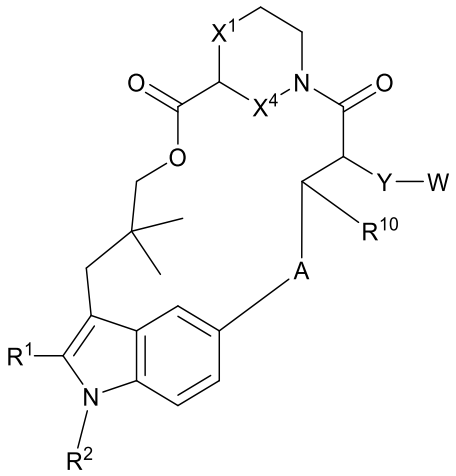
Summary

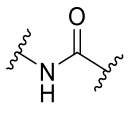
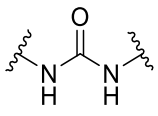
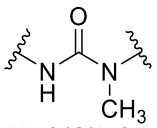
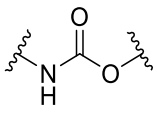
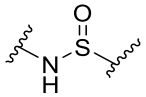
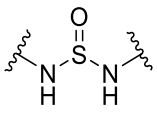
Provided herein are Ras inhibitors. These Ras inhibitors target, that is, selectively bind to or inhibit, Ras(ON) (e.g., selective over the GDP-bound, inactive state of Ras). The approach described herein entails formation of a high affinity three-component complex between a synthetic ligand and two intracellular proteins which do not interact under normal physiological conditions: the target protein of interest (e.g., Ras), and a widely expressed cytosolic chaperone (presenter protein) in the cell (e.g., cyclophilin A). More specifically, in some examples, the inhibitors of Ras described herein induce a new binding pocket in Ras by driving formation of a high affinity tri-complex between the Ras protein and the widely expressed cytosolic chaperone, cyclophilin A (CYPA). Without being bound by theory, the inventors believe that one way the inhibitory effect on Ras is effected by compounds of the disclosure and the complexes they form is by steric occlusion of the interaction site between Ras and downstream effector molecules, such as RAF and PI3K, which are required for propagating the oncogenic signal.

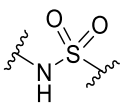
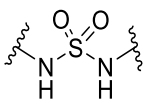
As such, in an aspect, the disclosure features a compound, or pharmaceutically acceptable salt thereof, of structural Formula Ia:



Formula Ia

wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, optionally substituted 5 to 6-membered heteroarylene, optionally substituted C_2-C_4 alkylene, or optionally substituted C_2-C_4 alkenylene;

Y is  -NHC(O)-,  -NHC(O)NH-,  -NHC(O)NCH$_3$-,  -NHC(O)O-,  -NHC(S)-,  -NHC(S)NH-,

 -NHS(O)$_2$-, or  -NHS(O)$_2$NH-;

W is hydrogen, C_1-C_4 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

X^1 and X^4 are each, independently, CH_2 or NH;

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 15-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

R^{10} is hydrogen, hydroxy, optionally substituted C_1-C_3 alkyl, or optionally substituted C_1-C_6 heteroalkyl. In some examples, R^{10} is hydrogen.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, of Table 1a.

In another aspect, there is provide a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, as defined above and a pharmaceutically acceptable excipient.

Also provided are pharmaceutical compositions comprising a compound of Formula Ia, or a pharmaceutically acceptable salt thereof, and a pharamceuticall acceptable excipient.

In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt thereof, as defined above, or a pharmaceutical composition as defined above, in the manufacture of a medicament for the treatment of cancer.

Also provided is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided the use of a compound, or a pharmaceutically acceptable salt thereof, as defined above, or a pharmaceutical composition as defined above, in the manufacture of a medicament for the treatment of a Ras protein related disorder.

In some examples, a method is provided of treating a Ras protein-related disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, as defined above, or a pharmaceutical composition as defined above.

Further provided is a method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound of the present disclosure, or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as defined above or a pharmaceutical composition as defined above, for use in therapy

It is specifically contemplated that any limitation discussed with respect to one example of the disclosure may apply to any other example of the

disclosure. Furthermore, any compound or composition of the invention may be used in any method of the disclosure, and any method of the disclosure may be used to produce or to utilize any compound or composition of the disclosure.

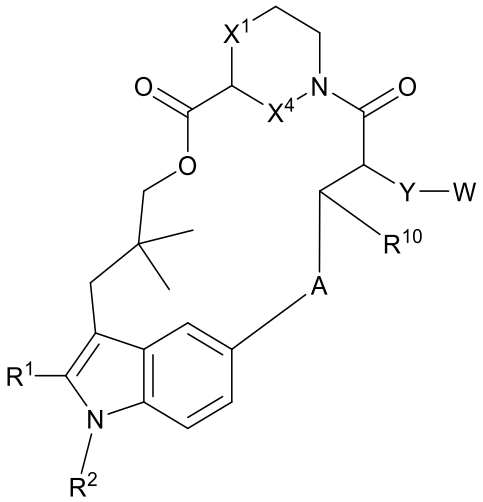
Definitions and Chemical Terms

In this application, unless otherwise clear from context, (i) the term “a” means “one or more”; (ii) the term "or" is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternative are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or"; (iii) the terms “comprising” and “including” are understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; and (iv) where ranges are provided, endpoints are included.

As used herein, the term “about” is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value. In certain embodiments, the term “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less

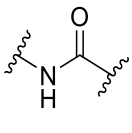
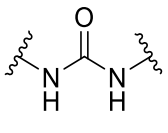
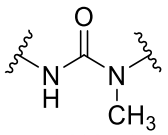
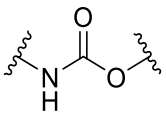
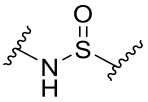
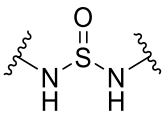
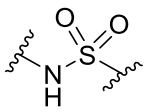
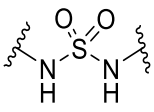
Claims

1. A compound, or pharmaceutically acceptable salt thereof, having the structure of Formula Ia:



Formula Ia

wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, optionally substituted 5 to 6-membered heteroarylene, optionally substituted C_2-C_4 alkylene, or optionally substituted C_2-C_4 alkenylene;

Y is  -NHC(O)-,  -NHC(O)NH-,  -NHC(O)NCH$_3$-,  -NHC(O)O-,  -NHC(S)-,  -NHC(S)NH-,  -NHS(O)$_2$-, or  -NHS(O)$_2$NH-;

W is hydrogen, C_1-C_4 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

X^1 and X^4 are each, independently, CH_2 or NH;

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

R^{10} is hydrogen, hydroxy, optionally substituted C_1-C_3 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

2. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted 6 to 10-membered aryl or optionally substituted 5 to 10-membered heteroaryl.

3. The compound of claim 2, or pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted phenyl or optionally substituted pyridine.

4. The compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, wherein A is optionally substituted thiazole, optionally substituted triazole, optionally substituted morpholino, optionally substituted piperidinyl, optionally substituted pyridine, or optionally substituted phenyl.

5. The compound of any one of claims 1-3, or pharmaceutically acceptable salt thereof, wherein A is not an optionally substituted phenyl or benzimidazole.

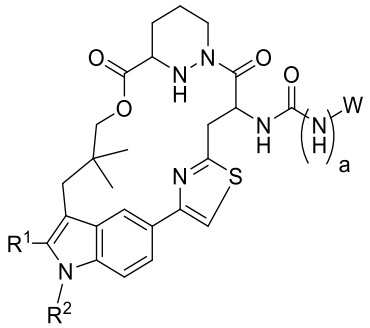
6. The compound of claim 5, or pharmaceutically acceptable salt thereof, wherein A is not hydroxyphenyl.

7. The compound of any one of claims 1-6, or pharmaceutically acceptable salt thereof, wherein the compound is not a compound of Table 2.

8. The compound of any one of claims 1-7, or pharmaceutically acceptable salt thereof, wherein the compound is not a compound of Table 3.

9. The compound of any one of claims 1-8, or pharmaceutically acceptable salt thereof, wherein Y is -NHC(O)- or -NHC(O)NH-.

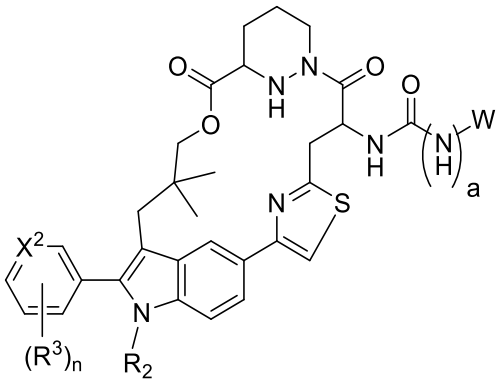
10. The compound of claim 9, or pharmaceutically acceptable salt thereof, having the structure of Formula IIa:



Formula IIa,

wherein a is 0 or 1.

11. The compound of claim 10, or pharmaceutically acceptable salt thereof, having the structure of Formula II-1a:



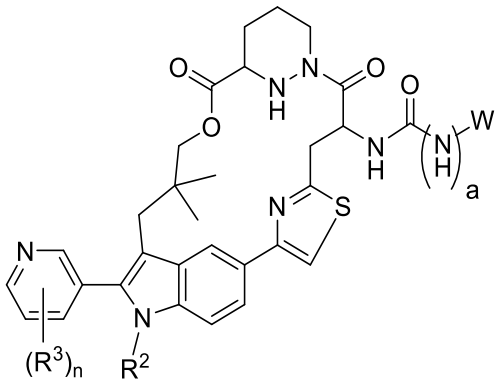
Formula II-1a,

wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

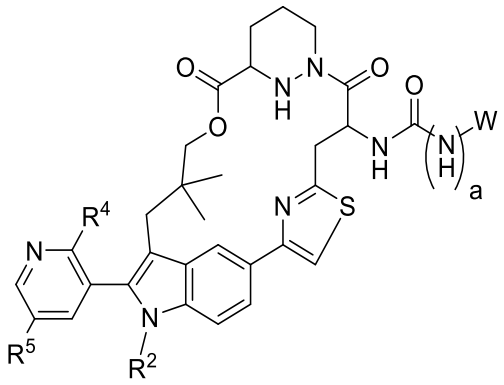
n is an integer from 1 to 4.

12. The compound of claim 11, or pharmaceutically acceptable salt thereof, having the structure of Formula IIa-2:



Formula IIa-2.

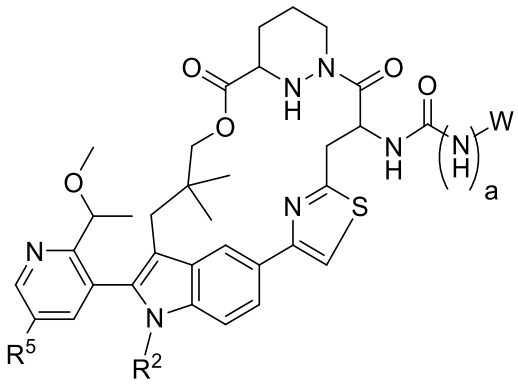
13. The compound of claim 12, or pharmaceutically acceptable salt thereof, having the structure of Formula IIa-3:



Formula IIa-3,

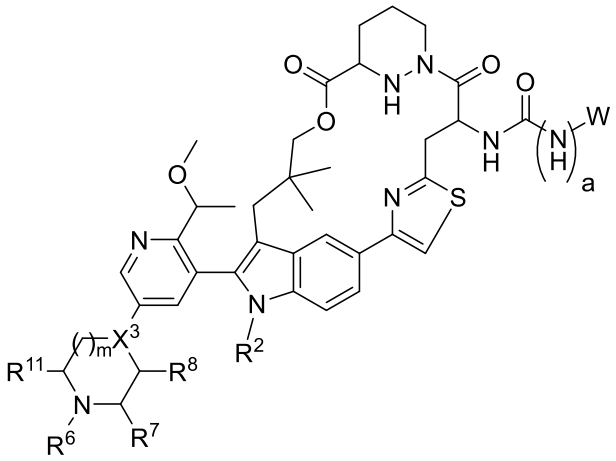
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

14. The compound of claim 13, or pharmaceutically acceptable salt thereof, having the structure of Formula IIa-4:



Formula IIa-4.

15. The compound of claim 14, or pharmaceutically acceptable salt thereof, having the structure of Formula IIa-5:



Formula IIa-5,

wherein X^3 is N or CH;

m is 1 or 2;

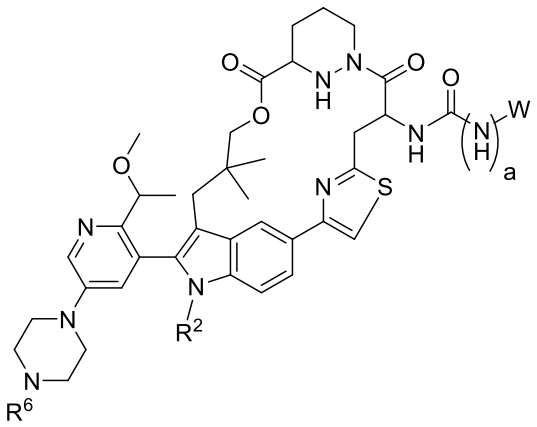
R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

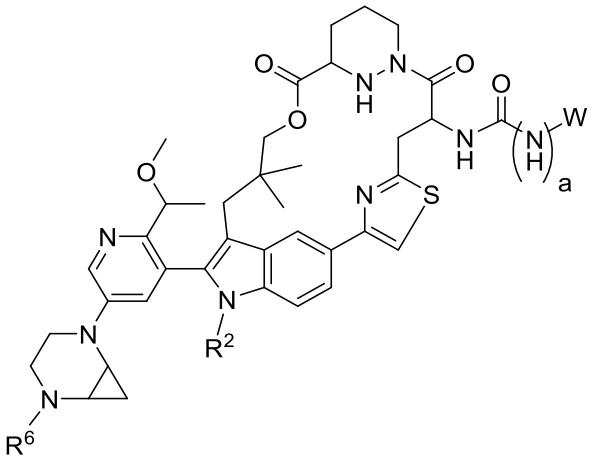
R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

16. The compound of claim 15, or pharmaceutically acceptable salt thereof, having the structure of Formula IIa-6:



Formula IIa-6.

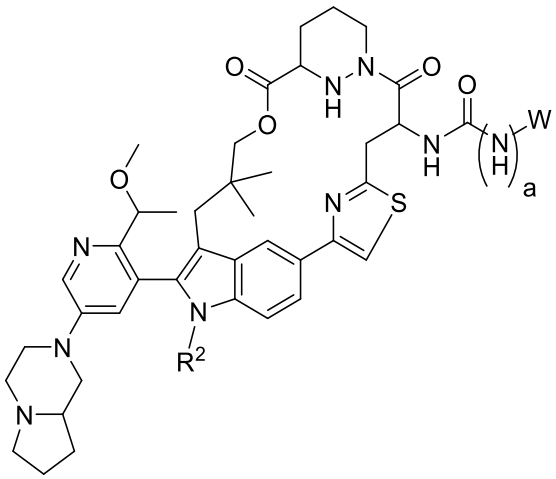
17. The compound of claim 15, or pharmaceutically acceptable salt thereof, having the structure of Formula IIa-7:



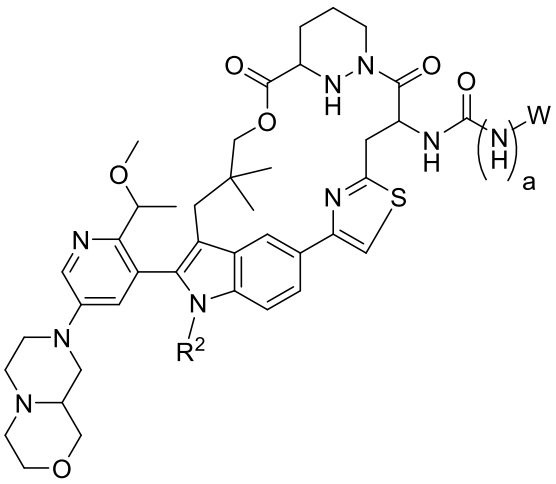
Formula IIa-7.

18. The compound of claim 16 or 17, wherein R^6 is methyl.

19. The compound of claim 15, or pharmaceutically acceptable salt thereof, having the structure of Formula IIa-8 or Formula IIa-9:

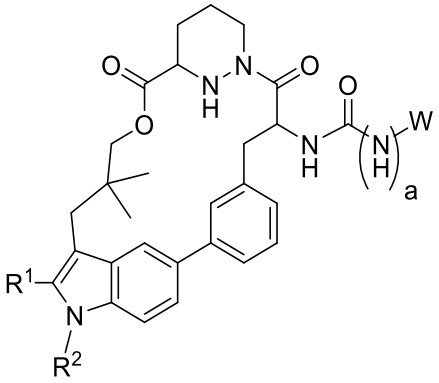


Formula IIa-8,



Formula IIa-9.

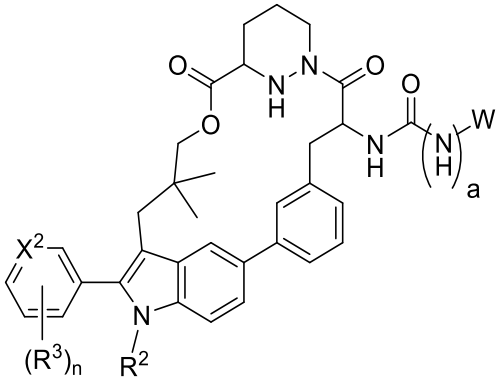
20. The compound of claim 9, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa:



Formula IIIa,

wherein a is 0 or 1.

21. The compound of claim 20, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa-1:



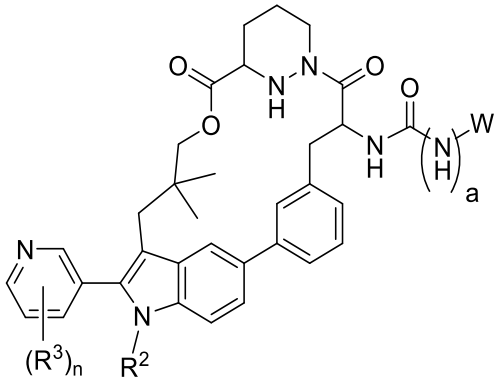
Formula IIIa-1,

wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

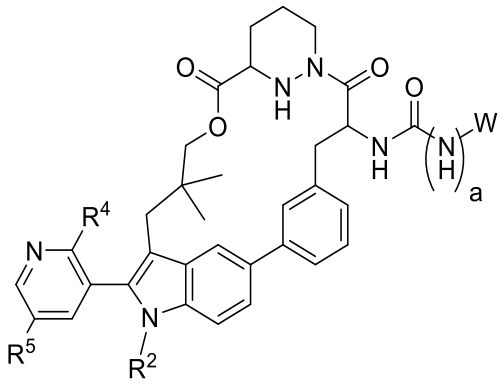
n is an integer from 1 to 4.

22. The compound of claim 21, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa-2:



Formula IIIa-2.

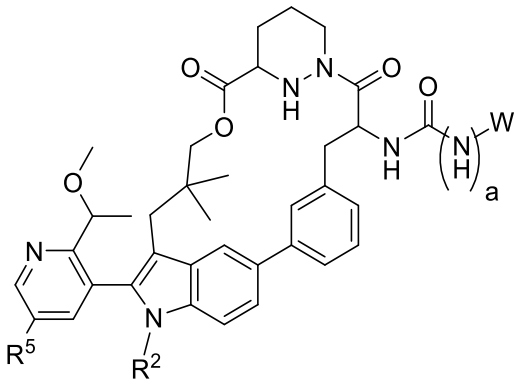
23. The compound of claim 22, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa-3:



Formula IIIa-3,

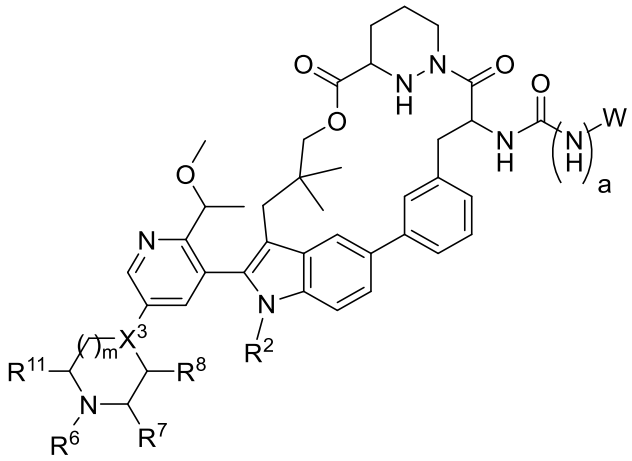
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

24. The compound of claim 23, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa-4:



Formula IIIa-4.

25. The compound of claim 24, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa-5:



Formula IIIa-5,

wherein X^3 is N or CH;

m is 1 or 2;

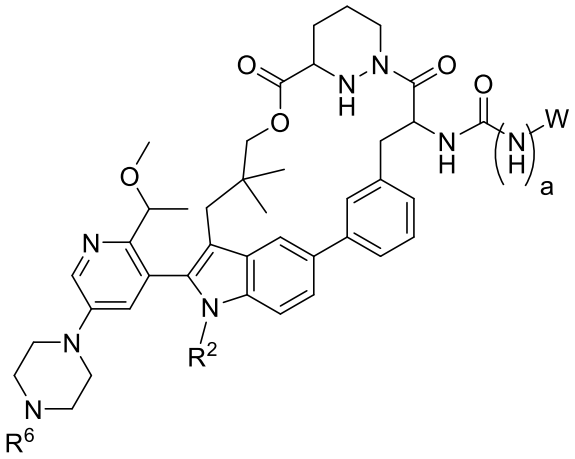
R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

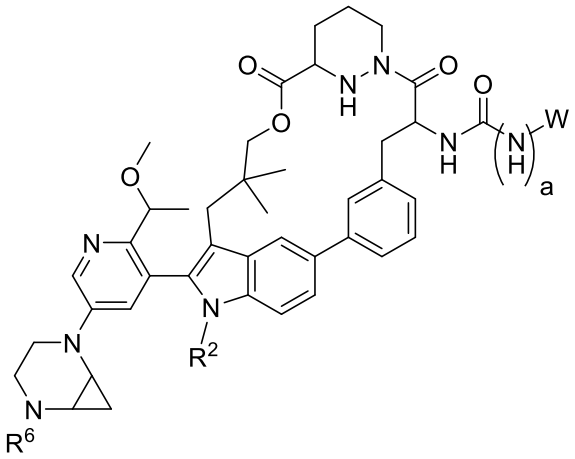
R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

26. The compound of claim 25, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa-6:



Formula IIIa-6.

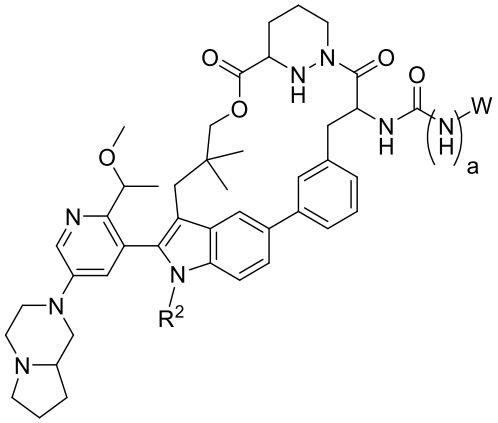
27. The compound of claim 25, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa-7:



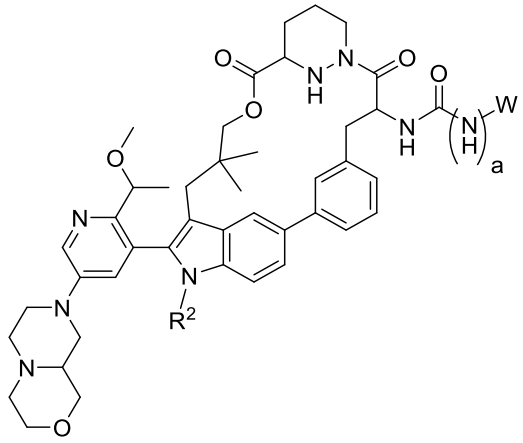
Formula IIIa-7.

28. The compound of claim 26 or 27, wherein R^6 is methyl.

29. The compound of claim 25, or pharmaceutically acceptable salt thereof, having the structure of Formula IIIa-8 or Formula IIIa-9:

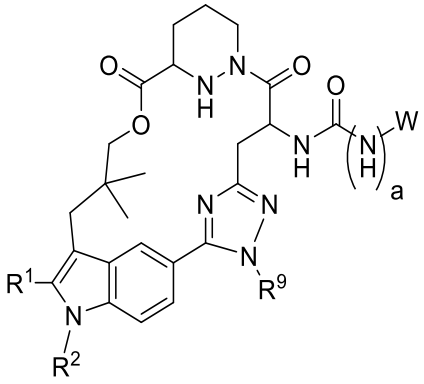


Formula IIIa-8,



Formula IIIa-9.

30. The compound of claim 9, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa:

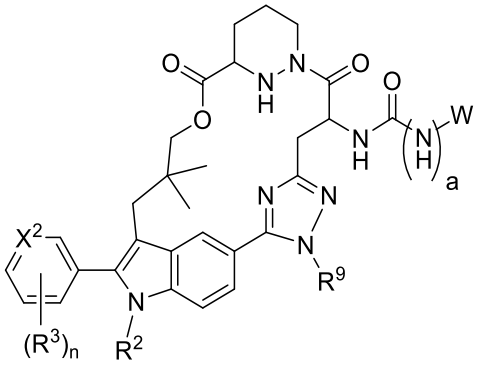


Formula IVa,

wherein R^9 is H or C_1-C_6 alkyl; and

a is 0 or 1.

31. The compound of claim 30, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa-1:



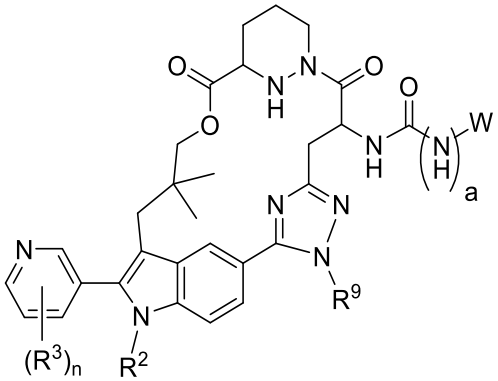
Formula IVa-1,

wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

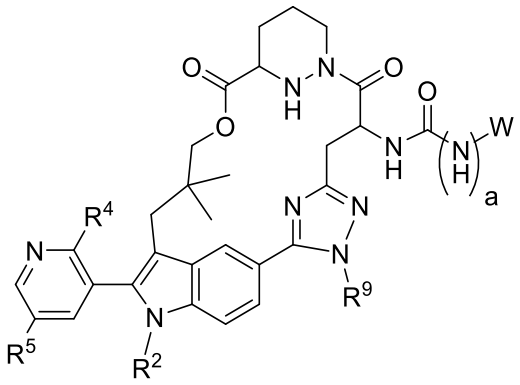
n is an integer from 1 to 4.

32. The compound of claim 31, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa-2:



Formula IVa-2.

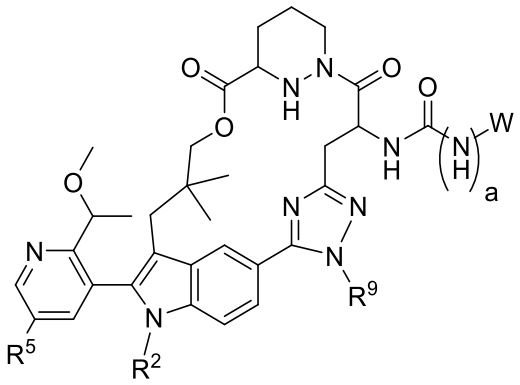
33. The compound of claim 32, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa-3:



Formula IVa-3,

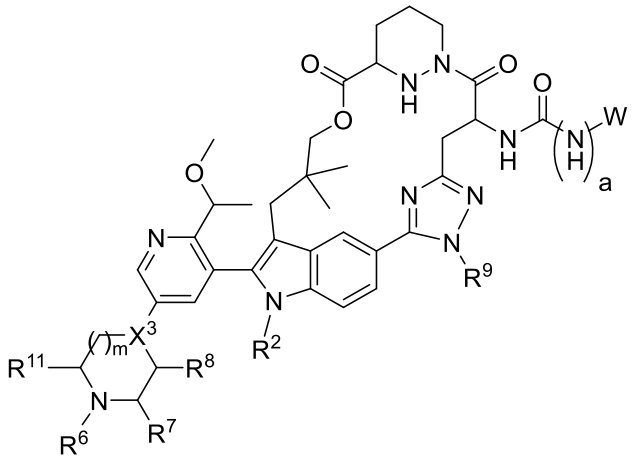
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

34. The compound of claim 33, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa-4:



Formula IVa-4.

35. The compound of claim 34, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa-5:



Formula IVa-5,

wherein X^3 is N or CH;

m is 1 or 2;

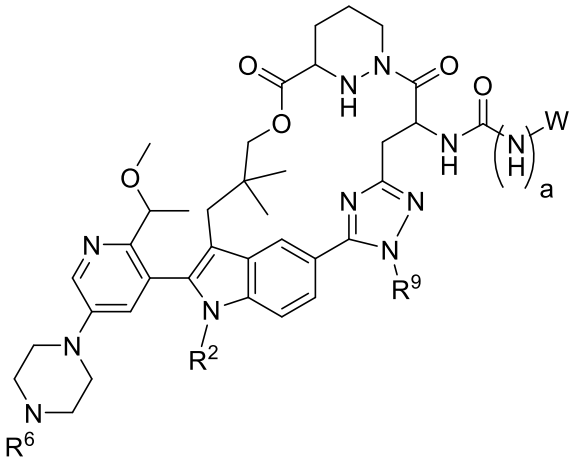
R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

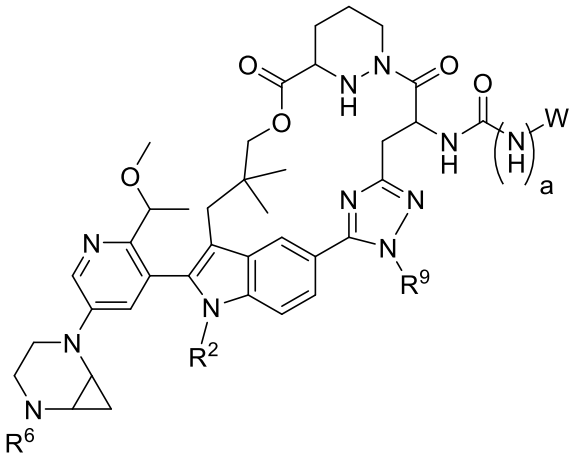
R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

36. The compound of claim 35, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa-6:



Formula IVa-6.

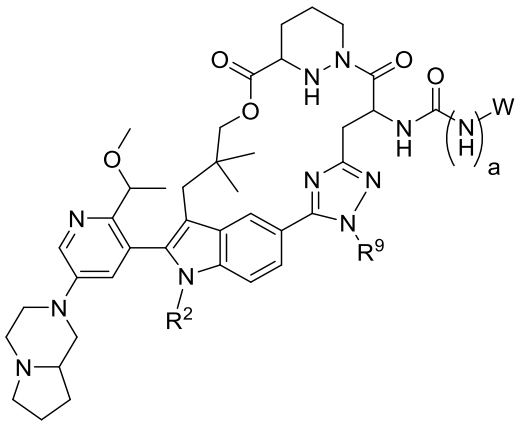
37. The compound of claim 35, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa-7:



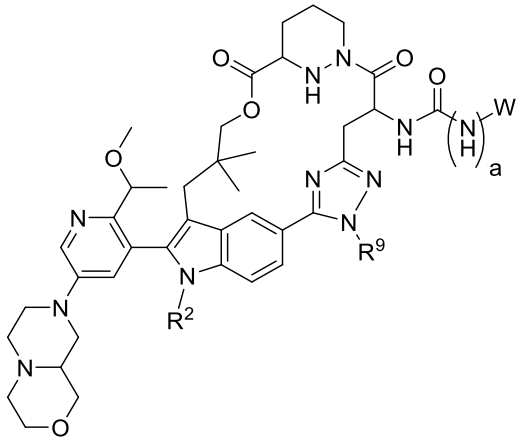
Formula IVa-7.

38. The compound of claim 36 or 37, wherein R^6 is methyl.

39. The compound of claim 35, or pharmaceutically acceptable salt thereof, having the structure of Formula IVa-8 or Formula IVa-9:



Formula IVa-8,

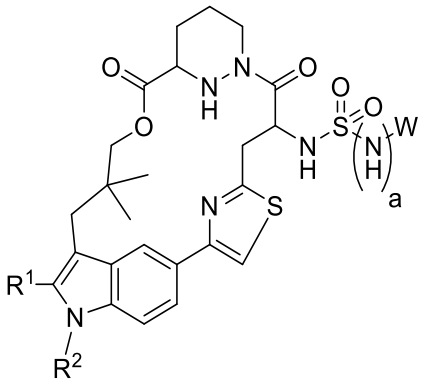


Formula IVa-9.

40. The compound of any one of claims 30-39, or pharmaceutically acceptable salt thereof, wherein R^9 is methyl.

41. The compound of any one of claims 1-8, or pharmaceutically acceptable salt thereof, wherein Y is $-NHS(O)_2-$ or $-NHS(O)_2NH-$.

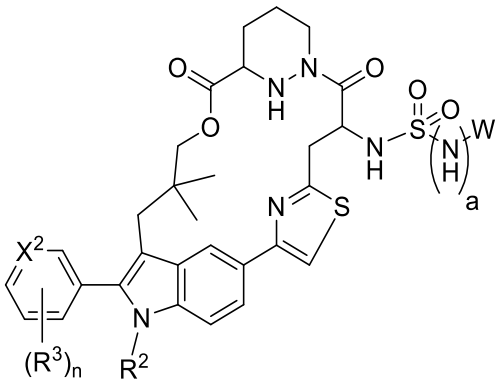
42. The compound of claim 41, or pharmaceutically acceptable salt thereof, having the structure of Formula Va:



Formula Va,

wherein a is 0 or 1.

43. The compound of claim 42, or pharmaceutically acceptable salt thereof, having the structure of Formula Va-1:



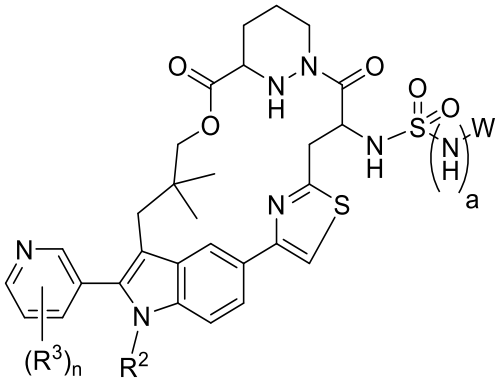
Formula Va-1,

wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

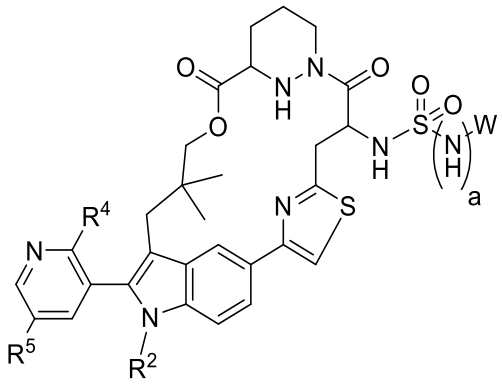
n is an integer from 1 to 4.

44. The compound of claim 43, or pharmaceutically acceptable salt thereof, having the structure of Formula Va-2:



Formula Va-2.

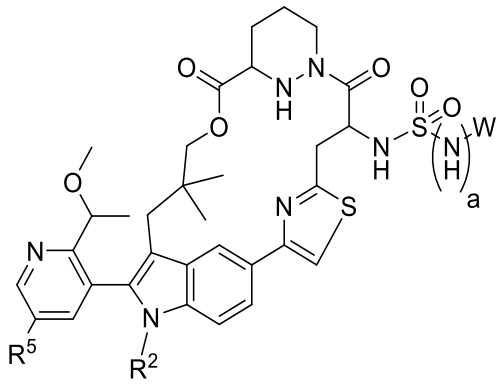
45. The compound of claim 44, or pharmaceutically acceptable salt thereof, having the structure of Formula Va-3:



Formula Va-3,

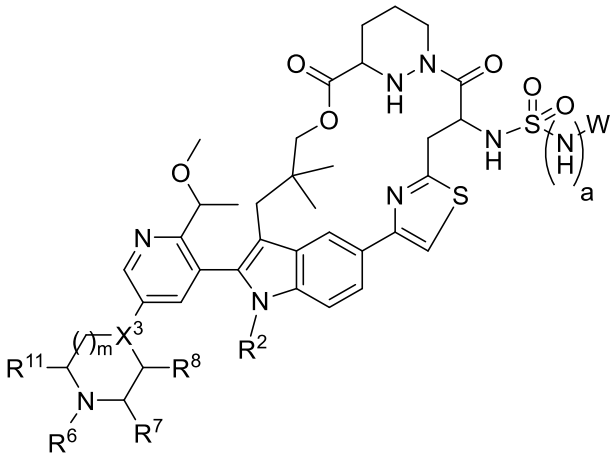
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

46. The compound of claim 45, or pharmaceutically acceptable salt thereof, having the structure of Formula Va-4:



Formula Va-4.

47. The compound of claim 46, or pharmaceutically acceptable salt thereof, having the structure of Formula Va-5:



Formula Va-5,

wherein X^3 is N or CH;

m is 1 or 2;

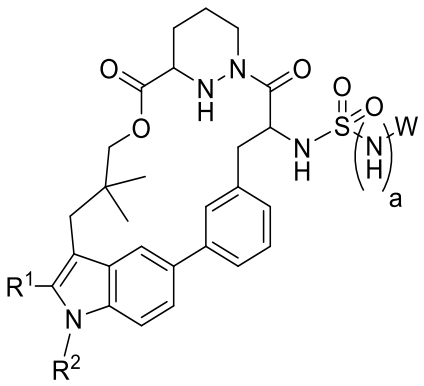
R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

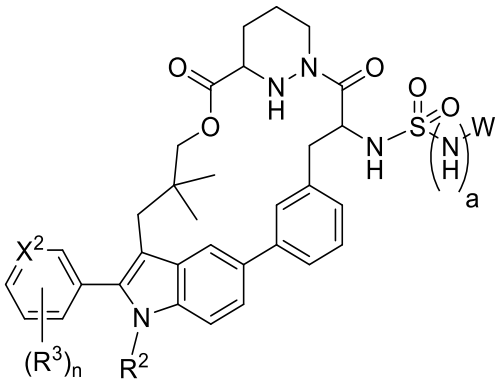
48. The compound of claim 41, or pharmaceutically acceptable salt thereof, having the structure of Formula VIa:



Formula VIa,

wherein a is 0 or 1.

49. The compound of claim 48, or pharmaceutically acceptable salt thereof, having the structure of Formula VIa-1:



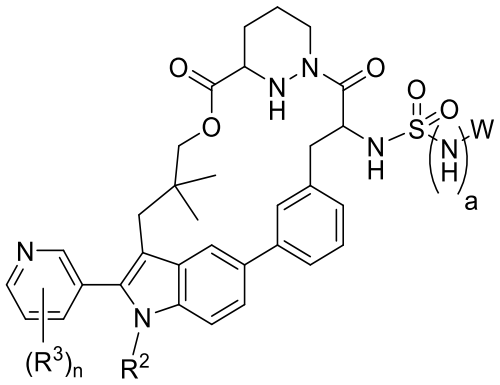
Formula VIa-1,

wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

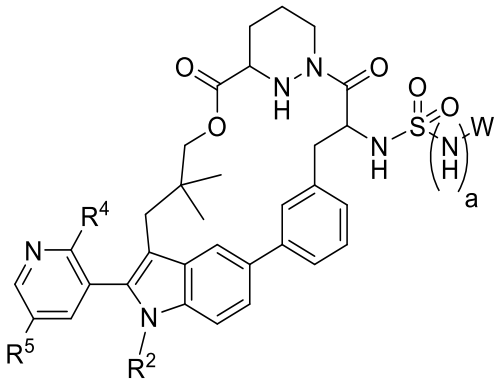
n is an integer from 1 to 4.

50. The compound of claim 49, or pharmaceutically acceptable salt thereof, having the structure of Formula VIa-2:



Formula VIa-2.

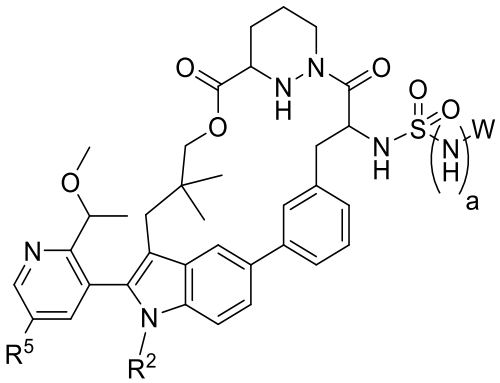
51. The compound of claim 50, or pharmaceutically acceptable salt thereof, having the structure of Formula VIa-3:



Formula VIa-3,

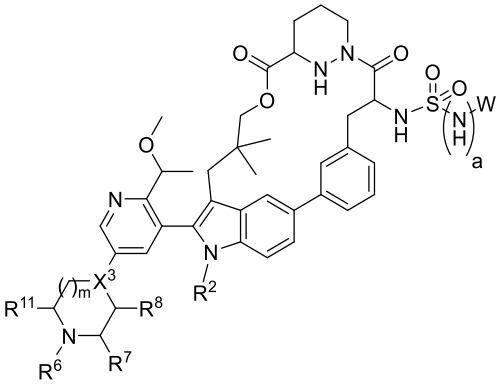
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

52. The compound of claim 51, or pharmaceutically acceptable salt thereof, having the structure of Formula VIa-4:



Formula VIa-4.

53. The compound of claim 52, or pharmaceutically acceptable salt thereof, having the structure of Formula VIa-5:



Formula VIa-5,

wherein X^3 is N or CH;

m is 1 or 2;

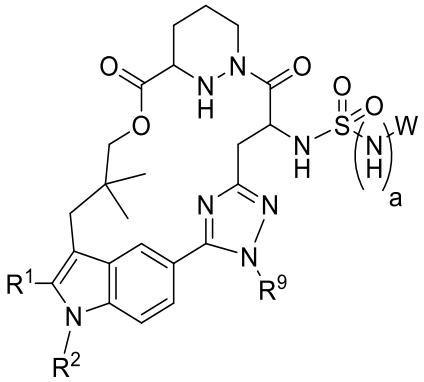
R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

54. The compound of claim 41, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIa:

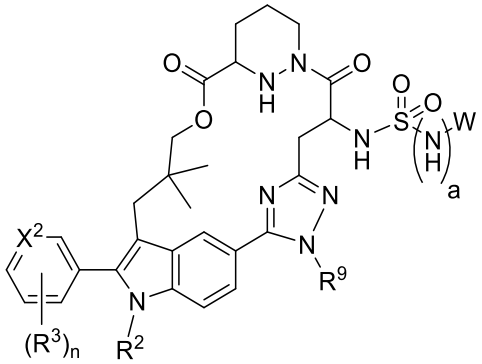


Formula VIIa,

wherein R^9 is H or C_1-C_6 alkyl; and

a is 0 or 1.

55. The compound of claim 54, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIa-1:



Formula VIIa-1,

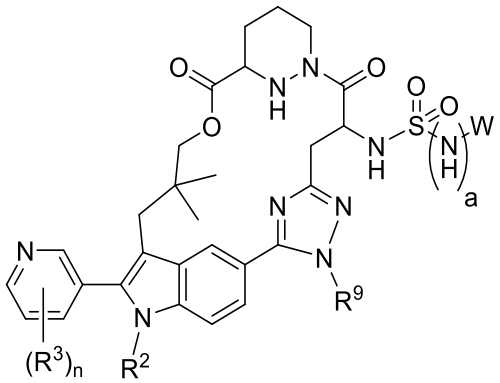
wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl,

optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

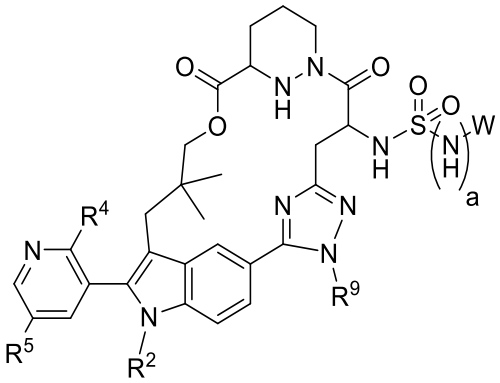
n is an integer from 1 to 4.

56. The compound of claim 55, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIa-2:



Formula VIIa-2.

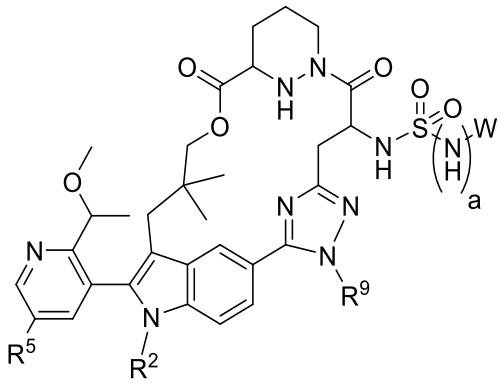
57. The compound of claim 56, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIa-3:



Formula VIIa-3,

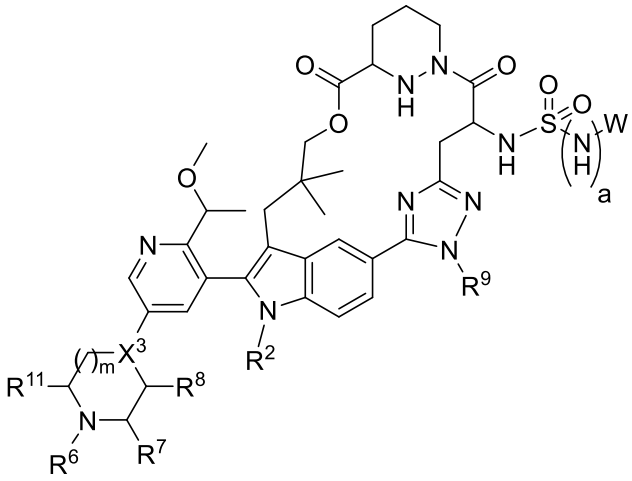
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

58. The compound of claim 57, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIa-4:



Formula VIIa-4.

59. The compound of claim 58, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIa-5:



Formula VIIa-5,

wherein X^3 is N or CH;

m is 1 or 2;

R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

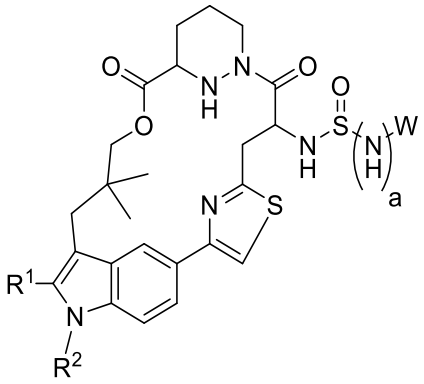
R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

60. The compound of any one of claims 54-59, or pharmaceutically acceptable salt thereof, wherein R^9 is methyl.

61. The compound of any one of claims 1-8, or pharmaceutically acceptable salt thereof, wherein Y is -NHS(O)- or -NHS(O)NH-.

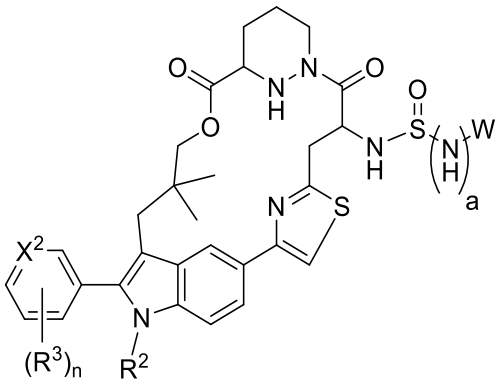
62. The compound of claim 61, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIIa:



Formula VIIIa,

wherein a is 0 or 1.

63. The compound of claim 62, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIIa-1:



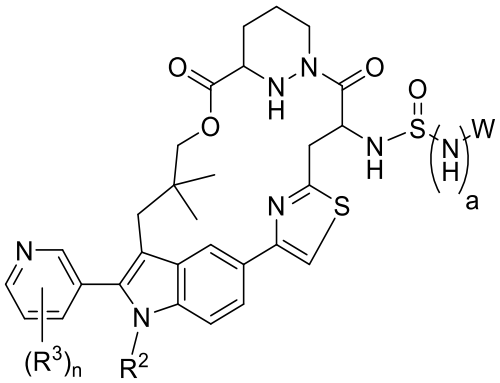
Formula VIIIa-1,

wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

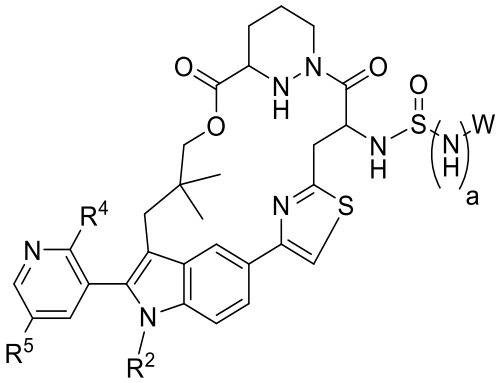
n is an integer from 1 to 4.

64. The compound of claim 63, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIIa-2:



Formula VIIIa-2.

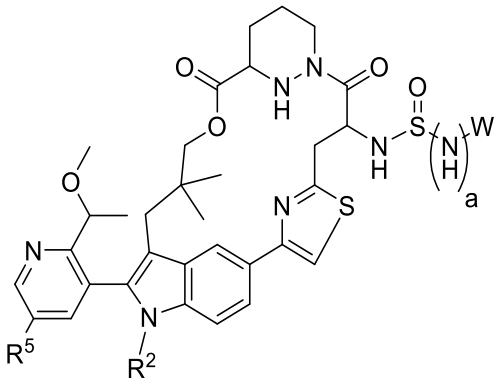
65. The compound of claim 64, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIIa-3:



Formula VIIIa-3,

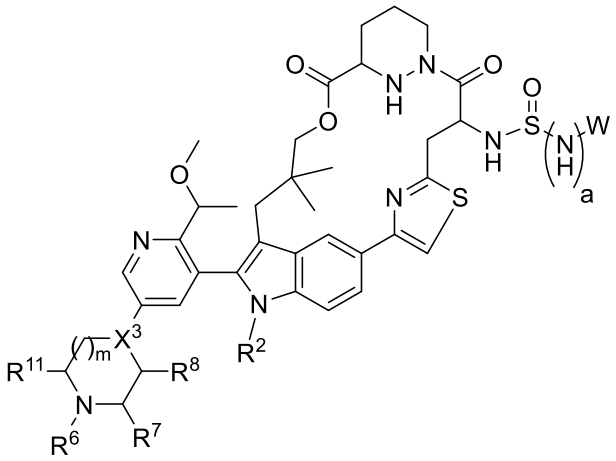
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

66. The compound of claim 65, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIIa-4:



Formula VIIIa-4.

67. The compound of claim 66, or pharmaceutically acceptable salt thereof, having the structure of Formula VIIIa-5:



Formula VIIIa-5,

wherein X^3 is N or CH;

m is 1 or 2;

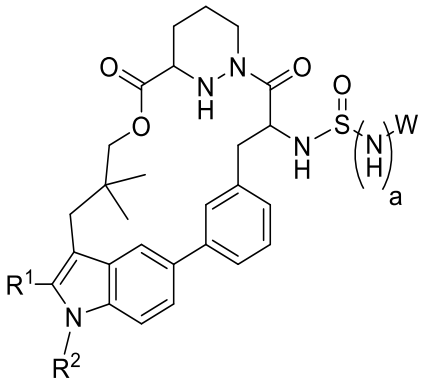
R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

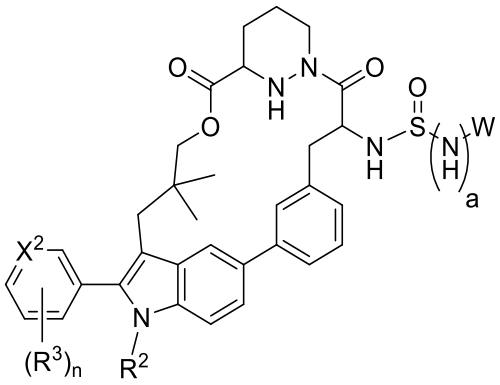
68. The compound of claim 61, or pharmaceutically acceptable salt thereof, having the structure of Formula IXa:



Formula IXa,

wherein a is 0 or 1.

69. The compound of claim 68, or pharmaceutically acceptable salt thereof, having the structure of Formula IXa-1:



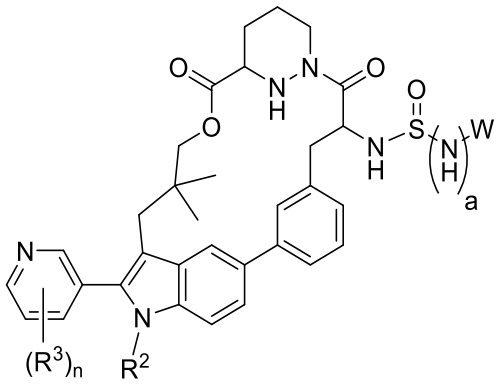
Formula IXa-1,

wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

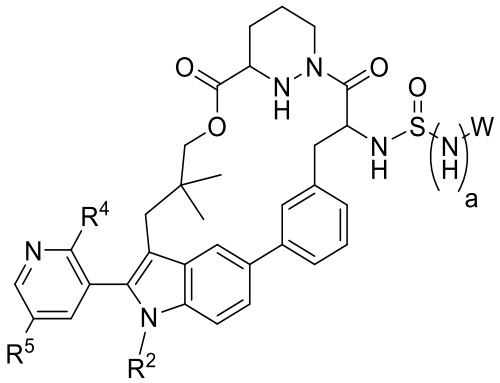
n is an integer from 1 to 4.

70. The compound of claim 69, or pharmaceutically acceptable salt thereof, having the structure of Formula IXa-2:



Formula IXa-2.

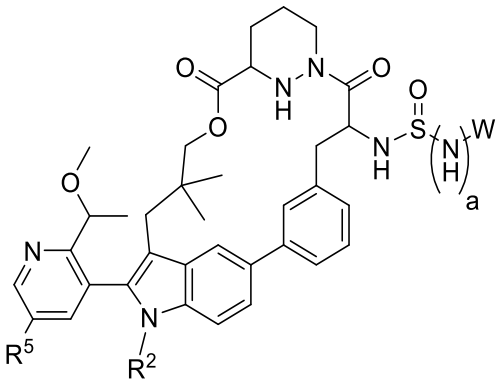
71. The compound of claim 70, or pharmaceutically acceptable salt thereof, having the structure of Formula IXa-3:



Formula IXa-3,

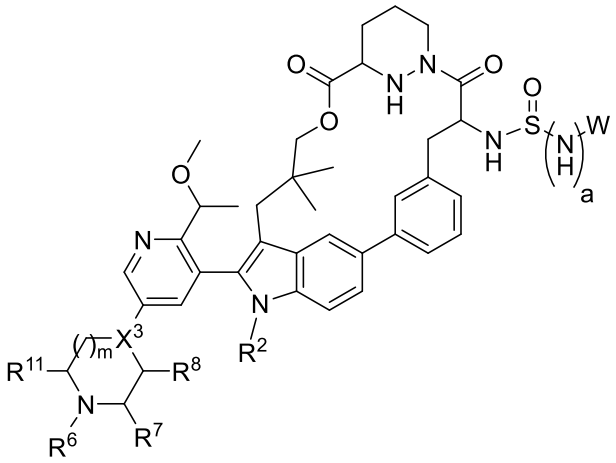
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

72. The compound of claim 71, or pharmaceutically acceptable salt thereof, having the structure of Formula IXa-4:



Formula IXa-4.

73. The compound of claim 72, or pharmaceutically acceptable salt thereof, having the structure of Formula IXa-5:



Formula IXa-5,

wherein X^3 is N or CH;

m is 1 or 2;

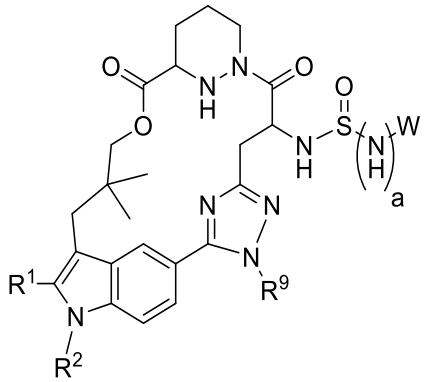
R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

74. The compound of claim 61, or pharmaceutically acceptable salt thereof, having the structure of Formula Xa:

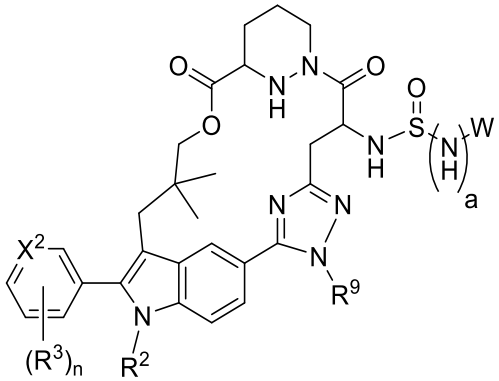


Formula Xa,

wherein R^9 is H or C_1-C_6 alkyl; and

a is 0 or 1.

75. The compound of claim 74, or pharmaceutically acceptable salt thereof, having the structure of Formula Xa-1:



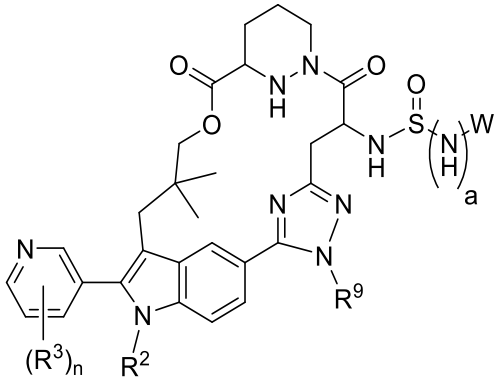
Formula Xa-1,

wherein X^2 is N or CH;

each R^3 is independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

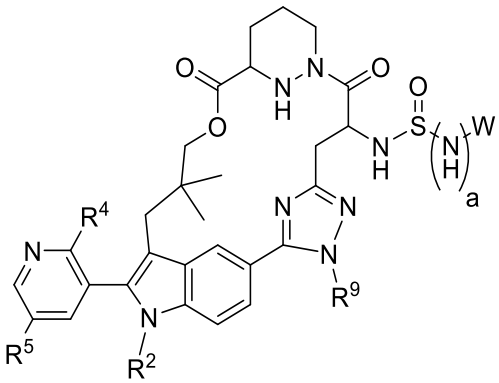
n is an integer from 1 to 4.

76. The compound of claim 75, or pharmaceutically acceptable salt thereof, having the structure of Formula Xa-2:



Formula Xa-2.

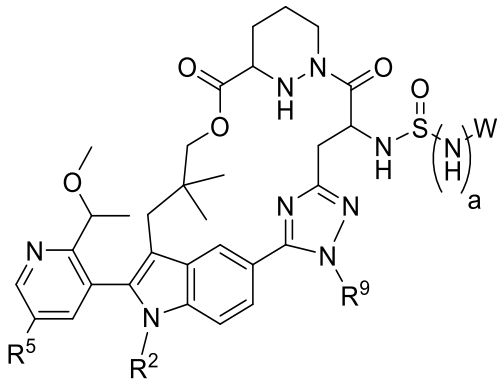
77. The compound of claim 76, or pharmaceutically acceptable salt thereof, having the structure of Formula Xa-3:



Formula Xa-3,

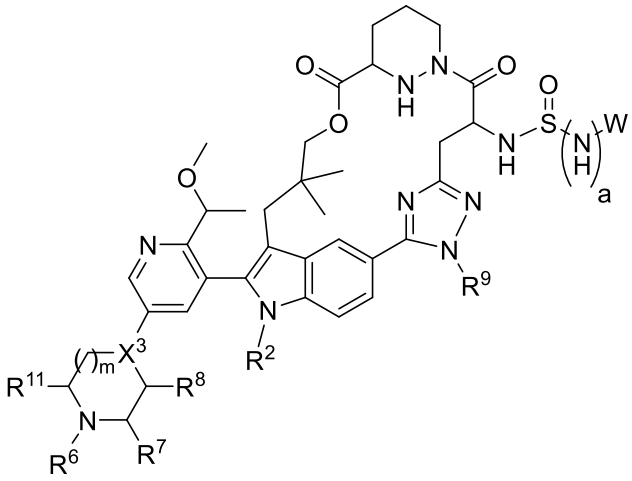
wherein R^4 and R^5 are each independently selected from halogen, cyano, hydroxy, optionally substituted amine, optionally substituted amido, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

78. The compound of claim 77, or pharmaceutically acceptable salt thereof, having the structure of Formula Xa-4:



Formula Xa-4.

79. The compound of claim 78, or pharmaceutically acceptable salt thereof, having the structure of Formula Xa-5:



Formula Xa-5,

wherein X^3 is N or CH;

m is 1 or 2;

R^6, R^7, R^8, and R^{11} are each independently selected from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; or

R^6 and R^7 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^8 combine with the atoms to which they are attached to form an optionally substituted 3 to 8-membered heterocycloalkyl; or

R^7 and R^{11} combine with the atoms to which they are attached to form an optionally substituted 4 to 8-membered heterocycloalkyl.

80. The compound of any one of claims 74-79, or pharmaceutically acceptable salt thereof, wherein R^9 is methyl.

81. The compound of any one of claims 10-40, 42-60, or 62-80, or pharmaceutically acceptable salt thereof, wherein a is 0.

82. The compound of any one of claims 10-40, 42-60, or 62-80, or pharmaceutically acceptable salt thereof, wherein a is 1.

83. The compound of any one of claims 1-82, or pharmaceutically acceptable salt thereof, wherein R^2 is optionally substituted C_1-C_6 alkyl.

84. The compound of claim 83, or pharmaceutically acceptable salt thereof, wherein R^2 is selected from $-CH_2CH_3$ or $-CH_2CF_3$.

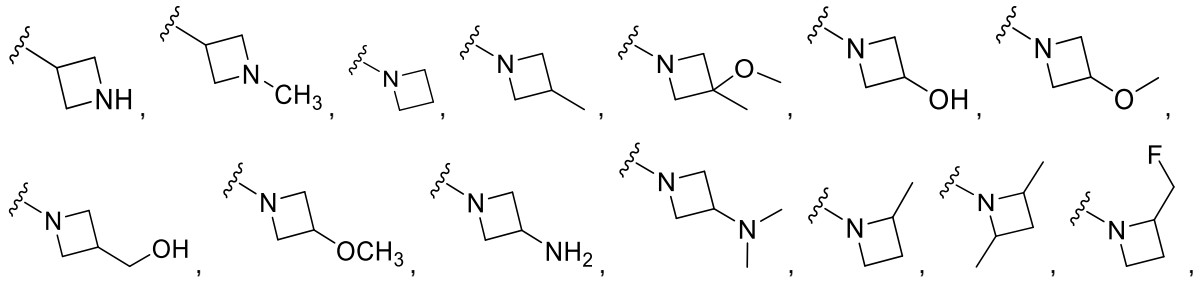
85. The compound of any one of claims 1-84, or pharmaceutically acceptable salt thereof, wherein W is C_1-C_4 alkyl.

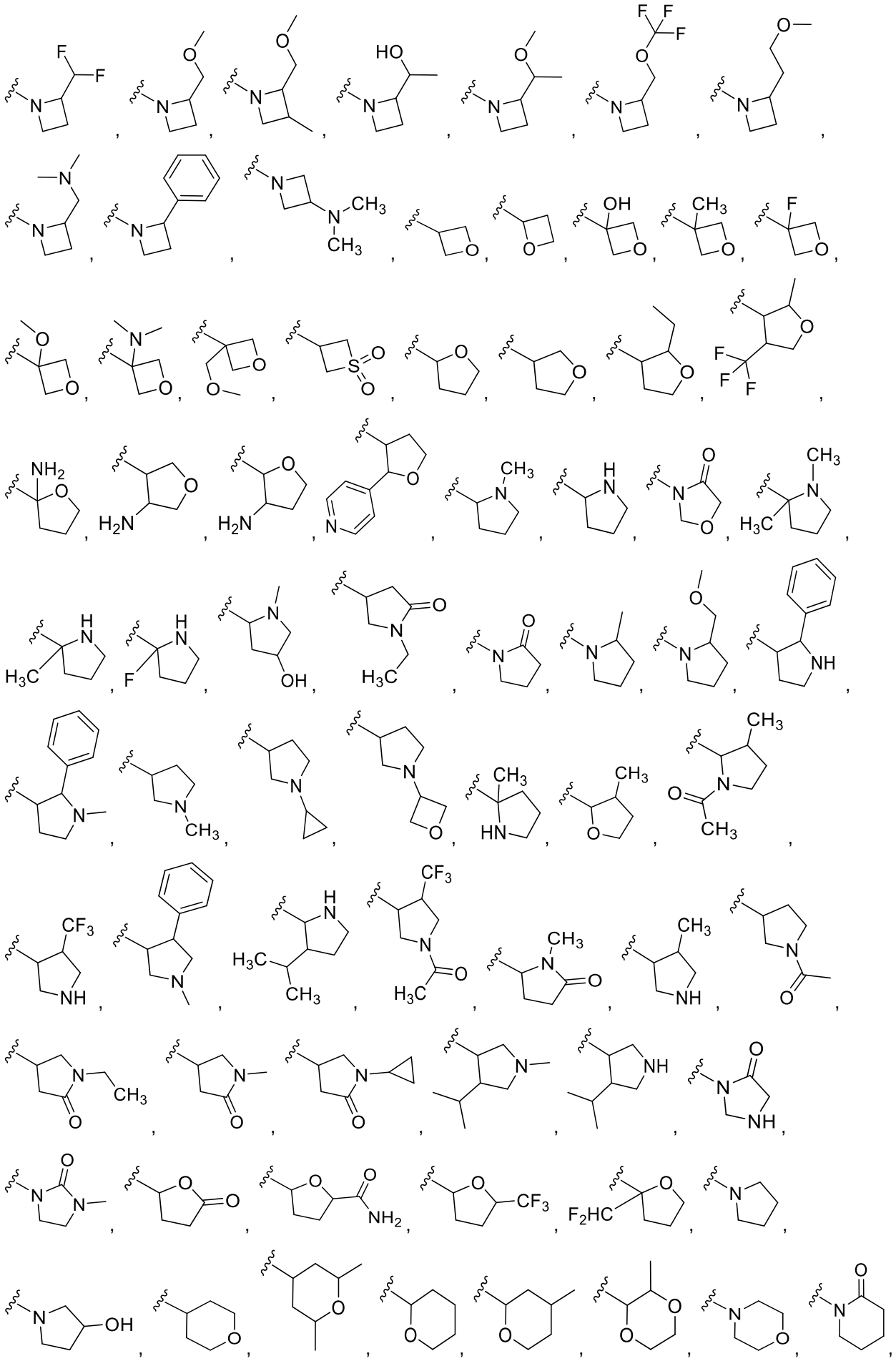
86. The compound of any one of claims 1-84, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, or optionally substituted cyclohexyl, optionally substituted piperidine, optionally substituted piperazine, optionally substituted pyridine, or optionally substituted phenyl.

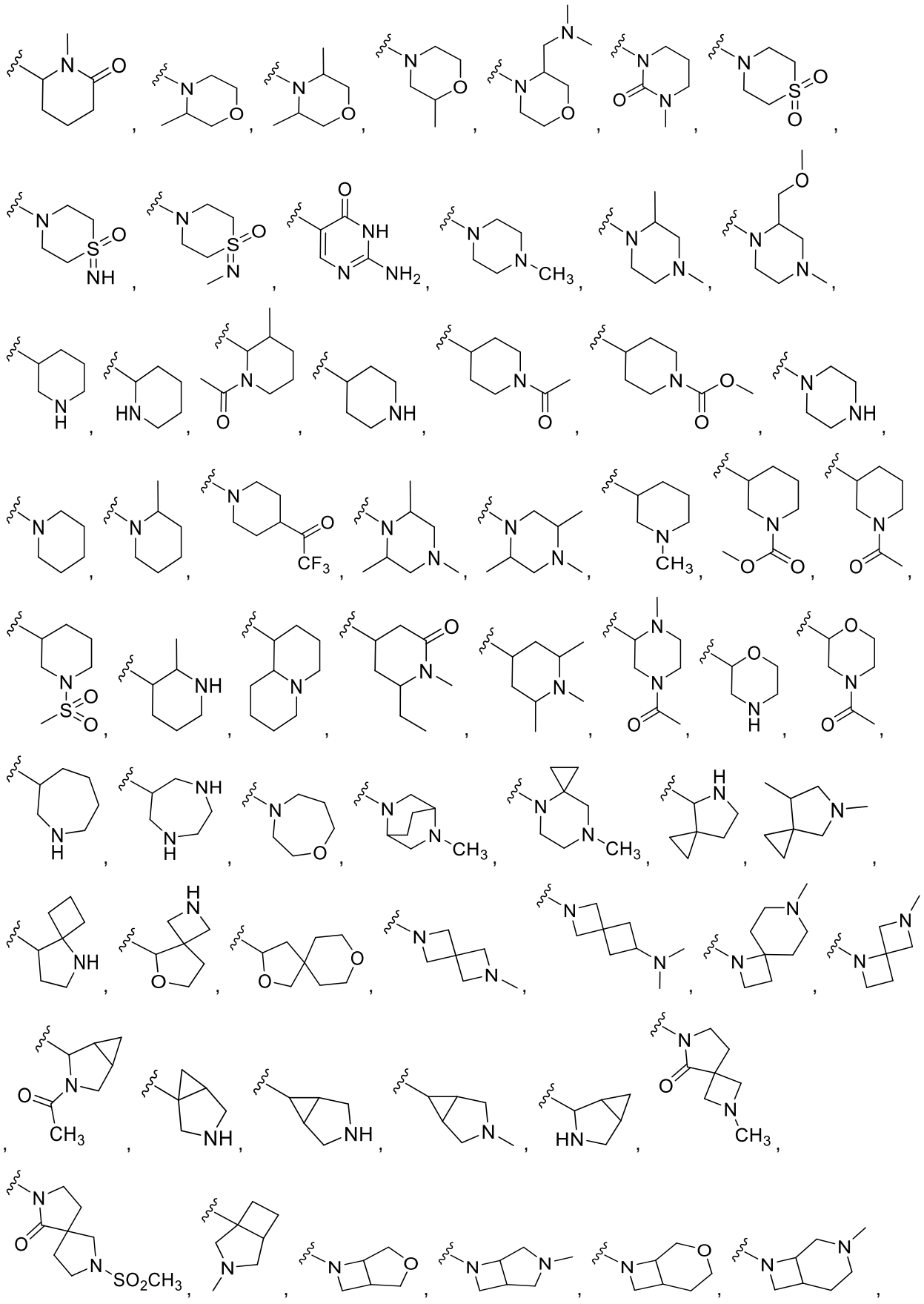
87. The compound of any one of claims 1-84, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl.

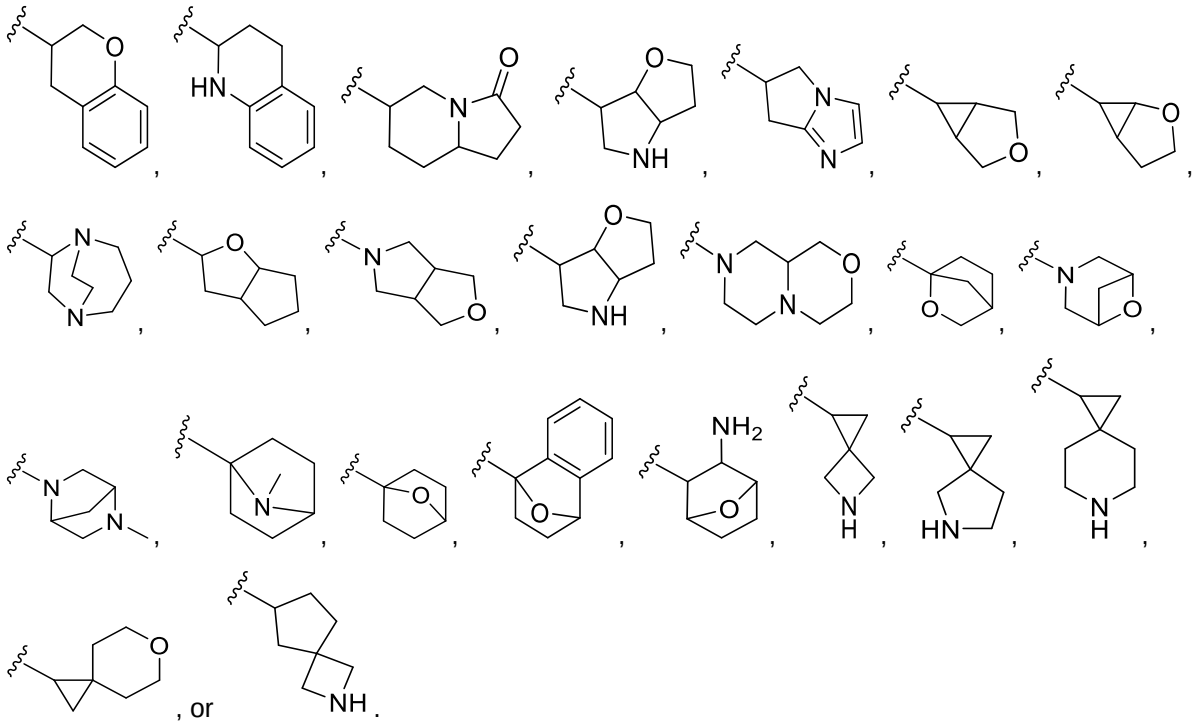
88. The compound of any one of claims 1-84, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted 3 to 10-membered heterocycloalkyl.

89. The compound of claim 88, or pharmaceutically acceptable salt thereof, wherein W is selected from the following, or a stereoisomer thereof:



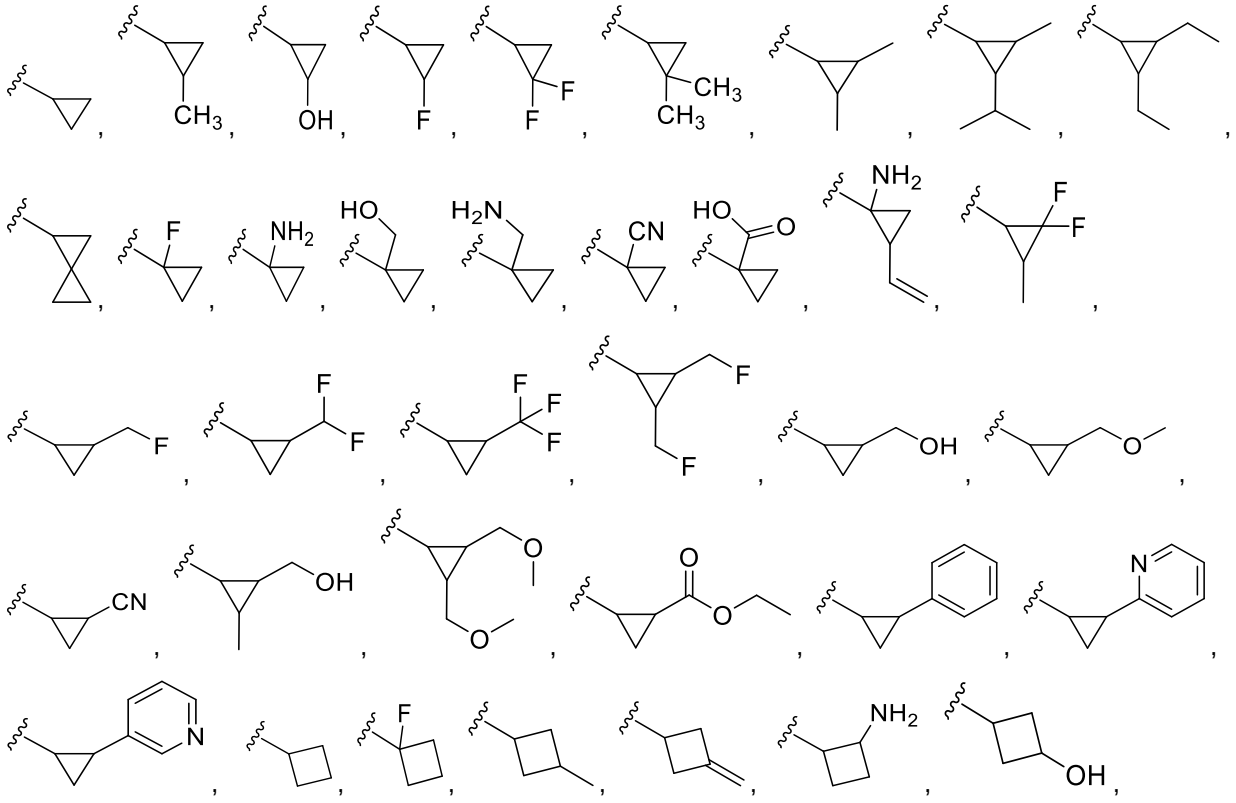


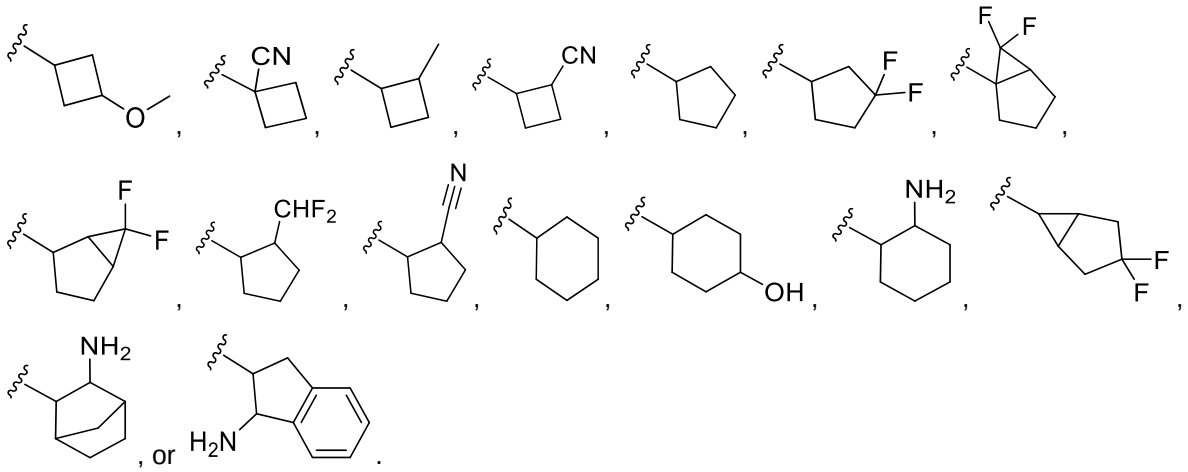




90. The compound of any one of claims 1-84, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted 3 to 10-membered cycloalkyl.

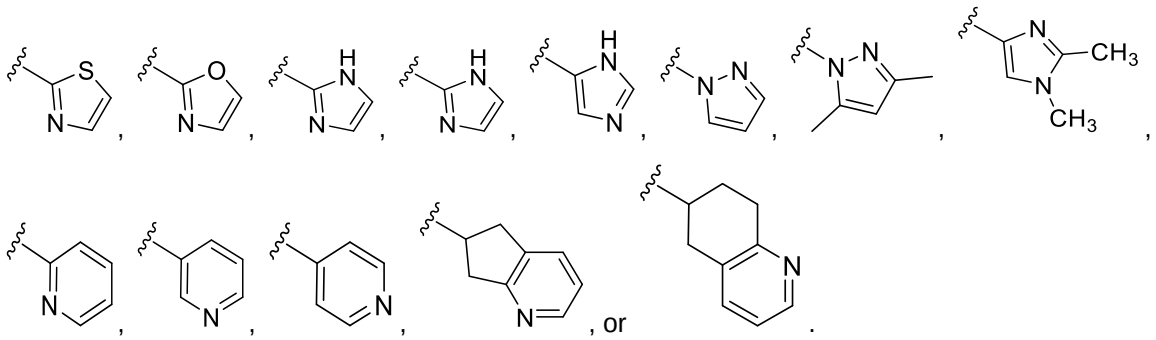
91. The compound of claim 90, or pharmaceutically acceptable salt thereof, wherein W is selected from the following, or a stereoisomer thereof:





92. The compound of any one of claims 1-84, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted 5 to 10-membered heteroaryl.

93. The compound of claim 92, or pharmaceutically acceptable salt thereof, wherein W is selected from the following, or a stereoisomer thereof:

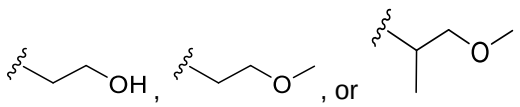


94. The compound of any one of claims 1-84, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted 6 to 10-membered aryl.

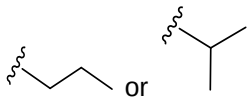
95. The compound of claim 94, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted phenyl.

96. The compound of any one of claims 1-84, or pharmaceutically acceptable salt thereof, wherein W is optionally substituted C_1-C_3 heteroalkyl.

97. The compound of claim 96, or pharmaceutically acceptable salt thereof, wherein W is selected from the following, or a stereoisomer thereof:



98. The compound of claim 85, or pharmaceutically acceptable salt thereof, wherein W is selected from the following:

 or .

99. A compound, or a pharmaceutically acceptable salt thereof, of Table 1a.

100. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-99 and a pharmaceutically acceptable excipient.

101. Use of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-99 or a pharmaceutical composition of claim 100, in the manufacture of a medicament for the treatment of cancer.

102. The use of claim 101, wherein the cancer comprises a Ras mutation.

103. The use of claim 102, wherein the Ras mutation is at position 12, 13 or 61.

104. The use of claim 102 or 103, wherein the Ras mutation is at position 12.

105. The use of claim 103, wherein the Ras mutation is at a position selected from the group consisting of G12C, G12D, G12V, G12R, G13C, G13D, and Q61K, or a combination thereof.

106. The use of claim 105, wherein the Ras mutation is at a position selected from the group consisting of G12D, G12V and G12R, or a combination thereof.

107. The use of claim 106, wherein the Ras mutation is at a position selected from the group consisting of G12D and G12V, or a combination thereof.

108. The use of any one of claims 101-107, wherein the cancer is pancreatic cancer.

109. The use of any one of claims 101-107, wherein the cancer is lung cancer.

110. The use of any one of claims 101-107, wherein the cancer is colorectal cancer.

111. Use of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-99 or a pharmaceutical composition of claim 100, in the manufacture of a medicament for the treatment of aRas protein related disorder.

112. A method of inhibiting a Ras protein in a cell, the method comprising contacting the cell with an effective amount of a compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-99 or a pharmaceutical composition of claim 100.

113. The method of claim 112, wherein more than one Ras protein is inhibited in the cell.

114. The method of claim 112 or 113, wherein the cell is a cancer cell.

115. The method of claim 114, wherein the cancer cell is a pancreatic cancer cell.

116. The method of claim 114, wherein the cancer cell is a lung cancer cell.

117. The method of claim 114, wherein the cancer cell is a colorectal cancer cell.

118. The method of any one of claims 101-117, wherein the Ras protein is KRAS.

119. The method or use of any one of claims 101-118, further comprising an additional anticancer therapy to be administered.

120. The method or use of claim 119, wherein the additional anticancer therapy is an EGFR inhibitor, a second Ras inhibitor, a SHP2 inhibitor, a SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, an mTORC1 inhibitor, a BRAF inhibitor, a PD-L1 inhibitor, a PD-1 inhibitor, a CDK4/6 inhibitor, a HER2 inhibitor, or a combination thereof.

121. The method or use of claim 119 or 120, wherein the additional anticancer therapy is a SHP2 inhibitor.

122. The method or use of claim 119 or 120, wherein the additional anticancer therapy comprises a SHP2 inhibitor and a PD-L1 inhibitor.

123. The method or use of claim 119 or 120, wherein the the additional therapy comprises a second Ras inhibitor and a PD-L1 inhibitor.

124. The method or use of claim 120 or 123, wherein the second Ras inhibitor is a $KRAS^{G12C}$ inhibitor.

125. The method or use of claim 123 or 124, wherein the second Ras inhibitor is a $KRAS^{G12C}$(ON) inhibitor.

126. The method or use of claim 123 or 124, wherein the second Ras inhibitor is a $KRAS^{G12C}$(OFF) inhibitor.

127. A compound, or a pharmaceutically acceptable salt thereof, of any one of claims 1-99 or a pharmaceutical composition of claim 100, for use in therapy.