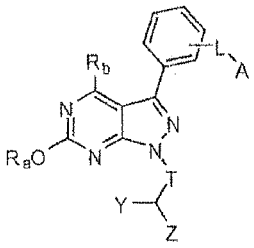
WHAT IS CLAIMED IS:

1. A compound of Formula (I) having the structure:



Formula (I);

wherein:

L is a bond, CH_2, O, NR_2, S, CO, C=NR_2, or C=N-OR_2;

T is a bond, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

A is aryl or heteroaryl wherein aryl or heteroaryl is optionally substituted with at least one R_1;

Y and Z are each independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_1-C_6heteroalkyl, C_2-C_6heteroalkenyl, C_4-C_{10}heterocycloalkenyl and C_2-C_{10}heterocycloalkyl, wherein C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_1-C_6heteroalkyl, C_2-C_6heteroalkenyl, C_4-C_{10}heterocycloalkenyl and C_2-C_{10}heterocycloalkyl are optionally substituted with at least one R_1; or

Y and Z together with the carbon atom to which they are attached form a C_3-C_{10}cycloalkyl, C_2-C_{10}heterocycloalkyl, C_4-C_{10}heterocycloalkenyl, aryl, or heteroaryl, wherein C_3-C_{10}cycloalkyl, C_2-C_{10}heterocycloalkyl, C_4-C_{10}heterocycloalkenyl, aryl, or heteroaryl, are optionally substituted with at least one X;

wherein when Y and Z together with the carbon atom to which they are attached form a nitrogen atom-containing C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl, the nitrogen atom of the C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl is optionally substituted with W and the carbon atoms of the C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl are optionally substituted with at least one X;

W is selected from J, C(=O)-J, C(=O)O-J, C(=O)NR_2-J, C(=NR_2)-J, -C(=NR_2)NR_2-J, C(=N-OR_3)-J, C(=S)-J, S(=O)$_v$-J, S(=O)$_v$O-J;

X is F, Cl, Br, I, -CN, -NO_2, -OR_3, -N(R_2)$_2$, -SR_2, -C_1-C_6alkyl, -C(=O)R_2, -OC(=O)R_2, -NR_2C(=O)R_2, -NR_2C(=O)N(R_2)$_2$, -C(=O)N(R_2)$_2$, -C(=NR_2)N(R_2)$_2$, -C(=N-OR_2)N(R_2)$_2$, -C(=S)R_2, -S(=O)$_v$$R_2$, -OS(=O)$_v$$R_2$, -$NR_2$C(=O)$OR_2$, -$NR_2$S(=O)$_v$$R_2$;

J is -C_1-C_6alkyl, C_3-C_6cycloalkyl, -C_2-C_6alkene, C_2-C_6heterocycloalkyl, aryl, or heteroaryl optionally substituted with at least one R_1;

v is 1 or 2;

R_a is H, -SO_3H, or C_1-C_4alkyl;

R_b is NH_2, OH, OSO_3H or $NHSO_3H$;

R_1 is selected from F, Cl, Br, I, -CN, -NO_2, -SR_2, -OR_3, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, -OC_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, -$NR_2S(=O)_2R_2$, -$S(=O)_2N(R_2)_2$, -$C(=O)CF_3$, -$C(=O)NR_2S(=O)_2R_2$, -$S(=O)_2NR_2C(=O)R_2$, -$N(R_2)_2$, wherein optionally the two R_2 groups of $N(R_2)_2$ and the nitrogen atom to which they are attached form a C_2-C_6 heterocycloalkyl ring; -$NR_2C(=O)R_2$, -$NR_2C(=O)N(R_2)_2$, -CO_2R_2, -$C(=O)R_2$, -$OC(=O)R_2$, -$C(=O)N(R_2)_2$, -$S(=O)R_2$, -$S(=O)_2R_2$, -SO_3H, and at least one amino acid fragment;

R_2 is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_3-C_6cycloalkyl;

R_3 is H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, or SO_3H; or a pharmaceutically acceptable salt, solvate, or tautomeric form thereof.

2. The compound of claim 1 wherein T is a bond.

3. The compound of claim 1 wherein T is C_1-C_6alkylene.

4. The compound of claim 3 wherein C_1-C_6alkylene is CH_2.

5. The compound of any of claims 1-4 wherein R_a is H, R_b is NH_2, and L is O.

6. The compound of any of claims 1-5 wherein A is aryl.

7. The compound of claim 6 wherein aryl is phenyl.

8. The compound of claim 7 wherein phenyl is substituted with one R_1 selected from F, Cl, Br, I, -CN, NO_2, -SR_2,–OR_3, -$N(R_2)_2$, methyl, and ethyl.

9. The compound of claim 8 wherein phenyl is substituted with –OH, or -OSO_3H.

10. The compound of any of claims 1-7 wherein phenyl is substituted with two R_1 selected from F, Cl, Br, I, -CN, NO_2, -SR_2, and –OR_3.

11. The compound of claim 10 wherein phenyl is substituted with two –OH, two -OSO_3H or –OH and -OSO_3H.

12. The compound of any of claims 1-11 wherein Y is C_1-C_6alkyl or C_2-C_6alkene.

13. The compound of any of claims 1-12 wherein C_1-C_6alkyl or C_2-C_6alkene is substituted with –$C(=O)R_2$ or -CO_2R_2.

14. The compound of claim 13 wherein R_2 is H.

15. The compound of any of claims 1-14 wherein Z is C_1-C_6alkyl.

16. The compound of claim 15 wherein C_1-C_6alkyl is substituted with -C(=O)R_2, -OC(=O)R_2, -NR_2C(=O)R_2, or -C(=O)N(R_2)$_2$.

17. The compound of claim 16 wherein C_1-C_6alkyl is substituted with –NR_2C(=O)R_2.

18. The compound of claim 17 wherein each R_2 is H.

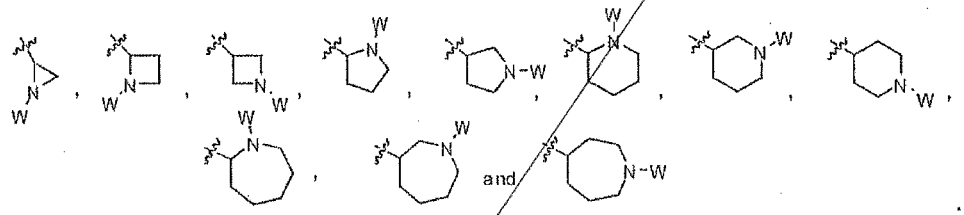
19. The compound of claim 15 wherein C_1-C_6alkyl is substituted with –NHC(=O)C_1-C_6alkyl.

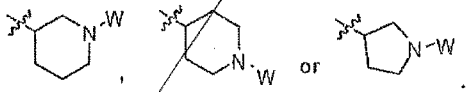
20. The compound of claim 19 wherein C_1-C_6alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl.

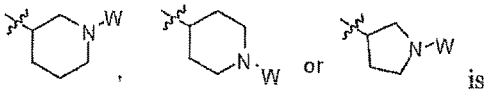
21. The compound of claim 17 wherein R_2 is C_1-C_6hydroxyalkyl.

22. The compound of any of claims 1-11 wherein Y and Z together with the carbon atom to which they are attached form a nitrogen atom-containing C_2-C_{10}heterocycloalkyl.

23. The compound of claim 22 wherein the nitrogen atom-containing C_2-C_{10}heterocycloalkyl is selected from:



24. The compound of claim 23 wherein the nitrogen atom-containing C_2-C_{10}heterocycloalkyl is 

25. The compound of claim 24 wherein 

is substituted with at least one X.

26. The compound of claim 25 wherein X is selected from F, Cl, Br, I, -CN, -OR_3, and NO_2.

27. The compound of claim 26 wherein X is –OH or -OSO_3H.

28. The compound of any of claims 22-27 wherein W is selected from J, C(=O)-J, C(=O)O-J, and C(=O)NR_2-J.

29. The compound of any of claims 22-28 wherein W is C(=O)-J.

30. The compound of claim 29 wherein J is C_1-C_6alkyl.

31. The compound of claim 30 wherein C_1-C_6alkyl is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl.

32. The compound of claim 30 or 31 wherein C_1-C_6alkyl is substituted with one R_1.

33. The compound of claim 30 or 31 wherein C_1-C_6alkyl is substituted with two R_1.

34. The compound of claim 32 or 33 wherein R_1 is selected from F, Cl, Br, I, -CN, NO_2, $-OR_3$, and at least one amino acid fragment.

35. The compound of any of claims 22-28 wherein W is J.

36. The compound of claim 35 wherein J is C_1-C_6alkyl.

37. The compound of claim 36 wherein C_1-C_6alkyl is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, and tert-butyl.

38. The compound of claim 35 or 36 wherein C_1-C_6alkyl is substituted with one R_1.

39. The compound of claim 35 or 36 wherein C_1-C_6alkyl is substituted with two R_1.

40. The compound of claim 38 or 39 wherein R_1 is selected from F, Cl, Br, I, -CN, NO_2, and OR_3.

41. The compound of claim 34 wherein R_1 is at least one amino acid fragment.

42. The compound of claim 41 wherein the at least one amino acid fragment is a cysteine or glutathione fragment.

43. The compound of claim 33 wherein one R_1 is at least one amino acid fragment and the other R_1 is selected from F, Cl, Br, I, -CN, NO_2, –OH, and $-OSO_3H$.

44. The compound of claim 41 wherein the at least one amino acid fragment is a di-peptide fragment.

45. The compound of claim 41 wherein the at least one amino acid fragment is a tri-peptide fragment.

46. The compound of claim 44 wherein the di-peptide fragment is a fragment of Cys-Gly.

47. The compound of claim 29 wherein J is C_2-C_6alkene.

48. The compound of claim 47 wherein C_2-C_6alkene is C_2H_3.

49. The compound of claim 47 wherein C_2-C_6alkene is substituted with at least one R_1 selected from F, Cl, Br, I, -CN, NO_2, OH, and $-OSO_3H$.

50. The compound of claim 29 wherein J is C_2-C_6heterocycloalkyl.

51. The compound of claim 50 wherein C_2-C_6heterocycloalkyl is an epoxide.

52. The compound of claim 1 wherein R_1 is selected from $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)NR_2S(=O)_2R_2$, $-S(=O)_2NR_2C(=O)R_2$, $-S(=O)R_2$, or $-S(=O)_2R_2$.

53. The compound of claim 52 wherein R_1 is $-S(=O)_2R_2$.

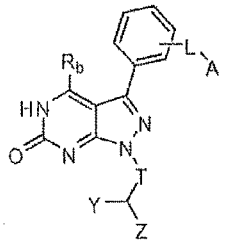
54. The compound of claim 53 wherein R_2 is C_1-C_6haloalkyl.

55. The compound of claim 54 wherein C_1-C_6haloalkyl is CF_3.

56. The pharmaceutically acceptable salt of a compound of claim 1.

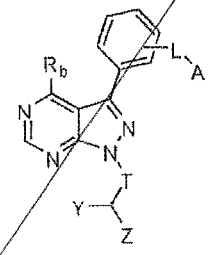
57. The pharmaceutically acceptable salt of claim 52 comprising at least one sulfate anion of the compound of claim 1 and at least one metal cation.

58. The compound of claim 1 wherein the tautomeric form of the compound of Formula (I) has the structure:



; or a pharmaceutically acceptable salt or solvate thereof.

59. A compound having the structure of Formula (II):



Formula (II);

wherein:

L is a bond, CH_2, O, NR_3, S, CO, $C=NR_2$, or $C=N\text{-}OR_2$;

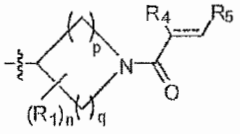
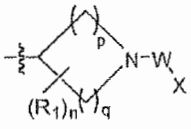
T is a bond, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

A is aryl or heteroaryl wherein aryl or heteroaryl is optionally substituted with at least one R_1;

Y is C_1-C_6alkylene-CO_2H or C_2-C_6alkenylene-C(=O)H;

Z is C_1-C_6alkylene-$NR_2C(=O)C_1$-C_6alkyl optionally substituted with at least one R_1; or

Y and Z together with the carbon atom to which they are attached form a

 or a  group;

 is a single bond or a cis or trans-double bond;

p is 0-6;

q is 0-6; wherein p+q is ≥1;

n is 0-4;

R_1 is selected from F, Cl, Br, I, -CN, -NO_2, -SR_2, -OR_3, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, -OC_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, -$NR_3S(=O)_2R_2$, -$S(=O)_2N(R_2)_2$, -$C(=O)CF_3$, -$C(=O)NR_3S(=O)_2R_2$, -$S(=O)_2NR_3C(=O)R_2$, -$N(R_2)_2$, wherein optionally the two R_2 groups of $N(R_2)_2$ and the nitrogen atom to which they are attached form a C_2-C_6 heterocycloalkyl ring, -$NR_2C(=O)R_2$, -$NR_2C(=O)NR_2$, -CO_2R_2, -$C(=O)R_2$, -$OC(=O)R_2$, -$C(=O)N(R_2)_2$, -$S(=O)R_2$, -$S(=O)_2R_2$, and at least one amino acid fragment;

R_6 is NH_2, OH, OSO_3H or $NHSO_3H$;

R_2 is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6dihydroxyalkyl, or C_3-C_6cycloalkyl;

R_3 is H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl or SO_3H;

R_4 and R_5 are each independently selected from H, F, Cl, Br, I, -CN, -NO_2, -SR_2, -OR_3, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, -OC_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, -OSO_3H, -$NR_2S(=O)_2R_2$, -$S(=O)_2N(R_2)_2$, -$C(=O)CF_3$, -$C(=O)NR_2S(=O)_2R_2$, -$S(=O)_2NR_2C(=O)R_2$, -$N(R_2)_2$, -$NR_2C(=O)R_2$, -CO_2R_2, -$C(=O)R_2$, -$OC(=O)R_2$, -$C(=O)N(R_2)_2$, -$S(=O)R_2$, -$S(=O)_2R_2$, and at least one amino acid fragment; or optionally when  is a single bond then R_4 and R_5 together with the carbon atoms to which they are attached form an epoxide; wherein when is a single bond then R_4 and R_5 are not both hydrogen;

W is selected from -C(=O)-, -$C(=O)R_2$-, -$C(=O)OR_2$-, -$C(=NR_2)$-, -$C(=N\text{-}OR_3)$-, -(C=S)-, -$S(=O)_v$-;

X is , wherein J is O, NR_6 or $C(R_2)_2$.

R_6 is selected from H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, $-S(=O)_2N(R_2)_2$, $-C(=O)CF_3$, $-CO_2R_2$, $-C(=O)R_2$, $-C(=O)N(R_2)_2$, $-S(=O)R_2$, $-S(=O)_2R_2$; or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

60. The compound of claim 59 wherein T is a bond.

61. The compound of claim 59 wherein T is C_1-C_6alkylene.

62. The compound of claim 61 wherein C_1-C_6alkylene is CH_2.

63. The compound of any of claims 59-62 wherein L is O and R_b is NH_2.

64. The compound of any of claims 59-63 wherein A is aryl.

65. The compound of claim 64 wherein aryl is phenyl.

66. The compound of claim 65 wherein phenyl is substituted with one R_1 selected from F, Cl, Br, I, -CN, NO_2, -OH, $-SR_2$, and $-OR_3$.

67. The compound of claim 66 wherein phenyl is substituted with –OH or $-OSO_3H$.

68. The compound of any of claims 59-65 wherein phenyl is substituted with two R_1 selected from F, Cl, Br, I, -CN, NO_2, $-SR_2$, and $-OR_3$.

69. The compound of claim 68 wherein phenyl is substituted with two –OH or two $-OSO_3H$ or –OH and $-OSO_3H$.

70. The compound of any of claims 59-69 wherein Y is C_1-C_6alkylene-CO_2H.

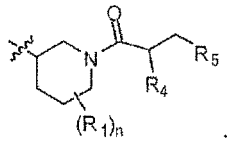
71. The compound of claim 70 wherein C_1-C_6alkylene is C_2H_5.

72. The compound of any of claims 59-69 wherein Y is C_2-C_6alkenylene-C(=O)H.

73. The compound of claim 69 wherein C_2-C_6alkenylene is C_2H_3.

74. The compound of any of claims 59-73 wherein Z is CH_2-$NHC(=O)C_1$-C_6alkyl.

75. The compound of claim 74 wherein C_1-C_6alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl.

76. The compound of any of claims 59-69 wherein Y and Z together with the carbon atom to which they are attached form 

.

77. The compound of claim 76 wherein R_4 and R_5 are each independently selected from H, F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, C_1-C_6alkyl, and at least one amino acid fragment.

78. The compound of claim 77 wherein R_4 is H and R_5 is –OH.

79. The compound of claim 77 wherein R_4 is –OH and R_5 is H.

80. The compound of claim 77 wherein R_4 and R_5 are both –OH.

81. The compound of claim 77 wherein R_4 is H and R_5 is at least one amino acid fragment.

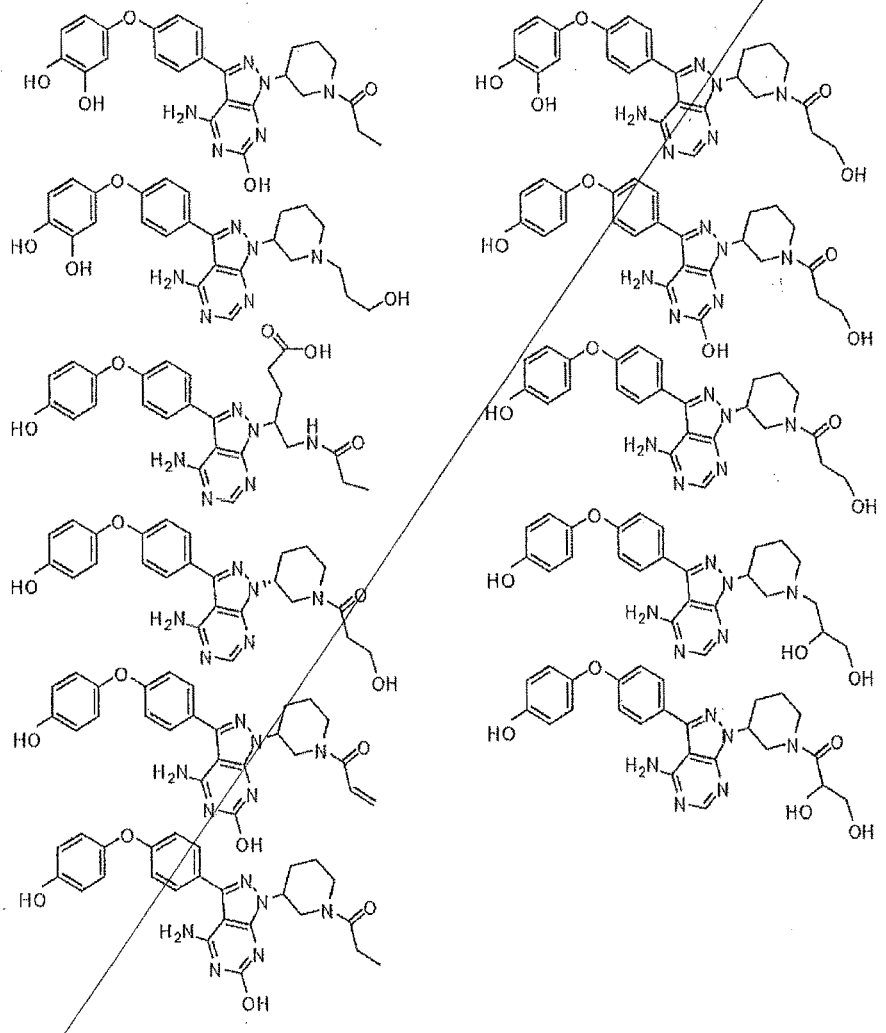
82. The compound of claim 81 wherein the at least one amino acid fragment is a cysteine or glutathione fragment.

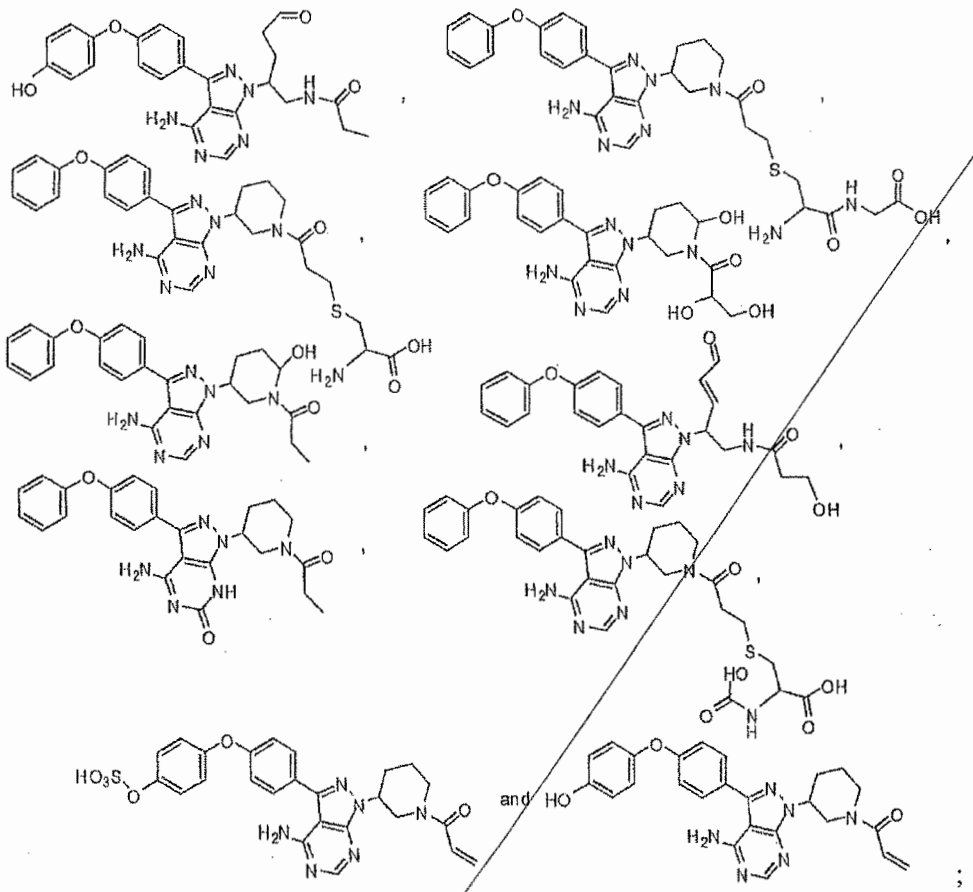
83. The compound of any of claims 76-82 wherein R_1 is selected from F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, and C_1-C_6alkyl.

84. The compound of claim 83 wherein R_1 is –OH or $-OSO_3H$.

85. The compound of claim 59 wherein X is morpholine or pyrrolidine.

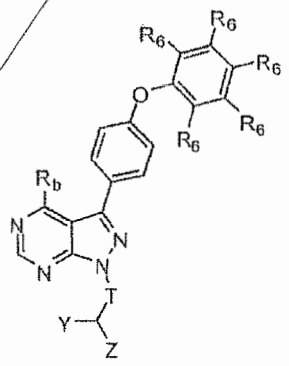
86. A compound selected from:





or a pharmaceutically acceptable salt, solvate, or tautomeric form thereof.

87. A compound having the structure of Formula (IV) having the structure:



Formula (IV);

wherein:

T is a bond, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

Y and Z are each independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_1-C_6heteroalkyl, C_2-C_6heteroalkenyl, C_4-C_{10}heterocycloalkenyl and C_2-C_{10}heterocycloalkyl, wherein C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_1-C_6heteroalkyl, C_2-C_6heteroalkenyl, C_4-C_{10}heterocycloalkenyl and C_2-C_{10}heterocycloalkyl are optionally substituted with at least one R_1; or

Y and Z together with the carbon atom to which they are attached form a C_3-C_{10}cycloalkyl, C_2-C_{10}heterocycloalkyl, C_4-C_{10}heterocycloalkenyl, aryl, or heteroaryl, wherein C_3-C_{10}cycloalkyl, C_2-C_{10}heterocycloalkyl, C_4-C_{10}heterocycloalkenyl, aryl, or heteroaryl, are optionally substituted with at least one X;

wherein when Y and Z together with the carbon atom to which they are attached form a nitrogen atom-containing C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl, the nitrogen atom of the C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl is optionally substituted with W and the carbon atoms of the C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl are optionally substituted with at least one X;

W is selected from J, C(=O)-J, C(=O)O-J, C(=O)NR_2-J, C(=NR_2)-J, -C(=NR_2)NR_2-J, C(=N-OR_3)-J, C(=S)-J, S(=O)$_v$-J, S(=O)$_v$O-J;

X is F, Cl, Br, I, -CN, -NO_2, -OR_3, -N(R_2)$_2$, -SR_2, -C_1-C_6alkyl, -C(=O)R_2, -OC(=O)R_2, -NR_2C(=O)R_5, -NR_2C(=O)N(R_2)$_2$, -C(=O)N(R_2)$_2$, -C(=NR_2)N(R_2)$_2$, -C(=N-OR_2)N(R_2)$_2$, -C(=S)R_2, -S(=O)$_v$$R_2$, -OS(=O)$_v$$R_2$, -$NR_2$C(=O)$OR_2$, -$NR_2$S(=O)$_v$$R_2$;

J is -C_1-C_6alkyl, C_3-C_6cycloalkyl, -C_2-C_6alkene, C_2-C_6heterocycloalkyl, aryl, or heteroaryl optionally substituted with at least one R_1;

v is 1 or 2;

R_b is NH_2, OH, OSO_3H or $NHSO_3H$, halogen, -CN, -NO_2, -SR_2, optionally substituted C_1-C_6alkyl; N(R_2)$_2$ or NHR_7;

R_1 is selected from F, Cl, Br, I, -CN, -NO_2, -SR_2, -OR_3, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, -OC_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, heteroaryl, phenyl, -NR_2S(=O)$_2$$R_2$, -S(=O)$_2$N($R_2$)$_2$, -C(=O)$CF_3$, -C(=O)$NR_2$S(=O)$_2$$R_2$, -S(=O)$_2$$NR_2$C(=O)$R_2$, -N($R_2$)$_2$, wherein optionally the two R_2 groups of N(R_2)$_2$ and the nitrogen atom to which they are attached form a C_2-C_6 heterocycloalkyl ring, -NR_2C(=O)R_2, -NR_2C(=O)R_8, -NR_2C(=O)N(R_2)$_2$, -CO_2R_2, -C(=O)R_2, -OC(=O)R_2, -

$C(=O)N(R_2)_2$, $-OS(=O)_2R_2$, $-OS(=O)_2OR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-SO_3H$, and at least one amino acid fragment;

R_2 is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_3-C_6cycloalkyl;

R_3 is H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, or SO_3H;

R_6 is selected from H, F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, $-OC_1$-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)CF_3$, $-C(=O)NR_2S(=O)_2R_2$, $-S(=O)_2NR_2C(=O)R_2$, $-N(R_2)_2$, wherein optionally the two R_2 groups of $N(R_2)_2$ and the nitrogen atom to which they are attached form a C_2-C_6 heterocycloalkyl ring, $-NR_2C(=O)R_2$, $-NR_2C(=O)N(R_2)_2$, $-CO_2R_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)N(R_2)_2$, $-OS(=O)_2R_2$, $-OS(=O)_2OR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-SO_3H$, and at least one amino acid fragment; wherein each R_6 cannot all be H;

R_7 is an amino protecting group;

R_8 is an optionally substituted C_1-C_6alkyl, an optionally substituted C_2-C_6alkenyl, an optionally substituted C_2-C_6alkynyl, or an optionally substituted C_3-C_6cycloalkyl; or a pharmaceutically acceptable salt, solvate, or metabolite thereof.

88. The compound of claim 86 wherein Y and Z together with the carbon atom to which they are attached form a C_3-C_{10}cycloalkyl or C_2-C_{10}heterocycloalkyl.

89. The compound of claim 87 or 88 wherein Y and Z together with the carbon atom to which they are attached form a C_2-C_{10}heterocycloalkyl.

90. The compound of claim 86 wherein W is C(=O)J.

91. The compound of claim 90 wherein J is $-C_1$-C_6alkyl or $-C_2$-C_6alkene.

92. The compound of claim 91 wherein J is substituted with at least one R_1.

93. The compound of claim 92 wherein R_1 is selected from F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, $-OC_1$-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, heteroaryl, or phenyl.

94. A pharmaceutical formulation comprising a therapeutically effective amount of a compound of any of claims 1-93, and a pharmaceutically acceptable excipient.

95. The pharmaceutical formulation of claim 94 that is formulated for a route of administration selected from oral administration, parenteral administration, buccal administration, nasal administration, topical administration, or rectal administration.

96. The compound of any of claims 1-93 wherein the compound forms a covalent bond with a Cys 481 residue of Btk or a cysteine residue in the homologous corresponding position of another tyrosine kinase.

97. The compound of any of claims 1-93 wherein the compound forms a covalent bond with an amino acid residue of Btk.

98. The compound of any of claims 1-93 wherein the compound is an irreversible inhibitor of Btk.

99. A method for treating an autoimmune disease or condition comprising administering to a patient in need the pharmaceutical formulation of claim 94.

100. The method of claim 99, wherein the autoimmune disease is selected from rheumatoid arthritis or lupus.

101. A method for treating a heteroimmune disease or condition comprising administering to a patient in need the pharmaceutical formulation of claim 94.

102. A method for treating a cancer comprising administering to a patient in need the pharmaceutical formulation of claim 94.

103. The method of claim 102, wherein the cancer is a B-cell proliferative disorder.

104. The method of claim 103, wherein the B-cell proliferative disorder is diffuse large B cell lymphoma, follicular lymphoma or chronic lymphocytic leukemia.

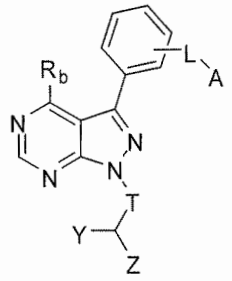
105. A method for treating mastocytosis comprising administering to a patient in need the pharmaceutical formulation of claim 94.

106. A method for treating osteoporosis or bone resorption disorders comprising administering to a patient in need the pharmaceutical formulation of claim 94.

107. A method for treating an inflammatory disease or condition comprising administering to a patient in need the pharmaceutical formulation of claim 94.

Claims

1. A compound having the structure of Formula (II):



Formula (II);

wherein:

L is a bond, CH_2, O, NR_3, S, CO, $C{=}NR_2$, or $C{=}N\text{-}OR_2$;

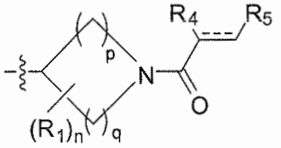
T is a bond, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

A is aryl or heteroaryl wherein aryl or heteroaryl is optionally substituted with at least one R_1;

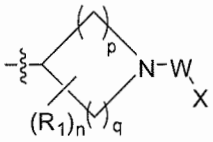
Y is C_1-C_6alkylene-CO_2H or C_2-C_6alkenylene-C(=O)H;

Z is C_1-C_6alkylene-$NR_2C(=O)C_1$-C_6alkyl optionally substituted with at least one R_1; or

Y and Z together with the carbon atom to which they are attached form a



or a



group;

is a single bond or a cis or trans-double bond;

p is 0-6;

q is 0-6; wherein p+q is ≥1;

n is 0-4;

R_1 is selected from F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, $-OC_1$-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, $-NR_3S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)CF_3$, $-C(=O)NR_3S(=O)_2R_2$, $-S(=O)_2NR_3C(=O)R_2$, $-N(R_2)_2$, wherein optionally the two R_2 groups of $N(R_2)_2$ and the nitrogen atom to which they are attached form a C_2-C_6 heterocycloalkyl

ring, $-NR_2C(=O)R_2$, $-NR_2C(=O)NR_2$, $-CO_2R_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)N(R_2)_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, and at least one amino acid fragment;

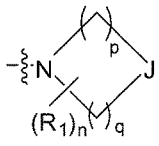
R_b is NH_2, OH, OSO_3H or $NHSO_3H$;

R_2 is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6dihydroxyalkyl, or C_3-C_6cycloalkyl;

R_3 is H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl or SO_3H;

R_4 and R_5 are each independently selected from H, F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, $-OC_1$-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, $-OSO_3H$, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)CF_3$, $-C(=O)NR_2S(=O)_2R_2$, $-S(=O)_2NR_2C(=O)R_2$, $-N(R_2)_2$, $-NR_2C(=O)R_2$, $-CO_2R_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)N(R_2)_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, and at least one amino acid fragment; or optionally when  is a single bond then R_4 and R_5 together with the carbon atoms to which they are attached form an epoxide; wherein when is a single bond then R_4 and R_5 are not both hydrogen;

W is selected from $-C(=O)-$, $-C(=O)R_2-$, $-C(=O)OR_2-$, $-C(=NR_2)-$, $-C(=N-OR_3)-$, $-(C=S)-$, $-S(=O)_v-$;

X is , wherein J is O, NR_6 or $C(R_2)_2$.

R_6 is selected from H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, $-S(=O)_2N(R_2)_2$, $-C(=O)CF_3$, $-CO_2R_2$, $-C(=O)R_2$, $-C(=O)N(R_2)_2$, $-S(=O)R_2$, $-S(=O)_2R_2$; or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1 wherein T is a bond.

3. The compound of claim 1 wherein T is C_1-C_6alkylene.

4. The compound of claim 3 wherein C_1-C_6alkylene is CH_2.

5. The compound of any of claims 1-4 wherein L is O and R_b is NH_2.

6. The compound of any of claims 1-5 wherein A is aryl.

7. The compound of claim 6 wherein aryl is phenyl.

8. The compound of claim 7 wherein phenyl is substituted with one R_1 selected from F, Cl, Br, I, -CN, NO_2, -OH, $-SR_2$, and $-OR_3$.

9. The compound of claim 7 wherein phenyl is substituted with –OH or $-OSO_3H$.

10. The compound of any of claims 1-7 wherein phenyl is substituted with two R_1 selected from F, Cl, Br, I, -CN, NO_2, $-SR_2$, and $-OR_3$.

11. The compound of claim 10 wherein phenyl is substituted with two –OH or two – OSO_3H or –OH and $-OSO_3H$.

12. The compound of any of claims 1-11 wherein Y is C_1-C_6alkylene-CO_2H.

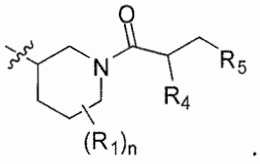
13. The compound of claim 12 wherein C_1-C_6alkylene is C_2H_5.

14. The compound of any of claims 1-11 wherein Y is C_2-C_6alkenylene-C(=O)H.

15. The compound of claim 14 wherein C_2-C_6alkenylene is C_2H_3.

16. The compound of any of claims 1-15 wherein Z is CH_2-NHC(=O)C_1-C_6alkyl.

17. The compound of claim 16 wherein C_1-C_6alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl.

18. The compound of any of claims 1-11 wherein Y and Z together with the carbon atom to which they are attached form 

.

19. The compound of claim 18 wherein R_4 and R_5 are each independently selected from H, F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, C_1-C_6alkyl, and at least one amino acid fragment.

20. The compound of claim 19 wherein R_4 is H and R_5 is –OH.

21. The compound of claim 19 wherein R_4 is –OH and R_5 is H.

22. The compound of claim 19 wherein R_4 and R_5 are both –OH.

23. The compound of claim 19 wherein R_4 is H and R_5 is at least one amino acid fragment.

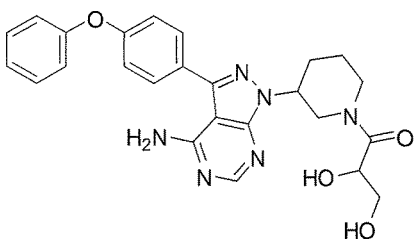
24. The compound of claim 23 wherein the at least one amino acid fragment is a cysteine or glutathione fragment.

25. The compound of any of claims 18-24 wherein R_1 is selected from F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, and C_1-C_6alkyl.

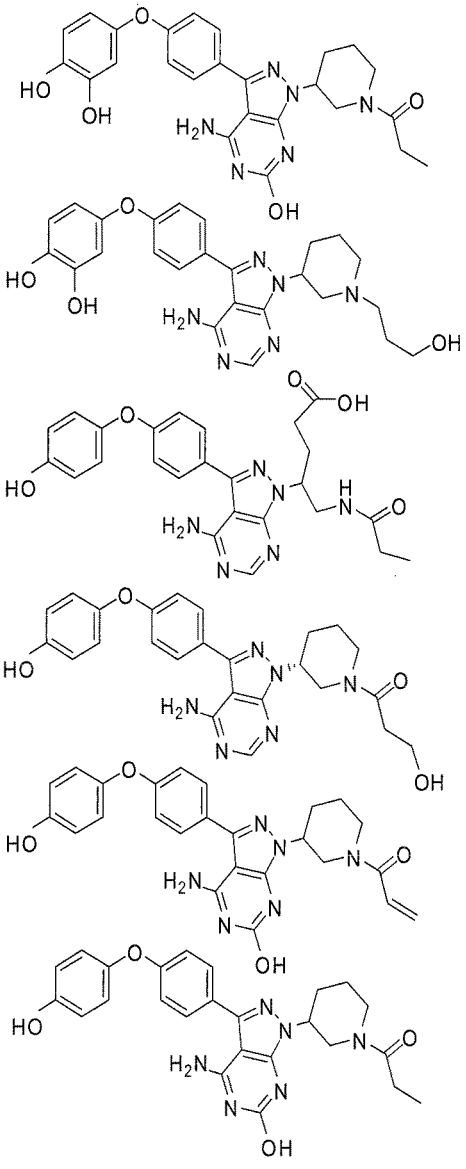
26. The compound of claim 25 wherein R_1 is –OH or $-OSO_3H$.

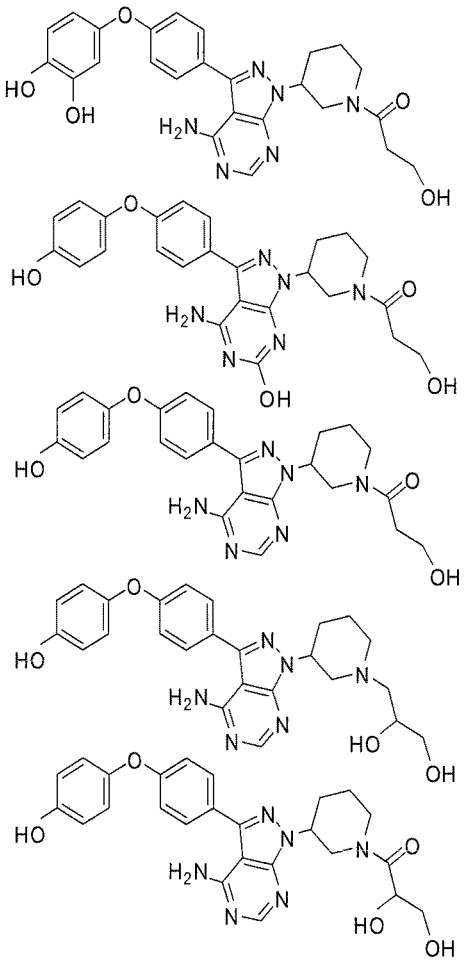
27. The compound of claim 1 wherein X is morpholine or pyrrolidine.

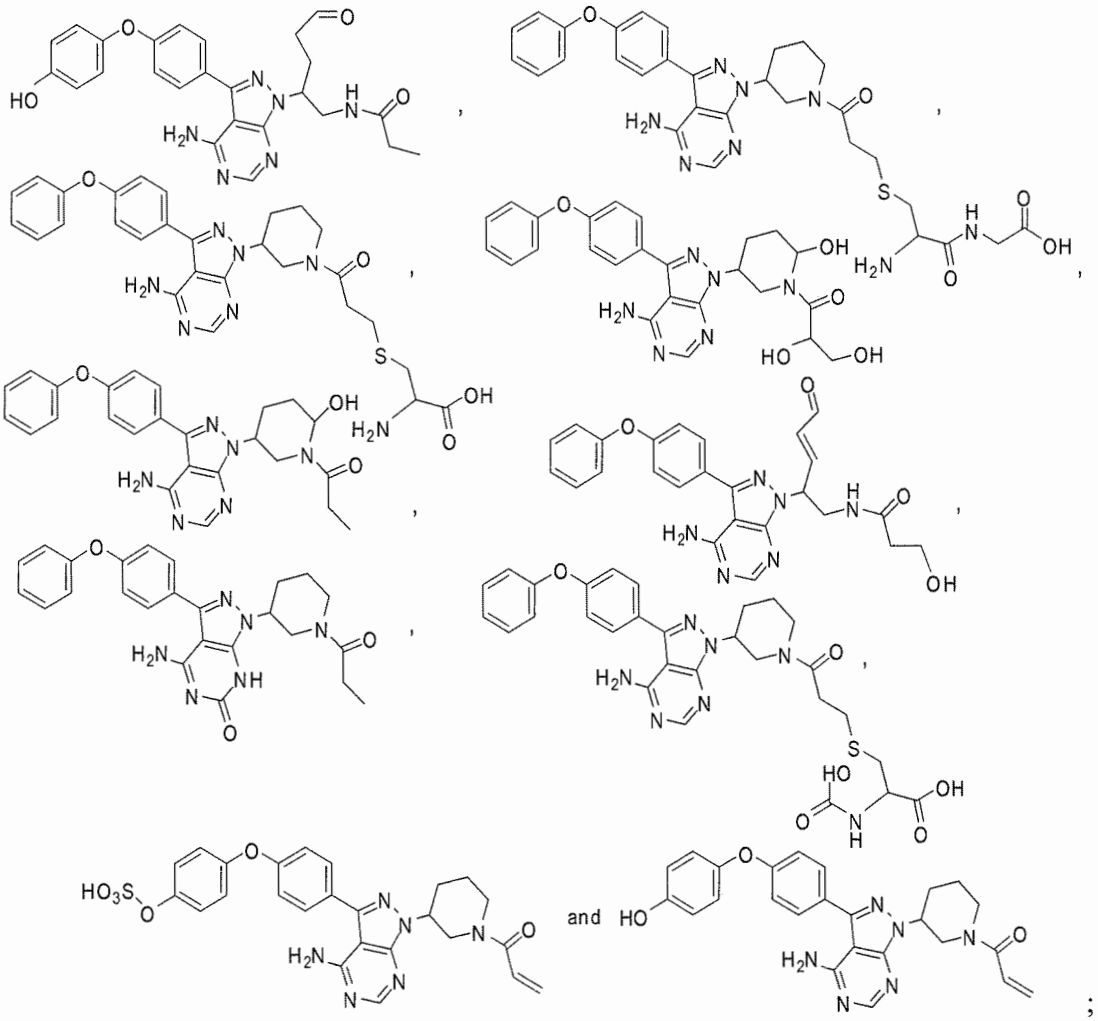
28. A compound having the structure:



29. A compound selected from:

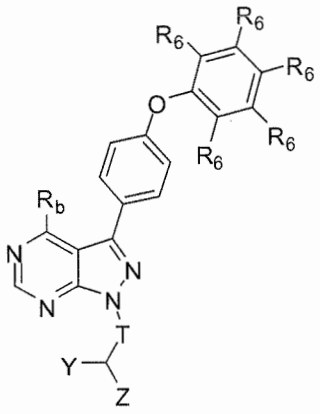






or a pharmaceutically acceptable salt or solvate thereof.

30. A compound having the structure of Formula (IV) having the structure:



Formula (IV);

wherein:

T is a bond, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

Y and Z are each independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_1-C_6heteroalkyl, C_2-C_6heteroalkenyl, C_4-C_{10}heterocycloalkenyl and C_2-C_{10}heterocycloalkyl, wherein C_1-C_6alkyl, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_1-C_6heteroalkyl, C_2-C_6heteroalkenyl, C_4-C_{10}heterocycloalkenyl and C_2-C_{10}heterocycloalkyl are optionally substituted with at least one R_1; or

Y and Z together with the carbon atom to which they are attached form a C_3-C_{10}cycloalkyl, C_2-C_{10}heterocycloalkyl, C_4-C_{10}heterocycloalkenyl, aryl, or heteroaryl, wherein C_3-C_{10}cycloalkyl, C_2-C_{10}heterocycloalkyl, C_4-C_{10}heterocycloalkenyl, aryl, or heteroaryl, are optionally substituted with at least one X;

wherein when Y and Z together with the carbon atom to which they are attached form a nitrogen atom-containing C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl, the nitrogen atom of the C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl is optionally substituted with W and the carbon atoms of the C_2-C_{10}heterocycloalkyl or C_4-C_{10}heterocycloalkenyl are optionally substituted with at least one X;

W is selected from J, C(=O)-J, C(=O)O-J, C(=O)NR_2-J, C(=NR_2)-J, -C(=NR_2)NR_2-J, C(=N-OR_3)-J, C(=S)-J, S(=O)$_v$-J, S(=O)$_v$O-J;

X is F, Cl, Br, I, -CN, -NO_2, -OR_3, -N(R_2)$_2$, -SR_2, -C_1-C_6alkyl, -C(=O)R_2, -OC(=O)R_2, -NR_2C(=O)R_5, -NR_2C(=O)N(R_2)$_2$, -C(=O)N(R_2)$_2$, -C(=NR_2)N(R_2)$_2$, -C(=N-OR_2)N(R_2)$_2$, -C(=S)R_2, -S(=O)$_v$$R_2$, -OS(=O)$_v$$R_2$, -$NR_2$C(=O)$OR_2$, -$NR_2$S(=O)$_v$$R_2$;

J is -C_1-C_6alkyl, C_3-C_6cycloalkyl, -C_2-C_6alkene, C_2-C_6heterocycloalkyl, aryl, or heteroaryl optionally substituted with at least one R_1;

v is 1 or 2;

R_b is NH_2, OH, OSO_3H or $NHSO_3H$, halogen, -CN, -NO_2, -SR_2, optionally substituted C_1-C_6alkyl; N(R_2)$_2$ or NHR_7;

R_1 is selected from F, Cl, Br, I, -CN, -NO_2, -SR_2, -OR_3, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, -OC_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, heteroaryl, phenyl, -NR_2S(=O)$_2$$R_2$, -S(=O)$_2$N($R_2$)$_2$, -C(=O)$CF_3$, -C(=O)$NR_2$S(=O)$_2$$R_2$, -S(=O)$_2$$NR_2$C(=O)$R_2$, -N($R_2$)$_2$, wherein optionally the two R_2 groups of N(R_2)$_2$ and the nitrogen atom to which they are attached form a C_2-C_6 heterocycloalkyl ring, -NR_2C(=O)R_2, -NR_2C(=O)R_8, -NR_2C(=O)N(R_2)$_2$, -CO_2R_2, -C(=O)R_2, -OC(=O)R_2, -

$C(=O)N(R_2)_2$, $-OS(=O)_2R_2$, $-OS(=O)_2OR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-SO_3H$, and at least one amino acid fragment;

R_2 is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, or C_3-C_6cycloalkyl;

R_3 is H, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, or SO_3H;

R_6 is selected from H, F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, $-OC_1$-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)CF_3$, $-C(=O)NR_2S(=O)_2R_2$, $-S(=O)_2NR_2C(=O)R_2$, $-N(R_2)_2$, wherein optionally the two R_2 groups of $N(R_2)_2$ and the nitrogen atom to which they are attached form a C_2-C_6 heterocycloalkyl ring, $-NR_2C(=O)R_2$, $-NR_2C(=O)N(R_2)_2$, $-CO_2R_2$, $-C(=O)R_2$, $-OC(=O)R_2$, $-C(=O)N(R_2)_2$, $-OS(=O)_2R_2$, $-OS(=O)_2OR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-SO_3H$, and at least one amino acid fragment; wherein each R_6 cannot all be H;

R_7 is an amino protecting group;

R_8 is an optionally substituted C_1-C_6alkyl, an optionally substituted C_2-C_6alkenyl, an optionally substituted C_2-C_6alkynyl, or an optionally substituted C_3-C_6cycloalkyl; or a pharmaceutically acceptable salt or solvate thereof.

31. The compound of claim 30 wherein Y and Z together with the carbon atom to which they are attached form a C_3-C_{10}cycloalkyl or C_2-C_{10}heterocycloalkyl.

32. The compound of claim 31 wherein Y and Z together with the carbon atom to which they are attached form a C_2-C_{10}heterocycloalkyl.

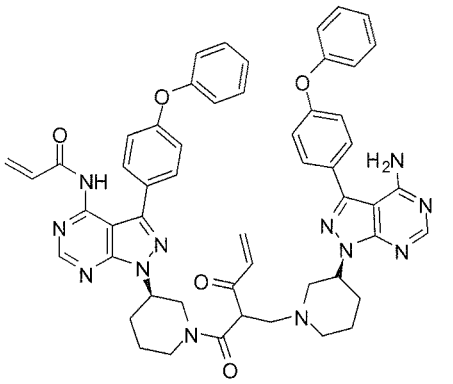
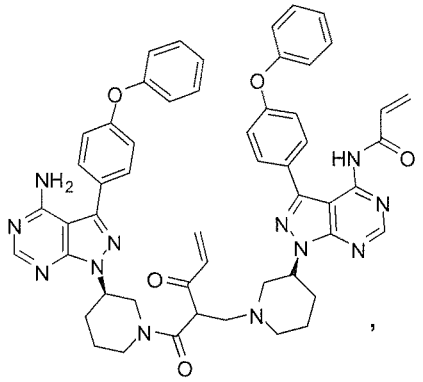
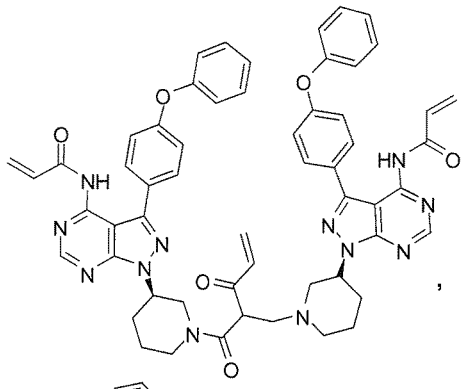
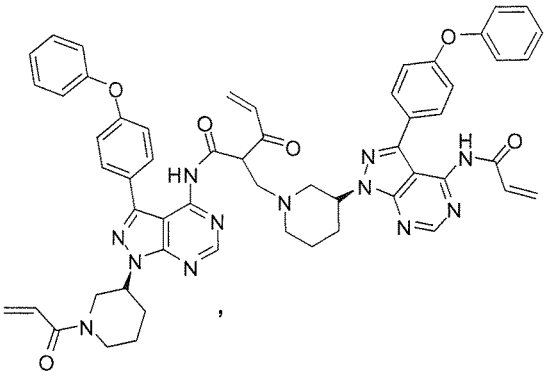
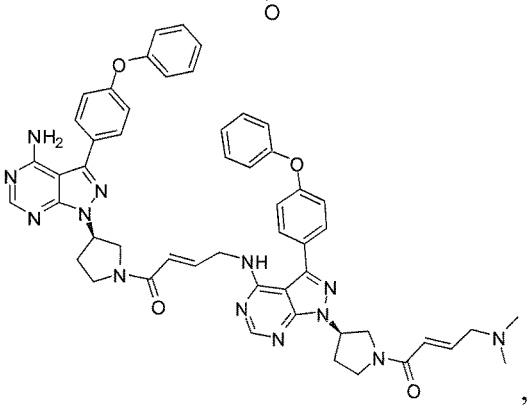
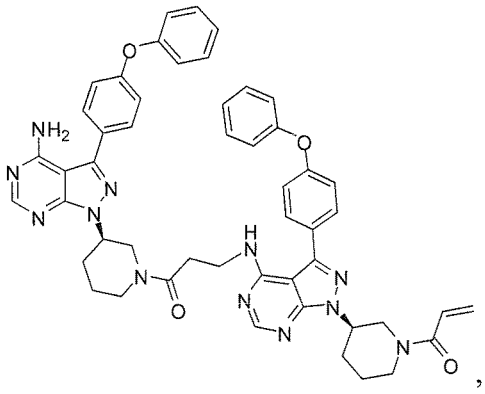
33. The compound of claim 32 wherein W is C(=O)J.

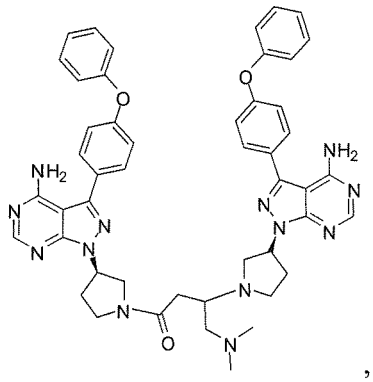
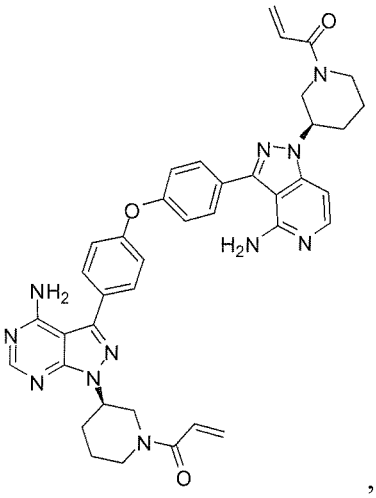
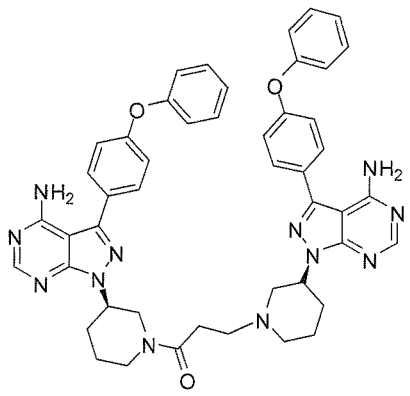
34. The compound of claim 33 wherein J is $-C_1$-C_6alkyl or $-C_2$-C_6alkene.

35. The compound of claim 34 wherein J is substituted with at least one R_1.

36. The compound of claim 35 wherein R_1 is selected from F, Cl, Br, I, -CN, $-NO_2$, $-SR_2$, $-OR_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, $-OC_1$-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, heteroaryl, or phenyl.

37. A compound selected from:


,

,

,

,

,

,


,

, and

; or a pharmaceutically acceptable salt or solvate thereof.

38. The compound of any one of claims 1-37 wherein the compound is isolated.

39. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any of claims 1-38, and a pharmaceutically acceptable excipient.