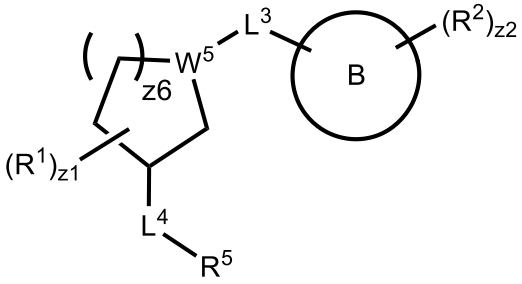
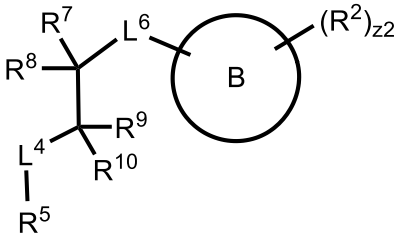
CLAIMS

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;

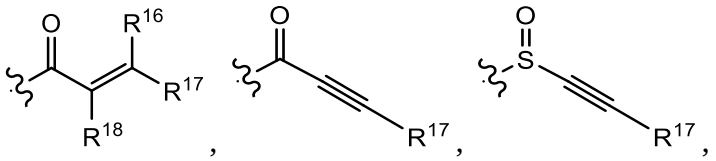
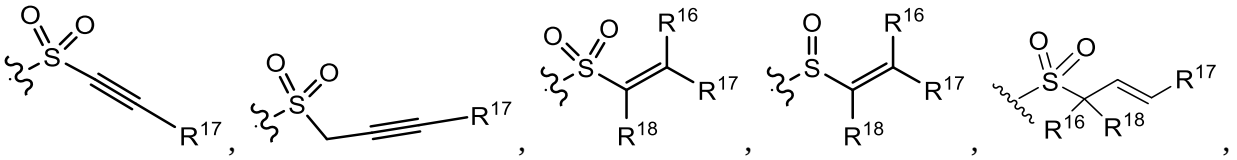
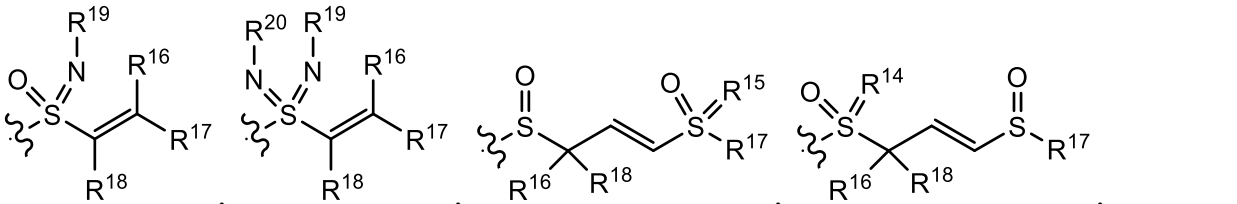
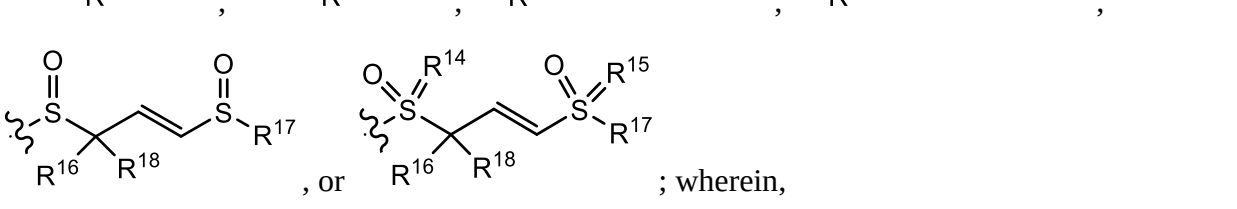
L^6 is $-N(R^6)-L^3-$ or –C(O)NH-;

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  ,  ,  ,  , , 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;

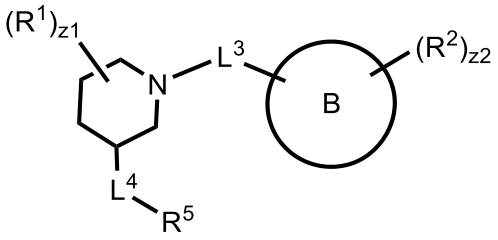
R^{1A}, R^{1B}, R^{1C}, R^{1D}, R^{2A}, R^{2B}, R^{2C}, and R^{2D} are independently hydrogen, -CCl_3, -CBr_3, -CF_3, -CI_3, $CHCl_2$, -$CHBr_2$, -CHF_2, -CHI_2, -CH_2Cl, -CH_2Br, -CH_2F, -CH_2I, -CN, -OH, -NH_2, -COOH, -$CONH_2$, -$OCCl_3$, -OCF_3, -$OCBr_3$, -OCI_3, -$OCHCl_2$, -$OCHBr_2$, -$OCHI_2$, -$OCHF_2$, -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:



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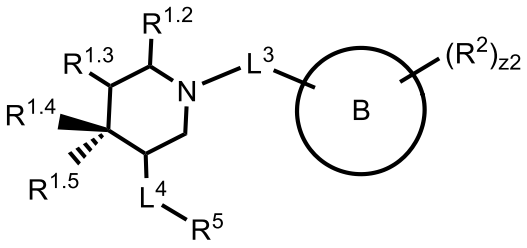
3. The compound of claim 2, having the formula:

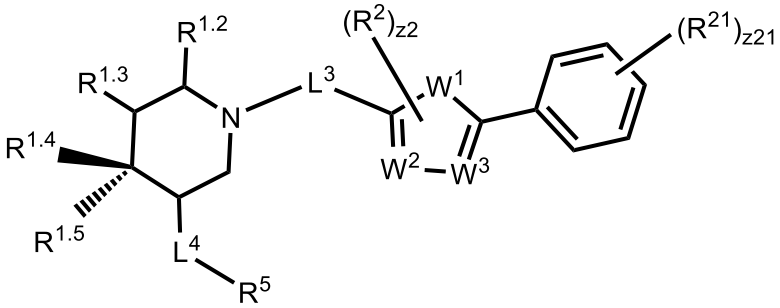


(Ia); wherein,

$R^{1.2}$ 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:



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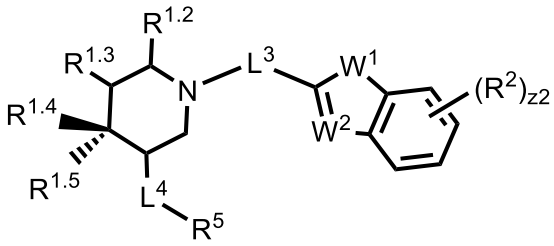

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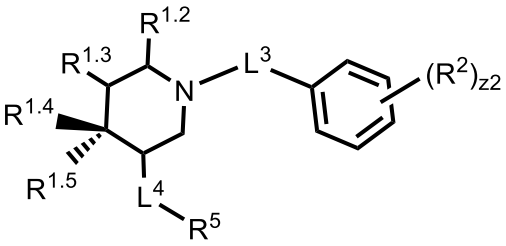

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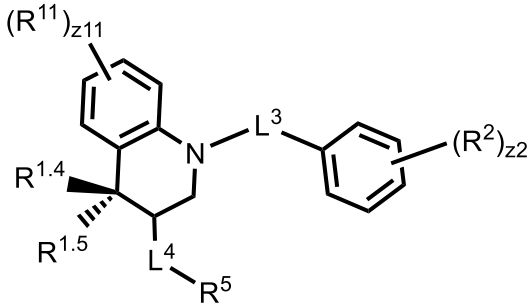


; wherein,

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;

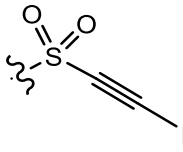
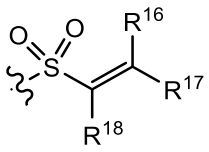
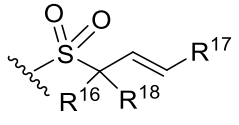
z2 is an integer from 0 to 6;

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 $-CH_2-$;

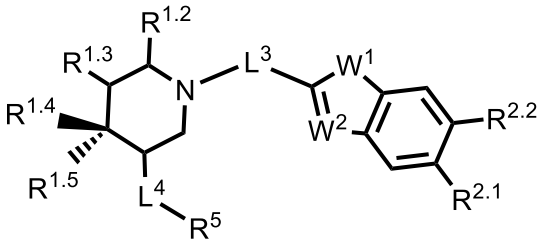
R^5 is independently  ,  , or  ;

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:



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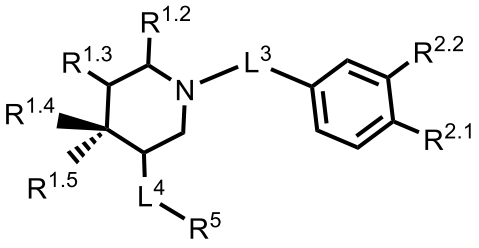

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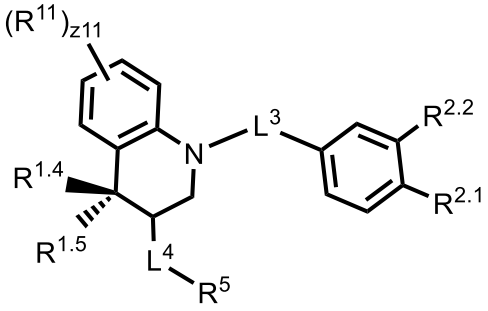


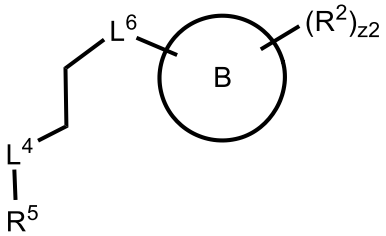
or ; wherein,

$R^{2.1}$ 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:



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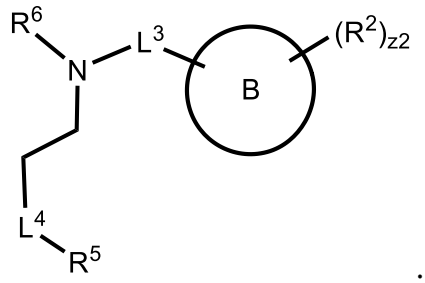
9. The compound of claim 1, having the formula:



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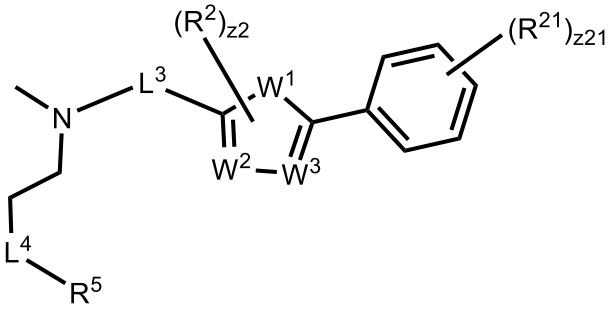
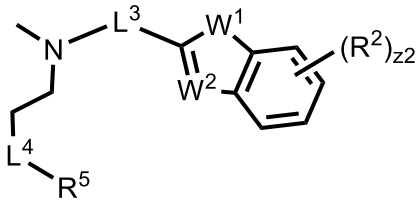
10. The compound of claim 9, having the formula:



or



; wherein,

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

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

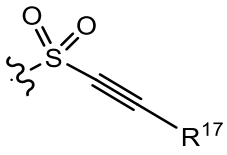
R^2 and R^{21} are independently halogen, -OCX^2_3, -OCH_2X^2, -$OCHX^2_2$, unsubstituted C_1-C_3 alkyl, or unsubstituted 5 to 6 membered heteroaryl;

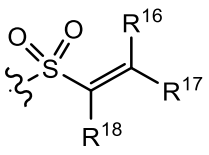
z2 is an integer from 0 to 6;

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 

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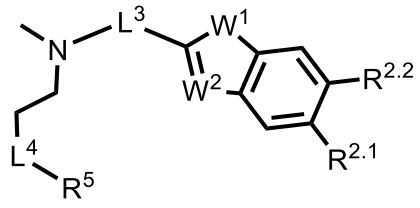
wherein R^{16}, R^{17}, and R^{18} are independently hydrogen, $–C(O)N(CH_3)_2$, or unsubstituted C_1-C_3 alkyl.

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



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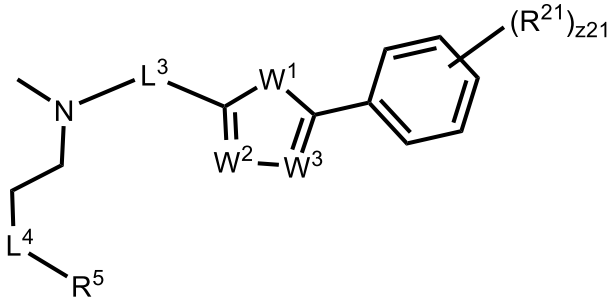
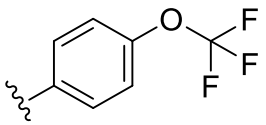
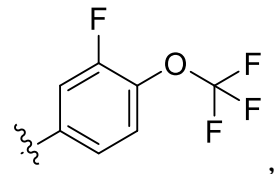


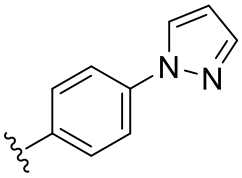
; wherein,

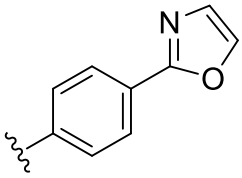
$R^{2.1}$ is independently hydrogen, $-OCX^2_3$, or unsubstituted 5 to 6 membered heteroaryl; and

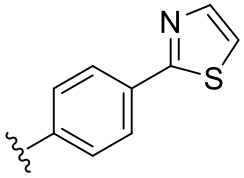
$R^{2.2}$ is independently hydrogen or halogen.

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

, 

, 

, 

, 

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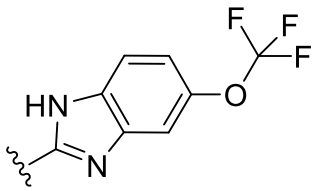
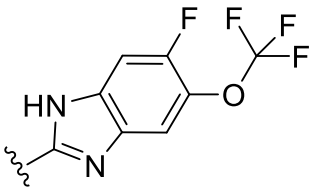
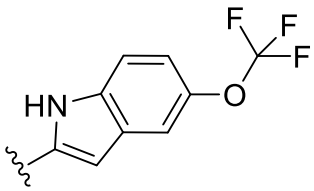
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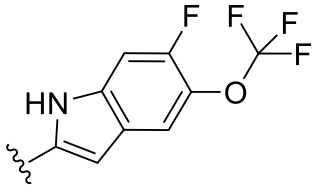
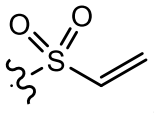
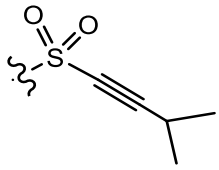
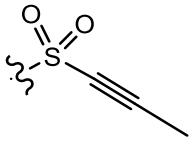

.

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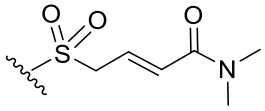
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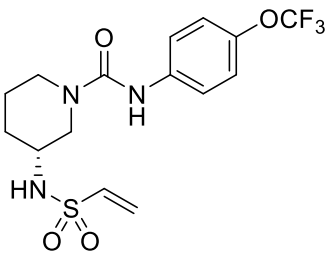
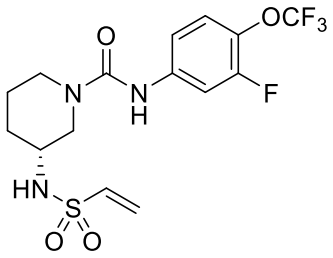
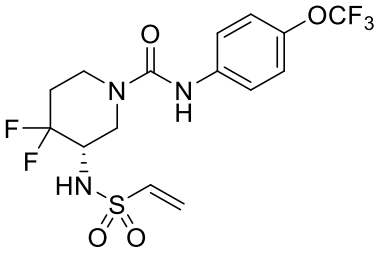
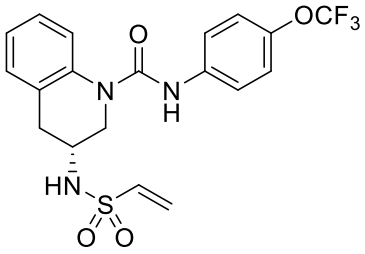
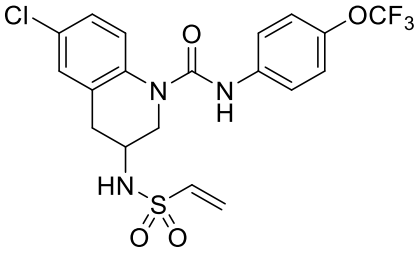
17. The compound of claim 1, wherein L^3 is -C(O)-, $-CH_2$-, -C(O)NH-, $-CH_2CH_2NH$-, $-C(O)CH_2NH$-, or $-CH_2C(O)NH$.

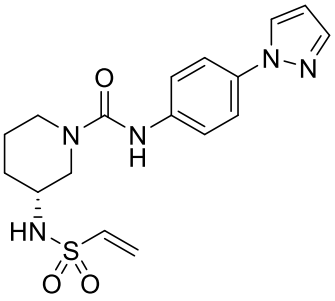
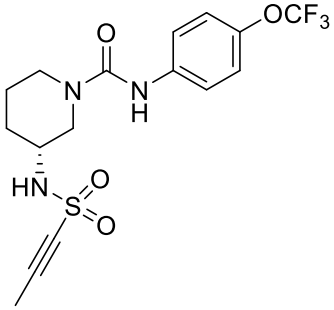
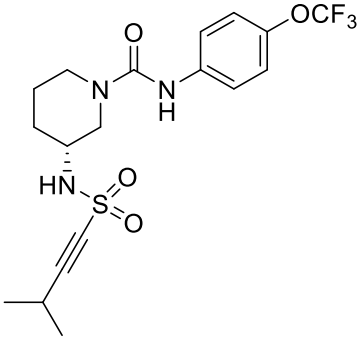
18. The compound of claim 1, wherein L^3 is $-CH_2$- or -C(O)NH-.

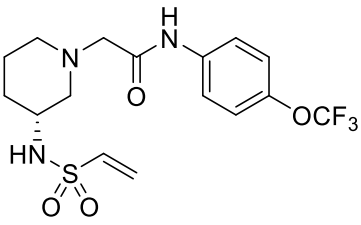
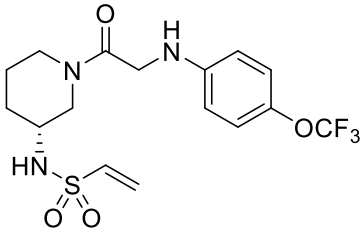
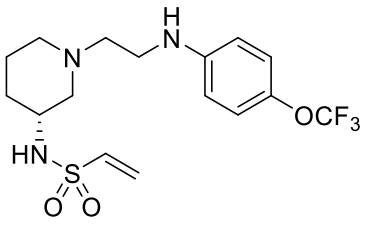
19. The compound of claim 1, wherein R^2 is independently -F or $-OCF_3$.

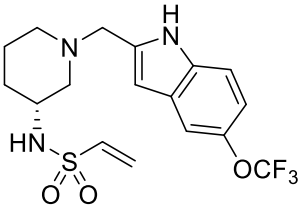
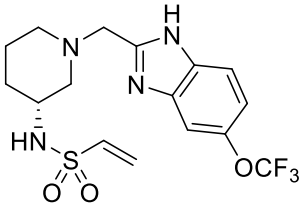
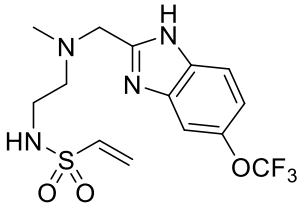
20. The compound of claim 1 having the formula:

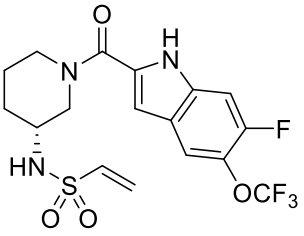
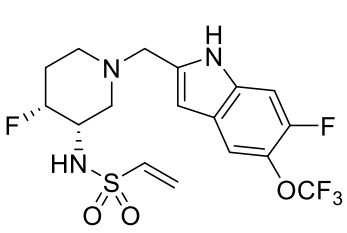
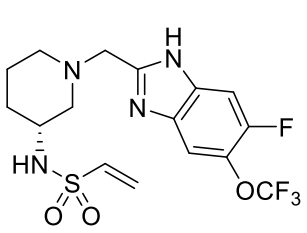
2  ,  ,

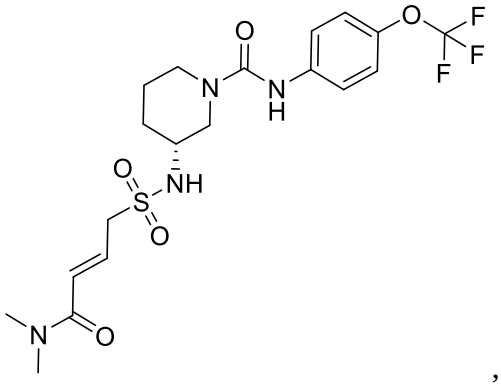
3  ,  ,  ,

4  ,  ,  ,

5  ,  ,  ,

6  ,  ,  ,

7  ,  ,  ,



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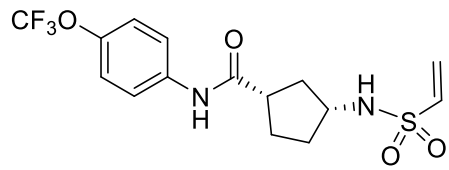

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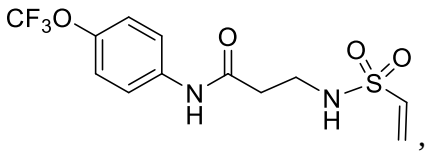

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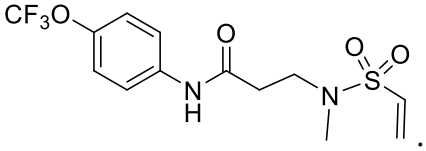

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21. A pharmaceutical composition comprising the compound of any one of claims 1 to 20 and a pharmaceutically acceptable excipient.

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. 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.

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

29. The use of claim 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.

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

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

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

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

38. A compound for the use of claim 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.

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

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

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

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

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

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