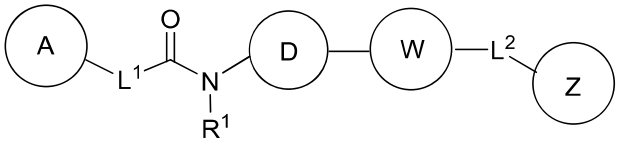
5233). The exchange of GDP with GTP in eIF2 is catalyzed by its dedicated guanine nucleotide exchange factor (GEF) eIF2B. eIF2B exists as a decamer ($B1_2\,B2_2\,B3_2\,B4_2\,B5_2$) or dimer of two pentamers in cells (Gordiyenko, Y. et al, Nat Commun (2014) 5:3902; Wortham, N.C. et al, *FASEB J* (2014) 28:2225-2237). Molecules such as ISRIB interact with and stabilize the eIF2B dimer conformation, thereby enhancing intrinsic GEF activity and making cells less sensitive to the cellular effects of phosphorylation of eIF2α (Sidrauski, C. et al, *eLife* (2015) e07314; Sekine, Y. et al, *Science* (2015) 348:1027-1030). As such, small molecule therapeutics that can modulate eIF2B activity may have the potential to attenuate the PERK branch of the UPR and the overall ISR, and therefore may be used in the prevention and/or treatment of various diseases, such as a neurodegenerative disease, a leukodystrophy, cancer, an inflammatory disease, a musculoskeletal disease, or a metabolic disease.

SUMMARY

In one aspect, the present disclosure refers to a compound of Formula (I):



Formula (I)

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

D is a bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, cubanyl, cyclohexyl, cyclobutyl, or tetrahydropyranyl wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, cubanyl, cyclohexyl, cyclobutyl, or tetrahydropyranyl is optionally substituted on one or more available carbons with 1-4 R^X; and wherein if the bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may optionally be substituted with R^{N1};

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

L^2 is C_1-C_6 alkylene, 2-7 membered heteroalkylene, a bond, $–NR^{N2}–$, –O–, or $–S(O)_w–$ (wherein w is 0, 1 or 2); wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L2};

R^1 is hydrogen or C_1-C_6 alkyl;

W is a 3-7-membered saturated, or partially unsaturated, monocyclic nitrogen-containing heterocyclyl; wherein the 3-7-membered saturated or partially unsaturated

monocyclic heterocyclyl is optionally substituted on one or more available carbons with 1-5 R^W; and wherein if the 3-7-membered saturated or partially unsaturated monocyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N3}; and wherein W is attached to D through an available nitrogen atom or carbon atom within W;

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

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

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

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

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

R^{N3} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

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

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

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

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

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

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

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

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

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

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

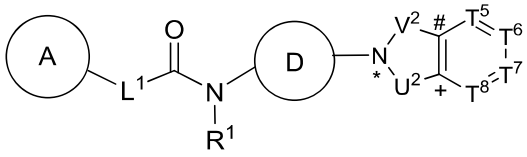
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

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

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

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

In another aspect, the present disclosure refers to a compound of Formula (II):



Formula (II)

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

D is bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane, cyclohexyl, cyclobutyl, or tetrahydropyranyl each of which is optionally substituted with 1-4 R^X groups;

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

R^1 is hydrogen or C_1-C_6 alkyl;

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

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

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

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

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

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

V^2 is selected from the group consisting of *–$C(R^{V21}R^{V22})$–$^\#$, *–$C(R^{V21}R^{V22})$–$C(R^{V23}R^{V24})$–$^\#$, *–$C(R^{V21}R^{V22})$–$C(R^{V23}R^{V24})$–$C(R^{V23}R^{V24})$–$^\#$, *–$C(R^{V21}R^{V22})$–$C(R^{V21}R^{V22})$–O–$^\#$, *–$C(R^{V21}R^{V22})$–$C(R^{V21}R^{V22})$–NR^{N4}–$^\#$, –$C(R^{V21}R^{V22})$–NR^{N4}–$^\#$, *–C(O)–$C(R^{V23}R^{V24})$–$^\#$, *–C(O)–$C(R^{V23}R^{V24})$–$C(R^{V23}R^{V24})$–$^\#$, *–C(O)–NR^{N4}–$^\#$, *–C(O)–$^\#$, and *–C(O)–O–$^\#$, wherein "*–" and "–$^\#$" indicate the attachment points of V^2 as indicated in Formula (II);

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

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

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

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

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

each R^{L1} 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

In yet another aspect, the present disclosure refers to a compound selected from any compound set forth in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof.

In a further aspect, the present disclosure refers to a pharmaceutically acceptable composition comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure refers to a use of a composition in the manufacture of a medicament for treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease in a subject, wherein the composition comprises a compound disclosed herein.

In yet another aspect, the present disclosure refers to a use of a composition in the manufacture of a medicament for treating a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway, wherein the composition comprises a compound disclosed herein.

In a further aspect, the present disclosure refers to a use of a composition in combination with an immunotherapeutic agent, in the manufacture of a medicament for treating cancer in a subject, wherein the composition comprises a compound disclosed herein.

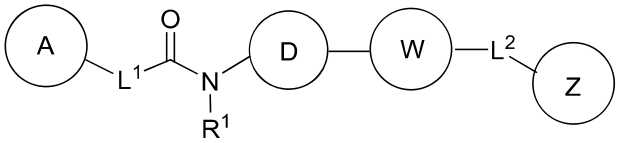
In another aspect, the present disclosure refers to a composition for use in treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease in a subject; or

for use in in treating a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway; or

for use in treating cancer in a subject in combination with an immunotherapeutic agent, wherein the composition comprises a compound disclosed herein.

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

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



Formula (I)

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

D is a bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, cubanyl, cyclohexyl, cyclobutyl, or tetrahydropyranyl wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, cubanyl, cyclohexyl, cyclobutyl, or tetrahydropyranyl is optionally substituted on

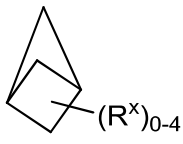
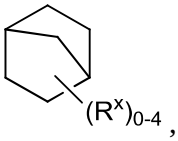
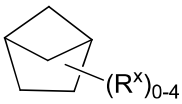
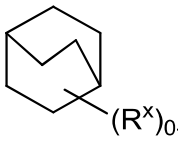
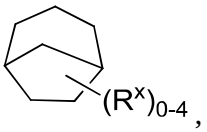
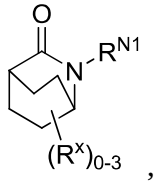
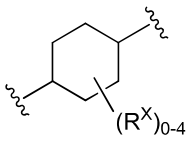
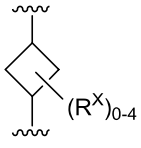
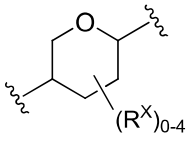
each R^F is independently hydrogen, C_1-C_6 alkyl, or halo; and

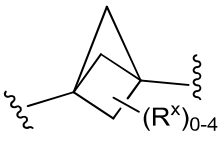
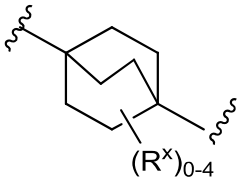
m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

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

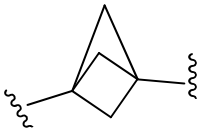
In some examples, D is a bridged bicyclic 5-8 membered cycloalkyl, a bridged bicyclic 5-8 membered heterocyclyl, a cyclohexyl, a cyclobutyl, or a tetrahydropyranyl, each optionally substituted with 1-4 R^X.

In some examples, D is bicyclo[1.1.1]pentane, bicyclo[2.2.1]heptane, bicyclo[2.1.1]hexane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, 2-azabicyclo[2.2.2]octane, cyclohexyl, cyclobutyl, or tetrahydropyranyl, each of which is optionally substituted with 1-4 R^X groups.

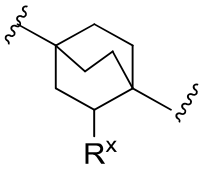
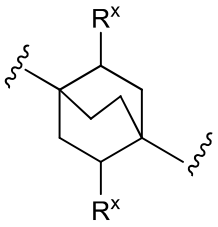
In some examples, D is , , , , , , , , or .

In some examples, D is  or .

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

In some examples, D is .

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

In some examples, D is  or .

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

In some examples, L^1 is 2-7 membered heteroalkylene optionally substituted by 1-5 R^{L1}; and L^2 is C_1-C_6 alkylene optionally substituted by 1-5 R^{L2}, 2-7 membered heteroalkylene optionally substituted by 1-5 R^{L2}, a bond, $–NR^{N2}–$, or –O–.

In some examples, L^1 is 2-7 membered heteroalkylene optionally substituted by 0 R^{L1}; and L^2 is C_1-C_6 alkylene optionally substituted by 0 R^{L2}, 2-7 membered heteroalkylene optionally substituted by 0 R^{L2}, a bond, $–NR^{N2}–$, or –O–.

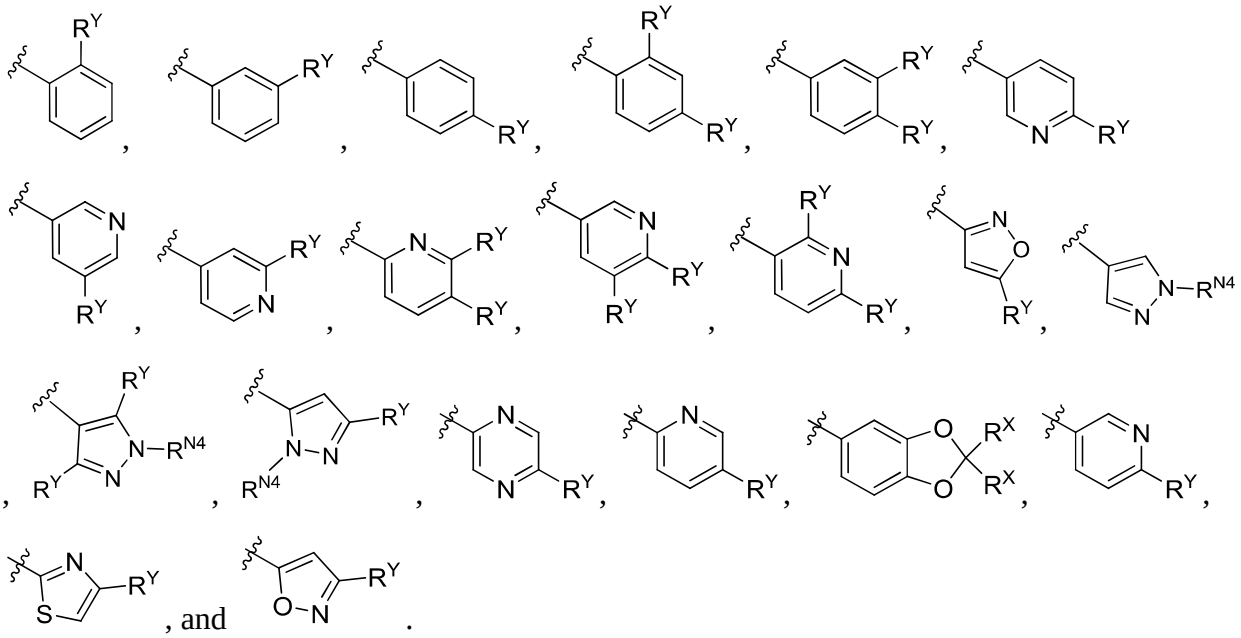
In some examples, L^1 is a bond, $CH_2O–*$, $CH_2CH_2O–*$ $OCH_2–*$ or $CH_2OCH_2–*$; and L^2 is selected from a bond, $CH_2O–*$, $–OCH_2–*$, $–CH_2–$, –NH–, $–NCH_3–$, or –O–, wherein "-*" indicates the attachment point to A or Z, respectively.

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

In some examples, each of A and Z is independently phenyl or 5-6-membered heteroaryl; wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y, and each R^Y is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, halo, cyano, $–OR^A$, or G^1.

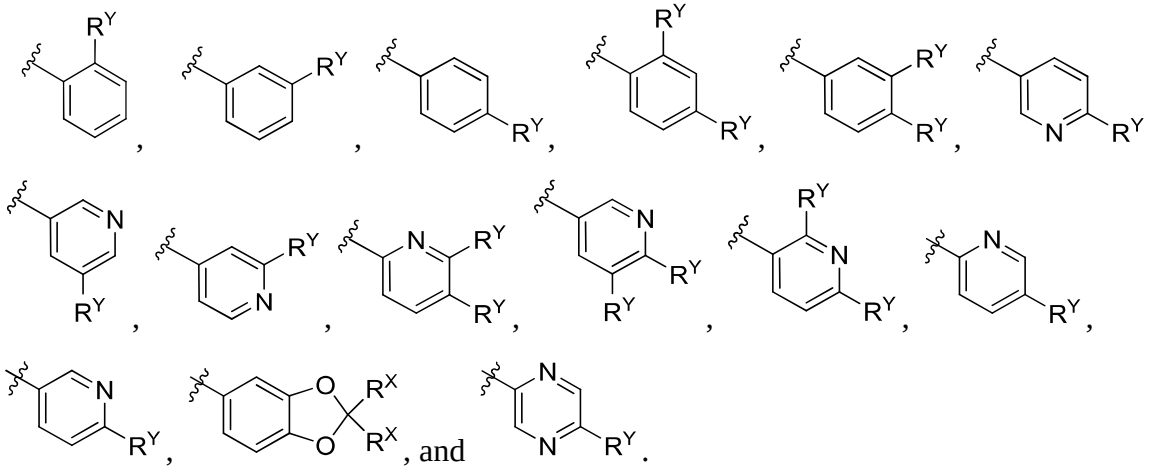
In some examples, each of A and Z is independently phenyl, pyridyl, isoxazolyl, pyrazinyl, thiazolyl, or pyrazolyl, each of which is optionally substituted with 1-5 R^Y groups.

In some examples, , each of A and Z is independently selected from the group consisting of:



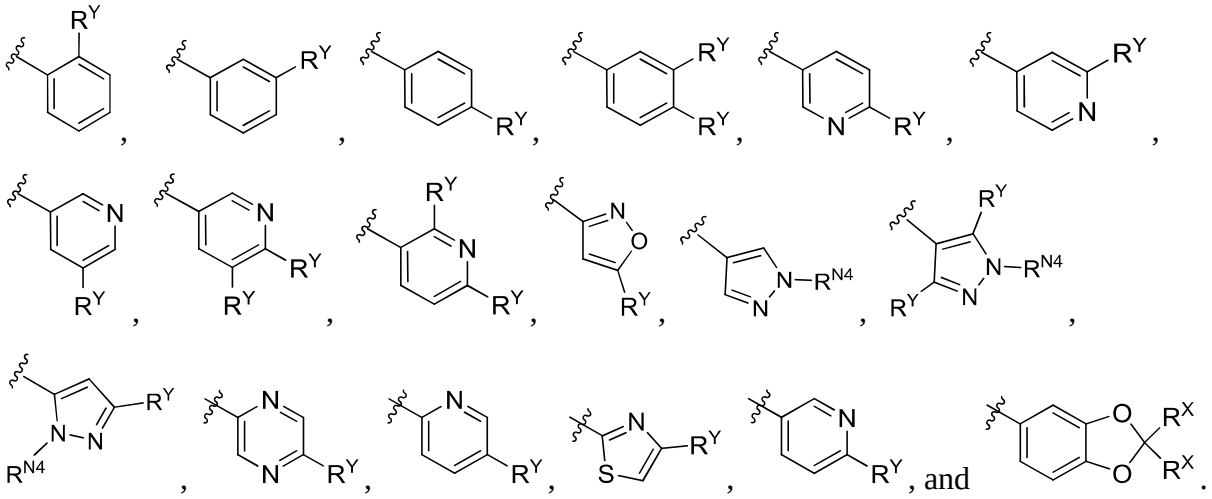
In some examples, A is phenyl or pyridyl, each of which is optionally substituted with 1-2 R^Y groups.

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



In some examples, Z is phenyl, pyridyl, isoxazolyl, thiazolyl, pyrazinyl or pyrazolyl, each of which is optionally substituted with 1-3 R^Y groups.

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



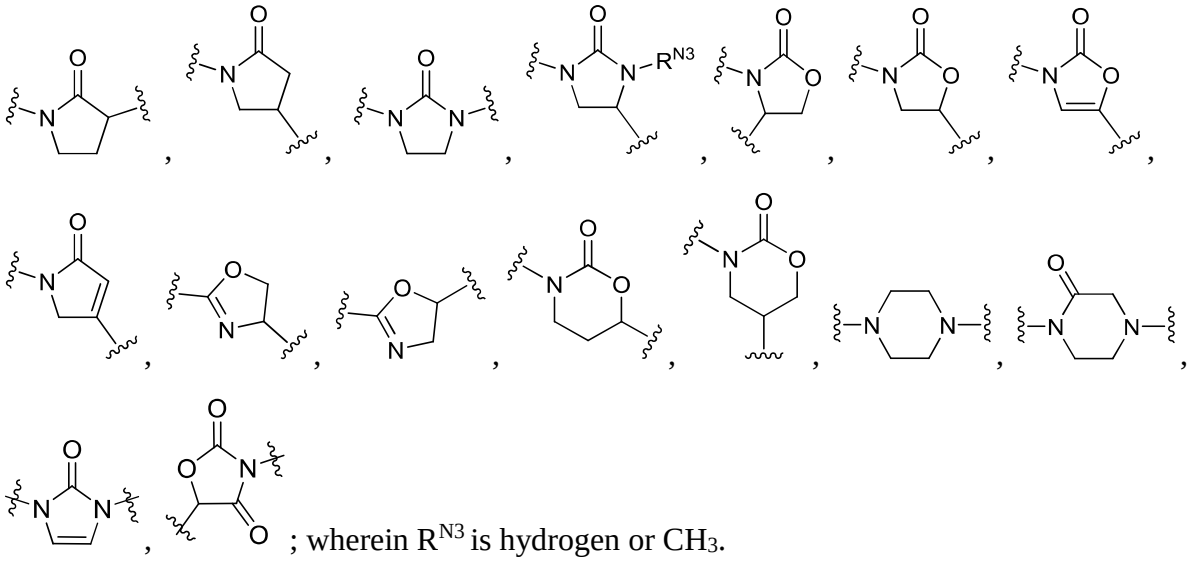
wherein R^{N4} is hydrogen or CH_3.

In some examples, each R^Y is independently hydrogen, chloro, fluoro, CF_3, CHF_2, CH_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, OCF_3, $OCH(CH_3)_2$, or CN.

In some examples, W is a pyrrolidinone, imidazolidinone, dihydroimidazolidinone, oxazolidinone, oxazolidinedione, oxazolone, dihydropyrrolone, piperazine, piperazinone, oxazinanone, or dihydrooxazole moiety, each of which is optionally substituted with 1-4 R^W groups.

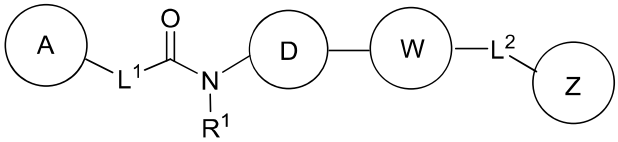
In some examples, W is a pyrrolidin-2-one, imidazolidin-2-one, oxazolidin-2-one, oxazol-2-one, 1,5-dihydropyrrol-2-one, piperazine, piperazinone, 1,3-oxazinan-2-one, 4,5-dihydrooxazole, 1,3-dihydro-2*H*-imidazol-2-one, oxazolidine-2,4-dione, moiety, each of which is optionally substituted with 1-4 R^W groups, and each R^W is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, oxo, cyano, or $–OR^A$.

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



; wherein R^{N3} is hydrogen or 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, *N*-oxide, or stereoisomer thereof, wherein:

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

L^1 is CH_2O–* or CH_2OCH_2–*, wherein "-*" indicates the attachment point to A;

L^2 is selected from a bond, CH_2O–*, –OCH_2–*, –CH_2–, –NH–, –NCH_3–, or –O–, wherein "-*" indicates the attachment point to Z;

W is a pyrrolidinone, imidazolidinone, dihydroimidazolidinone, oxazolidinone, oxazolidinedione, oxazolone, dihydropyrrolone, piperazine, piperazinone, oxazinanone, or dihydrooxazole moiety, each of which is optionally substituted with 1-4 R^W groups.and wherein the imidazolidinone may be optionally substituted on an available nitrogen with hydrogen or CH_3;

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

Z is phenyl, pyridyl, isoxazolyl, thiazolyl, pyrazinyl 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;

each R^W is independently fluoro, chloro, oxo, OH, OCH_3, CHF_2, OCF_3, CF_3, CH_3, CH_2CH_3, or $CH(CH_3)_2$;

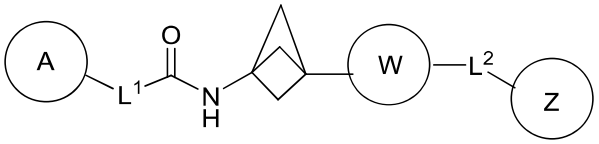
each R^X is independently fluoro, oxo, OH, OCH_3, C(O)OH, or $C(O)OCH_3$;

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

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

R^1 is hydrogen.

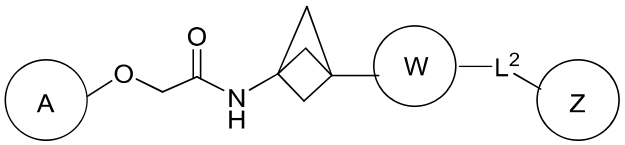
In some examples, the compound of Formula (I) is a compound of Formula (I-b):



Formula (I-b)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof, wherein each of A, W, Z, L^1, and L^2 is defined as for Formula (I).

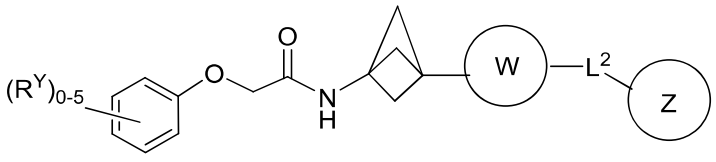
In some examples, the compound of Formula (I) is a compound of Formula (I-c):



Formula (I-c)

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

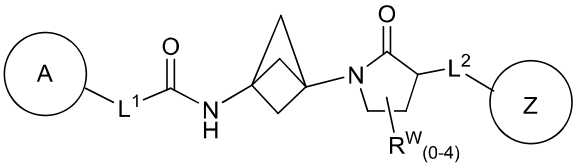
In some examples, the compound of Formula (I) is a compound of Formula (I-d):



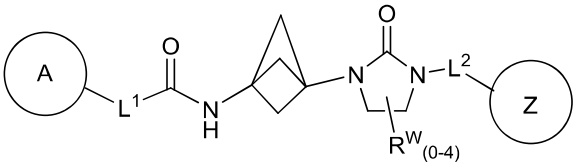
Formula (I-d)

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

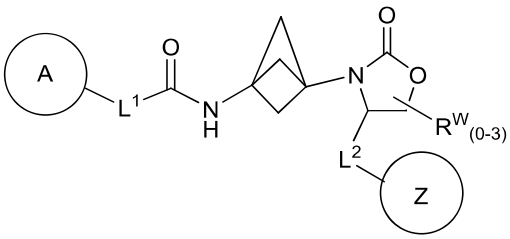
In some examples, the compound of Formula (I) is a compound of Formula (I-e-1), Formula (I-e-2), Formula (I-e-3), Formula (I-e-4), Formula (I-e-5), Formula (I-e-6), Formula (I-e-7), Formula (I-e-8), Formula (I-e-9), Formula (I-e-10), Formula (I-e-11), Formula (I-e-12), Formula (I-e-13), Formula (I-e-14), or Formula (I-e-15):



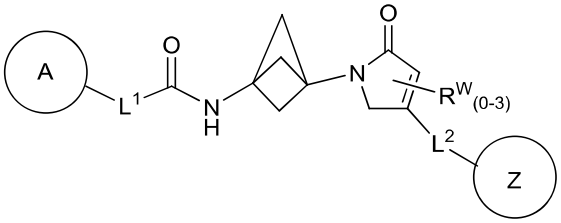
Formula (I-e-1)



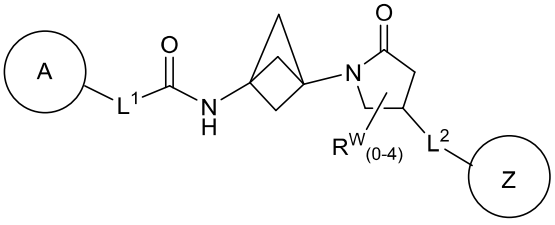
Formula (I-e-2)



Formula (I-e-3)

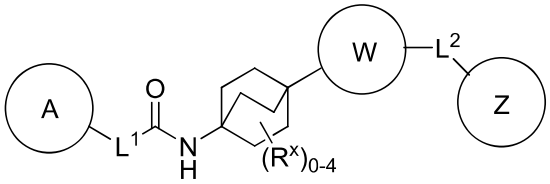


Formula (I-e-4)



Formula (I-e-5)

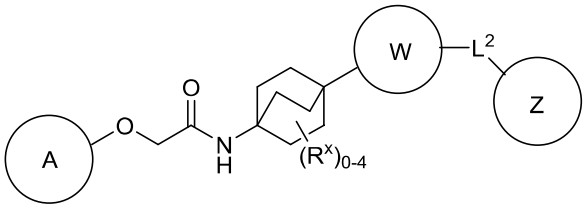
In some examples, the compound of Formula (I) is a compound of Formula (I-f):



Formula (I-f)

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

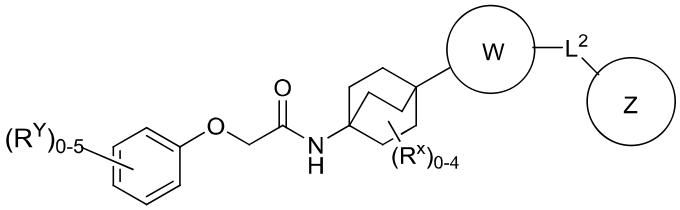
In some examples, the compound of Formula (I) is a compound of Formula (I-g):



Formula (I-g)

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

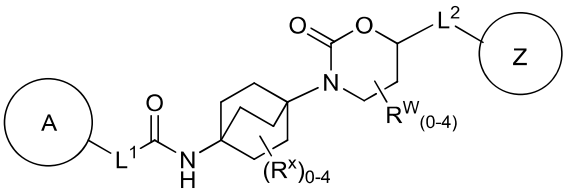
In some examples, the compound of Formula (I) is a compound of Formula (I-h):



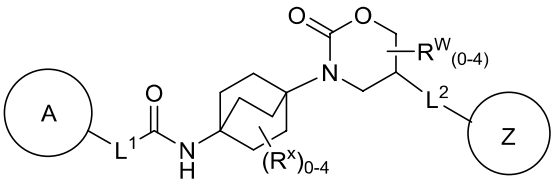
Formula (I-h)

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

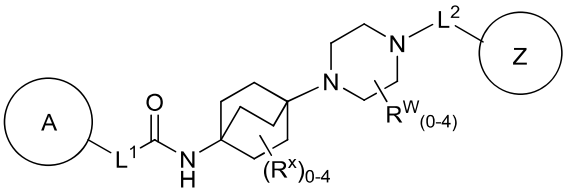
In some examples, the compound of Formula (I) is a compound of Formula (I-i-1), Formula (I-i-2), Formula (I-i-3), Formula (I-i-4), Formula (I-i-5), Formula (I-i-6), Formula (I-i-7), Formula (I-i-8), Formula (I-i-9), Formula (I-i-10), Formula (I-i-11), Formula (I-i-12), Formula (I-i-13), Formula (I-i-14), or Formula (I-i-15):



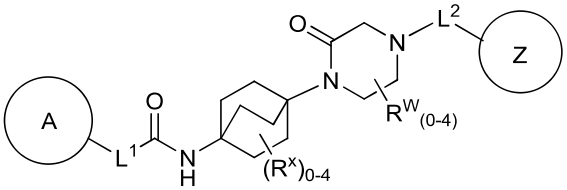
Formula (I-i-11)



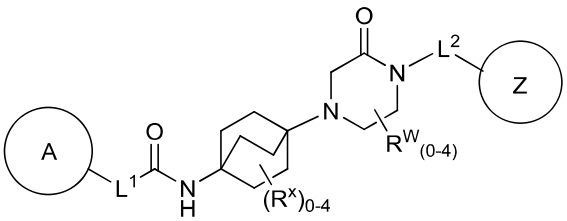
Formula (I-i-12)



Formula (I-i-13)



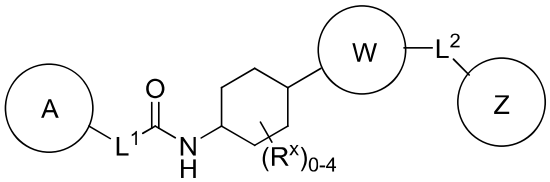
Formula (I-i-14)



Formula (I-i-15)

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

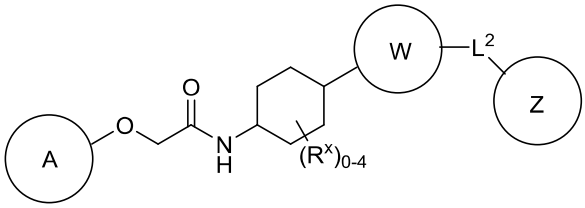
In some examples, the compound of Formula (I) is a compound of Formula (I-j):



Formula (I-j)

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

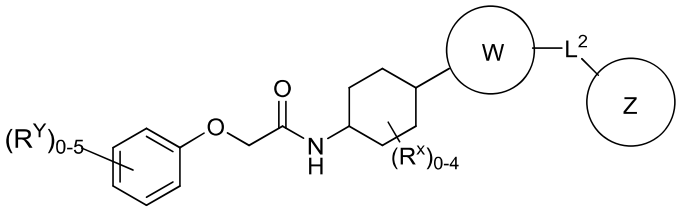
In some examples, the compound of Formula (I) is a compound of Formula (I-k):



Formula (I-k)

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

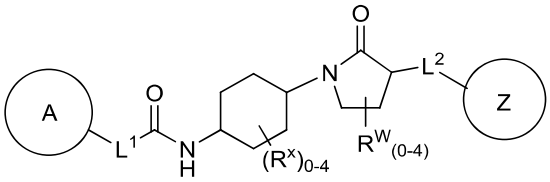
In some examples, the compound of Formula (I) is a compound of Formula (I-l):



Formula (I-l)

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

In some examples, the compound of Formula (I) is a compound of Formula (I-m-1), Formula (I-m-2), Formula (I-m-3), Formula (I-m-4), Formula (I-m-5), Formula (I-m-6), Formula (I-m-7), Formula (I-m-8), Formula (I-m-9), Formula (I-m-10), Formula (I-m-11), Formula (I-m-12), Formula (I-m-13), Formula (I-m-14), or Formula (I-m-15):



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

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

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

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

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

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

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

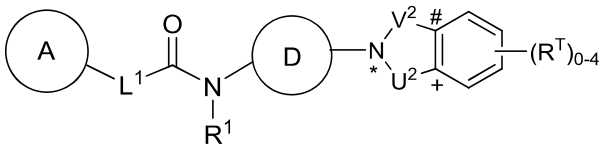
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

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

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

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

In some examples, the compound is represented by:



.

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

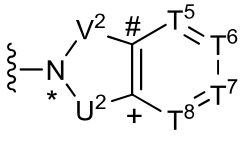
In some examples, each of R^{V21} and R^{V22} is independently selected from the group consisting of hydrogen, -OH, and C_1-C_3 alkyl.

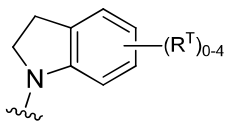
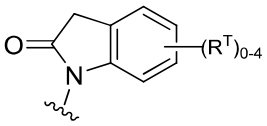
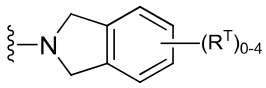
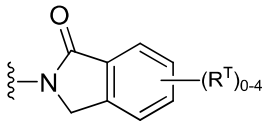
In some examples, each of R^{V21} and R^{V22} is hydrogen or -OH.

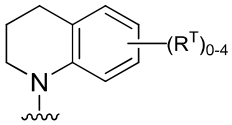
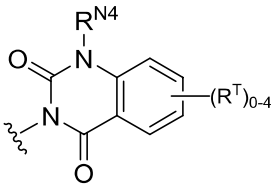
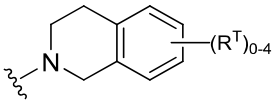
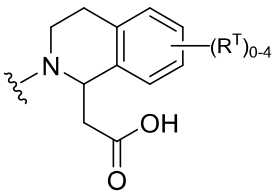
In some examples, each of R^{V23} and R^{V24} is independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, cyano, $–OR^A$, and $–NR^BR^C$.

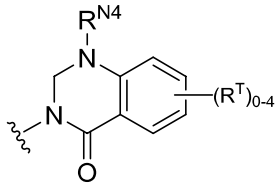
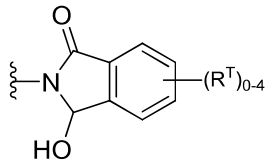
In some examples, each of R^{V23} and R^{V24} is hydrogen.

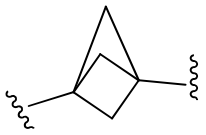
In some examples, U^2 is selected from the group consisting of a bond, $^*–C(O)–^+$, $^*–CH_2–^+$, and $^*–CH(CH_2CO_2H)–^+$, wherein "$^*–$" and "$–^+$" indicate the attachment points of U^2 as indicated in Formula (II); and V^2 is selected from the group consisting of $^*–CH_2–^\#$, $^*–CH_2–CH_2–^\#$,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

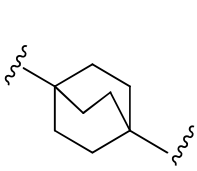
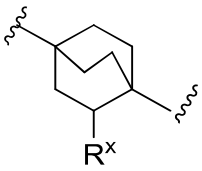
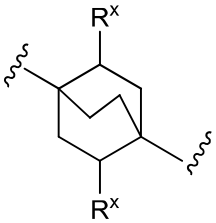
In some examples, the moiety  is selected from the group consisting of:

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, , , ,

, and ; wherein R^{N4} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and hydroxy-C_2-C_6 alkyl.

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

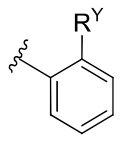
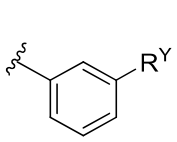
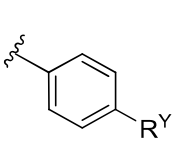
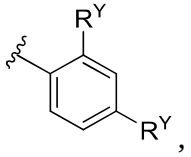
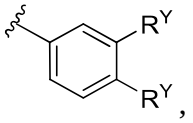
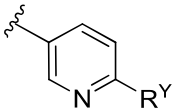
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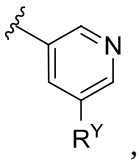
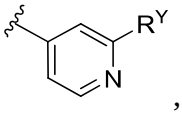
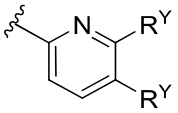
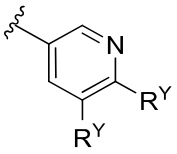
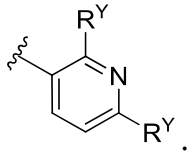
In some examples, each R^X is independently selected from the group consisting of oxo, –OH , –C(O)OH, –C(O)OR^D, halo, and hydroxy-C_1-C_6 alkyl.

In some examples, L^1 is CH_2O–* or CH_2OCH_2–*; wherein "-*" indicates the attachment point to A.

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

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

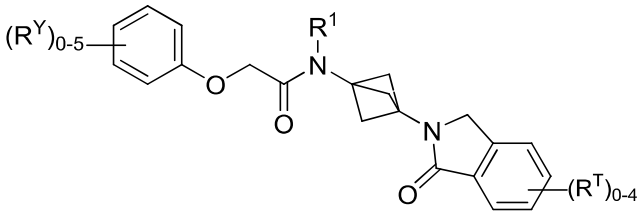
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, , , , and .

In some examples, each R^Y is independently hydrogen, chloro, fluoro, CF_3, CH_3, CHF_2, OCF_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, $OCH(CH_3)_2$, or CN.

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

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



Formula (II-a)

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

R^1 is hydrogen or CH_3;

each R^Y is independently hydrogen, chloro, fluoro, CF_3, CH_3, CH_2CH_3, $CH(CH_3)_2$, OCH_3, $OCH(CH_3)_2$, or CN; and

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

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

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

In another example, the present disclosure features a method of treating a neurodegenerative disease, a leukodystrophy, 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, N-oxide or stereoisomer thereof, or a composition thereof, to a subject.

In some examples, the method comprises the treatment of a neurodegenerative disease. In some examples, the neurodegenerative disease comprises 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 eIF2α activity or level, modulation (e.g., an increase) in eIF2α phosphorylation, modulation (e.g., an increase) of phosphorylated eIF2α pathway activity, or modulation (e.g., an increase) of ISR activity in a subject, wherein the method comprises administering a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide or stereoisomer thereof, or a composition thereof, to a subject. In some examples, the disease

may be caused by a mutation to a gene or protein sequence related to a member of the eIF2 pathway (e.g., the eIF2α signaling pathway or ISR pathway).

In another example, the present disclosure features a method of treating 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, N-oxide 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 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 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 eIF2α activity or level, modulation (e.g., an increase) in eIF2α phosphorylation, modulation (e.g., an increase) of phosphorylated eIF2α pathway activity, or modulation (e.g., an increase) of ISR activity in a subject, wherein the composition comprises a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, N-oxide 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 eIF2α 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, N-oxide or stereoisomer thereof for use, e.g., in the modulation (e.g., activation) of eIF2B and the attenuation of the ISR signaling pathway.

Definitions

Chemical Definitions

Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

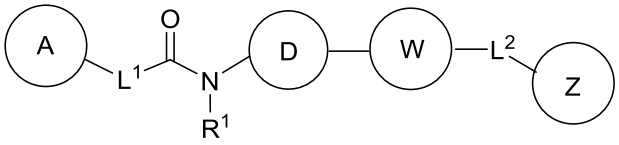
The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid

CLAIMS

We claim:

1. A compound of Formula (I):



Formula (I)

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

D is a bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, cubanyl, cyclohexyl, cyclobutyl, or tetrahydropyranyl wherein each bridged bicyclic cycloalkyl, bridged bicyclic heterocyclyl, cubanyl, cyclohexyl, cyclobutyl, or tetrahydropyranyl is optionally substituted on one or more available carbons with 1-4 R^X; and wherein if the bridged bicyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may optionally be substituted with R^{N1};

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

L^2 is C_1-C_6 alkylene, 2-7 membered heteroalkylene, a bond, $–NR^{N2}–$, –O–, or $–S(O)_w–$ (wherein w is 0, 1 or 2); wherein C_1-C_6 alkylene or 2-7 membered heteroalkylene is optionally substituted with 1-5 R^{L2};

R^1 is hydrogen or C_1-C_6 alkyl;

W is a 3-7-membered saturated, or partially unsaturated, monocyclic nitrogen-containing heterocyclyl; wherein the 3-7-membered saturated or partially unsaturated monocyclic heterocyclyl is optionally substituted on one or more available carbons with 1-5 R^W; and wherein if the 3-7-membered saturated or partially unsaturated monocyclic heterocyclyl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N3}; and wherein W is attached to D through an available nitrogen atom or carbon atom within W;

A and Z are each independently phenyl or 5-6-membered heteroaryl, wherein each phenyl or 5-6-membered heteroaryl is optionally substituted on one or more available carbons

with 1-5 R^Y; and wherein if the 5-6-membered heteroaryl contains a substitutable nitrogen moiety, the substitutable nitrogen may be optionally substituted by R^{N4};

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

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

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

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

R^{N3} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, hydroxy-C_2-C_6 alkyl, halo-C_2-C_6 alkyl, amino-C_2-C_6 alkyl, cyano-C_2-C_6 alkyl, $-C(O)NR^BR^C$, $–C(O)R^D$, $–C(O)OR^D$, and $–S(O)_2R^D$;

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

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

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

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

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

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

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

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

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

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

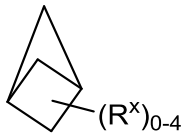
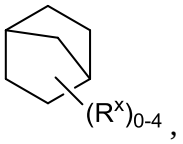
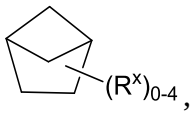
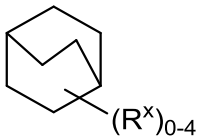
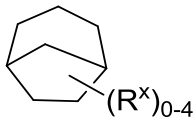
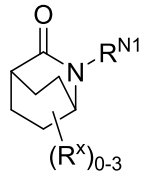
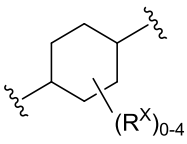
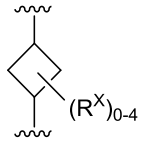
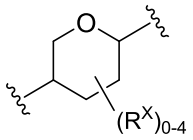
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

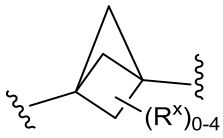
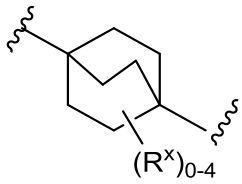
each R^E is independently hydrogen, C_1-C_6 alkyl, or halo-C_1-C_6 alkyl;

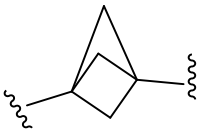
each R^F is independently hydrogen, C_1-C_6 alkyl, or halo; and

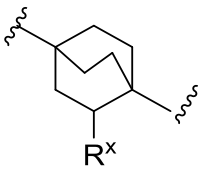
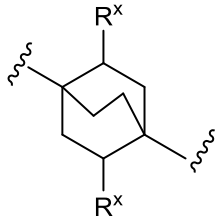
m is 1 when R^F is hydrogen or C_1-C_6 alkyl, 3 when R^F is C_1-C_6 alkyl, or 5 when R^F is halo.

2. The compound of claim 1, wherein D is a bridged bicyclic cycloalkyl (*e.g.*, a bridged bicyclic 5-8 membered cycloalkyl), a bridged bicyclic heterocyclyl (*e.g.*, a bridged bicyclic 5-8 membered heterocyclyl), a cyclohexyl, a cyclobutyl, or a tetrahydropyranyl, each optionally substituted with 1-4 R^X.

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

4. The compound of any one of claims 1-3, wherein D is  or .

5. The compound of any one of claims 1-4, wherein D is .

6. The compound of any one of claims 1-4, wherein D is  or .

7. The compound of claim 6, wherein each R^X is independently selected from the group consisting of oxo, $–OR^A$, –C(O)OH, $–C(O)OR^D$, halo, and hydroxy-C_1-C_6 alkyl.

8. The compound of any one of claims 1-7, wherein L^1 is 2-7 membered heteroalkylene optionally substituted by 1-5 R^{L1}; and L^2 is C_1-C_6 alkylene optionally substituted by 1-5 R^{L2}, 2-7 membered heteroalkylene optionally substituted by 1-5 R^{L2}, a bond, $–NR^{N2}–$, or –O–.

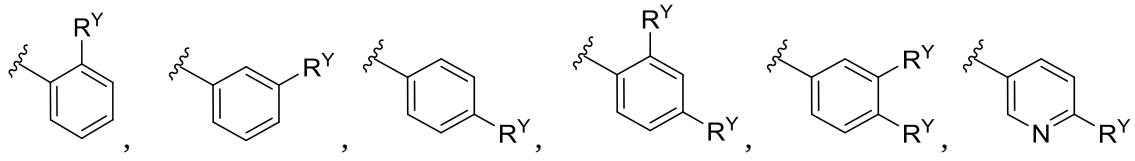
9. The compound of any one of claims 1-8, wherein L^1 is a bond, $CH_2O–*$, $CH_2CH_2O–*$ $OCH_2–*$ or $CH_2OCH_2–*$; and L^2 is selected from a bond, $CH_2O–*$, $–OCH_2–*$, $–CH_2–$, –NH–, $–NCH_3–$, or –O–, wherein "–*" indicates the attachment point to A or Z, respectively.

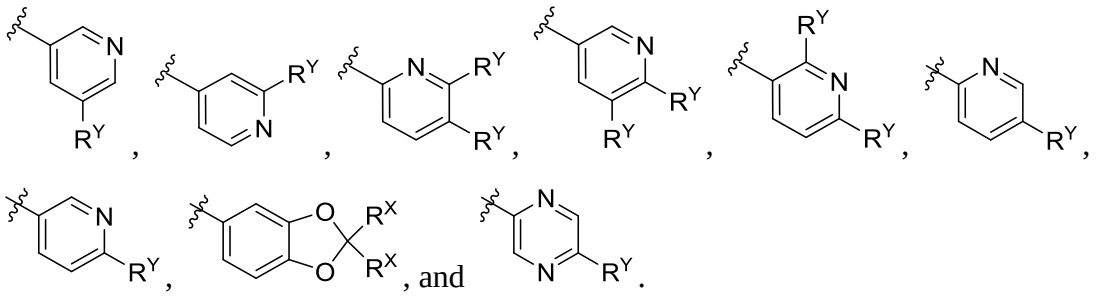
10. The compound of any one of claims 1-9, wherein R^1 is hydrogen or $–CH_3$.

11. The compound of any one of claims 1-10, wherein each of A and Z is independently phenyl or 5-6-membered heteroaryl; wherein each phenyl or 5-6-membered heteroaryl is optionally substituted with 1-5 R^Y, and each R^Y is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo-C_1-C_6 alkoxy, halo, cyano, $–OR^A$, or G^1.

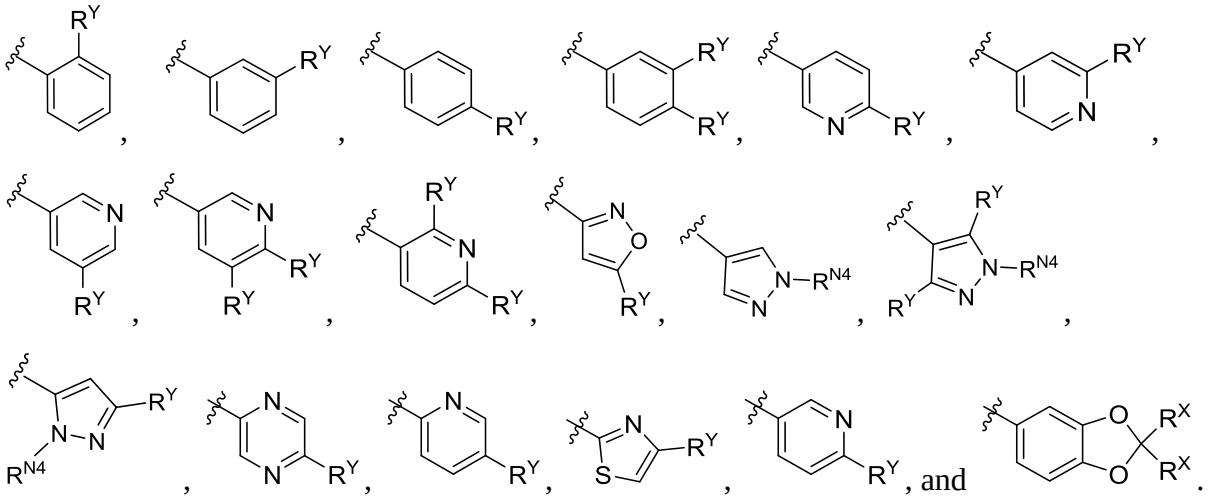
12. The compound of any one of claims 1-11, wherein each of A and Z is independently phenyl, pyridyl, isoxazolyl, pyrazinyl, thiazolyl, or pyrazolyl, each of which is optionally substituted with 1-5 R^Y groups.

13. The compound of any one of claims 1-12, wherein A is selected from the group consisting of:





14. The compound of any one of claims 1-13, wherein Z is selected from the group consisting of:



wherein R^{N4} is hydrogen or $–CH_3$.

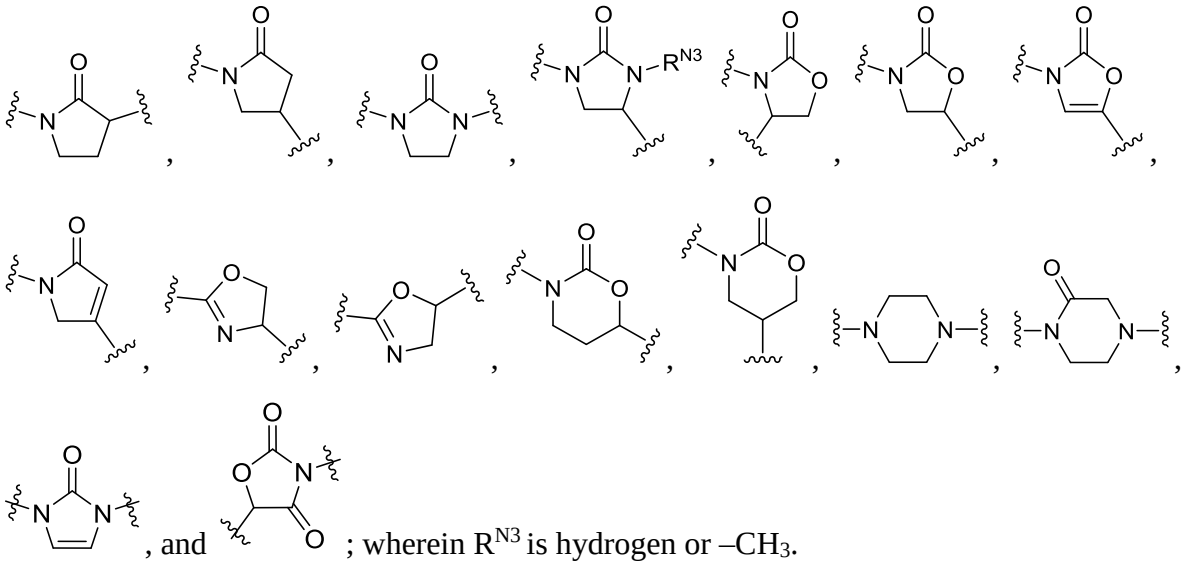
15. The compound of any one of claims 1-14, wherein each R^Y is independently hydrogen, chloro, fluoro, $–CF_3$, $–CHF_2$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCF_3$, $–OCH(CH_3)_2$, or –CN.

16. The compound of any one of claims 1-15, wherein W is a pyrrolidinone, imidazolidinone, dihydroimidazolidinone, oxazolidinone, oxazolidinedione, oxazolone, dihydropyrrolone, piperazine, piperazinone, oxazinanone, or dihydrooxazole moiety, each of which is optionally substituted with 1-4 R^W groups.

17. The compound of any one of claims 1-16, wherein W is a pyrrolidin-2-one, imidazolidin-2-one, oxazolidin-2-one, oxazol-2-one, 1,5-dihydropyrrol-2-one, piperazine, piperazinone, 1,3-

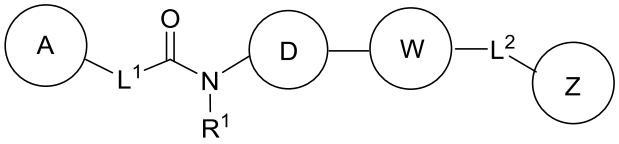
oxazinan-2-one, 4,5-dihydrooxazole, 1,3-dihydro-2*H*-imidazol-2-one, oxazolidine-2,4-dione, moiety, each of which is optionally substituted with 1-4 R^W groups, and each R^W is independently C_1-C_6 alkyl, halo-C_1-C_6 alkyl, halo, oxo, cyano, or $–OR^A$.

18. The compound of any one of claims 1-17, wherein W is selected from the group consisting of:



; wherein R^{N3} is hydrogen or $–CH_3$.

19. The compound of any one of claims 1-18, wherein the compound of Formula (I) is a compound of Formula (I-a):



Formula (I-a)

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

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

L^1 is CH_2O–* or CH_2OCH_2–*, wherein "–*" indicates the attachment point to A;

L^2 is selected from a bond, CH_2O–*, $–OCH_2$–*, $–CH_2–$, –NH–, $–NCH_3–$, or –O–, wherein "–*" indicates the attachment point to Z;

W is a pyrrolidinone, imidazolidinone, dihydroimidazolidinone, oxazolidinone, oxazolidinedione, oxazolone, dihydropyrrolone, piperazine, piperazinone, oxazinanone, or dihydrooxazole moiety, each of which is optionally substituted with 1-4 R^W groups; and wherein the imidazolidinone may be optionally substituted on an available nitrogen with hydrogen or $–CH_3$;

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

Z is phenyl, pyridyl, isoxazolyl, thiazolyl, pyrazinyl 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 $–CH_3$;

each R^W is independently fluoro, chloro, oxo, –OH, $–OCH_3$, $–CHF_2$, $–OCF_3$, $–CF_3$, $–CH_3$, $–CH_2CH_3$, or $–CH(CH_3)_2$;

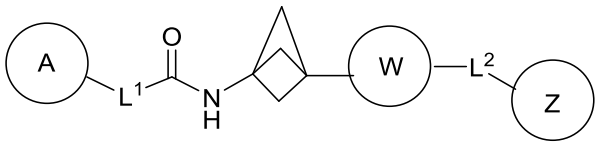
each R^X is independently fluoro, oxo, –OH, $–OCH_3$, –C(O)OH, or $–C(O)OCH_3$;

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

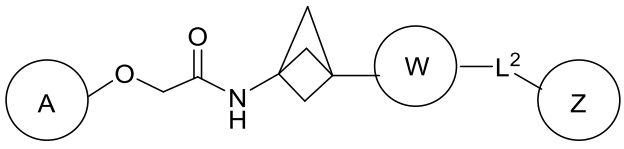
2 R^Y groups on adjacent atoms, together with the atoms to which they are attached form a furanyl, pyrrolyl, or dioxolanyl ring, each of which is optionally substituted with 1-2 R^X; and

R^1 is hydrogen.

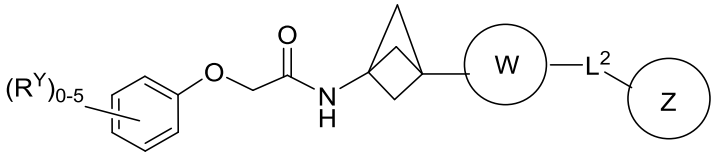
20. The compound of any one of claims 1-19, wherein the compound of Formula (I) is a compound of Formula (I-b), Formula (I-c), or Formula (I-d):



Formula (I-b)



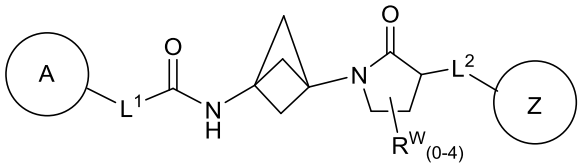
Formula (I-c)



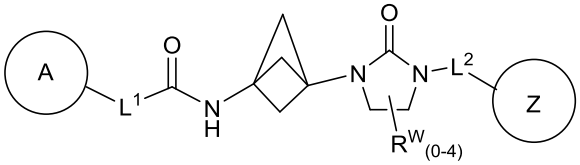
Formula (I-d)

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

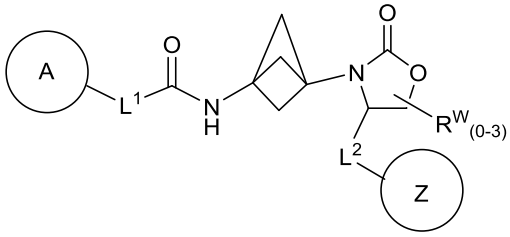
21. The compound of any one of claims 1-20, wherein the compound of Formula (I) is a compound of Formula (I-e-1), Formula (I-e-2), Formula (I-e-3), Formula (I-e-4), Formula (I-e-5), Formula (I-e-6), Formula (I-e-7), Formula (I-e-8), Formula (I-e-9), Formula (I-e-10), Formula (I-e-11), Formula (I-e-12), Formula (I-e-13), Formula (I-e-14), or Formula (I-e-15):



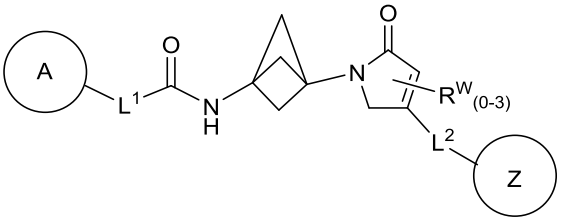
Formula (I-e-1)



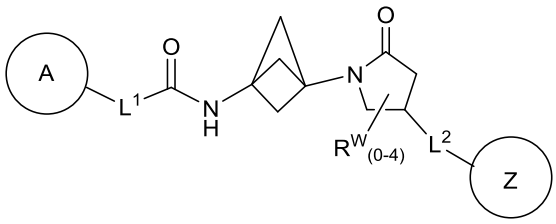
Formula (I-e-2)



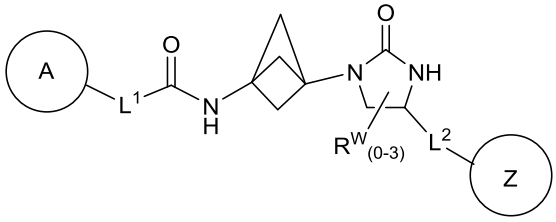
Formula (I-e-3)



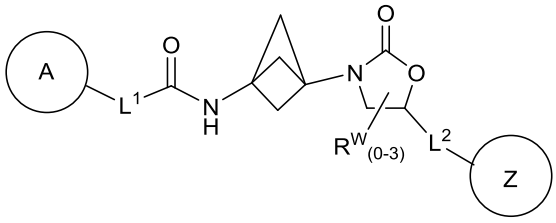
Formula (I-e-4)



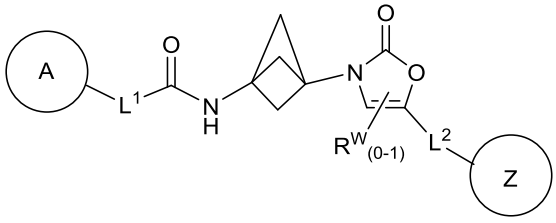
Formula (I-e-5)



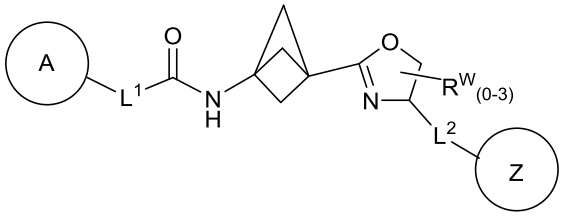
Formula (I-e-6)



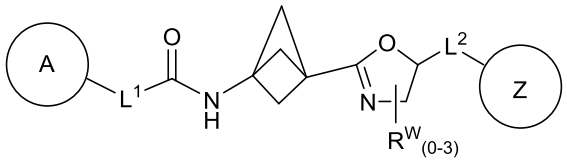
Formula (I-e-7)



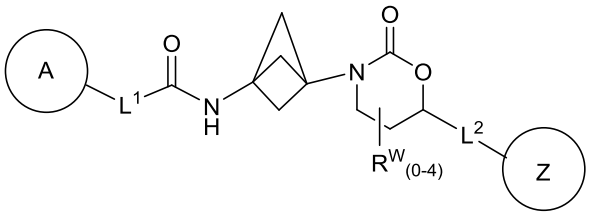
Formula (I-e-8)



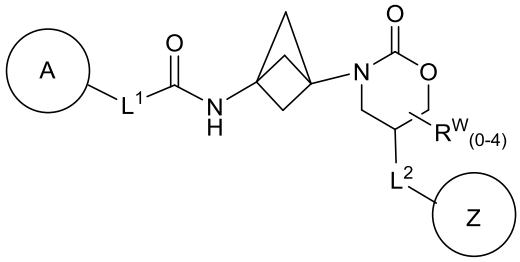
Formula (I-e-9)



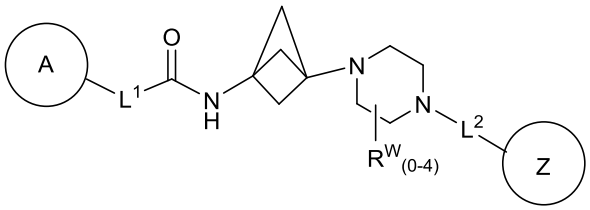
Formula (I-e-10)



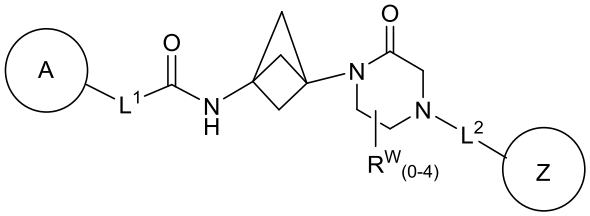
Formula (I-e-11)



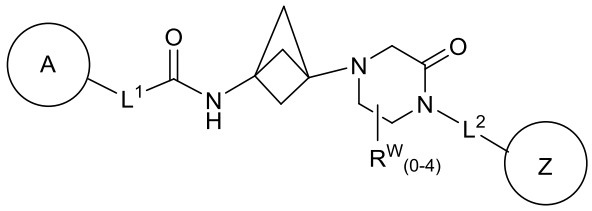
Formula (I-e-12)



Formula (I-e-13)



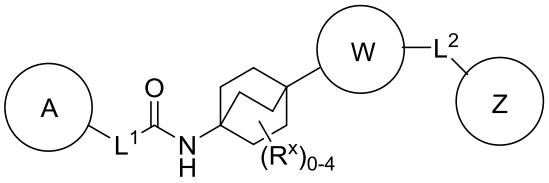
Formula (I-e-14)



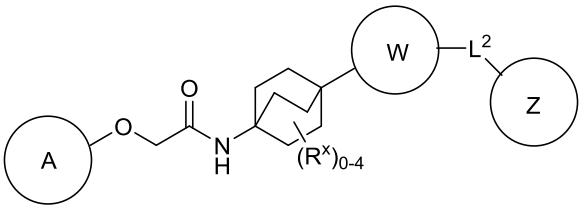
Formula (I-e-15)

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

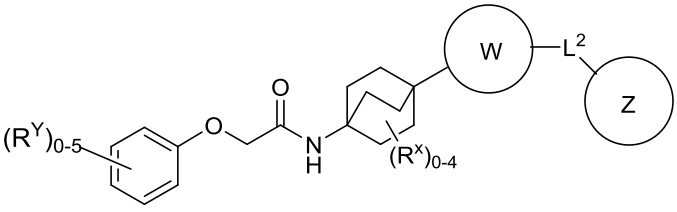
22. The compound of any one of claims 1-19, wherein the compound of Formula (I) is a compound of Formula (I-f), Formula (I-g), or Formula (I-h):



Formula (I-f)



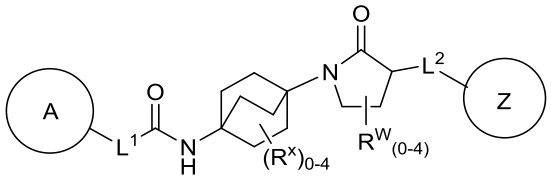
Formula (I-g)



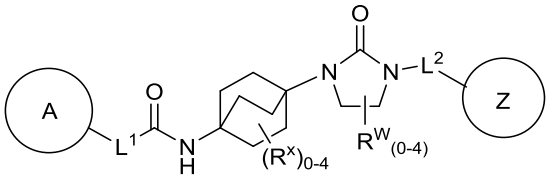
Formula (I-h)

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

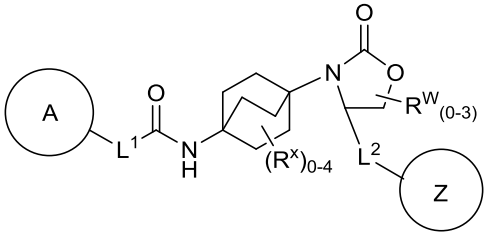
23. The compound of any one of claims 1-19 and 22, wherein the compound of Formula (I) is a compound of Formula (I-i-1), Formula (I-i-2), Formula (I-i-3), Formula (I-i-4), Formula (I-i-5), Formula (I-i-6), Formula (I-i-7), Formula (I-i-8), Formula (I-i-9), Formula (I-i-10), Formula (I-i-11), Formula (I-i-12), Formula (I-i-13), Formula (I-i-14), or Formula (I-i-15):



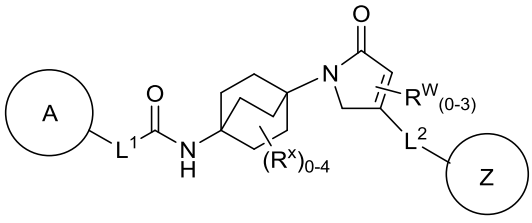
Formula (I-i-1)



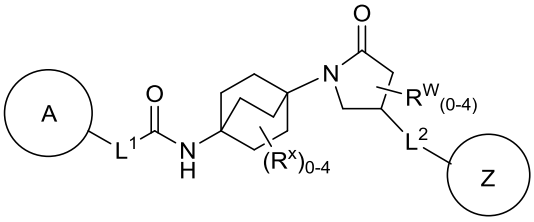
Formula (I-i-2)



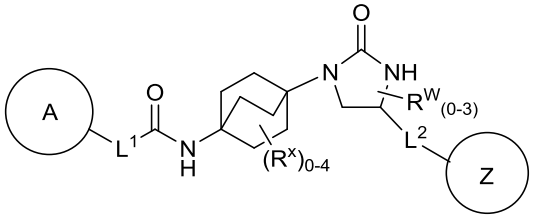
Formula (I-i-3)



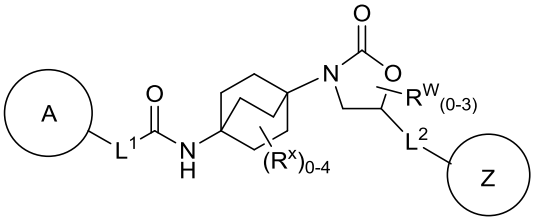
Formula (I-i-4)



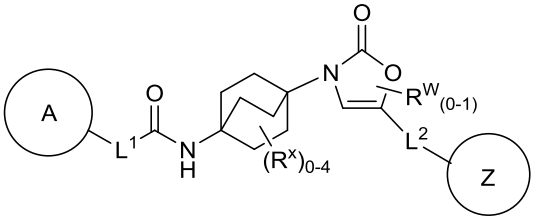
Formula (I-i-5)



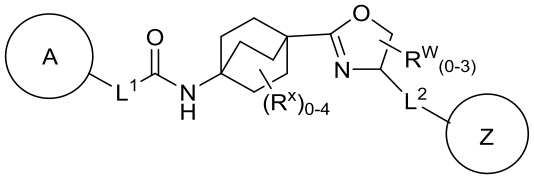
Formula (I-i-6)



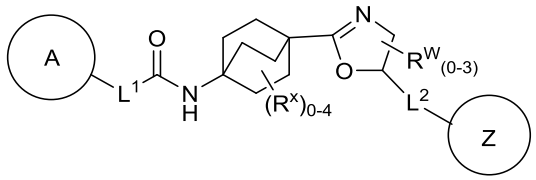
Formula (I-i-7)



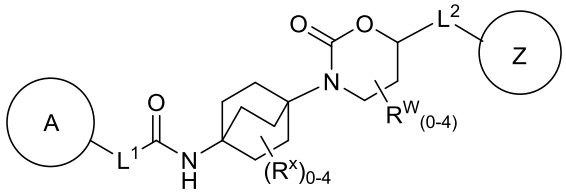
Formula (I-i-8)



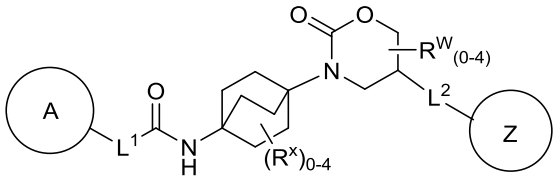
Formula (I-i-9)



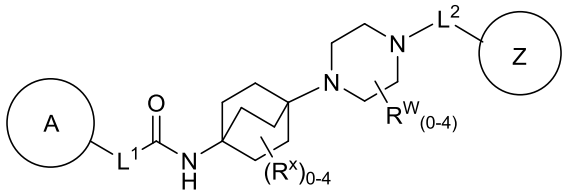
Formula (I-i-10)



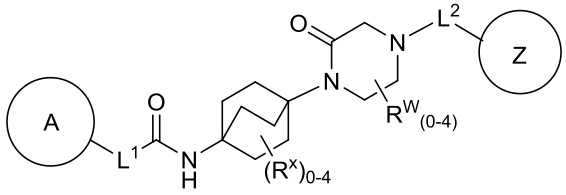
Formula (I-i-11)



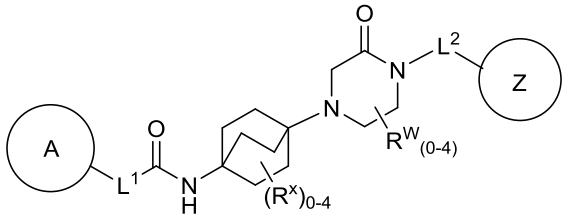
Formula (I-i-12)



Formula (I-i-13)



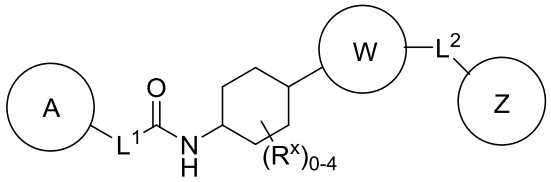
Formula (I-i-14)



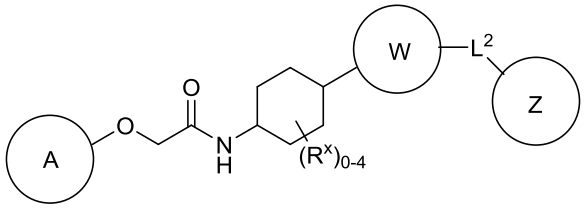
Formula (I-i-15)

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

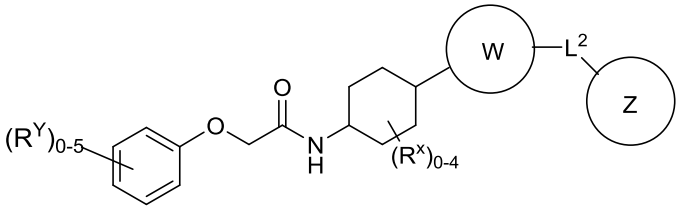
24. The compound of any one of claims 1-19, wherein the compound of Formula (I) is a compound of Formula (I-j), Formula (I-k), or Formula (I-l):



Formula (I-j)



Formula (I-k)

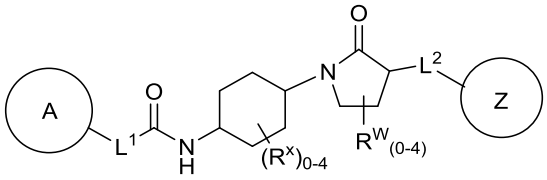


Formula (I-l)

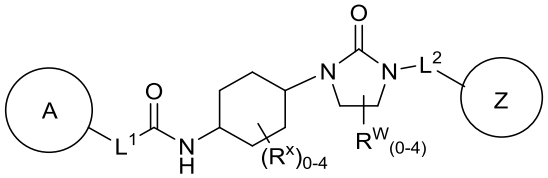
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof.

25. The compound of any one of claims 1-1 or 24, wherein the compound of Formula (I) is a compound of Formula (I-m-1), Formula (I-m-2), Formula (I-m-3), Formula (I-m-4), Formula (I-

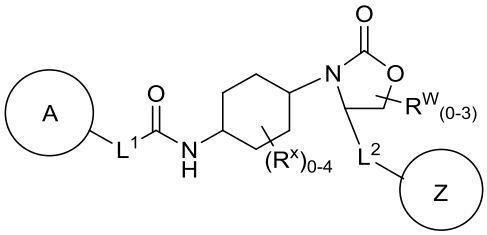
m-5), Formula (I-m-6), Formula (I-m-7), Formula (I-m-8), Formula (I-m-9), Formula (I-m-10), Formula (I-m-11), Formula (I-m-12), Formula (I-m-13), Formula (I-m-14), or Formula (I-m-15):



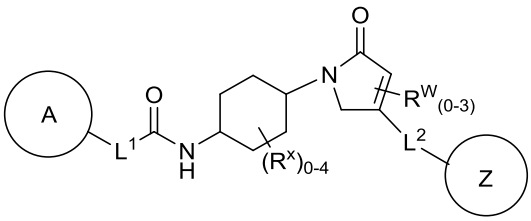
Formula (I-m-1)



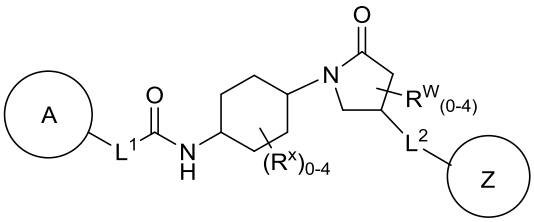
Formula (I-m-2)



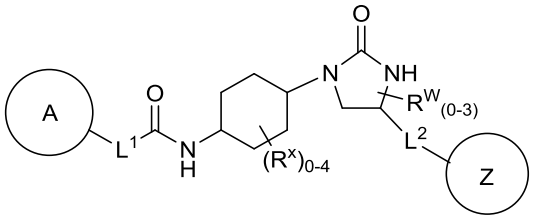
Formula (I-m-3)



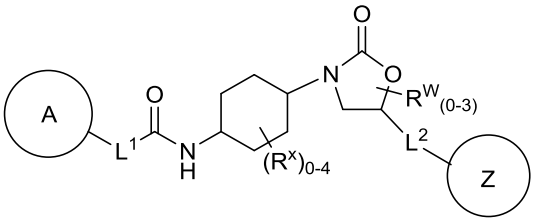
Formula (I-m-4)



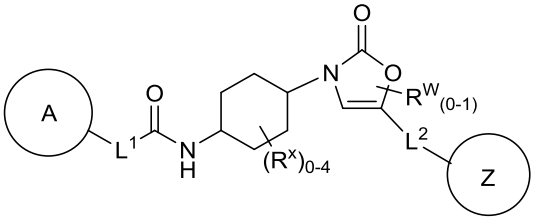
Formula (I-m-5)



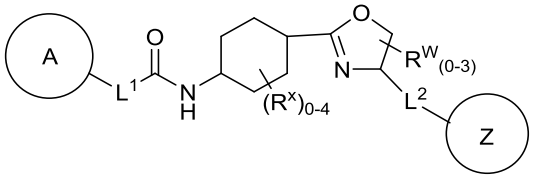
Formula (I-m-6)



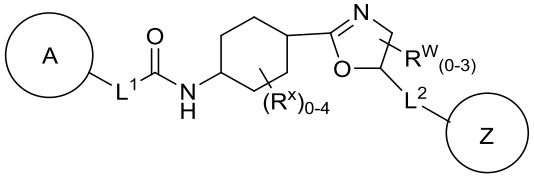
Formula (I-m-7)



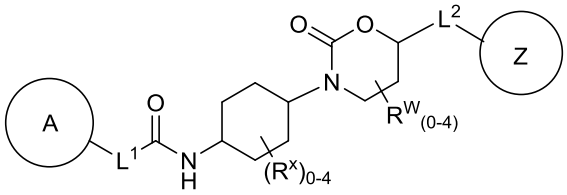
Formula (I-m-8)



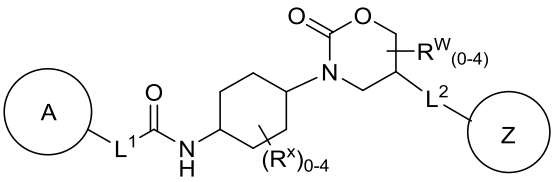
Formula (I-m-9)



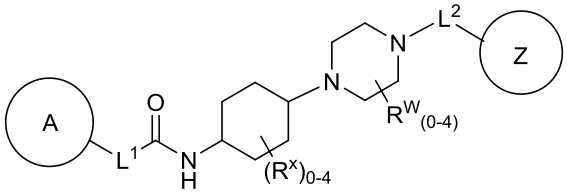
Formula (I-m-10)



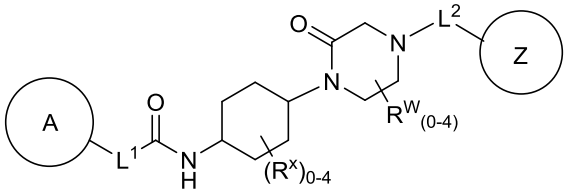
Formula (I-m-11)



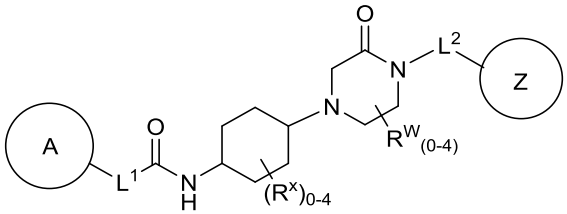
Formula (I-m-12)



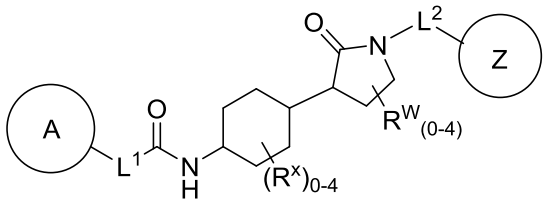
Formula (I-m-13)



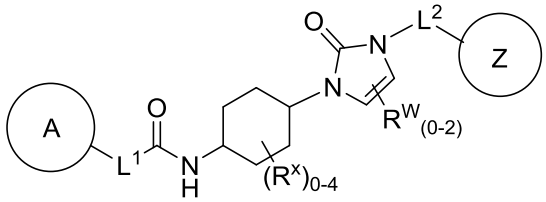
Formula (I-m-14)



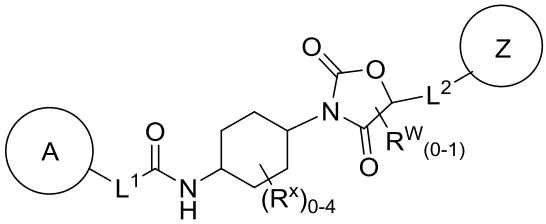
Formula (I-m-15)



Formula (I-m-16)



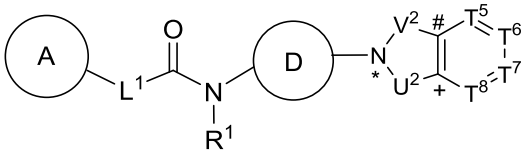
Formula (I-m-17)



Formula (I-m-18)

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

26. A compound of Formula (II):



Formula (II)

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

D is bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane, cyclohexyl, cyclobutyl, or tetrahydropyranyl each of which is optionally substituted with 1-4 R^X groups;

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

R^1 is hydrogen or C_1-C_6 alkyl;

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

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

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

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

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

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

V^2 is selected from the group consisting of *–$C(R^{V21}R^{V22})$–$^\#$, *–$C(R^{V21}R^{V22})$–$C(R^{V23}R^{V24})$–$^\#$, *–$C(R^{V21}R^{V22})$–$C(R^{V23}R^{V24})$–$C(R^{V23}R^{V24})$–$^\#$, *–$C(R^{V21}R^{V22})$–$C(R^{V21}R^{V22})$–O–$^\#$, *–$C(R^{V21}R^{V22})$–$C(R^{V21}R^{V22})$–NR^{N4}–$^\#$, –$C(R^{V21}R^{V22})$–NR^{N4}–$^\#$, *–C(O)–$C(R^{V23}R^{V24})$–$^\#$, *–C(O)–$C(R^{V23}R^{V24})$–$C(R^{V23}R^{V24})$–$^\#$, *–C(O)–NR^{N4}–$^\#$, *–C(O)–$^\#$, and *–C(O)–O–$^\#$, wherein "*–" and "–$^\#$" indicate the attachment points of V^2 as indicated in Formula (II);

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

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

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

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

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

each R^{L1} 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, $–OR^A$, $–NR^BR^C$, $–NR^BC(O)R^D$, $-C(O)NR^BR^C$, $–C(O)R^D$, –C(O)OH, $–C(O)OR^D$, $–SR^E$, $–S(O)R^D$, and $–S(O)_2R^D$;

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

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

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

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

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

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

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

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

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

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

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

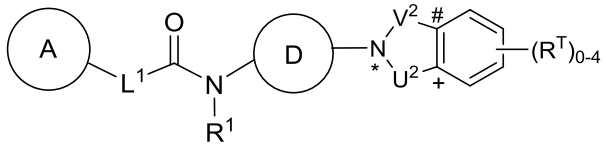
each R^D is independently C_1-C_6 alkyl or halo-C_1-C_6 alkyl;

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

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

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

27. The compound of claim 26, wherein the compound is represented by:



.

28. The compound of claim 26 or 27, wherein V^2 is selected from the group consisting of *–$C(R^{V21}R^{V22})$–$^{\#}$, *–$C(R^{V21}R^{V22})$–$C(R^{V23}R^{V24})$–$^{\#}$, *–C(O)–$C(R^{V23}R^{V24})$–$^{\#}$, and *–$C(R^{V21}R^{V22})$–$C(R^{V23}R^{V24})$–$C(R^{V23}R^{V24})$–$^{\#}$; wherein "*–" and "–$^{\#}$" indicate the attachment points of V^2 as indicated in Formula (II).

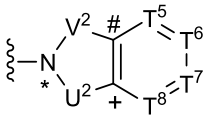
29. The compound of any one of claims 26-28, wherein each of R^{V21} and R^{V22} is independently selected from the group consisting of hydrogen, –OH, and C_1-C_3 alkyl.

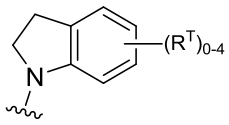
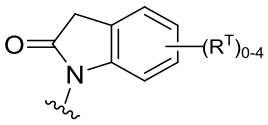
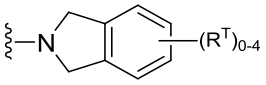
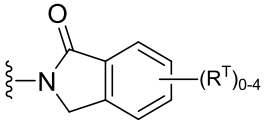
30. The compound of any one of claims 26-29, wherein each of R^{V21} and R^{V22} is hydrogen or –OH.

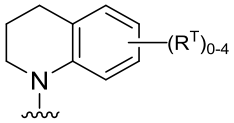
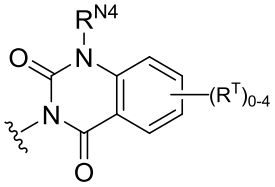
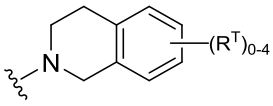
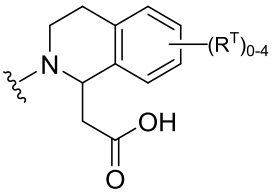
31. The compound of any one of claims 26-30, wherein each of R^{V23} and R^{V24} is independently selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, cyano, –OR^A, and –NR^BR^C.

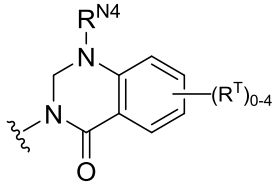
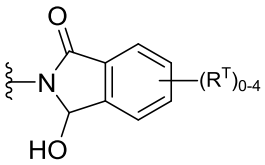
32. The compound of any one of claims 26-31, wherein each of R^{V23} and R^{V24} is hydrogen.

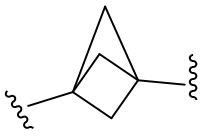
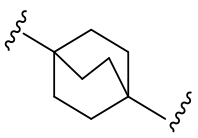
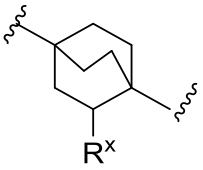
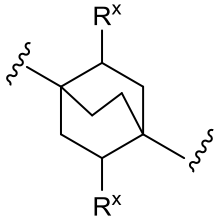
33. The compound of any one of claims 26-32, wherein U^2 is selected from the group consisting of a bond, *–C(O) –$^{+}$, *–CH_2 –$^{+}$, and *–$CH(CH_2CO_2H)$ –$^{+}$, wherein "*–" and "–$^{+}$" indicate the attachment points of U^2 as indicated in Formula (II); and V^2 is selected from the group consisting of *–CH_2–$^{\#}$, *–CH_2–CH_2–$^{\#}$, *–C(O)–CH_2–$^{\#}$, *–C(O)–NH–$^{\#}$, *–CH_2–NH–$^{\#}$, and *–CH_2–CH_2–CH_2–$^{\#}$; wherein "*–" and "–$^{\#}$" indicate the attachment points of V^2 as indicated in Formula (II).

34. The compound of any one of claims 26-33, wherein the moiety  is selected from the group consisting of:

, , , ,

, , , ,

, and ; wherein R^{N4} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and hydroxy-C_2-C_6 alkyl.

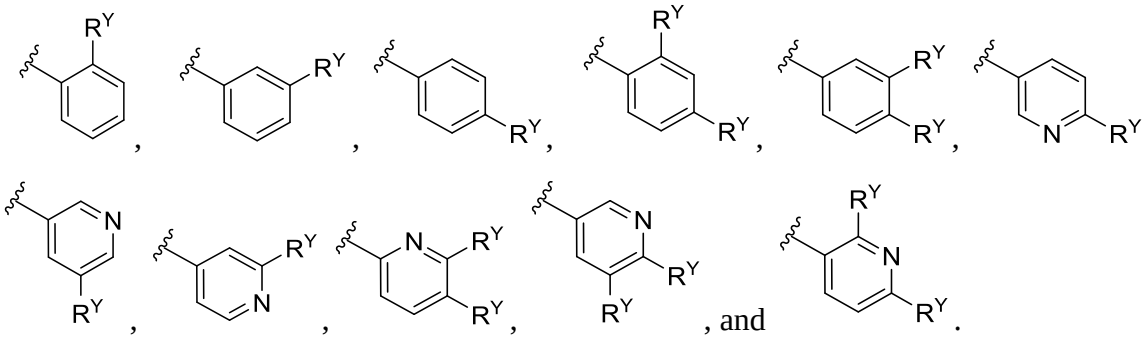
35. The compound of any one of claims 26-34, wherein D is selected from the group consisting of , , , and .

36. The compound of claim 35, wherein each R^X is independently selected from the group consisting of oxo, –OH , –C(O)OH, –C(O)OR^D, halo, and hydroxy-C_1-C_6 alkyl.

37. The compound of any one of claims 26-36, wherein L^1 is CH_2O–* or CH_2OCH_2–*; wherein "–*" indicates the attachment point to A.

38. The compound of any one of claims 26-37, wherein R^1 is hydrogen or $–CH_3$.

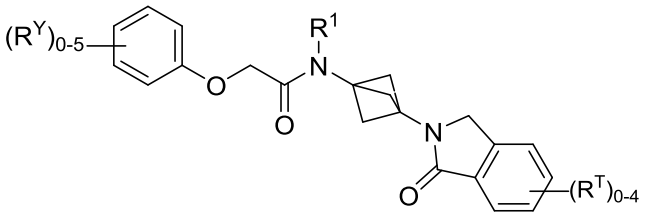
39. The compound of any one of claims 26-38, wherein A is selected from the group consisting of:


, and .

40. The compound of any one of claims 26-39, wherein each R^Y is independently hydrogen, chloro, fluoro, $–CF_3$, $–CH_3$, $–CHF_2$, $–OCF_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCH(CH_3)_2$, or –CN.

41. The compound of any one of claims 26-40, wherein each R^T is independently selected from the group consisting of hydrogen, chloro, fluoro, $–CHF_2$, $–CF_3$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCHF_2$, $–OCF_3$, $–OCH_2CF_3$, $–OCH(CH_3)_2$, and –CN.

42. The compound of any one of claims 26-41, wherein the compound of Formula (II) is a compound of Formula (II-a):



Formula (II-a)

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

R^1 is hydrogen or $–CH_3$;

each R^Y is independently hydrogen, chloro, fluoro, $–CF_3$, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–OCH_3$, $–OCH(CH_3)_2$, or –CN; and

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

43. A compound selected from any compound set forth in Table 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, *N*-oxide, or stereoisomer thereof.

44. A pharmaceutically acceptable composition comprising a compound of any one of claims 1-43 and a pharmaceutically acceptable carrier.

45. Use of a composition in the manufacture of a medicament for treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease in a subject, wherein the composition comprises a compound of any one of claims 1-43.

46. The use of claim 45, wherein:

the neurodegenerative disease comprises a leukodystrophy, a leukoencephalopathy, a hypomyelinating or demyelinating disease, an intellectual disability syndrome, a cognitive impairment, a glial cell dysfunction, a brain injury, vanishing white matter disease, childhood

ataxia with CNS hypo myelination, Alzheimer's disease, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, frontotemporal dementia, Gerstmann-Straussler-Scheinker disease, Huntington's disease, dementia, kuru, multiple sclerosis, Parkinson's disease, or a prion disease;

cancer comprises pancreatic cancer, breast cancer, multiple myeloma, or a cancer of the secretory cells;

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

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

the metabolic disease comprises non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes, phenylketonuria, proliferative retinopathy, or Kearns-Sayre disease;

the mitochondrial disease is associated with or is a result of mitochondrial dysfunction, one or more mitochondrial protein mutations, or one or more mitochondrial DNA mutations or is a mitochondrial myopathy, 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;

the autoimmune disease is selected from the group consisting of Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal

nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonnage-Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndrome type I, Polyglandular syndrome type II, Polyglandular syndrome type III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, Vogt-Koyanagi-Harada Disease, and Wegener's granulomatosis (or Granulomatosis with Polyangiitis (GPA));

the viral infection is selected from the group consisting of influenza, human immunodeficiency virus (HIV) and herpes;

the skin disease is selected from the group consisting of acne, alopecia areata, basal cell carcinoma, Bowen's disease, congenital erythropoietic porphyria, contact dermatitis, Darier's disease, disseminated superficial actinic porokeratosis, dystrophic epidermolysis bullosa, eczema (atopic eczema), extra-mammary Paget's disease, epidermolysis bullosa simplex, erythropoietic protoporphyria, fungal infections of nails, Hailey-Hailey disease, herpes simplex, hidradenitis suppurativa, hirsutism, hyperhidrosis, ichthyosis, impetigo, keloids, keratosis pilaris, lichen planus, lichen sclerosus, melanoma, melasma, mucous membrane pemphigoid, pemphigoid, pemphigus vulgaris, pityriasis lichenoides, pityriasis rubra pilaris, plantar warts (verrucas), polymorphic light eruption, psoriasis, plaque psoriasis, pyoderma gangrenosum, rosacea, scabies, scleroderma, shingles, squamous cell carcinoma, sweet's syndrome, urticaria and angioedema and vitiligo;

the fibrotic disease is selected from the group consisting of adhesive capsulitis, arterial stiffness, arthrofibrosis, atrial fibrosis, cardiac fibrosis, cirrhosis, congenital hepatic fibrosis,

Crohn's disease, cystic fibrosis, Dupuytren's contracture, endomyocardial fibrosis, glial scar, hepatitis C, hypertrophic cardiomyopathy, hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, idiopathic interstitial pneumonia, interstitial lung disease, keloid, mediastinal fibrosis, myelofibrosis, nephrogenic systemic fibrosis, non-alcoholic fatty liver disease, old myocardial infarction, Peyronie's disease, pneumoconiosis, pneumonitis, progressive massive fibrosis, pulmonary fibrosis, radiation-induced lung injury, retroperitoneal fibrosis, scleroderma/systemic sclerosis, silicosis and ventricular remodeling;

the hemoglobin disease is selected from the group consisting of "dominant" β-thalassemia, acquired (toxic) methemoglobinemia, carboxyhemoglobinemia, congenital Heinz body hemolytic anemia, HbH disease, HbS/β-thalassemia, HbE/β-thalassemia, HbSC disease, homozygous α^{+}-thalassemia (phenotype of α^{0}-thalassemia), Hydrops fetalis with Hb Bart's, sickle cell anemia/disease, sickle cell trait, sickle β-thalassemia disease, α^{+}-thalassemia, α^{0}-thalassemia, α-Thalassemia associated with myelodysplastic syndromes, α-Thalassemia with mental retardation syndrome (ATR), β^{0}-Thalassemia, β^{+}-Thalassemia, δ-Thalassemia, γ-Thalassemia, β-Thalassemia major, β-Thalassemia intermedia, δβ-Thalassemia, and εγδβ-Thalassemia;

the kidney disease is selected from the group consisting of Abderhalden–Kaufmann–Lignac syndrome (Nephropathic Cystinosis), Abdominal Compartment Syndrome, Acetaminophen-induced Nephrotoxicity, Acute Kidney Failure/Acute Kidney Injury, Acute Lobar Nephronia, Acute Phosphate Nephropathy, Acute Tubular Necrosis, Adenine Phosphoribosyltransferase Deficiency, Adenovirus Nephritis, Alagille Syndrome, Alport Syndrome, Amyloidosis, ANCA Vasculitis Related to Endocarditis and Other Infections, Angiomyolipoma, Analgesic Nephropathy, Anorexia Nervosa and Kidney Disease, Angiotensin Antibodies and Focal Segmental Glomerulosclerosis, Antiphospholipid Syndrome, Anti-TNF-α Therapy-related Glomerulonephritis, APOL1 Mutations, Apparent Mineralocorticoid Excess Syndrome, Aristolochic Acid Nephropathy, Chinese Herbal Nephropathy, Balkan Endemic Nephropathy, Arteriovenous Malformations and Fistulas of the Urologic Tract, Autosomal Dominant Hypocalcemia, Bardet-Biedl Syndrome, Bartter Syndrome, Bath Salts and Acute Kidney Injury, Beer Potomania, Beeturia, β-Thalassemia Renal Disease, Bile Cast Nephropathy, BK Polyoma Virus Nephropathy in the Native Kidney, Bladder Rupture, Bladder Sphincter Dyssynergia, Bladder Tamponade, Border-Crossers' Nephropathy, Bourbon Virus and Acute

Kidney Injury, Burnt Sugarcane Harvesting and Acute Renal Dysfunction, Byetta and Renal Failure, C1q Nephropathy, C3 Glomerulopathy, C3 Glomerulopathy with Monoclonal Gammopathy, C4 Glomerulopathy, Calcineurin Inhibitor Nephrotoxicity, Callilepsis Laureola Poisoning, Cannabinoid Hyperemesis Acute Renal Failure, Cardiorenal syndrome, Carfilzomib-Induced Renal Injury, CFHR5 nephropathy, Charcot–Marie–Tooth Disease with Glomerulopathy, Chinese Herbal Medicines and Nephrotoxicity, Cherry Concentrate and Acute Kidney Injury, Cholesterol Emboli, Churg–Strauss syndrome, Chyluria, Ciliopathy, Cocaine and the Kidney, Cold Diuresis, Colistin Nephrotoxicity, Collagenofibrotic Glomerulopathy, Collapsing Glomerulopathy, Collapsing Glomerulopathy Related to CMV, Combination Antiretroviral (cART) Related-Nephropathy, Congenital Anomalies of the Kidney and Urinary Tract (CAKUT), Congenital Nephrotic Syndrome, Congestive Renal Failure, Conorenal syndrome (Mainzer-Saldino Syndrome or Saldino-Mainzer Disease), Contrast Nephropathy, Copper Sulphate Intoxication, Cortical Necrosis, Crizotinib-related Acute Kidney Injury, Cryocrystalglobulinemia, Cryoglobuinemia, Crystalglobulin-Induced Nephropathy, Crystal-Induced Acute Kidney injury, Crystal-Storing Histiocytosis, Cystic Kidney Disease, Acquired, Cystinuria, Dasatinib-Induced Nephrotic-Range Proteinuria, Dense Deposit Disease (MPGN Type 2), Dent Disease (X-linked Recessive Nephrolithiasis), DHA Crystalline Nephropathy, Dialysis Disequilibrium Syndrome, Diabetes and Diabetic Kidney Disease, Diabetes Insipidus, Dietary Supplements and Renal Failure, Diffuse Mesangial Sclerosis, Diuresis, Djenkol Bean Poisoning (Djenkolism), Down Syndrome and Kidney Disease, Drugs of Abuse and Kidney Disease, Duplicated Ureter, EAST syndrome, Ebola and the Kidney, Ectopic Kidney, Ectopic Ureter, Edema, Swelling, Erdheim-Chester Disease, Fabry's Disease, Familial Hypocalciuric Hypercalcemia, Fanconi Syndrome, Fraser syndrome, Fibronectin Glomerulopathy, Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy, Fraley syndrome, Fluid Overload, Hypervolemia, Focal Segmental Glomerulosclerosis, Focal Sclerosis, Focal Glomerulosclerosis, Galloway Mowat syndrome, Giant Cell (Temporal) Arteritis with Kidney Involvement, Gestational Hypertension, Gitelman Syndrome, Glomerular Diseases, Glomerular Tubular Reflux, Glycosuria, Goodpasture Syndrome, Green Smoothie Cleanse Nephropathy, HANAC Syndrome, Harvoni (Ledipasvir with Sofosbuvir)-Induced Renal Injury, Hair Dye Ingestion and Acute Kidney Injury, Hantavirus Infection Podocytopathy, Heat Stress Nephropathy, Hematuria (Blood in Urine), Hemolytic Uremic Syndrome (HUS), Atypical Hemolytic Uremic Syndrome

(aHUS), Hemophagocytic Syndrome, Hemorrhagic Cystitis, Hemorrhagic Fever with Renal Syndrome (HFRS, Hantavirus Renal Disease, Korean Hemorrhagic Fever, Epidemic Hemorrhagic Fever, Nephropathis Epidemica), Hemosiderinuria, Hemosiderosis related to Paroxysmal Nocturnal Hemoglobinuria and Hemolytic Anemia, Hepatic Glomerulopathy, Hepatic Veno-Occlusive Disease, Sinusoidal Obstruction Syndrome, Hepatitis C-Associated Renal Disease, Hepatocyte Nuclear Factor 1β–Associated Kidney Disease, Hepatorenal Syndrome, Herbal Supplements and Kidney Disease, High Altitude Renal Syndrome, High Blood Pressure and Kidney Disease, HIV-Associated Immune Complex Kidney Disease (HIVICK), HIV-Associated Nephropathy (HIVAN), HNF1B-related Autosomal Dominant Tubulointerstitial Kidney Disease, Horseshoe Kidney (Renal Fusion), Hunner's Ulcer, Hydroxychloroquine-induced Renal Phospholipidosis, Hyperaldosteronism, Hypercalcemia, Hyperkalemia, Hypermagnesemia, Hypernatremia, Hyperoxaluria, Hyperphosphatemia, Hypocalcemia, Hypocomplementemic Urticarial Vasculitic Syndrome, Hypokalemia, Hypokalemia-induced renal dysfunction, Hypokalemic Periodic Paralysis, Hypomagnesemia, Hyponatremia, Hypophosphatemia, Hypophosphatemia in Users of Cannabis, Hypertension, Hypertension, Monogenic, Iced Tea Nephropathy, Ifosfamide Nephrotoxicity, IgA Nephropathy, IgG4 Nephropathy, Immersion Diuresis, Immune-Checkpoint Therapy-Related Interstitial Nephritis, Infliximab-Related Renal Disease, Interstitial Cystitis, Painful Bladder Syndrome (Questionnaire), Interstitial Nephritis, Interstitial Nephritis, Karyomegalic, Ivemark's syndrome, JC Virus Nephropathy, Joubert Syndrome, Ketamine-Associated Bladder Dysfunction, Kidney Stones, Nephrolithiasis, Kombucha Tea Toxicity, Lead Nephropathy and Lead-Related Nephrotoxicity, Lecithin Cholesterol Acyltransferase Deficiency (LCAT Deficiency), Leptospirosis Renal Disease, Light Chain Deposition Disease, Monoclonal Immunoglobulin Deposition Disease, Light Chain Proximal Tubulopathy, Liddle Syndrome, Lightwood-Albright Syndrome, Lipoprotein Glomerulopathy, Lithium Nephrotoxicity, LMX1B Mutations Cause Hereditary FSGS, Loin Pain Hematuria, Lupus, Systemic Lupus Erythematosis, Lupus Kidney Disease, Lupus Nephritis, Lupus Nephritis with Antineutrophil Cytoplasmic Antibody Seropositivity, Lupus Podocytopathy, Lyme Disease-Associated Glomerulonephritis, Lysinuric Protein Intolerance, Lysozyme Nephropathy, Malarial Nephropathy, Malignancy-Associated Renal Disease, Malignant Hypertension, Malakoplakia, McKittrick-Wheelock Syndrome, MDMA (Molly; Ecstacy; 3,4-Methylenedioxymethamphetamine) and Kidney Failure, Meatal

Stenosis, Medullary Cystic Kidney Disease, Urolodulin-Associated Nephropathy, Juvenile Hyperuricemic Nephropathy Type 1, Medullary Sponge Kidney, Megaureter, Melamine Toxicity and the Kidney, MELAS Syndrome, Membranoproliferative Glomerulonephritis, Membranous Nephropathy, Membranous-like Glomerulopathy with Masked IgG Kappa Deposits, MesoAmerican Nephropathy, Metabolic Acidosis, Metabolic Alkalosis, Methotrexate-related Renal Failure, Microscopic Polyangiitis, Milk-alkalai syndrome, Minimal Change Disease, Monoclonal Gammopathy of Renal Significance, Dysproteinemia, Mouthwash Toxicity, MUC1 Nephropathy, Multicystic dysplastic kidney, Multiple Myeloma, Myeloproliferative Neoplasms and Glomerulopathy, Nail-patella Syndrome, NARP Syndrome, Nephrocalcinosis, Nephrogenic Systemic Fibrosis, Nephroptosis (Floating Kidney, Renal Ptosis), Nephrotic Syndrome, Neurogenic Bladder, 9/11 and Kidney Disease, Nodular Glomerulosclerosis, Non-Gonococcal Urethritis, Nutcracker syndrome, Oligomeganephronia, Orofaciodigital Syndrome, Orotic Aciduria, Orthostatic Hypotension, Orthostatic Proteinuria, Osmotic Diuresis, Osmotic Nephrosis, Ovarian Hyperstimulation Syndrome, Oxalate Nephropathy, Page Kidney, Papillary Necrosis, Papillorenal Syndrome (Renal-Coloboma Syndrome, Isolated Renal Hypoplasia), PARN Mutations and Kidney Disease, Parvovirus B19 and the Kidney, The Peritoneal-Renal Syndrome, POEMS Syndrome, Posterior Urethral Valve, Podocyte Infolding Glomerulopathy, Post-infectious Glomerulonephritis, Post-streptococcal Glomerulonephritis, Post-infectious Glomerulonephritis, Atypical, Post-Infectious Glomerulonephritis (IgA-Dominant), Mimicking IgA Nephropathy, Polyarteritis Nodosa, Polycystic Kidney Disease, Posterior Urethral Valves, Post-Obstructive Diuresis, Preeclampsia, Propofol infusion syndrome, Proliferative Glomerulonephritis with Monoclonal IgG Deposits (Nasr Disease), Propolis (Honeybee Resin) Related Renal Failure, Proteinuria (Protein in Urine), Pseudohyperaldosteronism, Pseudohypobicarbonatemia, Pseudohypoparathyroidism, Pulmonary-Renal Syndrome, Pyelonephritis (Kidney Infection), Pyonephrosis, Pyridium and Kidney Failure, Radiation Nephropathy, Ranolazine and the Kidney, Refeeding syndrome, Reflux Nephropathy, Rapidly Progressive Glomerulonephritis, Renal Abscess, Peripnephric Abscess, Renal Agenesis, Renal Arcuate Vein Microthrombi-Associated Acute Kidney Injury, Renal Artery Aneurysm, Renal Artery Dissection, Spontaneous, Renal Artery Stenosis, Renal Cell Cancer, Renal Cyst, Renal Hypouricemia with Exercise-induced Acute Renal Failure, Renal Infarction, Renal Osteodystrophy, Renal Tubular Acidosis, Renin Mutations and Autosomal Dominant

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

the hearing loss condition is selected from the group consisting of 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; or

the ocular disease cataracts, glaucoma, endoplasmic reticulum (ER) stress, autophagy deficiency, age-related macular degeneration (AMD), or diabetic retinopathy.

47. The use of claim 45 or 46, wherein the neurodegenerative disease comprises vanishing white matter disease.

48. The use of any one of claims 45-47, further comprising a second agent (*e.g.*, agent for treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, a mitochondrial disease, or a disease or disorder associated with impaired function of eIF2B, eIF2α, or a component of the eIF2 pathway or ISR pathway).

49. Use of a composition in the manufacture of a medicament for treating a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway, wherein the composition comprises a compound of any one of claims 1-43.

50. Use of a composition in combination with an immunotherapeutic agent, in the manufacture of a medicament for treating cancer in a subject, wherein the composition comprises a compound of any one of claims 1-43.

51. A composition for use in treating a neurodegenerative disease, a leukodystrophy, a cancer, an inflammatory disease, an autoimmune disease, a viral infection, a skin disease, a fibrotic disease, a hemoglobin disease, a kidney disease, a hearing loss condition, an ocular disease, a musculoskeletal disease, a metabolic disease, or a mitochondrial disease in a subject; or

for use in in treating a disease related to a modulation of eIF2B activity or levels, eIF2α activity or levels, or the activity or levels of a component of the eIF2 pathway or the ISR pathway; or

for use in treating cancer in a subject in combination with an immunotherapeutic agent, wherein the composition comprises a compound of any one of claims 1-43.