.0 (M+H)⁺.

Example 201: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(pyridin-3-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 300)

The reaction and purification conditions described in Example 48 substituting 3-aminopyridine for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.80 (s, 1H), 8.81 – 8.78 (m, 2H), 8.26 (dd, J = 4.7, 1.5 Hz, 1H), 8.05 (ddd, J = 8.3, 2.6, 1.5 Hz, 1H), 7.51 (t, J = 8.9 Hz, 1H), 7.34 (ddd, J = 8.4, 4.7, 0.8 Hz, 1H), 7.09 (dd, J = 11.4, 2.9 Hz, 1H), 6.87 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.50 (s, 2H), 2.34 (s, 6H); MS (ESI⁺) *m/z* 390 (M+H)⁺.

Example 202: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(pyridin-4-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 301)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 4-aminopyridine for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.94 (s, 1H), 8.80 (s, 1H), 8.44 – 8.40 (m, 2H), 7.66 – 7.62 (m, 2H), 7.51 (t, J = 8.9 Hz, 1H), 7.09 (dd, J = 11.4, 2.8 Hz, 1H), 6.87 (ddd, J = 8.8, 2.8, 1.2 Hz, 1H), 4.50 (s, 2H), 2.35 (s, 6H); MS (ESI⁺) *m/z* 390 (M+H)⁺.

Example 203: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(5-methoxypyrimidin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 302)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 2-amino-5-methoxypyrimidine (Combi-Blocks) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.29 (s, 1H), 8.74 (s, 1H), 8.44 (s, 2H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (s, 2H), 3.88 (s, 3H), 2.32 (s, 6H); MS (ESI⁺) *m/z* 421 (M+H)⁺.

Example 204: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(5-methoxypyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 303)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 2-amino-5-methoxypyridine (ArkPharm) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.11 (s, 1H), 8.74 (s, 1H), 8.03 (dd, J = 3.2, 0.7 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.42 (dd, J = 9.1, 3.1 Hz, 1H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 (ddd, J = 8.9, 2.8, 1.2 Hz, 1H), 4.48 (s, 2H), 3.80 (s, 3H), 2.33 (s, 6H); MS (ESI⁺) *m/z* 420 (M+H)⁺.

Example 205: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(5-methylpyrazin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 304)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 5-methylpyrazin-2-amine (AK Scientific) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.51 (s, 1H), 9.14 (d, J = 1.5 Hz, 1H), 8.76 (s, 1H), 8.32 – 8.28 (m, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.49 (s, 2H), 2.45 (s, 3H), 2.36 (s, 6H); MS (ESI⁺) *m/z* 405 (M+H)⁺.

Example 206: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(5-cyanopyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 305)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 2-amino-5-cyanopyridine (Aldrich) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 10.86 (s, 1H), 8.81 (dd, J = 2.3, 0.9 Hz, 1H), 8.77 (s, 1H), 8.28 – 8.19 (m, 2H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (s, 2H), 2.38 (s, 6H); MS (ESI⁺) *m/z* 415 (M+H)⁺.

Example 207: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(5-cyclopropylpyridin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 306)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 5-cyclopropylpyridin-2-amine (CombiPhos) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 10.15 (s, 1H), 8.75 (s, 1H), 8.16 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.41 (dd, J = 8.7, 2.5 Hz, 1H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.48 (s, 2H), 2.33 (s, 6H), 1.92 (tt, J = 8.3, 5.1 Hz, 1H), 1.00 – 0.90 (m, 2H), 0.74 – 0.63 (m, 2H); MS (ESI⁺) *m/z* 430 (M+H)⁺.

Example 208: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(5-ethoxypyrazin-2-yl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 307)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 5-ethoxypyrazin-2-amine (ArkPharm) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.36 (s, 1H), 8.77 (d, J = 1.5 Hz, 1H), 8.75 (s, 1H), 8.08 (d, J = 1.5 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.48 (s, 2H), 4.32 (q, J = 7.0 Hz, 2H), 2.34 (s, 6H), 1.33 (t, J = 7.0 Hz, 3H); MS (ESI⁺) *m/z* 435 (M+H)⁺.

Example 209: 3-[2-(3,4-difluorophenoxy)acetamido]-N-[5-(trifluoromethoxy)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 308)

The reaction and purification conditions described in Example 48 substituting 2-(3,4-difluorophenoxy)acetic acid (Combi-Blocks) for the product of Example 18A, and the product of Example 195B for (5-(difluoromethoxy)pyridin-2-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.58 (s, 1H), 8.74 (s, 1H), 8.43 (d, J = 2.9 Hz, 1H), 8.17 (dd, J = 9.1, 0.6 Hz, 1H), 7.90 (dd, J = 8.9, 2.9 Hz, 1H), 7.37 (dt, J = 10.7, 9.3 Hz, 1H), 7.10 (ddd, J = 12.6, 6.7, 3.0 Hz, 1H), 6.83 – 6.78 (m, 1H), 4.45 (s, 2H), 2.36 (s, 6H); MS (APCI⁺) *m/z* 458 (M+H)⁺.

Example 210: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[5-(difluoromethoxy)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 309)

The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 5-(difluoromethoxy)pyridin-2-amine dihydrochloride (Oakwood) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.79 (s, 1H), 8.19 (d, J = 2.9 Hz, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.62 (dd, J = 9.1, 2.9 Hz, 1H), 7.38 (t, J = 8.7 Hz, 1H), 6.97 – 6.91 (m, 1H),

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6.84 (t, J = 73.0 Hz, 1H), 6.84 – 6.80 (m, 1H), 4.49 (s, 2H), 2.46 (s, 6H); MS (ESI⁺) *m/z* 456 (M+H)⁺.

Example 211: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(2,2,2-trifluoroethoxy)pyridin-3-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 310)

5 The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and 6-(2,2,2-trifluoroethoxy)pyridin-3-amine (Enamine) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.74 (s, 1H), 8.79 (s, 1H), 8.43 (d, J = 2.6 Hz, 1H), 8.01 (dd, J = 8.9, 2.7 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.09 (dd, J = 11.4, 2.8 Hz, 1H), 6.96 (d, J = 8.9 Hz, 10 1H), 6.87 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.94 (q, J = 9.1 Hz, 2H), 4.49 (s, 2H), 2.33 (s, 6H); MS (ESI⁺) *m/z* 488 (M+H)⁺.

Example 212: ethyl 6-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carbonyl}amino)pyridine-3-carboxylate (Compound 311)

 The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and ethyl 6-aminonicotinate 15 (ArkPharm) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.74 (s, 1H), 8.85 (dd, J = 2.4, 0.8 Hz, 1H), 8.77 (s, 1H), 8.28 (dd, J = 8.8, 2.4 Hz, 1H), 8.19 (dd, J = 8.9, 0.8 Hz, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.48 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 2.38 (s, 6H), 20 1.33 (t, J = 7.1 Hz, 3H); MS (ESI⁺) *m/z* 462 (M+H)⁺.

Example 213: ethyl 2-({3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carbonyl}amino)-1,3-thiazole-4-carboxylate (Compound 312)

 The reaction and purification conditions described in Example 180 substituting the product of Example 18A for the product of Example 158B, and ethyl 2-aminothiazole-4- 25 carboxylate (Alfa Aesar) for 5-(trifluoromethoxy)pyridin-2-amine gave the title compound. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 12.58 (s, 1H), 8.79 (s, 1H), 8.06 (s, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.3, 2.9 Hz, 1H), 6.86 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.49 (s, 2H), 4.28 (q, J = 7.1 Hz, 2H), 2.37 (s, 6H), 1.29 (t, J = 7.1 Hz, 3H); MS (ESI⁺) *m/z* 468 (M+H)⁺.

Example 214: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[4-(hydroxymethyl)pyridin-2-yl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 313)

30 The reaction and purification conditions described in Example 48 substituting 4-(*tert*-butyl-dimethyl-silanyloxymethyl)-pyridin-2-ylamine (Matrix) for 5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.16 (s,

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1H), 8.75 (s, 1H), 8.23 (dd, J = 5.0, 0.8 Hz, 1H), 8.03 8.01 (m, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 7.06 7.03 (m, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 5.40 (t, J = 5.7 Hz, 1H), 4.51 (d, J = 5.5 Hz, 2H), 4.48 (s, 2H), 2.34 (s, 6H); MS (ESI⁺) *m/z* 420 (M+H)⁺.

Example 215: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-(2-

5 fluorophenyl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 314)

To a mixture of 3-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[1.1.1]pentane-1-carboxylic acid (40 mg, 0.128 mmol, Example 18A), and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 48.5 mg, 0.128 mmol) was added 2-fluoroaniline (22.67 mg, 0.204 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (49.4 mg, 0.383 mmol) in *N,N*-dimethylformamide (1 mL). The mixture was stirred at room temperature for 60 minutes. Then water (0.02 mL) was added to quench the reaction. The product was purified by flash column chromatography on silica gel (40g) eluted with 20 to 60% ethyl acetate in heptane to give titled compound (23 mg, 0.057 mmol, 44%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.42 (s, 1H), 8.74 (s, 1H), 7.50 (m, 1H), 7.48 (t, J = 8 Hz, 1H), 7.17 (m, 3H), 7.05 (dd, J = 9, 3 Hz, 1H), 6.83 (br d, J = 8 Hz, 1H), 4.46 (s, 2H), 2.30 (s, 6H); MS (ESI⁺) *m/z* 407 (M+H)⁺.

Example 216: 5-(trifluoromethoxy)-*N*-(3-{[5-(trifluoromethoxy)pyridin-2-

yl]carbamoyl}bicyclo[1.1.1]pentan-1-yl)pyridine-2-carboxamide (Compound 315)

The reaction and purification conditions described in Example 48 substituting 5-(trifluoromethoxy)picolinic acid (ArkPharm) for the product of Example 18A, and the product of Example 195B for (5-(difluoromethoxy)pyridin-2-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 10.61 (s, 1H), 9.41 (s, 1H), 8.71 (dt, J = 2.7, 0.8 Hz, 1H), 8.44 (dt, J = 2.9, 0.8 Hz, 1H), 8.20 – 8.17 (m, 1H), 8.16 – 8.13 (m, 1H), 8.11 – 8.06 (m, 1H), 7.94 – 7.88 (m, 1H), 2.45 (s, 6H); MS (ESI⁺) *m/z* 477 (M+H)⁺.

25 Example 217: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-hydroxy-*N*-[5-

(trifluoromethyl)pyridin-2-yl]bicyclo[2.2.2]octane-1-carboxamide (Compound 316)

The title compound was prepared using the methodologies described in Example 7 substituting 5-(trifluoromethyl)pyridin-2-amine for (5-(trifluoromethyl)pyridin-2-yl)methanamine. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.73 (s, 1H), 8.91 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 8.7, 2.5 Hz, 1H), 7.80 (d, J = 8.7 Hz, 1H), 7.54 (s, 1H), 7.45 (t, J = 8.9 Hz, 1H), 7.00 (dd, J = 11.4, 2.8 Hz, 1H), 6.79 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 5.16 (d, J = 4.7 Hz, 1H), 4.42 (s, 2H), 4.23 (m, 1H), 2.34 2.23 (m, 1H), 2.18 (t, J = 11.4 Hz, 1H), 1.94 1.63 (m, 8H); MS (ESI⁺) *m/z* 516.2 (M+H)⁺.

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Example 218: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[2-(4-chlorophenyl)-2-hydroxypropyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 317)

3-(2-(4-Chloro-3-fluorophenoxy)acetamido)bicyclo[1.1.1]pentane-1-carboxylic acid (Example 18A, 200 mg, 0.638 mmol) triethylamine (0.267 mL, 1.913 mmol), and 1-amino-2-(4-chlorophenyl)propan-2-ol (142 mg, 0.765 mmol) were combined with *N,N*-dimethylformamide (3 mL) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 339 mg, 0.893 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 14 hours and purified by preparative 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 30 minutes, at a flow rate of 50 mL/minute) to give the title compound (273 mg, 0.567 mmol, 89 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.69 (s, 1H), 7.54 - 7.38 (m, 4H), 7.38 - 7.31 (m, 2H), 7.07 (dd, *J* = 11.3, 2.9 Hz, 1H), 6.85 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.46 (s, 2H), 3.36 - 3.23 (m, 2H), 2.11 (s, 6H), 1.36 (s, 3H); MS(APCI) *m/z* 481.2 (M+H)⁺.

Example 219: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[1-(4-chlorophenyl)-2-hydroxyethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 318) The title compound was prepared using the protocol described for Example 218 substituting 2-amino-2-(4-chlorophenyl)ethanol hydrochloride for 1-amino-2-(4-chlorophenyl)propan-2-ol. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.34 (t, *J* = 8.6 Hz, 3H), 7.25 (t, *J* = 9.0 Hz, 2H), 6.88 (s, 1H), 6.77 (dd, *J* = 10.2, 2.8 Hz, 1H), 6.68 (ddd, *J* = 8.9, 2.9, 1.3 Hz, 1H), 6.27 (d, *J* = 7.2 Hz, 1H), 5.03 (dt, *J* = 7.2, 4.6 Hz, 1H), 4.40 (s, 2H), 3.90 (d, *J* = 4.7 Hz, 2H), 2.44 (s, 6H) ; MS(APCI) *m/z* 467.2 (M+H)⁺.

Example 220: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(5,6-difluoro-1*H*-benzimidazol-2-yl)methyl]-3-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 319)

To a mixture of Example 175H (100 mg, 0.270 mmol), (5,6-difluoro-1*H*-benzo[*d*]imidazol-2-yl)methanamine (52.0 mg, 0.284 mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (0.142 mL, 0.811 mmol) in *N,N*-dimethylformamide (2.5 mL), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (129 mg, 0.338 mmol) was added and stirred at ambient temperature for 60 minutes. Volatiles were removed, and the residue was dissolved in a mixture of methanol/dichloromethane (1:1, 5 mL). To this solution, sodium tetrahydroborate (102 mg, 2.70 mmol) was added, and the mixture was stirred at ambient temperature for 30 minutes. Volatiles were removed, and the residue was purified by HPLC

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(Phenomenex® Luna® C18(2) 10 µm 100Å AXIA™ column (250 mm × 50 mm). A 20-95% gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used over 25 minutes, at a flow rate of 50 mL/minute) to give 63 mg of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.15 (t, J = 5.5 Hz, 1H), 7.67 (t, J = 8.8 Hz, 2H), 7.45 (t, J = 8.9 Hz, 1H), 7.27 (s, 1H), 7.02 (dd, J = 11.4, 2.9 Hz, 1H), 6.79 (dd, J = 9.1, 2.8 Hz, 1H), 4.46 (d, J = 8.0 Hz, 2H), 4.44 (s, 2H), 4.00 (dd, J = 9.4, 3.1 Hz, 1H), 2.17 – 2.07 (m, 1H), 1.98 (td, J = 11.8, 4.6 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.80 (t, J = 7.6 Hz, 1H), 1.79 – 1.71 (m, 1H), 1.74 – 1.65 (m, 3H), 1.64 (dd, J = 12.8, 4.6 Hz, 1H), 1.56 (dt, J = 13.5, 3.1 Hz, 1H); MS (ESI+) *m/z* 537.0 (M+H)⁺.

Example 221: *N*-(2-amino-2-oxoethyl)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(4-chloro-3-fluorophenyl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 320)

Example 221A: 2-((4-chloro-3-fluorobenzyl)amino)acetamide

A 20 mL vial was charged with dimethyl sulfoxide (5 mL), 4-chloro-3-fluorobenzyl bromide (500 mg, 2.24 mmol, Enamine), glycineamide hydrochloride (200 mg, 1.81 mmol, Enamine) and Hunig's base (2.0 mL). The vial was sealed and stirred at 85 °C for 18 hours. The reaction mixture was cooled to ambient temperature and methanol (3 mL) was added. The resulting solution was filtered through a glass microfiber frit 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 compound (80 mg, 0.37 mmol, 20 % yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.47 (t, J = 8.0 Hz, 1H), 7.37 (dd, J = 10.6, 1.9 Hz, 1H), 7.26 (br s, 1H), 7.16 (ddd, J = 8.2, 1.9, 0.8 Hz, 1H), 6.99 (br s, 1H), 3.64 (s, 2H), 2.98 (s, 2H), 2.62 (br s, 1H); MS (APCI⁺) *m/z* 217 (M+H)⁺.

Example 221B: N-(2-amino-2-oxoethyl)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-chloro-3-fluorophenyl)methyl]bicyclo[2.2.2]octane-1-carboxamide

To a 4ml vial was added *N,N*-dimethylformamide (1.5 mL), triethylamine (0.032 mL), the product of Example 211A (9.8 mg, 0.045 mmol), the product of Example 158B (16 mg, 0.045 mmol) and HATU (25.8 mg, 0.068 mmol) in sequential order. The resulting reaction mixture was stirred at ambient temperature for 1 hour and more product of Example 158B (16 mg, 0.045 mmol) was added followed by (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP, 24 mg, 0.045 mmol). After stirring at ambient temperature for 18

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hours, water (0.3 mL) was added, and the resulting solution was filtered through a glass microfiber frit 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 (8 mg, 0.014 mmol, 32 % yield). ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.45 (t, J = 8.0 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.13 (dd, J = 10.5, 2.0 Hz, 1H), 7.04 – 7.01 (m, 1H), 6.97 – 6.93 (m, 1H), 6.92 (br s, 1H), 6.83 – 6.78 (m, 1H), 6.69 (br s, 2H), 4.58 (s, 2H), 4.39 (d, J = 2.3 Hz, 2H), 3.92 (s, 2H), 1.94 – 1.83 (m, 12H); MS (APCI⁺) *m/z* 554 (M+H)⁺.

Example 222: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-hydroxy-*N*-[(6-methoxypyridazin-3-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 321)

To a mixture of Example 175H (0.028 g, 0.076 mmol), (6-methoxypyridazin-3-yl)methanamine hydrochloride (0.014 g, 0.080 mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (0.040 mL, 0.23 mmol) in *N,N*-dimethylformamide (0.7 mL) was added 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.036 g, 0.095 mmol) followed by stirring at ambient temperature for 16 hours. The reaction mixture was concentrated, and the residue was taken up in dichloromethane (0.7 mL) and methanol (0.7 mL). To this solution was added sodium tetrahydroborate (0.029 g, 0.76 mmol), and the reaction mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was concentrated, and 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 0.1% trifluoroacetic acid/water) to give the title compound (0.030 g, 0.061 mmol, 80% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.13 (t, J = 5.9 Hz, 1H), 7.48 (t, J = 8.9 Hz, 1H), 7.41 (d, J = 9.1 Hz, 1H), 7.30 (s, 1H), 7.20 (d, J = 9.1 Hz, 1H), 7.06 (dd, J = 11.4, 2.8 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (s, 2H), 4.42 (d, J = 5.9 Hz, 2H), 4.03 (dd, J = 9.6, 3.2 Hz, 1H), 4.00 (s, 3H), 2.14 (ddd, J = 13.4, 9.3, 2.3 Hz, 1H), 2.02 (ddd, J = 12.5, 10.8, 4.6 Hz, 1H), 1.89 (m, 1H), 1.93 1.61 (m, 5H), 1.57 (dt, J = 13.5, 3.0 Hz, 1H); MS (ESI⁺) *m/z* 493 (M+H)⁺.

Example 223: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(6-methoxypyridazin-3-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 322)

The methodologies described in Example 48, substituting (6-methoxypyridazin-3-yl)methanamine hydrochloride for (5-(difluoromethoxy)pyridin-2-yl)methanamine and purifying

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by preparative HPLC (Waters XBridge™ C18 5 μ m OBD column, 30 $\times$ 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 8.73 (s, 1H), 8.49 (t, J = 6.0 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.22 (d, J = 9.1 Hz, 1H), 7.07 (dd, J = 11.3, 2.9 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.47 (s, 2H), 4.45 (d, J = 6.0 Hz, 2H), 4.01 (s, 3H), 2.22 (s, 6H); MS (ESI $^+$) m/z 435 (M+H) $^+$.

Example 224: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5-fluoro-1-methyl-1H-benzimidazol-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 323)

The reaction and purification conditions described in Example 48 substituting the product of Example 158B for the product of Example 18A, and (5-fluoro-1-methyl-1H-benzo[d]imidazol-2-yl)methanamine dihydrochloride (Aldrich) for (5-(difluoromethoxy)pyridin-2-yl)methanamine gave the title compound. ^1H NMR (500 MHz, DMSO- d_6) δ ppm 8.03 (t, J = 5.4 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.38 (dd, J = 9.8, 2.5 Hz, 1H), 7.10 (ddd, J = 9.8, 8.8, 2.5 Hz, 1H), 7.03 (dd, J = 11.4, 2.9 Hz, 1H), 6.81 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.51 (d, J = 5.4 Hz, 2H), 4.44 (s, 2H), 3.73 (s, 3H), 1.89 – 1.73 (m, 12H); MS (APCI $^+$) m/z 517 (M+H) $^+$.

Example 225: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5,6-difluoro-1H-benzimidazol-2-yl)methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 324)

The title compound was prepared using the methodologies described above. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.12 (s, 1H), 8.02 (t, J = 5.7 Hz, 1H), 7.53 – 7.39 (m, 4H), 6.99 (dd, J = 11.4, 2.8 Hz, 1H), 6.78 (dd, J = 9.0, 2.8 Hz, 1H), 4.40 (s, 2H), 4.37 (d, J = 5.6 Hz, 2H), 1.85 – 1.70 (m, 12H); MS (APCI $^+$) m/z 521 (M+H) $^+$.

Example 226: N-[(6-chloro-1H-benzimidazol-2-yl)methyl]-4-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[2.2.2]octane-1-carboxamide (Compound 325)

The title compound was prepared using the methodologies described above. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 12.08 (br s, 1H), 8.02 (t, J = 5.7 Hz, 1H), 7.53 – 7.40 (m, 4H), 7.12 (dd, J = 8.5, 2.1 Hz, 1H), 6.99 (dd, J = 11.4, 2.9 Hz, 1H), 6.77 (ddd, J = 9.0, 3.0, 1.2 Hz, 1H), 4.44 – 4.35 (m, 4H), 1.85 – 1.70 (m, 12H); MS (APCI $^+$) m/z 519 (M+H) $^+$.

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Example 227: (2S)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(4-chloro-3-fluorophenyl)-2-oxoethyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 326)

The title compound was prepared using the methodologies described for Example 178. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.03 - 7.93 (m, 2H), 7.85 - 7.74 (m, 2H), 7.55 - 7.44 (m, 2H), 7.03 (dd, J = 11.4, 2.9 Hz, 1H), 6.81 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 5.00 (d, J = 3.8 Hz, 1H), 4.54 (dd, J = 5.4, 1.8 Hz, 2H), 4.45 (s, 2H), 4.06 (d, J = 9.2 Hz, 1H), 2.31 - 2.18 (m, 1H), 2.15 - 2.01 (m, 1H), 1.98 - 1.86 (m, 1H), 1.82 - 1.65 (m, 5H), 1.65 - 1.48 (m, 2H); MS (APCI) *m/z* 541.2 (M+H)⁺.

Example 228: N-[(1H-benzimidazol-2-yl)methyl]-4-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[2.2.2]octane-1-carboxamide (Compound 327)

The title compound was prepared using the methodologies described above. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.98 (s, 1H), 8.03 (t, J = 5.7 Hz, 1H), 7.53 - 7.44 (m, 4H), 7.16 - 7.10 (m, 2H), 7.03 (dd, J = 11.4, 2.8 Hz, 1H), 6.81 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.45 - 4.43 (m, 4H), 1.89 - 1.76 (m, 12H); MS (APCI⁺) *m/z* 485 (M+H)⁺.

Example 229: {2-[(3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carbonyl]amino)methyl]-5,6-difluoro-1H-benzimidazol-1-yl}acetic acid (Compound 328)

Example 229A: tert-butyl 2-(2-((3-(2-(4-chloro-3-fluorophenoxy)acetamido)bicyclo[1.1.1]pentane-1-carboxamido)methyl)-5,6-difluoro-1H-benzimidazol-1-yl)acetate

To a solution of potassium hydroxide (0.053 g, 0.95 mmol, crushed pellets) in dimethyl sulfoxide (0.53 mL), which had stirred for 15 minutes, was added Example 232 (0.114 g, 0.238 mmol). The reaction mixture stirred for 1 hour, and then *tert*-butyl bromoacetate (0.14 mL, 0.95 mmol) was added. This reaction mixture was allowed to stir at ambient temperature for 1 hour, was diluted with H₂O and diethyl ether, and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 5 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The residue was then 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 give the title compound (0.10 g, 0.17 mmol, 71% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.71 (s, 1H), 8.51 (t, J = 5.8 Hz, 1H), 7.70 (ddd, J = 11.0, 9.2, 7.3 Hz, 2H), 7.49 (t, J =

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8.9 Hz, 1H), 7.07 (dd, J = 11.4, 2.8 Hz, 1H), 6.85 (dt, J = 9.1, 1.9 Hz, 1H), 5.15 (s, 2H), 4.46 (s, 2H), 4.44 (d, J = 5.9 Hz, 2H), 2.19 (s, 6H), 2.07 (s, 2H), 1.42 (s, 9H); MS (ESI⁺) *m/z* 593 (M+H)⁺.

Example 229B: {2-[(3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-
5 carbonyl)amino)methyl]-5,6-difluoro-1H-benzimidazol-1-yl}acetic acid

To a solution of Example 229A (0.10 g, 0.17 mmol) in tetrahydrofuran (0.19 mL) and water (0.063 mL) was added lithium hydroxide (0.012 g, 0.51 mmol), and the resulting mixture was stirred at ambient temperature for 1 hour. Then the mixture was concentrated. The residue was diluted with *N,N*-dimethylformamide/water (3:1, 1.2 mL) and purified by preparative HPLC
10 [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 (0.020 g, 0.037 mmol, 22% yield). ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.73 (d, J = 2.1 Hz, 2H), 7.62 (ddd, J = 10.7, 7.4, 3.4 Hz, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.07 (dd, J = 11.4, 2.8 Hz, 1H), 6.85 (dd, J = 9.1, 2.8 Hz, 1H), 4.76
15 (s, 2H), 4.46 (s, 2H), 4.45 (d, J = 5.4 Hz, 2H), 2.18 (s, 6H); MS (ESI⁺) *m/z* 537 (M+H)⁺.

Example 230: 1-[2-(4-chloro-3-fluorophenoxy)acetamido]-2-(2-hydroxyethyl)-3-oxo-*N*-{[5-(trifluoromethyl)pyridin-2-yl]methyl}-2-azabicyclo[2.2.2]octane-4-carboxamide (Compound 329)

To a solution of Example 234 (80 mg, 0.151 mmol) in *N,N*-dimethylformamide (2.0 mL)
20 was added NaH (9.07 mg, 60% in mineral oil, 0.227 mmol), and the reaction was stirred at ambient temperature for 15 minutes. Then (2-bromoethoxy)(*tert*-butyl)dimethylsilane (0.049 mL, 0.073 mmol) was added to the mixture and stirring was continued for 16 hours. The reaction was quenched with methanol and volatiles were removed under vacuum. The residue was purified by HPLC (Phenomenex® Luna® C18(2) 10 μm 100Å AXIA™ column (250 mm ×
25 50 mm). A 40-100% gradient of acetonitrile (A) and 0.1% trifluoroacetic acid in water (B) was used over 25 minutes, at a flow rate of 50 mL/minute) to give 68 mg of intermediate (*tert*-butyl)dimethylsilyl ether. A solution of this intermediate (50 mg, 0.073 mmol) and hydrogen chloride (5.0 mL, 6.25 mmol) in methanol (5.0 mL) was stirred at ambient temperature for 16 hours. Solvent was removed, and the residue was purified by HPLC (Phenomenex® Luna®
30 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) was used over 25 minutes, at a flow rate of 50

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mL/minute) to give 8 mg of the title compound. ¹H NMR (501 MHz, methanol-*d*₄) δ ppm 8.75 – 8.70 (m, 1H), 8.04 – 7.98 (m, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.30 (t, J = 8.7 Hz, 1H), 6.84 (dd, J = 10.9, 2.9 Hz, 1H), 6.74 (ddd, J = 8.9, 2.9, 1.3 Hz, 1H), 4.51 (s, 2H), 3.63 (t, J = 5.7 Hz, 2H), 3.38 (t, J = 5.7 Hz, 2H), 2.70 – 2.62 (m, 2H), 2.21 (ddd, J = 13.8, 11.3, 4.5 Hz, 2H), 1.97 (qd, J = 11.4, 5.6 Hz, 4H); MS (ESI+) *m/z* 573.4 (M+H)⁺.

Example 231: *N*-[1-(5-chloro-1-benzofuran-2-yl)ethyl]-3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carboxamide (Compound 330)

The methodologies described in Example 48, substituting 1-(5-chlorobenzofuran-2-yl)ethanamine hydrochloride for (5-(difluoromethoxy)pyridin-2-yl)methanamine 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 8.74 (s, 1H), 8.34 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.28 (dd, J = 8.7, 2.3 Hz, 1H), 7.07 (dd, J = 11.4, 2.8 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 6.67 (d, J = 1.1 Hz, 1H), 5.14 (tt, J = 7.7, 6.4 Hz, 1H), 4.47 (s, 2H), 2.23 (s, 6H), 1.47 (d, J = 7.0 Hz, 3H); MS (ESI+) *m/z* 491 (M+H)⁺.

Example 232: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(5,6-difluoro-1*H*-benzimidazol-2-yl)methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 331)

The methodologies described in Example 48, substituting (5,6-difluoro-1*H*-benzo[*d*]imidazol-2-yl)methanamine for (5-(difluoromethoxy)pyridin-2-yl)methanamine 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 8.76 (s, 1H), 8.66 (t, J = 5.6 Hz, 1H), 7.80 (t, J = 8.7 Hz, 2H), 7.50 (t, J = 8.9 Hz, 1H), 7.11 6.99 (m, 1H), 6.86 (ddd, J = 9.0, 2.8, 1.2 Hz, 1H), 4.59 (d, J = 5.5 Hz, 2H), 4.48 (s, 2H), 2.25 (s, 6H); MS (ESI+) *m/z* 479 (M+H)⁺.

Example 233: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[[4-(trifluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 332)

The title compound was prepared using the methodologies described above. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.76 – 8.72 (m, 1H), 8.13 (t, J = 5.9 Hz, 1H), 7.61 – 7.58 (m, 1H),

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7.48 – 7.38 (m, 3H), 6.99 (dd, J = 11.5, 2.8 Hz, 1H), 6.78 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.41 (s, 2H), 4.38 (d, J = 5.9 Hz, 2H), 1.87 – 1.72 (m, 12H); MS (APCI⁺) *m/z* 514 (M+H)⁺.

Example 234: 1-[2-(4-chloro-3-fluorophenoxy)acetamido]-3-oxo-N-{{5-(trifluoromethyl)pyridin-2-yl)methyl}-2-azabicyclo[2.2.2]octane-4-carboxamide
(Compound 333)

Example 234A: 1-(ethoxycarbonyl)-4-oxocyclohexanecarboxylic acid

To a suspension of diethyl 4-oxocyclohexane-1,1-dicarboxylate (4.24 g, 17.5 mmol) in ethanol (20 mL) and dichloromethane (30 mL), potassium hydroxide (1.155 g, 17.50 mmol) was added at ambient temperature and stirred at reflux for 3 hours. The mixture was concentrated, and the residue was partitioned between water and ethyl acetate. The aqueous layer was then acidified with 3 N aqueous HCl solution to pH = 3, and then extracted with ethyl acetate (2×100 mL). The combined organic layers were dried over magnesium sulfate and filtered. The filtrate was concentrated to give 2.89 g of the title compound that was used without additional purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 13.01 (s, 1H), 4.24 – 4.02 (m, 2H), 2.32 (d, J = 5.5 Hz, 2H), 2.32 – 2.20 (m, 5H), 2.24 – 2.10 (m, 1H), 1.20 (t, J = 7.1 Hz, 3H).

Example 234B: ethyl 4-oxo-1-(((5-(trifluoromethyl)pyridin-2-yl)methyl)carbamoyl)cyclohexanecarboxylate

To a mixture of Example 234A (0.37 g, 1.727 mmol), (5-(trifluoromethyl)pyridin-2-yl)methanamine, hydrochloric acid (0.459 g, 2.159 mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (1.056 mL, 6.05 mmol) in *N,N*-dimethylformamide (7.5 mL), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.985 g, 2.59 mmol) was added, and the mixture was stirred at ambient temperature overnight. Water was added, and the aqueous phase was extracted with dichloromethane. The organic layer was dried over magnesium sulfate and filtered. The filtrate was concentrated, and the residue was purified on silica gel (5~100% ethyl acetate in heptane) to give 0.45 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.83 (d, J = 2.3 Hz, 1H), 8.64 (t, J = 5.9 Hz, 1H), 8.13 (ddd, J = 21.1, 8.4, 2.4 Hz, 1H), 7.39 (dd, J = 19.7, 8.3 Hz, 1H), 4.45 (d, J = 5.8 Hz, 2H), 4.20 – 4.03 (m, 2H), 2.38 – 2.21 (m, 8H), 1.15 (td, J = 7.1, 1.8 Hz, 3H); MS (ESI⁺) *m/z* 373.4 (M+H)⁺.

Example 234C: 1-amino-3-oxo-N-((5-(trifluoromethyl)pyridin-2-yl)methyl)-2-azabicyclo[2.2.2]octane-4-carboxamide

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A mixture of Example 234B (0.45 g, 1.088 mmol) and ammonia (10.0 mL, 7 M solution in methanol, 70.0 mmol) in methanol (10.0 mL) was stirred at ambient temperature for 48 hours. Volatiles were removed, and the residue was purified on silica gel (0~12% methanol/dichloromethane) to give 0.18 g of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.19 (t, J = 5.9 Hz, 1H), 8.88 (d, J = 2.3 Hz, 1H), 8.15 (dd, J = 8.4, 2.4 Hz, 1H), 7.93 (s, 1H), 7.72 (d, J = 8.3 Hz, 1H), 4.52 (d, J = 5.9 Hz, 2H), 2.64 (s, 2H), 1.98 – 1.80 (m, 4H), 1.72 (td, J = 11.2, 10.6, 4.4 Hz, 2H), 1.57 (td, J = 10.8, 5.2 Hz, 2H); MS (ESI-) *m/z* 340.9 (M-H)⁻.

Example 234: 1-(2-(4-chloro-3-fluorophenoxy)acetamido)-3-oxo-N-((5-(trifluoromethyl)pyridin-2-yl)methyl)-2-azabicyclo[2.2.2]octane-4-carboxamide

To a mixture of Example 234C (80 mg, 0.234 mmol), 2-(4-chloro-3-fluorophenoxy)acetic acid (59.8 mg, 0.292 mmol), and *N*-ethyl-*N*-isopropylpropan-2-amine (0.143 mL, 0.818 mmol) in *N,N*-dimethylformamide (2.0 mL), 2-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (133 mg, 0.351 mmol) was added, and the mixture was stirred at ambient temperature for 2 hours. *N,N*-Dimethylformamide and volatiles were removed under high vacuum, 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) was used over 25 minutes, at a flow rate of 50 mL/minute) to give 110 mg of the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.11 (t, J = 5.9 Hz, 1H), 8.88 (d, J = 2.3 Hz, 1H), 8.57 (s, 1H), 8.35 (s, 1H), 8.16 (dd, J = 8.3, 2.4 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.49 (t, J = 8.8 Hz, 1H), 7.09 (dd, J = 11.4, 2.9 Hz, 1H), 6.87 (dd, J = 9.3, 2.9 Hz, 1H), 4.53 (s, 2H), 4.52 (d, J = 6.1 Hz, 2H), 2.20 (dd, J = 10.8, 6.0 Hz, 2H), 2.02 – 1.82 (m, 6H); MS (ESI+) *m/z* 529.3 (M+H)⁺.

Example 235: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[(4-chloro-3-fluorophenyl)methyl]-2-oxabicyclo[2.2.2]octane-1-carboxamide (Compound 334)

Example 235A: tert-butyl (1-vinyl-2-oxabicyclo[2.2.2]octan-4-yl)carbamate

To a solution of 1-vinyl-2-oxabicyclo[2.2.2]octane-4-carboxylic acid (4.3 g, 23.60 mmol) in toluene (150 mL) was added 4Å molecular sieve (6 g), diphenylphosphoryl azide (7.14 g, 26.0 mmol) and triethylamine (3.62 mL, 26.0 mmol) in order at 20 °C. The mixture was stirred for 2 hours at 20 °C and 2 hours at 120 °C under N₂. After insoluble materials were filtered off, the filtrate was concentrated in vacuo. To a solution of the residue in anhydrous tetrahydrofuran

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(120 mL) was added potassium *tert*-butoxide (5.83 g, 51.9 mmol) under cooling with ice. The mixture was stirred at 20 °C for 12 hours. The reaction mixture was quenched with 10% aqueous citric acid and concentrated in vacuo. The residue was treated with ethyl acetate, washed with saturated sodium hydrogen carbonate solution, water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluted with petroleum ether and ethyl acetate from 100:1 to 10:1 to provide the title compound (5.2 g, yield 85%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.42 (s, 9H), 1.74-1.91 (m, 4H), 1.91-2.02 (m, 2H), 2.05-2.16 (m, 2H), 3.99 (s, 2H), 4.29 (br s, 1H), 5.03 (d, J=10.96 Hz, 1H), 5.15 (d, J=17.54 Hz, 1H), 5.81 (dd, J=17.54, 10.96 Hz, 1H).

10 *Example 235B: tert-butyl (1-formyl-2-oxabicyclo[2.2.2]octan-4-yl)carbamate*

To a solution of Example 235A (2.6 g, 9.75 mmol) in tetrahydrofuran (90 mL) and water (60 mL) was added sodium periodate (6.26 g, 29.2 mmol) and osmium tetroxide (1.239 g, 4.87 mmol) in order at 0 °C, and the mixture was stirred for 12 hours at 20 °C. The reaction mixture was diluted with water and extracted with ethyl acetate (2 ×). The combined organic phases were dried with Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with petroleum ether:ethyl acetate (100:1 to 4:1) to provide the title compound (1.85 g, yield 70.6%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.42 (s, 9H), 1.81-1.92 (m, 4H), 1.94-2.05 (m, 2H), 2.08-2.20 (m, 2H), 4.06 (s, 2H), 4.33 (br s, 1H), 7.26 (s, 1H), 9.57 (s, 1H).

20 *Example 235C: 4-((tert-butoxycarbonyl)amino)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid*

To a solution of Example 235B (1.9 g, 7.07 mmol) in tetrahydrofuran (60 mL), 2-methylpropan-2-ol (60 mL, 656 mmol) and water (20 mL) was added sodium dihydrogen phosphate (3.39 g, 28.3 mmol), 2-methyl-2-butene (7.49 mL, 70.7 mmol), and sodium chlorite (1.279 g, 14.14 mmol) in order at 20 °C, and the mixture was stirred for 12 hours at 20 °C. The reaction mixture was concentrated under reduced pressure to remove most of the volatiles. The remaining mixture was diluted with water (50 mL), adjusted to pH = 12 by aqueous NaOH (1 M), and extracted with methyl *tert*-butyl ether (50 mL) and ethyl acetate (50 mL) in order. The aqueous layer was adjusted to pH=1 with aqueous HCl (1 M) and extracted with ethyl acetate (2 × 100 mL). The combined organic phases were dried with Na₂SO₄ and concentrated under reduced pressure to provide the title compound (1.84 g, yield 91%). ¹H NMR (400 MHz,

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DMSO- d_6) δ ppm 1.35 (s, 9H), 1.73-1.84 (m, 2H), 1.85-1.99 (m, 1H), 1.85-1.99 (m, 5H), 3.80 (s, 2H), 6.68 (br s, 1H), 12.42 (br s, 1H).

Example 235D: methyl 4-((tert-butoxycarbonyl)amino)-2-oxabicyclo[2.2.2]octane-1-carboxylate

5 A solution of Example 235C (1.00 g, 3.69 mmol) in methanol (MeOH) (10 mL) was treated with 2 N (diazomethyl)trimethylsilane (1.843 mL, 3.69 mmol) in ether drop-wise. After 10 minutes, the reaction mixture was concentrated and purified on an 80 g column using the Biotage® Isolera One flash system eluted with heptanes/ethyl acetate (7:3 to 6:4) to provide the title compound (0.358 g, 34%). MS (DCI⁺) m/z 303.2 (M+NH₄)⁺.

10 *Example 235E: methyl 4-amino-2-oxabicyclo[2.2.2]octane-1-carboxylate hydrochloric acid*

 A suspension of Example 235D (0.350 g, 1.227 mmol) and trifluoroacetic acid (0.945 mL, 12.27 mmol) in CH₂Cl₂ (4 mL) was stirred overnight. The reaction mixture was concentrated. The residue was dissolved in methanol and concentrated again. The residue was suspended in 2 mL of methanol and treated with 2 mL of 2 N HCl in ether. The suspension was
15 stirred for 15 minutes, diluted with ether, collected by filtration, washed with ether, and vacuum oven-dried to provide the title compound as an HCl salt (0.245 g, 90%). MS (DCI⁺) m/z 203.1 (M+NH₄)⁺.

Example 235F: methyl 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-2-oxabicyclo[2.2.2]octane-1-carboxylate

20 A mixture of Example 235E (0.230 g, 1.038 mmol), triethylamine (0.434 mL, 3.11 mmol), 2-(4-chloro-3-fluorophenoxy)acetic acid (0.255 g, 1.245 mmol) and HATU (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (0.473 g, 1.245 mmol) in *N,N*-dimethylformamide (DMF) (6 mL) was stirred for 6 hours. The reaction mixture was quenched with brine and saturated NaHCO₃, and
25 extracted with ethyl acetate (2×). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified on a 25 g column using the Biotage® Isolera One flash system eluted with heptanes/ethyl acetate (3:7 to 2:8) to provide the title compound (0.333 g, 86%). MS (ESI⁺) m/z 372.2 (M+H)⁺.

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Example G: 4-(2-(4-chloro-3-fluorophenoxy)acetamido)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid

A mixture of Example 235F (0.310 g, 0.834 mmol) in tetrahydrofuran (THF) (6 mL) and methanol (MeOH) (4 mL) was treated with a solution of lithium hydroxide (0.070 g, 2.92 mmol) in water (2 mL). The mixture was stirred for 4 hours. Most of the volatiles were evaporated. The residue was diluted with water (2 mL) and treated with 5% citric acid until pH=4. The resulting suspension was filtered, and the collected solid was rinsed with water and vacuum oven-dried to provide the title compound (0.255g, 85%). MS (ESI⁺) *m/z* 358.2 (M+H)⁺.

Example 235H: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-chloro-3-fluorophenyl)methyl]-2-oxabicyclo[2.2.2]octane-1-carboxamide

A mixture of Example 235G (40.0 mg, 0.112 mmol), HATU (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (51.0 mg, 0.134 mmol), (4-chloro-3-fluorophenyl)methanamine (0.015 mL, 0.123 mmol), and triethylamine (0.031 mL, 0.224 mmol) in *N,N*-dimethylformamide (DMF) (1.5 mL) was stirred for 3 hours. The reaction mixture was quenched with brine and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by HPLC performed on a Phenomenex® Luna® C18 column (250 × 30 mm, 10 μm particle size) using a gradient of 20% to 100% acetonitrile:0.1% aqueous trifluoroacetic acid over 26 minutes at a flow rate of 50 mL/minute to provide the title compound (49.6 mg, yield 89%). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.29 (t, *J* = 6.3 Hz, 1H), 7.75 (s, 1H), 7.50 (dt, *J* = 15.1, 8.5 Hz, 2H), 7.20 (dd, *J* = 10.4, 2.0 Hz, 1H), 7.11 – 6.99 (m, 2H), 6.82 (ddd, *J* = 9.0, 2.9, 1.1 Hz, 1H), 4.48 (s, 2H), 4.23 (d, *J* = 6.3 Hz, 2H), 4.03 (s, 2H), 2.13 – 1.95 (m, 4H), 1.95 – 1.77 (m, 4H); MS (ESI⁺) *m/z* 449.3 (M+H)⁺.

Example 236: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[[5-(trifluoromethyl)pyridin-2-yl]methyl]-2-oxabicyclo[2.2.2]octane-1-carboxamide (Compound 335)

A mixture of Example 235G (40.0 mg, 0.112 mmol), HATU (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (51.0 mg, 0.134 mmol), (5-(trifluoromethyl)pyridin-2-yl)methanamine (21.66 mg, 0.123 mmol), and triethylamine (0.031 mL, 0.224 mmol) in *N,N*-dimethylformamide

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(DMF) (1.5 mL) was stirred for 3 hours. The reaction mixture was quenched with brine and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by HPLC (see protocol in Example 235H) to provide the title compound as a trifluoroacetic acid salt (29.2 mg, 42%). ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.88 (d, J = 2.3 Hz, 1H), 8.36 (t, J = 6.1 Hz, 1H), 8.16 (dd, J = 8.3, 2.4 Hz, 1H), 7.77 (s, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.04 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.1 Hz, 1H), 4.48 (s, 2H), 4.44 (d, J = 5.0 Hz, 2H), 4.06 (s, 2H), 2.19 – 1.97 (m, 4H), 1.92 (q, J = 9.3, 7.6 Hz, 4H); MS (ESI⁺) *m/z* 516.3 (M+H)⁺.

Example 237: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[4-(trifluoromethoxy)phenyl]-2-oxabicyclo[2.2.2]octane-1-carboxamide (Compound 336)

A mixture of Example 235G (0.040 g, 0.112 mmol), 4-(trifluoromethoxy)aniline (0.024 g, 0.134 mmol), PyBOP® ((1*H*-benzo[*d*][1,2,3]triazol-1-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V)) (0.070 g, 0.134 mmol), and triethylamine (0.023 mL, 0.168 mmol) in *N,N*-dimethylformamide (DMF) (1.5 mL) was stirred for 6 hours. The reaction mixture was quenched with brine and saturated NaHCO₃ and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by HPLC (see protocol in Example 235H) to provide the title compound (31.8 mg, 55%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.65 (s, 1H), 7.91 – 7.74 (m, 3H), 7.49 (t, J = 8.9 Hz, 1H), 7.34 – 7.23 (m, 2H), 7.04 (dd, J = 11.4, 2.9 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.49 (s, 2H), 4.10 (s, 2H), 2.21 – 1.82 (m, 8H); MS (ESI⁺) *m/z* 517.1 (M+H)⁺.

Example 238: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-*N*-[4-(trifluoromethyl)phenyl]-2-oxabicyclo[2.2.2]octane-1-carboxamide (Compound 337)

The reaction described in Example 237 substituting 4-aminobenzotrifluoride for 4-(trifluoromethoxy)aniline gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.81 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.80 (s, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.49 (t, J = 8.9 Hz, 1H), 7.05 (dd, J = 11.4, 2.9 Hz, 1H), 6.83 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.50 (s, 2H), 4.11 (s, 2H), 2.19 – 1.82 (m, 8H); MS (ESI⁺) *m/z* 501.4 (M+H)⁺.

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Example 239: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-(4-chloro-3-fluorophenyl)-2-oxabicyclo[2.2.2]octane-1-carboxamide (Compound 338)

The reaction described in Example 237 substituting 4-chloro-3-fluoroaniline for 4-(trifluoromethoxy)aniline gave the title compound. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 9.81 (s, 1H), 7.88 (dd, J = 12.1, 2.4 Hz, 1H), 7.81 (s, 1H), 7.61 (ddd, J = 8.9, 2.4, 1.0 Hz, 1H), 7.49 (td, J = 8.8, 1.2 Hz, 2H), 7.04 (dd, J = 11.4, 2.9 Hz, 1H), 6.82 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.49 (s, 2H), 4.10 (d, J = 1.6 Hz, 2H), 2.16 – 1.89 (m, 8H); MS (ESI⁺) *m/z* 485.3 (M+H)⁺.

Example 240: 6-[(3-[2-(4-chloro-3-fluorophenoxy)acetamido]bicyclo[1.1.1]pentane-1-carbonyl)amino)methyl]pyridine-3-carboxamide (Compound 339)

The title compound was prepared using the methodologies described above. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.94 (d, J = 2.2 Hz, 1H), 8.74 (s, 1H), 8.47 (t, J = 6.1 Hz, 1H), 8.17 (dd, J = 8.2, 2.3 Hz, 1H), 8.10 (s, 1H), 7.53 (s, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 6.91 – 6.81 (m, 1H), 4.48 (s, 2H), 4.38 (d, J = 6.0 Hz, 2H), 2.24 (s, 6H); MS (ESI⁺) *m/z* 447 (M+H)⁺.

Example 241: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(4-chloro-3-fluorophenoxy)ethyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 340)

The title compound was prepared using the methodologies described above. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.71 (s, 1H), 8.01 (t, J = 5.7 Hz, 1H), 7.49 (t, J = 8.9 Hz, 1H), 7.46 (t, J = 8.9 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.88 – 6.81 (m, 2H), 4.47 (s, 2H), 4.02 (t, J = 5.9 Hz, 2H), 3.39 (q, J = 5.9 Hz, 2H), 2.17 (s, 6H); MS (ESI⁺) *m/z* 485 (M+H)⁺.

Example 242: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(trifluoromethoxy)pyridin-3-yl]-2-oxabicyclo[2.2.2]octane-1-carboxamide (Compound 341)

Example 242A: tert-butyl (1-((6-(trifluoromethoxy)pyridin-3-yl)carbamoyl)-2-oxabicyclo[2.2.2]octan-4-yl)carbamate

A mixture of Example 235C (0.095 g, 0.350 mmol), PyBOP® ((1*H*-benzo[*d*][1,2,3]triazol-1-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V)) (0.219 g, 0.420 mmol), 6-(trifluoromethoxy)pyridin-3-amine (0.075 g, 0.420 mmol), and triethylamine (0.073 mL, 0.525 mmol) in *N,N*-dimethylformamide (DMF) (3 mL) was stirred for 3 hours. The reaction mixture was quenched with brine and saturated NaHCO₃, and extracted

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with ethyl acetate (2×). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified on a 12 g column using the Biotage® Isolera One flash system eluted with heptanes/ethyl acetate (7:3 to 6:4) to provide the title compound (65.1 mg, 43%). MS (ESI⁺) *m/z* 432.3 (M+H)⁺.

5 *Example 242B: 4-amino-N-(6-(trifluoromethoxy)pyridin-3-yl)-2-oxabicyclo[2.2.2]octane-1-carboxamide, hydrochloric acid*

A mixture of Example 242A (62.0 mg, 0.144 mmol) and trifluoroacetic acid (0.111 mL, 1.437 mmol) in CH₂Cl₂ (2 mL) was stirred for 4 hours. The reaction mixture was concentrated, and the residue was dissolved in 1 mL of methanol. The solution was treated with 1 mL of 2 M
10 HCl in ether and stirred for 15 minutes. The solution was concentrated to provide the title compound as an HCl salt (60.8 mg, quantitative yield) that was used in the next step without further purifications. MS (ESI⁺) *m/z* 332.2 (M+H)⁺.

Example 242C 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[6-(trifluoromethoxy)pyridin-3-yl]-2-oxabicyclo[2.2.2]octane-1-carboxamide, trifluoroacetic acid salt

15 A mixture of Example 242B (59.0 mg, 0.146 mmol), HATU (1-bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (66.6 mg, 0.175 mmol), 2-(4-chloro-3-fluorophenoxy)acetic acid (35.8 mg, 0.175 mmol), and triethylamine (0.081 mL, 0.584 mmol) in *N,N*-dimethylformamide (DMF) (2 mL) was stirred for 3 hours. The reaction mixture was quenched with brine and saturated
20 NaHCO₃, and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by HPLC (see protocol in Example 235H) to provide the title compound as a trifluoroacetic acid salt (43.5 mg, 47%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.94 (s, 1H), 8.66 (d, *J* = 2.6 Hz, 1H), 8.32 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.81 (s, 1H), 7.49 (t, *J* = 8.9 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.05 (dd, *J* =
25 11.4, 2.8 Hz, 1H), 6.83 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.50 (s, 2H), 4.12 (s, 2H), 2.23 – 1.77 (m, 8H); MS (ESI⁺) *m/z* 518.4 (M+H)⁺.

Example 243: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5-chloropyridin-2-yl)methyl]-2-oxabicyclo[2.2.2]octane-1-carboxamide (Compound 342)

Example 243A: tert-butyl (1-(((5-chloropyridin-2-yl)methyl)carbamoyl)-2-oxabicyclo[2.2.2]octan-4-yl)carbamate
30

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A mixture of Example 235C (0.150 g, 0.553 mmol), HATU (1-bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (0.231 g, 0.608 mmol), (5-chloropyridin-2-yl)methanamine hydrochloride (0.109 g, 0.608 mmol), and triethylamine (0.193 mL, 1.382 mmol) in *N,N*-dimethylformamide (DMF) (2.5 mL) was stirred overnight. The reaction mixture was quenched with brine and saturated NaHCO₃ and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified on a 12 g column using the Biotage® Isolera One flash system eluting with heptanes/ethyl acetate (4:6 to 3:7) to provide the title compound (0.165 g, 75%). MS (ESI⁺) *m/z* 396.2 (M+H)⁺.

10 *Example 243B: 4-amino-N-((5-chloropyridin-2-yl)methyl)-2-oxabicyclo[2.2.2]octane-1-carboxamide*

A mixture of Example 243A (0.160 g, 0.404 mmol) and trifluoroacetic acid (0.311 mL, 4.04 mmol) in CH₂Cl₂ (3 mL) was stirred for 4 hours. The reaction mixture was concentrated, and the residue was dissolved in 2 mL of methanol. The solution was treated with 1.5 mL of 2 M HCl in ether and stirred for 15 minutes. The solution was concentrated to provide the title compound as an HCl salt (0.140 g, 94%) that was used in the next step without further purification. MS (ESI⁺) *m/z* 296.2 (M+H)⁺.

Example 243C: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(5-chloropyridin-2-yl)methyl]-2-oxabicyclo[2.2.2]octane-1-carboxamide

20 A mixture of Example 243B (0.070 g, 0.190 mmol), HATU (1-bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (0.087 g, 0.228 mmol), 2-(4-chloro-3-fluorophenoxy)acetic acid (0.047 g, 0.228 mmol), and triethylamine (0.106 mL, 0.759 mmol) in *N,N*-dimethylformamide (DMF) (2.5 mL) was stirred for 3 hours. The reaction mixture was quenched with brine and saturated NaHCO₃ and extracted with ethyl acetate (2×). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was purified by HPLC (see protocol in Example 235H) to provide the title compound as a trifluoroacetic acid salt (46.3 mg, 41%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.53 (d, *J* = 2.4 Hz, 1H), 8.25 (t, *J* = 6.1 Hz, 1H), 7.88 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.76 (s, 1H), 7.49 (t, *J* = 8.9 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.04 (dd, *J* = 11.4, 2.9 Hz, 1H), 6.82 (ddd, *J* = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (s, 2H), 4.34 (d, *J* = 6.1 Hz, 2H), 4.04 (s, 2H), 2.17 – 1.81 (m, 8H); MS (ESI⁺) *m/z* 482.3 (M+H)⁺.

Example 244: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-chloro-3-fluorophenyl)methyl]-N-(2-hydroxyethyl)bicyclo[1.1.1]pentane-1-carboxamide (Compound 343)

Example 244A: 2-((4-chloro-3-fluorobenzyl)amino)ethanol

5 To a solution of (4-chloro-3-fluorophenyl)methanamine (266 mg, 1.67 mmol, Alfa) in a methanol buffer (3.6 weight % sodium acetate trihydrate and 2.4 weight % acetic acid in methanol, 15mL) was added 1,4-dioxane-2,5-diol (100 mg, 0.833 mmol, Aldrich) in one portion followed by sodium cyanoborohydride (105 mg, 1.67 mmol) and trifluoroacetic acid (0.1 mL). After stirring at ambient temperature for 10 minutes, the reaction mixture was concentrated
10 under reduced pressure to less than 5 mL and was filtered through a glass microfiber frit. Then the filtrate was purified by preparative HPLC [YMC TriArt™ C18 Hybrid 5 µm column, 50 × 100 mm, flow rate 140 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 (0.18 g, 0.88 mmol, 53.0 % yield). MS (ESI⁺) *m/z* 204 (M+H)⁺.

15 *Example 244B: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-chloro-3-fluorophenyl)methyl]-N-(2-hydroxyethyl)bicyclo[1.1.1]pentane-1-carboxamide*

The reaction and purification conditions described in Example 48 substituting the product of Example 244A for (5-(difluoromethoxy)pyridin-2-yl)methanamine, and (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP) for (1-
20 [bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate) (HATU) gave the title compound. ¹H NMR (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 8.19 (s, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 10.4, 1.9 Hz, 1H), 7.04 (ddd, *J* = 8.3, 2.0, 0.9 Hz, 1H), 6.97 (dd, *J* = 11.3, 2.8 Hz, 1H), 6.82 (ddd, *J* = 8.9, 2.8, 1.2 Hz, 1H), 4.60 (s, 2H), 4.42 (s, 2H), 4.30 (br s, 1H), 3.51 (q, *J* = 5.8 Hz, 2H), 3.42 – 3.37
25 (m, 2H), 2.30 (s, 6H); MS (ESI⁺) *m/z* 499 (M+H)⁺.

Example 245: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[(4-chloro-3-fluorophenyl)methyl]-N-(2-hydroxyethyl)bicyclo[2.2.2]octane-1-carboxamide (Compound 344)

The title compound was prepared using the methodologies described above. ¹H NMR
30 (400 MHz, DMSO-*d*₆, 120 °C) δ ppm 7.44 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.8 Hz, 1H), 7.09 (dd,

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J = 10.5, 1.9 Hz, 1H), 7.01 (dd, J = 8.3, 1.9 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.80 (ddd, J = 8.9, 2.9, 1.2 Hz, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 4.25 (br s, 1H), 3.55 – 3.50 (m, 2H), 3.46 – 3.40 (m, 2H), 1.96 – 1.83 (m, 12H); MS (APCI⁺) *m/z* 541 (M+H)⁺.

Example 246: 3-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[[5-(difluoromethyl)pyridin-2-yl]methyl]bicyclo[1.1.1]pentane-1-carboxamide (Compound 345)

The title compound was prepared using the methodologies described above. ¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 8.75 (s, 1H), 8.71 – 8.68 (m, 1H), 8.50 (t, J = 6.1 Hz, 1H), 8.00 – 7.97 (m, 1H), 7.50 (t, J = 8.9 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.13 (t, J = 55.4 Hz, 1H), 7.08 (dd, J = 11.4, 2.9 Hz, 1H), 6.86 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.48 (s, 2H), 4.39 (d, J = 6.0 Hz, 2H), 2.24 (s, 6H); MS (ESI⁺) *m/z* 454 (M+H)⁺.

Example 247: 4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[[5-(difluoromethyl)pyridin-2-yl]methyl]bicyclo[2.2.2]octane-1-carboxamide (Compound 346)

The title compound was prepared using the methodologies described above. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.69 – 8.66 (m, 1H), 8.12 (t, J = 6.0 Hz, 1H), 7.98 – 7.93 (m, 1H), 7.52 – 7.45 (m, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.12 (t, J = 55.4 Hz, 1H), 7.03 (dd, J = 11.5, 2.8 Hz, 1H), 6.81 (ddd, J = 9.0, 2.9, 1.2 Hz, 1H), 4.44 (s, 2H), 4.37 (d, J = 5.9 Hz, 2H), 1.90 – 1.75 (m, 12H); MS (ESI⁺) *m/z* 496 (M+H)⁺.

Example 248: (2R)-4-[2-(4-chloro-3-fluorophenoxy)acetamido]-N-[2-(4-chloro-3-fluorophenyl)-2-oxoethyl]-2-hydroxybicyclo[2.2.2]octane-1-carboxamide (Compound 347)

The title compound was prepared using the methodologies described for Example 177. ¹H NMR (501 MHz, DMSO-*d*₆) δ ppm 8.00 (t, J = 5.4 Hz, 1H), 7.96 (dd, J = 9.9, 1.8 Hz, 1H), 7.82 (dd, J = 8.4, 1.9 Hz, 1H), 7.78 (dd, J = 8.4, 7.1 Hz, 1H), 7.53 (s, 1H), 7.48 (t, J = 8.9 Hz, 1H), 7.03 (dd, J = 11.4, 2.8 Hz, 1H), 6.81 (ddd, J = 9.0, 2.9, 1.1 Hz, 1H), 4.60 - 4.48 (m, 2H), 4.45 (s, 2H), 4.12 - 4.01 (m, 1H), 2.24 (ddd, J = 12.6, 9.1, 3.0 Hz, 1H), 2.17 - 2.01 (m, 1H), 1.98 - 1.84 (m, 1H), 1.84 - 1.65 (m, 5H), 1.66 - 1.52 (m, 2H); MS (APCI) *m/z* 541.2 (M+H)⁺.

Example 249: 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

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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

5 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

10 maintained in DMEM with L-glutamine supplemented with 10% heat-inactivated FBS (Gibco) and Antibiotic-Antimycotic solution (Gibco).

Table 2 below summarizes the EC₅₀ data obtained using the ATF4-Luc assay for exemplary compounds of the invention. In this table, "A" represents an EC₅₀ of less than 250 nM; "B" an EC₅₀ of between 250 nM and 500 nM; "C" an EC₅₀ of between 500 nM and 1 µM; "D" an EC₅₀ of between 1 µM and 2 µM; "E" an EC₅₀ of greater than 2 µM; and "F" indicates

15 that data is not available.

Table 2: EC₅₀ values of exemplary compounds of the invention in the ATF4-Luc assay.

Compound No.	ATF4-Luc EC ₅₀
100	A
101	D
102	B
103	B
104	B
105	C

Compound No.	ATF4-Luc EC ₅₀
106	A
107	A
108	A
109	C
110	A
111	E

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Compound No.	ATF4-Luc EC ₅₀
112	E
113	A
114	A
115	E
116	E
117	A
118	A
119	D
120	A
121	E
122	A
123	A
124	C
125	A
126	E
127	D
128	A
129	B
130	A
131	B

Compound No.	ATF4-Luc EC ₅₀
132	A
133	A
134	A
135	A
136	C
137	C
138	A
139	D
140	E
141	A
142	C
143	A
144	E
145	A
146	A
147	B
148	A
149	B
150	A
151	E

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Compound No.	ATF4-Luc EC ₅₀
152	E
153	E
154	E
155	E
156	A
157	E
158	A
159	E
160	E
161	E
162	E
163	E
164	E
165	E
166	E
167	E
168	D
169	C
170	E
171	D

Compound No.	ATF4-Luc EC ₅₀
172	E
173	E
174	E
175	E
176	E
177	E
178	E
179	E
180	E
181	E
182	E
183	E
184	E
185	E
186	E
187	E
188	E
189	E
190	E
191	D

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Compound No.	ATF4-Luc EC ₅₀
192	E
193	B
194	A
195	E
196	E
197	C
198	E
199	E
200	E
201	D
202	E
203	E
204	A
205	E
206	E
207	E
208	E
209	E
210	E
211	D

Compound No.	ATF4-Luc EC ₅₀
212	E
213	E
214	E
215	E
216	E
217	E
218	F
219	E
220	E
221	E
222	E
223	E
224	E
225	E
226	E
227	E
228	E
229	E
230	E
231	E

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Compound No.	ATF4-Luc EC ₅₀
232	E
233	E
234	E
235	E
236	E
237	E
238	E
239	E
240	E
241	E
242	E
243	E
244	E
245	E
246	E
247	E
248	E
249	E
250	E
251	E

Compound No.	ATF4-Luc EC ₅₀
252	E
253	D
254	D
255	A
256	D
257	A
258	C
259	C
260	A
261	A
262	A
263	A
264	A
265	A
266	A
267	A
268	B
269	A
270	A
271	A

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Compound No.	ATF4-Luc EC ₅₀
272	A
273	A
274	A
275	A
276	A
277	A
278	A
279	A
280	A
281	E
282	A
283	A
284	A
285	A
286	E
287	A
288	A
289	A
290	A
291	A

Compound No.	ATF4-Luc EC ₅₀
292	A
293	B
294	A
295	A
296	A
297	A
298	A
299	A
300	A
301	A
302	B
303	B
304	A
305	A
306	A
307	B
308	A
309	A
310	A
311	B

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Compound No.	ATF4-Luc EC ₅₀
312	B
313	D
314	C
315	C
316	C
317	D
318	E
319	A
320	C
321	E
322	E
323	A
324	A
325	A
326	A
327	A
328	D
329	A

Compound No.	ATF4-Luc EC ₅₀
330	D
331	A
332	A
333	A
334	B
335	A
336	A
337	A
338	A
339	E
340	A
341	A
342	A
343	D
344	D
345	B
346	A
347	A

VWMD mutations were introduced into the genome of the HEK293T ATF4-Fluc stable cell lines by using Gene Art CRISPR nuclease vector with OFP Reporter kit (ThermoFisher; see

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Table 3 below). Guide RNAs were designed using the CRISPR Design Tool (<http://crispr.mit.edu>) and ligated into the CRISPR OFP Nuclease Vector. To obtain homology directed repair (HDR) incorporating VWMD point mutations in the genome, 150 bp ssDNA ultramer oligos were synthesized by Integrated DNA Technologies containing specific mutations of interest. In addition to the VWMD mutations, the ssDNA HDR templates contained a silent mutation to the PAM site of the CRISPR gRNA sequence (to avoid further Cas9 cutting) and 75 bp of homology on each side of the mutation.

HEK293T ATF4-Fluc cells were transfected with 500 ng of the CRISPR OFP Nuclease Vector and 1 μ L of 10 μ M ssDNA HDR template using lipofectamine 3000 (ThermoFisher) or SF Cell Line 4D-nucleofector X Kit (Lonza) according to the manufacturer's instructions. After 2-3 days of recovery, single cells were sorted for positive OFP expression on a FACS Aria II (BD Biosciences) into wells of a 96 well plate and allowed to recover for 1-2 weeks.

The resulting clones were surveyed for CRISPR editing and HDR by harvesting the genomic DNA with the PureLink Genomic DNA kit (ThermoFisher), amplifying a ~500bp locus near the editing site, and sequencing the amplicon. Clones that displayed an ambiguous chromatogram signal near the expected CRISPR editing site were further examined by TA cloning (Invitrogen) and sequencing of the amplicon, yielding the sequence of each allele in the clone. Typical clones obtained were hemizygous for the VWMD point mutation, with one or two alleles harboring the desired mutation, and the remaining alleles knocked out (edited to produce a premature stop codon).

Table 3: Exemplary VWMD point mutations introduced into eIF2B

eIF2B Subunit	Mutation
eIF2B1	V183F
eIF2B3	H341Q
eIF2B3	I346T
eIF2B4	R483W
eIF2B5	R113H
eIF2B5	R195H

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 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

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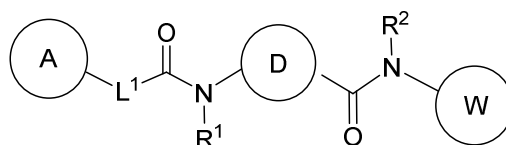
be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

Those skilled in the art will recognize or be able to ascertain using no more than routine
5 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

What is claimed is:

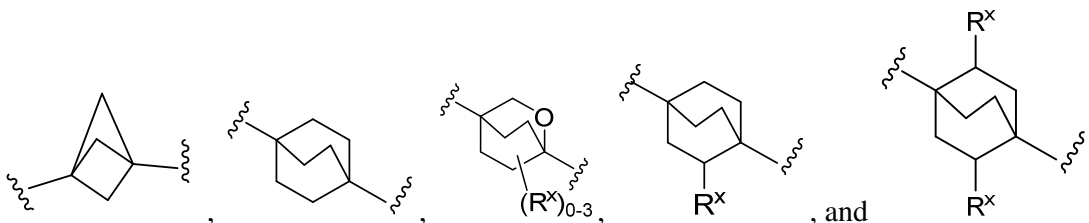
1. A compound of Formula (II):



Formula (II)

or a pharmaceutically acceptable salt thereof, wherein:

D is selected from the group consisting of:



L^1 is CH_2O^* or $CH_2CH_2O^*$, wherein “ * ” indicates the attachment point to A;

R^1 and R^2 are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy- C_2 - C_6 alkyl, hydroxy- C_2 - C_6 alkyl, or silyloxy- C_2 - C_6 alkyl;

A and W are each independently phenyl or 5-6 membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y ;

each R^X 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, amino- C_1 - C_6 alkyl, cyano- C_1 - C_6 alkyl, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-SR^E$, $-S(O)R^D$, and $-S(O)_2 R^D$;

each R^Y is independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, hydroxy- C_1 - C_6 alkyl, C_1 - C_6 alkoxy- 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, oxo, halo, cyano, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, $-S(R^F)_m$, $-S(O)R^D$, $-S(O)_2 R^D$, 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 heterocyclyl, aryl, or 5-6 membered heteroaryl, optionally substituted with 1-5 R^X ;

each G^1 is independently C_3 - C_6 cycloalkyl, 4-7-membered heterocyclyl, aryl, or 5-6-membered heteroaryl, wherein each C_3 - C_6 cycloalkyl, 4-7-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, $-OR^A$, $-NR^B R^C$, $-NR^B C(O)R^D$, $-C(O)NR^B R^C$, $-C(O)R^D$, $-C(O)OH$, $-C(O)OR^D$, and $-S(O)_2 R^D$;

R^A is, at each occurrence, independently hydrogen, C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, $-C(O)NR^B R^C$, $-C(O)R^D$, 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 optionally substituted with 1-3 R^Z ;

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, halo, or halo- C_1 - C_6 alkyl;

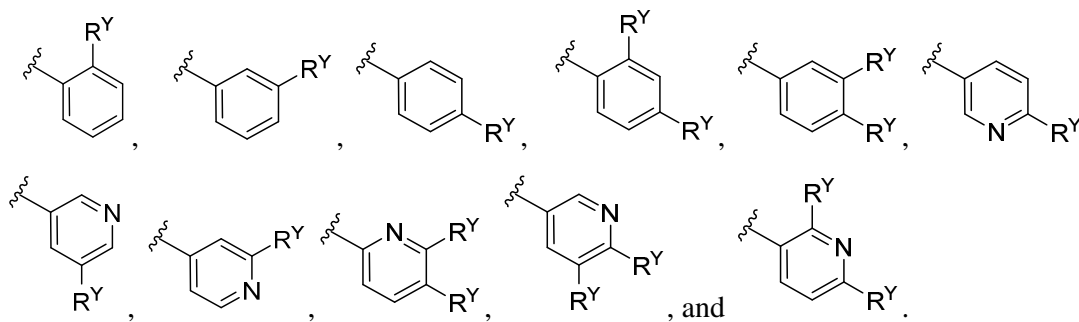
each of R^{B1} and R^{C1} is independently hydrogen or C_1 - C_6 alkyl; and

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.

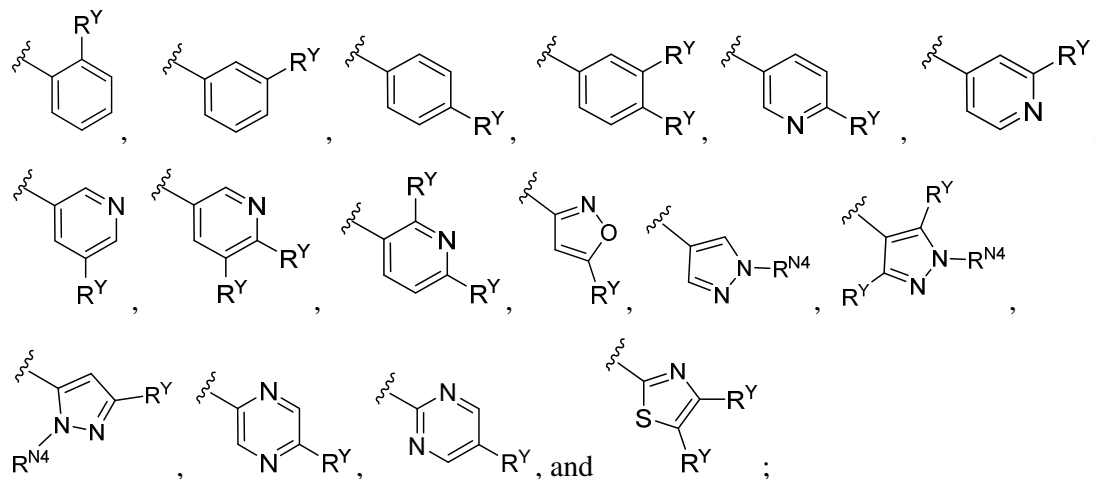
2. The compound of claim 1, wherein each R^X is independently selected from the group consisting of oxo, $-OH$, $-OCH_3$, $-C(O)OH$, $-C(O)OCH_3$, halo, and hydroxy- C_1 - C_6 alkyl.

3. The compound of claim 1 or 2, wherein each of R^1 and R^2 is hydrogen or $-CH_3$.

4. The compound of any one of claims 1-3, wherein A is selected from the group consisting of:



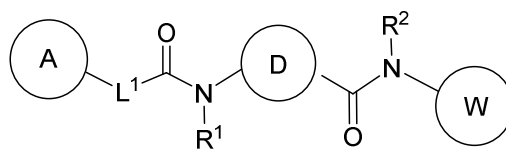
5. The compound of any one of claims 1-4, wherein W is selected from the group consisting of:



wherein R^{N4} is hydrogen or $-CH_3$.

6. The compound of any one of claims 1-5, wherein each R^Y is independently hydrogen, bromo, chloro, fluoro, iodo, $-CF_3$, $-CHF_2$, $-CH_2CF_3$, $-CH_3$, $-CH_2CH_3$, $-OH$, $-CH_2OH$, $-C(CH_3)_2OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$, $-OCH_2CF_3$, $-S(O)_2CH_3$, $-S(O)_2CH_2CH_2CH_3$, $-CN$, $N(CH_3)_2$, $-SF_5$, SCH_3 , $-NH_2$, $-C(CH_3)_3$, $-CH(CH_3)_2$, $-CH_2CN$, $-CH_2NH_2$, $-CH(OH)CH_3$, $-C(OH)(CH_3)CF_3$, $-S(O)_2CH_3$, $-C(O)CH_3$, $-C(O)OCH_3$, $-C(O)OH$, $-OCHF_2$, or G^1 .

7. A compound of Formula (II-a):



Formula (II-a)

or a pharmaceutically acceptable salt thereof, wherein:

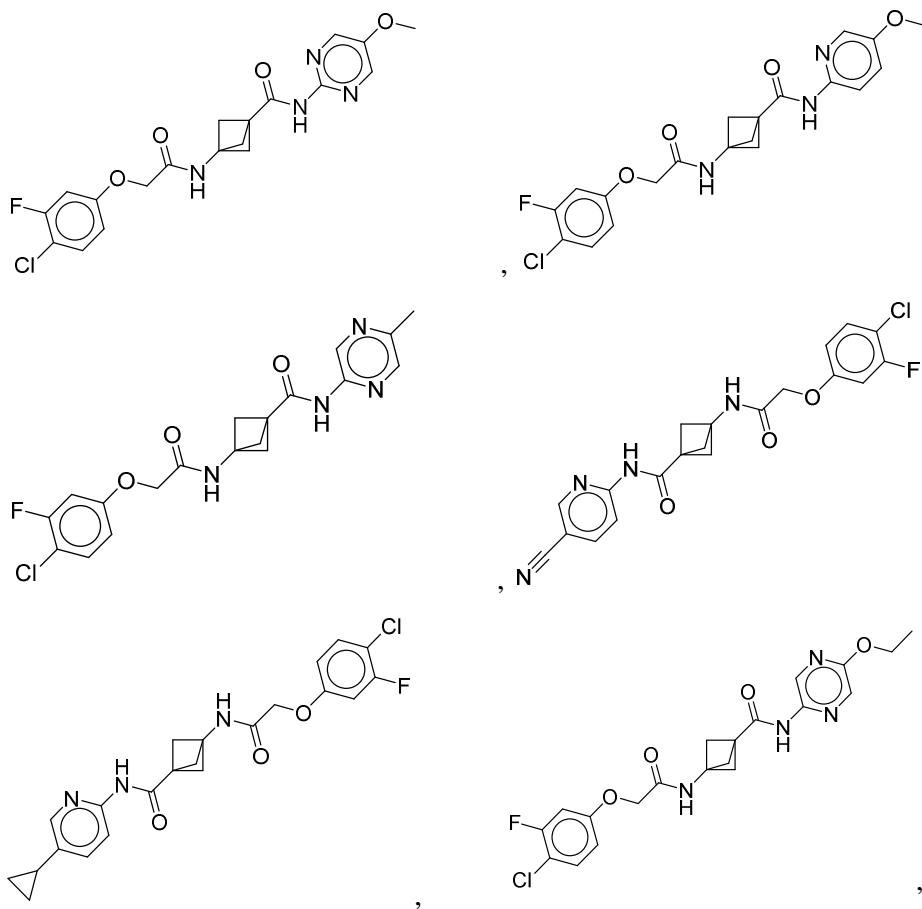
D is bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or 2-oxabicyclo[2.2.2]octane, each of which is optionally substituted with 1-4 R^X groups;

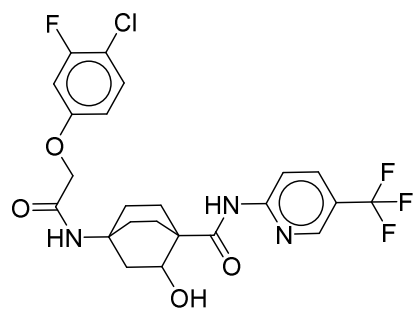
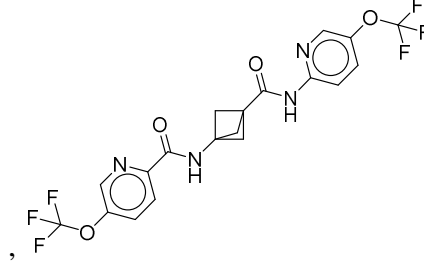
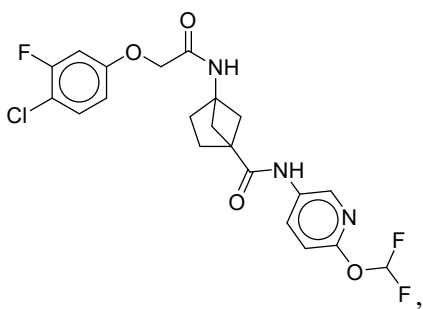
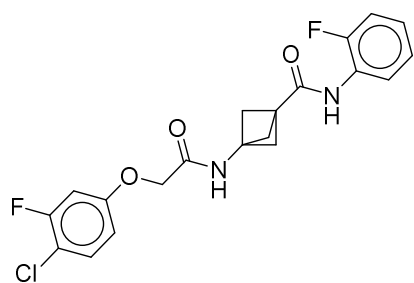
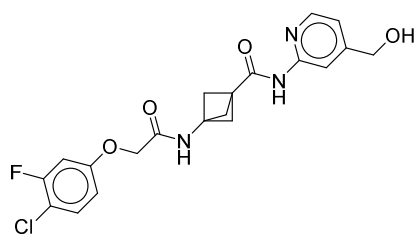
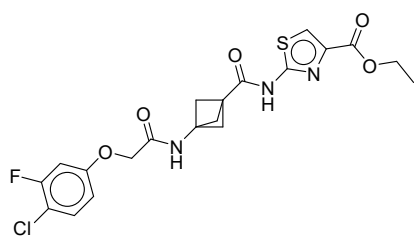
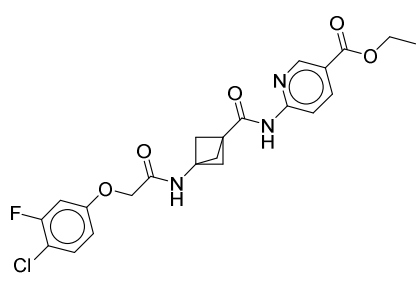
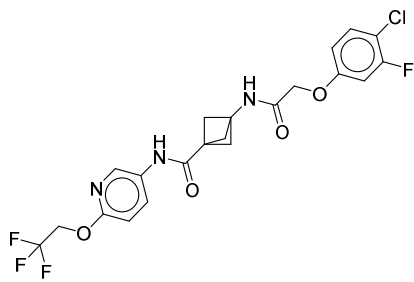
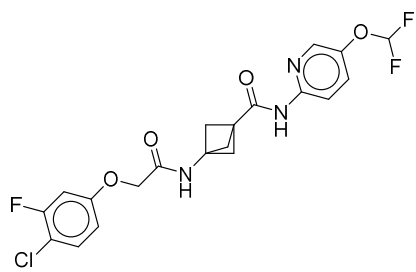
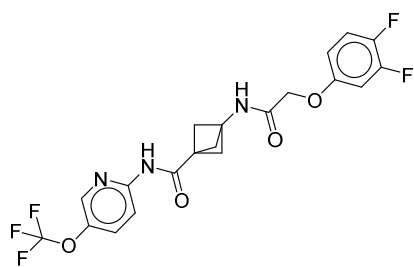
A is phenyl or pyridyl, each of which is optionally substituted with 1-5 R^Y groups;

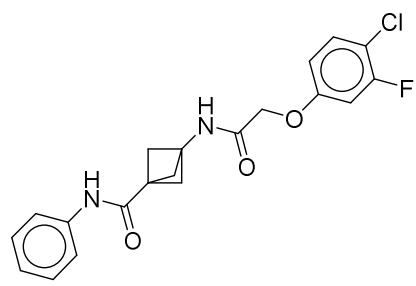
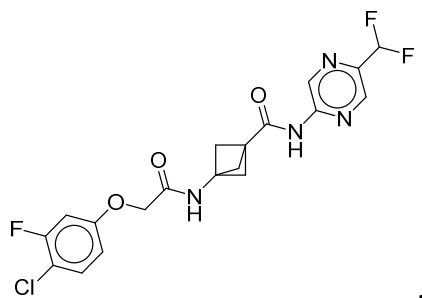
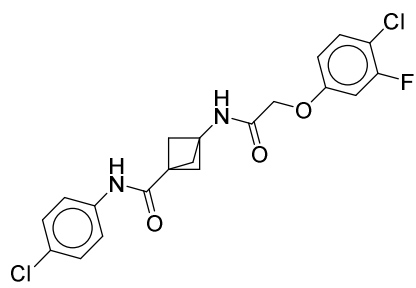
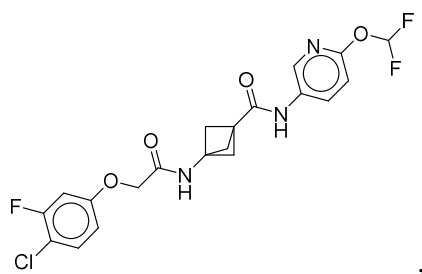
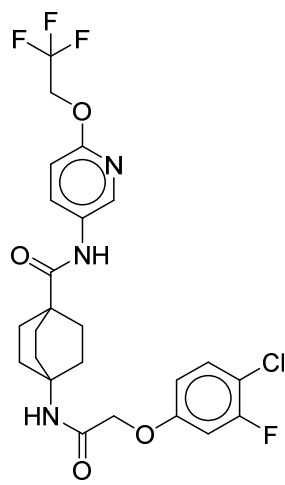
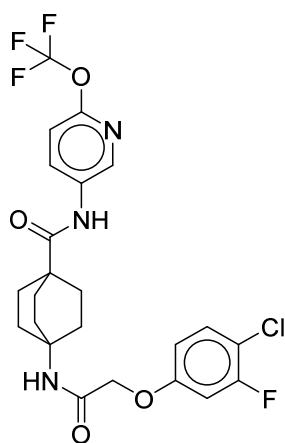
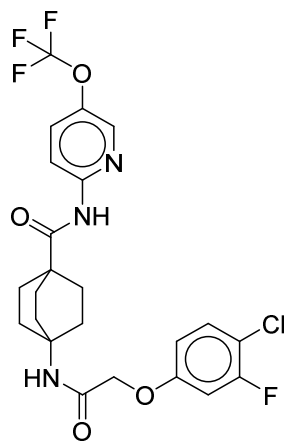
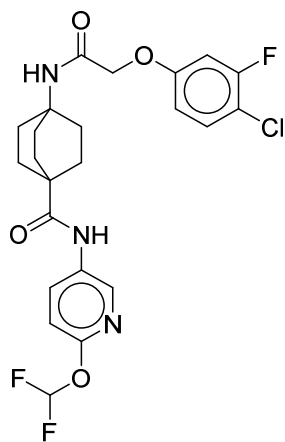
W is phenyl, pyridyl, pyrazinyl, pyrimidinyl, thiazolyl, isoxazolyl, or pyrazolyl, each of which is optionally substituted on one or more available carbons with 1-5 R^Y groups; and wherein pyrazolyl may be optionally substituted on an available nitrogen with hydrogen or $-CH_3$;

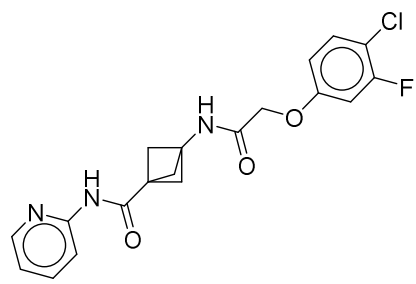
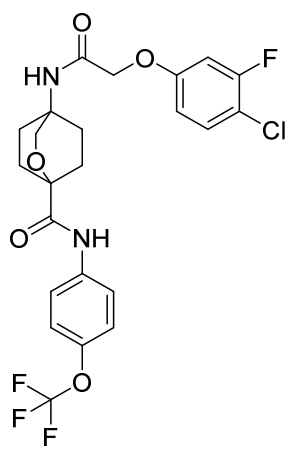
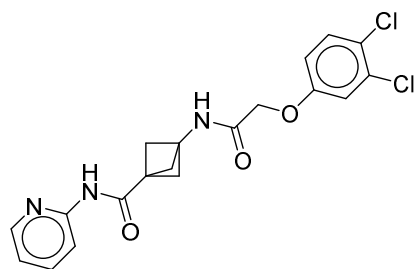
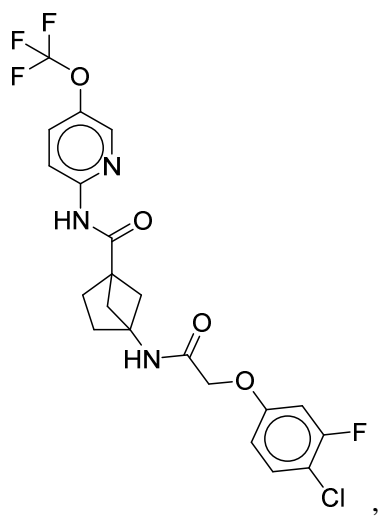
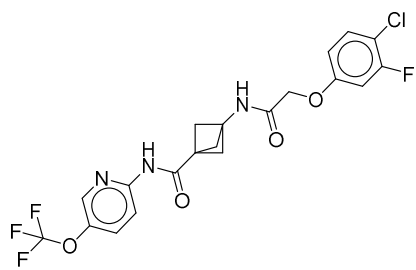
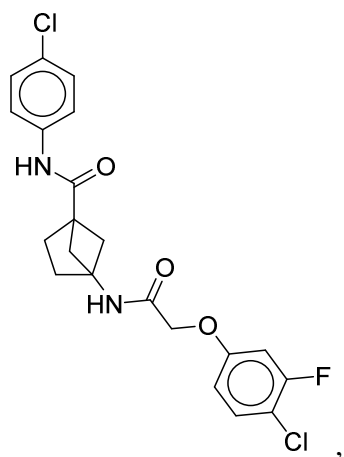
L^1 is CH_2O^* or $CH_2CH_2O^*$, wherein “ * ” indicates the attachment point to A;
 each R^X is independently fluoro, oxo, $-OH$, $-OCH_3$, $-C(O)OH$, or $-C(O)OCH_3$;
 each R^Y is independently hydrogen, bromo, chloro, fluoro, iodo, $-CF_3$, $-CHF_2$,
 $-CH_2CF_3$, $-CH_3$, $-CH_2CH_3$, $-OH$, $-CH_2OH$, $-C(CH_3)_2OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCF_3$,
 $-OCH_2CF_3$, $-S(O)_2CH_3$, $-S(O)_2CH_2CH_2CH_3$, $-CN$, $-N(CH_3)_2$, $-SF_5$, $-SCH_3$, $-NH_2$, $-C(CH_3)_3$,
 $-CH(CH_3)_2$, $-CH_2CN$, $-CH_2NH_2$, $-CH(OH)CH_3$, $-C(OH)(CH_3)CF_3$, $-S(O)_2CH_3$, $-C(O)CH_3$,
 $-C(O)OCH_3$, $-C(O)OH$, $-OCHF_2$ or G^1 ; or
 2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a
 furanyl, pyrrolyl, or dioxolanyl ring, each of which is optionally substituted with 1-2 R^X ; and
 each of R^1 and R^2 is hydrogen or $-CH_3$.

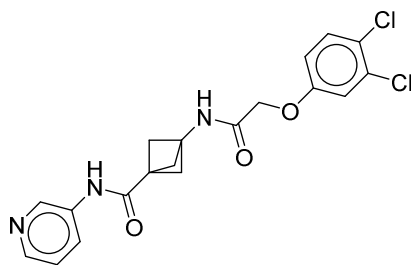
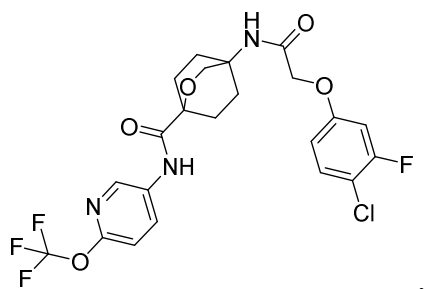
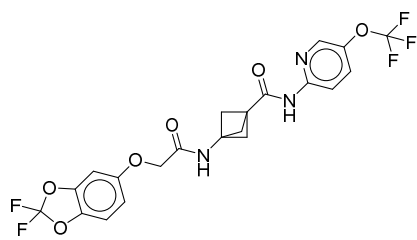
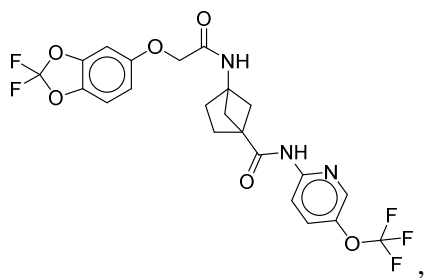
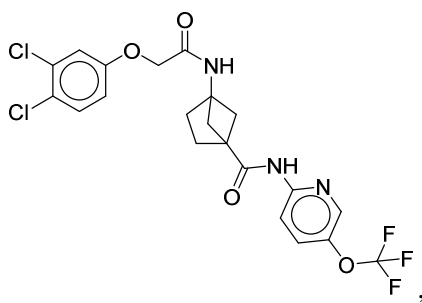
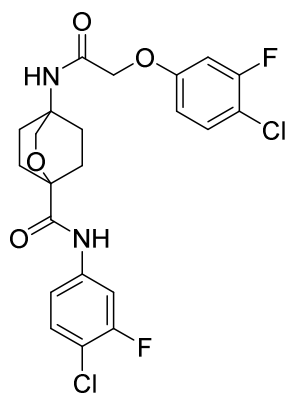
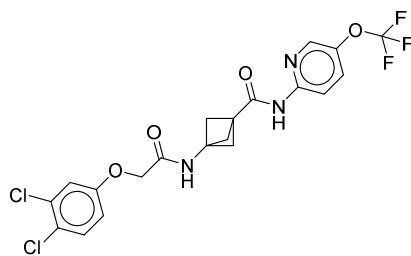
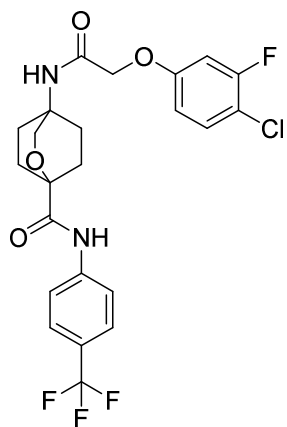
8. A compound, wherein the compound is selected from the group consisting of:

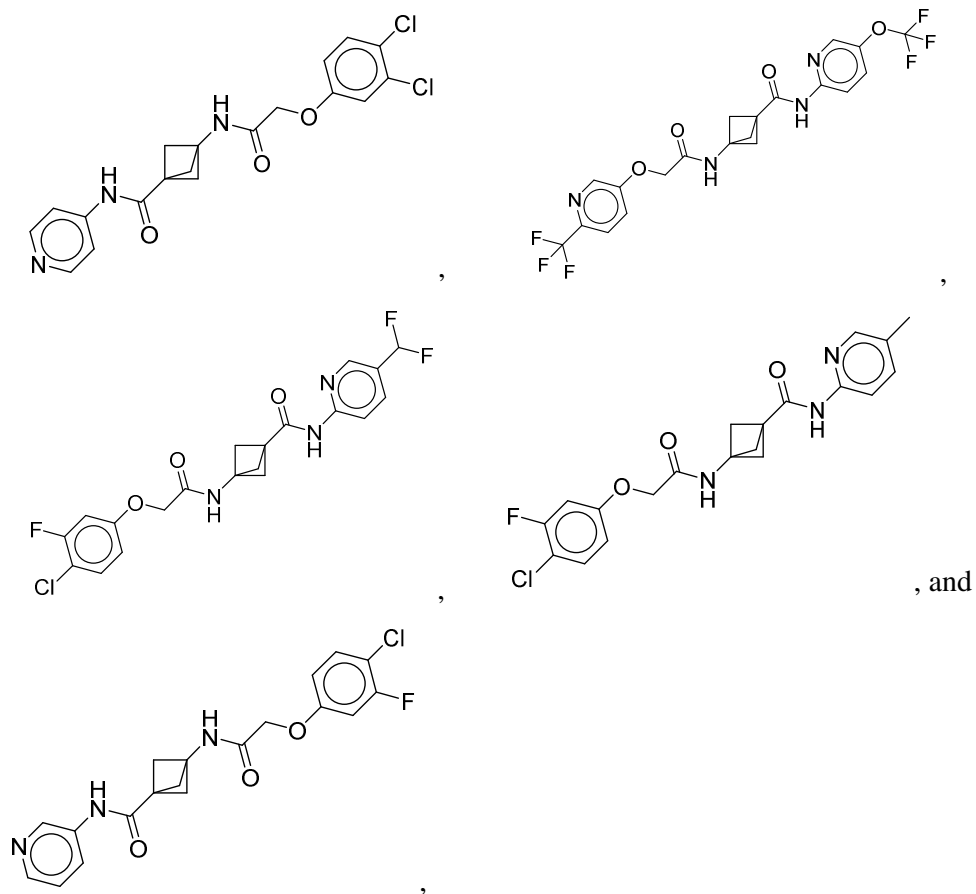












or a pharmaceutically acceptable salt thereof.