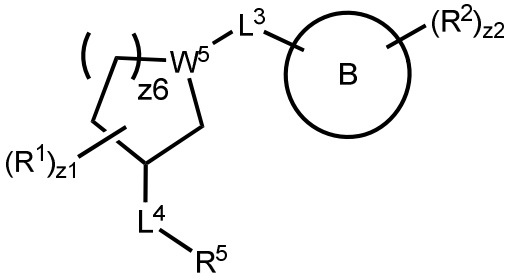
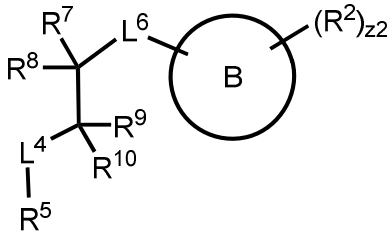
~~**WHAT IS CLAIMED IS:**~~**CLAIMS**

1. A compound having the formula:





(I),, or (III); wherein,

R^1 is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, -CN, $-SO_{n1}R^{1D}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NR^{1C}NR^{1A}R^{1B}$, $-ONR^{1A}R^{1B}$, $-NHC(O)NR^{1C}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$, $-C(O)-OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$, $-NR^{1A}OR^{1C}$, $-SF_5$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; two adjacent R^1 substituents on adjacent carbons may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or two R^1 substituents bonded to the same carbon atom may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl;

z1 is an integer from 0 to 9;

R^2 is independently oxo, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, -CN, $-SO_{n2}R^{2D}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NR^{2C}NR^{2A}R^{2B}$, $-ONR^{2A}R^{2B}$, $-NHC(O)NR^{2C}NR^{2A}R^{2B}$,$-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-C(O)R^{2C}$, $-C(O)-OR^{2C}$, $-C(O)NR^{2A}R^{2B}$, $-OR^{2D}$, $-NR^{2A}SO_2R^{2D}$, $-NR^{2A}C(O)R^{2C}$, $-NR^{2A}C(O)OR^{2C}$, $-NR^{2A}OR^{2C}$, $-SF_5$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

z2 is an integer from 0 to 6;

L^3 is a bond, $-S(O)_2-$, $-NR^3-$, -NH-, -O-, -S-, -C(O)-, $-C(O)NR^3-$, $-NR^3C(O)-$, $-N(R^3)CH_2-$, $-NR^3C(O)NH-$, $-NHC(O)NR^3-$, -C(O)O-, -OC(O)-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene;

L^4 is a bond, -NH-, $-NR^4-$, or substituted or unsubstituted alkylene;

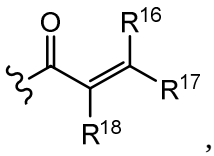
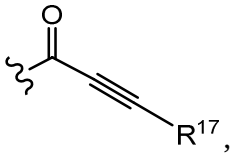
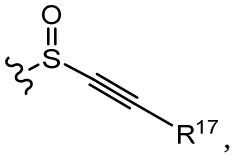
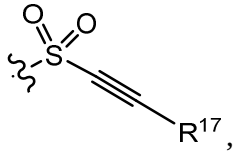
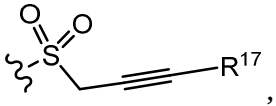
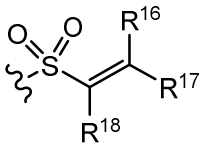
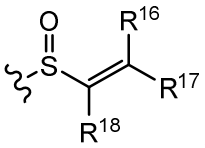
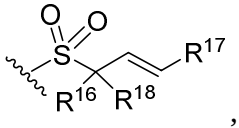
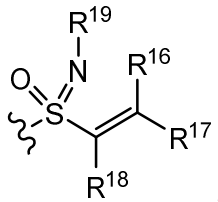
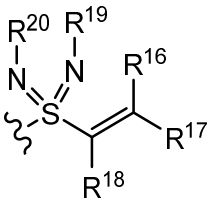
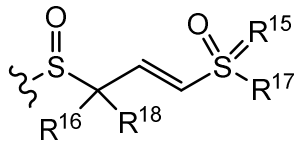
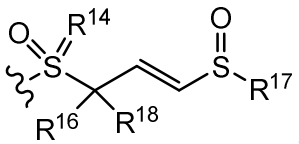
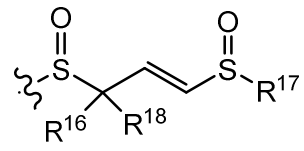
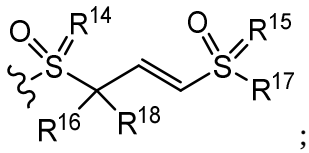
L^6 is $–N(R^6)-L^3-$ or –C(O)NH-;

W^5 is CH or N;

z6 is 1 or 2;

R^3, R^4, and R^6 are independently hydrogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, -CN, -OH, $-NH_2$, -COOH, $-COCH_3$, $-CONH_2$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, or unsubstituted heterocycloalkyl;

R^7, R^8, R^9, and R^{10} are independently hydrogen or unsubstituted C_1-C_{10} alkyl;Ring B is aryl, or membered heteroaryl;

R^5 is independently , , , , , , , , , , , , and , or ; wherein,

R^{14} is independently =O or =NR^{19};

R^{15} is independently =O or =NR^{20};

R^{16}, R^{17}, and R^{18} are independently hydrogen, oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-C(O)N(CH_3)_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{19} and R^{20} are independently hydrogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, -CN, -COOH, $-CONH_2$, $-C(O)N(CH_3)_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

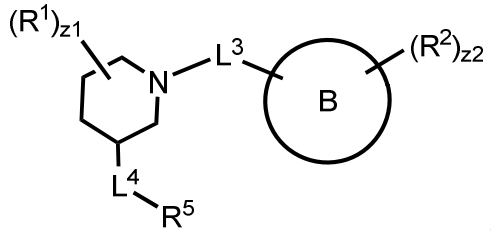
R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are independently hydrogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X^1 and X^2 are independently –F, -Cl, -Br, or –I;

n1 and n2 are independently an integer from 0 to 4; and

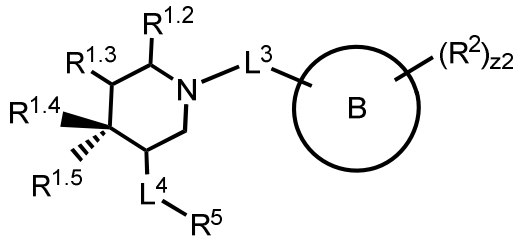
m1, m2, v1, and v2 are independently 1 or 2.

2. The compound of claim 1, having the formula:



.

3. The compound of claim 2, having the formula:

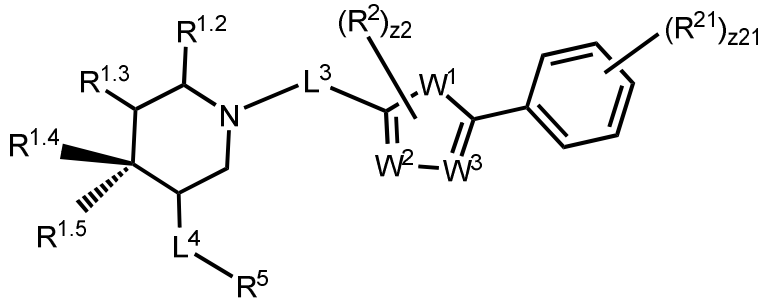


(Ia); wherein,

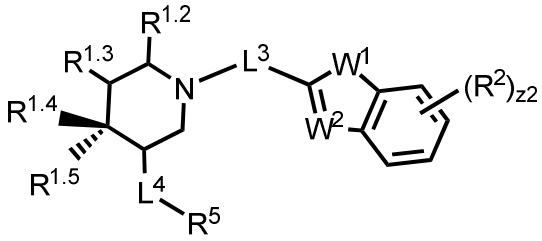
$R^{1.2}$ and $R^{1.3}$ are independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-N_3$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl; or $R^{1.2}$ and $R^{1.3}$ substituents on adjacent carbons may optionally be joined to form a substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl; and

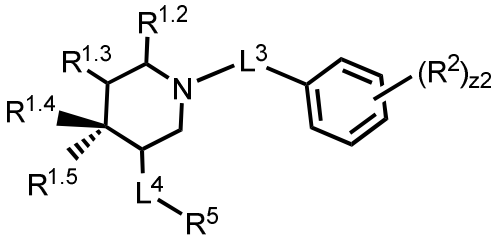
$R^{1.4}$ and $R^{1.5}$ are independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-N_3$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

4. The compound of claim 3, having the formula:

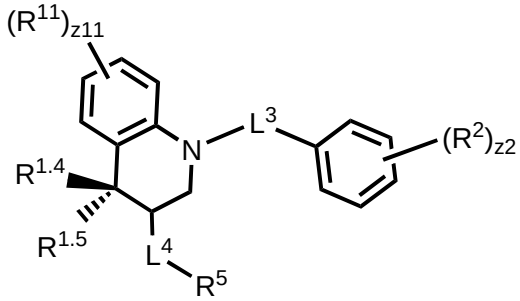


,



, 

, or



; wherein,

W^1 is independently –O-, -NH-, or -NR^2-;

W^2 and W^3 are independently =N-, =CH-, or =CR^2-;

$R^{1.2}$, $R^{1.3}$, $R^{1.4}$ and $R^{1.5}$ are independently hydrogen or halogen;

R^2 is independently oxo, halogen, -CX^2_3, -CHX^2_2, -CH_2X^2, -OCX^2_3, -OCH_2X^2, -$OCHX^2_2$, -CN, -OH, -NH_2, -COOH, -$CONH_2$, –$C(O)N(CH_3)_2$, -NO_2, -SH, -SO_3H, -SO_4H, -SO_2NH_2, –$NHNH_2$, –ONH_2, –$NHC(O)NHNH_2$, –$NHC(O)NH_2$, -$NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, -N_3, unsubstituted C_1-C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3-C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted C_6-C_{12} aryl, or unsubstituted 5 to 12 membered heteroaryl;

R^{11} is independently oxo, halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-C(O)N(CH_3)_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-N_3$, unsubstituted C_1-C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3-C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted C_6-C_{12} aryl, or unsubstituted 5 to 12 membered heteroaryl;

R^{21} is independently oxo, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, -CN, -OH, $-NH_2$, -COOH, $-CONH_2$, $-C(O)N(CH_3)_2$, $-NO_2$, -SH, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -NHC(O)H, -NHC(O)OH, -NHOH, $-N_3$, unsubstituted C_1-C_6 alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C_3-C_6 cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted C_6-C_{12} aryl, or unsubstituted 5 to 12 membered heteroaryl;

X^{11} and X^{21} are independently -F, -Cl, -Br, or –I;

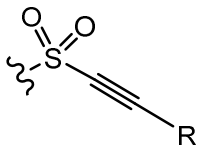
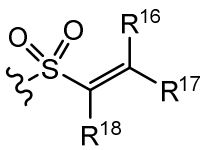
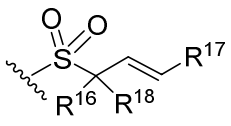
z2 is an integer from 0 to 6;

z11 is an integer from 0 to 4;

z21 is an integer from 0 to 5;

L^3 is -C(O)-, $-CH_2$-, -C(O)NH-, $-NHC(O)$-, $-NHCH_2$-, $-CH_2CH_2NH$-, $-C(O)CH_2NH$-, or $-CH_2C(O)NH$-;

L^4 is a bond, -NH-, or $-CH_2$-;

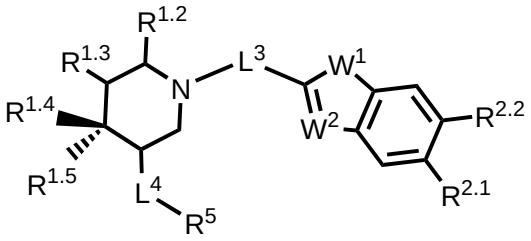
R^5 is independently , , or ;

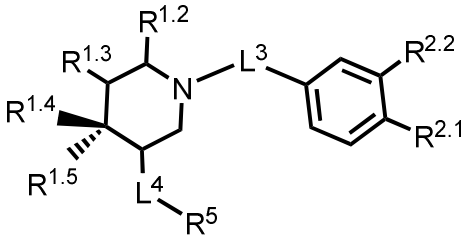
wherein R^{16}, R^{17}, and R^{18} are independently hydrogen, $-C(O)N(CH_3)_2$, or unsubstituted C_1-C_3 alkyl.

5. The compound of claim 4, wherein: R^2 is independently halogen, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, unsubstituted C_1-C_3 alkyl, or unsubstituted 5 to 6 membered heteroaryl; R^{11}

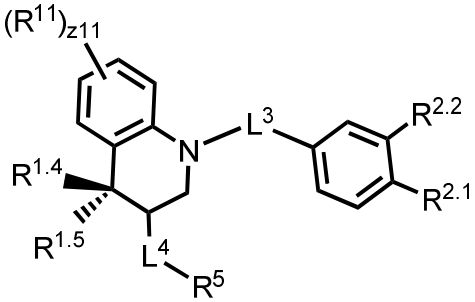
is independently halogen, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, unsubstituted C_1-C_3 alkyl, or unsubstituted 5 to 6 membered heteroaryl; and R^{21} is independently halogen, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, unsubstituted C_1-C_3 alkyl, or unsubstituted 5 to 6 membered heteroaryl.

6. The compound of claim 4, having the formula:



,


,



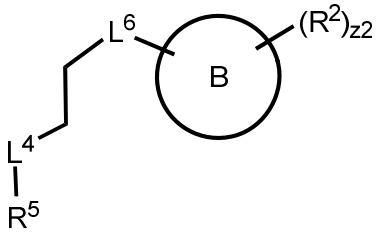
or ; wherein,

$R^{2.1}$ is independently hydrogen, $-OCX^2_3$, or unsubstituted 5 to 6 membered heteroaryl; and

$R^{2.2}$ is independently hydrogen or halogen.

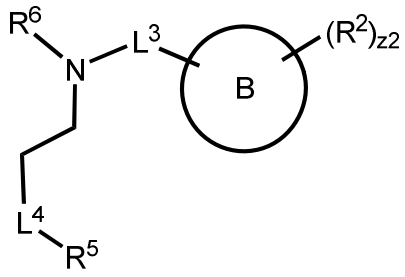
7. The compound of claim 4, wherein R^{11} is independently halogen.

8. The compound of claim 1, having the formula:



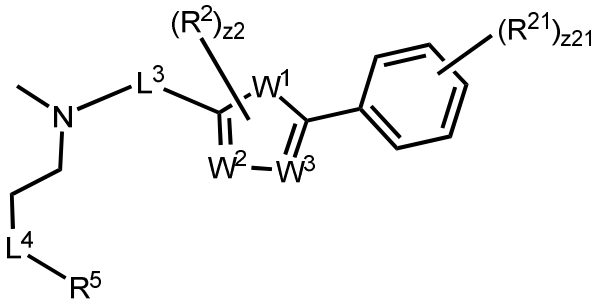
.

9. The compound of claim 1, having the formula:

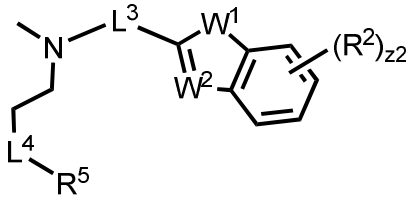


.

10. The compound of claim 9, having the formula:



or



; wherein,

W^1 is independently –O-, -NH-, or -NR^2-;

W^2 and W^3 are independently =N-, =CH-, or =CR^2-;

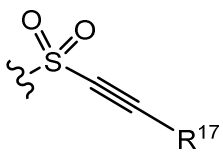
R^2 and R^{21} are independently halogen, -OCX^2_3, -OCH_2X^2, -$OCHX^2_2$, unsubstituted C_1-C_3 alkyl, or unsubstituted 5 to 6 membered heteroaryl;

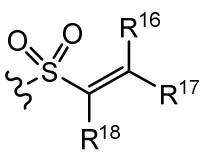
z2 is an integer from 0 to 6;

z21 is an integer from 0 to 5;

L^3 is -C(O)- or -CH_2-;

L^4 is a bond, -NH-, -NR^4-, or -CH_2-;

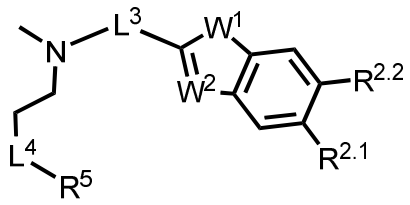
R^5 is independently 

or 

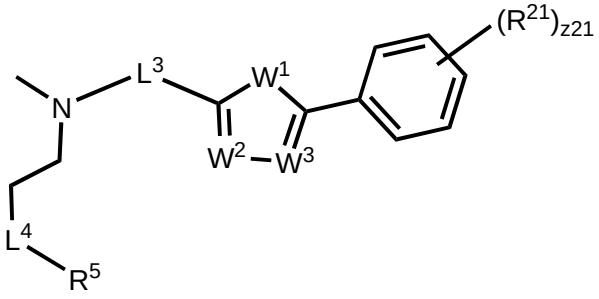
;

wherein R^{16}, R^{17}, and R^{18} are independently hydrogen, –C(O)N(CH_3)$_2$, or unsubstituted C_1-C_3 alkyl.

11. The compound of claim 10, having the formula:



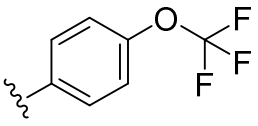
or

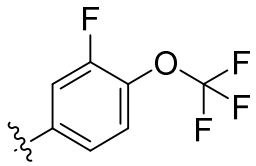


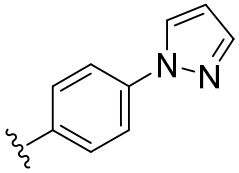
; wherein,

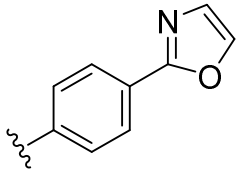
$R^{2.1}$ is independently hydrogen, -OCX^2_3, or unsubstituted 5 to 6 membered heteroaryl; and

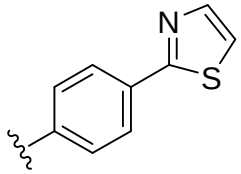
$R^{2.2}$ is independently hydrogen or halogen.

12. The compound of claim 1, wherein (Ring B)-$(R^2)_{z2}$ is 

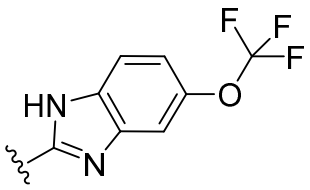
, 

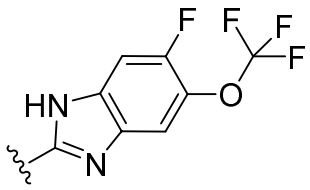
, 

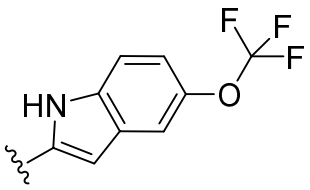
, 

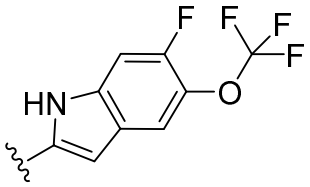
, 

,



, 

, 

, or 

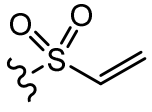
.

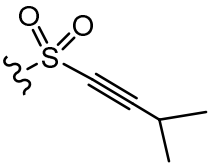
13. The compound of claim 1, wherein L^4 is -NH-.

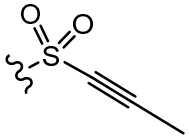
14. The compound of claim 1, wherein L^4 is $–CH_2$-.

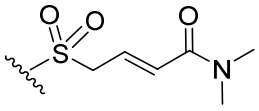
15. The compound of claim 1, wherein L^4 is $-N(CH_3)$-.

16. The compound of claim 1, wherein

R^5 is independently 

, 

, 

, or 

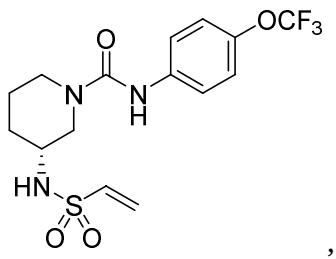
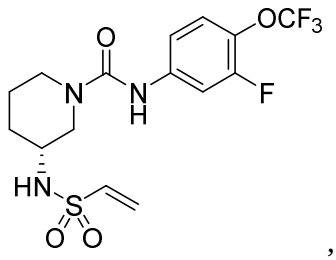
.

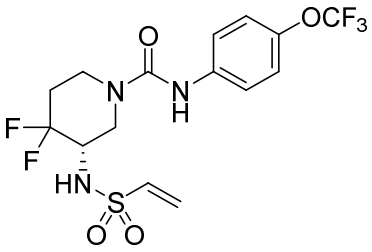
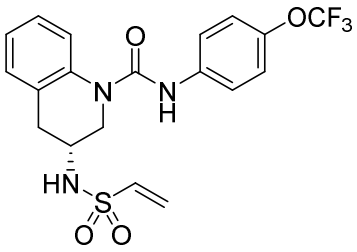
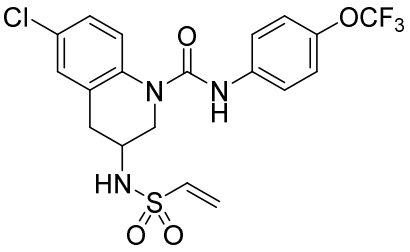
17. The compound of claim 1, wherein L^3 is -C(O)-, $-CH_2$-, -C(O)NH-, $-CH_2CH_2NH$-, $-C(O)CH_2NH$-, or $-CH_2C(O)NH$.

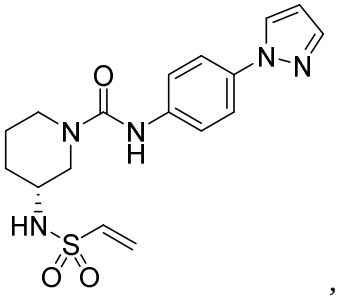
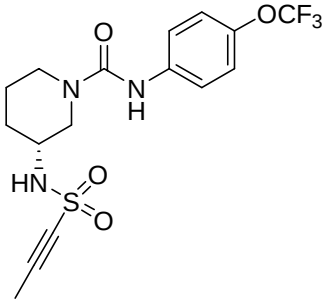
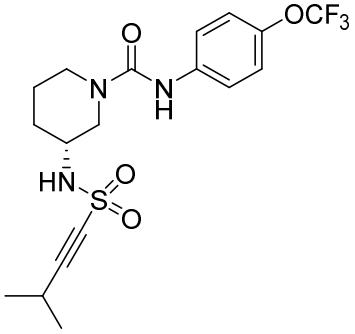
18. The compound of claim 1, wherein L^3 is $-CH_2$- or -C(O)NH-.

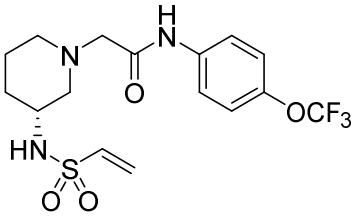
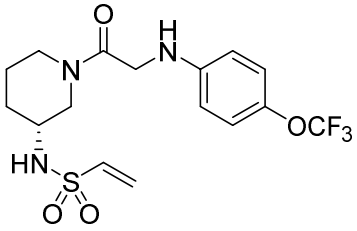
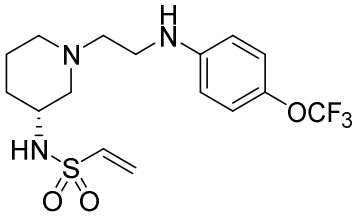
19. The compound of claim 1, wherein R^2 is independently -F or $-OCF_3$.

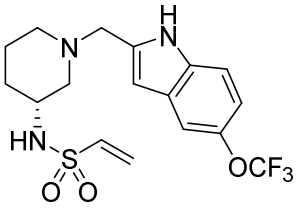
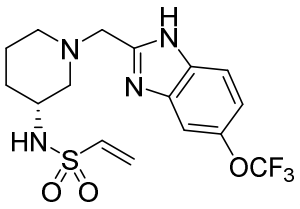
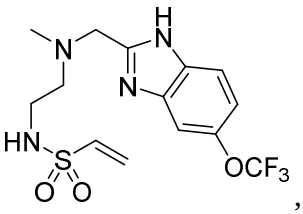
20. The compound of claim 1 having the formula:

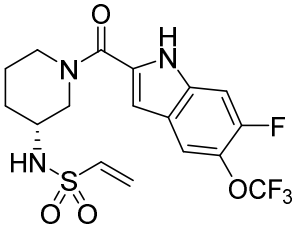
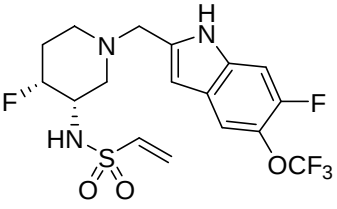
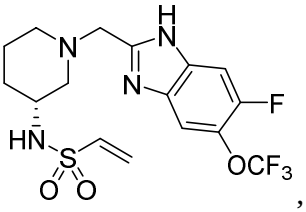
2  ,  ,

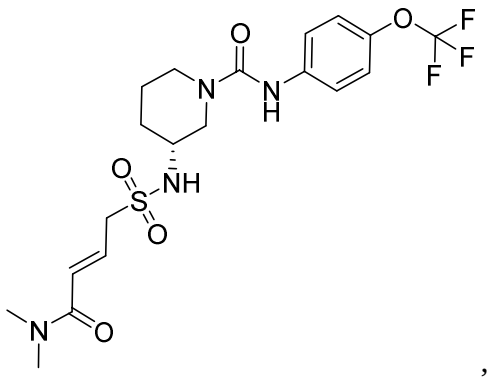
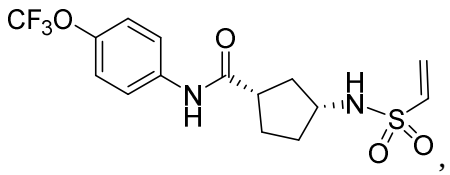
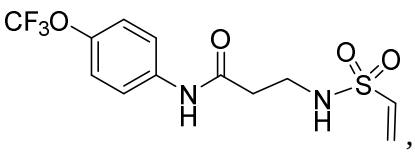
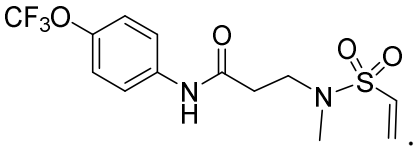
3  ,  ,  ,

4  ,  ,  ,

5  ,  ,  ,

6  ,  ,  ,

7  ,  ,  ,

21. A pharmaceutical composition comprising the compound of any one of claims 1 to 20 and a pharmaceutically acceptable excipient.

22. A method of inhibiting human Caspase 6 protein activity, said method comprising: contacting the human Caspase 6 protein with a compound of one of claims 1 to 20.

23. The method of claim 22, wherein the compound covalently binds C264 of the human Caspase 6 protein.

24. The method of claim 22, wherein the compound inhibits the activity of human Caspase 6 protein more than other human Caspase proteins.

25. The method of claim 22, wherein the compound inhibits the activity of human Caspase 6 protein more than human Caspase 2 and human Caspase 3.

26. The compound of one of claims 1 to 20 for use in therapy.

27. ~~A method of treating a neurodegenerative disease, said method comprising administering to a subject in need thereof an effective amount of a~~ Use of the compound of one of claims 1 to 20 in the manufacture of a medicament for the treatment of a neurodegenerative disease, wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~27~~28. The ~~method~~ use of claim ~~26~~ 27, wherein the neurodegenerative disease is a tauopathy.

~~28~~29. The ~~method~~ use of claim ~~26~~ 27, wherein the neurodegenerative disease is Alzheimer's disease, Huntington's disease, Amyotrophic lateral sclerosis, Lewy body disease, Progressive Supranuclear Palsy, or Parkinson's disease.

~~29~~30. The ~~method~~ use of claim ~~26~~ 27, wherein the neurodegenerative disease is Alzheimer's disease.

~~30~~31. ~~A method of treating a memory loss, said method comprising administering to a subject in need thereof an effective amount of a~~ Use of the compound of one of claims 1 to 20 in the manufacture of a medicament for the treatment of a memory loss, wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~31~~32. ~~A method of treating axonal degradation, said method comprising administering to a subject in need thereof an effective amount of a~~ Use of the compound of one of claims 1 to 20 in the manufacture of a medicament for the treatment of axonal degradation, wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~32~~33. ~~A method of treating neuroinflammation, said method comprising administering to a subject in need thereof an effective amount of a~~ Use of the compound of one of claims 1 to 20 in the manufacture of a medicament for the treatment of neuroinflammation, wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~33~~34. ~~A method of treating liver disease, said method comprising administering to a subject in need thereof an effective amount of a~~ Use of the compound of one of claims 1 to 20 in the manufacture of a medicament for the treatment of liver disease, wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~34~~35. ~~A method of treating nonalcoholic steatohepatitis or nonalcoholic fatty liver disease, said method comprising administering to a subject in need thereof an effective amount of a~~ Use of the compound of one of claims 1 to 20 in the manufacture of a medicament

for the treatment of nonalcoholic steatohepatitis or nonalcoholic fatty liver disease, wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~35~~36. A compound of any one of claims 1 to 20, or pharmaceutically acceptable salt thereof, for use in a method of treating a neurodegenerative disease, ~~comprising administering to a subject in need thereof~~ wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~36~~37. A compound for the use of claim ~~35~~ 36, wherein the neurodegenerative disease is a tauopathy.

~~37~~38. A compound for the use of claim ~~35~~ 36, wherein the neurodegenerative disease is Alzheimer's disease, Huntington's disease, Amyotrophic lateral sclerosis, Lewy body disease, Progressive Supranuclear Palsy, or Parkinson's disease.

~~38~~39. A compound for the use of claim ~~35~~ 36, wherein the neurodegenerative disease is Alzheimer's disease.

~~39~~40. A compound of any one of claims 1 to 20, or pharmaceutically acceptable salt thereof, for use in a method of treating a memory loss, ~~comprising administering to a subject in need thereof~~ wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~40~~41. A compound of any one of claims 1 to 20, or pharmaceutically acceptable salt thereof, for use in a method of treating axonal degradation, ~~comprising administering to a subject in need thereof~~ wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~41~~42. A compound of any one of claims 1 to 20, or pharmaceutically acceptable salt thereof, for use in a method of treating neuroinflammation, ~~comprising administering to a subject in need thereof~~ wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~42~~43. A compound of any one of claims 1 to 20, or pharmaceutically acceptable salt thereof, for use in a method of treating liver disease, ~~comprising administering to a subject in~~

~~need thereof~~ wherein an effective amount of the compound is to be administered to a subject in need thereof.

~~43~~44. A compound of any one of claims 1 to 20, or pharmaceutically acceptable salt thereof, for use in a method of treating nonalcoholic steatohepatitis or nonalcoholic fatty liver disease, ~~comprising administering to a subject in need thereof~~ wherein an effective amount of the compound is to be administered to a subject in need thereof.