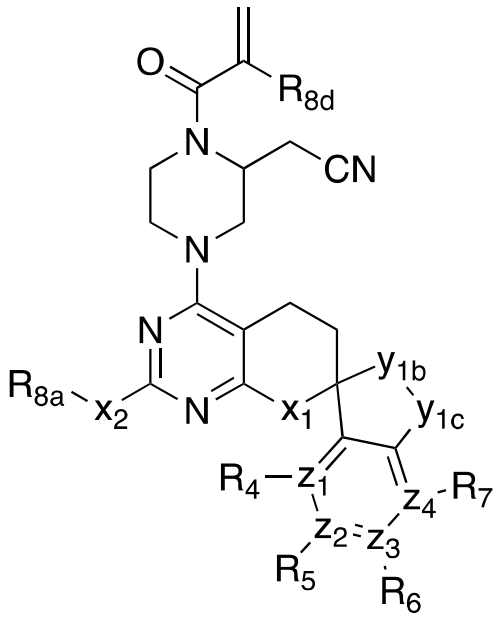
CLAIMS

1. A compound having structural formula IV:



(Formula IV)

or a pharmaceutically acceptable salt thereof,

wherein:

x_1 is $C(R_1)(R_2)$ or C=O;

x_2 is O, bond, $C(R_3)_2$, C=O, $N(R_3)$, S, S(O), or $S(O)_2$;

y_{1b} and y_{1c} are each independently $(C(R_{11})_2)_m$, $C=CH_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$, with the proviso that both y_{1b} and y_{1c} cannot be heteroatoms, the proviso that both y_{1b} and y_{1c} cannot be $C=CH_2$, and the further proviso that both y_{1b} and y_{1c} cannot be C=O;

z_1, z_2, z_3 and z_4 are each independently C or N;

R_1 and R_2 are each independently H or F;

R_3 in each occurrence is independently H or C_1-C_4 alkyl;

R_4, R_5, R_6 and R_7 are each independently H, OH, F, Cl, Br, $N(R_3)_2$, CF_3, CH_3, $OCFH_2$ or OCH_3, or each of R_4, R_5, R_6 and R_7 is absent when the respective z to which each is attached is N;

R_{8a} is C_1-C_4 alkyl, H, cycloalkyl, heterocyclyl, aralkyl, aryl or heteroaryl, wherein each of C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl and heteroaryl may be optionally substituted with one or more R_9;

R_{8d} is H, cyano, halogen, C_1-C_3 alkyl, haloalkyl, heteroalkyl, hydroxyalkyl or $C(O)N(R_3)_2$;

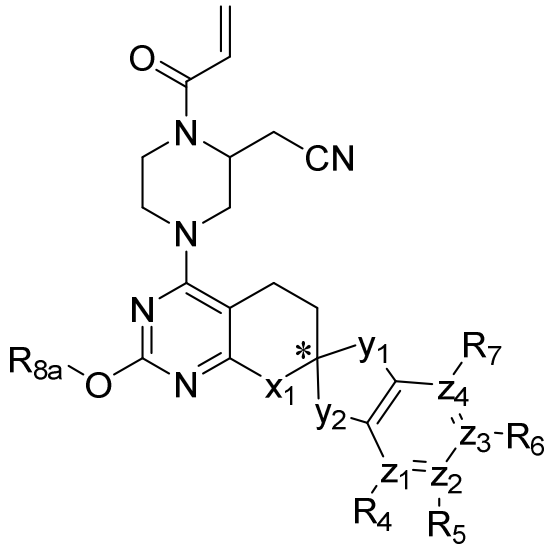
R_9 in each occurrence is independently heterocyclyl, halogen, hydroxyl, C_1-C_3 alkyl, C_1-C_6 alkyl, cycloalkyl, aryl, heteroaryl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl, wherein each of cycloalkyl, heterocyclyl, aryl and heteroaryl may be optionally substituted with one or more R_{10};

R_{10} in each occurrence is independently C_1-C_3 alkyl, halogen, hydroxyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl;

R_{11} in each occurrence is independently H, F, Cl, C_1-C_3 alkyl or OCH_3; and

m, when present, is 1.

2. A compound having the structure of Formula Id:



(Formula Id)

or a pharmaceutically acceptable salt thereof,

wherein:

* is the quaternary carbon atom;

x_1 is C=O or $C(R_1)(R_2)$;

y_1 is y_{1a} and y_2 is y_{2a}, with the proviso that both y_{1a} and y_{2a} cannot be heteroatoms; or

y_1 is *—y_{1b}—y_{1c} and y_2 is y_{2a}, with the proviso that both y_{1b} and y_{2a} cannot be heteroatoms, and the further proviso that both y_{1b} and y_{1c} cannot be heteroatoms; or

y_1 is y_{1a} and y_2 is *—y_{2b}—y_{2c}, with the proviso that both y_{1a} and y_{2b} cannot be heteroatoms, and the further proviso that both y_{2b} and y_{2c} cannot be heteroatoms; or

y_1 is *—y_{1d}═y_{1e} and y_2 is y_{2a}, with the proviso that both y_{1d} and y_{2a} cannot be heteroatoms; or

y_1 is y_{1a} and y_2 is *—y_{2d}═y_{2e}, with the proviso that both y_{1a} and y_{2d} cannot be heteroatoms;

y_{1a} and y_{2a} are each independently $C(R_{11})_2$, O, $N(R_3)$ or S;

y_{1b}, y_{1c}, y_{2b} and y_{2c} are each independently $C(R_{11})_2$, O, $N(R_3)$ or S;

y_{1d}, y_{1e}, y_{2d} and y_{2e} are each independently $C(R_3)$ or N;

z_1, z_2, z_3 and z_4 are each independently C or N;

R_1 and R_2 are each independently H or F;

R_3 in each occurrence is independently H or CH_3;

R_4, R_5, R_6 and R_7 are each independently H, F, Cl, CH_3 or OCH_3, or each of R_4, R_5, R_6 and R_7 is absent when the respective z to which each is attached is N;

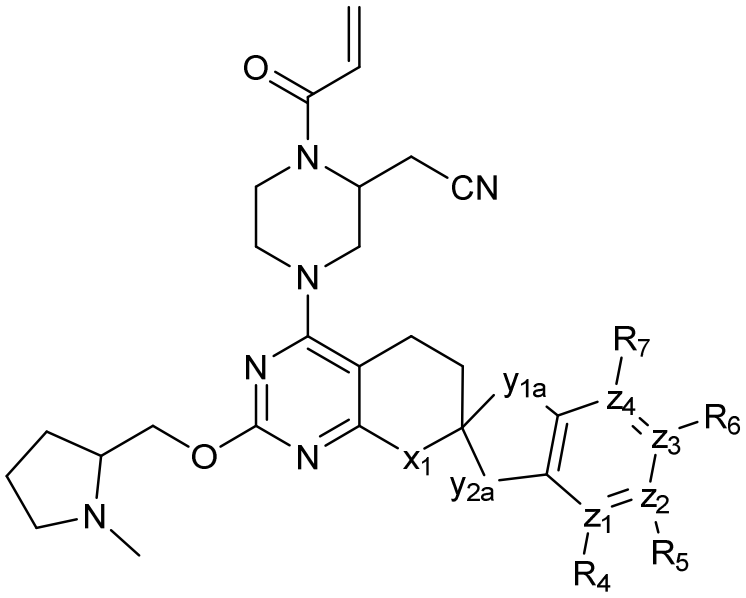
R_{8a} is H, C_1-C_3 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl or heteroaryl, wherein each of C_1-C_3 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl and heteroaryl may be optionally substituted with one or more R_9;

R_9 in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl, wherein each of cycloalkyl, heterocyclyl, aryl and heteroaryl may be optionally substituted with one or more R_{10};

R_{10} in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl; and

R_{11} in each occurrence is independently H, F, Cl, CH_3 or OCH_3.

3. A compound having the structure of Formula IIa:



(Formula IIa)

or a pharmaceutically acceptable salt thereof,

wherein:

x_1 is C=O or $C(R_1)(R_2)$;

y_{1a} and y_{2a} are each independently $C(R_{11})_2$, O, $N(R_3)$ or S, with the proviso that both y_{1a} and y_{2a} cannot be heteroatoms;

z_1, z_2, z_3 and z_4 are each independently C or N;

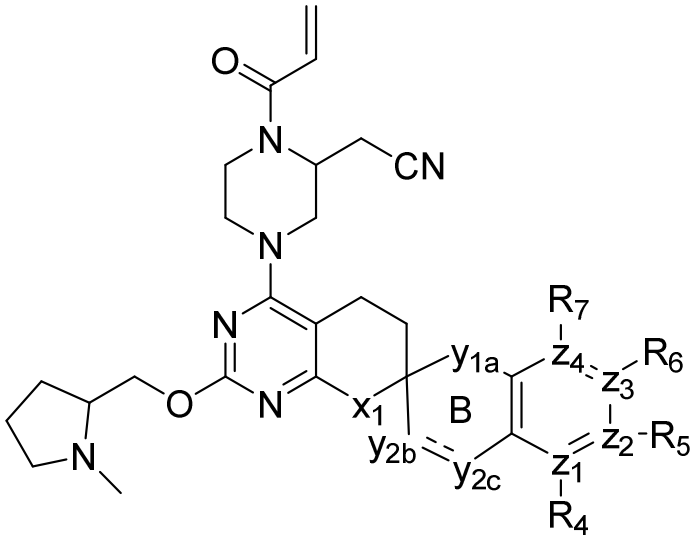
R_1 and R_2 are each independently H or F;

R_3 is H or CH_3;

R_4, R_5, R_6 and R_7 are each independently H, F, Cl, CH_3 or OCH_3, or each of R_4, R_5, R_6 and R_7 is absent when the respective z to which each is attached is N; and

R_{11} in each occurrence is independently H, F, Cl, CH_3 or OCH_3.

4. A compound having the structure of Formula IIIa:



(Formula IIIa)

or a pharmaceutically acceptable salt thereof,

wherein:

x_1 is C=O or $C(R_1)(R_2)$;

y_{1a} is $C(R_{11})_2$, O, $N(R_3)$ or S;

$\equiv$ is a single or double bond such that all valences are satisfied;

when $\equiv$ is a single bond, y_{2b} and y_{2c} are each independently $C(R_{11})_2$, O, $N(R_3)$ or S, with the proviso that both y_{1a} and y_{2b} cannot be heteroatoms, and the further proviso that both y_{2b} and y_{2c} cannot be heteroatoms; or

when $\equiv$ is a double bond, y_{2b} and y_{2c} are each independently $C(R_3)$ or N, with the proviso that both y_{1a} and y_{2b} cannot be heteroatoms;

z_1, z_2, z_3 and z_4 are each independently C or N;

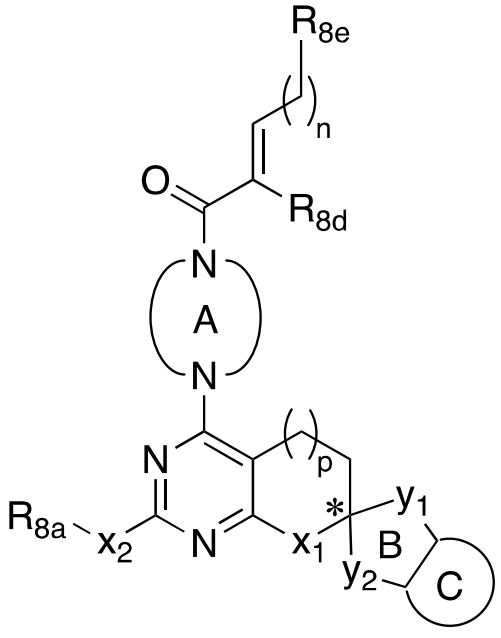
R_1 and R_2 are each independently H or F;

R_3 in each occurrence is independently H or CH_3;

R_4, R_5, R_6 and R_7 are each independently H, F, Cl, CH_3 or OCH_3, or each of R_4, R_5, R_6 and R_7 is absent when the respective z to which each is attached is N; and

R_{11} in each occurrence is independently H, F, Cl, CH_3 or OCH_3.

5. A compound having the structure of Formula I:



(Formula I)

or a pharmaceutically acceptable salt thereof,

wherein:

* is the quaternary carbon atom;

A is a 4 – 12 membered saturated or partially saturated monocyclic, bridged or spirocyclic ring substituted with one R_{8b} and one R_{8c};

B is a 5 – 7 membered saturated or partially saturated cycloalkyl or heterocyclyl;

C is an aryl or heteroaryl optionally substituted with one or more R_4;

x_1 is C=O or $C(R_1)(R_2)$;

x_2 is bond, $C(R_3)_2$, C=O, O, $N(R_3)$, S, S(O), or or $S(O)_2$;

y_1 is y_{1a} and y_2 is y_{2a}; or

y_1 is *—y_{1b}—y_{1c} and y_2 is y_{2a}; or

y_1 is y_{1a} and y_2 is *—y_{2b}—y_{2c}; or

y_1 is *—y_{1d}═y_{1e} and y_2 is y_{2a}; or

y_1 is y_{1a} and y_2 is *—y_{2d}═y_{2e}; or

y_1 is *y_{1a}—y_{1b}—y_{1c} and y_2 is bond; or

y_1 is bond and y_2 is *y_{2a}—y_{2b}—y_{2c};

y_{1a} and y_{2a} are each independently bond, $(C(R_{11})_2)_m$, $C=CH_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$;

y_{1b}, y_{1c}, y_{2b} and y_{2c} are each independently bond, $(C(R_{11})_2)_m$, $C{=}CH_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$;

y_{1d}, y_{1e}, y_{2d} and y_{2e} are each independently $C(R_3)$ or N;

with the proviso that both y_{1a} and y_{2a} cannot be heteroatoms;

with the proviso that both y_{1b} and y_{2a} cannot be heteroatoms, and the proviso that both y_{1b} and y_{1c} cannot be heteroatoms;

with the proviso that both y_{1a} and y_{2b} cannot be heteroatoms, and the proviso that both y_{2b} and y_{2c} cannot be heteroatoms;

with the proviso that both y_{1d} and y_{2a} cannot be heteroatoms;

with the proviso that both y_{1a} and y_{2d} cannot be heteroatoms;

with the proviso that both y_{1a} and y_{1b} cannot be heteroatoms, the proviso that both y_{1b} and y_{1c} cannot be heteroatoms; and

with the proviso that both y_{2a} and y_{2b} cannot be heteroatoms, the proviso that both y_{2b} and y_{2c} cannot be heteroatoms;

R_1 and R_2 are each independently H or F;

R_3 in each occurrence is independently H or C_1-C_4 alkyl;

R_4 in each instance is independently H, OH, F, Cl, Br, $N(R_3)_2$, CF_3, CH_3, $OCFH_2$ or OCH_3;

R_{8a} is H, C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl or heteroaryl, wherein each of C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl and heteroaryl may be optionally substituted with one or more R_9;

R_{8b} is H, C_1-C_3 alkyl-CN or C_1-C_3 alkyl-OCH_3;

R_{8c} is H or C_1-C_4 alkyl;

R_{8d} is H, cyano, halogen, C_1-C_3 alkyl, haloalkyl, heteroalkyl, hydroxyalkyl or $C(O)N(R_3)_2$;

R_{8e} is H, cyano, C_1-C_3 alkyl, hydroxyalkyl, heteroalkyl, C_1-C_3 alkoxy, halogen, haloalkyl, haloalkoxy, $(CH_2)_mN(R_3)_2$, $N(R_3)_2$, $C(O)N(R_3)_2$, $N(H)C(O)C_1$-C_3 alkyl, $CH_2N(H)C(O)C_1$-C_3 alkyl, heteroaryl or heterocyclyl;

R_9 in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or

hydroxyalkyl, wherein each of cycloalkyl, heterocyclyl, aryl and heteroaryl may be optionally substituted with one or more R_{10};

R_{10} in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl;

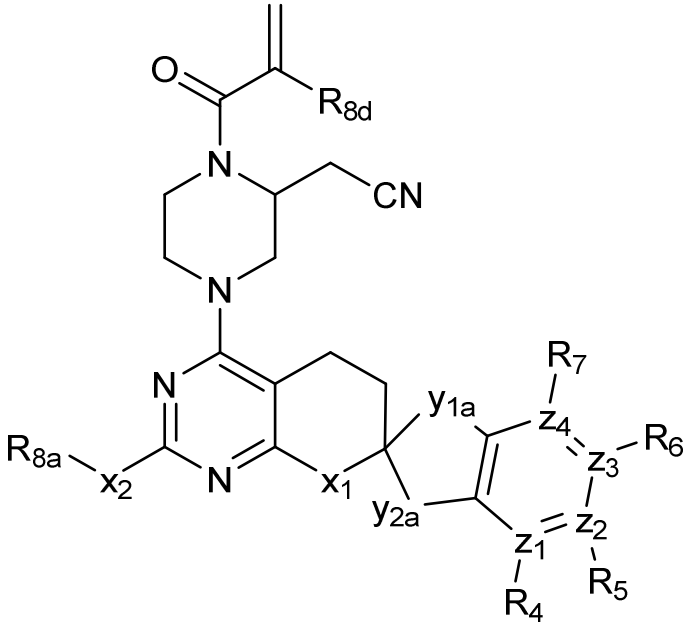
R_{11} in each occurrence is independently H, F, Cl, C_1-C_3 alkyl or OCH_3;

m in each occurrence is independently 1, 2 or 3;

n is 0, 1, 2 or 3; and

p is 0 or 1.

6. A compound having the structure of Formula II:



(Formula II)

or a pharmaceutically acceptable salt thereof,

wherein:

x_1 is C=O or $C(R_1)(R_2)$;

x_2 is bond, $C(R_3)_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$;

y_{1a} and y_{2a} are each independently $(C(R_{11})_2)_m$, $C=CH_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$, with the proviso that both y_{1a} and y_{2a} cannot be heteroatoms;

z_1, z_2, z_3 and z_4 are each independently C or N;

R_1 and R_2 are each independently H or F;

R_3 in each occurrence is independently H or C_1-C_4 alkyl;

R_4, R_5, R_6 and R_7 are each independently H, OH, F, Cl, Br, $N(R_3)_2$, CF_3, CH_3, $OCFH_2$ or OCH_3, or each of R_4, R_5, R_6 and R_7 is absent when the respective z to which each is attached is N;

R_{8a} is H, C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl or heteroaryl, wherein each of C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl and heteroaryl may be optionally substituted with one or more R_9;

R_{8d} is H, cyano, halogen, C_1-C_3 alkyl, haloalkyl, heteroalkyl, hydroxyalkyl or $C(O)N(R_3)_2$;

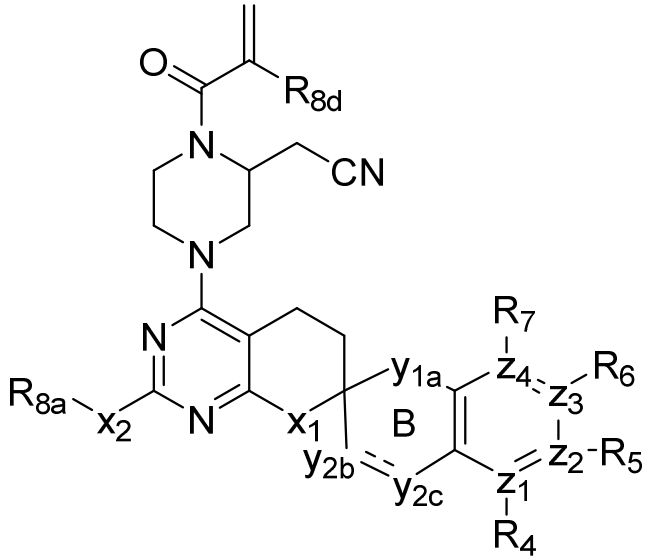
R_9 in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl, wherein each of cycloalkyl, heterocyclyl, aryl and heteroaryl may be optionally substituted with one or more R_{10};

R_{10} in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl;

R_{11} in each occurrence is independently H, F, Cl, C_1-C_3 alkyl or OCH_3; and

m, when present, is 1.

7. A compound having the structure of Formula III:



(Formula III)

or a pharmaceutically acceptable salt thereof,

wherein:

B is a 5 – 7 membered saturated or partially saturated cycloalkyl or heterocyclyl;

x_1 is C=O or $C(R_1)(R_2)$;

x_2 is bond, $C(R_3)_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$;

$\overline{---}$ is a single or double bond such that all valences are satisfied;

y_{1a} is bond, $(C(R_{11})_2)_m$, $C=CH_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$;

when $\overline{---}$ is a single bond, y_{2b} and y_{2c} are each independently bond, $(C(R_{11})_2)_m$, $C=CH_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$, with the proviso that both y_{1a} and y_{2b} cannot be heteroatoms, and the proviso that both y_{2b} and y_{2c} cannot be heteroatoms; or

when $\overline{---}$ is a double bond, y_{2b} and y_{2c} are each independently $C(R_3)$ or N, with the proviso that both y_{1a} and y_{2b} cannot be heteroatoms;

z_1, z_2, z_3 and z_4 are each independently C or N;

R_1 and R_2 are each independently H or F;

R_3 in each occurrence is independently H or C_1-C_4 alkyl;

R_4, R_5, R_6 and R_7 are each independently H, OH, F, Cl, Br, $N(R_3)_2$, CF_3, CH_3, $OCFH_2$ or OCH_3, or each of R_4, R_5, R_6 and R_7 is absent when the respective z to which each is attached is N;

R_{8a} is H, C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl or heteroaryl, wherein each of C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl and heteroaryl may be optionally substituted with one or more R_9;

R_{8d} is H, cyano, halogen, C_1-C_3 alkyl, haloalkyl, heteroalkyl, hydroxyalkyl or $C(O)N(R_3)_2$;

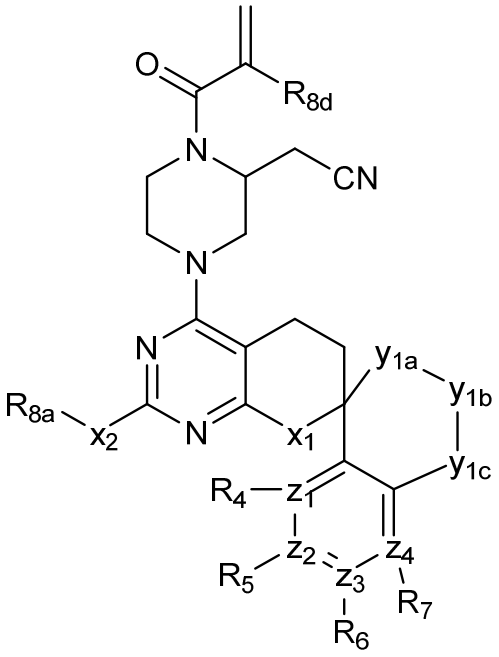
R_9 in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl, wherein each of cycloalkyl, heterocyclyl, aryl and heteroaryl may be optionally substituted with one or more R_{10};

R_{10} in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl;

R_{11} in each occurrence is independently H, F, Cl, C_1-C_3 alkyl or OCH_3; and

m in each occurrence is independently 1, 2 or 3.

8. A compound having the structure of Formula V:



(Formula V)

or a pharmaceutically acceptable salt thereof,

wherein:

x_1 is C=O or $C(R_1)(R_2)$;

x_2 is bond, $C(R_3)_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$;

y_{1a}, y_{1b} and y_{1c} are each independently $(C(R_{11})_2)_m$, $C=CH_2$, C=O, O, $N(R_3)$, S, S(O), or $S(O)_2$, with the proviso that both y_{1a} and y_{1b} cannot be heteroatoms, the proviso that both y_{1b} and y_{1c} cannot be heteroatoms, the proviso that both y_{1a} and y_{1b} cannot be $C=CH_2$, the proviso that both y_{1b} and y_{1c} cannot be $C=CH_2$, the proviso that both y_{1a} and y_{1b} cannot be C=O, and the further proviso that both y_{1b} and y_{1c} cannot be C=O;

z_1, z_2, z_3 and z_4 are each independently C or N;

R_1 and R_2 are each independently H or F;

R_3 in each occurrence is independently H or C_1-C_4 alkyl;

R_4, R_5, R_6 and R_7 are each independently H, OH, F, Cl, Br, $N(R_3)_2$, CF_3, CH_3, $OCFH_2$ or OCH_3, or each of R_4, R_5, R_6 and R_7 is absent when the respective z to which each is attached is N;

R_{8a} is H, C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl or heteroaryl, wherein each of C_1-C_4 alkyl, cycloalkyl, heterocyclyl, aralkyl, aryl and heteroaryl may be optionally substituted with one or more R_9;

R_{8d} is H, cyano, halogen, C_1-C_3 alkyl, haloalkyl, heteroalkyl, hydroxyalkyl or $C(O)N(R_3)_2$;

R_9 in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, C_1-C_6 alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl, wherein each of cycloalkyl, heterocyclyl, aryl and heteroaryl may be optionally substituted with one or more R_{10};

R_{10} in each occurrence is independently halogen, hydroxyl, C_1-C_3 alkyl, alkoxy, haloalkyl, amino, cyano, heteroalkyl or hydroxyalkyl;

R_{11} in each occurrence is independently H, F, Cl, C_1-C_3 alkyl or OCH_3; and

m, when present, is 1.

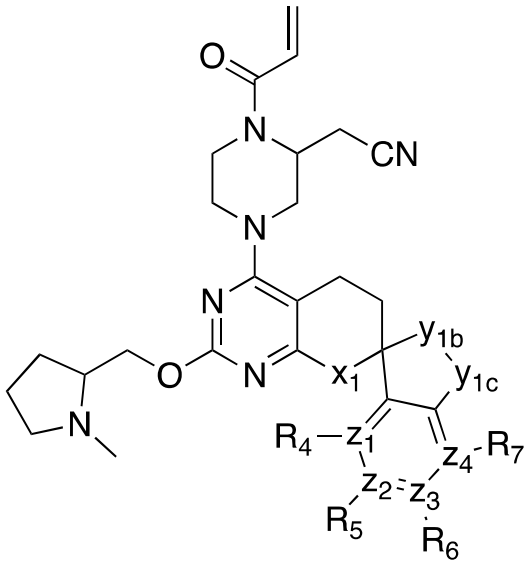
9. The compound of any one of claims 1-8, wherein the compound has a has a KRASG12C k_{obs}/[i] of about 1000 $M^{-1}s^{-1}$ or greater.

10. The compound of any one of claims 1-8, wherein the compound has an average IC_{50} of greater than 1000 nM for the drug-resistant cell lines of Table 5.

11. The compound of any one of claims 1-8, wherein the compound has an average IC_{50} of about 1000 nM or lower for the drug-sensitive cell lines of Table 5.

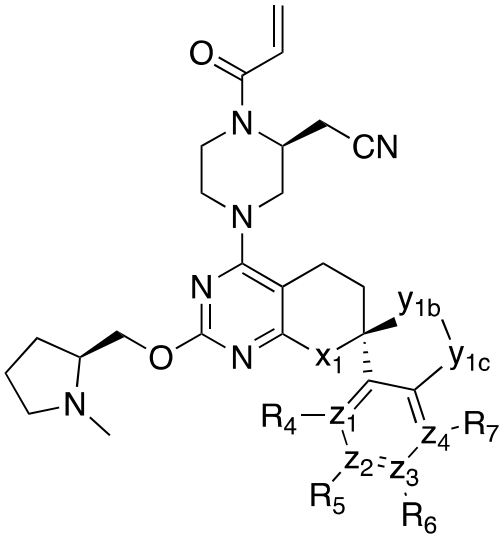
12. The compound of claim 1, wherein R_{8d} is H or F.

13. The compound of claim 1, wherein the compound of Formula IV has the structure of Formula IVa:



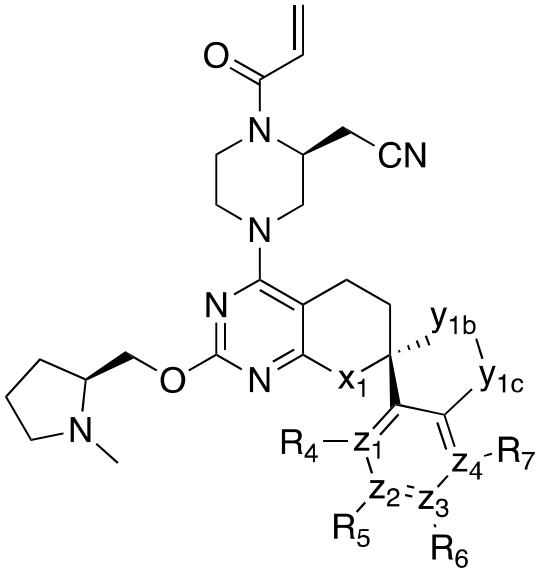
(Formula IVa)

Formula IVb:



(Formula IVb), or

Formula IVc:



(Formula IVc),

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, wherein R_{8d} is F.

15. The compound of claim 1, wherein R_{8d} is H.

16. A pharmaceutical composition comprising a compound of any one of claims 1-8 and a pharmaceutically acceptable diluent or excipient.

17. Use of a compound of any one of claims 1-8 in the manufacture of a medicament for treating cancer.

18. The compound of claim 1, wherein R_7 is Cl.

19. The compound of claim 1, wherein R_7 is F.

20. The compound of claim 1, wherein R_9 is heterocyclyl optionally substituted with one R_{10}.

21. The compound of claim 1, wherein

R_{8a} is C_1 alkyl substituted with one R_9; and

R_9 is heterocyclyl optionally substituted with one or more R_{10}.

22. The compound of claim 21, wherein R_9 is a 3- to 10-membered heterocyclyl ring structure, which ring structure includes one or two heteroatoms; and R_9 is optionally substituted with one or more R_{10}.

23. The compound of claim 21, wherein R_9 is 5- to 6-membered heterocyclyl ring structure, which ring structure includes one or two heteroatoms; and R_9 is optionally substituted with one or more R_{10}.

24. The compound of claim 21, wherein R_9 includes a five-membered heterocyclyl ring structure, which ring structure includes one or two heteroatoms; and R_9 is optionally substituted with one or more R_{10}.

25. The compound of claim 24, wherein R_9 is pyrrolidine; and R_9 is optionally substituted with one or more R_{10}.

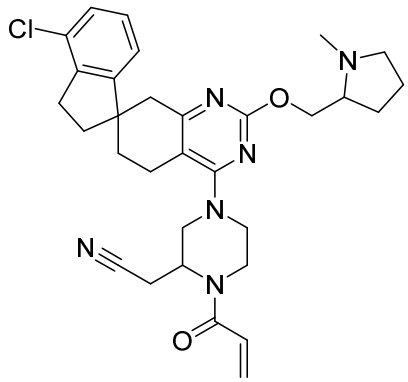
26. The compound of claim 24, wherein R_9 is pyrrolidine; and R_9 is substituted with one or more R_{10}.

27. The compound of claim 24, wherein R_9 is pyrrolidine; R_9 is substituted with one R_{10}; and R_{10} is C_1-C_3 alkyl.

28. The compound of claim 21, wherein R_9 is a polycyclic heterocycle; and R_9 is optionally substituted with one or more R_{10}.

29. The compound of claim 21, wherein R_9 is substituted with one or more R_{10}.

30. A compound having the following structure:



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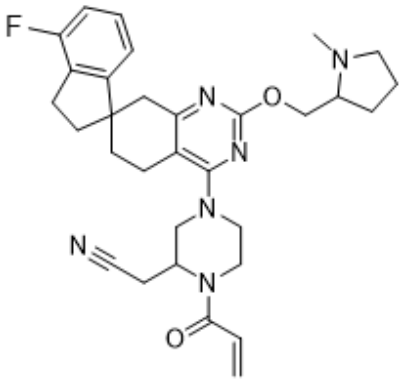
31. A compound having the following structure:



.

32. The compound of claim 1, wherein the compound is a single enantiomer.

33. The compound of claim 30, wherein the compound is a single enantiomer.

34. A compound of any one of claims 1-8 for use in therapy.

35. A compound of any one of claims 1-8 for use as a medicament.

36. A compound of any one of claims 1-8 for use in treating cancer.