ORIGINAL

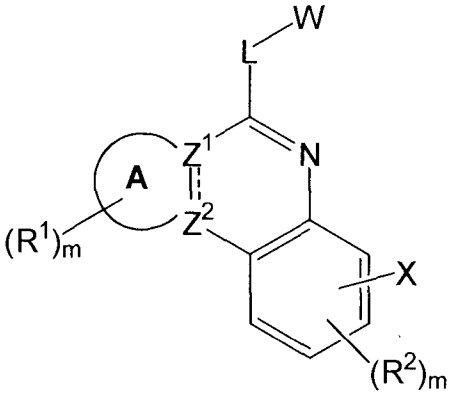
ABSTRACT

NOVEL TRICYCLIC PROTEIN KINASE MODULATORS

The invention provides compounds that inhibit CK2 and/or Pim kinases and compositions containing such compounds. These tricyclic compounds and compositions containing them are useful for treating proliferative disorders such as cancer, as well as other kinase-associated conditions including inflammation, pain, pathogenic infections, and certain immunological disorders.

I/WE CLAIM:

1. A compound having a structure of Formula I:



(I)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

L is a linker selected from a bond, NR^3, O, S, CR^4R^5, CR^4R^5-NR^3, CR^4R^5-O-, and CR^4R^5-S;

each R^1, R^2, R^3, R^4 and R^5 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group,

or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3-8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected

from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R', $SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3-7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3-8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

and R^4 and R^5, when on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3 to 8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

and each m is independently 0, 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

2. The compound of claim 1, wherein L is NH or NMe.

3. The compound of claim 1 or 2, wherein W is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl.

4. The compound of claim 1, 2 or 3, wherein Z^1 and Z^2 are C and ----- represents a double bond.

5. The compound of claim 1, 2 or 3, wherein Z^1 is N, Z^2 is C and ----- represents a single bond.

6. The compound of claim 1, 2 or 3, wherein Z^1 is C, Z^2 is N and ----- represents a single bond.

7. The compound of any one of claims 1 to 6, wherein W is optionally substituted phenyl, optionally substituted heterocyclyl, or C1-C4 alkyl substituted with at least one member selected from the group consisting of optionally substituted phenyl, optionally substituted heteroalkyl, optionally substituted heteroaryl, halo, hydroxy and $-NR"_2$,

where each R" is independently H or optionally substituted C1-C6 alkyl;

and two R" taken together with the N to which they are attached can be linked together to form an optionally substituted 3 to 8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

8. The compound of claim 7, wherein L is NH or NMe.

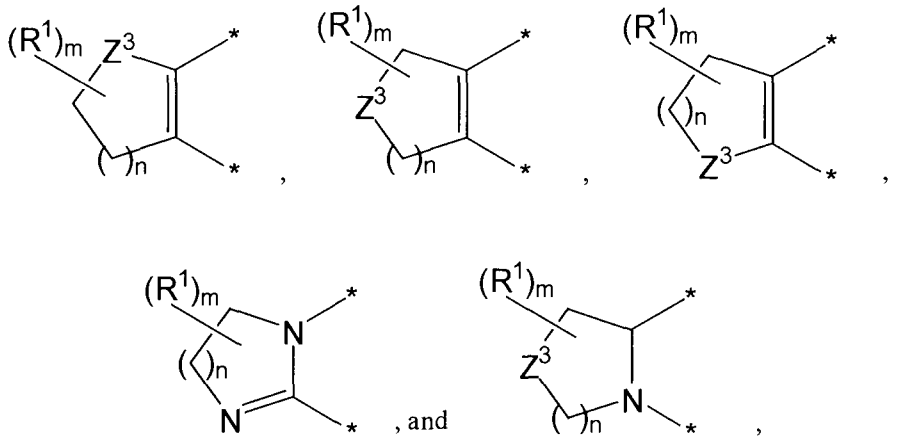
9. The compound of claim 7 or 8, wherein W comprises at least one group of the formula $-(CH_2)_p-NR^x_2$,

where p is 1, 2, 3, or 4,

R^x is independently at each occurrence H or optionally substituted alkyl;

and two R^x taken together with the N to which they are attached can be linked together to form an optionally substituted 3 to 8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

10. The compound of any one of claims 1 to 9, wherein A is selected from the group consisting of:

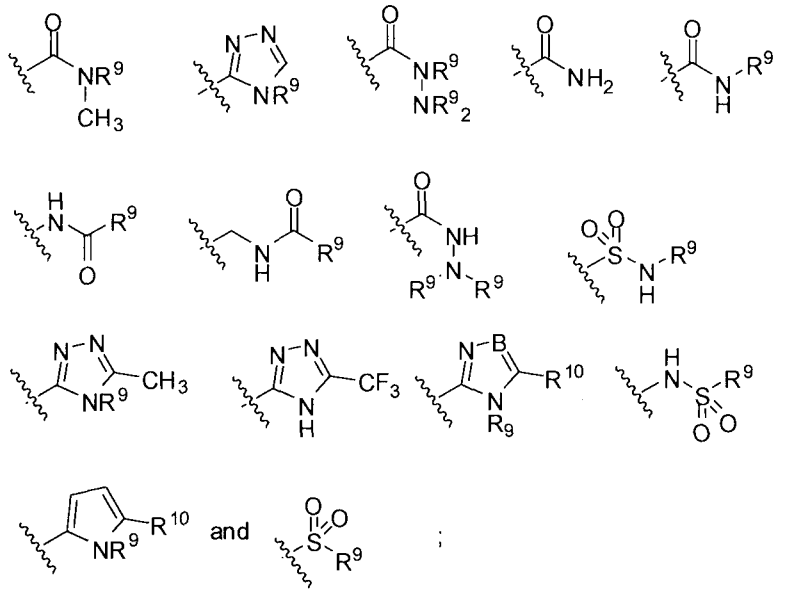


wherein Z^3 is CR^1_2, NR^1, $S(=O)_p$, or O;

n is 1, 2, or 3; and

p is 0,1, or 2.

11. The compound of any one of claims 1 to 10, wherein X is selected from the group consisting of $COOR^9$, $C(O)NR^9$-OR^9, triazole, tetrazole, CN, imidazole, carboxylate, a carboxylate bioisostere,



wherein each R^9 is independently H or an optionally substituted member selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, and heteroarylalkyl,

and two R^9 on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

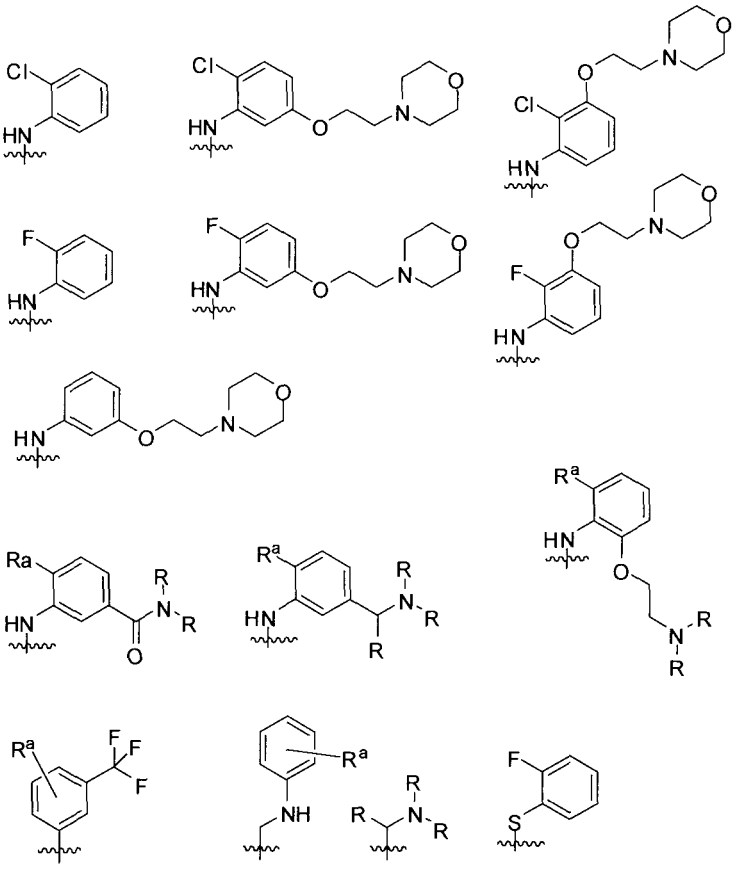
R^{10} is halo, CF_3, CN, SR, OR, NR_2, or R, where each R is independently H or optionally substituted C1-C6 alkyl, and two R on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

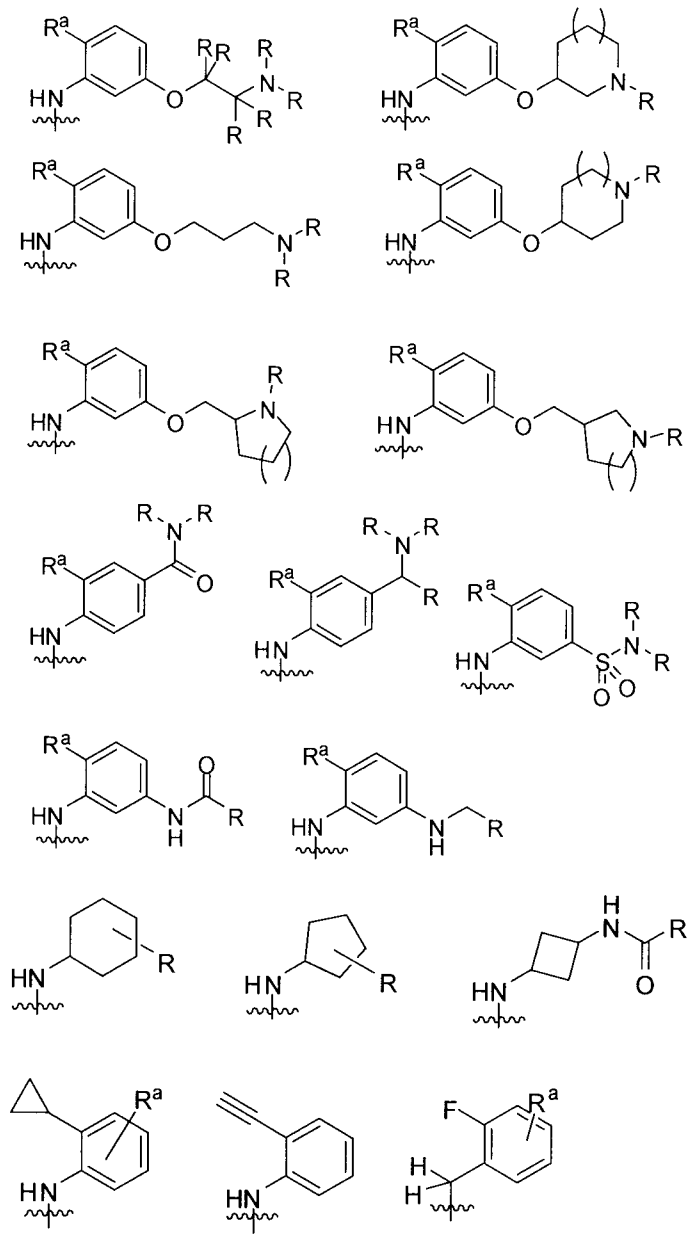
and B is N or CR^{10}.

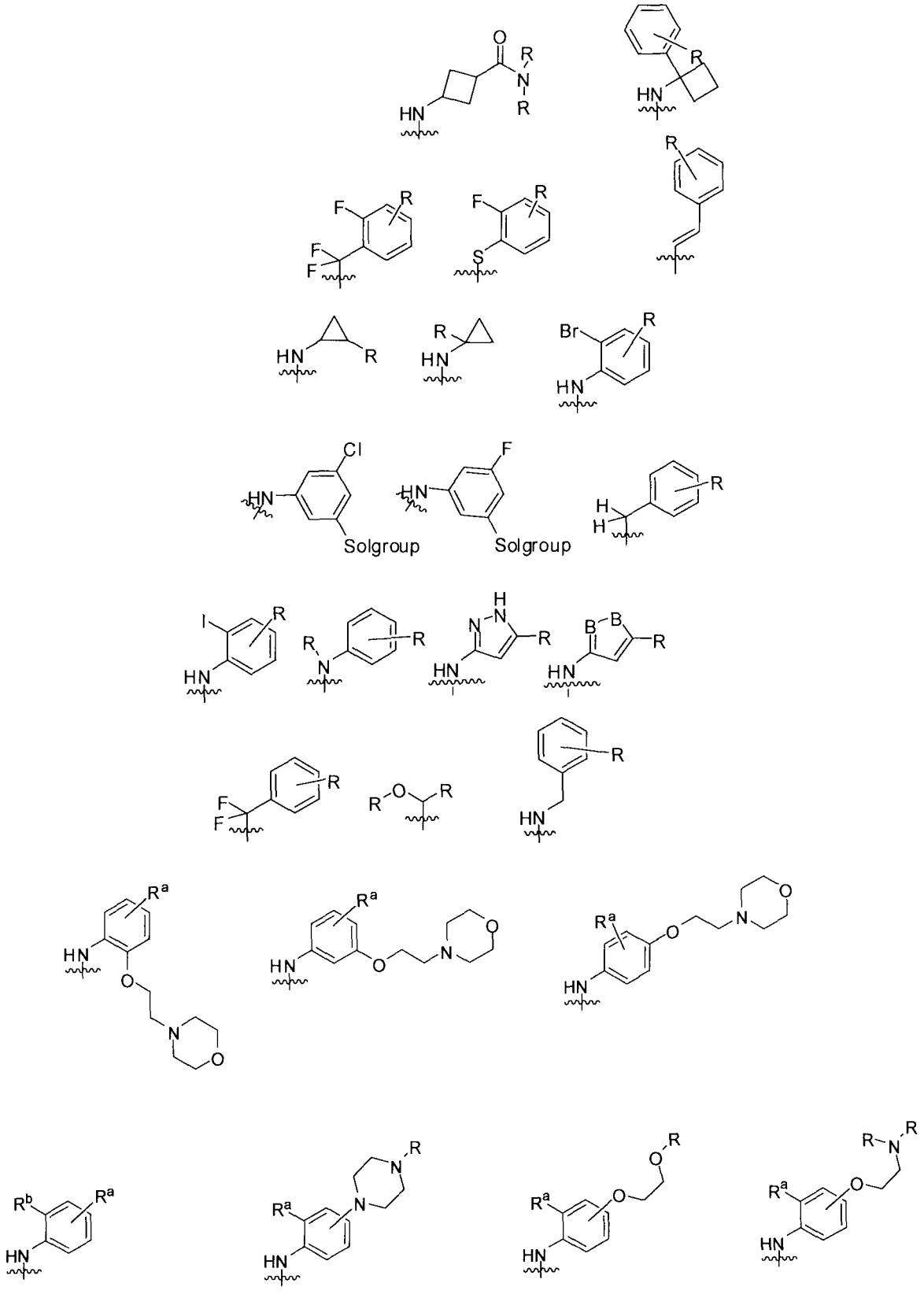
12. The compound of claim 11, wherein the polar substituent X is located at position 3 on the phenyl ring.

13. The compound of claim 11, wherein the polar substituent X is located at position 4 on the phenyl ring.

14. The compound of any one of claims 1 to 13, wherein –L-W is selected from:







wherein each R^a is independently H, Cl or F;

each R^b is independently Me, F, or Cl;

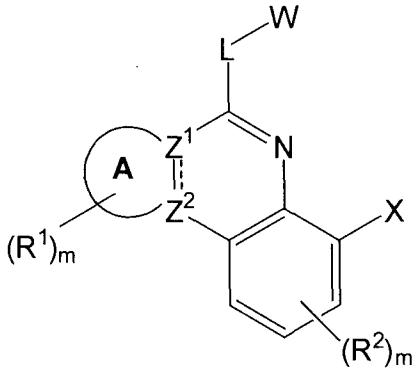
each R is independently selected from H, halo, C1-C4 alkyl, C1-C4 alkoxy, and C1-C4 haloalkyl,

and two R groups on the same or adjacent connected atoms can optionally be linked together to form a 3 to 8 membered ring;

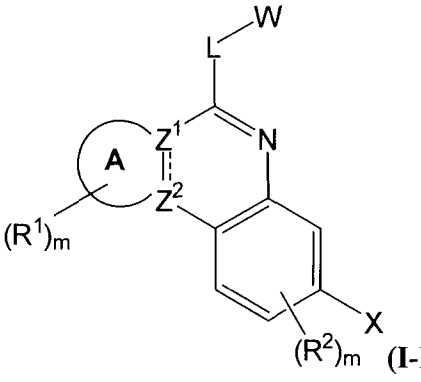
each B is N or CR;

and each Solgroup is a solubility-enhancing group.

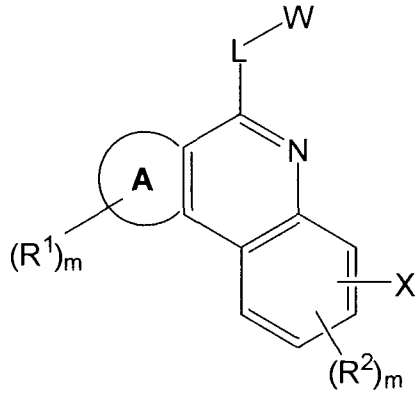
15. The compound of claim 1, having the Formula I-A, I-B, I-C, I-D or I-E:



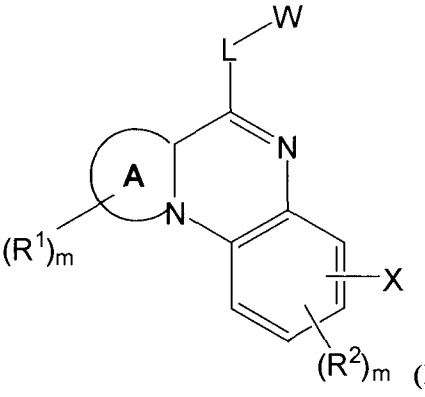
(I-A),



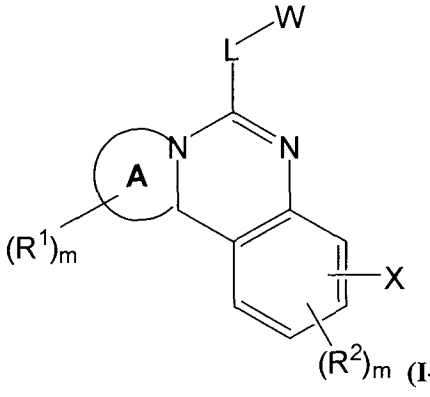
(I-B)



(I-C),



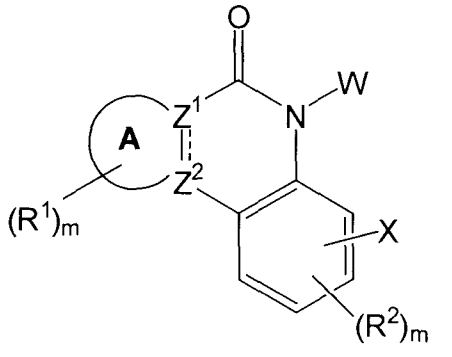
(I-D), or



(I-E),

or a pharmaceutically acceptable salt thereof.

16. A compound having a structure of Formula II:



(II)

wherein:

A is a saturated or partially saturated optionally substituted 5, 6 or 7 membered ring;

----- represents a single bond or a double bond;

Z^1 and Z^2 are independently N or C when ----- represents a single bond, provided Z^1 and Z^2 are not both N; and

Z^1 and Z^2 are C when ----- represents a double bond;

each of R^1 and R^2 is independently H, or an optionally substituted member selected from the group consisting of C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C12 heteroaryl, C7-C12 arylalkyl, and C6-C12 heteroarylalkyl group,

or halo, OR, NR_2, NROR, $NRNR_2$, SR, SOR, SO_2R, SO_2NR_2, $NRSO_2R$, $NRCONR_2$, $NRCSNR_2$, $NRC(=NR)NR_2$, NRCOOR, NRCOR, CN, COOR, $CONR_2$, OOCR, COR, or NO_2,

wherein each R is independently H or C1-C8 alkyl, C2-C8 heteroalkyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-C12 arylalkyl, or C6-C12 heteroarylalkyl,

and wherein two R on the same atom or on adjacent atoms can be linked to form a 3 to 8 membered ring, optionally containing one or more N, O or S;

and each R group, and each ring formed by linking two R groups together, is optionally substituted with one or more substituents selected from halo, =O, =N-CN, =N-OR', =NR', OR', NR'_2, SR', SO_2R',

$SO_2NR'_2$, $NR'SO_2R'$, $NR'CONR'_2$, $NR'CSNR'_2$, $NR'C(=NR')NR'_2$, NR'COOR', NR'COR', CN, COOR', $CONR'_2$, OOCR', COR', and NO_2,

wherein each R' is independently H, C1-C6 alkyl, C2-C6 heteroalkyl, C1-C6 acyl, C2-C6 heteroacyl, C6-C10 aryl, C5-C10 heteroaryl, C7-12 arylalkyl, or C6-12 heteroarylalkyl, each of which is optionally substituted with one or more groups selected from halo, C1-C4 alkyl, C1-C4 heteroalkyl, C1-C6 acyl, C1-C6 heteroacyl, hydroxy, amino, and =O;

and wherein two R' on the same atom or on adjacent atoms can be linked to form a 3 to 7 membered ring optionally containing up to three heteroatoms selected from N, O and S;

and R^1 can be =O, or two R^1 groups on the same atom or on adjacent connected atoms, can optionally be linked together to form a 3 to 8 membered cycloalkyl or heterocycloalkyl, which is optionally substituted;

W is alkyl, heteroalkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, arylalkyl or heteroarylalkyl, each of which can be optionally substituted;

X is a polar substituent;

and each m is independently 0, 1, 2, or 3;

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

17. The compound of claim 16, wherein W is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl.

18. The compound of claim 16 or 17, wherein Z^1 and Z^2 are C and ----- represents a double bond.

19. The compound of claim 16 or 17, wherein Z^1 is N, Z^2 is C and ----- represents a single bond.

20. The compound of claim 16 or 17, wherein Z^1 is C, Z^2 is N and ----- represents a single bond.

21. The compound of any one of claims 16 to 20, wherein W is optionally substituted phenyl, optionally substituted heterocyclyl, or C1-C4 alkyl substituted with at least one member selected from the group consisting of optionally substituted phenyl, optionally substituted heteroalkyl, optionally substituted heteroaryl, halo, hydroxy and -NR''_2,

where each R" is independently H or optionally substituted C1-C6 alkyl;

and two R" taken together with the N to which they are attached can be linked together to form an optionally substituted 3to 8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

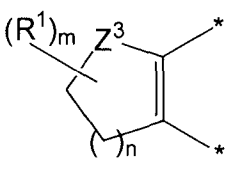
22. The compound of claim 21, wherein W comprises at least one group of the formula $-(CH_2)_p$-NR^x_2,

where p is 1, 2, 3, or 4,

R^x is independently at each occurrence H or optionally substituted alkyl;

and two R^x taken together with the N to which they are attached can be linked together to form an optionally substituted 3 to 8 membered ring, which can contain another heteroatom selected from N, O and S as a ring member, and can be saturated, unsaturated or aromatic.

23. The compound of any one of claims 16 to 22, wherein A is selected from the group consisting of: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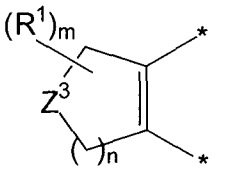
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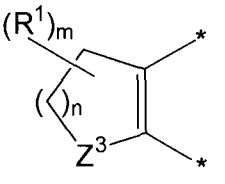
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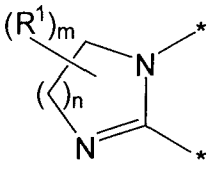
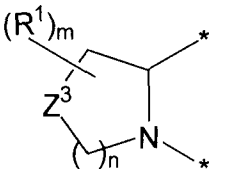
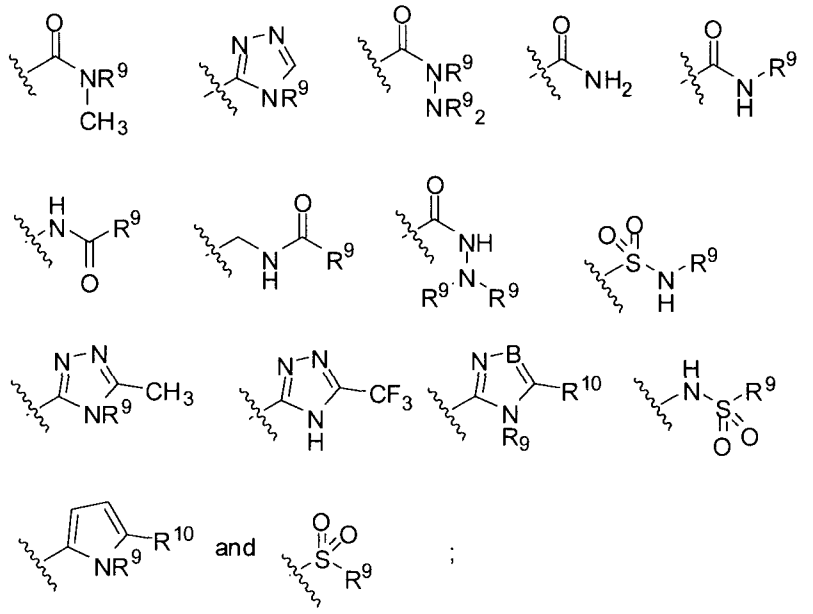

, and

,

wherein Z^3 is CR^1_2, NR^1, $S(=O)_p$, or O;

n is 1, 2, or 3; and

p is 0, 1, or 2.

24. The compound of any one of claims 16 to 23, wherein X is selected from the group consisting of $COOR^9$, $C(O)NR^9$-OR^9, triazole, tetrazole, CN, imidazole, carboxylate, a carboxylate bioisostere,



wherein each R^9 is independently H or an optionally substituted member selected from the group consisting of alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, arylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, and heteroarylalkyl,

and two R^9 on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

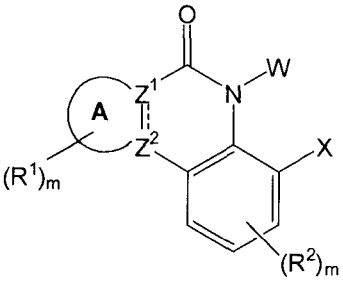
R^{10} is halo, CF_3, CN, SR, OR, NR_2, or R, where each R is independently H or optionally substituted C1-C6 alkyl, and two R on the same or adjacent atoms can optionally be linked together to form an optionally substituted ring that can also contain an additional heteroatom selected from N, O and S as a ring member;

and B is N or CR^{10}.

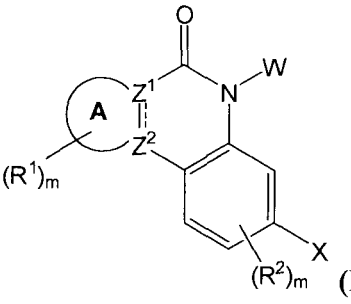
25. The compound of claim 24, wherein the polar substituent X is located at position 3 on the phenyl ring.

26. The compound of claim 24, wherein the polar substituent X is located at position 4 on the phenyl ring.

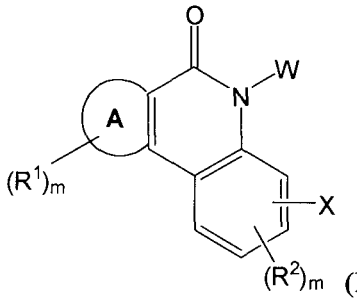
27. The compound of claim 1, having the Formula II-A, II-B, II-C, II-D or II-E:



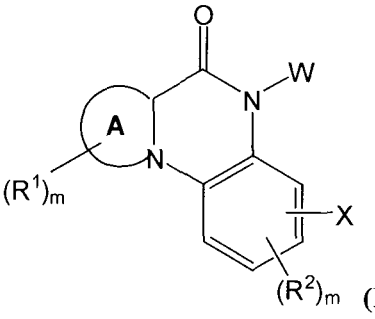
(II-A),



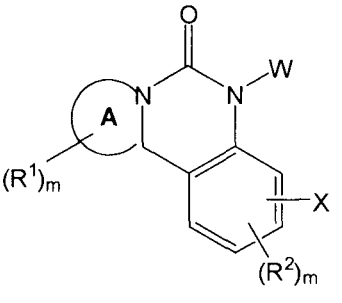
(II-B)



(II-C),



(II-D), or



(II-E),

or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof; and a pharmaceutically acceptable excipient.

29. A method of inhibiting cell proliferation, which comprises contacting cells with a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof in an amount effective to inhibit proliferation of the cells.

30. The method of claim 29, wherein the cells are in a cancer cell line.

31. The method of claim 29, wherein the cells are in a tumor in a subject, or from an eye of a subject having macular degeneration, or in a subject having macular degeneration.

32. A method of treating a condition related to aberrant cell proliferation, which comprises administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, to a subject in need thereof in an amount effective to treat the cell proliferative condition.

33. The method of claim 32, wherein the cell proliferative condition is a tumor-associated cancer, a non-tumor cancer, or macular degeneration.

34. The method of claim 33, wherein the non-tumor cancer is a hematopoietic cancer.

35. A method of treating a condition or disease associated with casein kinase 2 activity, Pim kinase activity, and/or Fms-like tyrosine kinase activity comprising administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, to a subject in need thereof in a therapeutically effective amount.

36. The method of claim 35, wherein the condition or disease is a cancer of colorectum, breast, lung, liver, pancreas, lymph node, colon, prostate, brain, head and neck, skin, liver, kidney, blood and heart.

37. A method of treating pain or inflammation in a subject, which comprises administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, to a subject in need thereof in an amount effective to treat the pain or the inflammation.

38. A method of inhibiting angiogenesis in a subject, which comprises administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, to a subject in need thereof in an amount effective to inhibit the angiogenesis.

39. A method of treating an infection in a subject, which comprises administering a compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof to a subject in need thereof, in an amount effective to treat the infection.

40. The method of claim 39, wherein the infection is selected from *Theileria parva, Trypanosoma cruzi, Leishmania donovani, Herpetomonas muscarum muscarum, Plasmodium falciparum, Trypanosoma brucei, Toxoplasma gondii* and *Schistosoma mansoni*, human immunodeficiency virus type 1 (HIV-1), human papilloma virus, herpes simplex virus, human cytomegalovirus, hepatitis C and B viruses, Epstein-Barr virus, Borna disease virus, adenovirus, coxsackievirus, coronavirus, influenza, and varicella zoster virus.

41. A method of modulating casein kinase 2 activity, Pim kinase activity, and/or Fms-like tyrosine kinase activity in a cell comprising contacting the cell with a compound any one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

42. A pharmaceutical composition comprising a compound of any of one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof; and at least one additional therapeutic agent.

43. A method to treat a condition related to aberrant cell proliferation, which comprises co-administering to a subject in need of treatment for such condition a compound of any of one of claims 1 to 27, or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof; and at least one additional therapeutic agent.

Date **13 April 2012**

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IN/PA - 1760
Agent for the Applicant

To
The Controller of Patents
The Patent Office at New Delhi