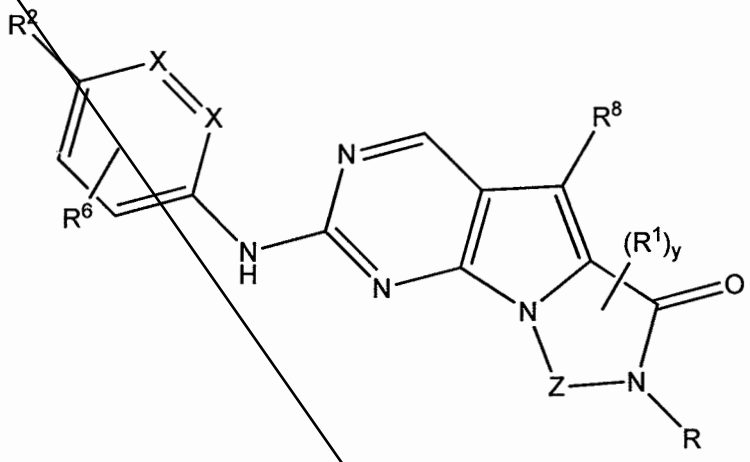
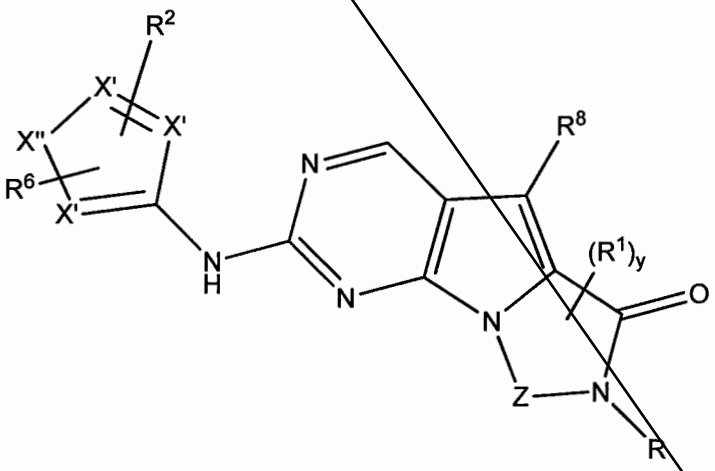
CLAIMS:

1. A compound of formula I or formula II:



I



II

or a pharmaceutically acceptable salt thereof, wherein:

Z is $-(CH_2)_x-$ wherein x is 1, 2, 3 or 4 or $-O-(CH_2)_z-$ wherein z is 2, 3 or 4;

each X is independently CH or N;

each X′ is independently, C, S or N;

X″ is CH_2, S or NH;

each of R and R^8 are independently H, C_1-C_3 alkyl or haloalkyl;

each R^1 is independently aryl, alkyl, cycloalkyl or haloalkyl, wherein each of said alkyl, cycloalkyl and haloalkyl groups optionally includes O or N heteroatoms in place of a carbon in the chain and two R^1's on adjacent ring atoms or on the same ring atom together with the ring atom(s) to which they are attached optionally form a 3-8-membered cycle;

y is 0, 1, 2, 3 or 4;

R^2 is –(alkylene)$_m$–heterocyclo, –(alkylene)$_m$–heteroaryl, –(alkylene)$_m$–NR^3R^4, –(alkylene)$_m$–C(O)–NR^3R^4; –(alkylene)$_m$–C(O)–O-alkyl; –(alkylene)$_m$–O–R^5, –(alkylene)$_m$–S(O)$_n$–R^5, or –(alkylene)$_m$–S(O)$_n$–NR^3R^4 any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring and wherein m is 0 or 1 and n is 0, 1 or 2;

R^3 and R^4 at each occurrence are independently:

(i) hydrogen or

(ii) alkyl, cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring; or R^3 and R^4 together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring;

R^5 and R^{5*} at each occurrence is:

(i) hydrogen or

(ii) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance;

R^x at each occurrence is independently, halo, cyano, nitro, oxo, alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkyl, -(alkylene)$_m$-OR^5, -(alkylene)$_m$-O-alkylene-OR^5, -(alkylene)$_m$-S(O)$_n$–R^5, -(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-CN, -(alkylene)$_m$-C(O)–R^5, -(alkylene)$_m$-C(S)–R^5, -(alkylene)$_m$-C(O)–OR^5, -(alkylene)$_m$-O–C(O)–R^5, -(alkylene)$_m$-C(S)–OR^5, -(alkylene)$_m$-C(O)-(alkylene)$_m$-NR^3R^4, -(alkylene)$_m$-C(S)–NR^3R^4, -(alkylene)$_m$-N(R^3)–C(O)–NR^3R^4, -(alkylene)$_m$-N(R^3)–C(S)–NR^3R^4, -(alkylene)$_m$-N(R^3)–C(O)–R^5, -(alkylene)$_m$-N(R^3)–C(S)–R^5, -(alkylene)$_m$-O–C(O)–NR^3R^4, -(alkylene)$_m$–O–C(S)–NR^3R^4, -(alkylene)$_m$–SO_2–NR^3R^4, -(alkylene)$_m$–N(R^3)–SO_2–R^5,

-(alkylene)$_m$-N(R^3)–SO_2–NR^3R^4, -(alkylene)$_m$-N(R^3)–C(O)–OR^5) -(alkylene)$_m$-N(R^3)–C(S)–OR^5, or -(alkylene)$_m$-N(R^3)–SO_2–R^5; wherein:

said alkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclo, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, and heterocycloalkyl groups may be further independently substituted with one or more -(alkylene)$_m$-CN, -(alkylene)$_m$-OR^5*, -(alkylene)$_m$-S(O)$_n$–R^5*, -(alkylene)$_m$-NR^3*R^4*, -(alkylene)$_m$-C(O)–R^5*, -(alkylene)$_m$-C(=S)R^5*, -(alkylene)$_m$-C(=O)O R^5*, -(alkylene)$_m$-OC(=O)R^5*, -(alkylene)$_m$-C(S)–OR^5*, -(alkylene)$_m$-C(O)–NR^3*R^4*, -(alkylene)$_m$-C(S)–NR^3*R^4*, -(alkylene)$_m$-N(R^3*)–C(O)–NR^3*R^4*, -(alkylene)$_m$-N(R^3*)–C(S)–NR^3*R^4*, -(alkylene)$_m$-N(R^3*)–C(O)–R^5*, -(alkylene)$_m$-N(R^3*)–C(S)–R^5*, -(alkylene)$_m$-O–C(O)–NR^3*R^4*, -(alkylene)$_m$-O–C(S)–NR^3*R^4*, -(alkylene)$_m$-SO_2–NR^3*R^4*, -(alkylene)$_m$-N(R^3*)–SO_2–R^5*, -(alkylene)$_m$-N(R^3*)–SO_2–NR^3*R^4*, -(alkylene)$_m$-N(R^3*)–C(O)–OR^5*, -(alkylene)$_m$-N(R^3*)–C(S)–OR^5*, or -(alkylene)$_m$-N(R^3*)–SO_2–R^5*,

n is 0, 1 or 2, and

m is 0 or 1; and

R^3* and R^4* at each occurrence are independently:

(i) hydrogen or

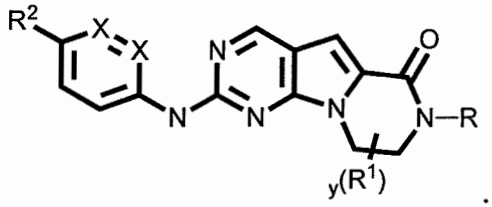
(ii) alkyl, alkenyl, alkynyl cycloalkyl, heterocyclo, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkyl, arylalkyl, or heteroarylalkyl any of which may be optionally independently substituted with one or more R^x groups as allowed by valance; or R^3* and R^4* together with the nitrogen atom to which they are attached may combine to form a heterocyclo ring optionally independently substituted with one or more R^x groups as allowed by valance.

2. The compound of claim 1, having formula I.

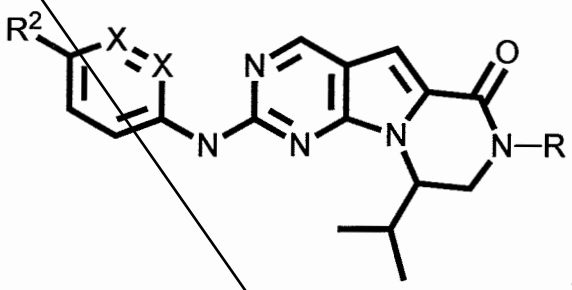
3. The compound of any previous claim wherein R^8 is hydrogen or C_1-C_3 alkyl.

4. The compound of claim 1 having formula I or formula II and selected from the structures shown in FIGS. 4-8.

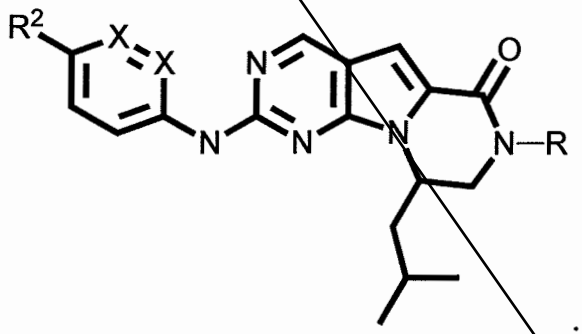
5. The compound of claim 1 having formula Ia:



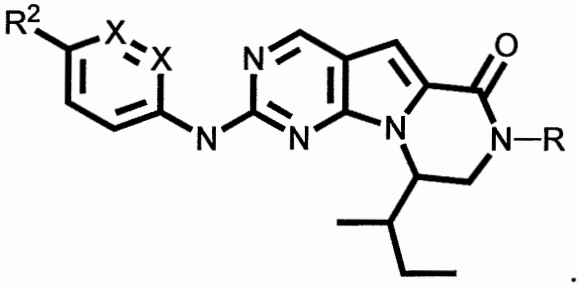
6. The compound of claim 1 having formula Ib:



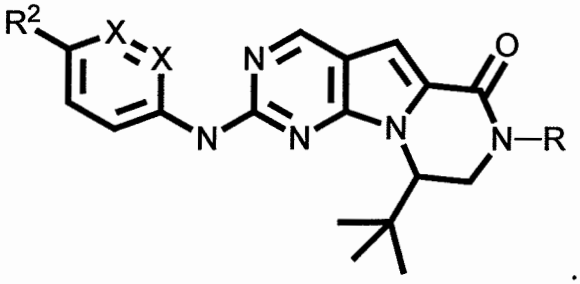
7. The compound of claim 1 having formula Ic:



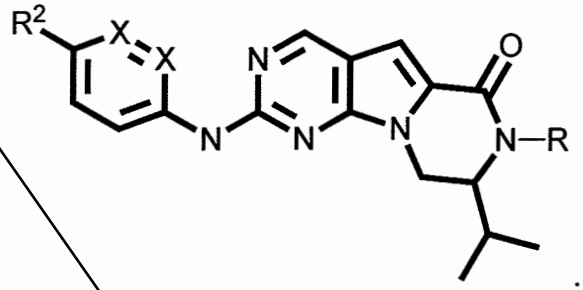
8. The compound of claim 1 having formula Id:



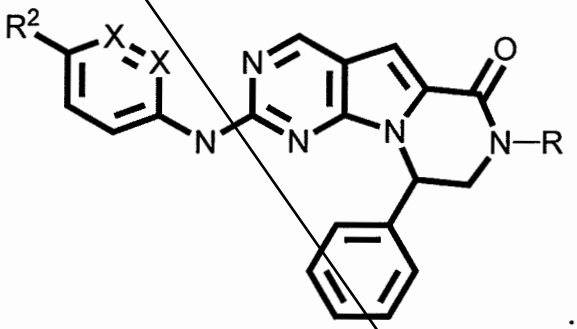
9. The compound of claim 1 having formula Ie:



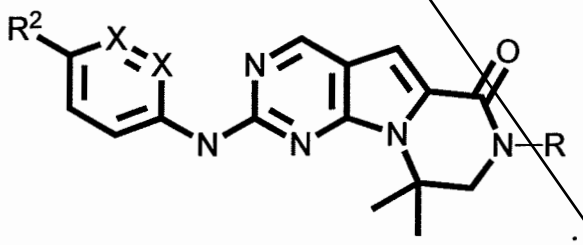
10. The compound of claim 1 having formula If:



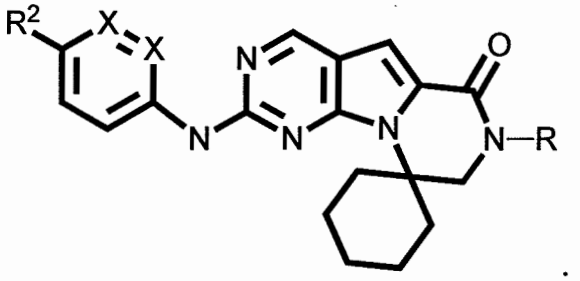
11. The compound of claim 1 having formula Ig:



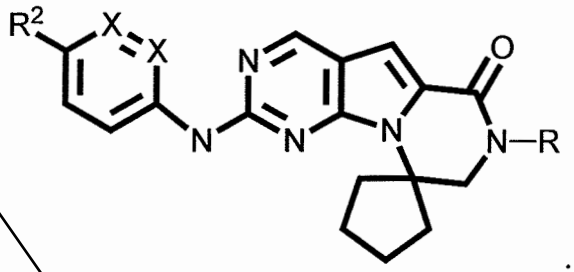
12. The compound of claim 1 having formula Ih:



13. The compound of claim 1 having formula Ii:



14. The compound of claim 1 having formula Ij:

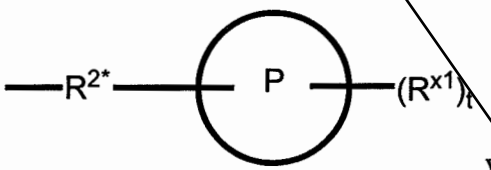


15. The compound of any one of claims 5-14 wherein both of X are N.

16. The compound of any previous claim wherein R^2 is selected from the structures of FIGS. 1-3.

17. The compound of any one of claims 1-15 wherein R^2 is $-(alkylene)_m-$heterocyclo, $-(alkylene)_m-NR^3R^4$, $-(alkylene)_m-C(O)-NR^3R^4$, $-(alkylene)_m-C(O)-O$-alkyl or $-(alkylene)_m-OR^5$ any of which may be optionally independently substituted with one or more R^x groups as allowed by valance, and wherein two R^x groups bound to the same or adjacent atom may optionally combine to form a ring.

18. The compound of any one of claims 1-14 wherein R^2 is



wherein:

R^{2*} is a bond, alkylene, $-(alkylene)_m-O-(alkylene)_m-$, $-(alkylene)_m-C(O)-(alkylene)_m-$, $-(alkylene)_m-S(O)_2-(alkylene)_m-$ and $-(alkylene)_m-NH-(alkylene)_m-$ wherein each m is independently 0 or 1;

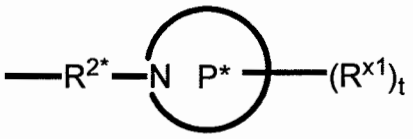
P is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group;

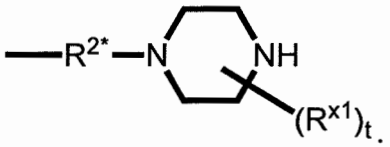
each R^{x1} is independently $-(alkylene)_m-(C(O))_m-(alkylene)_m-(N(R^N))_m-(alkyl)_m$ wherein each m is independently 0 or 1 provided at least one m is 1, -(C(O))-O-alkyl, $-(alkylene)_m$-cycloalkyl wherein m is 0 or 1, $-N(R^N)$-cycloalkyl, -C(O)-cycloalkyl, $-(alkylene)_m$-heterocyclyl wherein m is 0 or 1, or $-N(R^N)$-heterocyclyl, -C(O)-heterocyclyl,$-S(O)_2-(alkylene)_m$ wherein:

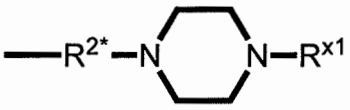
R^N is H, C_1 to C_4 alkyl or C_1 to C_6 heteroalkyl, and

wherein two R^{x1} can, together with the atoms to which they attach on R, which may be the same atom, form a ring; and

t is 0, 1 or 2.

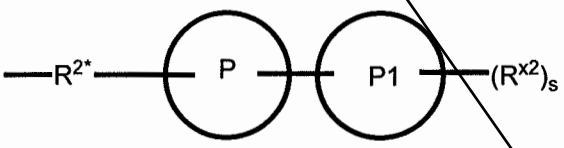
19. The compound of claim 17 wherein R^2 is  wherein P* is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group and R^{2*}, R^{x1} and t are as previously defined.

20. The compound of claim 18 wherein R^2 is .

21. The compound of claim 19 wherein R^2 is .

22. The compound of 18-21 wherein each R^{x1} is only optionally substituted by C_1-C_4 alkyl, halogen or hydroxy.

23. The compound of any one of claims 1-15 wherein R^2 is



wherein:

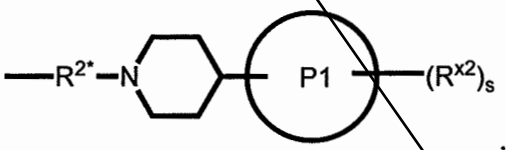
R^{2*} is a bond, alkylene, -(alkylene)$_m$-O-(alkylene)$_m$-, -(alkylene)$_m$-C(O)-(alkylene)$_m$-, -(alkylene)$_m$-S(O)$_2$-(alkylene)$_m$- and -(alkylene)$_m$-NH-(alkylene)$_m$- wherein each m is independently 0 or 1;

P is a 4- to 8-membered mono- or bicyclic saturated heterocyclyl group;

P1 is a 4- to 6-membered monocyclic saturated heterocyclyl group;

each R^{x2} is independently hydrogen or alkyl; and

s is 0, 1 or 2.

24. The compound of claim 21 wherein R^2 is .

25. The compound of any previous claim wherein R^x is not further substituted.

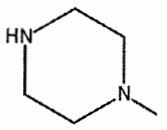
26. The compound of any one of claims 18-24 wherein R^{2*} is not further substituted.

27. The compound of any previous claim wherein R is hydrogen or C_1-C_3 alkyl.

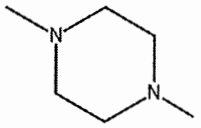
28. The compound of any previous claim wherein the alkylene in R^2 is methylene.

29. A pharmaceutical composition comprising an effective amount of a compound of claims 1-28 or 30-46.

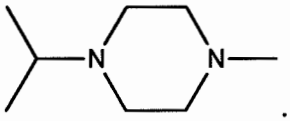
30. The compound of claim 21, wherein R^{x1} is isopropyl.

31. The compound of claim 20, wherein R^2 is 

.

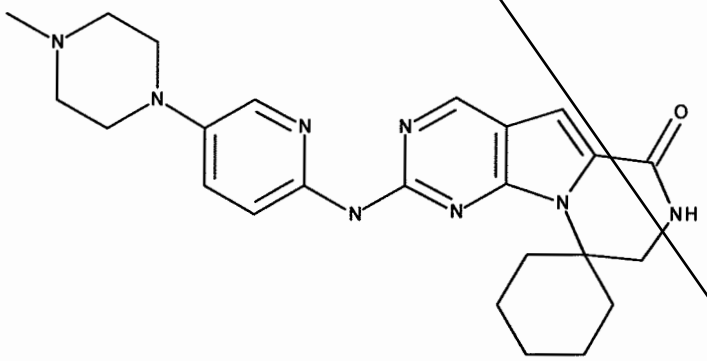
32. The compound of claim 20, wherein R^2 is 

.

33. The compound of claim 21, wherein R^2 is 

.

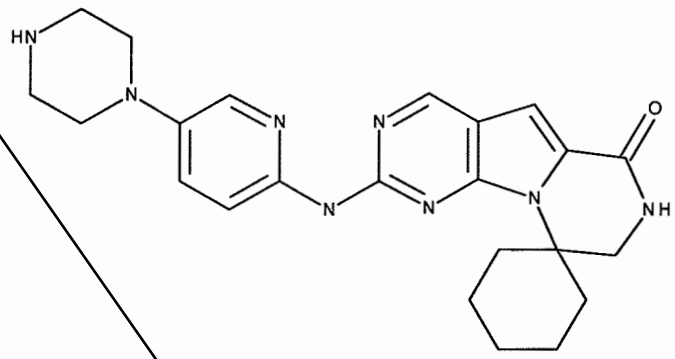
34. A compound of the formula:



,

or a pharmaceutically acceptable salt thereof.

35. A compound of the formula:

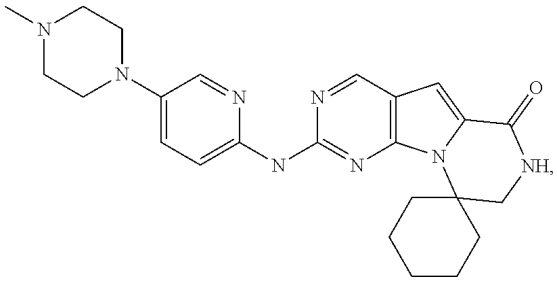


or a pharmaceutically acceptable salt thereof.

36. The compound of claim 13, wherein R^2 is -(alkylene)$_m$-heterocyclo and R is hydrogen.
37. The compound of claim 14, wherein R^2 is -(alkylene)$_m$-heterocyclo and R is hydrogen.
38. The compound of claim 36 or 37, wherein m is 0.
39. The compound of claim 36 or 37, wherein m is 1.
40. The compound of claim 36 or 37, wherein the heterocyclo is not substituted.
41. The compound of claim 13, wherein R^2 is -(alkylene)$_m$-heteroaryl and R is hydrogen.
42. The compound of claim 14, wherein R^2 is -(alkylene)$_m$-heteroaryl and R is hydrogen.
43. The compound of claim 41 or 42, wherein m is 0.
44. The compound of claim 41 or 42, wherein m is 1.
45. The compound of claim 41 or 42, wherein the heterocyclo is not substituted.
46. The compound of any previous claim, wherein the compound or pharmaceutically acceptable salt thereof is in the form of a dosage unit.
47. A method of inhibiting a cyclin dependent kinase in a subject comprising administering to the subject in need thereof, a compound of any of the previous claims.
48. Any of the compounds described in claims 1-28 or 30-46 for use in medical therapy.
49. The compound of claim 43 for use to inhibit a cyclin dependent kinase in a subject in need thereof.

CLAIMS

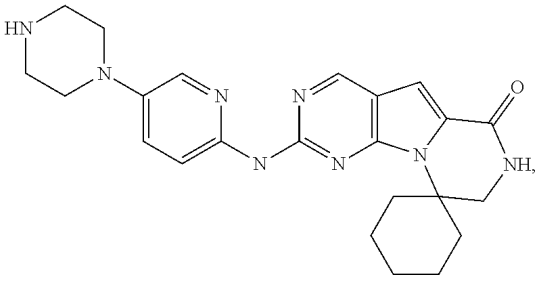
1. A compound of the formula:



or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising an effective amount of the compound of claim 1 in a pharmaceutically acceptable carrier.

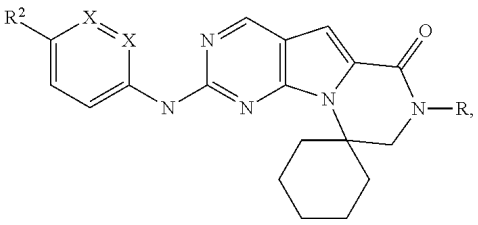
3. A compound of the formula:



or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising an effective amount of the compound of claim 3 in a pharmaceutically acceptable carrier.

5. A compound of the structure:



wherein R^2 is -(alkylene)$_m$-heterocyclo or -(alkylene)$_m$-heteroaryl,

R is hydrogen, and

X is independently CH or N.

6. The compound of claim 5, wherein R^2 is -(alkylene)$_m$-heterocyclo.

7. The compound of claim 5, wherein m is 0.

8. The compound of claim 6, wherein m is 0.

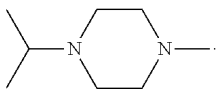
9. The compound of claim 5, wherein m is 1.

10. The compound of claim 6, wherein m is 1.

11. The compound of claim 5, wherein the heterocyclo is not substituted.

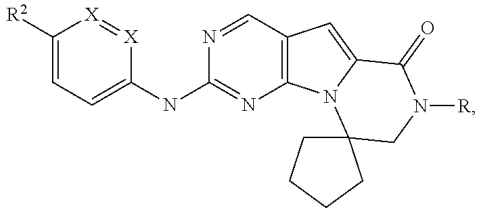
12. The compound of claim 6, wherein the heterocyclo is not substituted.

13. The compound of claim 5, wherein R^2 is



14. A pharmaceutical composition comprising an effective amount of the compound of claim 5 in a pharmaceutically acceptable carrier.

15. A compound of the structure:



wherein R^2 is -(alkylene)$_m$-heterocyclo or -(alkylene)$_m$-heteroaryl,

R is hydrogen, and

X is independently CH or N.

16. The compound of claim 15, wherein R^2 is -(alkylene)$_m$-heterocyclo.

17. The compound of claim 15, wherein m is 0.

18. The compound of claim 16, wherein m is 0.

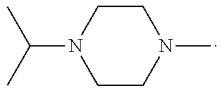
19. The compound of claim 15, wherein m is 1.

20. The compound of claim 16, wherein m is 1.

21. The compound of claim 15, wherein the heterocyclo is not substituted.

22. The compound of claim 16, wherein the heterocyclo is not substituted.

23. The compound of claim 15, wherein R^2 is



24. A pharmaceutical composition comprising an effective amount of the compound of claim 15 in a pharmaceutically acceptable carrier.