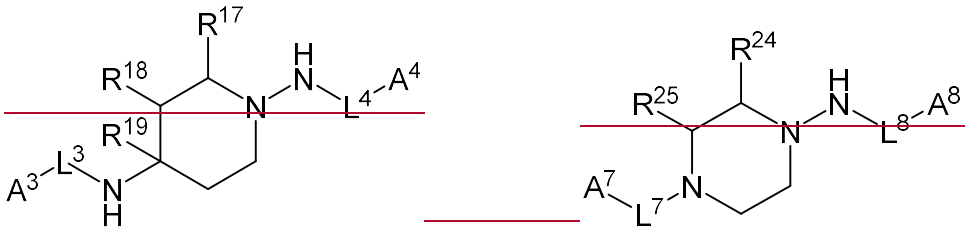
Huntington disease, or prior disease), metabolic diseases (metabolic syndrome), autoimmune diseases, inflammatory diseases (such as cystic fibrosis), musculoskeletal diseases (such as myopathy), vascular diseases, and ocular diseases.

BRIEF SUMMARY

[0005] Inhibitors of the Integrated Stress Response (ISR) pathway are described, as are methods of making and using the compounds, or salts thereof.

~~**[0005a]** In one aspect, the present disclosure refers to a compound of formula (IV) or a compound of formula (VI):~~



~~(IV) (VI)~~

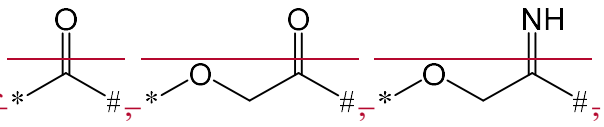
~~or a pharmaceutically acceptable salt thereof,~~

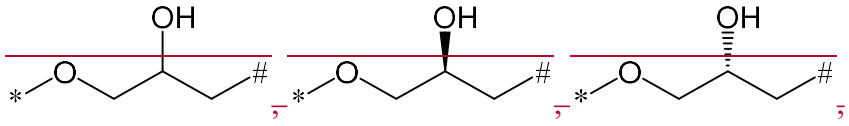
~~wherein in the compound of formula (IV), or the pharmaceutically acceptable salt thereof:~~

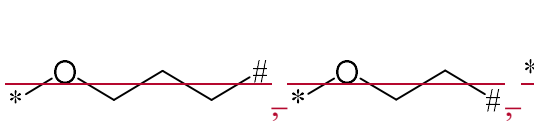
~~R^{17} is hydrogen or C(O)OH;~~

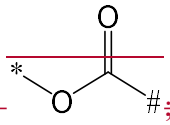
~~R^{18} is hydrogen or halogen;~~

~~R^{19} is hydrogen or C_2-C_6 alkynyl;~~

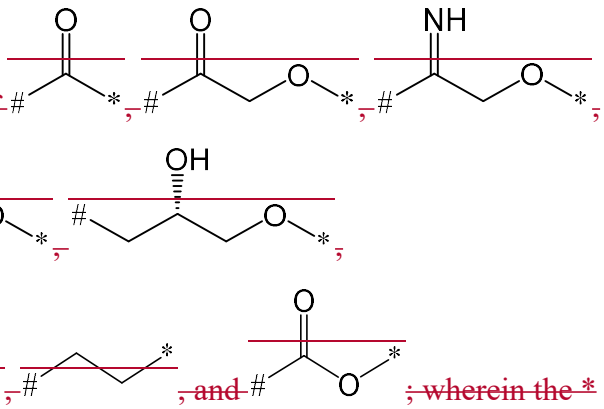
~~L^3 is selected from the group consisting of~~ 





~~, and~~ 

~~; wherein the * represents the attachment point to A^3, and the # represents the attachment point to the remainder of the molecule;~~

L^4 is selected from the group consisting of  , and ; wherein the * represents the attachment point to A^4, and the # represents the attachment point to the remainder of the molecule;

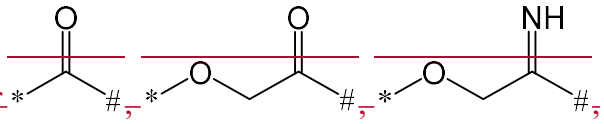
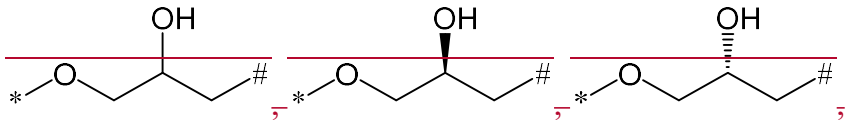
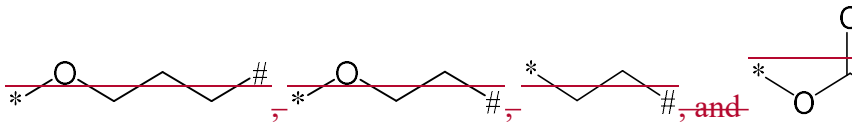
A^3 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

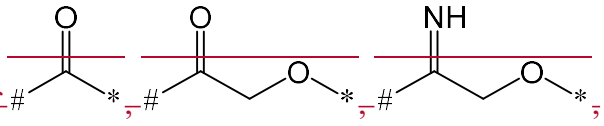
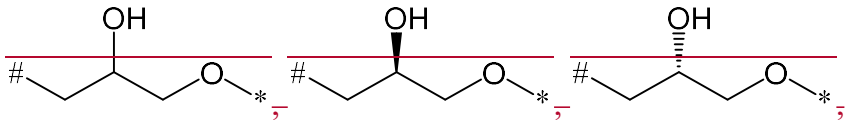
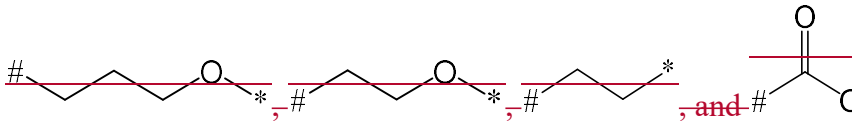
A^4 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

and wherein in the compound of formula (VI), or the pharmaceutically acceptable salt thereof:

R^{24} is hydrogen or -C(O)OH;

R^{25} is hydrogen or halogen;

L^7 is selected from the group consisting of  ,  ,  , and ; wherein the * represents the attachment point to A^7, and the # represents the attachment point to the remainder of the molecule;

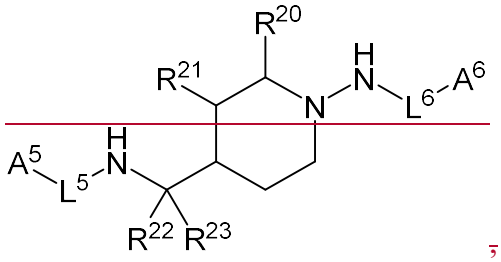
L^8 is selected from the group consisting of  ,  ,  , and ; wherein the * represents the attachment point to A^8, and the # represents the attachment point to the remainder of the molecule;

A^7 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

A^8 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents

selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.

[0005b] In one aspect, the present disclosure refers to a compound of formula (V):



(V)

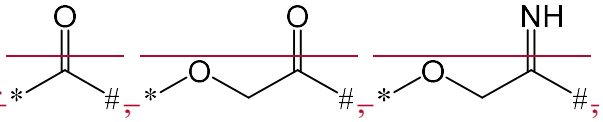
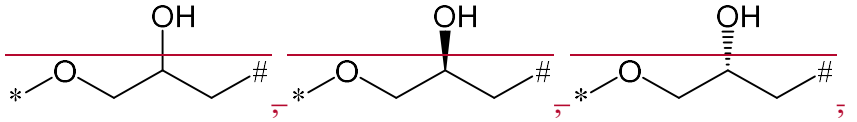
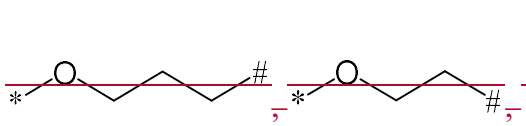
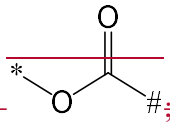
or a pharmaceutically acceptable salt thereof,

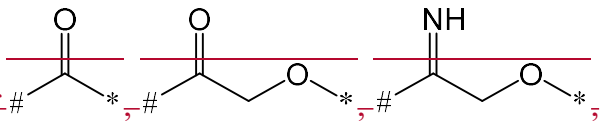
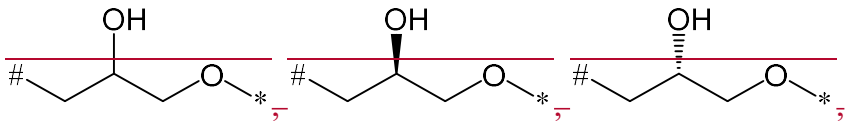
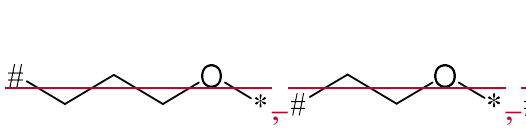
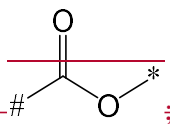
wherein:

R^{20} is hydrogen or -C(O)OH;

R^{21} is hydrogen or halogen;

R^{22} and R^{23} are both hydrogen or R^{22} and R^{23} are taken together to form an oxo (=O) subsitituent;

L^5 is selected from the group consisting of 


, and  ; wherein the * represents the attachment point to A^5, and the # represents the attachment point to the remainder of the molecule;

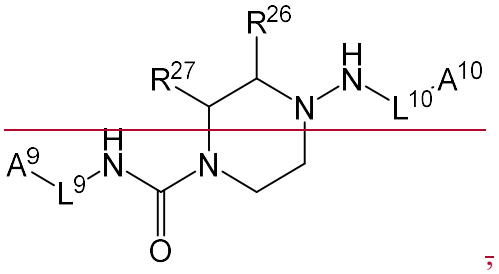
L^6 is selected from the group consisting of 


, and  ; wherein the *

represents the attachment point to A^6, and the # represents the attachment point to the remainder of the molecule;

A^5 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

A^6 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.

[0005c] In one aspect, the present disclosure refers to a compound of formula (VII):



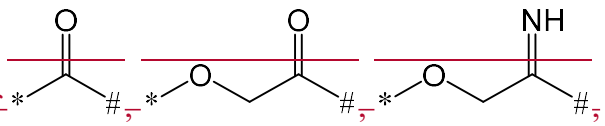
(VII)

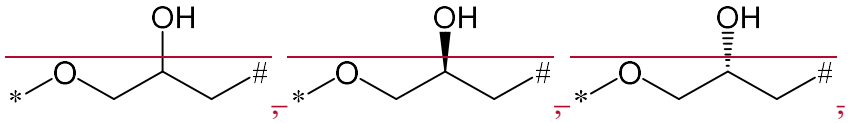
or a pharmaceutically acceptable salt thereof,

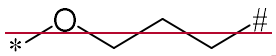
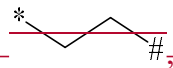
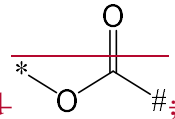
wherein:

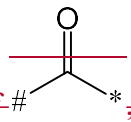
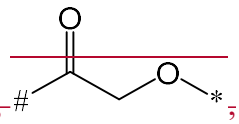
R^{26} is hydrogen or -C(O)OH;

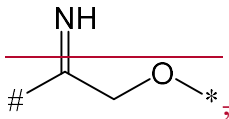
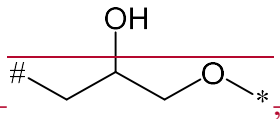
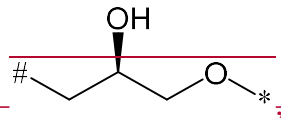
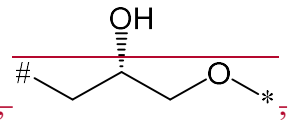
R^{27} is hydrogen or halogen;

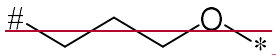
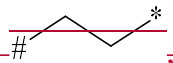
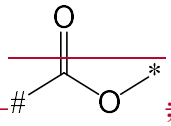
L^9 is selected from the group consisting of 



 ,  ,  , and  ; wherein the * represents the attachment point to A^9, and the # represents the attachment point to the remainder of the molecule;

L^{10} is selected from the group consisting of  ,  ,

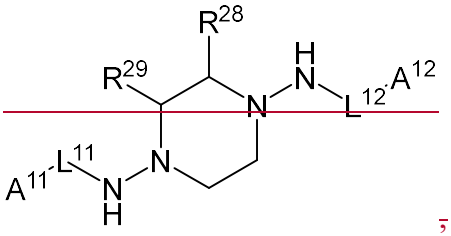
 ,  ,  ,  ,

 ,  ,  , and  ; wherein the * represents the attachment point to A^{10}, and the # represents the attachment point to the remainder of the molecule;

A^9 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

A^{10} is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.

[0005d] In one aspect, the present disclosure refers to a compound of formula (VIII):



,

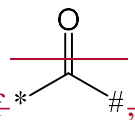
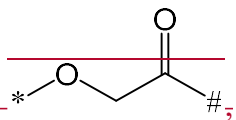
~~(VIII)~~

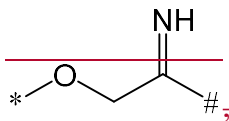
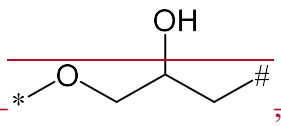
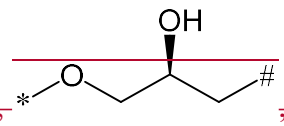
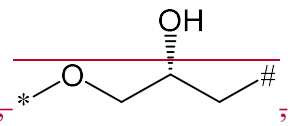
~~or a pharmaceutically acceptable salt thereof,~~

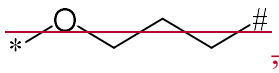
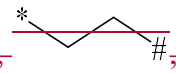
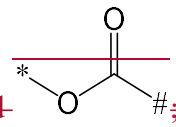
~~wherein:~~

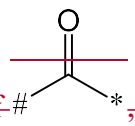
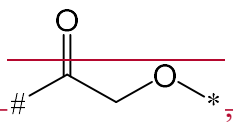
~~R^{28} is hydrogen or –C(O)OH;~~

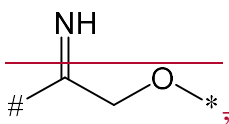
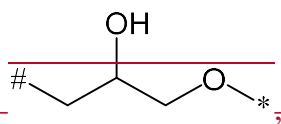
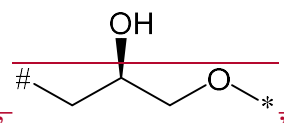
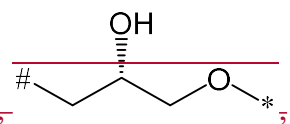
~~R^{29} is hydrogen or halogen;~~

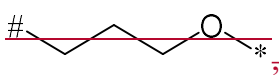
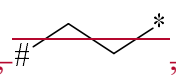
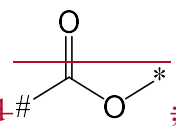
~~L^{11} is selected from the group consisting of~~  ,  ,

 ,  ,  ,  ,

 ,  ,  , and  ; wherein the * represents the attachment point to A^{11}, and the # represents the attachment point to the remainder of the molecule;

~~L^{12} is selected from the group consisting of~~  ,  ,

 ,  ,  ,  ,

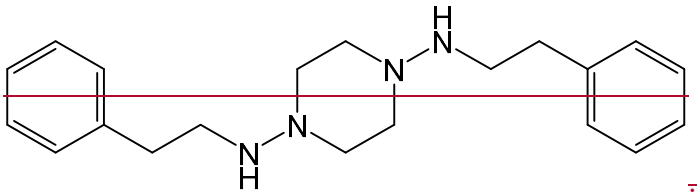
 ,  ,  , and  ; wherein the * represents the attachment point to A^{12}, and the # represents the attachment point to the remainder of the molecule;

~~A^{11} is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl,~~

quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

A^{12} is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

provided that the compound of formula (VIII) is not



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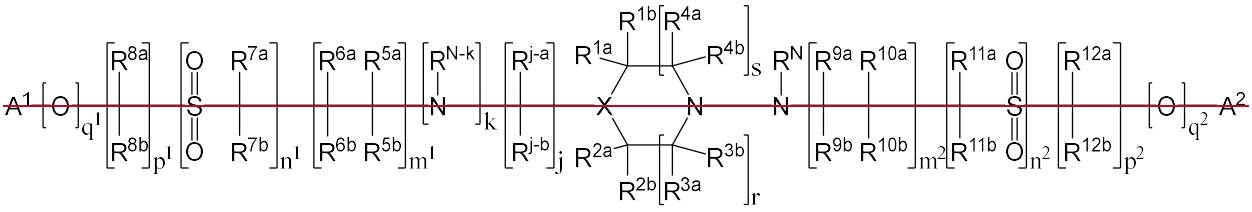
[0005e] In one aspect, the present disclosure refers to a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

m^1, m^2, n^1, n^2, p^1, p^2, q^1, and q^2, independently of each other, are 0 or 1;

r and s, independently of each other, are 0, 1, or 2;

X is N or CR^X;

R^X is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

j is 0 or 1;

R^{j-a} and R^{j-b} are taken together to form an oxo (=O) substituent, or R^{j-a} and R^{j-b} are both hydrogen;

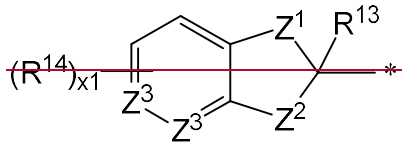
k is 0 or 1;

R^{N-k} is H or C_1-C_6 alkyl;

R^N is H or C_1-C_6 alkyl;

A^1 is selected from the group consisting of:

a substituent of formula (A^1-a)



(A^1-a)

wherein

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

Z^1 is selected from the group consisting of $CR^{Z1-1}R^{Z1-2}$, NR^{Z1-2}, $C(R^{Z1-1}R^{Z1-2})N(R^{Z1-2})$, O, $C(R^{Z1-1}R^{Z1-2})O$, S, $C(R^{Z1-1}R^{Z1-2})S$, and $-CR^{Z1-1}=CR^{Z1-1}-$;

wherein R^{Z1-1} is H or R^{14}; and R^{Z1-2} is H or R^{14};

Z^2 is selected from the group consisting of $CR^{Z2-1}R^{Z2-2}$, NR^{Z2-2}, $C(R^{Z2-1}R^{Z2-2})N(R^{Z2-2})$, O, $C(R^{Z2-1}R^{Z2-2})O$, S, $C(R^{Z2-1}R^{Z2-2})S$, and $-CR^{Z2-1}=CR^{Z2-1}-$;

wherein R^{Z2-1} is H or R^{14}; and R^{Z2-2} is H or R^{14};

Z^3, independently at each occurrence, is CH, CR^{14}, or N;

R^{13} is hydrogen or R^{14}, or R^{13} and R^{Z1-2} are taken together to form a double bond between the carbon atom bearing R^{13} and Z^1, or R^{13} and R^{Z2-2} are taken together to form a double bond between the carbon atom bearing R^{13} and Z^2; and

x1 is 0, 1, 2, 3, or 4;

C_6-C_{14} aryl optionally substituted with one or more R^{14} substituents; and

5-14 membered heteroaryl optionally substituted with one or more R^{14} substituents;

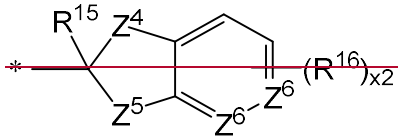
R^{14} is selected, independently at each occurrence, from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), $-NH_2$, -NH(C_1-C_6 alkyl), -NH(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$,

~~$-NR^{14-a}R^{14-b}$, -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)$_2$, $-C(O)NR^{14-a}R^{14-b}$, $-S(O)_2OH$, $-S(O)_2O$(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)$_2$, $-S(O)_2NR^{14-a}R^{14-b}$, -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^{14-a} and R^{14-b} are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;~~

~~A^2 is selected from the group consisting of:~~

~~a substituent of formula (A^2-a)~~



~~(A^2-a)~~

~~wherein~~

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

~~Z^4 is selected from the group consisting of $CR^{Z4-1}R^{Z4-2}$, NR^{Z4-2}, $C(R^{Z4-1}R^{Z4-2})N(R^{Z4-2})$, O, $C(R^{Z4-1}R^{Z4-2})O$, S, $C(R^{Z4-1}R^{Z4-2})S$, and $-CR^{Z4-1}=CR^{Z4-1}-$;~~

~~wherein R^{Z4-1} is H or R^{16}; and R^{Z4-2} is H or R^{16};~~

~~Z^5 is selected from the group consisting of $CR^{Z5-1}R^{Z5-2}$, NR^{Z5-2}, $C(R^{Z5-1}R^{Z5-2})N(R^{Z5-2})$, O, $C(R^{Z5-1}R^{Z5-2})O$, S, $C(R^{Z5-1}R^{Z5-2})S$, and $-CR^{Z5-1}=CR^{Z5-1}-$;~~

~~wherein R^{Z5-1} is H or R^{16}; and R^{Z5-2} is H or R^{16};~~

~~Z^6, independently at each occurrence, is CH, CR^{16}, or N;~~

R^{15} is hydrogen or R^{16}, or R^{15} and R^{Z4-2} are taken together to form a double bond between the carbon atom bearing R^{15} and Z^4, or R^{15} and R^{Z5-2} are taken together to form a double bond between the carbon atom bearing R^{15} and Z^5; and

x2 is 0, 1, 2, 3, or 4;

C_6-C_{14} aryl optionally substituted with one or more R^{16} substituents; and

5-14 membered heteroaryl optionally substituted with one or more R^{16} substituents;

R^{16} is selected, independently at each occurrence, 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)$_2$, $-NR^{16-a}R^{16-b}$, -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)$_2$, $-C(O)NR^{16-a}R^{16-b}$, $-S(O)_2OH$, -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)$_2$, $-S(O)_2NR^{16-a}R^{16-b}$, -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^{16-a} and R^{16-b} are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen, or

R^{1a} is taken together with R^{2a} to form a C_1-C_6 alkylene moiety, or

R^{1a} is taken together with an R^{3a} moiety to form a C_1-C_6 alkylene moiety;

R^{1b} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{2a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{2b} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{3a} independently at each occurrence is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen, or R^{3a} is taken together with R^{4a} to form a C_1-C_6 alkylene moiety;

R^{3b} independently at each occurrence is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{4a} independently at each occurrence is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{4b} independently at each occurrence is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{5a} and R^{5b} are taken together to form an oxo (=O) substituent or an imido (=NH) substituent, or R^{5a} and R^{5b} are both hydrogen;

R^{6a} is selected from the group consisting of hydrogen, $-OR^{6a-a}$, and $-NR^{6a-b}R^{6a-c}$;

R^{6b} is hydrogen;

or R^{6a} and R^{6b} are taken together to form a moiety selected from the group consisting of -O-CH_2-CH_2-, -CH_2-O-CH_2-, -CH_2-CH_2-O-, -O-CH_2-CH_2-CH_2-, -CH_2-O-CH_2-CH_2-, -CH_2-CH_2-O-CH_2-, -CH_2-CH_2-CH_2-O-, -O-CH_2-CH_2-CH_2-CH_2-, -CH_2-O-CH_2-CH_2-CH_2-, -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-CH_2-CH_2-O-CH_2-, and -CH_2-CH_2-CH_2-CH_2-O-;

R^{7a} and R^{7b} are both hydrogen;

R^{8a} and R^{8b} are taken together to form an oxo (=O) substituent, or R^{8a} and R^{8b} are both hydrogen;

R^{9a} and R^{9b} are taken together to form an oxo (=O) substituent or an imido (=NH) substituent, or R^{9a} and R^{9b} are both hydrogen;

R^{10a} is selected from the group consisting of hydrogen, $-OR^{10a-a}$, and $-NR^{10a-b}R^{10a-c}$ and R^{10b} is hydrogen, or R^{10a} and R^{10b} are taken together to form a moiety selected from the group consisting of -O-CH_2-CH_2-, -CH_2-O-CH_2-, -CH_2-CH_2-O-,

-O-CH_2-CH_2-CH_2-, -CH_2-O-CH_2-CH_2-, -CH_2-CH_2-O-CH_2-, -CH_2-CH_2-CH_2-O-, -O-CH_2-CH_2-CH_2-CH_2-, -CH_2-O-CH_2-CH_2-CH_2-, -CH_2-CH_2-O-CH_2-CH_2-, -CH_2-CH_2-CH_2-O-CH_2-, and -CH_2-CH_2-CH_2-CH_2-O-;

R^{11a} and R^{11b} are both hydrogen;

R^{12a} and R^{12b} are taken together to form an oxo (=O) substituent, or R^{12a} and R^{12b} are both hydrogen;

R^{6a-a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, or R^{6a-a} is taken together with R^{N-k} to form a carbonyl (C=O) moiety;

R^{10a-a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, or R^{10a-a} is taken together with R^{N} to form a carbonyl (C=O) moiety;

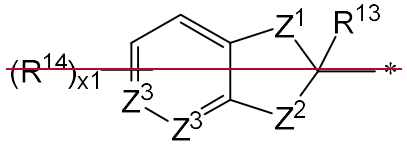
R^{6a-b} and R^{6a-c}, independently of each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

R^{10a-b} and R^{10a-c}, independently of each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

provided that:

(i) when j is 1, then k is 1;

(ii) when m^1 is 0, n^1 is 0, q^1 is 0, and p^1 is 1, then R^{8a} and R^{8b} are taken together to form an oxo (=O) substituent, and A^1 is a substituent of formula (A^1-a)



(A^1-a)

wherein

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

Z^1 is selected from the group consisting of $CR^{Z1-1}R^{Z1-2}$, NR^{Z1-2}, $C(R^{Z1-1}R^{Z1-2})N(R^{Z1-2})$, O, $C(R^{Z1-1}R^{Z1-2})O$, S, $C(R^{Z1-1}R^{Z1-2})S$, and -CR^{Z1-1}=CR^{Z1-1}-;

wherein R^{Z1-1} is H or R^{14}; and R^{Z1-2} is H or R^{14};

Z^2 is selected from the group consisting of $CR^{Z2-1}R^{Z2-2}$, NR^{Z2-2}, $C(R^{Z2-1}R^{Z2-2})N(R^{Z2-2})$, O, $C(R^{Z2-1}R^{Z2-2})O$, S, $C(R^{Z2-1}R^{Z2-2})S$, and -CR^{Z2-1}=CR^{Z2-1}-;

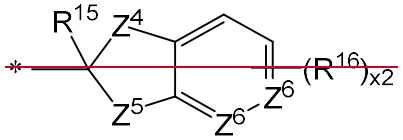
wherein R^{Z2-1} is H or R^{14}; and R^{Z2-2} is H or R^{14};

~~Z^3, independently at each occurrence, is CH, CR^{14}, or N;~~

~~R^{13} is hydrogen or R^{14}, or R^{13} and R^{Z1-2} are taken together to form a double bond between the carbon atom bearing R^{13} and Z^1, or R^{13} and R^{Z2-2} are taken together to form a double bond between the carbon atom bearing R^{13} and Z^2; and~~

~~x1 is 0, 1, 2, 3, or 4; and~~

~~(iii) when m^2 is 0, n^2 is 0, q^2 is 0, and p^2 is 1, then R^{12a} and R^{12b} are taken together to form an oxo (=O) substituent, and A^2 is a substituent of formula (A^2-a)~~



~~(A^2-a)~~

~~wherein~~

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

~~Z^4 is selected from the group consisting of $CR^{Z4-1}R^{Z4-2}$, NR^{Z4-2}, $C(R^{Z4-1}R^{Z4-2})N(R^{Z4-2})$, O, $C(R^{Z4-1}R^{Z4-2})O$, S, $C(R^{Z4-1}R^{Z4-2})S$, and $-CR^{Z4-1}=CR^{Z4-1}-$;~~

~~wherein R^{Z4-1} is H or R^{16}; and R^{Z4-2} is H or R^{16};~~

~~Z^5 is selected from the group consisting of $CR^{Z5-1}R^{Z5-2}$, NR^{Z5-2}, $C(R^{Z5-1}R^{Z5-2})N(R^{Z5-2})$, O, $C(R^{Z5-1}R^{Z5-2})O$, S, $C(R^{Z5-1}R^{Z5-2})S$, and $-CR^{Z5-1}=CR^{Z5-1}-$;~~

~~wherein R^{Z5-1} is H or R^{16}; and R^{Z5-2} is H or R^{16};~~

~~Z^6, independently at each occurrence, is CH, CR^{16}, or N;~~

~~R^{15} is hydrogen or R^{16}, or R^{15} and R^{Z4-2} are taken together to form a double bond between the carbon atom bearing R^{15} and Z^4, or R^{15} and R^{Z5-2} are taken together to form a double bond between the carbon atom bearing R^{15} and Z^5; and~~

~~x2 is 0, 1, 2, 3, or 4;~~

~~(iv) when X is CR^X, then k is 1;~~

~~(v) when X is N, j is 1, and k is 1, then R^{j-a} and R^{j-b} are taken together to form an oxo (=O) substituent;~~

(vi) when X is N, j is 0 and k is 1; then at least one of (vi-a), (vi-b), (vi-c), or (vi-d) applies:

(vi-a) A^1 is C_6-C_{14} aryl substituted with one or more R^{14} substituents;

(vi-b) A^1 is 5-14 membered heteroaryl optionally substituted with one or more R^{14} substituents;

(vi-c) A^2 is C_6-C_{14} aryl substituted with one or more R^{16} substituents;

(vi-d) A^2 is 5-14 membered heteroaryl optionally substituted with one or more R^{16} substituents; and

(vii) when X is N, j is 0, k is 0, m^1 is 1, n^1 is 0, p^1 is 0, and q^1 is 0, then A^1 is a substituent of formula (A^1-a).

[0005f] In one aspect, the present disclosure refers to a compound selected from the group consisting of a compound of Table 1, or a pharmaceutically acceptable salt thereof, for example, a compound selected from the group consisting of compounds 1 to 75, or a pharmaceutically acceptable salt thereof.

[0005g] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0005h] In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of a pharmaceutical composition as 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;

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.

[0005i] In one aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as 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.

[0005j] In one aspect, the present disclosure refers to a method of producing a protein, comprising contacting a eukaryotic cell comprising a nucleic acid encoding the protein with the compound or salt as disclosed herein; and optionally comprising culturing the cell in an *in vitro* culture medium comprising the compound or salt.

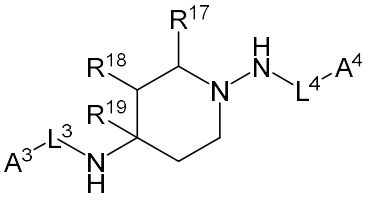
[0005k] In one aspect, the present disclosure refers to a method of culturing a eukaryotic cell comprising a nucleic acid encoding a protein, comprising contacting the eukaryotic cell with an *in vitro* culture medium comprising a compound or salt as disclosed herein; and wherein:
(a) the nucleic acid encoding the protein is a recombinant nucleic acid; and/or
(b) the cell is a human embryonic kidney (HEK) cell, a Chinese hamster ovary (CHO) cell, 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.

[0005l] In one aspect, the present disclosure refers to 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 as disclosed herein.

[0005m] In one aspect, the present disclosure refers to an *in vitro* cell culture medium, comprising the compound or salt as disclosed herein and nutrients for cellular growth, wherein the cell culture medium optionally comprises a eukaryotic cell comprising a nucleic acid encoding a protein; and wherein the cell culture medium optionally further comprises a compound for inducing protein expression;
for example, wherein:
(a) the nucleic acid encoding the protein is a recombinant nucleic acid and/or
(b) the protein is:
(b-1) an antibody or a fragment thereof; or
(b-2) 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; and/or
(c) the eukaryotic cell is a human embryonic kidney (HEK) cell, a Chinese hamster ovary (CHO) cell, 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.

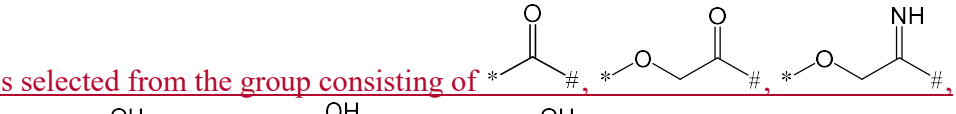
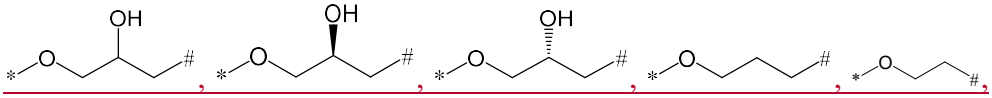
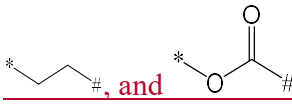
[0005n] In one aspect, the present disclosure refers to a cell-free protein synthesis (CFPS) system comprising eukaryotic initiation factor 2 (eIF2) and a nucleic acid encoding a protein with the compound or salt as disclosed herein; wherein the CFPS system optionally comprises a eukaryotic cell extract comprising eIF2; and wherein the CFPS system optionally further comprises eIF2B;
for example, wherein:
(a) the protein is an antibody or a fragment thereof; or

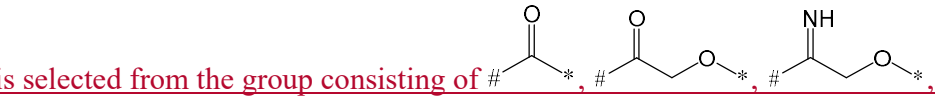
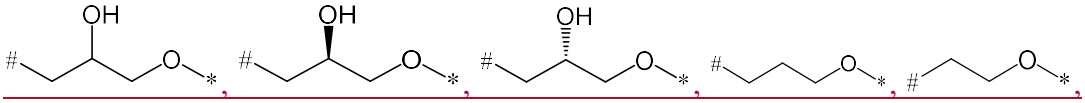
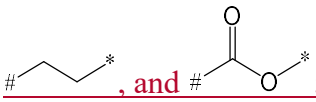
[0005a] In one aspect, the present disclosure refers to a compound of formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein: R^{17} is hydrogen or –C(O)OH; R^{18} is hydrogen or halogen; R^{19} is hydrogen or C_2-C_6 alkynyl;

L^3 is selected from the group consisting of  ,  , and  ; wherein the * represents the attachment point to A^3, and the # represents the attachment point to the remainder of the molecule;

L^4 is selected from the group consisting of  ,  , and  ; wherein the * represents the attachment point to A^4, and the # represents the attachment point to the remainder of the molecule;

A^3 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, $–NO_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

A^4 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, $–NO_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.

[0005b] In one aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0005c] In one aspect, the present disclosure refers to 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; 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; optionally 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; 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, 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.

[0005d] In one aspect, the present disclosure refers to 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; optionally 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; 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, 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.

[0005e] In one aspect, the present disclosure refers to 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, and culturing the cell in an *in vitro* culture medium comprising the compound or salt.

[0005f] In one aspect, the present disclosure refers to 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; and wherein: (a) the nucleic acid encoding the protein is a recombinant nucleic acid; and/or (b) the cell is a human embryonic kidney (HEK) cell, a Chinese hamster ovary (CHO) cell, 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.

[0005g] In one aspect, the present disclosure refers to 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.

[0005h] In one aspect, the present disclosure refers to an *in vitro* cell culture medium, comprising the compound or salt disclosed herein and nutrients for cellular growth, wherein the cell culture medium optionally comprises a eukaryotic cell comprising a nucleic acid encoding a protein; and wherein the cell culture medium optionally further comprises a compound for inducing protein expression; for example, wherein: (a) the nucleic acid encoding the protein is a recombinant nucleic acid and/or

(b) the protein is: (b-1) an antibody or a fragment thereof; or

(b-2) 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; and/or (c) the eukaryotic cell is a human embryonic kidney (HEK) cell, a Chinese hamster ovary (CHO) cell, 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.

[0005i] In one aspect, the present disclosure refers to 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; wherein the CFPS system optionally comprises a eukaryotic cell extract comprising eIF2; and wherein the CFPS system optionally further comprises eIF2B; for example, wherein: (a) the protein is an antibody or a fragment thereof; or (b) 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.

~~(b) 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.~~

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] FIG. 1 shows an IC_{50} titration for inhibition of ATF4 in stressed HEK293T cells using a luciferase assay for ISRIB (trans-N,N′-1,4-cyclohexanediylbis[2-(4-chlorophenoxy)-acetamide). ISRIB was found to have an IC_{50} of 5 nM.

[0005] FIG. 2 shows the percent recovery of protein translation in stressed HEK293T cells after exposure to 10 nM, 31.6 nM, 100 nM, 316 nM, or 1000 nM of ISRIB.

[0006] FIG. 3 shows an IC_{50} titration for inhibition of ATF4 in stressed HEK293T cells using a luciferase assay for compound 4. Compound 4 was found to have an IC_{50} of 3.1 nM.

[0007] FIG. 4 shows the percent recovery of protein translation in stressed HEK293T cells after exposure to 1 μM of ISRIB or compound 4.

FIG. 5A shows long-term potentiation (LTP) of a stimulated hippocampal slice from a WT C57BL/6 mouse or a transgenic APP/PS1 mouse with or without incubation with ISRIB. LTP was based on field excitatory postsynaptic potential (fEPSP) slope, measured from 20 minutes prior to theta burst stimulation (TBS) to 60 minutes after TBS.

FIG. 5B shows the LTP (based on fEPSP) for the stimulated hippocampal slices after 60 minutes.

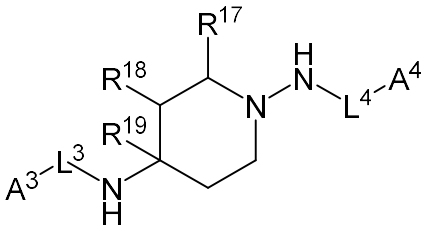
FIG. 6 shows ATF4 expression in unstressed condition (Veh) or under Tg stress alone or in the presence of compound 58 at the indicated concentration.

FIG. 7 shows ATF4 expression in SH-SY5Y cells after incubation with CM from the 7PA2 CHO cells alone or in the presence of compound 58 at the indicated concentrations.

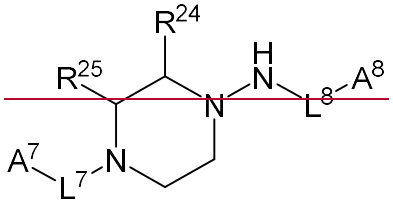
FIG. 8A shows weight of fed mice and fasted mice treated either with vehicle or compound 58.

CLAIMS

1. A compound of formula (IV) ~~or a compound of formula (VI)~~:



(IV)



~~(VI)~~

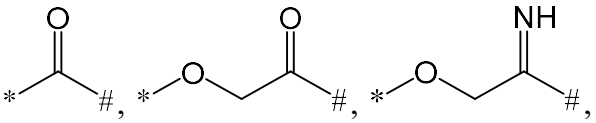
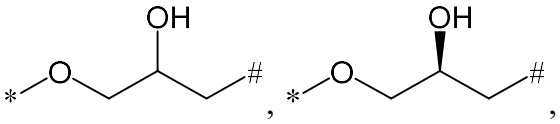
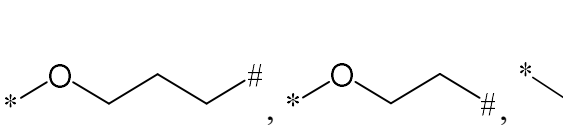
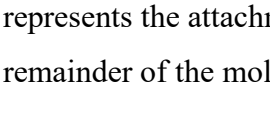
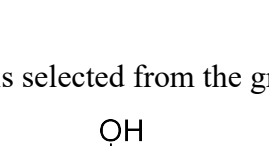
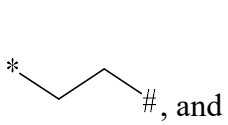
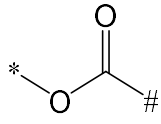
or a pharmaceutically acceptable salt thereof,

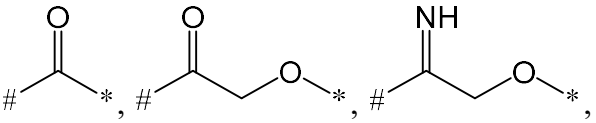
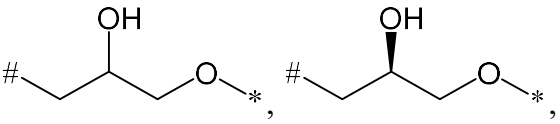
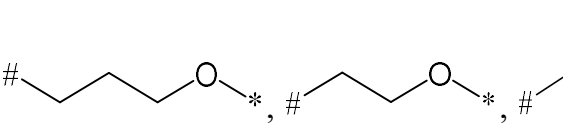
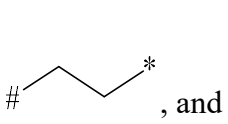
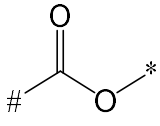
wherein ~~in the compound of formula (IV), or the pharmaceutically acceptable salt thereof~~:

R^{17} is hydrogen or –C(O)OH;

R^{18} is hydrogen or halogen;

R^{19} is hydrogen or C_2-C_6 alkynyl;

L^3 is selected from the group consisting of  ,  ,  ,  ,  ,  , and  ; wherein the * represents the attachment point to A^3, and the # represents the attachment point to the remainder of the molecule;

L^4 is selected from the group consisting of  ,  ,  , , ,  , and  ; wherein the *

represents the attachment point to A^4, and the # represents the attachment point to the remainder of the molecule;

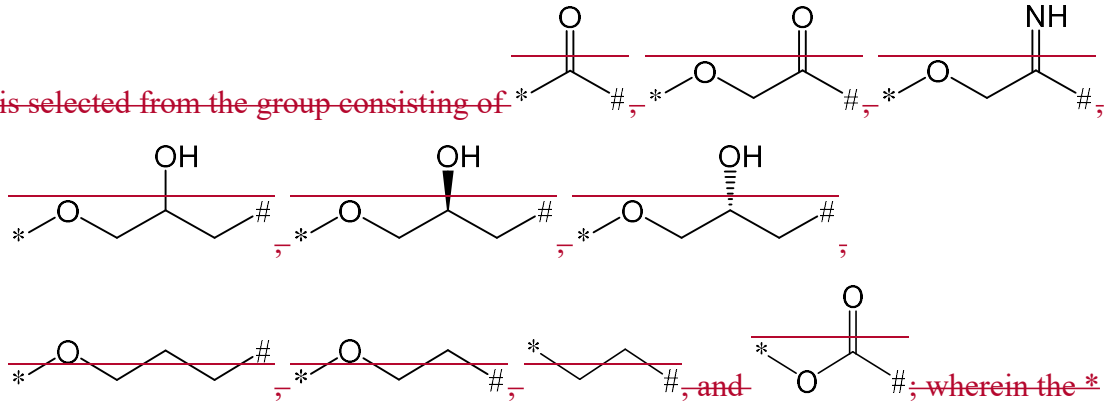
A^3 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, $–NO_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

A^4 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, $–NO_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.;

and wherein in the compound of formula (VI), or the pharmaceutically acceptable salt thereof:

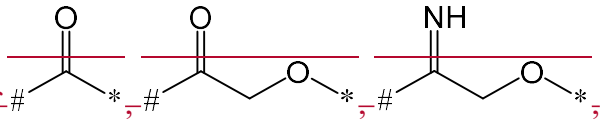
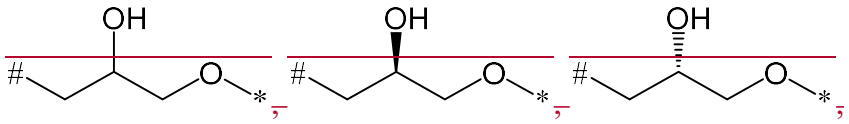
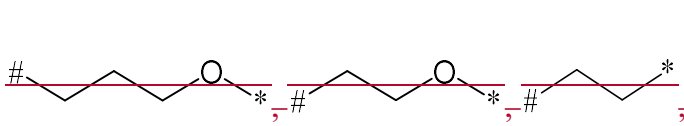
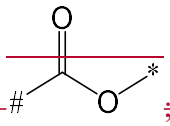
R^{24} is hydrogen or –C(O)OH;

R^{25} is hydrogen or halogen;

L^7 is selected from the group consisting of 

, and

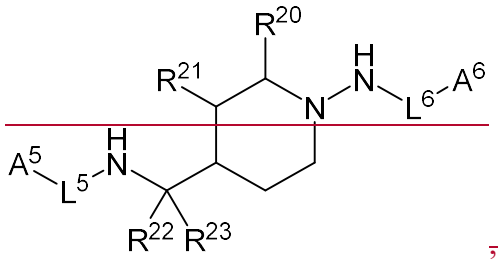
; wherein the * represents the attachment point to A^7, and the # represents the attachment point to the remainder of the molecule;

L^8 is selected from the group consisting of  ,  ,  , and  ; wherein the * represents the attachment point to A^8, and the # represents the attachment point to the remainder of the molecule;

A^7 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

A^8 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.

2. A compound of formula (V):



(V)

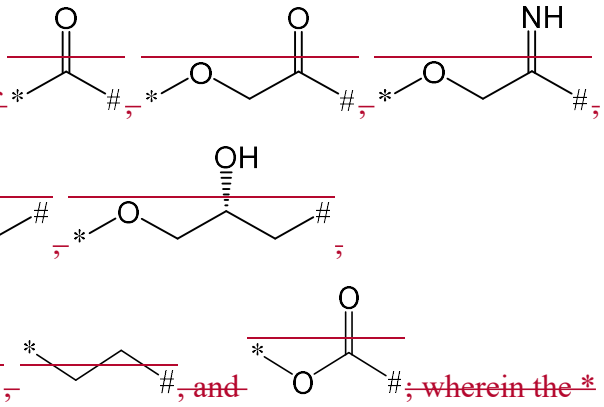
or a pharmaceutically acceptable salt thereof,

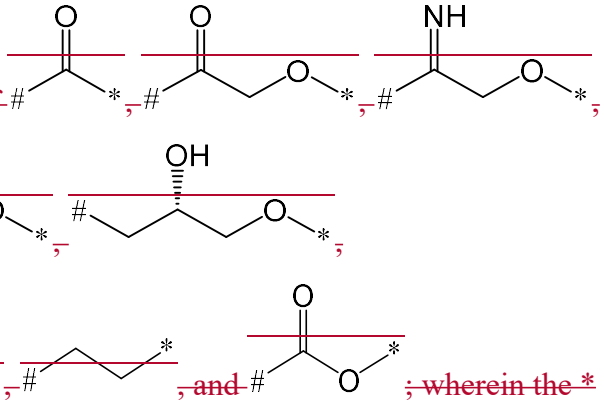
wherein:

R^{20} is hydrogen or –C(O)OH;

R^{21} is hydrogen or halogen;

R^{22} and R^{23} are both hydrogen or R^{22} and R^{23} are taken together to form an oxo (=O) subsitituent;

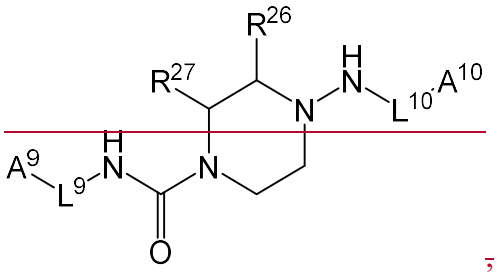
L^5 is selected from the group consisting of  ; wherein the * represents the attachment point to A^5, and the # represents the attachment point to the remainder of the molecule;

L^6 is selected from the group consisting of  ; wherein the * represents the attachment point to A^6, and the # represents the attachment point to the remainder of the molecule;

A^5 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –O-C_1-C_6 alkyl, –O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

~~A^6 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.~~

~~3. A compound of formula (VII):~~



~~,~~

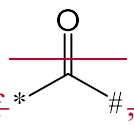
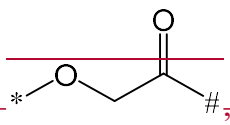
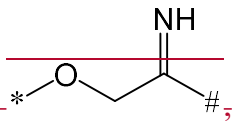
~~(VII)~~

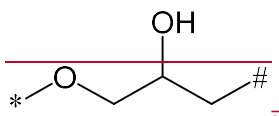
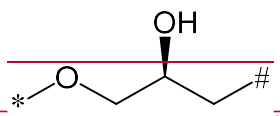
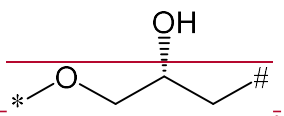
~~or a pharmaceutically acceptable salt thereof,~~

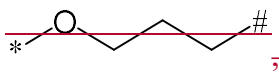
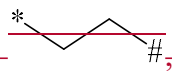
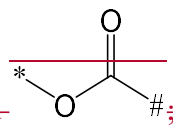
~~wherein:~~

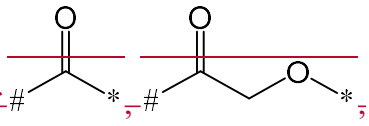
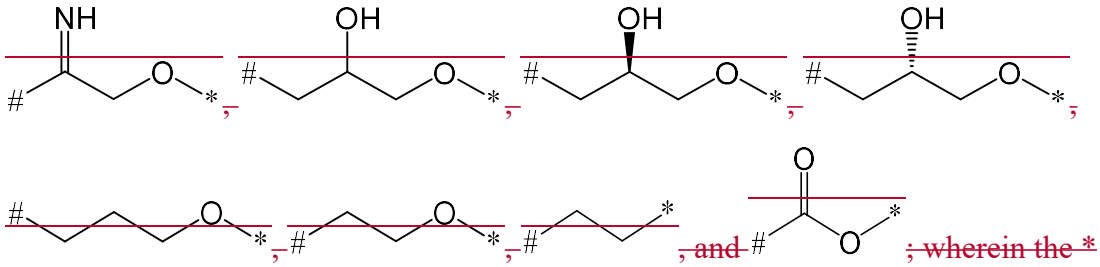
~~R^{26} is hydrogen or -C(O)OH;~~

~~R^{27} is hydrogen or halogen;~~

~~L^9 is selected from the group consisting of~~  ~~,~~  ~~,~~  ~~,~~

 ~~,~~  ~~,~~  ~~,~~

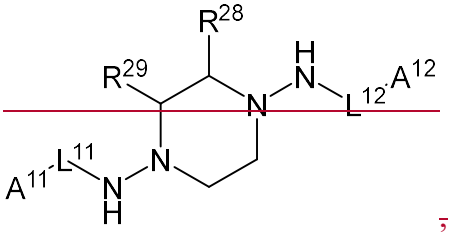
 ~~,~~  ~~,~~  ~~, and~~  ~~; wherein the * represents the attachment point to A^9, and the # represents the attachment point to the remainder of the molecule;~~

L^{10} is selected from the group consisting of  ,  ; wherein the * represents the attachment point to A^{10}, and the # represents the attachment point to the remainder of the molecule;

A^9 is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

A^{10} is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.

4. A compound of formula (VIII):



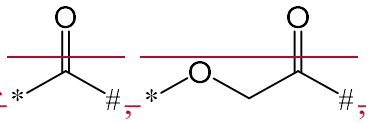
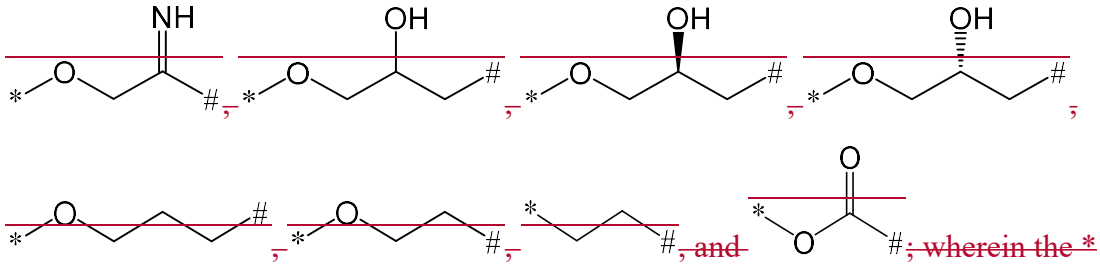
(VIII)

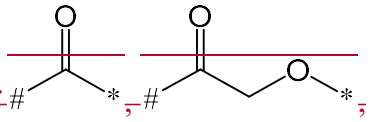
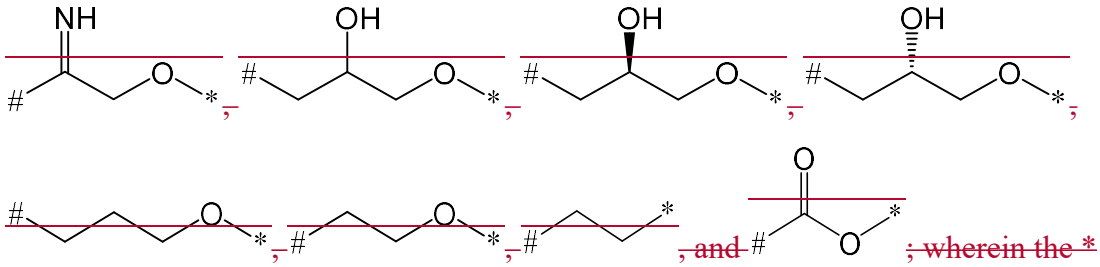
or a pharmaceutically acceptable salt thereof,

wherein:

R^{28} is hydrogen or –C(O)OH;

R^{29} is hydrogen or halogen;

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

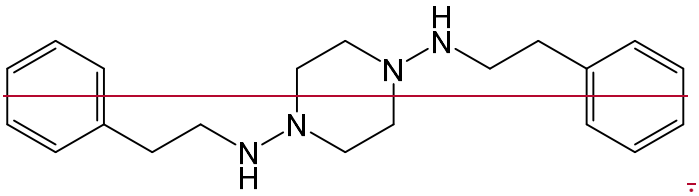
L^{12} is selected from the group consisting of  ,  , , and ; wherein the * represents the attachment point to A^{12}, and the # represents the attachment point to the remainder of the molecule;

A^{11} is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, $-NO_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, –O-C_1-C_6 alkyl, –O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

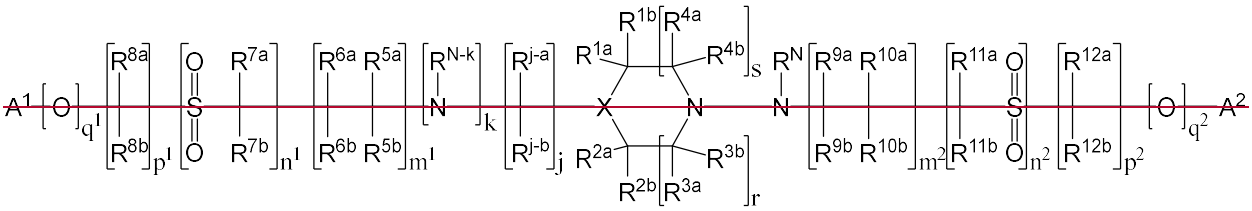
A^{12} is selected from the group consisting of phenyl, naphthyl, pyridyl, pyrazinyl, quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, and 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, wherein each of the phenyl, naphthyl, pyridyl, pyrazinyl,

quinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothiazolyl, or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl;

provided that the compound of formula (VIII) is not



5. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

m^1, m^2, n^1, n^2, p^1, p^2, q^1, and q^2, independently of each other, are 0 or 1;

r and s, independently of each other, are 0, 1, or 2;

X is N or CR^X;

R^X is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

j is 0 or 1;

R^{j-a} and R^{j-b} are taken together to form an oxo (=O) substituent, or R^{j-a} and R^{j-b} are both hydrogen;

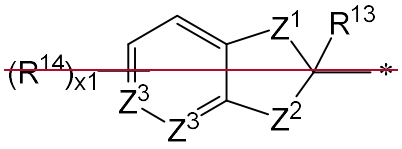
k is 0 or 1;

R^{N-k} is H or C_1-C_6 alkyl;

R^N is H or C_1-C_6 alkyl;

A^1 is selected from the group consisting of:

a substituent of formula (A^1-a)



(A^1-a)

wherein

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

Z^1 is selected from the group consisting of $CR^{Z1-1}R^{Z1-2}$, NR^{Z1-2}, $C(R^{Z1-1}R^{Z1-2})N(R^{Z1-2})$, O, $C(R^{Z1-1}R^{Z1-2})O$, S, $C(R^{Z1-1}R^{Z1-2})S$, and $-CR^{Z1-1}=CR^{Z1-1}-$;

wherein R^{Z1-1} is H or R^{14}; and R^{Z1-2} is H or R^{14};

Z^2 is selected from the group consisting of $CR^{Z2-1}R^{Z2-2}$, NR^{Z2-2}, $C(R^{Z2-1}R^{Z2-2})N(R^{Z2-2})$, O, $C(R^{Z2-1}R^{Z2-2})O$, S, $C(R^{Z2-1}R^{Z2-2})S$, and $-CR^{Z2-1}=CR^{Z2-1}-$;

wherein R^{Z2-1} is H or R^{14}; and R^{Z2-2} is H or R^{14};

Z^3, independently at each occurrence, is CH, CR^{14}, or N;

R^{13} is hydrogen or R^{14}, or R^{13} and R^{Z1-2} are taken together to form a double bond between the carbon atom bearing R^{13} and Z^1, or R^{13} and R^{Z2-2} are taken together to form a double bond between the carbon atom bearing R^{13} and Z^2; and

x1 is 0, 1, 2, 3, or 4;

C_6-C_{14} aryl optionally substituted with one or more R^{14} substituents; and

5-14 membered heteroaryl optionally substituted with one or more R^{14} substituents;

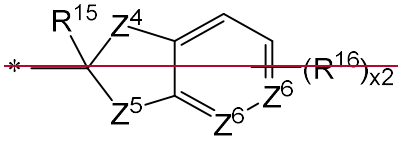
R^{14} is selected, independently at each occurrence, from the group consisting of halogen, NO_2, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 haloalkyl, -OH, -O(C_1-C_6 alkyl), -O(C_1-C_6 haloalkyl), -SH, -S(C_1-C_6 alkyl), -S(C_1-C_6 haloalkyl), $-NH_2$, -NH(C_1-C_6 alkyl), -NH(C_1-C_6 haloalkyl), -N(C_1-C_6 alkyl)$_2$, -N(C_1-C_6 haloalkyl)$_2$, $-NR^{14-a}R^{14-b}$, -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)$_2$, $-C(O)NR^{14-a}R^{14-b}$, $-S(O)_2OH$, $-S(O)_2O$(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)$_2$, $-S(O)_2NR^{14-a}R^{14-b}$, -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^{14-a} and R^{14-b} are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

A^2 is selected from the group consisting of:

a substituent of formula (A^2-a)



(A^2-a)

wherein

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

Z^4 is selected from the group consisting of $CR^{Z4\text{-}1}R^{Z4\text{-}2}$, $NR^{Z4\text{-}2}$, $C(R^{Z4\text{-}1}R^{Z4\text{-}2})N(R^{Z4\text{-}2})$, O, $C(R^{Z4\text{-}1}R^{Z4\text{-}2})O$, S, $C(R^{Z4\text{-}1}R^{Z4\text{-}2})S$, and $-CR^{Z4\text{-}1}=CR^{Z4\text{-}1}-$;

wherein $R^{Z4\text{-}1}$ is H or R^{16}; and $R^{Z4\text{-}2}$ is H or R^{16};

Z^5 is selected from the group consisting of $CR^{Z5\text{-}1}R^{Z5\text{-}2}$, $NR^{Z5\text{-}2}$, $C(R^{Z5\text{-}1}R^{Z5\text{-}2})N(R^{Z5\text{-}2})$, O, $C(R^{Z5\text{-}1}R^{Z5\text{-}2})O$, S, $C(R^{Z5\text{-}1}R^{Z5\text{-}2})S$, and $-CR^{Z5\text{-}1}=CR^{Z5\text{-}1}-$;

wherein $R^{Z5\text{-}1}$ is H or R^{16}; and $R^{Z5\text{-}2}$ is H or R^{16};

Z^6, independently at each occurrence, is CH, CR^{16}, or N;

R^{15} is hydrogen or R^{16}, or R^{15} and $R^{Z4\text{-}2}$ are taken together to form a double bond between the carbon atom bearing R^{15} and Z^4, or R^{15} and $R^{Z5\text{-}2}$ are taken together to form a double bond between the carbon atom bearing R^{15} and Z^5; and

x2 is 0, 1, 2, 3, or 4;

C_6-C_{14} aryl optionally substituted with one or more R^{16} substituents; and

5-14 membered heteroaryl optionally substituted with one or more R^{16} substituents;

R^{16} is selected, independently at each occurrence, 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)$_2$, $-NR^{16\text{-}a}R^{16\text{-}b}$, -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)$NR^{16\text{-}a}R^{16\text{-}b}$, -$S(O)_2OH$, -$S(O)_2O$($C_1$-$C_6$ 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)$_2$, -$S(O)_2NR^{16\text{-}a}R^{16\text{-}b}$, -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 $R^{16\text{-}a}$ and $R^{16\text{-}b}$ are taken together with the nitrogen atom to which they are attached to form a 3-10 membered heterocycle;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen, or

R^{1a} is taken together with R^{2a} to form a C_1-C_6 alkylene moiety, or

R^{1a} is taken together with an R^{3a} moiety to form a C_1-C_6 alkylene moiety;

R^{1b} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{2a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{2b} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{3a} independently at each occurrence is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen, or R^{3a} is taken together with R^{4a} to form a C_1-C_6 alkylene moiety;

R^{3b} independently at each occurrence is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{4a} independently at each occurrence is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{4b} independently at each occurrence is selected from the group consisting of hydrogen, C_1-C_6 alkyl, -C(O)OH, -C(O)O(C_1-C_6 alkyl), -C(O)O(C_1-C_6 haloalkyl), and halogen;

R^{5a} and R^{5b} are taken together to form an oxo (=O) substituent or an imido (=NH) substituent, or R^{5a} and R^{5b} are both hydrogen;

R^{6a} is selected from the group consisting of hydrogen, $-OR^{6a-a}$, and $-NR^{6a-b}R^{6a-c}$;

R^{6b} is hydrogen;

or R^{6a} and R^{6b} are taken together to form a moiety selected from the group consisting of $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-CH_2-$, $-CH_2-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-O-CH_2-$, and $-CH_2-CH_2-CH_2-CH_2-O-$;

R^{7a} and R^{7b} are both hydrogen;

R^{8a} and R^{8b} are taken together to form an oxo (=O) substituent, or R^{8a} and R^{8b} are both hydrogen;

R^{9a} and R^{9b} are taken together to form an oxo (=O) substituent or an imido (=NH) substituent, or R^{9a} and R^{9b} are both hydrogen;

R^{10a} is selected from the group consisting of hydrogen, $-OR^{10a-a}$, and $-NR^{10a-b}R^{10a-c}$ and R^{10b} is hydrogen, or R^{10a} and R^{10b} are taken together to form a moiety selected from the group consisting of $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-CH_2-CH_2-O-$, $-O-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-CH_2-$, $-CH_2-CH_2-O-CH_2-$, $-CH_2-CH_2-CH_2-O-$, $-O-CH_2-CH_2-CH_2-CH_2-$, $-CH_2-O-CH_2-CH_2-CH_2-$, $-CH_2-CH_2-O-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-O-CH_2-$, and $-CH_2-CH_2-CH_2-CH_2-O-$;

R^{11a} and R^{11b} are both hydrogen;

R^{12a} and R^{12b} are taken together to form an oxo (=O) substituent, or R^{12a} and R^{12b} are both hydrogen;

R^{6a-a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, or R^{6a-a} is taken together with R^{N-k} to form a carbonyl (C=O) moiety;

R^{10a-a} is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl, or R^{10a-a} is taken together with R^{N} to form a carbonyl (C=O) moiety;

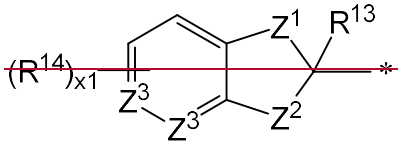
R^{6a-b} and R^{6a-c}, independently of each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl; and

R^{10a-b} and R^{10a-c}, independently of each other, are selected from the group consisting of hydrogen, C_1-C_6 alkyl, and C_1-C_6 haloalkyl;

provided that:

(i) when j is 1, then k is 1;

(ii) when m^1 is 0, n^1 is 0, q^1 is 0, and p^1 is 1, then R^{8a} and R^{8b} are taken together to form an oxo (=O) substituent, and A^1 is a substituent of formula (A^1-a)



(A^1-a)

wherein

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

Z^1 is selected from the group consisting of $CR^{Z1-1}R^{Z1-2}$, NR^{Z1-2}, $C(R^{Z1-1}R^{Z1-2})N(R^{Z1-2})$, O, $C(R^{Z1-1}R^{Z1-2})O$, S, $C(R^{Z1-1}R^{Z1-2})S$, and $-CR^{Z1-1}=CR^{Z1-1}-$;

wherein R^{Z1-1} is H or R^{14}; and R^{Z1-2} is H or R^{14};

Z^2 is selected from the group consisting of $CR^{Z2-1}R^{Z2-2}$, NR^{Z2-2}, $C(R^{Z2-1}R^{Z2-2})N(R^{Z2-2})$, O, $C(R^{Z2-1}R^{Z2-2})O$, S, $C(R^{Z2-1}R^{Z2-2})S$, and $-CR^{Z2-1}=CR^{Z2-1}-$;

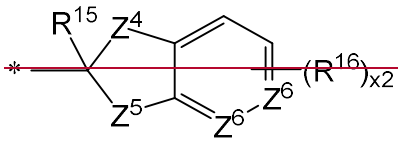
wherein R^{Z2-1} is H or R^{14}; and R^{Z2-2} is H or R^{14};

Z^3, independently at each occurrence, is CH, CR^{14}, or N;

R^{13} is hydrogen or R^{14}, or R^{13} and R^{Z1-2} are taken together to form a double bond between the carbon atom bearing R^{13} and Z^1, or R^{13} and R^{Z2-2} are taken together to form a double bond between the carbon atom bearing R^{13} and Z^2; and

x1 is 0, 1, 2, 3, or 4; and

(iii) when m^2 is 0, n^2 is 0, q^2 is 0, and p^2 is 1, then R^{12a} and R^{12b} are taken together to form an oxo (=O) substituent, and A^2 is a substituent of formula (A^2-a)



(A^2-a)

wherein

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

~~Z^4 is selected from the group consisting of $CR^{Z4\text{-}1}R^{Z4\text{-}2}$, $NR^{Z4\text{-}2}$, $C(R^{Z4\text{-}1}R^{Z4\text{-}2})N(R^{Z4\text{-}2})$, O, $C(R^{Z4\text{-}1}R^{Z4\text{-}2})O$, S, $C(R^{Z4\text{-}1}R^{Z4\text{-}2})S$, and $-CR^{Z4\text{-}1}=CR^{Z4\text{-}1}-$;~~

~~wherein $R^{Z4\text{-}1}$ is H or R^{16}; and $R^{Z4\text{-}2}$ is H or R^{16};~~

~~Z^5 is selected from the group consisting of $CR^{Z5\text{-}1}R^{Z5\text{-}2}$, $NR^{Z5\text{-}2}$, $C(R^{Z5\text{-}1}R^{Z5\text{-}2})N(R^{Z5\text{-}2})$, O, $C(R^{Z5\text{-}1}R^{Z5\text{-}2})O$, S, $C(R^{Z5\text{-}1}R^{Z5\text{-}2})S$, and $-CR^{Z5\text{-}1}=CR^{Z5\text{-}1}-$;~~

~~wherein $R^{Z5\text{-}1}$ is H or R^{16}; and $R^{Z5\text{-}2}$ is H or R^{16};~~

~~Z^6, independently at each occurrence, is CH, CR^{16}, or N;~~

~~R^{15} is hydrogen or R^{16}, or R^{15} and $R^{Z4\text{-}2}$ are taken together to form a double bond between the carbon atom bearing R^{15} and Z^4, or R^{15} and $R^{Z5\text{-}2}$ are taken together to form a double bond between the carbon atom bearing R^{15} and Z^5; and~~

~~x2 is 0, 1, 2, 3, or 4;~~

~~(iv) when X is CR^X, then k is 1;~~

~~(v) when X is N, j is 1, and k is 1, then $R^{j\text{-}a}$ and $R^{j\text{-}b}$ are taken together to form an oxo (=O) substituent;~~

~~(vi) when X is N, j is 0 and k is 1; then at least one of (vi-a), (vi-b), (vi-c), or (vi-d) applies:~~

~~(vi-a) A^1 is C_6-C_{14} aryl substituted with one or more R^{14} substituents;~~

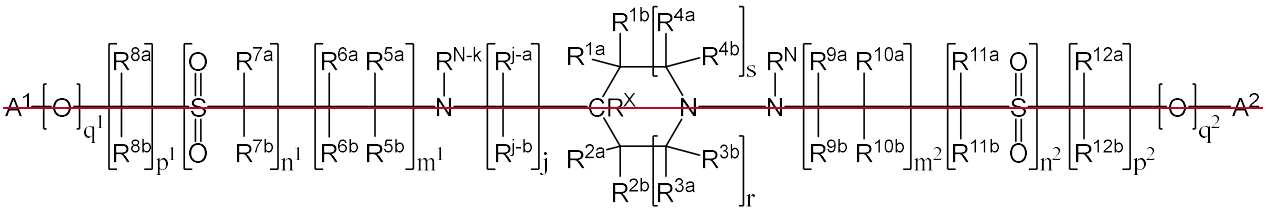
~~(vi-b) A^1 is 5-14 membered heteroaryl optionally substituted with one or more R^{14} substituents;~~

~~(vi-c) A^2 is C_6-C_{14} aryl substituted with one or more R^{16} substituents;~~

~~(vi-d) A^2 is 5-14 membered heteroaryl optionally substituted with one or more R^{16} substituents; and~~

~~(vii) when X is N, j is 0, k is 0, m^1 is 1, n^1 is 0, p^1 is 0, and q^1 is 0, then A^1 is a substituent of formula (A^1-a).~~

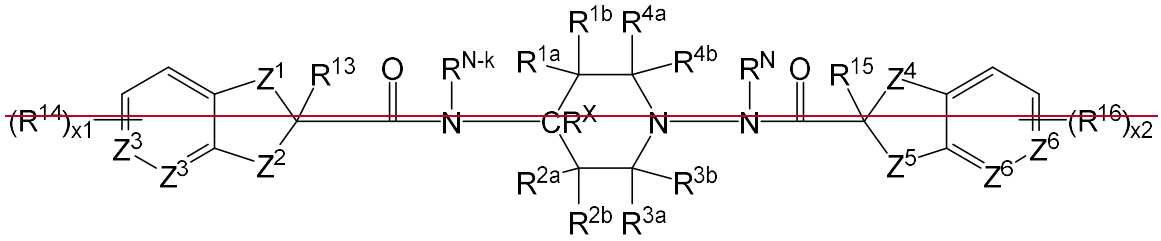
~~6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein k is 1, X is CR^X and the compound of formula (I) is a compound of formula (II), or a pharmaceutically acceptable salt thereof:~~



(II);

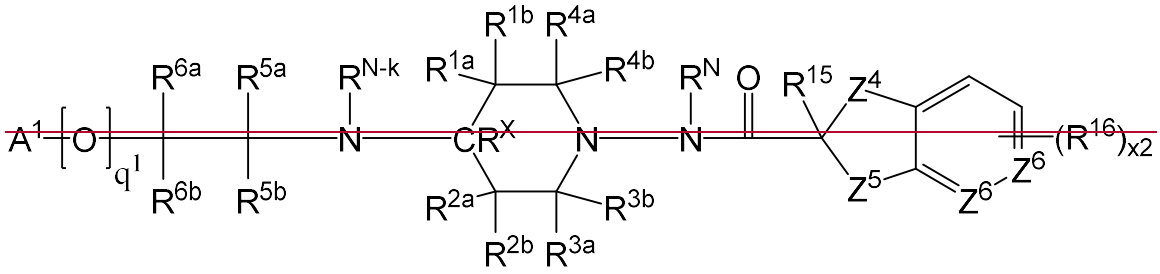
for example, wherein the compound of formula (II), or the pharmaceutically acceptable salt thereof, is either:

(a) a compound of formula (II-1-1), or a pharmaceutically acceptable salt thereof:



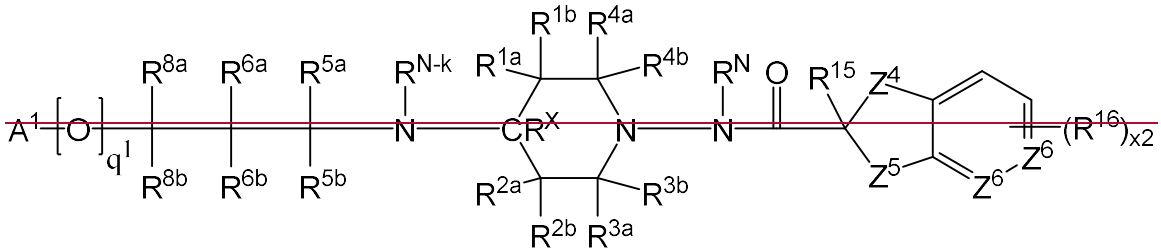
(II-1-1); or

(b) a compound of formula (II-1-2), or a pharmaceutically acceptable salt thereof:



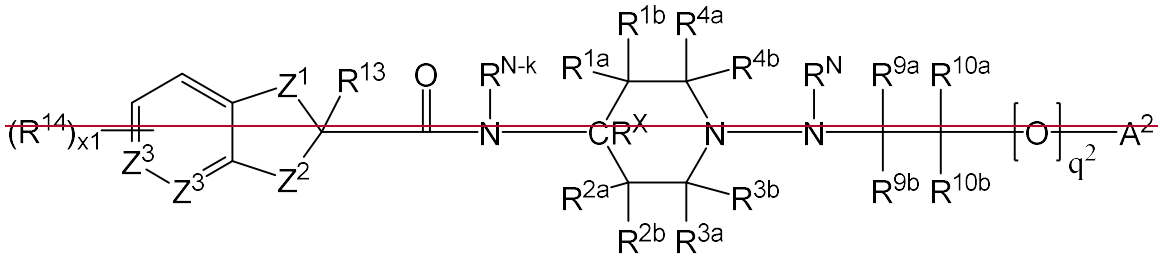
(II-1-2); or

(c) a compound of formula (II-1-3), or a pharmaceutically acceptable salt thereof:



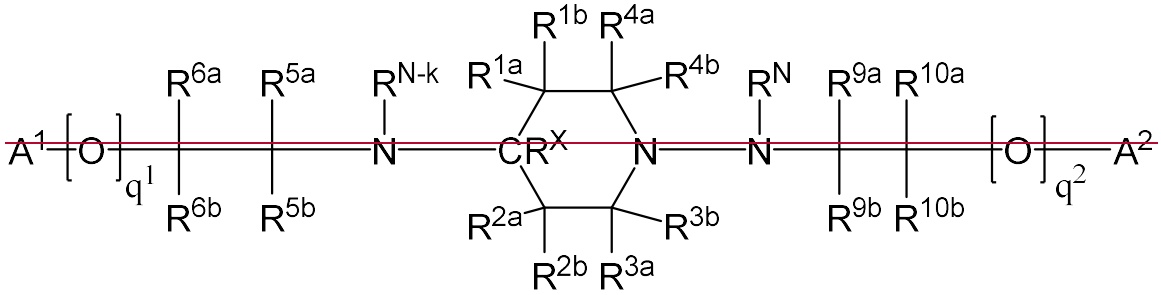
(II-1-3); or

(d) a compound of formula (II-2-1), or a pharmaceutically acceptable salt thereof:



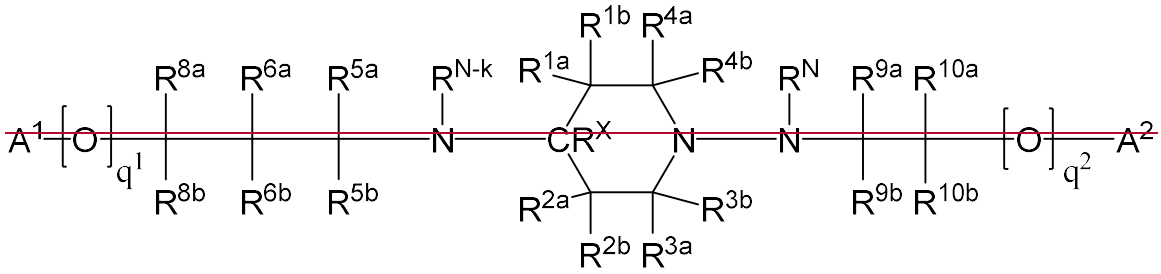
~~(II-2-1); or~~

~~(e) a compound of formula (II-2-2), or a pharmaceutically acceptable salt thereof:~~



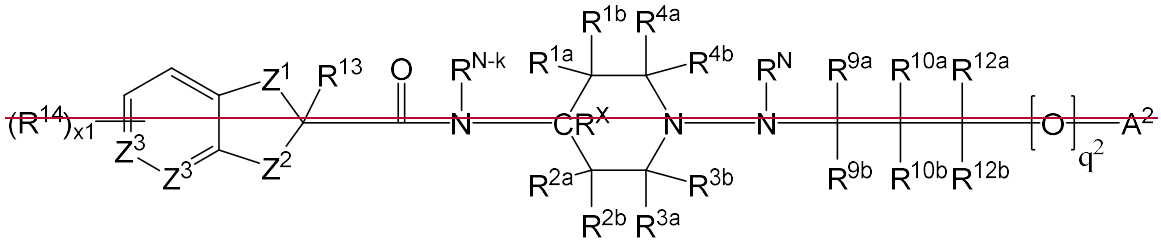
~~(II-2-2); or~~

~~(f) a compound of formula (II-2-3), or a pharmaceutically acceptable salt thereof:~~



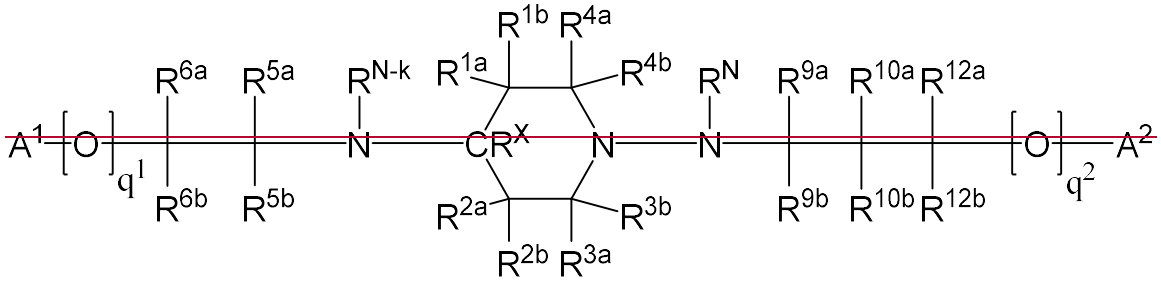
~~(II-2-3); or~~

~~(g) a compound of formula (II-3-1), or a pharmaceutically acceptable salt thereof:~~



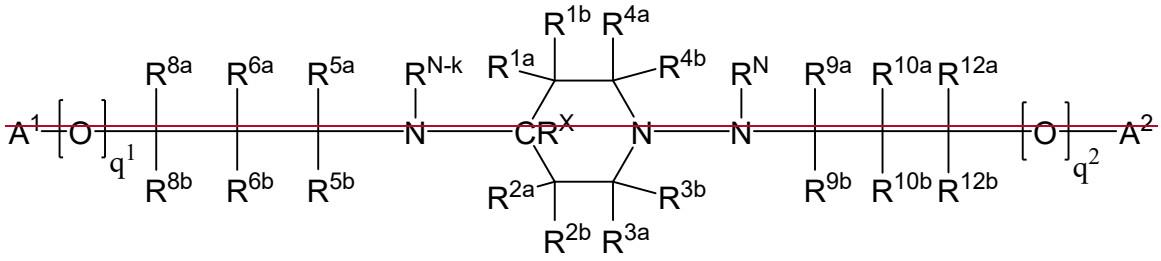
~~(II-3-1); or~~

~~(h) a compound of formula (II-3-2), or a pharmaceutically acceptable salt thereof:~~



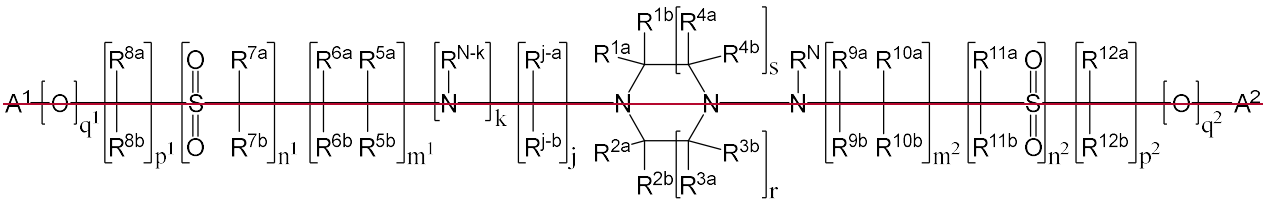
(II-3-2); or

(i) a compound of formula (II-3-3), or a pharmaceutically acceptable salt thereof:



(II-3-3).

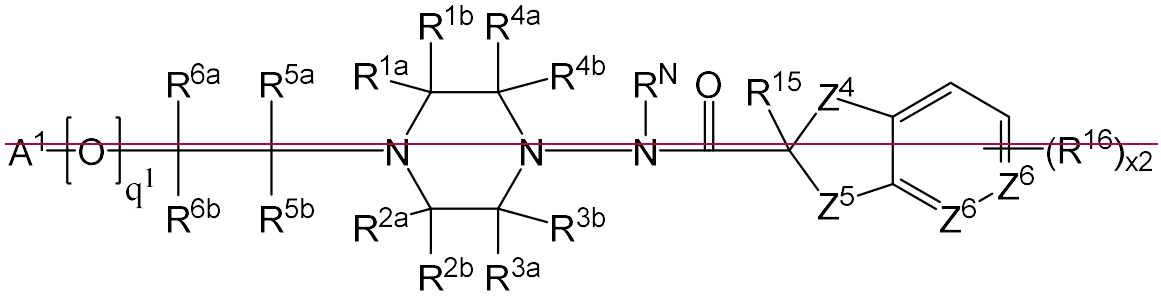
7. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein X is N and the compound of formula (I), or the pharmaceutically acceptable salt thereof, is a compound of formula (III), or a pharmaceutically acceptable salt thereof:



(III)

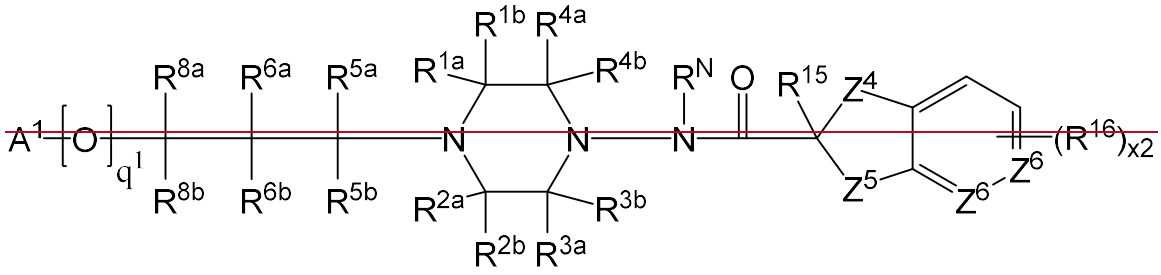
for example, the compound of formula (III), or the pharmaceutically acceptable salt thereof, is either:

(a) a compound of formula (III-1-2), or a pharmaceutically acceptable salt thereof:



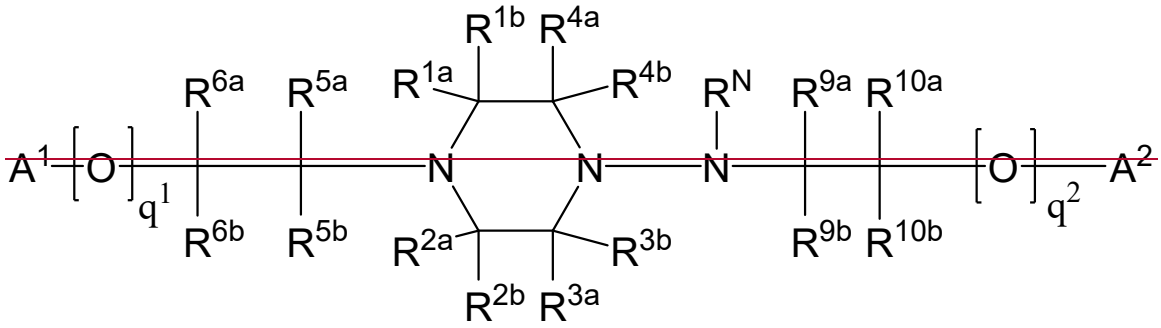
~~(III-1-2); or~~

~~(b) a compound of formula (III-1-3), or a pharmaceutically acceptable salt thereof:~~



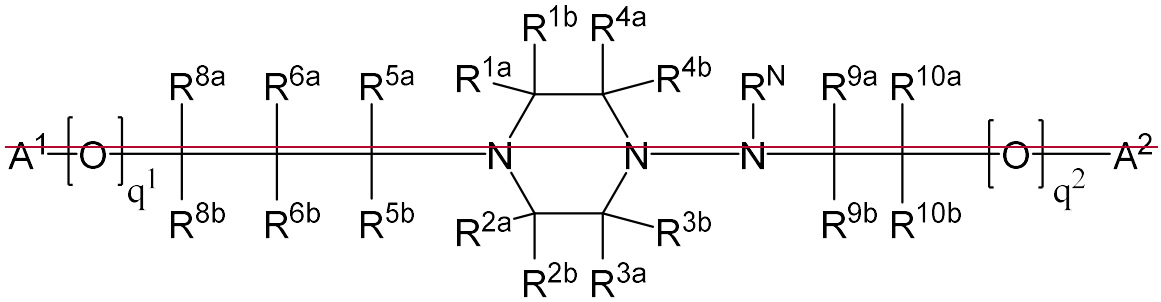
~~(III-1-3); or~~

~~(c) a compound of formula (III-2-2), or a pharmaceutically acceptable salt thereof:~~



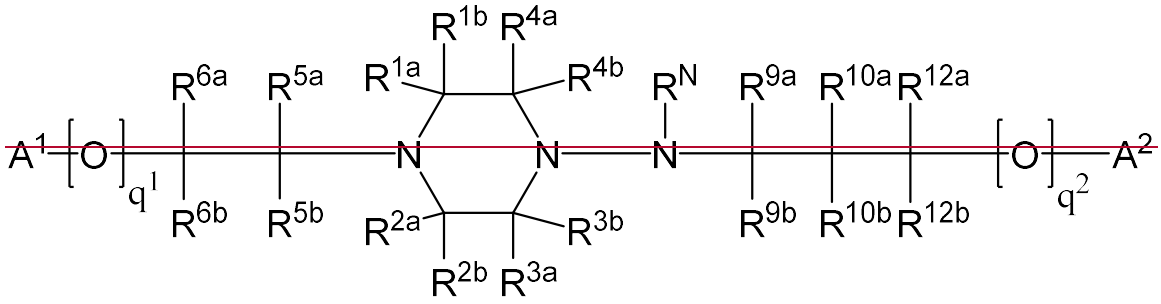
~~(III-2-2); or~~

~~(d) a compound of formula (III-2-3), or a pharmaceutically acceptable salt thereof:~~



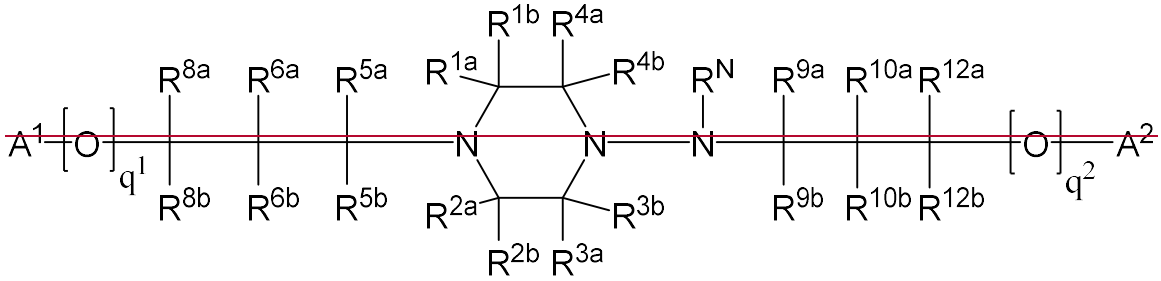
~~(III-2-3); or~~

~~(e) a compound of formula (III-3-2), or a pharmaceutically acceptable salt thereof:~~



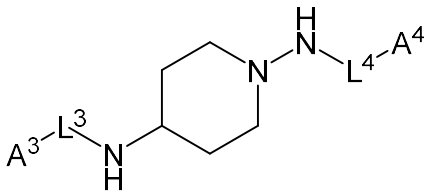
~~(III-3-2); or~~

~~(f) a compound of formula (III-3-3), or a pharmaceutically acceptable salt thereof:~~

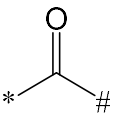
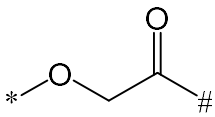


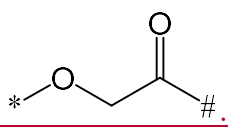
~~(III-3-3).~~

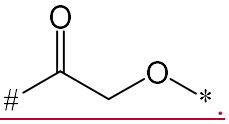
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of formula (IV) is a compound of formula (IV-a):



(IV-a).

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein L^3 is  or  .

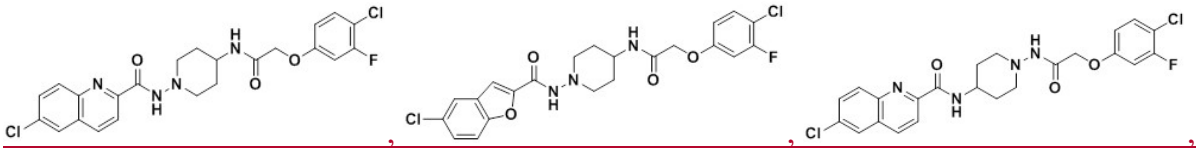
4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein L^3 is  .

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein L^4 is  .

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein A^3 is phenyl or 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, each of which is optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, $–NO_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein A^4 is phenyl optionally substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen, CN, $–NO_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O-C_1-C_6 alkyl, -O-C_1-C_6 haloalkyl, and C_1-C_6 haloalkyl.

8. ~~A~~The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of: ~~a compound of Table 1, or a pharmaceutically acceptable salt thereof, for example, a compound selected from the group consisting of compounds 1 to 75, or a pharmaceutically acceptable salt thereof.~~

 ,
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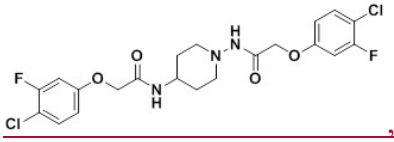
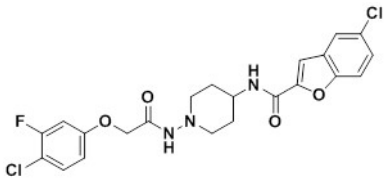
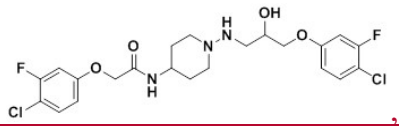
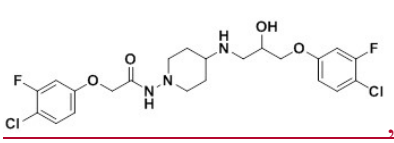
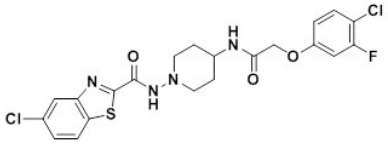
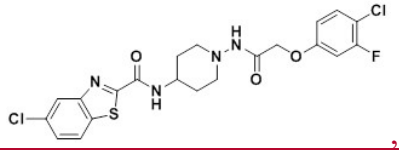
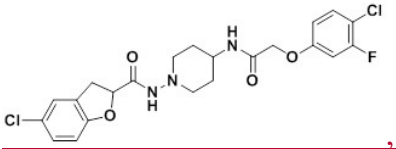
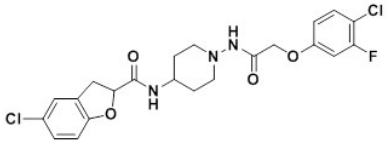
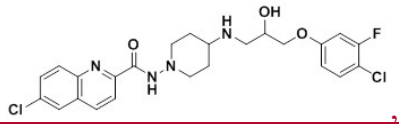
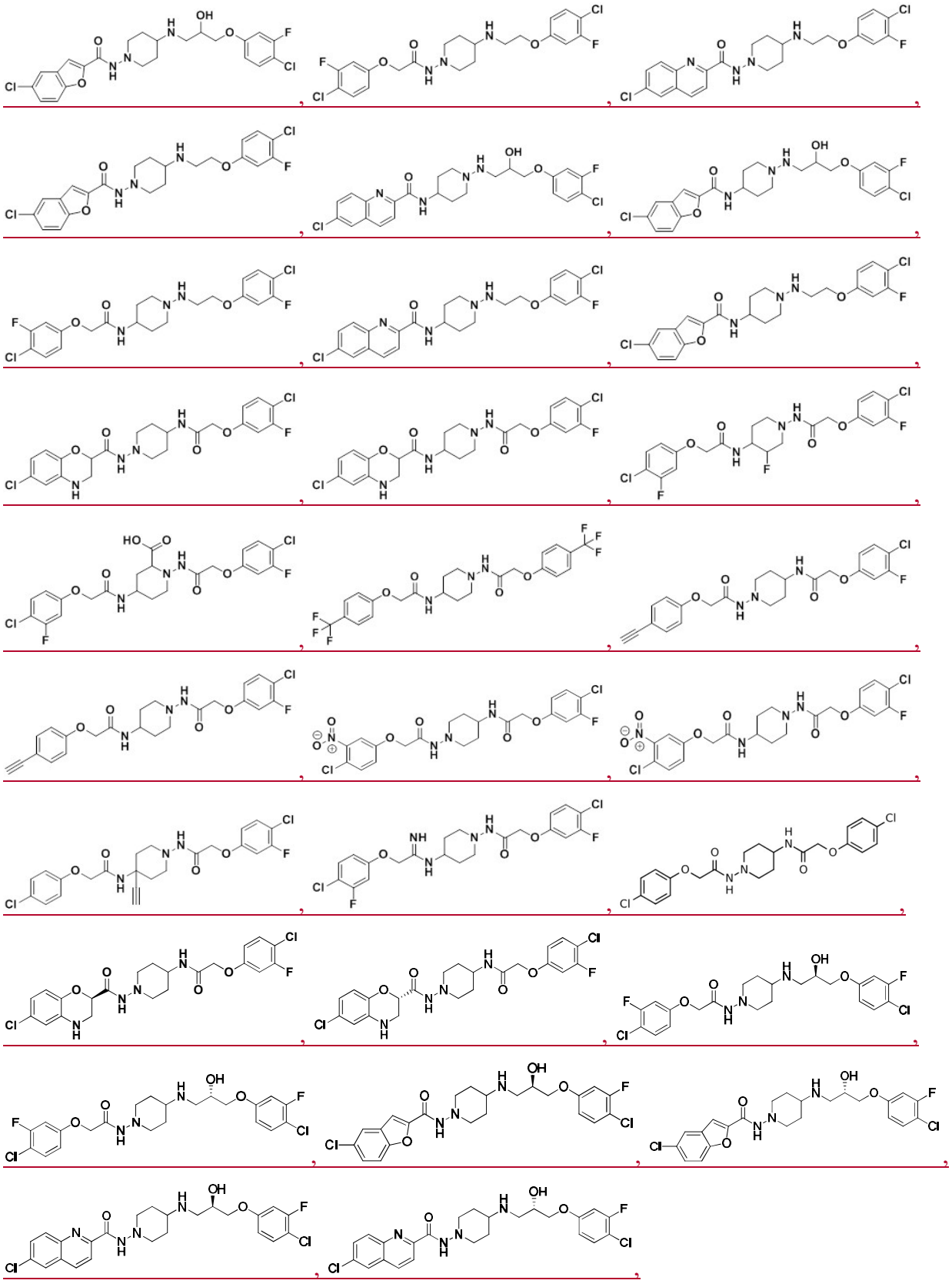
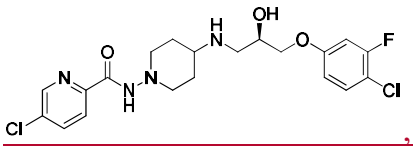
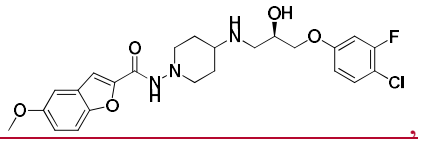
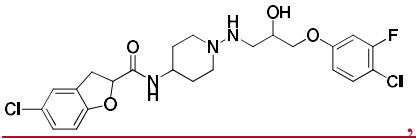
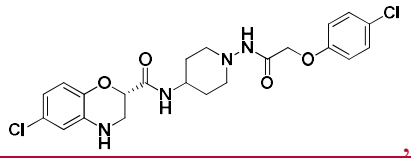
 ,
 ,
 ,

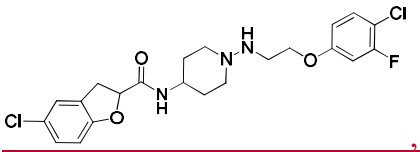
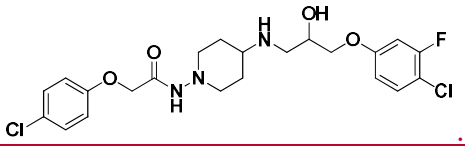
 ,
 ,
 ,

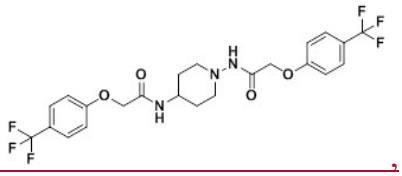
 ,
 ,
 ,

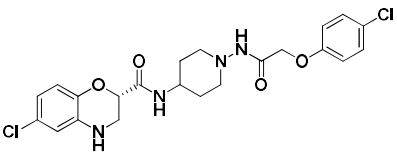


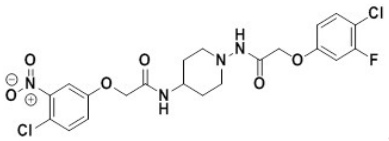
 ,  ,

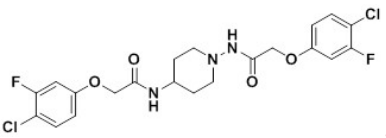
 ,  ,

 , and  .

9. The compound of claim 1 or 8, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1 or 8, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1 or 8, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1 or 8, wherein the compound is  , or a pharmaceutically acceptable salt thereof.

~~9~~13. A pharmaceutical composition comprising a compound of any of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

140. Use of a compound of any one of claims 1 to 128, or a pharmaceutically acceptable salt thereof, or a therapeutically effective amount of a pharmaceutical composition of claim 139, 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;
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;
optionally 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;

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, 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.

~~11. The use of claim 10, 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.~~

~~12. The use of claim 10 or 11, 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, 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.~~

153. A compound according to any one of claims 1 to 128, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 139, 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;

optionally 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;

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, 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.

~~14. The compound or pharmaceutical composition of claim 13, 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.~~

~~15. The compound or pharmaceutical composition of claim 13 or 14, 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, 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.~~

16. 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 12,~~8;~~ and ~~optionally comprising~~ culturing the cell in an *in vitro* culture medium comprising the compound or salt.

17. 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 12~~8~~; and wherein:

(a) the nucleic acid encoding the protein is a recombinant nucleic acid; and/or

(b) the cell is a human embryonic kidney (HEK) cell, a Chinese hamster ovary (CHO) cell, 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.

18. 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 128.

19. The method of claim 17 or 18, wherein:
(a) the protein is an antibody or a fragment thereof; or
(b) 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.

20. The method of any one of claims 17 to 19, comprising purifying the protein.

21. An *in vitro* cell culture medium, comprising the compound or salt of any one of claims 1 to 128 and nutrients for cellular growth, wherein the cell culture medium optionally comprises a eukaryotic cell comprising a nucleic acid encoding a protein; and wherein the cell culture medium optionally further comprises a compound for inducing protein expression;
for example, wherein:
(a) the nucleic acid encoding the protein is a recombinant nucleic acid and/or
(b) the protein is:
(b-1) an antibody or a fragment thereof; or
(b-2) 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; and/or
(c) the eukaryotic cell is a human embryonic kidney (HEK) cell, a Chinese hamster ovary (CHO) cell, 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.

22. 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 128; wherein the CFPS system optionally comprises a eukaryotic cell extract comprising eIF2; and wherein the CFPS system optionally further comprises eIF2B;
for example, wherein:
(a) the protein is an antibody or a fragment thereof; or
(b) 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.