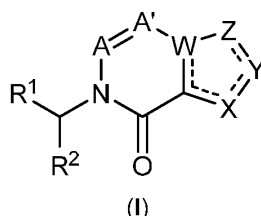


CLAIMS

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof;

wherein:

== represents a single or double bond;

A and A' are each, independently, CH, CR⁸, or N;

W is N or C;

Z is selected from the group consisting of S, O, N, NH, N-Me, CH₂, CH, C-halo, C-(C₁-C₃ alkyl), or C-(C₁-C₃ alkoxy);

X and Y are each, independently, S, O, N, CH, NR³, or CR³;

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

R¹ is selected from the group consisting of C(O)NHR⁹, 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 R⁸;

R² 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 R⁶;

R³ is independently, at each occurrence, selected from the group consisting of halogen, OR⁴, NR⁴R⁴, SO₂R⁴, SO₂NHR⁴, NH₂SO₂R⁴, C(O)OR⁴, C(O)NHR⁴, NHC(O)R⁴, C(O)R⁴, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, 3-7 membered cycloalkyl, C₄-C₇ cycloalkenyl, C₆-C₁₀ 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 R⁴, and wherein aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁵;

R⁴ is independently, at each occurrence, selected from the group consisting of H, C₁-C₆ alkyl, (CH₂)₀₋₃-(C₃-C₇ cycloalkyl), (CH₂)₀₋₃-(C₄-C₇ cycloalkenyl), (CH₂)₀₋₃-(C₆-C₁₀ aryl), (CH₂)₀₋₃-(5-6 membered heteroaryl), and (CH₂)₀₋₃-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁵;

R⁵ is independently, at each occurrence, selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₃ alkylamine, 3-10 membered cycloalkyl, halogen, COOH, C(O)O(C₁-C₆ alkyl), O(CH₂)₁₋₃-OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, OH, CN, (CH₂)₀₋₃-(C₆-C₁₀ aryl), (CH₂)₀₋₃-(5-6 membered heteroaryl), and (CH₂)₀₋₃-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁷;

alternatively, two R⁵, 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 R⁷;

R⁶ is independently, at each occurrence, selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₁-C₃ alkylamine, halogen, OH, NO₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, (CH₂)₁₋₄OH, S(O)₀₋₂H, S(O)₀₋₂NH₂, or CN;

alternatively, two R⁶, 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;

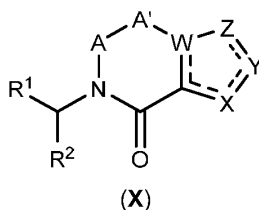
R⁷ is independently, at each occurrence, selected from the group consisting of substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, SO₂NH₂, SO₂NH(C₁-C₆ alkyl), SO₂N(C₁-C₆ alkyl)₂, (CH₂)₁₋₂-OH, C(O)(CH₂)₁₋₂-OH, C(O)(C₁-C₆ alkyl), and C(O)O(C₁-C₆ alkyl);

alternatively, two R⁷, 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;

R⁸ is independently, at each occurrence, selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₁-C₃ alkylamine, 3-6 membered cycloalkyl, halogen, OH, NO₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, (CH₂)₁₋₄OH, S(O)₀₋₂H, S(O)₀₋₂NH₂, or CN; and

R⁹ 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 R⁸.

2. A compound of Formula X:



or a pharmaceutically acceptable salt thereof;

wherein:

== represents a single or double bond;

A and A' are each, independently, CH, CR⁸, 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, CH₂, CH, C-halo, C-(C₁-C₃ alkyl), or C-(C₁-C₃ alkoxy);

X and Y are each, independently, S, O, N, CH, NR³, or CR³;

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

R¹ is selected from the group consisting of C(O)NHR⁹, 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 R⁸;

R² 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 R⁶;

R³ is independently, at each occurrence, selected from the group consisting of halogen, OR⁴, NR⁴R⁴, SO₂R⁴, SO₂NHR⁴, NHSO₂R⁴, C(O)OR⁴, C(O)NHR⁴, NHC(O)R⁴, C(O)R⁴, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, 3-7 membered cycloalkyl, C₄-C₇ cycloalkenyl, C₆-C₁₀ 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 R⁴, and wherein aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁵;

R⁴ is independently, at each occurrence, selected from the group consisting of H, C₁-C₆ alkyl, (CH₂)₀₋₃-(C₃-C₇ cycloalkyl), (CH₂)₀₋₃-(C₄-C₇ cycloalkenyl), (CH₂)₀₋₃-(C₆-C₁₀ aryl), (CH₂)₀₋₃-(5-6 membered heteroaryl), and (CH₂)₀₋₃-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁵;

R⁵ is independently, at each occurrence, selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₃ alkylamine, 3-10 membered

cycloalkyl, halogen, COOH, C(O)O(C₁-C₆ alkyl), O(CH₂)₁₋₃-OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, OH, CN, (CH₂)₀₋₃-(C₆-C₁₀ aryl), (CH₂)₀₋₃-(5-6 membered heteroaryl), and (CH₂)₀₋₃-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁷;

alternatively, two R⁵, 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 R⁷;

R⁶ is independently, at each occurrence, selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₁-C₃ alkylamine, halogen, OH, NO₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, (CH₂)₁₋₄OH, S(O)₀₋₂H, S(O)₀₋₂NH₂, or CN;

alternatively, two R⁶, 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;

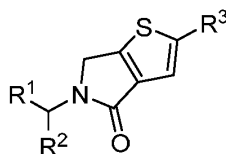
R⁷ is independently, at each occurrence, selected from the group consisting of substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, SO₂NH₂, SO₂NH(C₁-C₆ alkyl), SO₂N(C₁-C₆ alkyl)₂, (CH₂)₁₋₂-OH, C(O)(CH₂)₁₋₂-OH, C(O)(C₁-C₆ alkyl), and C(O)O(C₁-C₆ alkyl);

alternatively, two R⁷, 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;

R⁸ is independently, at each occurrence, selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₁-C₃ alkylamine, 3-6 membered cycloalkyl, halogen, OH, NO₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, (CH₂)₁₋₄OH, S(O)₀₋₂H, S(O)₀₋₂NH₂, or CN; and

R⁹ 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 R⁸.

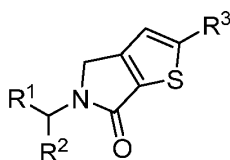
3. The compound of claim 2, wherein the compound of Formula X is a compound of Formula Xa:



(Xa)

or a pharmaceutically acceptable salt thereof.

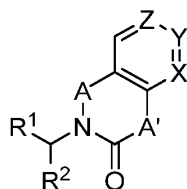
4. The compound of claim 2, wherein the compound of Formula X is a compound of Formula Xb:



(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, CH₂, CHR⁸, NH, or NR⁸;

alternatively, A is absent;

Z is selected from the group consisting of N, CH, C-halo, C-(C₁-C₃ alkyl), or C-(C₁-C₃ alkoxy);

X and Y are each, independently, N, CH, or CR³;

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

R¹ is selected from the group consisting of C(O)NHR⁹, 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 R⁸;

R² 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 R⁶;

R³ is independently, at each occurrence, selected from the group consisting of halogen, OR⁴, NR⁴R⁴, SO₂R⁴, SO₂NHR⁴, NHSO₂R⁴, C(O)OR⁴, C(O)NHR⁴, NHC(O)R⁴,

C(O)R⁴, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, 3-7 membered cycloalkyl, C₄-C₇ cycloalkenyl, C₆-C₁₀ 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 R⁴, and wherein aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁵;

R⁴ is independently, at each occurrence, selected from the group consisting of H, C₁-C₆ alkyl, (CH₂)₀₋₃-(C₃-C₇ cycloalkyl), (CH₂)₀₋₃-(C₄-C₇ cycloalkenyl), (CH₂)₀₋₃-(C₆-C₁₀ aryl), (CH₂)₀₋₃-(5-6 membered heteroaryl), and (CH₂)₀₋₃-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁵;

R⁵ is independently, at each occurrence, selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₃ alkylamine, 3-10 membered cycloalkyl, halogen, COOH, C(O)O(C₁-C₆ alkyl), O(CH₂)₁₋₃-OH, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, OH, CN, (CH₂)₀₋₃-(C₆-C₁₀ aryl), (CH₂)₀₋₃-(5-6 membered heteroaryl), and (CH₂)₀₋₃-(5-7 membered heterocyclyl), wherein the aryl, heteroaryl, or heterocyclyl are each optionally substituted one, two, or three times with R⁷;

alternatively, two R⁵, 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 R⁷;

R⁶ is independently, at each occurrence, selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₁-C₃ alkylamine, halogen, OH, NO₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, (CH₂)₁₋₄OH, S(O)₀₋₂H, S(O)₀₋₂NH₂, or CN;

alternatively, two R⁶, 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;

R⁷ is independently, at each occurrence, selected from the group consisting of substituents independently selected from C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, halogen, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, SO₂NH₂, SO₂NH(C₁-C₆ alkyl), SO₂N(C₁-C₆ alkyl)₂, (CH₂)₁₋₂-OH, C(O)(CH₂)₁₋₂-OH, C(O)(C₁-C₆ alkyl), and C(O)O(C₁-C₆ alkyl);

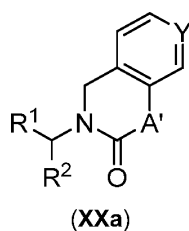
alternatively, two R⁷, together with the atoms to which they are attached, can form 5-10 membered heteroaryl, 6-10 membered aryl, 3-10 membered heterocycloalkyl, or 3-10 membered cycloalkyl;

R⁸ is independently, at each occurrence, selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkoxy, C₁-C₃ alkylamine, 3-6 membered

cycloalkyl, halogen, OH, NO₂, NH₂, NH(C₁-C₆ alkyl), N(C₁-C₆ alkyl)₂, (CH₂)₁₋₄OH, S(O)₀₋₂H, S(O)₀₋₂NH₂, or CN; and

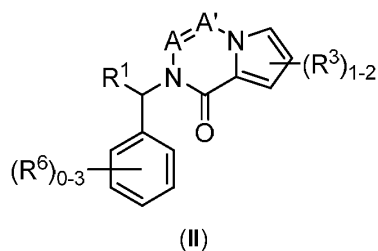
R⁹ is selected from the group consisting of 6-10 membered aryl, 5-10 membered heteroaryl, 3-10 membered heterocycloalkyl, and 3-10 membered cycloalkyl all of which are optionally substituted with one, two, or three R⁸.

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



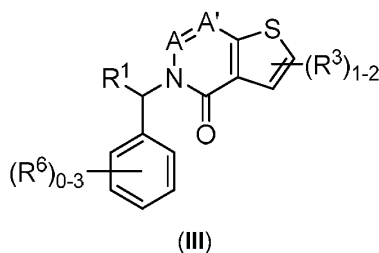
or a pharmaceutically acceptable salt thereof.

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



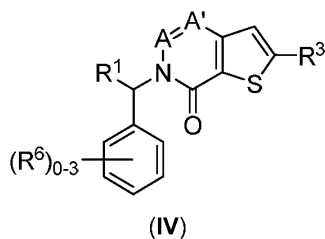
or a pharmaceutically acceptable salt thereof.

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



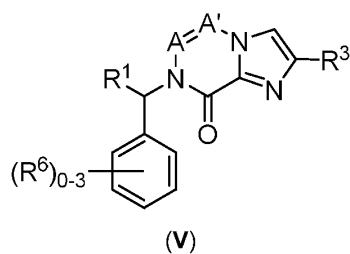
or a pharmaceutically acceptable salt thereof.

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



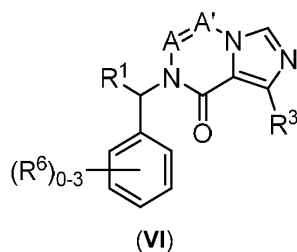
or a pharmaceutically acceptable salt thereof.

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



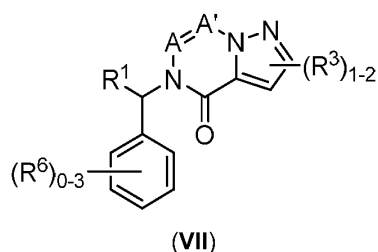
or a pharmaceutically acceptable salt thereof.

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



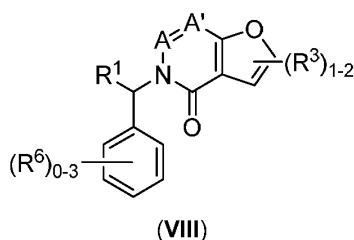
or a pharmaceutically acceptable salt thereof.

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



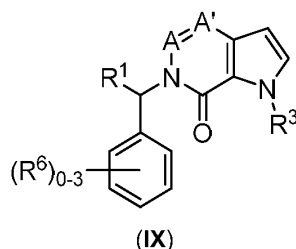
or a pharmaceutically acceptable salt thereof.

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



or a pharmaceutically acceptable salt thereof.

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

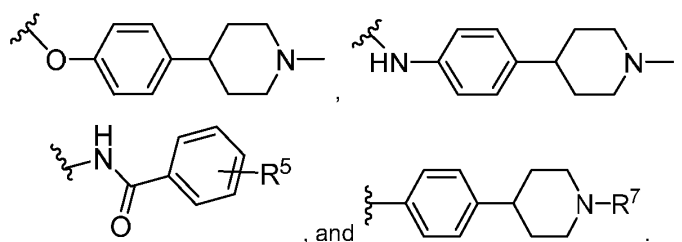


or a pharmaceutically acceptable salt thereof.

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, C₂-C₆ alkynyl, and C₆-C₁₀ aryl, wherein alkyl and alkynyl are optionally substituted one, two, or three times with R⁴, and aryl is optionally substituted one, two, or three times with R⁵.

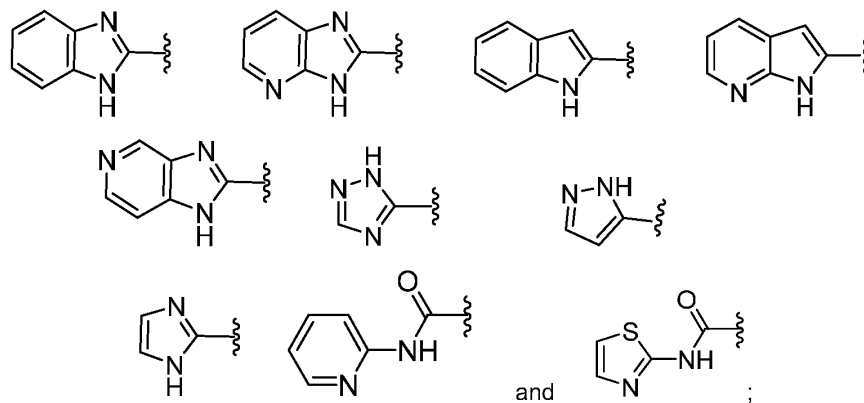
18. The compound of any one of claims 1-17, wherein R³ is independently at each occurrence selected from the group consisting of halogen, methyl,



19. The compound of any one of claims 1-18, wherein R⁶ is independently, at each occurrence, hydroxy or halo.

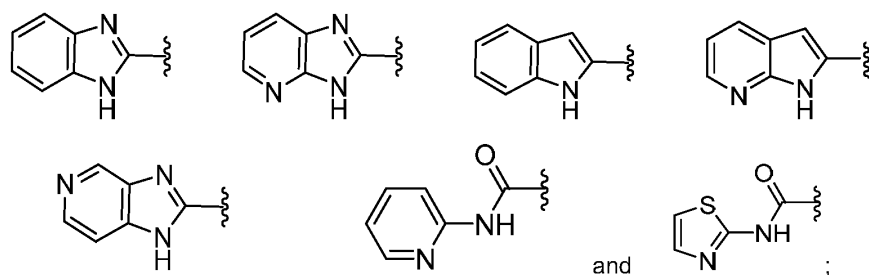
20. The compound of any one of claims 1-19, wherein R¹ is selected from the group consisting of benzimidazole, imidazopyridine, indole, triazole, pyrazole, imidazole, pyridinylamide, and thiazolylamide, all of which are optionally substituted with one, two, or three R⁸.

21. The compound of any one of claims 1-19, wherein R¹ is selected from the group consisting of:



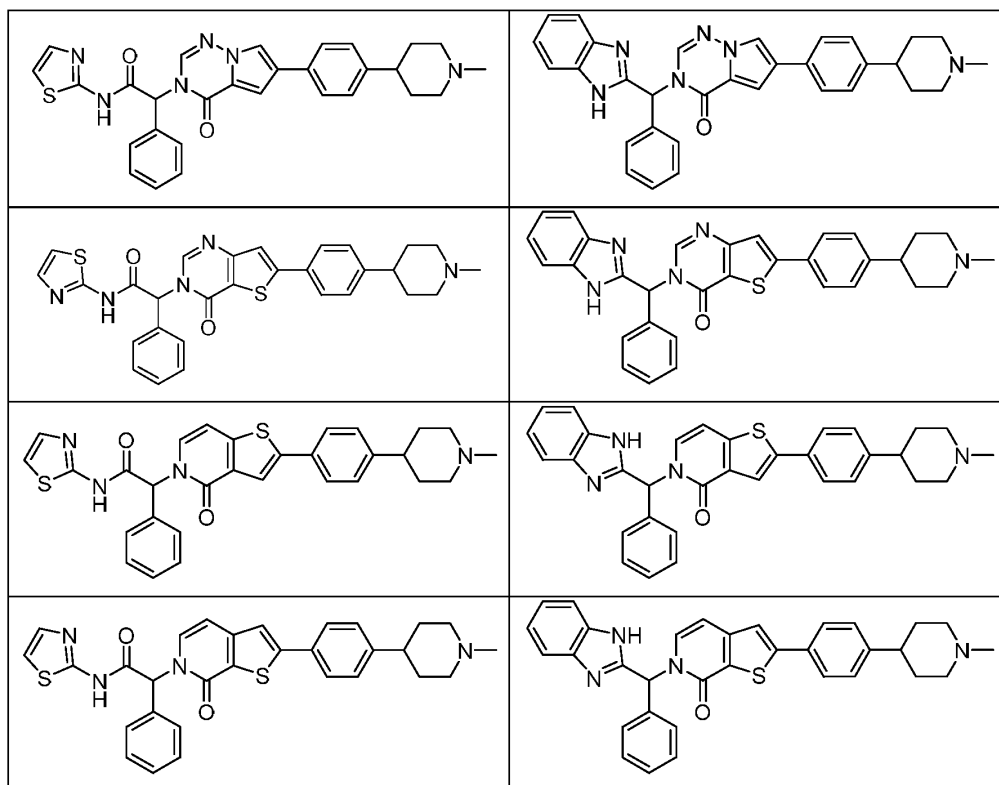
all of which are optionally substituted with one, two, or three R⁸.

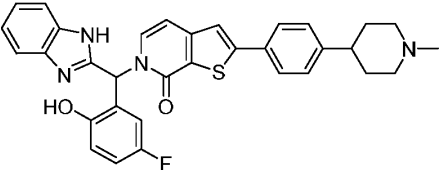
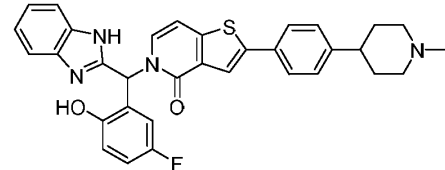
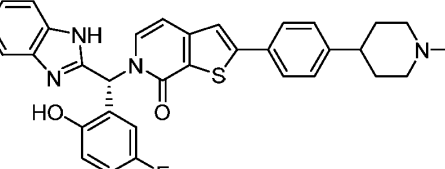
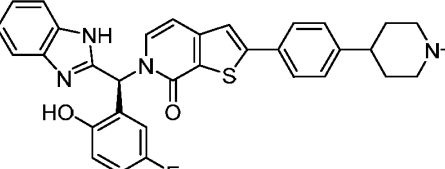
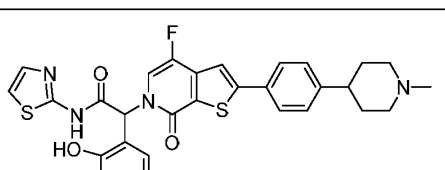
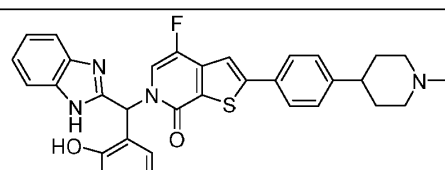
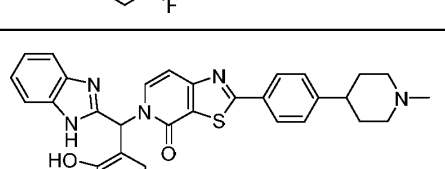
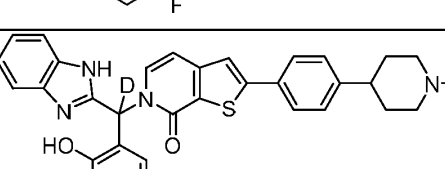
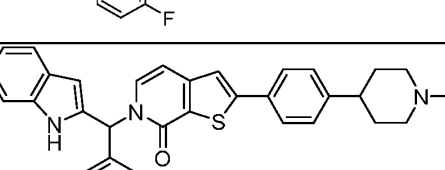
22. The compound of any one of claims 1-21, wherein R¹ is selected from the group consisting of:



all of which are optionally substituted with one, two, or three R⁸.

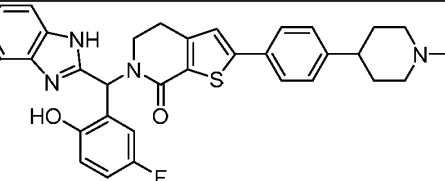
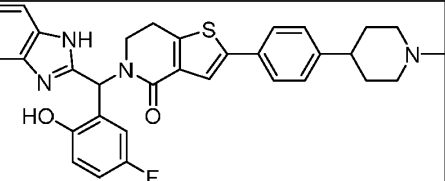
23. The compound of any one of claims 1-22, wherein R⁷ is C₁-C₃ alkyl.
24. The compound of any one of claims 1-23, wherein R⁸ is independently, at each occurrence, selected from the group consisting of C₁-C₃ alkyl, C₁-C₃ haloalkyl, C₁-C₃ alkoxy, halogen, OH, and NH₂.
25. The compound of claim 1, wherein the compound of Formula I is selected from the group consisting of:

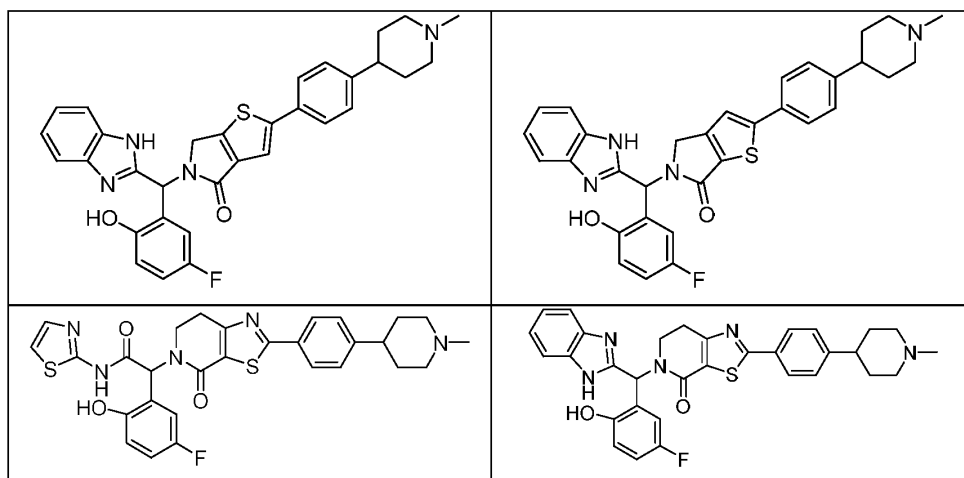


or a pharmaceutically acceptable salt thereof.

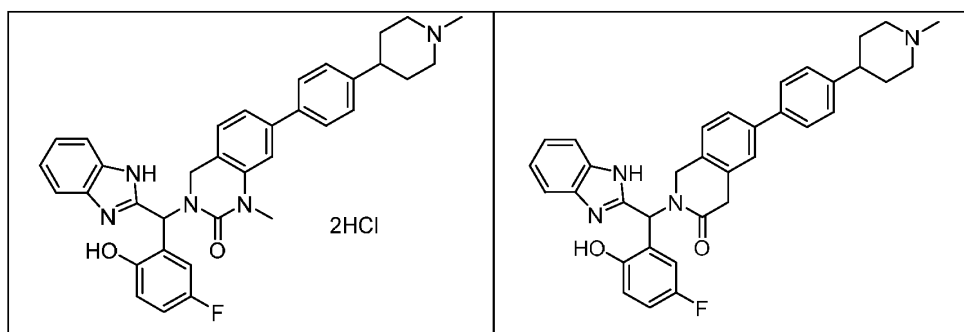
26. The compound of claim 2 selected from the group consisting of

	
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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. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-27 or a composition according to any one of claims 28-34.
36. The method according to claim 35, 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.
37. The method according to claim 35, wherein the cancer is non-small cell lung cancer (NSCLC).
38. A method of inhibiting a kinase in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-27 or a composition according to any one of claims 28-34.
39. The method according to claim 38, wherein the kinase is EGFR.
40. A method of treating or preventing a kinase-mediated disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-27 or a composition according to any one of claims 28-34.
41. The method according to claim 40, wherein the kinase-mediated disorder is resistant to an EGFR-targeted therapy.

42. The method according to claim 41, wherein the EGFR-treated therapy is selected from the group consisting of gefitinib, erlotinib, and osimertinib.