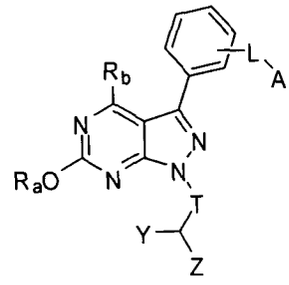
INHIBITORS OF BRUTON'S TYROSINE KINASE

ABSTRACT

Described herein are kinase inhibitor compounds, methods for synthesizing such inhibitors, and methods for using such inhibitors in the treatment of diseases. Further described herein are methods, assays and systems for determining an appropriate inhibitor of a protein, including a kinase.

We Claim:

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, $S(=O)_vO$-J;

X is F, Cl, Br, I, -CN, $-NO_2$, $-OR_3$, $-N(R_2)_2$, $-SR_2$, $-C_1$-C_6alkyl, $-C(=O)R_2$, $-OC(=O)R_2$, $-NR_2C(=O)R_2$, $-NR_2C(=O)N(R_2)_2$, $-C(=O)N(R_2)_2$, $-C(=NR_2)N(R_2)_2$, $-C(=N{-}OR_2)N(R_2)_2$, $-C(=S)R_2$, $-S(=O)_vR_2$, $-OS(=O)_vR_2$, $-NR_2C(=O)OR_2$, $-NR_2S(=O)_vR_2$;

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.

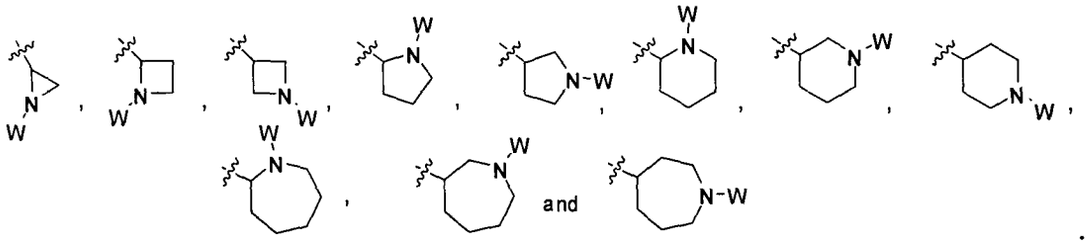
19. The compound of claim 15 wherein C_1-C_6alkyl is substituted with –NHC(=O)C_1-C_6alkyl.

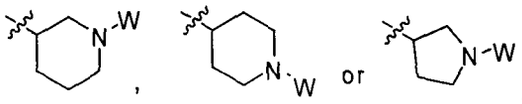
20. The compound of claim 19 wherein C_1-C_6alkyl is selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, or tert-butyl.

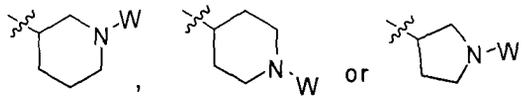
21. The compound of claim 17 wherein R_2 is C_1-C_6hydroxyalkyl.

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 $-S(=O)_2R_2$.

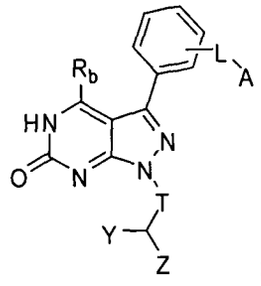
54. The compound of claim 53 wherein R_2 is C_1-C_6haloalkyl.

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.

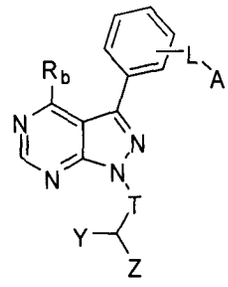
57. The pharmaceutically acceptable salt of claim 52 comprising at least one sulfate anion of the compound of claim 1 and at least one metal cation.

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 $C=N-OR_2$;

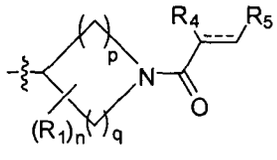
T is a bond, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

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

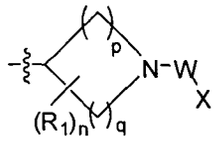
Y is C_1-C_6alkylene-CO_2H or C_2-C_6alkenylene-C(=O)H;

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

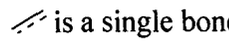
Y and Z together with the carbon atom to which they are attached form a



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;

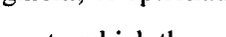
n is 0-4;

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;

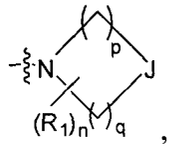
R_b is NH_2, OH, OSO_3H or $NHSO_3H$;

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, 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.

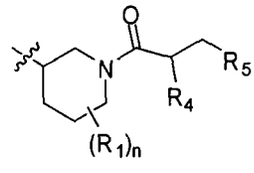
71. The compound of claim 70 wherein C_1-C_6alkylene is C_2H_5.

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 

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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.

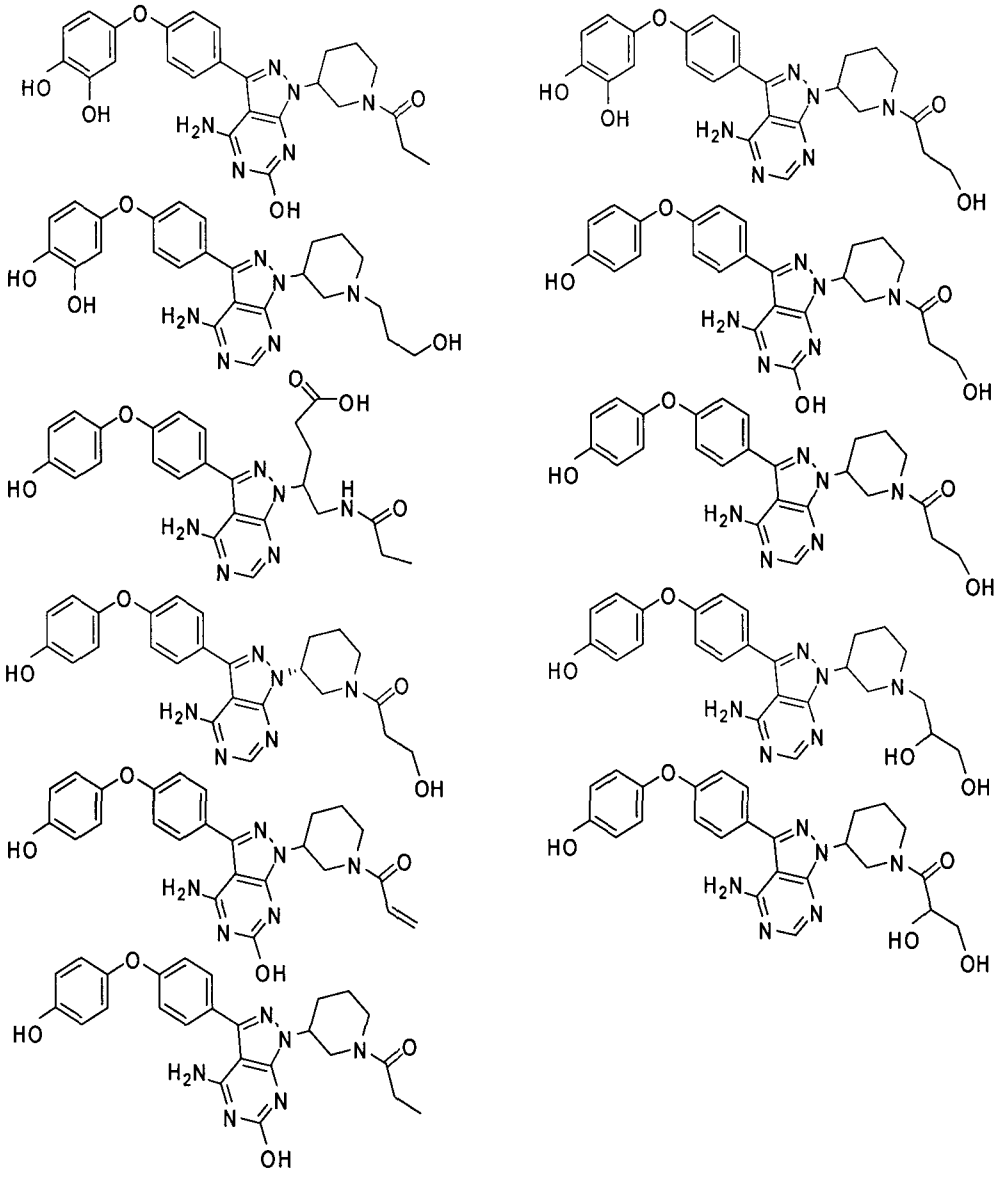
82. The compound of claim 81 wherein the at least one amino acid fragment is a cysteine or glutathione fragment.

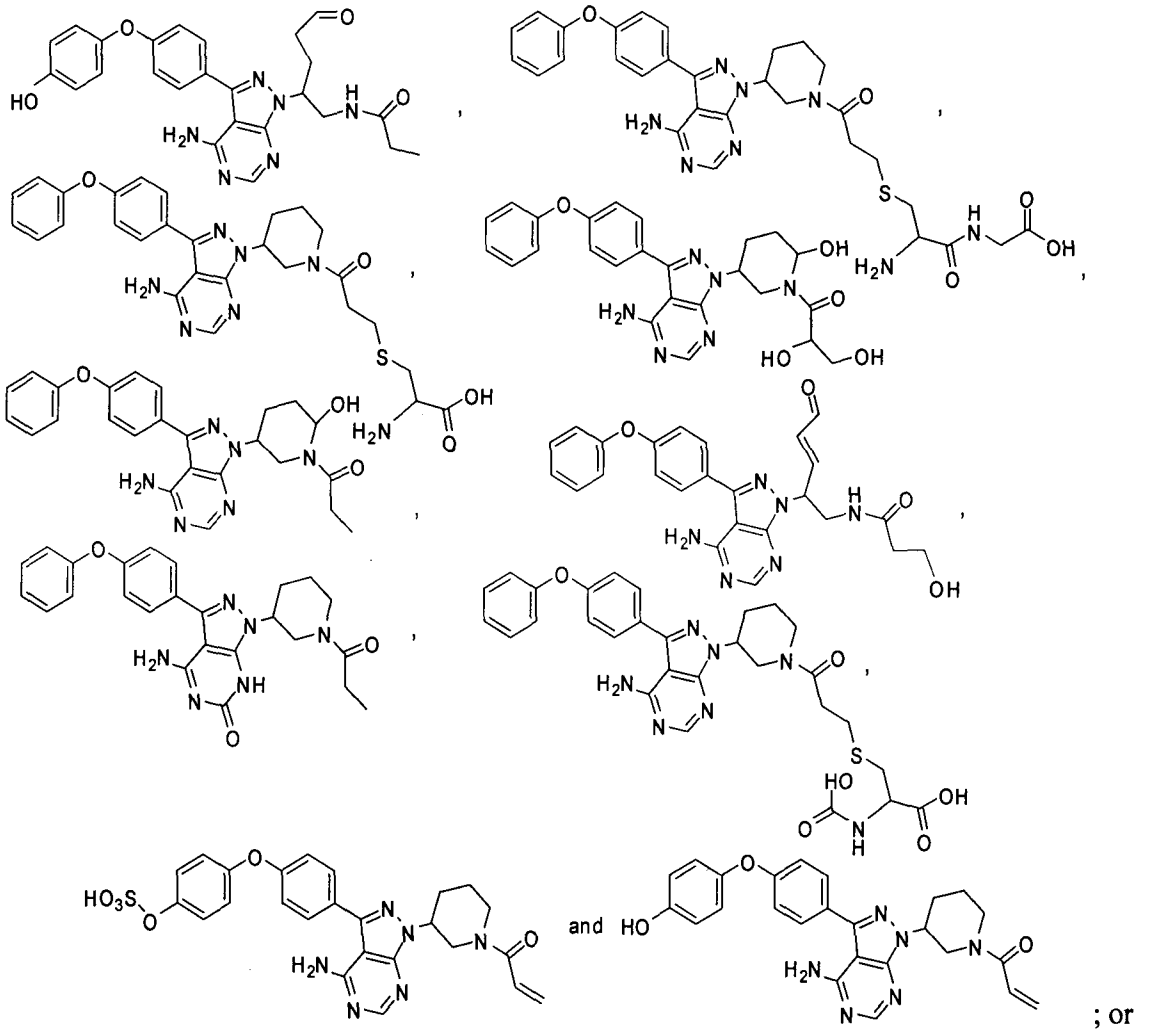
83. The compound of any of claims 76-82 wherein R_1 is selected from F, Cl, Br, I, -CN, -NO_2, -SR_2, -OR_3, and C_1-C_6alkyl.

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:

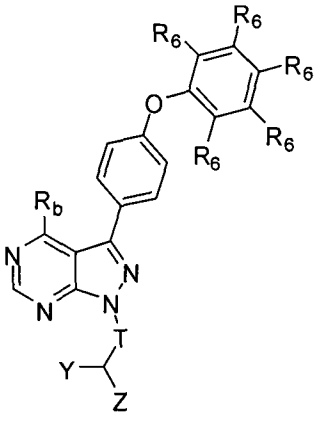




; or

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, $S(=O)_vO$-J;

X is F, Cl, Br, I, -CN, $-NO_2$, $-OR_3$, $-N(R_2)_2$, $-SR_2$, -C_1-C_6alkyl, $-C(=O)R_2$, $-OC(=O)R_2$, $-NR_2C(=O)R_5$, $-NR_2C(=O)N(R_2)_2$, $-C(=O)N(R_2)_2$, $-C(=NR_2)N(R_2)_2$, $-C(=N\text{-}OR_2)N(R_2)_2$, $-C(=S)R_2$, $-S(=O)_vR_2$, $-OS(=O)_vR_2$, $-NR_2C(=O)OR_2$, $-NR_2S(=O)_vR_2$;

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, $-NR_2S(=O)_2R_2$, $-S(=O)_2N(R_2)_2$, $-C(=O)CF_3$, $-C(=O)NR_2S(=O)_2R_2$, $-S(=O)_2NR_2C(=O)R_2$, $-N(R_2)_2$, 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, $-NR_2C(=O)R_2$, $-NR_2C(=O)R_8$, $-NR_2C(=O)N(R_2)_2$, $-CO_2R_2$, $-C(=O)R_2$, $-OC(=O)R_2$, -

$C(=O)N(R_2)_2$, $-OS(=O)_2R_2$, $-OS(=O)_2OR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$, $-SO_3H$, 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.

Dated this the 09th day of April 2012

NEHA CHUGH
PATENT AGENT

INHIBITORS OF BRUTON'S TYROSINE KINASE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/250,787, filed October 12, 2009; U.S. Application No. 12/581,044 filed October 16, 2009, now U.S. Patent No. 7,718,662; and U.S. Application No. 12/581,062, filed October 16, 2009, now U.S. Patent No. 7,741,330; which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] Described herein are kinase inhibitor compounds, methods for synthesizing such inhibitors, and methods for using such inhibitors in the treatment of diseases.

BACKGROUND OF THE INVENTION

[0003] A kinase, alternatively known as a phosphotransferase, is a type of enzyme that transfers phosphate groups from high-energy donor molecules, such as ATP, to specific target molecules; the process is termed phosphorylation. Protein kinases, which act on and modify the activity of specific proteins, are used to transmit signals and control complex processes in cells. Up to 518 different kinases have been identified in humans. Their enormous diversity and role in signaling makes them attractive targets for drug design.

[0004] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

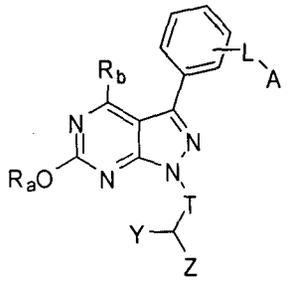
[0005] Btk is a key regulator of B-cell development, activation, signaling, and survival (Kurosaki, Curr Op Imm, 2000, 276-281; Schaeffer and Schwartzberg, Curr Op Imm 2000, 282-288). In addition, Btk plays a role in a number of other hematopoetic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF-.alpha. production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation. See, e.g., C. A. Jeffries, et al., (2003), Journal of Biological Chemistry

278:26258-26264; N. J. Horwood, et al., (2003), The Journal of Experimental Medicine 197:1603-1611; Iwaki et al. (2005), Journal of Biological Chemistry 280(48):40261-40270; Vassilev et al. (1999), Journal of Biological Chemistry 274(3):1646-1656, and Quek et al. (1998), Current Biology 8(20):1137-1140.

SUMMARY OF THE INVENTION

[0006] Described herein are inhibitors of Bruton's tyrosine kinase (Btk). Also described herein are irreversible inhibitors of Btk. Further described are irreversible inhibitors of Btk that form a covalent bond with a cysteine residue on Btk. Further described herein are irreversible inhibitors of other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with the irreversible inhibitor (such tyrosine kinases, are referred herein as "Btk tyrosine kinase cysteine homologs"). Yet further described herein are methods for synthesizing such inhibitors, methods for using such inhibitors in the treatment of diseases (including diseases wherein inhibition of Btk provides therapeutic benefit to a patient having the disease). Further described are pharmaceutical formulations that include an inhibitor of Btk.

[0007] In one aspect, provided herein are compounds of Formula (I) having the structure:



Formula (I);

wherein:

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

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 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 $NHSO_3$H;

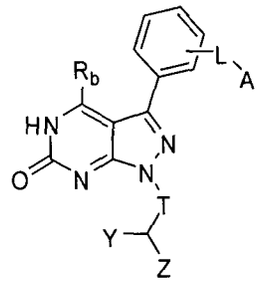
R_1 is selected from F, Cl, Br, I, -CN, -NO_2, -SR_2, -OR_3, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6hydroxyalkyl, -OC_1-C_6haloalkyl, C_1-C_6heteroalkyl, C_3-C_6cycloalkyl, C_2-C_6heterocycloalkyl, phenyl, -NR_2S(=O)$_2$$R_2$, -S(=O)$_2$N($R_2$)$_2$, -C(=O)$CF_3$, -C(=O)$NR_2$S(=O)$_2$$R_2$, -S(=O)$_2$$NR_2$C(=O)$R_2$, -N($R_2$)$_2$, wherein optionally the two R_2 groups of N(R_2)$_2$ and the nitrogen atom to which they are attached form a C_2-C_6 heterocycloalkyl ring, -NR_2C(=O)R_2, -NR_2C(=O)N(R_2)$_2$, -CO_2R_2, -C(=O)R_2, -OC(=O)R_2, -C(=O)N(R_2)$_2$, -OS(=O)$_2$$R_2$, -OS(=O)$_2$$OR_2$, -S(=O)$R_2$, -S(=O)$_2$$R_2$, -$SO_3$H, 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.

[0008] For any and all of the embodiments, substituents are optionally selected from among a subset of the listed alternatives.

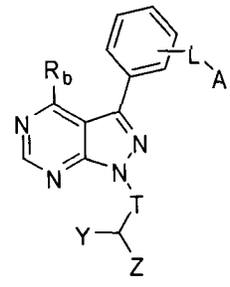
[0009] In one embodiment, the tautomeric form of the compound of Formula (I) has the structure of Formula (IA):



Formula (IA).

[0010] Any combination of the groups described above for the various variables is contemplated herein.

[0011] In another aspect is 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 $C{=}N\text{-}OR_2$;

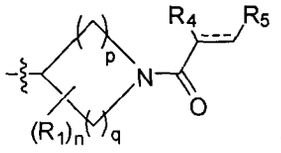
T is a bond, C_1-C_6alkylene, or C_3-C_6cycloalkylene;

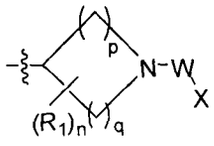
A is aryl or heteroaryl wherein aryl or heteroaryl is optionally substituted with at least one R_1;

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

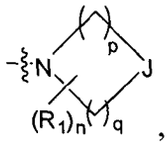
R_b is NH_2, OH, OSO_3H or $NHSO_3H$;

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, -$C(=O)R_2$, -$OC(=O)R_2$, -$C(=O)N(R_2)_2$, -$OS(=O)_2R_2$, -$OS(=O)_2OR_2$, -$S(=O)R_2$, -$S(=O)_2R_2$, 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, $-S(=O)_2N(R_2)_2$, $-C(=O)CF_3$, $-CO_2R_2$, $-C(=O)R_2$, $-C(=O)N(R_2)_2$, $-OS(=O)_2R_2$, $-OS(=O)_2OR_2$, $-S(=O)R_2$, $-S(=O)_2R_2$; or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

[0012] In one embodiment is a compound selected from: