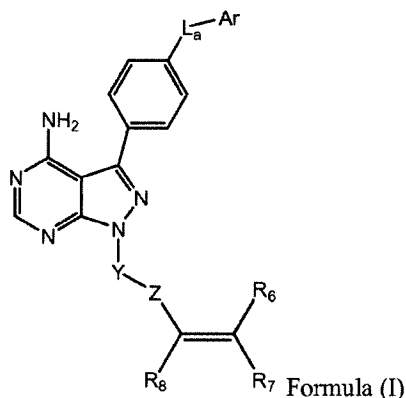


WHAT IS CLAIMED IS:

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



wherein:

5 L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; and either

- (i) Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, alkylenearylene, alkyleneheteroarylene, alkyleneheterocycloalkylene and alkyleneheterocycloalkylene;

10 Z is $C(=O)$, $NHC(=O)$, $NR^aC(=O)$, $NR^aS(=O)_x$, where x is 1 or 2, and R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

- (a) R_7 and R_8 are H;

R_6 is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, C_1 - C_8 alkylaminoalkyl, C_1 - C_8 hydroxyalkylaminoalkyl, C_1 - C_8 alkoxyalkylaminoalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_1 - C_8 alkyl C_3 - C_6 cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2 - C_8 heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1 - C_4 alkyl(aryl), C_1 - C_4 alkyl(heteroaryl), C_1 - C_8 alkylethers, C_1 - C_8 alkylamides, or C_1 - C_4 alkyl(C_2 - C_8 heterocycloalkyl);

- (b) R_6 and R_8 are H;

R_7 is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, C_1 - C_8 alkylaminoalkyl, C_1 - C_8 hydroxyalkylaminoalkyl, C_1 - C_8 alkoxyalkylaminoalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_1 - C_8 alkyl C_3 - C_6 cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2 - C_8 heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1 - C_4 alkyl(aryl), C_1 - C_4 alkyl(heteroaryl), C_1 - C_8 alkylethers, C_1 - C_8 alkylamides, or C_1 - C_4 alkyl(C_2 - C_8 heterocycloalkyl); or

- (c) R_7 and R_8 taken together form a bond;

R_6 is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, C_1 - C_8 alkylaminoalkyl, C_1 - C_8 hydroxyalkylaminoalkyl, C_1 - C_8 alkoxyalkylaminoalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted C_1 - C_8 alkyl C_3 - C_6 cycloalkyl, substituted or unsubstituted aryl, substituted or

unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl); or

(ii) Y is an optionally substituted group selected from cycloalkylene or heterocycloalkylene;

Z is C(=O), NHC(=O), NR^aC(=O), NR^aS(=O)_x, where x is 1 or 2, and R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

(a) R₇ and R₈ are H;

R₆ is substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl);

(b) R₆ and R₈ are H;

R₇ is substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl); or

(c) R₇ and R₈ taken together form a bond;

R₆ is substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl); and

pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

2. The compound of Claim 1, wherein L_a is O.
3. The compound of Claim 2, wherein Ar is phenyl.
4. The compound of Claim 3, wherein:
Z is C(=O), NHC(=O), or NCH₃C(=O).

5. The compound of any of claims 1-4, wherein

Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, alkylenearylene, alkyleneheteroarylene, alkyleneheterocycloalkylene and alkyleneheterocycloalkylene;

5 Z is C(=O), NHC(=O), NR^aC(=O), NR^aS(=O)_x, where x is 1 or 2, and R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either

(a) R₇ and R₈ are H;

10 R₆ is H, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl);

15 (b) R₆ and R₈ are H;

20 R₇ is H, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl); or

(c) R₇ and R₈ taken together form a bond;

25 R₆ is H, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

6. The compound of claim 5, wherein

R₇ and R₈ are H; and

35 R₆ is H, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

7. The compound of claim 6, wherein Y is alkyleneheterocycloalkylene.

8. The compound of claim 6, wherein:
R₆ is H, substituted or unsubstituted C₁-C₄alkyl, C₁-C₈alkylaminoalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl)
9. The compound of claim 5, wherein
5 R₆ and R₈ are H; and
R₇ is H, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or
10 unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).
10. The compound of claim 9, wherein Y is alkyleneheterocycloalkylene.
11. The compound of claim 9, wherein:
R₇ is H, substituted or unsubstituted C₁-C₄alkyl, C₁-C₈alkylaminoalkyl, substituted or unsubstituted
15 C₁-C₈alkylC₃-C₆cycloalkyl, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl)
12. The compound of claim 5, wherein
R₇ and R₈ taken together form a bond; and
R₆ is H, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or
20 unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).
13. The compound of claim 12, wherein Y is alkyleneheterocycloalkylene.
- 25 14. The compound of claim 12, wherein:
R₆ is H, substituted or unsubstituted C₁-C₄alkyl, C₁-C₈alkylaminoalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl)
15. The compound of any of claims 1-4, wherein
Y is an optionally substituted group selected from cycloalkylene or heterocycloalkylene;
30 Z is C(=O), NHC(=O), NR^aC(=O), NR^aS(=O)_x, where x is 1 or 2, and R^a is H, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl; and either
(a) R₇ and R₈ are H;
R₆ is substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or
35 unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl);
(b) R₆ and R₈ are H;

R₇ is substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl); or

(c) R₇ and R₈ taken together form a bond;

R₆ is substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

16. The compound of claim 15, wherein:

R₇ and R₈ are H; and

R₆ is substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

17. The compound of claim 16, wherein:

R₆ is substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

18. The compound of claim 15, wherein:

R₆ and R₈ are H; and

R₇ is substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

19. The compound of claim 18, wherein:

R₇ is substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

20. The compound of claim 15, wherein:

R₇ and R₈ taken together form a bond; and

R₆ is substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₈alkylethers, C₁-C₈alkylamides, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

21. The compound of claim 16, wherein:

R₆ is substituted or unsubstituted C₁-C₄alkyl, C₁-C₈alkylaminoalkyl, substituted or unsubstituted C₁-C₈alkylC₃-C₆cycloalkyl, or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

22. A compound selected from among:

- 5 (E)-4-(N-(2-hydroxyethyl)-N-methylamino)-1-(3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)but-2-en-1-one (Compound 3); (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-3-(1H-imidazol-4-yl)prop-2-en-1-one (Compound 4); (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)-4-morpholinobut-2-en-1-one (Compound 5); (E)-1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Compound 7); (E)-*N*-((1*s*,4*s*)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide (Compound 8); *N*-((1*r*,4*r*)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl)acrylamide (Compound 10); (E)-1-((*R*)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Compound 11); (E)-1-((*S*)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Compound 12); 1-((*R*)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)prop-2-en-1-one (Compound 13); 1-((*S*)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)prop-2-en-1-one (Compound 14); 1-((*R*)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)but-2-yn-1-one (Compound 15); 1-((*S*)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)but-2-yn-1-one (Compound 16); 1-((*R*)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)but-2-yn-1-one (Compound 17); (E)-*N*-((1*r*,4*r*)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide (Compound 18); *N*-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)-*N*-methylacrylamide (Compound 19); (E)-1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)-4-morpholinobut-2-en-1-one (Compound 20); (E)-1-((*S*)-2-((4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)methyl)pyrrolidin-1-yl)-4-morpholinobut-2-en-1-one (Compound 21); *N*-((1*s*,4*s*)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl)but-2-ynamide (Compound 22); *N*-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)ethyl)acrylamide (Compound 23); (E)-1-((*R*)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)-4-morpholinobut-2-en-1-one (Compound 24); (E)-*N*-((1*s*,4*s*)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-*d*]pyrimidin-1-yl)cyclohexyl)-4-morpholinobut-2-enamide (Compound 25).

23. A pharmaceutical formulation comprising a therapeutically effective amount of a compound of any of Claims 1-22, and a pharmaceutically acceptable excipient.

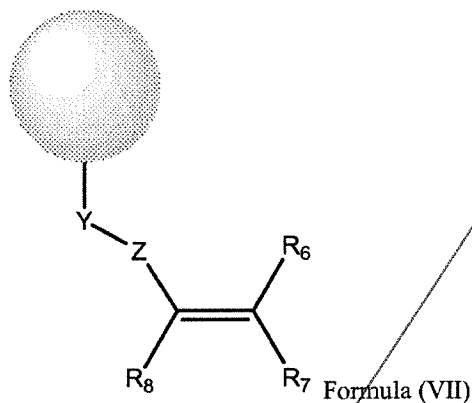
24. The pharmaceutical formulation of claim 23 that is formulated for a route of administration selected from oral administration, parenteral administration, buccal administration, nasal administration, topical administration, or rectal administration.

25. A method for treating an autoimmune disease or condition comprising administering to a patient in need the pharmaceutical formulation of claim 23.

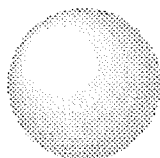
26. The method of Claim 25, wherein the autoimmune disease is selected from rheumatoid arthritis or lupus.

27. A method for treating a heteroimmune disease or condition comprising administering to a patient in need the pharmaceutical formulation of claim 23.
28. A method for treating a cancer comprising administering to a patient in need the pharmaceutical formulation of claim 23.
- 5 29. The method of claim 28, wherein the cancer is a B-cell proliferative disorder.
30. The method of claim 29, wherein the B-cell proliferative disorder is diffuse large B cell lymphoma, follicular lymphoma or chronic lymphocytic leukemia.
31. A method for treating mastocytosis comprising administering to a patient in need the pharmaceutical formulation of claim 23.
- 10 32. A method for treating osteoporosis or bone resorption disorders comprising administering to a patient in need the pharmaceutical formulation of claim 23.
33. A method for treating an inflammatory disease or condition comprising administering to a patient in need the pharmaceutical formulation of claim 23.
34. A method for treating lupus comprising administering to a subject in need thereof a composition
- 15 containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase or a Bruton's tyrosine kinase homolog.
35. A method for treating a heteroimmune disease or condition comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase or a Bruton's tyrosine kinase homolog.
- 20 36. A method for treating diffuse large B cell lymphoma, follicular lymphoma or chronic lymphocytic leukemia comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase or a Bruton's tyrosine kinase homolog.
37. A method for treating mastocytosis, comprising administering to a subject in need thereof a composition
- 25 containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase or a Bruton's tyrosine kinase homolog.
38. A method for treating osteoporosis or bone resorption disorders comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase or a Bruton's tyrosine kinase homolog.
- 30 39. A method for treating an inflammatory disease or condition comprising administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Bruton's tyrosine kinase or a Bruton's tyrosine kinase homolog.
40. A kinase inhibitor that selectively and irreversibly binds to a protein tyrosine kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog, in which the kinase inhibitor reversibly and non-selectively
- 35 binds to a multiplicity of protein tyrosine kinases, and further in which the plasma half life of the kinase inhibitor is less than about 4 hours.
41. The kinase inhibitor of claim 40 that selectively and irreversibly binds to at least one of Btk, Jak3, Blk, Bmx, Tec, and Itk.
42. The kinase inhibitor of claim 41 that selectively and irreversibly binds to Btk.
- 40 43. The kinase inhibitor of claim 41 that selectively and irreversibly binds to Jak3.

44. The kinase inhibitor of claim 41 that selectively and irreversibly binds to Tec.
 45. The kinase inhibitor of claim 41 that selectively and irreversibly binds to Btk and Tec.
 46. The kinase inhibitor of claim 41 that selectively and irreversibly binds to Blk.
 47. The kinase inhibitor of claim 40 that reversibly and non-selectively binds to a multiplicity of src-family
 5 protein kinase inhibitors.
 48. The kinase inhibitor of claim 40, in which the plasma half life of the kinase inhibitor is less than about 3
 hours.
 49. The kinase inhibitor of claim 40, having the structure of Formula (VII):



10 wherein:



is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

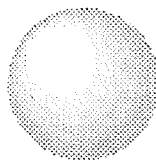
Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, heterocycloalkylene, cycloalkylene, alkylenearylene, alkyleneheteroarylene, alkylenecycloalkylene, and alkyleneheterocycloalkylene;

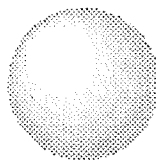
Z is C(=O), OC(=O), NHC(=O), NCH₂C(=O), C(=S), S(=O)_x, OS(=O)_x, NHS(=O)_x, where x is 1 or 2;

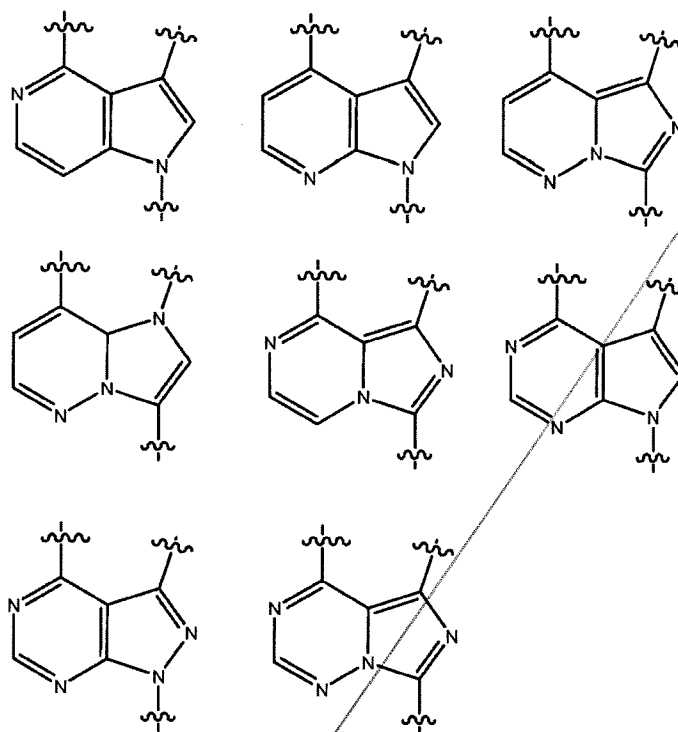
R₇ and R₈ are independently selected from among H, unsubstituted C₁-C₄ alkyl, substituted C₁-C₄ alkyl, unsubstituted C₁-C₄ heteroalkyl, substituted C₁-C₄ heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, unsubstituted C₂-C₆ heterocycloalkyl, and substituted C₂-C₆ heterocycloalkyl; or

R₇ and R₈ taken together form a bond;

R₆ is H, substituted or unsubstituted C₁-C₄ alkyl, substituted or unsubstituted C₁-C₄ heteroalkyl, C₁-C₆ alkoxyalkyl, C₁-C₈ alkylaminoalkyl, C₁-C₈ hydroxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₆ heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄ alkyl(aryl), C₁-C₄ alkyl(heteroaryl), C₁-C₄ alkyl(C₃-C₈ cycloalkyl), or C₁-C₄ alkyl(C₂-C₈ heterocycloalkyl); and
 pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.



50. The kinase inhibitor of Claim 49, wherein  is a substituted fused biaryl moiety selected from



51. The kinase inhibitor of Claim 49, wherein:

5 Z is C(=O), NHC(=O), NCH₃C(=O), or S(=O)₂.

52. The kinase inhibitor of Claim 49, wherein:

each of R₇ and R₈ is H; or

R₇ and R₈ taken together form a bond.

53. The kinase inhibitor of Claim 49, wherein:

10 R₆ is H, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₆alkoxyalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₄alkyl(C₃-C₈cycloalkyl), or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

54. The kinase inhibitor of Claim 49, wherein:

15 Y is a 4-, 5-, 6-, or 7-membered cycloalkylene ring; or

Y is a 4-, 5-, 6-, or 7-membered heterocycloalkylene ring; or

Y is a C₁-C₄ alkylene, or 4-, 5-, 6-, or 7-membered heterocycloalkylene ring.

55. A pharmaceutical formulation comprising the kinase inhibitor of any of claims 40-54 and a pharmaceutically acceptable excipient.

56. The pharmaceutical formulation of claim 55 that is formulated for a route of administration selected from oral administration, parenteral administration, buccal administration, nasal administration, topical administration, or rectal administration.

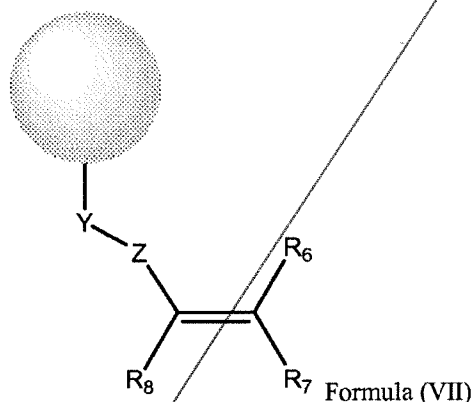
57. The pharmaceutical formulation of claim 56 that is formulated for oral administration.

58. A method for treating rheumatoid arthritis comprising administering to a subject the kinase inhibitor of claim 41 that selectively and irreversibly binds to Btk and Tec.

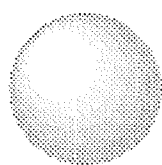
59. A method for increasing the selectivity of a test protein tyrosine kinase inhibitor that irreversibly and selectively binds to at least one protein kinase inhibitor selected from Btk, a Btk homolog, or a Btk kinase cysteine homolog, in which the test protein tyrosine kinase inhibitor is chemically modified to decrease the plasma half life to less than about 4 hours.

60. The method of claim 59, in which the test protein tyrosine kinase inhibitor is chemically modified to decrease the plasma half life to less than about 3 hours.

61. The method of claim 59 or claim 60, in which the test protein tyrosine kinase inhibitor has the structure of Formula (VII):



wherein:



is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, heterocycloalkylene, cycloalkylene, alkylenearylene, alkyleneheteroarylene, alkylenecycloalkylene, and alkyleneheterocycloalkylene;

Z is C(=O), OC(=O), NHC(=O), NCH₃C(=O), C(=S), S(=O)_x, OS(=O)_x, NHS(=O)_x, where x is 1 or 2;

R₇ and R₈ are independently selected from among H, unsubstituted C₁-C₄ alkyl, substituted C₁-C₄ alkyl, unsubstituted C₁-C₄ heteroalkyl, substituted C₁-C₄ heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, unsubstituted C₂-C₆ heterocycloalkyl, and substituted C₂-C₆ heterocycloalkyl; or

R₇ and R₈ taken together form a bond; and

R₆ is H, substituted or unsubstituted C₁-C₄alkyl, substituted or unsubstituted C₁-C₄heteroalkyl, C₁-C₆alkoxyalkyl, C₁-C₈alkylaminoalkyl, C₁-C₈hydroxyalkylaminoalkyl, C₁-C₈alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₄alkyl(C₃-C₈cycloalkyl), or C₁-C₄alkyl(C₂-C₈heterocycloalkyl).

62. The method of claim 59, in which the test protein tyrosine kinase inhibitor non-selectively and reversibly binds to a multiplicity of src-family protein tyrosine kinases.

63. A method for treating a B-cell proliferative disorder or a mast cell proliferative disorder comprising administering to a patient in need the pharmaceutical composition of claim 55.

64. A method for treating a rheumatoid arthritis or condition comprising administering to a patient in need the pharmaceutical composition of claim 55.

65. A method for treating a disease characterized by hyperactive B cells comprising administering to a patient in need the pharmaceutical composition of claim 55.

66. A method for treating a disease characterized by hyperactive mast cells comprising administering to a patient in need the pharmaceutical composition of claim 55.

67. A method for treating a disease characterized by both hyperactive B cells and hyperactive mast cells comprising administering to a patient in need the pharmaceutical composition of claim 55.

68. The methods of any of claims 63 to 67, in which the pharmaceutical composition is administered once a day.

69. A method of identifying an irreversible inhibitor of a kinase selected from Btk, a Btk homolog, or a Btk kinase cysteine homolog comprising:

(1) contacting a multiplicity of kinases selected from Btk, a Btk homolog, or a Btk kinase cysteine homolog with a compound that comprises a Michael acceptor moiety;

(2) contacting at least one non-kinase molecule having at least one accessible SH group with the compound that comprises a Michael acceptor moiety; and

(3) determining the covalent binding of the compound that comprises a Michael acceptor with the multiplicity of kinases and the at least one non-kinase molecule; and repeating steps (1), (2), and (3) for at least one other compound that comprises a Michael acceptor moiety.

70. The method of claim 69, further comprising

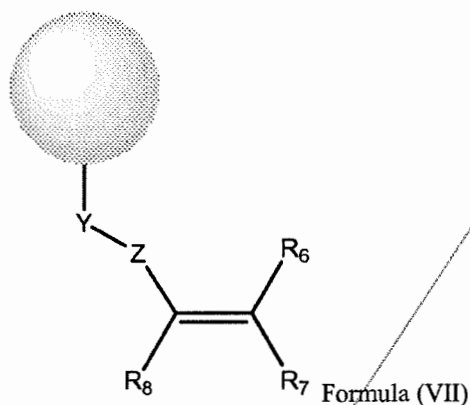
(4) comparing the covalent binding of the compound that comprises a Michael acceptor with the multiplicity of kinases and the at least one non-kinase molecule; and repeating steps (1), (2), (3) and (4) for at least one other compound that comprises a Michael acceptor moiety.

71. The method of claim 69, wherein the at least one non-kinase molecule having at least one accessible SH group includes glutathione and/or hemoglobin.

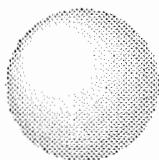
72. The method of claim 71, wherein a desired irreversible inhibitor is selective for a particular kinase relative to other kinases, glutathione and hemoglobin.

73. The method of claim 69, further comprising contacting each kinase with an Activity Probe.

74. The method of claim 69, wherein steps (1) and (2) are conducted in vivo and step (3) is conducted in part using an Activity Probe.
75. The method of claim 69, wherein the determining step uses mass spectrometry.
76. The method of claim 69, wherein the determining step uses fluorescence.
- 5 77. The method of claim 70, wherein the compound further comprises an active site binding moiety.
78. The method of claim 77, wherein the compound further comprises a linker moiety that links the Michael acceptor moiety to the active site binding moiety.
79. The method of claim 69, wherein the at least one compound has the structure of Formula (VII):



10 wherein:



is a moiety that binds to the active site of a kinase, including a tyrosine kinase, further including a Btk kinase cysteine homolog;

Y is an optionally substituted group selected from among alkylene, heteroalkylene, arylene, heteroarylene, heterocycloalkylene, cycloalkylene, alkylenearylene, alkyleneheteroarylene, alkylenecycloalkylene, and alkyleneheterocycloalkylene;

Z is C(=O), OC(=O), NHC(=O), NHC(=O), C(=S), S(=O)_x, OS(=O)_x, NHS(=O)_x, where x is 1 or 2;

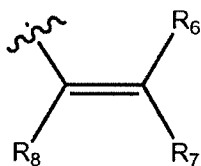
R₇ and R₈ are independently selected from among H, unsubstituted C₁-C₄ alkyl, substituted C₁-C₄ alkyl, unsubstituted C₁-C₄ heteroalkyl, substituted C₁-C₄ heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, substituted C₃-C₆ cycloalkyl, unsubstituted C₂-C₆ heterocycloalkyl, and substituted C₂-C₆ heterocycloalkyl; or

R₇ and R₈ taken together form a bond; and

R₆ is H, substituted or unsubstituted C₁-C₄ alkyl, substituted or unsubstituted C₁-C₄ heteroalkyl, C₁-C₆ alkoxyalkyl, C₁-C₈ alkylaminoalkyl, C₁-C₈ hydroxyalkylaminoalkyl, C₁-C₈ alkoxyalkylaminoalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C₂-C₈ heterocycloalkyl, substituted or unsubstituted heteroaryl, C₁-C₄ alkyl(aryl), C₁-C₄ alkyl(heteroaryl), C₁-C₄ alkyl(C₃-C₈ cycloalkyl), or C₁-C₄ alkyl(C₂-C₈ heterocycloalkyl).

80. The method of claim 78, further comprising analyzing the structure-function activity relationship between the structure of the linker moiety and/or the Michael acceptor moiety of each compound, and the binding and/or selectivity of each compound to at least one kinase.

81. The method of claim 79, further comprising analyzing the structure-function activity relationship



5 between the structure of Y-Z and/or of each compound, and the binding and/or selectivity of each compound to at least one kinase.

82. The method of claim 80, wherein the structure of the active site binding moiety of each compound is not varied.

83. The method of claim 79, wherein the structure of of each compound is not varied.

10 84. An assay comprising the method of any of claims 70 to 83.

85. A system comprising the assay of claim 80 or any method of claims 70 to 63.

86. An irreversible inhibitor of a kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog, wherein the inhibitor is identified using any method of claims 70 to 83, the assay of claim 84, or the system of claim 85.

15 87. The irreversible inhibitor of claim 86, wherein the inhibitor is selective for one kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog over at least one other kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog.

88. The irreversible inhibitor of claim 87, wherein the inhibitor is at least 5 times more selective for one kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog over at least one other kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog.

20 89. The irreversible inhibitor of claim 88, wherein the inhibitor is at least 50 times more selective for one kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog over at least one other kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog.

90. The irreversible inhibitor of claim 86, wherein the inhibitor is selective for at least one kinase selected from Btk, a Btk homolog, and a Btk kinase cysteine homolog over at least one other non-kinase molecule having an accessible SH group.

25 91. A pharmaceutical composition comprising the compound of any of claim 86, 87, or 88.

92. A method for improving the kinase selectivity of an inhibitor comprising use of the methods of claims 70 to 83.

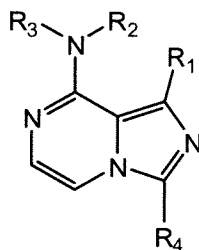
30 93. A method for treating an autoimmune disease or condition comprising administering to a patient in need a composition containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Btk or a Btk homolog.

94. The method of Claim 91, wherein the autoimmune disease is selected from rheumatoid arthritis or lupus.

95. A method for treating a B-cell proliferative disorder comprising administering to a patient in need a composition containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Blk or a Blk homolog.
96. The method of claim 93, wherein the B-cell proliferative disorder is diffuse large B cell lymphoma, follicular lymphoma or chronic lymphocytic leukemia.
97. A method for treating an inflammatory disease or condition comprising administering to a patient in need a composition containing a therapeutically effective amount of a compound that forms a covalent bond with a cysteine sidechain of a Blk or a Blk homolog.
98. A method for identifying biomarkers suitable for determining patient response to a compound of Formula (I) comprising administering to a test subject a composition containing an amount of compound of Formula (I) sufficient to inhibit B cell receptor signaling and correlating B cell receptor signaling with apoptosis.
99. A method for selecting a patient for treatment for lymphoma with a compound of Formula (I) comprising measuring pErk levels or Erk transcriptional target levels in a patient sample, correlating a high level of pERK or ERK transcriptional target levels with a positive response to the treatment, and selecting or excluding the patient for treatment based on the pErk level or Erk transcriptional target levels.
100. A method for measuring a patient's response to treatment comprising administering to the patient a compound of Formula (I), measuring pErk levels or Erk transcriptional target levels in a patient sample, correlating a reduced level of pERK or Erk transcriptional targets with a positive response to the administration of the compound of Formula (I), and continuing or stopping treatment of the patient with the compound based on the pErk levels or the Erk transcriptional target levels.

CLAIMS

1. A compound of Formula (A5) having the structure:



Formula (A5),

5 wherein:

 R₁ is H, L₂-(substituted or unsubstituted alkyl), L₂-(substituted or unsubstituted cycloalkyl), L₂-(substituted or unsubstituted alkenyl), L₂-(substituted or unsubstituted cycloalkenyl), L₂-(substituted or unsubstituted heterocycle), L₂-(substituted or unsubstituted heteroaryl), or L₂-(substituted or unsubstituted aryl), where L₂ is a bond, O, S, -S(=O), -S(=O)₂, C(=O), -(substituted or unsubstituted C₁-C₆ alkyl), or -(substituted or unsubstituted C₂-C₆ alkenyl);

 R₂ and R₃ are independently selected from H, lower alkyl and substituted lower alkyl;

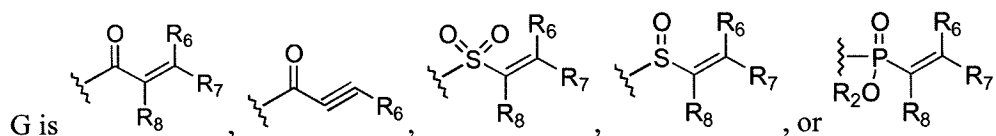
 R₄ is L₃-X-L₄-G, wherein,

 L₃ is optional, and when present is a bond, optionally substituted or unsubstituted alkyl, optionally substituted or unsubstituted cycloalkyl, optionally substituted or unsubstituted alkenyl, optionally substituted or unsubstituted alkynyl;

 X is optional, and when present is a bond, O, -C(=O), S, -S(=O), -S(=O)₂, -NH, -NR₉, -NHC(O), -C(O)NH, -NR₉C(O), -C(O)NR₉, -S(=O)₂NH, -NHS(=O)₂, -S(=O)₂NR₉, -NR₉S(=O)₂, -OC(O)NH-, -NHC(O)O-, -OC(O)NR₉-, -NR₉C(O)O-, -CH=NO-, -ON=CH-, -NR₁₀C(O)NR₁₀-, heteroaryl, aryl, -NR₁₀C(=NR₁₁)NR₁₀-, -NR₁₀C(=NR₁₁)-, -C(=NR₁₁)NR₁₀-, -OC(=NR₁₁)-, or -C(=NR₁₁)O-;

 L₄ is optional, and when present is a bond, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycle;

 or L₃, X and L₄ taken together form a nitrogen containing heterocyclic ring;



wherein,

R₆, R₇ and R₈ are independently selected from among H, lower alkyl or substituted lower alkyl, lower heteroalkyl or substituted lower heteroalkyl, substituted or unsubstituted lower cycloalkyl, and substituted or unsubstituted lower heterocycloalkyl;

R₅ is H, halogen, -L₆-(substituted or unsubstituted C₁-C₃ alkyl), -L₆-(substituted or unsubstituted C₂-C₄ alkenyl), -L₆-(substituted or unsubstituted heteroaryl), or -L₆-(substituted or unsubstituted aryl), wherein L₆ is a bond, O, S, -S(=O), S(=O)₂, NH, C(O), -NHC(O)O, -OC(O)NH, -NHC(O), or -C(O)NH;

each R₉ is independently selected from among H, substituted or unsubstituted lower alkyl, and substituted or unsubstituted lower cycloalkyl;

each R₁₀ is independently H, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower cycloalkyl; or

two R₁₀ groups can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or

R₉ and R₁₀ can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or

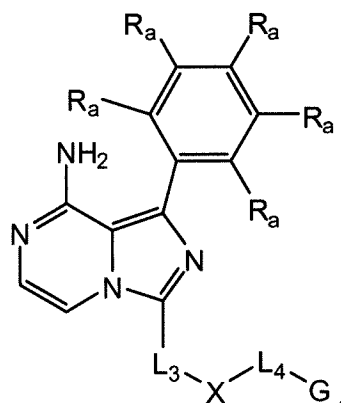
each R₁₁ is independently selected from H, -S(=O)₂R₈, -S(=O)₂NH₂, -C(O)R₈, -CN, -NO₂, heteroaryl, or heteroalkyl; or

pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein R₂ and R₃ are H.

3. The compound of claim 2, wherein R₁ is L₂-(substituted or unsubstituted heteroaryl), or L₂-(substituted or unsubstituted aryl).

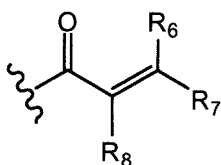
4. The compound of claim 3 having the structure



wherein each R_a is independently H, halogen, $-CF_3$, $-CN$, $-NO_2$, OH, NH_2 , $-L_a$ -(substituted or unsubstituted alkyl), or $-L_a$ -(substituted or unsubstituted alkenyl), wherein L_a is a bond, O, S, $-S(=O)$, $-S(=O)_2$, NH, C(O), CH_2 , $-NHC(O)O$, $-NHC(O)$, or $-C(O)NH$.

5. The compound of claim 4, wherein L_3 , X and L_4 taken together form a nitrogen containing heterocyclic ring.

6. The compound of claim 5, wherein G is



7. The compound of claim 6, wherein R_6 , R_7 , and R_8 are H.

8. The compound of claim 6, wherein

R_7 and R_8 are H; and

R_6 is selected from lower alkyl or substituted lower alkyl, lower heteroalkyl or substituted lower heteroalkyl, substituted or unsubstituted lower cycloalkyl, and substituted or unsubstituted lower heterocycloalkyl.

9. The compound of claim 8, wherein R_6 is substituted lower alkyl.

10. The compound of claim 9, wherein lower alkyl is substituted with a disubstituted amino group.

11. The compound of claim 6, wherein

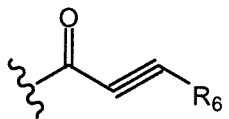
R_6 and R_8 are H; and

R_7 is selected from lower alkyl or substituted lower alkyl, lower heteroalkyl or substituted lower heteroalkyl, substituted or unsubstituted lower cycloalkyl, and substituted or unsubstituted lower heterocycloalkyl.

12. The compound of claim 11, wherein R_7 is substituted lower alkyl.

13. The compound of claim 12, wherein lower alkyl is substituted with a disubstituted amino group.

14. The compound of claim 5, wherein G is



15. The compound of claim 14, wherein R_6 is H.

16. The compound of claim 14, wherein R_6 is selected from lower alkyl or substituted lower alkyl, lower heteroalkyl or substituted lower heteroalkyl, substituted or unsubstituted lower cycloalkyl, and substituted or unsubstituted lower heterocycloalkyl.
17. The compound of claim 16, wherein R_6 is substituted lower alkyl.
- 5 18. The compound of claim 17, wherein lower alkyl is substituted with a disubstituted amino group.
19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, and a pharmaceutically acceptable excipient.
20. The pharmaceutical composition of claim 19 that is formulated for a route of administration
10 selected from oral administration, parenteral administration, buccal administration, nasal administration, topical administration, or rectal administration.