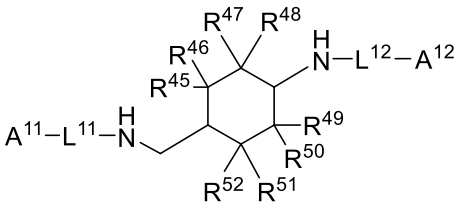
extrinsic stresses, such as viral infections, hypoxia, glucose and amino acid deprivation, oncogene activation, UV radiation, and endoplasmic reticulum stress. Upon activation of ISR by one or more of these factors, the eukaryotic initiation factor 2 (eIF2, which is comprised of three subunits, α, β and γ) becomes phosphorylated in its α-subunit and rapidly reduces overall protein translation by binding to the eIF2B complex. This phosphorylation inhibits the eIF2B-mediated exchange of GDP for GTP (i.e., a guanine nucleotide exchange factor (GEF) activity), sequestering eIF2B in a complex with eIF2 and reducing general protein translation of most mRNA in the cell. Paradoxically, eIF2α phosphorylation also increases translation of a subset of mRNAs that contain one or more upstream open reading frames (uORFs) in their 5' untranslated region (UTR). These transcripts include the transcriptional modulator activating transcription factor 4 (ATF4), the transcription factor CHOP, the growth arrest and DNA damage-inducible protein GADD34 and the β-secretase BACE-1.

[0006] Additionally, compounds useful in modulating the ISR pathway may also be useful in treating a large number of diseases. In animals, the ISR pathway modulates a broad translational and transcriptional program involved in diverse processes such as learning memory, immunity, intermediary metabolism, insulin production and resistance to unfolded protein stress in the endoplasmic reticulum, among others. Activation of the ISR pathway has also been associated with numerous pathological conditions including cancer, neurodegenerative diseases, metabolic diseases (metabolic syndrome), autoimmune diseases, inflammatory diseases, musculoskeletal diseases (such as myopathy), vascular diseases, ocular diseases, and genetic disorders. Aberrant protein synthesis through eIF2α phosphorylation is also characteristic of several other human genetic disorders, cystic fibrosis, amyotrophic lateral sclerosis, Huntington disease and prion disease.

BRIEF SUMMARY

[0007] Inhibitors of the Integrated Stress Response (ISR) pathway are described, as are methods of making and using the compounds, or salts thereof.

[0007a] In an aspect of the present disclosure, there is provided a compound of formula (F-1)



(F-1)

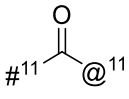
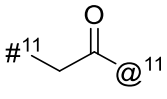
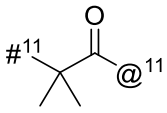
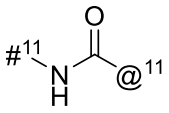
or a pharmaceutically acceptable salt thereof,

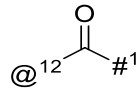
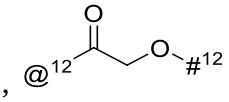
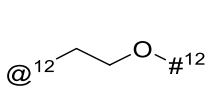
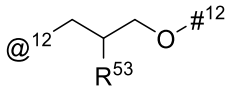
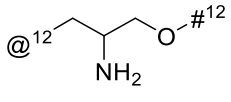
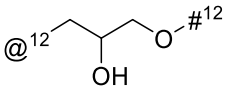
wherein:

R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, and R^{52}, independently from each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

or, one of R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, and R^{52}, and another one of R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, and R^{52}, are taken together to form a C_1-C_6 alkylene moiety;

or, two geminal substituents selected from the group consisting of R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, and R^{52} are taken together to form an oxo group;

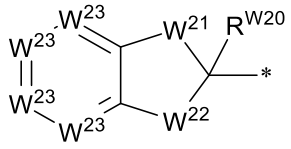
L^{11} is selected from the group consisting of a bond,  ,  ,  ,  , and , wherein $\#^{11}$ represents to attachment point to A^{11} and $@^{11}$ represents the attachment point to the remainder of the molecule;

L^{12} is selected from the group consisting of  ,  ,  ,  ,  , and  , wherein $\#^{12}$ represents to attachment point to A^{12} and $@^{12}$ represents the attachment point to the remainder of the molecule;

R^{53} is H, OH, or NH_2;

A^{11} is selected from the group consisting of:

a substituent of formula (A^{11}-1)



(A^{11}-1)

wherein * represents the attachment point to the remainder of the molecule;

W^{21} is selected from the group consisting of -C($R^{W21-1}R^{W21-2}$)-, -N(R^{W21-2})-, -C($R^{W21-1}R^{W21-2}$)N(R^{W21-2})-, -N(R^{W21-1})C($R^{W21-1}R^{W21-2}$)-, -C(R^{W21-1})=N-, -N=C(R^{W21-1})-, -O-, -C($R^{W21-1}R^{W21-1}$)O-, -OC($R^{W21-1}R^{W21-2}$) -, -S-, -C($R^{W21-1}R^{W21-1}$)S-, -SC($R^{W21-1}R^{W21-2}$) -, -C($R^{W21-1}R^{W21-1}$)C($R^{W21-1}R^{W21-2}$)-, and -CR^{W21-1}=CR^{W21-1}-,

wherein R^{W21-1} is H or R^{A11}, and R^{W21-2} is H or R^{A11};

W^{22} is selected from the group consisting of -C($R^{W22-1}R^{W22-2}$)-, -N(R^{W22-2})-, -C($R^{W22-1}R^{W22-1}$)N(R^{W22-2})-, -N(R^{W22-1})C($R^{W22-1}R^{W22-2}$)-, -C(R^{W22-1})=N-, -N=C(R^{W22-1})-, -O-, -C($R^{W22-1}R^{W22-1}$)O-, -OC($R^{W22-1}R^{W22-2}$)-, -S-, -C($R^{W22-1}R^{W22-1}$)S-, -SC($R^{W22-1}R^{W22-2}$)-, -C($R^{W22-1}R^{W22-1}$)C($R^{W22-1}R^{W22-2}$)-, and -CR^{W22-1}=CR^{W22-1}-,

wherein R^{W22-1} is H or R^{A11}, and R^{W22-2} is H or R^{A11};

W^{23}, independently at each occurrence, is CR^{W23} or N, wherein R^{W23} is H or R^{A11};

R^{W20} is hydrogen or R^{A11}, or R^{W20} and R^{W21-2} are taken together to form a double bond between the carbon atom bearing R^{W20} and the atom bearing R^{W21-2}, or R^{W20} and R^{W22-2} are taken together to form a double bond between the carbon atom bearing R^{W20} and the atom bearing R^{W21-2};

C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents; and

5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents;

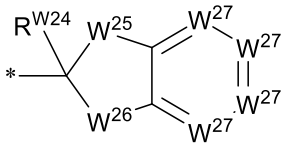
R^{A11}, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl,

OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, $C(O)NR^aR^b$, $S(O)_2OH$, $S(O)_2O$(C_1-C_6 alkyl), $S(O)_2O$(C_1-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2$NH(C_1-C_6 alkyl), $S(O)_2$NH(C_1-C_6 haloalkyl), $S(O)_2$N(C_1-C_6 alkyl)$_2$, $S(O)_2$N(C_1-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), $OS(O)_2$(C_1-C_6 alkyl), $OS(O)_2$(C_1-C_6 haloalkyl), N(H)$S(O)_2$(C_1-C_6 alkyl), N(H)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

and

A^{12} is selected from the group consisting of:

a substituent of formula (A^{12}-1)



(A^{12}-1)

wherein * represents the attachment point to the remainder of the molecule;

W^{25} is selected from the group consisting of -C($R^{W25-1}R^{W25-2}$)-, -N(R^{W25-2})-, -C($R^{W25-1}R^{W25-2}$)N(R^{W25-2})-, -N(R^{W25-1})C($R^{W25-1}R^{W25-2}$)-, -C(R^{W25-1})=N-, -N=C(R^{W25-1})-, -O-, -C($R^{W25-1}R^{W25-1}$)O-, -OC($R^{W25-1}R^{W25-2}$) -, -S-, -C($R^{W25-1}R^{W25-1}$)S-, -SC($R^{W25-1}R^{W25-2}$) -, -C($R^{W25-1}R^{W25-1}$)C($R^{W25-1}R^{W25-2}$)-, and -CR^{W25-1}=CR^{W25-1}-,

wherein R^{W25-1} is H or R^{A12}, and R^{W25-2} is H or R^{A12};

W^{26} is selected from the group consisting of -C($R^{W26-1}R^{W26-2}$)-, -N(R^{W26-2})-, -C($R^{W26-1}R^{W26-1}$)N(R^{W26-2})-, -N(R^{W26-1})C($R^{W26-1}R^{W26-2}$)-, -C(R^{W26-1})=N-, -N=C(R^{W26-1})-, -O-, -C($R^{W26-1}R^{W26-1}$)O-, -OC($R^{W26-1}R^{W26-2}$)-, -S-, -C($R^{W26-1}R^{W26-1}$)S-, -SC($R^{W26-1}R^{W26-2}$)-, -C($R^{W26-1}R^{W26-1}$)C($R^{W26-1}R^{W26-2}$)-, and -CR^{W26-1}=CR^{W26-1}-,

wherein R^{W26-1} is H or R^{A12}, and R^{W26-2} is H or R^{A12};

W^{27}, independently at each occurrence, is CR^{W27} or N, wherein R^{W27} is H or R^{A12};

R^{W24} is hydrogen or R^{A12}, or R^{W24} and R^{W25-2} are taken together to form a double bond between the carbon atom bearing R^{W24} and the atom bearing R^{W25-2}, or R^{W24} and R^{W26-2} are taken together to form a double bond between the carbon atom bearing R^{W24} and the atom bearing R^{W26-2};

C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A12} substituents; and

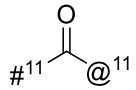
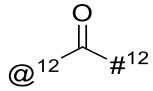
5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A12} substituents;

R^{A12}, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), C(O)NH_2, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, C(O)NR^aR^b, S(O)$_2$OH, S(O)$_2$O(C_1-C_6 alkyl), S(O)$_2$O(C_1-C_6 haloalkyl), S(O)$_2$NH_2, S(O)$_2$NH(C_1-C_6 alkyl), S(O)$_2$NH(C_1-C_6 haloalkyl), S(O)$_2$N(C_1-C_6 alkyl)$_2$, S(O)$_2$N(C_1-C_6 haloalkyl)$_2$, S(O)$_2$NR^aR^b,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6

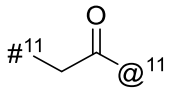
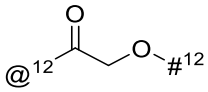
haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), OS(O)$_2$(C_1-C_6 alkyl), OS(O)$_2$(C_1-C_6 haloalkyl), N(H)S(O)$_2$(C_1-C_6 alkyl), N(H)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 alkyl), and N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

provided that

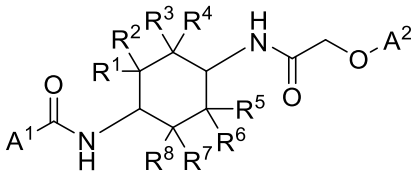
when L^{11} is a bond, then A^{11} is (A^{11}-1) optionally substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents;

when L^{11} is  and L^{12} is  , then A^{11} is (A^{11}-1) substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents or A^{12} is (A^{11}-1) substituted by 2, 3, 4, 5, 6, 7, 8, or 9 R^{A12} substituents;

and

when L^{11} is  and L^{12} is  , then A^{11} is substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents.

[0007b] In another aspect of the present disclosure, there is provided a compound of formula (A-1)



(A-1)

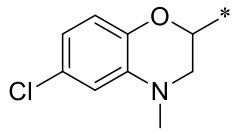
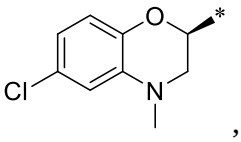
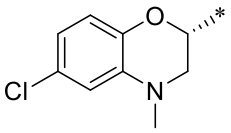
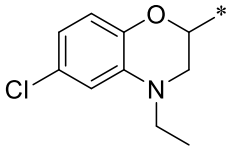
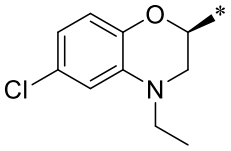
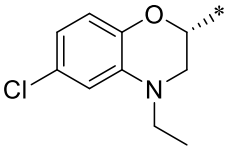
or a pharmaceutically acceptable salt thereof,

wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, independently from each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

or, one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, and another one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, are taken together to form a C_1-C_6 alkylene moiety;

or, two geminal substituents selected from the group consisting of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are taken together to form an oxo group;

A^1 is selected from the group consisting of  ,  ,  ,  ,  , and  ;

wherein * represents the attachment point to the remainder of the molecule;

and

A^2 is selected from the group consisting of:

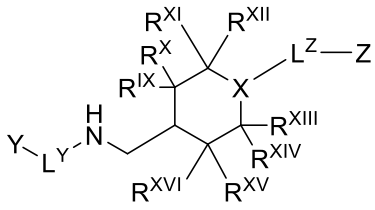
C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A2} substituents; and

5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A2} substituents;

R^{A2}, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, $C(O)NR^aR^b$, $S(O)_2OH$, $S(O)_2O$(C_1-C_6 alkyl), $S(O)_2O$(C_1-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2$NH(C_1-C_6 alkyl), $S(O)_2$NH(C_1-C_6 haloalkyl), $S(O)_2$N(C_1-C_6 alkyl)$_2$, $S(O)_2$N(C_1-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), $OS(O)_2$(C_1-C_6 alkyl), $OS(O)_2$(C_1-C_6 haloalkyl), N(H)$S(O)_2$(C_1-C_6 alkyl), N(H)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and

$N(C_1\text{-}C_6$ haloalkyl)$S(O)_2(C_1\text{-}C_6$ haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle.

[0007c] In a further aspect of the present disclosure, there is provided a compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof,

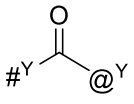
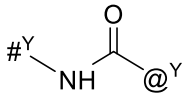
wherein:

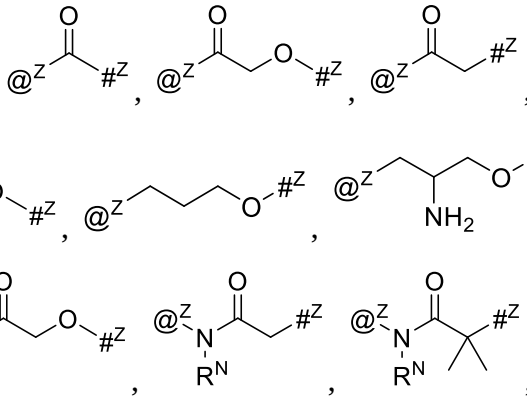
X is N;

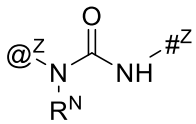
R^{IX}, R^X, R^{XI}, R^{XII}, R^{XIII}, R^{XIV}, R^{XV}, and R^{XVI}, independently from each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

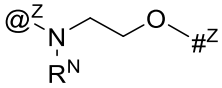
or, one of R^{IX}, R^X, R^{XI}, R^{XII}, R^{XIII}, R^{XIV}, R^{XV}, and R^{XVI}, and another one of R^{IX}, R^X, R^{XI}, R^{XII}, R^{XIII}, R^{XIV}, R^{XV}, and R^{XVI}, are taken together to form a C_1-C_6 alkylene moiety;

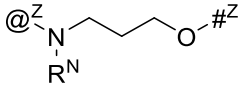
or, two geminal substituents selected from the group consisting of R^{IX}, R^X, R^{XI}, R^{XII}, R^{XIII}, R^{XIV}, R^{XV}, and R^{XVI} are taken together to form an oxo group;

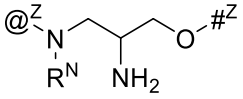
L^Y is  or  , wherein $\#^Y$ represents the attachment point to Y and $@^Y$ represents the attachment point to the remainder of the molecule;

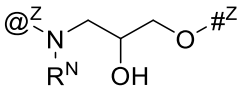
L^Z is selected from the group consisting of 



, 

, 

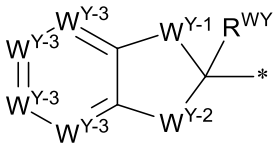
, 

, and 

; wherein $\#^{Z}$ represents the attachment point to Z and $@^{Z}$ represents the attachment point to the remainder of the molecule;

R^{N}, independently at each occurrence, is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl,

Y is a substituent of formula (Y-I)



(Y-I)

wherein * represents the attachment point to the remainder of the molecule;

W^{Y-1} is selected from the group consisting of $-C(R^{WY-1-1}R^{WY-1-2})-$, $-N(R^{WY-1-2})-$, $-C(R^{WY-1-1}R^{WY-1-1})N(R^{WY-1-2})-$, $-N(R^{WY-1-1})C(R^{WY-1-1}R^{WY-1-2})-$, $-C(R^{WY-1-1})=N-$, $-N=C(R^{WY-1-1})-$, $-O-$, $-C(R^{WY-1-1}R^{WY-1-1})O-$, $-OC(R^{WY-1-1}R^{WY-1-2})-$, $-S-$, $-C(R^{WY-1-1}R^{WY-1-1})S-$, $-SC(R^{WY-1-1}R^{WY-1-2})-$, $-C(R^{WY-1-1}R^{WY-1-1})C(R^{WY-1-1}R^{WY-1-2})-$, and $-CR^{WY-1-1}=CR^{WY-1-1}-$,

wherein R^{WY-1-1} is H or R^{Y}, and R^{WY-1-2} is H or R^{Y};

W^{Y-2} is selected from the group consisting of $-C(R^{WY-2-1}R^{WY-2-2})-$, $-N(R^{WY-2-2})-$, $-C(R^{WY-2-1}R^{WY-2-1})N(R^{WY-2-2})-$, $-N(R^{WY-2-1})C(R^{WY-2-1}R^{WY-2-2})-$, $-C(R^{WY-2-1})=N-$, $-N=C(R^{WY-2-1})-$, $-O-$, $-C(R^{WY-2-1}R^{WY-2-1})O-$, $-OC(R^{WY-2-1}R^{WY-2-2})-$, $-S-$, $-C(R^{WY-2-1}R^{WY-2-1})S-$, $-SC(R^{WY-2-1}R^{WY-2-2})-$, $-C(R^{WY-2-1}R^{WY-2-1})C(R^{WY-2-1}R^{WY-2-2})-$, and $-CR^{WY-2-1}=CR^{WY-2-1}-$,

wherein R^{WY-2-1} is H or R^{Y}, and R^{WY-2-2} is H or R^{Y};

W^{Y-3}, independently at each occurrence, is CR^{WY-3} or N, wherein R^{WY-3} is H or R^{Y};

R^{WY} is hydrogen or R^{Y}, or R^{WY} and R^{WY-1-2} are taken together to form a double bond between the carbon atom bearing R^{WY} and the atom bearing R^{WY-1-2}, or R^{WY} and R^{WY-2-2} are taken together to form a double bond between the carbon atom bearing R^{WY} and the atom bearing R^{WY-2-2};

C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Y substituents; and

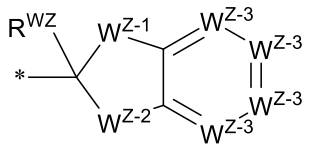
5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Y substituents;

R^Y, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, $C(O)NR^aR^b$, $S(O)_2OH$, $S(O)_2O$(C_1-C_6 alkyl), $S(O)_2O$(C_1-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_1-C_6 alkyl), $S(O)_2NH$(C_1-C_6 haloalkyl), $S(O)_2N$(C_1-C_6 alkyl)$_2$, $S(O)_2N$(C_1-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), OS(O)$_2$(C_1-C_6 alkyl), OS(O)$_2$(C_1-C_6 haloalkyl), N(H)S(O)$_2$(C_1-C_6 alkyl), N(H)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 alkyl), and N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

and

Z is selected from the group consisting of:

a substituent of formula (Z-I)



(Z-I)

wherein * represents the attachment point to the remainder of the molecule;

W^{Z-1} is selected from the group consisting of $-C(R^{WZ-1-1}R^{WZ-1-2})-$, $-N(R^{WZ-1-2})-$, $-C(R^{WZ-1-1}R^{WZ-1-2})N(R^{WZ-1-2})-$, $-N(R^{WZ-1-1})C(R^{WZ-1-1}R^{WZ-1-2})-$, $-C(R^{WZ-1-1})=N-$, $-N=C(R^{WZ-1-1})-$, $-O-$, $-C(R^{WZ-1-1}R^{WZ-1-1})O-$, $-OC(R^{WZ-1-1}R^{WZ-1-2})-$, $-S-$, $-C(R^{WZ-1-1}R^{WZ-1-1})S-$, $-SC(R^{WZ-1-1}R^{WZ-1-2})-$, $-C(R^{WZ-1-1}R^{WZ-1-1})C(R^{WZ-1-1}R^{WZ-1-2})-$, and $-CR^{WZ-1-1}=CR^{WZ-1-1}-$,

wherein R^{WZ-1-1} is H or R^Z, and R^{WZ-1-2} is H or R^Z;

W^{Z-2} is selected from the group consisting of $-C(R^{WZ-2-1}R^{WZ-2-2})-$, $-N(R^{WZ-2-2})-$, $-C(R^{WZ-2-1}R^{WZ-2-1})N(R^{WZ-2-2})-$, $-N(R^{WZ-2-1})C(R^{WZ-2-1}R^{WZ-2-2})-$, $-C(R^{WZ-2-1})=N-$, $-N=C(R^{WZ-2-1})-$, $-O-$, $-C(R^{WZ-2-1}R^{WZ-2-1})O-$, $-OC(R^{WZ-2-1}R^{WZ-2-2})-$, $-S-$, $-C(R^{WZ-2-1}R^{WZ-2-1})S-$, $-SC(R^{WZ-2-1}R^{WZ-2-2})-$, $-C(R^{WZ-2-1}R^{WZ-2-1})C(R^{WZ-2-1}R^{WZ-2-2})-$, and $-CR^{WZ-2-1}=CR^{WZ-2-1}-$,

wherein R^{WZ-2-1} is H or R^Z, and R^{WZ-2-2} is H or R^Z;

W^{Z-3}, independently at each occurrence, is CR^{WZ-3} or N, wherein R^{WZ-3} is H or R^Z;

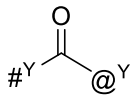
R^{WZ} is hydrogen or R^Z, or R^{WZ} and R^{WZ-1-2} are taken together to form a double bond between the carbon atom bearing R^{WZ} and the atom bearing R^{WZ-1-2}, or R^{WZ} and R^{WZ-2-2} are taken together to form a double bond between the carbon atom bearing R^{WZ} and the atom bearing R^{WZ-2-2};

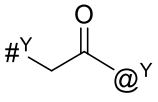
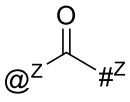
C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Z substituents; and

5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Z substituents;

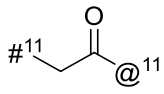
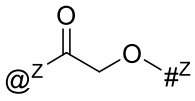
R^Z, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b,

CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), C(O)NH_2, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, C(O)NR^aR^b, $S(O)_2OH$, $S(O)_2O$(C_1-C_6 alkyl), $S(O)_2O$(C_1-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_1-C_6 alkyl), $S(O)_2NH$(C_1-C_6 haloalkyl), $S(O)_2N$(C_1-C_6 alkyl)$_2$, $S(O)_2N$(C_1-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), $OS(O)_2$(C_1-C_6 alkyl), $OS(O)_2$(C_1-C_6 haloalkyl), N(H)$S(O)_2$(C_1-C_6 alkyl), N(H)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

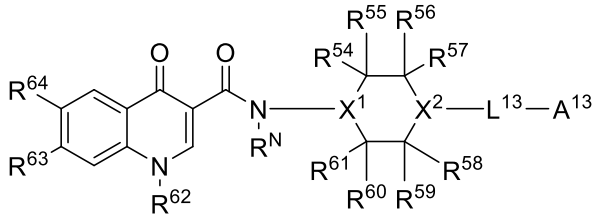
provided that when L^Y is  , Y is (Y-I);

when L^Y is  and L^Z is  , then Y is (Y-I) substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Y substituents or Z is (Z-I) substituted by 2, 3, 4, 5, 6, 7, 8, or 9 R^Z substituents;

and

when L^Y is  and L^Z is  , then Y is substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Y substituents.

[0007d] In another aspect of the present disclosure, there is provided a compound of formula (III)



(III)

or a salt thereof,

wherein:

X^1 is N or CR^{X1};

X^2 is N or CR^{X2};

when present, R^{X1} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

when present, R^{X2} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, and R^{61}, independently from each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

or, one of R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, and R^{61}, and another one of R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, and R^{61}, are taken together to form a C_1-C_6 alkylene moiety;

or, two geminal substituents selected from the group consisting of R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, and R^{61} are taken together to form an oxo group;

or, two of R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{X1} when present, and $R^{X2,}$ when present, are taken together to form a C_1-C_6 alkylene moiety;

R^{63} and R^{64}, independently from each other, are selected from the group consisting of hydrogen, halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), $-NH_2$, -NH(C_1-C_6 alkyl),-NH(C_1-C_6 haloalkyl),-N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, $-NR^{B\text{-}a}R^{B\text{-}b}$, -CN, -C(O)OH, -C(O)O($C_1$-$C_6$ alkyl), -C(O)O(C_1-C_6 haloalkyl), $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_1-C_6 haloalkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)N(C_1-C_6 haloalkyl)$_2$, $-C(O)NR^{B\text{-}a}R^{B\text{-}b}$, $-S(O)_2OH$, -S(O)$_2$O(C_1-C_6 alkyl), -S(O)$_2$O(C_1-C_6 haloalkyl), $-S(O)_2NH_2$, -S(O)$_2$NH(C_1-C_6 alkyl), -S(O)$_2$NH(C_1-C_6 haloalkyl), -S(O)$_2$N(C_1-C_6 alkyl)$_2$, -S(O)$_2$N(C_1-C_6 haloalkyl)$_2$,

-$S(O)_2NR^{B\text{-}a}R^{B\text{-}b}$,-OC(O)H, -OC(O)($C_1$-$C_6$ alkyl), -OC(O)(C_1-C_6 haloalkyl), -N(H)C(O)H, -N(H)C(O)(C_1-C_6 alkyl), -N(H)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)C(O)H, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)C(O)H, -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), -$OS(O)_2$(C_1-C_6 alkyl), -$OS(O)_2$(C_1-C_6 haloalkyl), -N(H)$S(O)_2$(C_1-C_6 alkyl), -N(H)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl);

wherein $R^{B\text{-}a}$ and $R^{B\text{-}b}$ are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

R^{62} is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -(C_1-C_6 alkylene)-(C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents), -(C_1-C_6 alkylene)-(5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents), C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -(C_1-C_6 alkylene)-OH, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), -NH_2, -NH(C_1-C_6 alkyl),-NH(C_1-C_6 haloalkyl),-N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, -CN, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), -$C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_1-C_6 haloalkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)N(C_1-C_6 haloalkyl)$_2$, -$C(O)NR^{62\text{-}a}R^{62\text{-}b}$, -$S(O)_2OH$, -$S(O)_2O$($C_1$-$C_6$ alkyl), -$S(O)_2O$(C_1-C_6 haloalkyl), -$S(O)_2NH_2$, -$S(O)_2NH$(C_1-C_6 alkyl), -$S(O)_2NH$(C_1-C_6 haloalkyl), -$S(O)_2N$(C_1-C_6 alkyl)$_2$, -$S(O)_2N$(C_1-C_6 haloalkyl)$_2$, -$S(O)_2NR^{62\text{-}a}R^{62\text{-}b}$,-OC(O)H, -OC(O)($C_1$-$C_6$ alkyl), -OC(O)(C_1-C_6 haloalkyl), -N(H)C(O)H, -N(H)C(O)(C_1-C_6 alkyl), -N(H)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)C(O)H, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)C(O)H, -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), -$OS(O)_2$(C_1-C_6 alkyl), -$OS(O)_2$(C_1-C_6 haloalkyl), -N(H)$S(O)_2$(C_1-C_6 alkyl), -N(H)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl);

wherein $R^{62\text{-}a}$ and $R^{62\text{-}b}$ are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

L^{13} is a linker selected from the group consisting of $@^{13}$-C_1-C_6 alkylene-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-CH_2-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-CH_2-NR^N-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-NR^N-NR^N -(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-CH_2-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-CH_2-NR^N-NR^N -(C_1-C_6 alkylene)-O-$\#^{13}$, and $@^{13}$-(C_1-C_6 alkylene)-O-$\#^{13}$;

wherein $@^{13}$ represents the attachment point to X^2 and $\#^{13}$ represents the attachment point to A^{13};

the C_1-C_6 alkylene moiety of each of the $@^{13}$-C_1-C_6 alkylene-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-CH_2-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-CH_2-NR^N-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-NR^N-NR^N -(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-CH_2-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-CH_2-NR^N-NR^N -(C_1-C_6 alkylene)-O-$\#^{13}$, and $@^{13}$-(C_1-C_6 alkylene)-O-$\#^{13}$ is optionally substituted with 1 to 12 R^{66};

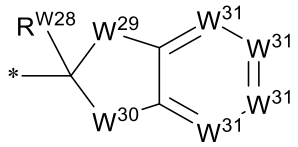
R^N, independently at each occurrence, is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl,

R^{66}, independently at each occurrence, is selected from the group consisting of oxo, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), $-NH_2$, -NH(C_1-C_6 alkyl),-NH(C_1-C_6 haloalkyl),-N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, $-NR^{B\text{-}a}R^{B\text{-}b}$, -CN, -C(O)OH, -C(O)O($C_1$-$C_6$ alkyl), -C(O)O(C_1-C_6 haloalkyl), $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_1-C_6 haloalkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)N(C_1-C_6 haloalkyl)$_2$, $-C(O)NR^{B\text{-}a}R^{B\text{-}b}$, $-S(O)_2OH$, -$S(O)_2$O(C_1-C_6 alkyl), -$S(O)_2$O(C_1-C_6 haloalkyl), $-S(O)_2NH_2$, -$S(O)_2$NH(C_1-C_6 alkyl), -$S(O)_2$NH(C_1-C_6 haloalkyl), -$S(O)_2$N(C_1-C_6 alkyl)$_2$, -$S(O)_2$N(C_1-C_6 haloalkyl)$_2$, $-S(O)_2NR^{B\text{-}a}R^{B\text{-}b}$,-OC(O)H, -OC(O)($C_1$-$C_6$ alkyl), -OC(O)(C_1-C_6 haloalkyl), -N(H)C(O)H, -N(H)C(O)(C_1-C_6 alkyl), -N(H)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)C(O)H, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)C(O)H, -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), -$OS(O)_2$(C_1-C_6 alkyl), -$OS(O)_2$(C_1-C_6 haloalkyl), -N(H)$S(O)_2$(C_1-C_6 alkyl), -N(H)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6

alkyl)$S(O)_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl);

A^{13} is selected from the group consisting of:

a substituent of formula (A^{13}-1)



(A^{13}-1)

W^{29} is selected from the group consisting of -C($R^{W29-1}R^{W29-2}$)-, -N(R^{W29-2})-, -C($R^{W29-1}R^{W29-1}$)N(R^{W29-2})-, -N(R^{W29-1})C($R^{W29-1}R^{W29-2}$)-, -C(R^{W29-1})=N-, -N=C(R^{W29-1})-, -O-, -C($R^{W29-1}R^{W29-1}$)O-, -OC($R^{W29-1}R^{W29-2}$)-, -S-, -C($R^{W29-1}R^{W29-1}$)S-, -SC($R^{W29-1}R^{W29-2}$) -, -C($R^{W29-1}R^{W29-1}$)C($R^{W29-1}R^{W29-2}$)-, and -CR^{W29-1}=CR^{W29-1}-, wherein R^{W29-1} is H or R^{A13}, and R^{W29-2} is H or R^{A13};

W^{30} is selected from the group consisting of -C($R^{W30-1}R^{W30-2}$)-, -N(R^{W30-2})-, -C($R^{W30-1}R^{W30-1}$)N(R^{W30-2})-, -N(R^{W30-1})C($R^{W30-1}R^{W30-2}$)-, -C(R^{W30-1})=N-, -N=C(R^{W30-1})-, -O-, -C($R^{W30-1}R^{W30-1}$)O-, -OC($R^{W30-1}R^{W30-2}$)-, -S-, -C($R^{W30-1}R^{W30-1}$)S-, -SC($R^{W30-1}R^{W30-2}$)-, -C($R^{W30-1}R^{W30-1}$)C($R^{W30-1}R^{W30-2}$)-, and -CR^{W30-1}=CR^{W30-1}-, wherein R^{W30-1} is H or R^{A13}, and R^{W30-2} is H or R^{A13};

W^{31}, independently at each occurrence, is CR^{W31} or N, wherein R^{W31} is H or R^{A13};

R^{W28} is hydrogen or R^{A13}, or R^{W28} and R^{W29-2} are taken together to form a double bond between the carbon atom bearing R^{W28} and the atom bearing R^{W29-2}, or R^{W28} and R^{W30-2} are taken together to form a double bond between the carbon atom bearing R^{W28} and the atom bearing R^{W30-2};

C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents; and

5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents;

R^{A13}, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), -NH_2, -NH(C_1-C_6 alkyl),-NH(C_1-C_6 haloalkyl),-N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, -$NR^{A13\text{-}a}R^{A13\text{-}b}$, -CN, -C(O)OH, -C(O)O($C_1$-$C_6$ alkyl), -C(O)O(C_1-C_6 haloalkyl), -C(O)NH_2, -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_1-C_6 haloalkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)N(C_1-C_6 haloalkyl)$_2$, -C(O)$NR^{A13\text{-}a}R^{A13\text{-}b}$, -S(O)$_2$OH, -S(O)$_2$O($C_1$-$C_6$ alkyl), -S(O)$_2$O(C_1-C_6 haloalkyl), -S(O)$_2$$NH_2$, -S(O)$_2$NH($C_1$-$C_6$ alkyl), -S(O)$_2$NH(C_1-C_6 haloalkyl), -S(O)$_2$N(C_1-C_6 alkyl)$_2$, -S(O)$_2$N(C_1-C_6 haloalkyl)$_2$, -S(O)$_2$$NR^{A13\text{-}a}R^{A13\text{-}b}$,-OC(O)H, -OC(O)($C_1$-$C_6$ alkyl), -OC(O)(C_1-C_6 haloalkyl), -N(H)C(O)H, -N(H)C(O)(C_1-C_6 alkyl), -N(H)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)C(O)H, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)C(O)H, -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), -OS(O)$_2$(C_1-C_6 alkyl), -OS(O)$_2$(C_1-C_6 haloalkyl), -N(H)S(O)$_2$(C_1-C_6 alkyl), -N(H)S(O)$_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 alkyl), and -N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 haloalkyl);

wherein $R^{A13\text{-}a}$ and $R^{A13\text{-}b}$ are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

provided that when X^2 is N, then L^{13} is a linker selected from the group consisting of @^{13}-C_1-C_6 alkylene-#^{13}, @^{13}-NR^N-(C_1-C_6 alkylene)-#^{13}, @^{13}-NR^N-(C_1-C_6 alkylene)-O-#^{13}, and @^{13}-(C_1-C_6 alkylene)-O-#^{13}; and further provided that when X^1 is CH, X^2 is N, R^{62} is methyl, and L^{13} is @^{13}-CH_2-#^{13}, then A^{13} is then A^{13} is (A^{13}-1), C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents, or 5-14 membered heteroaryl substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents.

[0007e] In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of a compound of Table 1, or a pharmaceutically acceptable salt thereof.

[0007f]In another aspect of the present disclosure, there is provided a compound selected from the group consisting of compounds 1 to 34, or a pharmaceutically acceptable salt thereof.

[0007g] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0007h] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a salt thereof, for use in enhancing protein synthesis in a living organism.

[0007i] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a salt thereof, for enhancing protein synthesis in a living organism.

[0007j] In another aspect of the present disclosure, there is provided a method for enhancing protein synthesis in a living organism, comprising administering to the living organism an effective amount of a compound disclosed herein, or a salt thereof, wherein the living organism is selected from the group consisting of a cell suspension, a hairy root culture, moss protonema, an aquatic plant and a terrestrial plant.

[0007k] In a further aspect of the present disclosure, there is provided a method for accelerating growth of a plant, comprising administering to the plant an effective amount of a compound disclosed herein, or a salt thereof.

[0007l] In another aspect of the present disclosure, thereis provided a method for improving protein yield or quality in a plant, comprising administering to the plant an effective amount of a compound disclosed herein, or a salt thereof.

[0007m] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease or disorder mediated by an integrated stress response (ISR) pathway in an individual in need thereof.

[0007n] In another aspect of the present disclosure, there is provided a method of producing a protein, comprising contacting a eukaryotic cell comprising a nucleic acid encoding the protein with the compound or salt disclosed herein.

[0007o] In a further aspect of the present disclosure, there is provided a method of culturing a eukaryotic cell comprising a nucleic acid encoding a protein, comprising contacting the eukaryotic cell with an *in vitro* culture medium comprising a compound or salt disclosed herein.

[0007p] In another aspect of the present disclosure, there is provided a method of producing a protein, comprising contacting a cell-free protein synthesis (CFPS) system

comprising eukaryotic initiation factor 2 (eIF2) and a nucleic acid encoding a protein with the compound or salt disclosed herein.

[0007q] In a further aspect of the present disclosure, there is provided an *in vitro* cell culture medium, comprising the compound or salt disclosed herein and nutrients for cellular growth.

[0007r] In another aspect of the present disclosure, there is provided a cell-free protein synthesis (CFPS) system comprising eukaryotic initiation factor 2 (eIF2) and a nucleic acid encoding a protein with the compound or salt disclosed herein.

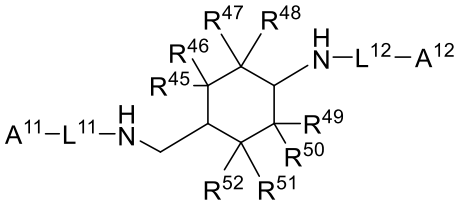
[0007s] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, for use in treating a disease or disorder mediated by an integrated stress response (ISR) pathway in an individual in need thereof, optionally wherein the compound, the pharmaceutically acceptable salt, or the pharmaceutical composition is to be administered in combination with a therapeutically effective amount of one or more additional anti-cancer agents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] FIG. 1A shows percent of protein synthesis in mouse quadriceps from fed or fasted animals treated with vehicle or compound 11.

CLAIMS

Claim 1. A compound of formula (F-1)



(F-1)

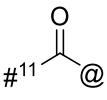
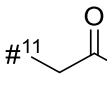
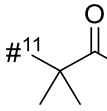
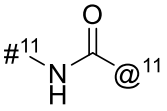
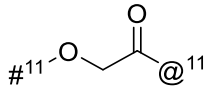
or a pharmaceutically acceptable salt thereof,

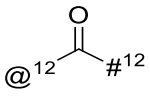
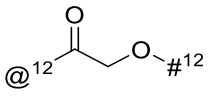
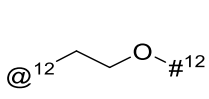
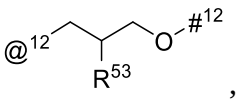
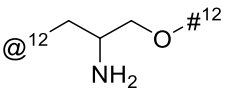
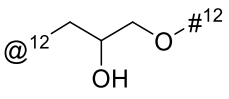
wherein:

R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, and R^{52}, independently from each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

or, one of R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, and R^{52}, and another one of R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, and R^{52}, are taken together to form a C_1-C_6 alkylene moiety;

or, two geminal substituents selected from the group consisting of R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{51}, and R^{52} are taken together to form an oxo group;

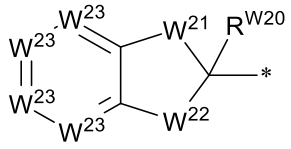
L^{11} is selected from the group consisting of a bond,  ,  ,  ,  , and  , wherein $\#^{11}$ represents to attachment point to A^{11} and $@^{11}$ represents the attachment point to the remainder of the molecule;

L^{12} is selected from the group consisting of  ,  ,  ,  ,  , and  , wherein $\#^{12}$ represents to attachment point to A^{12} and $@^{12}$ represents the attachment point to the remainder of the molecule;

R^{53} is H, OH, or NH_2;

A^{11} is selected from the group consisting of:

a substituent of formula (A^{11}-1)



(A^{11}-1)

wherein * represents the attachment point to the remainder of the molecule;

W^{21} is selected from the group consisting of -C($R^{W21-1}R^{W21-2}$)-, -N(R^{W21-2})-, -C($R^{W21-1}R^{W21-2}$)N(R^{W21-2})-, -N(R^{W21-1})C($R^{W21-1}R^{W21-2}$)-, -C(R^{W21-1})=N-, -N=C(R^{W21-1})-, -O-, -C($R^{W21-1}R^{W21-1}$)O-, -OC($R^{W21-1}R^{W21-2}$) -, -S-, -C($R^{W21-1}R^{W21-1}$)S-, -SC($R^{W21-1}R^{W21-2}$) -, -C($R^{W21-1}R^{W21-1}$)C($R^{W21-1}R^{W21-2}$)-, and -CR^{W21-1}=CR^{W21-1}-,

wherein R^{W21-1} is H or R^{A11}, and R^{W21-2} is H or R^{A11};

W^{22} is selected from the group consisting of -C($R^{W22-1}R^{W22-2}$)-, -N(R^{W22-2})-, -C($R^{W22-1}R^{W22-1}$)N(R^{W22-2})-, -N(R^{W22-1})C($R^{W22-1}R^{W22-2}$)-, -C(R^{W22-1})=N-, -N=C(R^{W22-1})-, -O-, -C($R^{W22-1}R^{W22-1}$)O-, -OC($R^{W22-1}R^{W22-2}$)-, -S-, -C($R^{W22-1}R^{W22-1}$)S-, -SC($R^{W22-1}R^{W22-2}$)-, -C($R^{W22-1}R^{W22-1}$)C($R^{W22-1}R^{W22-2}$)-, and -CR^{W22-1}=CR^{W22-1}-,

wherein R^{W22-1} is H or R^{A11}, and R^{W22-2} is H or R^{A11};

W^{23}, independently at each occurrence, is CR^{W23} or N, wherein R^{W23} is H or R^{A11};

R^{W20} is hydrogen or R^{A11}, or R^{W20} and R^{W21-2} are taken together to form a double bond between the carbon atom bearing R^{W20} and the atom bearing R^{W21-2}, or R^{W20} and R^{W22-2} are taken together to form a double bond between the carbon atom bearing R^{W20} and the atom bearing R^{W21-2};

C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents; and

5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents;

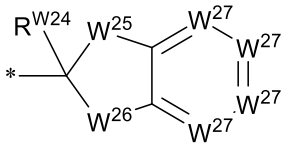
R^{A11}, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl,

OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, $C(O)NR^aR^b$, $S(O)_2OH$, $S(O)_2O$(C_1-C_6 alkyl), $S(O)_2O$(C_1-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2$NH(C_1-C_6 alkyl), $S(O)_2$NH(C_1-C_6 haloalkyl), $S(O)_2$N(C_1-C_6 alkyl)$_2$, $S(O)_2$N(C_1-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), $OS(O)_2$(C_1-C_6 alkyl), $OS(O)_2$(C_1-C_6 haloalkyl), N(H)$S(O)_2$(C_1-C_6 alkyl), N(H)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

and

A^{12} is selected from the group consisting of:

a substituent of formula (A^{12}-1)



(A^{12}-1)

wherein * represents the attachment point to the remainder of the molecule;

W^{25} is selected from the group consisting of -C($R^{W25-1}R^{W25-2}$)-, -N(R^{W25-2})-, -C($R^{W25-1}R^{W25-2}$)N(R^{W25-2})-, -N(R^{W25-1})C($R^{W25-1}R^{W25-2}$)-, -C(R^{W25-1})=N-, -N=C(R^{W25-1})-, -O-, -C($R^{W25-1}R^{W25-1}$)O-, -OC($R^{W25-1}R^{W25-2}$) -, -S-, -C($R^{W25-1}R^{W25-1}$)S-, -SC($R^{W25-1}R^{W25-2}$) -, -C($R^{W25-1}R^{W25-1}$)C($R^{W25-1}R^{W25-2}$)-, and -CR^{W25-1}=CR^{W25-1}-,

wherein R^{W25-1} is H or R^{A12}, and R^{W25-2} is H or R^{A12};

W^{26} is selected from the group consisting of $-C(R^{W26-1}R^{W26-2})-$, $-N(R^{W26-2})-$, $-C(R^{W26-1}R^{W26-1})N(R^{W26-2})-$, $-N(R^{W26-1})C(R^{W26-1}R^{W26-2})-$, $-C(R^{W26-1})=N-$, $-N=C(R^{W26-1})-$, $-O-$, $-C(R^{W26-1}R^{W26-1})O-$, $-OC(R^{W26-1}R^{W26-2})-$, $-S-$, $-C(R^{W26-1}R^{W26-1})S-$, $-SC(R^{W26-1}R^{W26-2})-$, $-C(R^{W26-1}R^{W26-1})C(R^{W26-1}R^{W26-2})-$, and $-CR^{W26-1}=CR^{W26-1}-$,

wherein R^{W26-1} is H or R^{A12}, and R^{W26-2} is H or R^{A12};

W^{27}, independently at each occurrence, is CR^{W27} or N, wherein R^{W27} is H or R^{A12};

R^{W24} is hydrogen or R^{A12}, or R^{W24} and R^{W25-2} are taken together to form a double bond between the carbon atom bearing R^{W24} and the atom bearing R^{W25-2}, or R^{W24} and R^{W26-2} are taken together to form a double bond between the carbon atom bearing R^{W24} and the atom bearing R^{W26-2};

C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A12} substituents; and

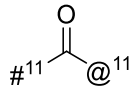
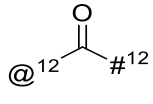
5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A12} substituents;

R^{A12}, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, $C(O)NR^aR^b$, $S(O)_2OH$, $S(O)_2O(C_1$-C_6 alkyl), $S(O)_2O(C_1$-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2NH(C_1$-C_6 alkyl), $S(O)_2NH(C_1$-C_6 haloalkyl), $S(O)_2N(C_1$-C_6 alkyl)$_2$, $S(O)_2N(C_1$-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6

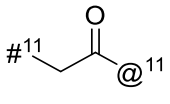
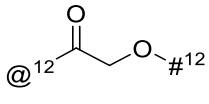
haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), OS(O)$_2$(C_1-C_6 alkyl), OS(O)$_2$(C_1-C_6 haloalkyl), N(H)S(O)$_2$(C_1-C_6 alkyl), N(H)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 alkyl), and N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

provided that

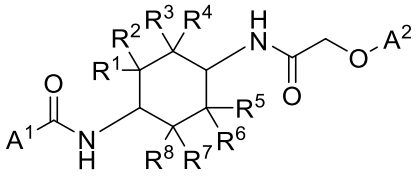
when L^{11} is a bond, then A^{11} is (A^{11}-1) optionally substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents;

when L^{11} is  and L^{12} is  , then A^{11} is (A^{11}-1) substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents or A^{12} is (A^{11}-1) substituted by 2, 3, 4, 5, 6, 7, 8, or 9 R^{A12} substituents;

and

when L^{11} is  and L^{12} is  , then A^{11} is substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A11} substituents.

Claim 2. A compound of formula (A-1)



(A-1)

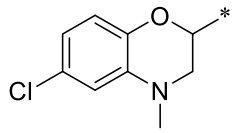
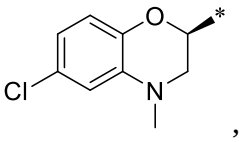
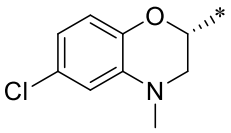
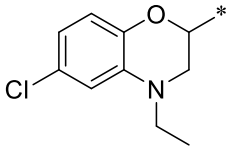
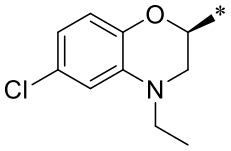
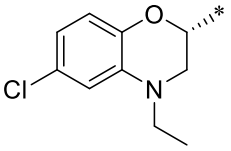
or a pharmaceutically acceptable salt thereof,

wherein:

R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, independently from each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

or, one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, and another one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8, are taken together to form a C_1-C_6 alkylene moiety;

or, two geminal substituents selected from the group consisting of R^1, R^2, R^3, R^4, R^5, R^6, R^7, and R^8 are taken together to form an oxo group;

A^1 is selected from the group consisting of  ,  ,  ,  ,  , and  ;

wherein * represents the attachment point to the remainder of the molecule;

and

A^2 is selected from the group consisting of:

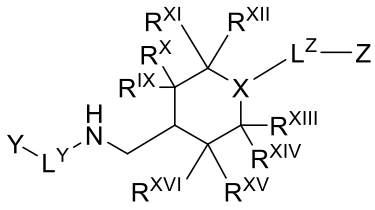
C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A2} substituents; and

5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A2} substituents;

R^{A2}, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, $C(O)NR^aR^b$, $S(O)_2OH$, $S(O)_2O$(C_1-C_6 alkyl), $S(O)_2O$(C_1-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2$NH(C_1-C_6 alkyl), $S(O)_2$NH(C_1-C_6 haloalkyl), $S(O)_2$N(C_1-C_6 alkyl)$_2$, $S(O)_2$N(C_1-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), $OS(O)_2$(C_1-C_6 alkyl), $OS(O)_2$(C_1-C_6 haloalkyl), N(H)$S(O)_2$(C_1-C_6 alkyl), N(H)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and

$N(C_1\text{-}C_6$ haloalkyl)$S(O)_2(C_1\text{-}C_6$ haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle.

Claim 3. A compound of formula (II)



(II)

or a pharmaceutically acceptable salt thereof,

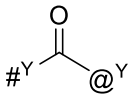
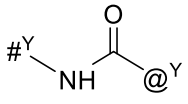
wherein:

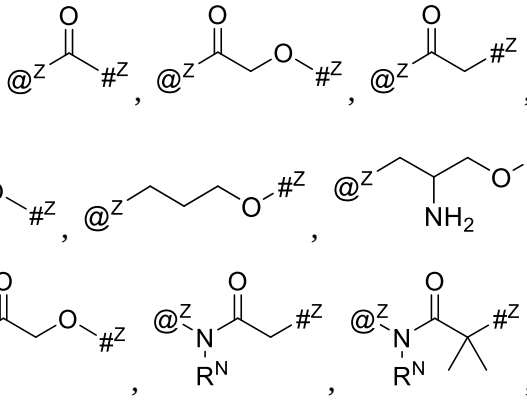
X is N;

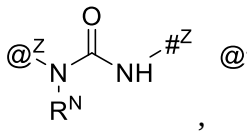
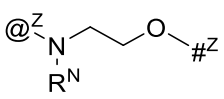
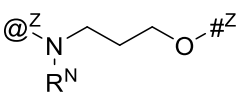
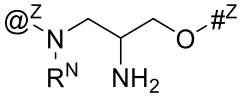
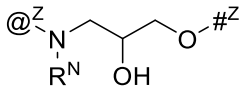
R^{IX}, R^X, R^{XI}, R^{XII}, R^{XIII}, R^{XIV}, R^{XV}, and R^{XVI}, independently from each other, are selected from the group consisting of hydrogen, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ haloalkyl, -C(O)OH, -C(O)O($C_1\text{-}C_6$ alkyl), -C(O)O($C_1\text{-}C_6$ haloalkyl), and halogen;

or, one of R^{IX}, R^X, R^{XI}, R^{XII}, R^{XIII}, R^{XIV}, R^{XV}, and R^{XVI}, and another one of R^{IX}, R^X, R^{XI}, R^{XII}, R^{XIII}, R^{XIV}, R^{XV}, and R^{XVI}, are taken together to form a $C_1\text{-}C_6$ alkylene moiety;

or, two geminal substituents selected from the group consisting of R^{IX}, R^X, R^{XI}, R^{XII}, R^{XIII}, R^{XIV}, R^{XV}, and R^{XVI} are taken together to form an oxo group;

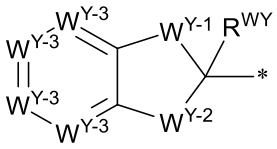
L^Y is  or  , wherein $\#^Y$ represents the attachment point to Y and $@^Y$ represents the attachment point to the remainder of the molecule;

L^Z is selected from the group consisting of 





, and

; wherein $\#^Z$ represents the attachment point to Z and $@^Z$ represents the attachment point to the remainder of the molecule;

R^N, independently at each occurrence, is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl,

Y is a substituent of formula (Y-I)



(Y-I)

wherein * represents the attachment point to the remainder of the molecule;

W^{Y-1} is selected from the group consisting of $-C(R^{WY-1-1}R^{WY-1-2})-$, $-N(R^{WY-1-2})-$, $-C(R^{WY-1-1}R^{WY-1-1})N(R^{WY-1-2})-$, $-N(R^{WY-1-1})C(R^{WY-1-1}R^{WY-1-2})-$, $-C(R^{WY-1-1})=N-$, $-N=C(R^{WY-1-1})-$, $-O-$, $-C(R^{WY-1-1}R^{WY-1-1})O-$, $-OC(R^{WY-1-1}R^{WY-1-2})-$, $-S-$, $-C(R^{WY-1-1}R^{WY-1-1})S-$, $-SC(R^{WY-1-1}R^{WY-1-2})-$, $-C(R^{WY-1-1}R^{WY-1-1})C(R^{WY-1-1}R^{WY-1-2})-$, and $-CR^{WY-1-1}=CR^{WY-1-1}-$,

wherein R^{WY-1-1} is H or R^Y, and R^{WY-1-2} is H or R^Y;

W^{Y-2} is selected from the group consisting of $-C(R^{WY-2-1}R^{WY-2-2})-$, $-N(R^{WY-2-2})-$, $-C(R^{WY-2-1}R^{WY-2-1})N(R^{WY-2-2})-$, $-N(R^{WY-2-1})C(R^{WY-2-1}R^{WY-2-2})-$, $-C(R^{WY-2-1})=N-$, $-N=C(R^{WY-2-1})-$, $-O-$, $-C(R^{WY-2-1}R^{WY-2-1})O-$, $-OC(R^{WY-2-1}R^{WY-2-2})-$, $-S-$, $-C(R^{WY-2-1}R^{WY-2-1})S-$, $-SC(R^{WY-2-1}R^{WY-2-2})-$, $-C(R^{WY-2-1}R^{WY-2-1})C(R^{WY-2-1}R^{WY-2-2})-$, and $-CR^{WY-2-1}=CR^{WY-2-1}-$,

wherein R^{WY-2-1} is H or R^Y, and R^{WY-2-2} is H or R^Y;

W^{Y-3}, independently at each occurrence, is CR^{WY-3} or N, wherein R^{WY-3} is H or R^Y;

R^{WY} is hydrogen or R^Y, or R^{WY} and R^{WY-1-2} are taken together to form a double bond between the carbon atom bearing R^{WY} and the atom bearing R^{WY-1-2}, or R^{WY} and R^{WY-2-2} are taken together to form a double bond between the carbon atom bearing R^{WY} and the atom bearing R^{WY-2-2};

C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Y substituents; and

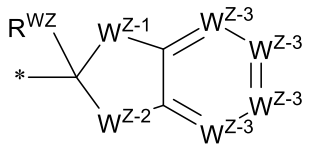
5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Y substituents;

R^Y, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b, CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), $C(O)NH_2$, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, $C(O)NR^aR^b$, $S(O)_2OH$, $S(O)_2O$(C_1-C_6 alkyl), $S(O)_2O$(C_1-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_1-C_6 alkyl), $S(O)_2NH$(C_1-C_6 haloalkyl), $S(O)_2N$(C_1-C_6 alkyl)$_2$, $S(O)_2N$(C_1-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), OS(O)$_2$(C_1-C_6 alkyl), OS(O)$_2$(C_1-C_6 haloalkyl), N(H)S(O)$_2$(C_1-C_6 alkyl), N(H)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 alkyl), and N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

and

Z is selected from the group consisting of:

a substituent of formula (Z-I)



(Z-I)

wherein * represents the attachment point to the remainder of the molecule;

W^{Z-1} is selected from the group consisting of $-C(R^{WZ-1-1}R^{WZ-1-2})-$, $-N(R^{WZ-1-2})-$, $-C(R^{WZ-1-1}R^{WZ-1-2})N(R^{WZ-1-2})-$, $-N(R^{WZ-1-1})C(R^{WZ-1-1}R^{WZ-1-2})-$, $-C(R^{WZ-1-1})=N-$, $-N=C(R^{WZ-1-1})-$, $-O-$, $-C(R^{WZ-1-1}R^{WZ-1-1})O-$, $-OC(R^{WZ-1-1}R^{WZ-1-2})-$, $-S-$, $-C(R^{WZ-1-1}R^{WZ-1-1})S-$, $-SC(R^{WZ-1-1}R^{WZ-1-2})-$, $-C(R^{WZ-1-1}R^{WZ-1-1})C(R^{WZ-1-1}R^{WZ-1-2})-$, and $-CR^{WZ-1-1}=CR^{WZ-1-1}-$,

wherein R^{WZ-1-1} is H or R^Z, and R^{WZ-1-2} is H or R^Z;

W^{Z-2} is selected from the group consisting of $-C(R^{WZ-2-1}R^{WZ-2-2})-$, $-N(R^{WZ-2-2})-$, $-C(R^{WZ-2-1}R^{WZ-2-1})N(R^{WZ-2-2})-$, $-N(R^{WZ-2-1})C(R^{WZ-2-1}R^{WZ-2-2})-$, $-C(R^{WZ-2-1})=N-$, $-N=C(R^{WZ-2-1})-$, $-O-$, $-C(R^{WZ-2-1}R^{WZ-2-1})O-$, $-OC(R^{WZ-2-1}R^{WZ-2-2})-$, $-S-$, $-C(R^{WZ-2-1}R^{WZ-2-1})S-$, $-SC(R^{WZ-2-1}R^{WZ-2-2})-$, $-C(R^{WZ-2-1}R^{WZ-2-1})C(R^{WZ-2-1}R^{WZ-2-2})-$, and $-CR^{WZ-2-1}=CR^{WZ-2-1}-$,

wherein R^{WZ-2-1} is H or R^Z, and R^{WZ-2-2} is H or R^Z;

W^{Z-3}, independently at each occurrence, is CR^{WZ-3} or N, wherein R^{WZ-3} is H or R^Z;

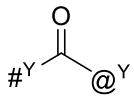
R^{WZ} is hydrogen or R^Z, or R^{WZ} and R^{WZ-1-2} are taken together to form a double bond between the carbon atom bearing R^{WZ} and the atom bearing R^{WZ-1-2}, or R^{WZ} and R^{WZ-2-2} are taken together to form a double bond between the carbon atom bearing R^{WZ} and the atom bearing R^{WZ-2-2};

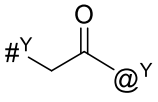
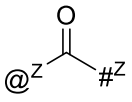
C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Z substituents; and

5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Z substituents;

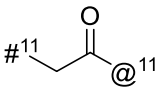
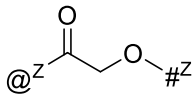
R^Z, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, OH, O(C_1-C_6 alkyl), O(C_1-C_6 haloalkyl), SH, S(C_1-C_6 alkyl), S(C_1-C_6 haloalkyl), NH_2, NH(C_1-C_6 alkyl), NH(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)$_2$, N(C_1-C_6 haloalkyl)$_2$, NR^aR^b,

CN, C(O)OH, C(O)O(C_1-C_6 alkyl), C(O)O(C_1-C_6 haloalkyl), C(O)NH_2, C(O)NH(C_1-C_6 alkyl), C(O)NH(C_1-C_6 haloalkyl), C(O)N(C_1-C_6 alkyl)$_2$, C(O)N(C_1-C_6 haloalkyl)$_2$, C(O)NR^aR^b, $S(O)_2OH$, $S(O)_2O$(C_1-C_6 alkyl), $S(O)_2O$(C_1-C_6 haloalkyl), $S(O)_2NH_2$, $S(O)_2NH$(C_1-C_6 alkyl), $S(O)_2NH$(C_1-C_6 haloalkyl), $S(O)_2N$(C_1-C_6 alkyl)$_2$, $S(O)_2N$(C_1-C_6 haloalkyl)$_2$, $S(O)_2NR^aR^b$,OC(O)H, OC(O)(C_1-C_6 alkyl), OC(O)(C_1-C_6 haloalkyl), N(H)C(O)H, N(H)C(O)(C_1-C_6 alkyl), N(H)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)C(O)H, N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)C(O)H, N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), OS(O)$_2$(C_1-C_6 alkyl), OS(O)$_2$(C_1-C_6 haloalkyl), N(H)S(O)$_2$(C_1-C_6 alkyl), N(H)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 alkyl), N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 haloalkyl), N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 alkyl), and N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 haloalkyl); wherein R^a and R^b are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

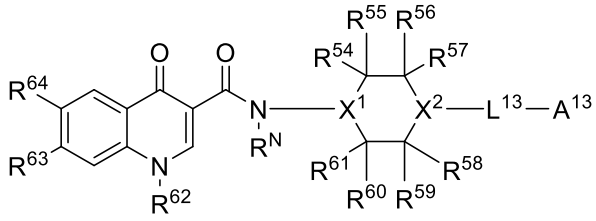
provided that when L^Y is  , Y is (Y-I);

when L^Y is  and L^Z is  , then Y is (Y-I) substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Y substituents or Z is (Z-I) substituted by 2, 3, 4, 5, 6, 7, 8, or 9 R^Z substituents;

and

when L^Y is  and L^Z is  , then Y is substituted by 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^Y substituents.

Claim 4. A compound of formula (III)



(III)

or a salt thereof,

wherein:

X^1 is N or CR^{X1};

X^2 is N or CR^{X2};

when present, R^{X1} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

when present, R^{X2} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, and R^{61}, independently from each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

or, one of R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, and R^{61}, and another one of R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, and R^{61}, are taken together to form a C_1-C_6 alkylene moiety;

or, two geminal substituents selected from the group consisting of R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, and R^{61} are taken together to form an oxo group;

or, two of R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{X1} when present, and $R^{X2,}$ when present, are taken together to form a C_1-C_6 alkylene moiety;

R^{63} and R^{64}, independently from each other, are selected from the group consisting of hydrogen, halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), $-NH_2$, -NH(C_1-C_6 alkyl),-NH(C_1-C_6 haloalkyl),-N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, $-NR^{B\text{-}a}R^{B\text{-}b}$, -CN, -C(O)OH, -C(O)O($C_1$-$C_6$ alkyl), -C(O)O(C_1-C_6 haloalkyl), $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_1-C_6 haloalkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)N(C_1-C_6 haloalkyl)$_2$, $-C(O)NR^{B\text{-}a}R^{B\text{-}b}$, $-S(O)_2OH$, -S(O)$_2$O(C_1-C_6 alkyl), -S(O)$_2$O(C_1-C_6 haloalkyl), $-S(O)_2NH_2$, -S(O)$_2$NH(C_1-C_6 alkyl), -S(O)$_2$NH(C_1-C_6 haloalkyl), -S(O)$_2$N(C_1-C_6 alkyl)$_2$, -S(O)$_2$N(C_1-C_6 haloalkyl)$_2$,

$-S(O)_2NR^{B-a}R^{B-b}$,-OC(O)H, -OC(O)(C_1-C_6 alkyl), -OC(O)(C_1-C_6 haloalkyl), -N(H)C(O)H, -N(H)C(O)(C_1-C_6 alkyl), -N(H)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)C(O)H, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)C(O)H, -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), $-OS(O)_2$(C_1-C_6 alkyl), $-OS(O)_2$(C_1-C_6 haloalkyl), -N(H)$S(O)_2$(C_1-C_6 alkyl), -N(H)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl);

wherein R^{B-a} and R^{B-b} are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

R^{62} is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -(C_1-C_6 alkylene)-(C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents), -(C_1-C_6 alkylene)-(5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents), C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -(C_1-C_6 alkylene)-OH, -(C_1-C_6 alkylene)-O-(C_1-C_6 alkyl), -(C_1-C_6 alkylene)-O-(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), $-NH_2$, -NH(C_1-C_6 alkyl),-NH(C_1-C_6 haloalkyl),-N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, -CN, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_1-C_6 haloalkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)N(C_1-C_6 haloalkyl)$_2$, $-C(O)NR^{62-a}R^{62-b}$, $-S(O)_2OH$, -S(O)$_2$O(C_1-C_6 alkyl), -S(O)$_2$O(C_1-C_6 haloalkyl), $-S(O)_2NH_2$, -S(O)$_2$NH(C_1-C_6 alkyl), -S(O)$_2$NH(C_1-C_6 haloalkyl), -S(O)$_2$N(C_1-C_6 alkyl)$_2$, -S(O)$_2$N(C_1-C_6 haloalkyl)$_2$, $-S(O)_2NR^{62-a}R^{62-b}$,-OC(O)H, -OC(O)(C_1-C_6 alkyl), -OC(O)(C_1-C_6 haloalkyl), -N(H)C(O)H, -N(H)C(O)(C_1-C_6 alkyl), -N(H)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)C(O)H, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)C(O)H, -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), $-OS(O)_2$(C_1-C_6 alkyl), $-OS(O)_2$(C_1-C_6 haloalkyl), -N(H)$S(O)_2$(C_1-C_6 alkyl), -N(H)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl);

wherein R^{62-a} and R^{62-b} are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

L^{13} is a linker selected from the group consisting of $@^{13}$-C_1-C_6 alkylene-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-CH_2-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-CH_2-NR^N-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-NR^N-NR^N -(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-CH_2-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-CH_2-NR^N-NR^N -(C_1-C_6 alkylene)-O-$\#^{13}$, and $@^{13}$-(C_1-C_6 alkylene)-O-$\#^{13}$;

wherein $@^{13}$ represents the attachment point to X^2 and $\#^{13}$ represents the attachment point to A^{13};

the C_1-C_6 alkylene moiety of each of the $@^{13}$-C_1-C_6 alkylene-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-CH_2-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-CH_2-NR^N-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-NR^N-NR^N -(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-CH_2-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, $@^{13}$-CH_2-NR^N-NR^N -(C_1-C_6 alkylene)-O-$\#^{13}$, and $@^{13}$-(C_1-C_6 alkylene)-O-$\#^{13}$ is optionally substituted with 1 to 12 R^{66};

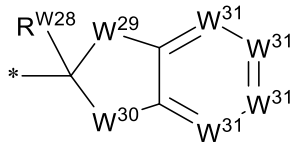
R^N, independently at each occurrence, is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl,

R^{66}, independently at each occurrence, is selected from the group consisting of oxo, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), $-NH_2$, -NH(C_1-C_6 alkyl),-NH(C_1-C_6 haloalkyl),-N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, $-NR^{B\text{-}a}R^{B\text{-}b}$, -CN, -C(O)OH, -C(O)O($C_1$-$C_6$ alkyl), -C(O)O(C_1-C_6 haloalkyl), $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_1-C_6 haloalkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)N(C_1-C_6 haloalkyl)$_2$, $-C(O)NR^{B\text{-}a}R^{B\text{-}b}$, $-S(O)_2OH$, -$S(O)_2$O(C_1-C_6 alkyl), -$S(O)_2$O(C_1-C_6 haloalkyl), $-S(O)_2NH_2$, -$S(O)_2$NH(C_1-C_6 alkyl), -$S(O)_2$NH(C_1-C_6 haloalkyl), -$S(O)_2$N(C_1-C_6 alkyl)$_2$, -$S(O)_2$N(C_1-C_6 haloalkyl)$_2$, $-S(O)_2NR^{B\text{-}a}R^{B\text{-}b}$,-OC(O)H, -OC(O)($C_1$-$C_6$ alkyl), -OC(O)(C_1-C_6 haloalkyl), -N(H)C(O)H, -N(H)C(O)(C_1-C_6 alkyl), -N(H)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)C(O)H, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)C(O)H, -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), -OS$(O)_2$(C_1-C_6 alkyl), -OS$(O)_2$(C_1-C_6 haloalkyl), -N(H)S$(O)_2$(C_1-C_6 alkyl), -N(H)S$(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6

alkyl)$S(O)_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$S(O)_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 alkyl), and -N(C_1-C_6 haloalkyl)$S(O)_2$(C_1-C_6 haloalkyl);

A^{13} is selected from the group consisting of:

a substituent of formula (A^{13}-1)



(A^{13}-1)

W^{29} is selected from the group consisting of -C($R^{W29\text{-}1}R^{W29\text{-}2}$)-, -N($R^{W29\text{-}2}$)-, -C($R^{W29\text{-}1}R^{W29\text{-}1}$)N($R^{W29\text{-}2}$)-, -N($R^{W29\text{-}1}$)C($R^{W29\text{-}1}R^{W29\text{-}2}$)-, -C($R^{W29\text{-}1}$)=N-, -N=C($R^{W29\text{-}1}$)-, -O-, -C($R^{W29\text{-}1}R^{W29\text{-}1}$)O-, -OC($R^{W29\text{-}1}R^{W29\text{-}2}$)-, -S-, -C($R^{W29\text{-}1}R^{W29\text{-}1}$)S-, -SC($R^{W29\text{-}1}R^{W29\text{-}2}$) -, -C($R^{W29\text{-}1}R^{W29\text{-}1}$)C($R^{W29\text{-}1}R^{W29\text{-}2}$)-, and -C$R^{W29\text{-}1}$=C$R^{W29\text{-}1}$-, wherein $R^{W29\text{-}1}$ is H or R^{A13}, and $R^{W29\text{-}2}$ is H or R^{A13};

W^{30} is selected from the group consisting of -C($R^{W30\text{-}1}R^{W30\text{-}2}$)-, -N($R^{W30\text{-}2}$)-, -C($R^{W30\text{-}1}R^{W30\text{-}1}$)N($R^{W30\text{-}2}$)-, -N($R^{W30\text{-}1}$)C($R^{W30\text{-}1}R^{W30\text{-}2}$)-, -C($R^{W30\text{-}1}$)=N-, -N=C($R^{W30\text{-}1}$)-, -O-, -C($R^{W30\text{-}1}R^{W30\text{-}1}$)O-, -OC($R^{W30\text{-}1}R^{W30\text{-}2}$)-, -S-, -C($R^{W30\text{-}1}R^{W30\text{-}1}$)S-, -SC($R^{W30\text{-}1}R^{W30\text{-}2}$)-, -C($R^{W30\text{-}1}R^{W30\text{-}1}$)C($R^{W30\text{-}1}R^{W30\text{-}2}$)-, and -C$R^{W30\text{-}1}$=C$R^{W30\text{-}1}$-, wherein $R^{W30\text{-}1}$ is H or R^{A13}, and $R^{W30\text{-}2}$ is H or R^{A13};

W^{31}, independently at each occurrence, is CR^{W31} or N, wherein R^{W31} is H or R^{A13};

R^{W28} is hydrogen or R^{A13}, or R^{W28} and $R^{W29\text{-}2}$ are taken together to form a double bond between the carbon atom bearing R^{W28} and the atom bearing $R^{W29\text{-}2}$, or R^{W28} and $R^{W30\text{-}2}$ are taken together to form a double bond between the carbon atom bearing R^{W28} and the atom bearing $R^{W30\text{-}2}$;

C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents; and

5-14 membered heteroaryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents;

R^{A13}, independently at each occurrence, is selected from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), $-NH_2$, -NH(C_1-C_6 alkyl),-NH(C_1-C_6 haloalkyl),-N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, $-NR^{A13\text{-}a}R^{A13\text{-}b}$, -CN, -C(O)OH, -C(O)O($C_1$-$C_6$ alkyl), -C(O)O(C_1-C_6 haloalkyl), $-C(O)NH_2$, -C(O)NH(C_1-C_6 alkyl), -C(O)NH(C_1-C_6 haloalkyl), -C(O)N(C_1-C_6 alkyl)$_2$, -C(O)N(C_1-C_6 haloalkyl)$_2$, $-C(O)NR^{A13\text{-}a}R^{A13\text{-}b}$, $-S(O)_2OH$, -S(O)$_2$O(C_1-C_6 alkyl), -S(O)$_2$O(C_1-C_6 haloalkyl), $-S(O)_2NH_2$, -S(O)$_2$NH(C_1-C_6 alkyl), -S(O)$_2$NH(C_1-C_6 haloalkyl), -S(O)$_2$N(C_1-C_6 alkyl)$_2$, -S(O)$_2$N(C_1-C_6 haloalkyl)$_2$, $-S(O)_2NR^{A13\text{-}a}R^{A13\text{-}b}$,-OC(O)H, -OC(O)($C_1$-$C_6$ alkyl), -OC(O)(C_1-C_6 haloalkyl), -N(H)C(O)H, -N(H)C(O)(C_1-C_6 alkyl), -N(H)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)C(O)H, -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)C(O)H, -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 alkyl), -N(C_1-C_6 haloalkyl)C(O)(C_1-C_6 haloalkyl), -OS(O)$_2$(C_1-C_6 alkyl), -OS(O)$_2$(C_1-C_6 haloalkyl), -N(H)S(O)$_2$(C_1-C_6 alkyl), -N(H)S(O)$_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)S(O)$_2$(C_1-C_6 haloalkyl), -N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 alkyl), and -N(C_1-C_6 haloalkyl)S(O)$_2$(C_1-C_6 haloalkyl);

wherein $R^{A13\text{-}a}$ and $R^{A13\text{-}b}$ are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

provided that when X^2 is N, then L^{13} is a linker selected from the group consisting of $@^{13}$-C_1-C_6 alkylene-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-$\#^{13}$, $@^{13}$-NR^N-(C_1-C_6 alkylene)-O-$\#^{13}$, and $@^{13}$-(C_1-C_6 alkylene)-O-$\#^{13}$; and further provided that when X^1 is CH, X^2 is N, R^{62} is methyl, and L^{13} is $@^{13}$-CH_2-$\#^{13}$, then A^{13} is then A^{13} is (A^{13}-1), C_6-C_{14} aryl optionally substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents, or 5-14 membered heteroaryl substituted with 1, 2, 3, 4, 5, 6, 7, 8, or 9 R^{A13} substituents.

Claim 5. A compound selected from the group consisting of a compound of Table 1, or a pharmaceutically acceptable salt thereof.

Claim 6. A compound selected from the group consisting of compounds 1 to 34, or a pharmaceutically acceptable salt thereof.

Claim 7. A pharmaceutical composition comprising a compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Claim 8. A compound of any one of claims 1 to 6, or a salt thereof, for use in enhancing protein synthesis in a living organism.

Claim 9. A compound of any one of claims 1 to 6, or a salt thereof, for enhancing protein synthesis in a living organism.

Claim 10. A method for enhancing protein synthesis in a living organism, comprising administering to the living organism an effective amount of a compound of any one of claims 1 to 6, or a salt thereof, wherein the living organism is selected from the group consisting of a cell suspension, a hairy root culture, moss protonema, an aquatic plant and a terrestrial plant.

Claim 11. A method for accelerating growth of a plant, comprising administering to the plant an effective amount of a compound of any one of claims 1 to 6, or a salt thereof.

Claim 12. A method for improving protein yield or quality in a plant, comprising administering to the plant an effective amount of a compound of any one of claims 1 to 6, or a salt thereof.

Claim 13. The method of claim 10, wherein the plant is selected from soybean, sunflower, grain legume, rice, wheat germ, maize, tobacco, a cereal, and a lupin crop.

Claim 14. Use of a compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of a pharmaceutical composition of claim 7, in the manufacture of a medicament for treating a disease or disorder mediated by an integrated stress response (ISR) pathway in an individual in need thereof.

Claim 15. The use of claim 14, wherein the compound, the pharmaceutically acceptable salt, or the pharmaceutical composition is to be administered in combination with a therapeutically effective amount of one or more additional anti-cancer agents.

Claim 16. The use of claim 14, wherein the disease or disorder is mediated by phosphorylation of eIF2α and/or the guanine nucleotide exchange factor (GEF) activity of eIF2B.

Claim 17. The use of any one of claims 14 to 16, wherein the disease or disorder is mediated by a decrease in protein synthesis.

Claim 18. The use of any one of claims 14 to 17, wherein the disease or disorder is mediated by the expression of ATF4, CHOP or BACE-1.

Claim 19. The use of any one of claims 14 to 17, wherein the disease or disorder is a neurodegenerative disease, an inflammatory disease, an autoimmune disease, a metabolic syndrome, a cancer, a vascular disease, an ocular disease, a musculoskeletal disease, or a genetic disorder.

Claim 20. The use of claim 19, wherein the disease is vanishing white matter disease, childhood ataxia with CNS hypomyelination, intellectual disability syndrome, Alzheimer's disease, prion disease, Creutzfeldt-Jakob disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) disease, cognitive impairment, frontotemporal dementia (FTD), traumatic brain injury, postoperative cognitive dysfunction (PCD), neuro-otological syndromes, hearing loss, Huntington's disease, stroke, chronic traumatic encephalopathy, spinal cord injury, dementias or cognitive impairment, arthritis, psoriatic arthritis, psoriasis, juvenile idiopathic arthritis, asthma, allergic asthma, bronchial asthma, tuberculosis, chronic airway disorder, cystic fibrosis, glomerulonephritis, membranous nephropathy, sarcoidosis, vasculitis, ichthyosis, transplant rejection, interstitial cystitis, atopic dermatitis or inflammatory bowel disease, Crohn's disease, ulcerative colitis, celiac disease, systemic lupus erythematosus, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, acute pancreatitis, chronic pancreatitis, alcoholic liver steatosis, obesity, glucose intolerance, insulin resistance, hyperglycemia, fatty liver, dyslipidemia, hyperlipidemia, type 2 diabetes, pancreatic cancer, breast cancer, kidney cancer, bladder cancer, prostate cancer, testicular cancer, urothelial cancer, endometrial cancer, ovarian cancer, cervical cancer, renal cancer, esophageal cancer, gastrointestinal stromal tumor (GIST), multiple

myeloma, cancer of secretory cells, thyroid cancer, gastrointestinal carcinoma, chronic myeloid leukemia, hepatocellular carcinoma, colon cancer, melanoma, malignant glioma, glioblastoma, glioblastoma multiforme, astrocytoma, dysplastic gangliocytoma of the cerebellum, Ewing's sarcoma, rhabdomyosarcoma, ependymoma, medulloblastoma, ductal adenocarcinoma, adenosquamous carcinoma, nephroblastoma, acinar cell carcinoma, lung cancer, non-Hodgkin's lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia, monoclonal gammopathy of undetermined significance (MGUS), plasmocytoma, lymphoplasmacytic lymphoma, acute lymphoblastic leukemia, Pelizaeus-Merzbacher disease, atherosclerosis, abdominal aortic aneurism, carotid artery disease, deep vein thrombosis, Buerger's disease, chronic venous hypertension, vascular calcification, telangiectasia or lymphoedema, glaucoma, age-related macular degeneration, inflammatory retinal disease, retinal vascular disease, diabetic retinopathy, uveitis, rosacea, Sjogren´s syndrome or neovascularization in proliferative retinopathy, hyperhomocysteinemia, skeletal muscle atrophy, myopathy, muscular dystrophy, muscular wasting, sarcopenia, Duchenne muscular dystrophy (DMD), Becker's disease, myotonic dystrophy, X-linked dilated cardiomyopathy, spinal muscular atrophy (SMA), Down syndrome, MEHMO syndrome, metaphyseal chondrodysplasia, Schmid type (MCDS), depression, or social behavior impairment.

Claim 21. A method of producing a protein, comprising contacting a eukaryotic cell comprising a nucleic acid encoding the protein with the compound or salt of any one of claims 1 to 6.

Claim 22. The method of claim 21, comprising culturing the cell in an *in vitro* culture medium comprising the compound or salt.

Claim 23. A method of culturing a eukaryotic cell comprising a nucleic acid encoding a protein, comprising contacting the eukaryotic cell with an *in vitro* culture medium comprising a compound or salt of any one of claims 1 to 6.

Claim 24. The method of any one of claims 21 to 23, wherein the nucleic acid encoding the protein is a recombinant nucleic acid.

Claim 25. The method of any one of claims 21 to 24, wherein the cell is a human embryonic kidney (HEK) cell, a Chinese hamster ovary (CHO) cell, or a HeLa cell.

Claim 26. The method of any one of claims 21 to 25, wherein the cell is a yeast cell, a wheat germ cell, an insect cell, a rabbit reticulocyte, a cervical cancer cell, a baby hamster kidney cell, a murine myeloma cell, an HT-1080 cell, a PER.C6 cell, a plant cell, a hybridoma cell, or a human blood derived leukocyte

Claim 27. A method of producing a protein, comprising contacting a cell-free protein synthesis (CFPS) system comprising eukaryotic initiation factor 2 (eIF2) and a nucleic acid encoding a protein with the compound or salt of any one of claims 1 to 6.

Claim 28. The method of any one of claims 21 to 27, wherein the protein is an antibody or a fragment thereof.

Claim 29. The method of any one of claims 21 to 28, wherein the protein is a recombinant protein, an enzyme, an allergenic peptide, a cytokine, a peptide, a hormone, erythropoietin (EPO), an interferon, a granulocyte-colony stimulating factor (G-CSF), an anticoagulant, or a clotting factor.

Claim 30. The method of any one of claims 21 to 29, comprising purifying the protein.

Claim 31. An *in vitro* cell culture medium, comprising the compound or salt of any one of claims 1 to 6 and nutrients for cellular growth.

Claim 32. The cell culture medium of claim 31, comprising a eukaryotic cell comprising a nucleic acid encoding a protein.

Claim 33. The cell culture medium of claim 31 or 32, further comprising a compound for inducing protein expression.

Claim 34. The cell culture medium of any one of claims 31 to 33, wherein the nucleic acid encoding the protein is a recombinant nucleic acid.

Claim 35. The cell culture medium of any one of claims 31 to 34, wherein the protein is an antibody or a fragment thereof.

Claim 36. The cell culture medium of any one of claims 31 to 34, wherein the protein is a recombinant protein, an enzyme, an allergenic peptide, a cytokine, a peptide, a hormone, erythropoietin (EPO), an interferon, a granulocyte-colony stimulating factor (G-CSF), an anticoagulant, or a clotting factor.

Claim 37. The cell culture medium of any one of claims 31 to 36, wherein the eukaryotic cell is a human embryonic kidney (HEK) cell, a Chinese hamster ovary (CHO) cell, or a HeLa cell.

Claim 38. The cell culture medium of any one of claims 31 to 36, wherein the cell is a yeast cell, a wheat germ cell, an insect cell, a rabbit reticulocyte, a cervical cancer cell, a baby hamster kidney cell, a murine myeloma cell, an HT-1080 cell, a PER.C6 cell, a plant cell, a hybridoma cell, or a human blood derived leukocyte

Claim 39. A cell-free protein synthesis (CFPS) system comprising eukaryotic initiation factor 2 (eIF2) and a nucleic acid encoding a protein with the compound or salt of any one of claims 1 to 6.

Claim 40. The CFPS system of claim 39, comprising a eukaryotic cell extract comprising eIF2.

Claim 41. The CFPS system of claim 39 or 40, further comprising eIF2B.

Claim 42. The CFPS system of any one of claims 39 to 41, wherein the protein is an antibody or a fragment thereof.

Claim 43. The CFPS system of any one of claims 39 to 42, wherein the protein is a recombinant protein, an enzyme, an allergenic peptide, a cytokine, a peptide, a hormone, erythropoietin (EPO), an interferon, a granulocyte-colony stimulating factor (G-CSF), an anticoagulant, or a clotting factor.

Claim 44. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 7, for use in treating a disease or disorder mediated by an integrated stress response (ISR) pathway in an individual in need thereof, optionally wherein the compound, the pharmaceutically acceptable salt, or the pharmaceutical composition is to be administered in combination with a therapeutically effective amount of one or more additional anti-cancer agents.

Claim 45. The compound or pharmaceutical composition of claim 44, wherein:
(a) the disease or disorder is mediated by phosphorylation of eIF2α and/or the guanine nucleotide exchange factor (GEF) activity of eIF2B; and/or
(b) the disease or disorder is mediated by a decrease in protein synthesis; and/or
(c) the disease or disorder is mediated by the expression of ATF4, CHOP or BACE-1.

Claim 46. The compound or pharmaceutical composition of claim 44 or 45, wherein the disease or disorder is a neurodegenerative disease, an inflammatory disease, an autoimmune disease, a metabolic syndrome, a cancer, a vascular disease, an ocular disease, a musculoskeletal disease, or a genetic disorder, for example, wherein the disease is vanishing white matter disease, childhood ataxia with CNS hypomyelination, intellectual disability syndrome, Alzheimer's disease, prion disease, Creutzfeldt-Jakob disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) disease, cognitive impairment, frontotemporal dementia (FTD), traumatic brain injury, postoperative cognitive dysfunction (PCD), neuro-otological syndromes, hearing loss, Huntington's disease, stroke, chronic traumatic encephalopathy, spinal cord injury, dementias or cognitive impairment, arthritis, psoriatic arthritis, psoriasis, juvenile idiopathic arthritis, asthma, allergic asthma, bronchial asthma, tuberculosis, chronic airway disorder, cystic fibrosis, glomerulonephritis, membranous nephropathy, sarcoidosis, vasculitis, ichthyosis, transplant rejection, interstitial cystitis, atopic dermatitis or inflammatory bowel disease, Crohn's disease, ulcerative colitis, celiac disease, systemic lupus erythematosus, type 1 diabetes, multiple

sclerosis, rheumatoid arthritis, acute pancreatitis, chronic pancreatitis, alcoholic liver steatosis, obesity, glucose intolerance, insulin resistance, hyperglycemia, fatty liver, dyslipidemia, hyperlipidemia, type 2 diabetes, pancreatic cancer, breast cancer, kidney cancer, bladder cancer, prostate cancer, testicular cancer, urothelial cancer, endometrial cancer, ovarian cancer, cervical cancer, renal cancer, esophageal cancer, gastrointestinal stromal tumor (GIST), multiple myeloma, cancer of secretory cells, thyroid cancer, gastrointestinal carcinoma, chronic myeloid leukemia, hepatocellular carcinoma, colon cancer, melanoma, malignant glioma, glioblastoma, glioblastoma multiforme, astrocytoma, dysplastic gangliocytoma of the cerebellum, Ewing's sarcoma, rhabdomyosarcoma, ependymoma, medulloblastoma, ductal adenocarcinoma, adenosquamous carcinoma, nephroblastoma, acinar cell carcinoma, lung cancer, non-Hodgkin's lymphoma, Burkitt's lymphoma, chronic lymphocytic leukemia, monoclonal gammopathy of undetermined significance (MGUS), plasmocytoma, lymphoplasmacytic lymphoma, acute lymphoblastic leukemia, Pelizaeus-Merzbacher disease, atherosclerosis, abdominal aortic aneurism, carotid artery disease, deep vein thrombosis, Buerger's disease, chronic venous hypertension, vascular calcification, telangiectasia or lymphoedema, glaucoma, age-related macular degeneration, inflammatory retinal disease, retinal vascular disease, diabetic retinopathy, uveitis, rosacea, Sjogren´s syndrome or neovascularization in proliferative retinopathy, hyperhomocysteinemia, skeletal muscle atrophy, myopathy, muscular dystrophy, muscular wasting, sarcopenia, Duchenne muscular dystrophy (DMD), Becker's disease, myotonic dystrophy, X-linked dilated cardiomyopathy, spinal muscular atrophy (SMA), Down syndrome, MEHMO syndrome, metaphyseal chondrodysplasia, Schmid type (MCDS), depression, or social behavior impairment.