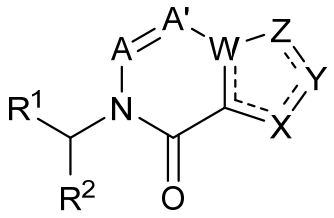
CLAIMS

1. A compound of Formula I:



(**I**)

or a pharmaceutically acceptable salt thereof;

wherein:

---- represents a single or double bond;

A and A' are each, independently, CH, CR^8, or N;

W is N or C;

Z is selected from the group consisting of S, O, N, NH, N-Me, CH_2, CH, C-halo, C-(C_1-C_3 alkyl), or C-(C_1-C_3 alkoxy);

X and Y are each, independently, S, O, N, CH, NR^3, or CR^3;

provided that at least one of X, Y, or Z is CH;

R^1 is selected from the group consisting of $C(O)NHR^9$, 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl, wherein aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one, two, or three R^8;

R^2 is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl, all of which are optionally substituted with one, two, or three R^6;

R^3 is independently, at each occurrence, selected from the group consisting of halogen, OR^4, NR^4R^4, SO_2R^4, SO_2NHR^4, $NHSO_2R^4$, $C(O)OR^4$, $C(O)NHR^4$, $NHC(O)R^4$, $C(O)R^4$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, 3-7 membered cycloalkyl, C_4-C_7 cycloalkenyl, C_6-C_{10} aryl, 5-6 membered heteroaryl, and 5-7 membered heterocyclyl, wherein alkyl, alkenyl, or alkynyl are each optionally substituted one, two, or three times with R^4, and wherein aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^5;

R^4 is independently, at each occurrence, selected from the group consisting of H, C_1-C_6 alkyl, $(CH_2)_{0-3}$-(C_3-C_7 cycloalkyl), $(CH_2)_{0-3}$-(C_4-C_7 cycloalkenyl), $(CH_2)_{0-3}$-(C_6-C_{10} aryl), $(CH_2)_{0-3}$-(5-6 membered heteroaryl), and $(CH_2)_{0-3}$-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^5;

R^5 is independently, at each occurrence, selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_3 alkylamine, 3-10 membered cycloalkyl, halogen, COOH, C(O)O(C_1-C_6 alkyl), O$(CH_2)_{1-3}$-OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, OH, CN, $(CH_2)_{0-3}$-(C_6-C_{10} aryl), $(CH_2)_{0-3}$-(5-6 membered heteroaryl), and $(CH_2)_{0-3}$-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^7;

alternatively, two R^5, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl all of which can be optionally substituted one, two, or three times with R^7;

R^6 is independently, at each occurrence, selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, C_1-C_3 alkylamine, halogen, OH, NO_2, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, $(CH_2)_{1-4}$OH, $S(O)_{0-2}$H, $S(O)_{0-2}NH_2$, or CN;

alternatively, two R^6, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl;

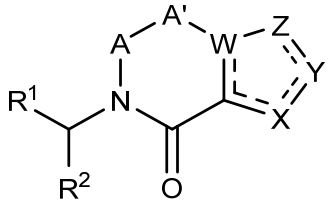
R^7 is independently, at each occurrence, selected from the group consisting of substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halogen, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, SO_2NH_2, SO_2NH(C_1-C_6 alkyl), SO_2N(C_1-C_6 alkyl)$_2$, $(CH_2)_{1-2}$-OH, C(O)$(CH_2)_{1-2}$-OH, C(O)(C_1-C_6 alkyl), and C(O)O(C_1-C_6 alkyl);

alternatively, two R^7, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl;

R^8 is independently, at each occurrence, selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, C_1-C_3 alkylamine, 3-6 membered cycloalkyl, halogen, OH, NO_2, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, $(CH_2)_{1-4}$OH, $S(O)_{0-2}$H, $S(O)_{0-2}NH_2$, or CN; and

R^9 is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl all of which are optionally substituted with one, two, or three R^8.

2. A compound of Formula X:



(**X**)

or a pharmaceutically acceptable salt thereof;

wherein:

---- represents a single or double bond;

A and A' are each, independently, CH, CR^8, or N;

alternatively, A is absent;

W is N, C, or CH;

Z is selected from the group consisting of S, O, N, NH, N-Me, CH_2, CH, C-halo, C-(C_1-C_3 alkyl), or C-(C_1-C_3 alkoxy);

X and Y are each, independently, S, O, N, CH, NR^3, or CR^3;

provided that at least one of X, Y, or Z is CH;

R^1 is selected from the group consisting of $C(O)NHR^9$, 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl, wherein aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one, two, or three R^8;

R^2 is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl, all of which are optionally substituted with one, two, or three R^6;

R^3 is independently, at each occurrence, selected from the group consisting of halogen, OR^4, NR^4R^4, SO_2R^4, SO_2NHR^4, $NHSO_2R^4$, $C(O)OR^4$, $C(O)NHR^4$, $NHC(O)R^4$, $C(O)R^4$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, 3-7 membered cycloalkyl, C_4-C_7 cycloalkenyl, C_6-C_{10} aryl, 5-6 membered heteroaryl, and 5-7 membered heterocyclyl, wherein alkyl, alkenyl, or alkynyl are each optionally substituted one, two, or three times with R^4, and wherein aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^5;

R^4 is independently, at each occurrence, selected from the group consisting of H, C_1-C_6 alkyl, $(CH_2)_{0-3}$-(C_3-C_7 cycloalkyl), $(CH_2)_{0-3}$-(C_4-C_7 cycloalkenyl), $(CH_2)_{0-3}$-(C_6-C_{10} aryl), $(CH_2)_{0-3}$-(5-6 membered heteroaryl), and $(CH_2)_{0-3}$-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^5;

R^5 is independently, at each occurrence, selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_3 alkylamine, 3-10 membered

cycloalkyl, halogen, COOH, C(O)O(C_1-C_6 alkyl), O(CH_2)$_{1-3}$-OH, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, OH, CN, (CH_2)$_{0-3}$-(C_6-C_{10} aryl), (CH_2)$_{0-3}$-(5-6 membered heteroaryl), and (CH_2)$_{0-3}$-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^7;

alternatively, two R^5, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl all of which can be optionally substituted one, two, or three times with R^7;

R^6 is independently, at each occurrence, selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, C_1-C_3 alkylamine, halogen, OH, NO_2, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, (CH_2)$_{1-4}$OH, S(O)$_{0-2}$H, S(O)$_{0-2}$$NH_2$, or CN;

alternatively, two R^6, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl;

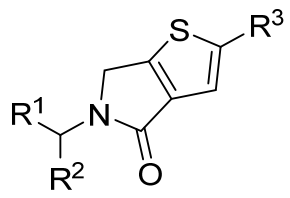
R^7 is independently, at each occurrence, selected from the group consisting of substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halogen, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, SO_2NH_2, SO_2NH(C_1-C_6 alkyl), SO_2N(C_1-C_6 alkyl)$_2$, (CH_2)$_{1-2}$-OH, C(O)(CH_2)$_{1-2}$-OH, C(O)(C_1-C_6 alkyl), and C(O)O(C_1-C_6 alkyl);

alternatively, two R^7, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl;

R^8 is independently, at each occurrence, selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, C_1-C_3 alkylamine, 3-6 membered cycloalkyl, halogen, OH, NO_2, NH_2, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, (CH_2)$_{1-4}$OH, S(O)$_{0-2}$H, S(O)$_{0-2}$$NH_2$, or CN; and

R^9 is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl all of which are optionally substituted with one, two, or three R^8.

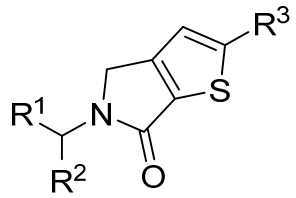
3. The compound of claim 2, wherein the compound of Formula X is a compound of Formula Xa:



(**Xa**)

or a pharmaceutically acceptable salt thereof.

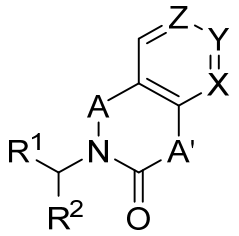
4. The compound of claim 2, wherein the compound of Formula X is a compound of Formula Xb:



(**Xb**)

or a pharmaceutically acceptable salt thereof.

5. A compound of Formula XX:



(**XX**)

or a pharmaceutically acceptable salt thereof;

wherein:

A and A' are each, independently, CH_2, CHR^8, NH, or NR^8;

alternatively, A is absent;

Z is selected from the group consisting of N, CH, C-halo, C-(C_1-C_3 alkyl), or C-(C_1-C_3 alkoxy);

X and Y are each, independently, N, CH, or CR^3;

provided that at least one of X, Y, or Z is CH;

R^1 is selected from the group consisting of $C(O)NHR^9$, 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl, wherein aryl, heteroaryl, cycloalkyl, and heterocycloalkyl are optionally substituted with one, two, or three R^8;

R^2 is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl, all of which are optionally substituted with one, two, or three R^6;

R^3 is independently, at each occurrence, selected from the group consisting of halogen, OR^4, NR^4R^4, SO_2R^4, SO_2NHR^4, $NHSO_2R^4$, $C(O)OR^4$, $C(O)NHR^4$, $NHC(O)R^4$,

$C(O)R^4$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, 3-7 membered cycloalkyl, C_4-C_7 cycloalkenyl, C_6-C_{10} aryl, 5-6 membered heteroaryl, and 5-7 membered heterocyclyl, wherein alkyl, alkenyl, or alkynyl are each optionally substituted one, two, or three times with R^4, and wherein aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^5;

R^4 is independently, at each occurrence, selected from the group consisting of H, C_1-C_6 alkyl, $(CH_2)_{0-3}$-(C_3-C_7 cycloalkyl), $(CH_2)_{0-3}$-(C_4-C_7 cycloalkenyl), $(CH_2)_{0-3}$-(C_6-C_{10} aryl), $(CH_2)_{0-3}$-(5-6 membered heteroaryl), and $(CH_2)_{0-3}$-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^5;

R^5 is independently, at each occurrence, selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_3 alkylamine, 3-10 membered cycloalkyl, halogen, COOH, $C(O)O(C_1$-C_6 alkyl), $O(CH_2)_{1-3}$-OH, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, OH, CN, $(CH_2)_{0-3}$-(C_6-C_{10} aryl), $(CH_2)_{0-3}$-(5-6 membered heteroaryl), and $(CH_2)_{0-3}$-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R^7;

alternatively, two R^5, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl all of which can be optionally substituted one, two, or three times with R^7;

R^6 is independently, at each occurrence, selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, C_1-C_3 alkylamine, halogen, OH, NO_2, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, $(CH_2)_{1-4}OH$, $S(O)_{0-2}H$, $S(O)_{0-2}NH_2$, or CN;

alternatively, two R^6, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl;

R^7 is independently, at each occurrence, selected from the group consisting of substituents independently selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, halogen, NH_2, $NH(C_1$-C_6 alkyl), $N(C_1$-C_6 alkyl)$_2$, SO_2NH_2, $SO_2NH(C_1$-C_6 alkyl), $SO_2N(C_1$-C_6 alkyl)$_2$, $(CH_2)_{1-2}$-OH, $C(O)(CH_2)_{1-2}$-OH, $C(O)(C_1$-C_6 alkyl), and $C(O)O(C_1$-C_6 alkyl);

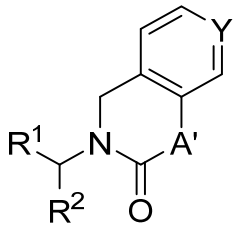
alternatively, two R^7, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl;

R^8 is independently, at each occurrence, selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, C_1-C_3 haloalkoxy, C_1-C_3 alkylamine, 3-6 membered

cycloalkyl, halogen, OH, NO_2, NH_2, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl)$_2$, $(CH_2)_{1\text{-}4}OH$, $S(O)_{0\text{-}2}H$, $S(O)_{0\text{-}2}NH_2$, or CN; and

R^9 is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl all of which are optionally substituted with one, two, or three R^8.

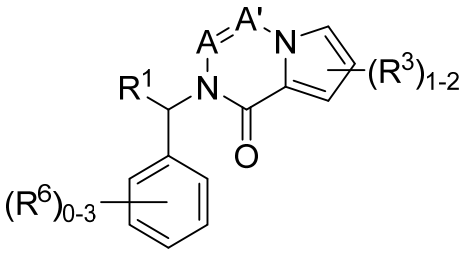
6. The compound of claim 5, wherein the compound of Formula XX is a compound of Formula XXa:



(**XXa**)

or a pharmaceutically acceptable salt thereof.

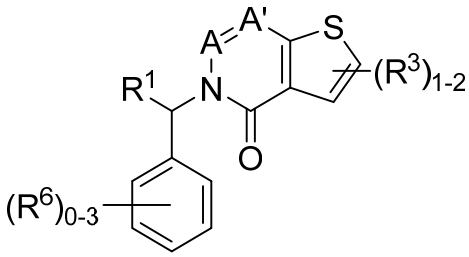
7. The compound of claim 1, wherein the compound of Formula I is a compound of Formula II:



(**II**)

or a pharmaceutically acceptable salt thereof.

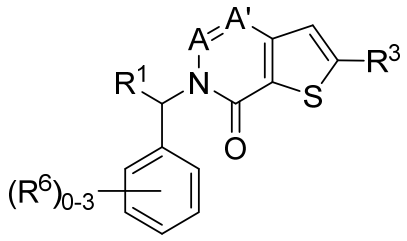
8. The compound of claim 1, wherein the compound of Formula I is a compound of Formula III:



(**III**)

or a pharmaceutically acceptable salt thereof.

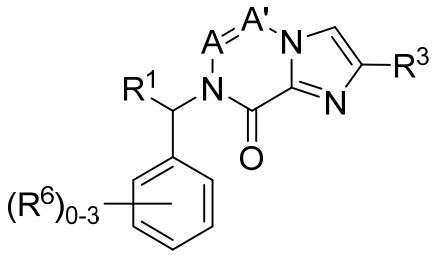
9. The compound of claim 1, wherein the compound of Formula I is a compound of Formula IV:



(**IV**)

or a pharmaceutically acceptable salt thereof.

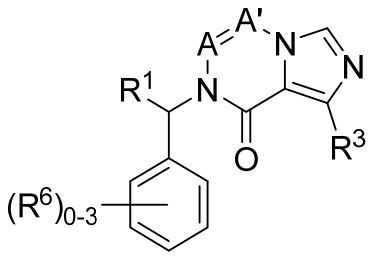
10. The compound of claim 1, wherein the compound of Formula I is a compound of Formula V:



(**V**)

or a pharmaceutically acceptable salt thereof.

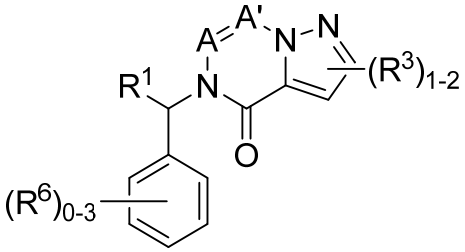
11. The compound of claim 1, wherein the compound of Formula I is a compound of Formula VI:



(**VI**)

or a pharmaceutically acceptable salt thereof.

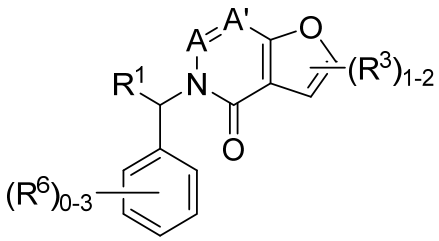
12. The compound of claim 1, wherein the compound of Formula I is a compound of Formula VII:



(**VII**)

or a pharmaceutically acceptable salt thereof.

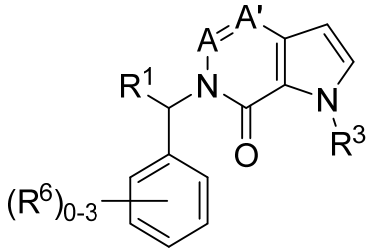
13. The compound of claim 1, wherein the compound of Formula I is a compound of Formula VIII:



(**VIII**)

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, wherein the compound of Formula I is a compound of Formula IX:



(**IX**)

or a pharmaceutically acceptable salt thereof.

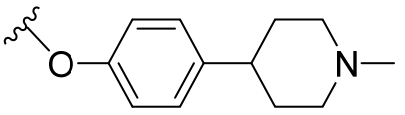
15. The compound of any one of claims 1-14, wherein R^2 is 6-10 membered aryl or 5-10 membered heteroaryl, both of which are optionally substituted with one, two, or three R^6.

16. The compound of any one of claims 1-14, wherein R^2 is phenyl optionally substituted with one, two, or three R^6.

17. The compound of any one of claims 1-16, wherein R^3 is independently at each occurrence selected from the group consisting of halogen, OR^4, NR^4R^4, $C(O)NHR^4$, C_1-C_6

alkyl, C_2-C_6 alkynyl, and C_6-C_{10} aryl, wherein alkyl and alkynyl are optionally substituted one, two, or three times with R^4, and aryl is optionally substituted one, two, or three times with R^5.

18. The compound of any one of claims 1-17, wherein R^3 is independently at each occurrence selected from the group consisting of halogen, methyl,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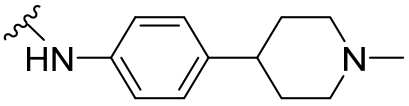
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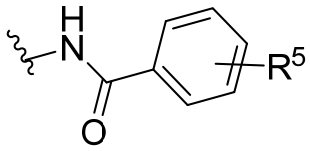
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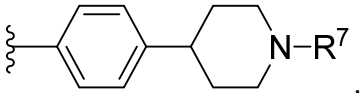
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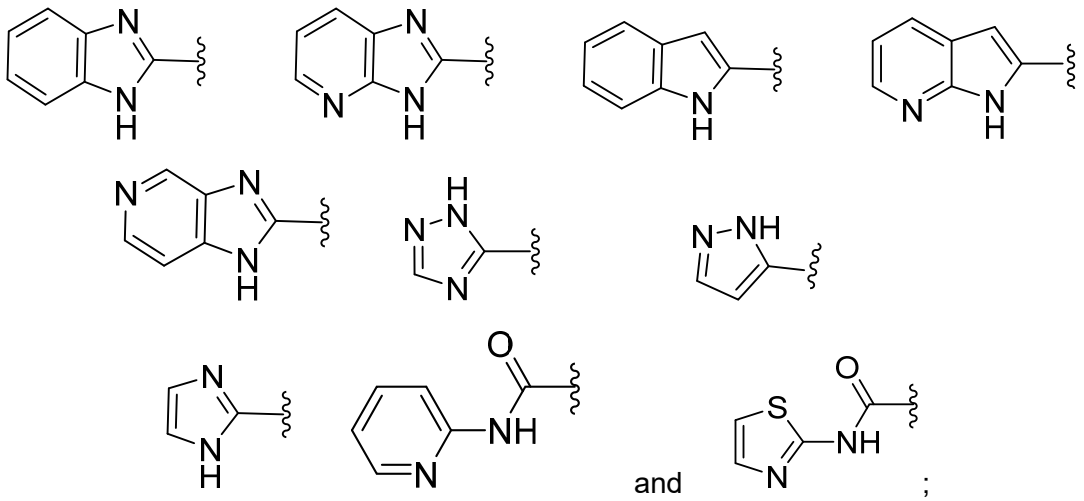
19. The compound of any one of claims 1-18, wherein R^6 is independently, at each occurrence, hydroxy or halo.

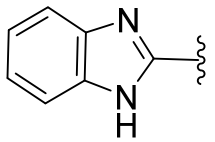
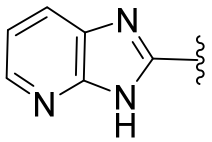
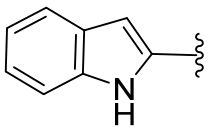
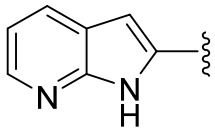
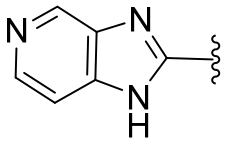
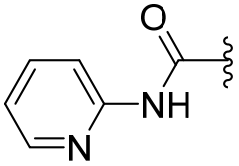
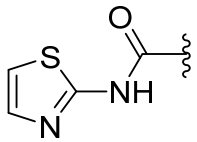
20. The compound of any one of claims 1-19, wherein R^1 is selected from the group consisting of benzimidazole, imidazopyridine, indole, triazole, pyrazole, imidazole, pyridinylamide, and thiazolylamide, all of which are optionally substituted with one, two, or three R^8.

21. The compound of any one of claims 1-19, wherein R^1 is selected from the group consisting of:


and
;

all of which are optionally substituted with one, two, or three R^8.

22. The compound of any one of claims 1-21, wherein R^1 is selected from the group consisting of:

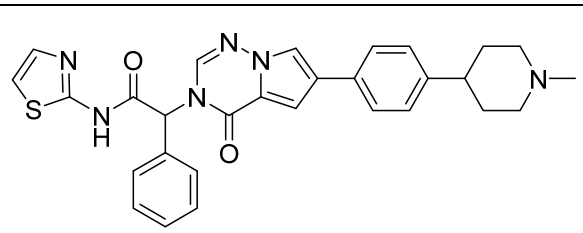
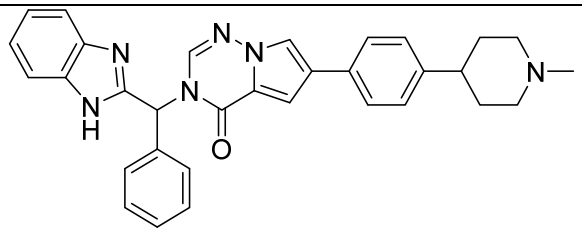
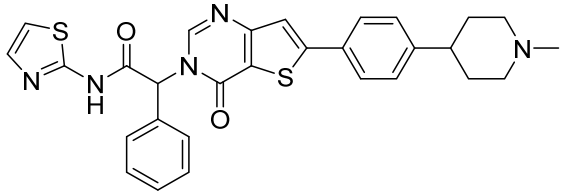
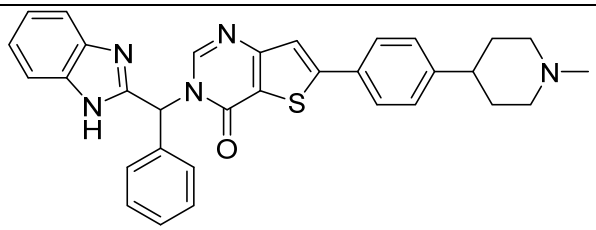
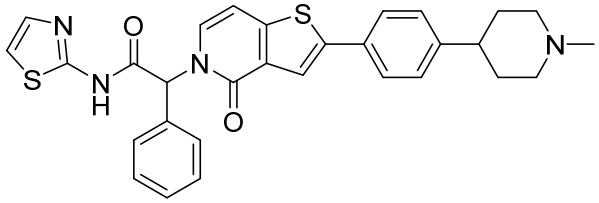
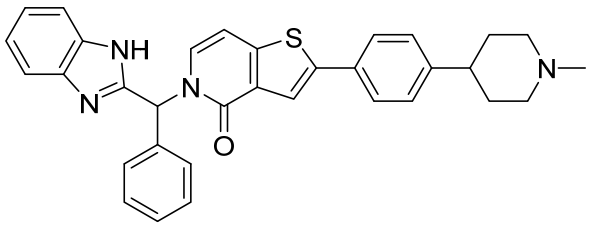






and

;

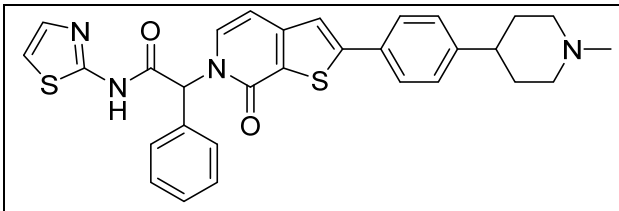
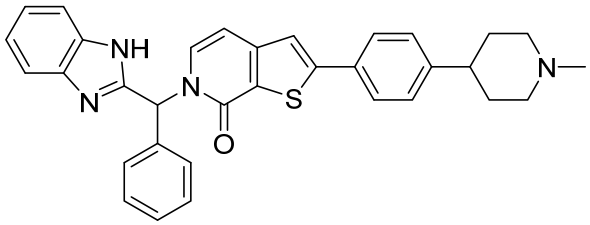
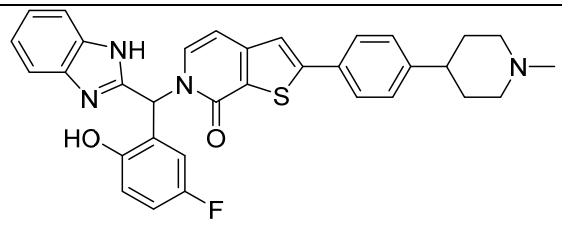
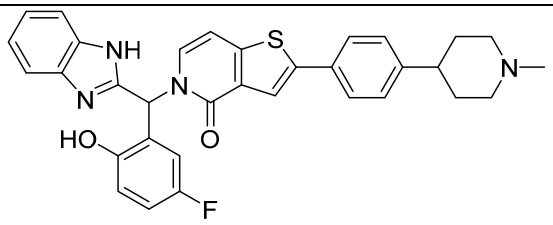
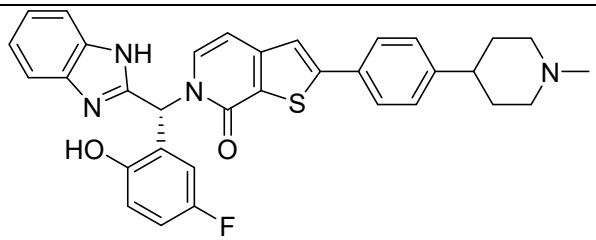
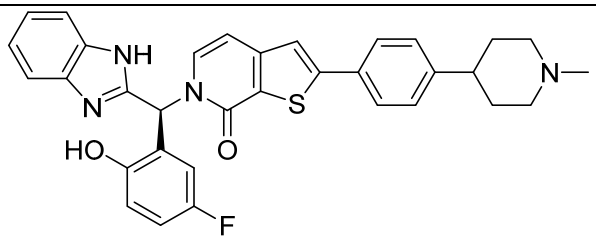
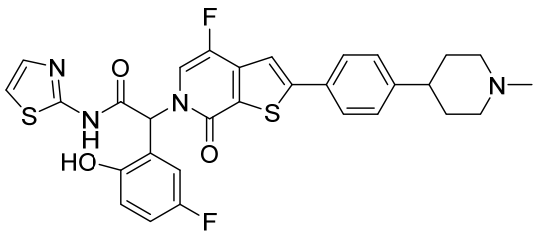
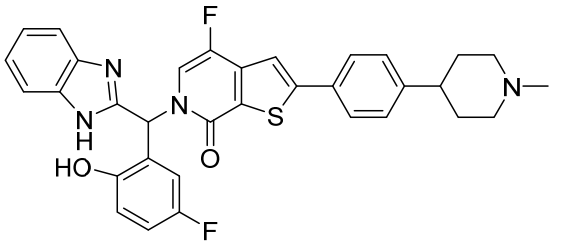
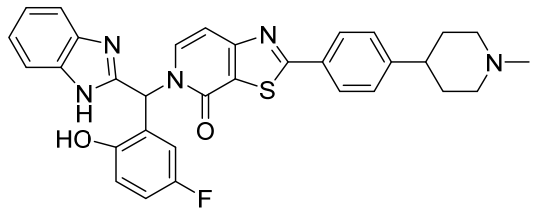
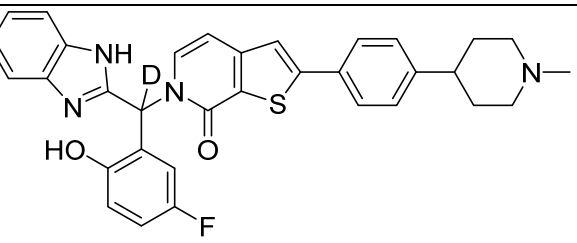
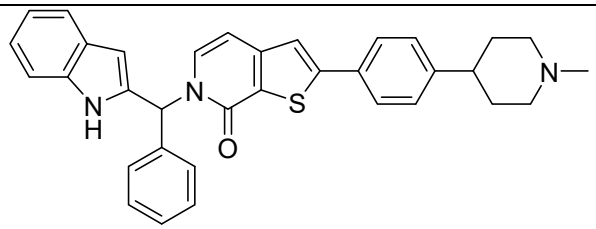
all of which are optionally substituted with one, two, or three R^8.

23. The compound of any one of claims 1-22, wherein R^7 is C_1-C_3 alkyl.

24. The compound of any one of claims 1-23, wherein R^8 is independently, at each occurrence, selected from the group consisting of C_1-C_3 alkyl, C_1-C_3 haloalkyl, C_1-C_3 alkoxy, halogen, OH, and NH_2.

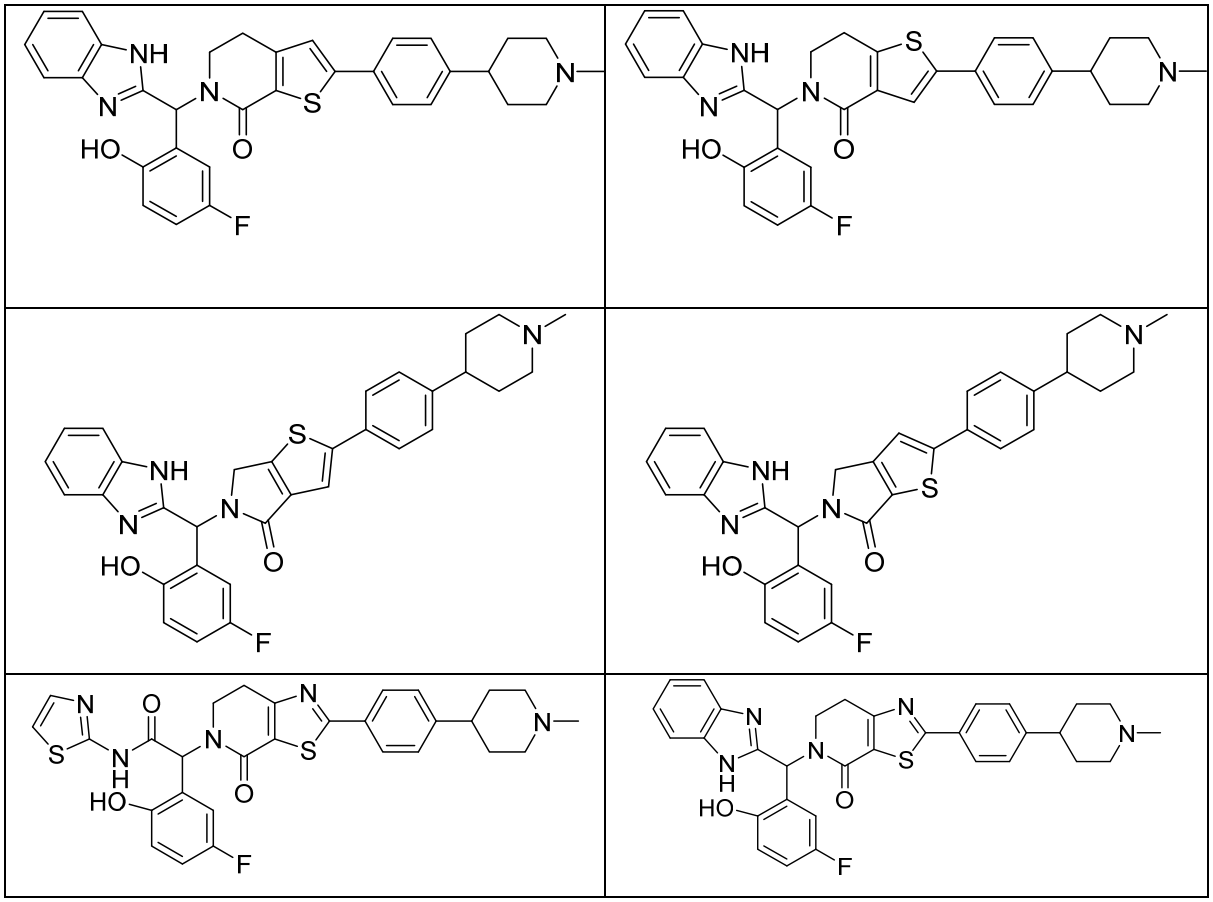
25. The compound of claim 1, wherein the compound of Formula I is selected from the group consisting of:

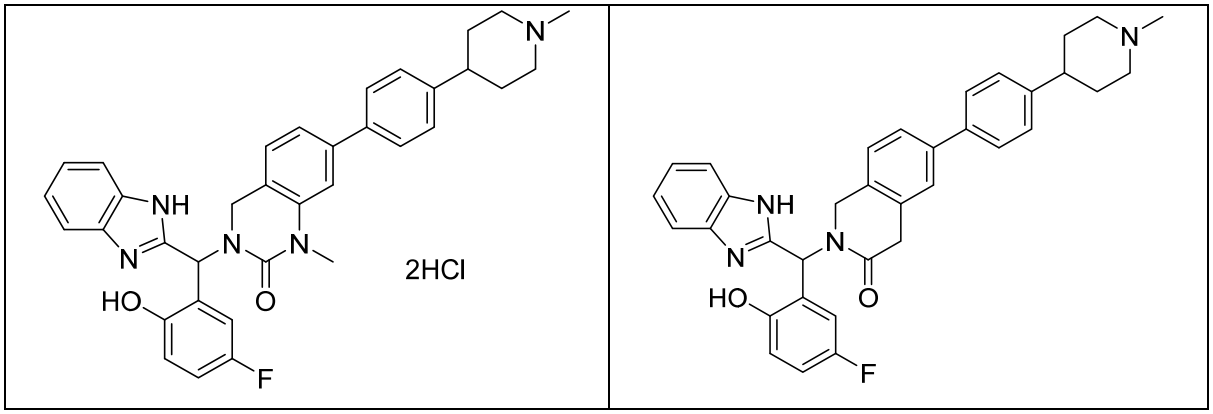
or a pharmaceutically acceptable salt thereof.

26. The compound of claim 2 selected from the group consisting of



or a pharmaceutically acceptable salt thereof.

27. The compound of claim 5, wherein the compound of Formula XX is selected from the group consisting of



or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

29. The pharmaceutical composition according to claim 28, wherein the composition further comprises a second active agent.

30. The pharmaceutical composition according to claim 28, wherein the second active agent is selected from the group consisting of a MEK inhibitor, a PI3K inhibitor, and an mTor inhibitor.

31. The pharmaceutical composition according to claim 28, wherein the second active agent prevents EGFR dimer formation in a subject.

32. The pharmaceutical composition according to claim 28, wherein the second active agent is selected from the group consisting of cetuximab, trastuzumab, and panitumumab.

33. The pharmaceutical composition according to claim 28, wherein the second active agent is an ATP competitive EGFR inhibitor.

34. The pharmaceutical composition according to claim 28, wherein the ATP competitive EGFR inhibitor is osimertinib, gefitinib, or erlotinib.

35. The compound of any one of claims 1-27 or the composition according to any one of claims 28-34 for use as a medicament.

36. Use of the compound of any one of claims 1-27 or the a composition according to any one of claims 28-34 in the preparation of a medicament for treating cancer wherein the medicament is to be administered to a subject in need thereof.

37. The use according to claim 36, wherein the cancer is selected from the group consisting of lung cancer, colon cancer, breast cancer, endometrial cancer, thyroid cancer, glioma, squamous cell carcinoma, and prostate cancer.

38. The method according to claim 36, wherein the cancer is non-small cell lung cancer (NSCLC).

39. Use of the compound of any one of claims 1-27 or the composition according to any one of claims 28-34 in the preparation of a medicament for inhibiting a kinase in a subject in need thereof, wherein a therapeutically effective amount of the compound or composition is to be administered to the subject.

40. The use according to claim 39, wherein the kinase is EGFR.

41. Use of the compound of any one of claims 1-27 or the composition according to any one of claims 28-34 in the preparation of a medicament for treating or preventing a kinase-mediated disorder, wherein the medicament is to be administered to a subject in need thereof.

42. The method according to claim 41, wherein the kinase-mediated disorder is resistant to an EGFR-targeted therapy.

43. The method according to claim 42, wherein the EGFR-treated therapy is selected from the group consisting of gefitinib, erlotinib, and osimertinib.