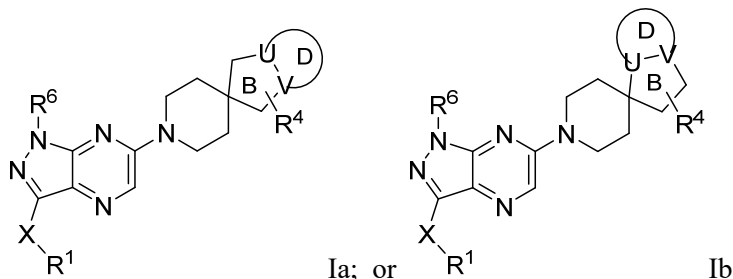


syndrome, where nearly all mutated forms of SHP2 demonstrate increased PTP activity. Thus, there is a need for SHP2 phosphatase inhibitor compounds and methods for treating cancer and other disorders with these compounds.

SUMMARY

- 5 [0004] In some embodimentsexamples, the present disclosure provides a compound of Formula Ia or Ib, or a pharmaceutically acceptable salt or stereoisomer thereof, represented by:



wherein

- 10 D is selected from the group consisting of: phenyl, a 5- or 6-membered heteroaryl having one or two heteroatoms each independently selected from the group consisting of S, O or N, and C₃₋₆cycloalkyl, wherein D is optionally substituted on an available carbon with one or two substituents each independently selected from R^{D1}, and, optionally substituted, on nitrogen, if present, with one or two substituents each independently selected from R^{D2};

U is C, CR⁴ or N;

- 15 V is C, CR⁴ or N; wherein at least one of U or V must be C, CR⁴ or N;

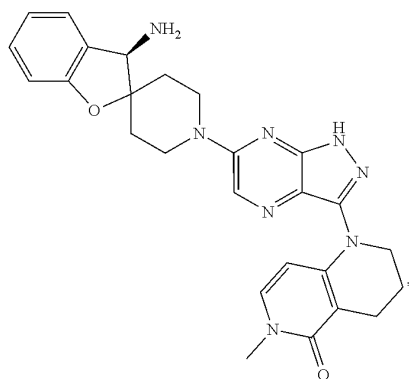
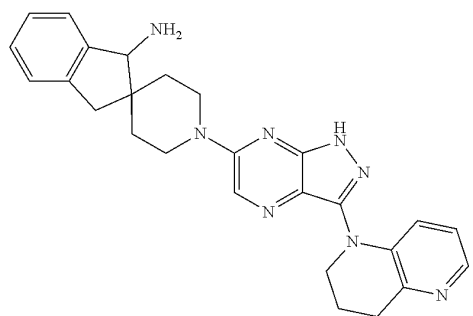
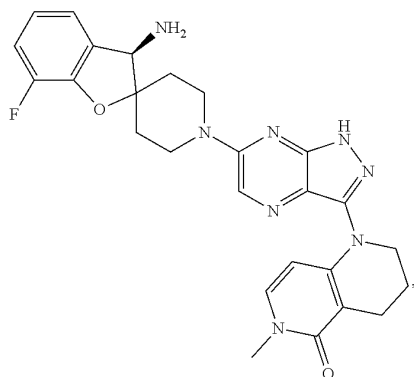
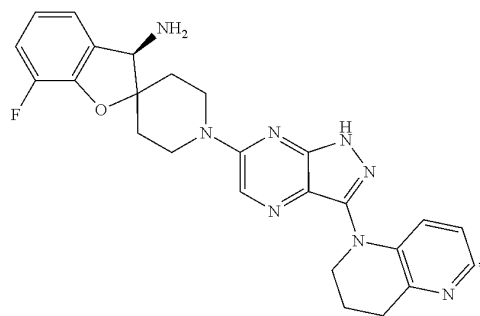
B is fused to D such that the two atoms shared by D and B are both carbon or one carbon and one nitrogen;

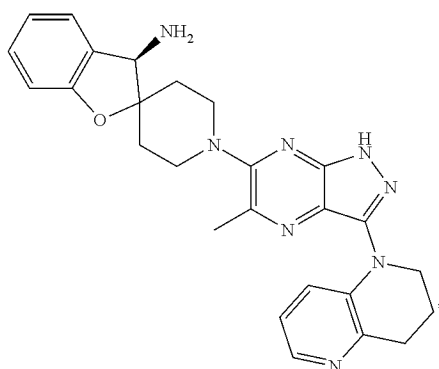
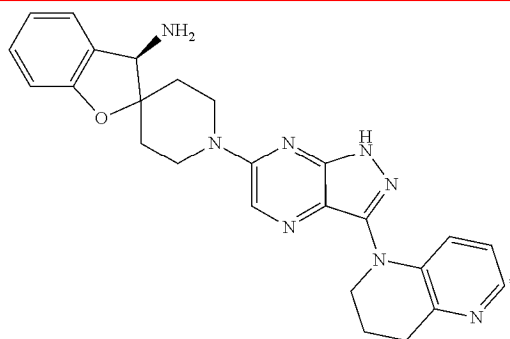
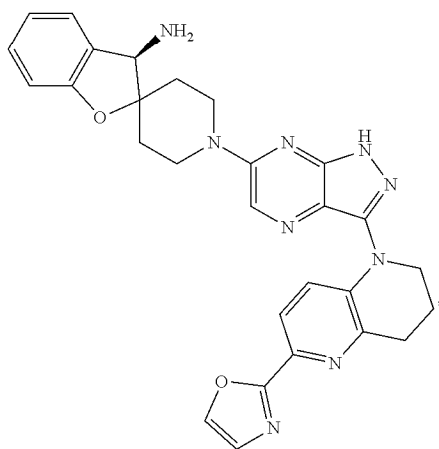
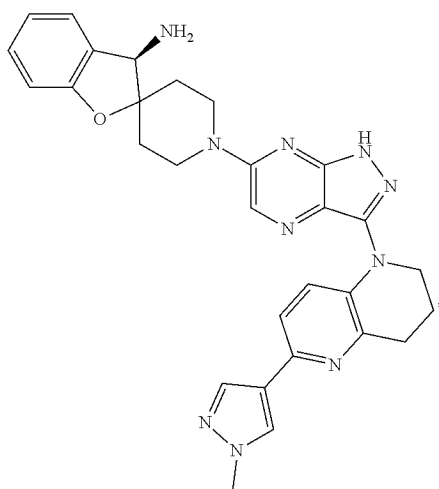
R⁴ is independently selected from the group consisting of hydrogen, -C(O)N(R⁶)₂, -N(R⁶)₂, and -C₁₋₃alkyl-N(R⁶)₂;

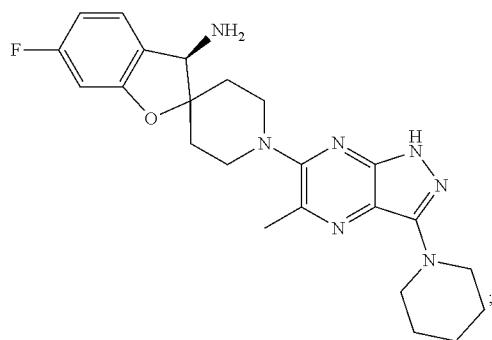
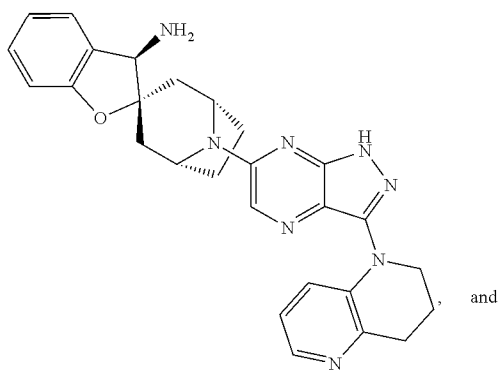
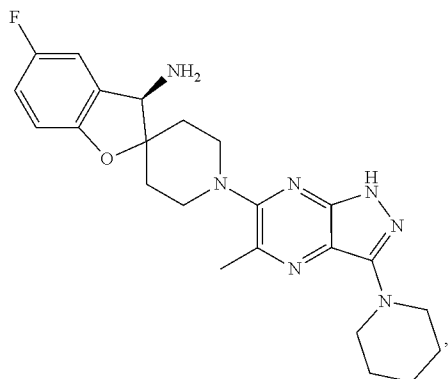
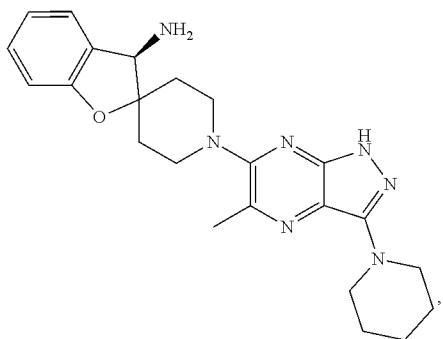
- 20 R⁶ is independently for each occurrence selected from the group consisting of H, -(C₁₋₆)alkyl, -C(O)OC₁₋₄alkyl, and phenyl;

R^{D1} is selected from the group consisting of hydroxyl, cyano, halogen, and -N(R⁶)₂;

[0005a] In one aspect of the present disclosure, there is provided a compound selected from the group consisting of:

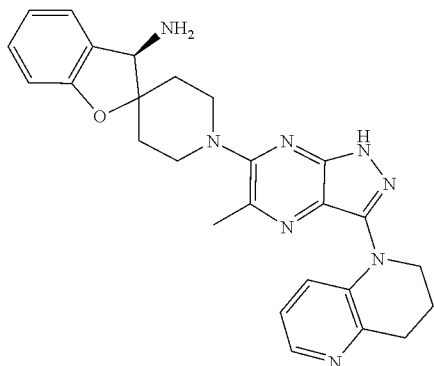






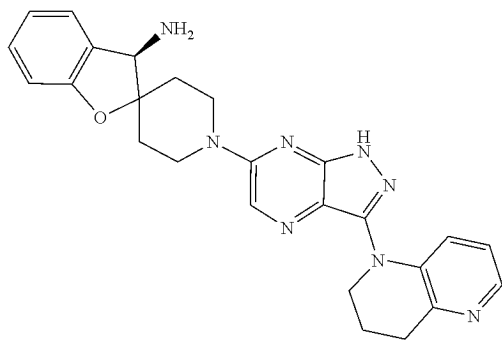
or a pharmaceutically acceptable salt thereof.

[0005b] In another aspect of the present disclosure, there is provided a compound represented by:



or a pharmaceutically acceptable salt thereof.

5 [0005c] In a further aspect of the present disclosure, there is provided a compound represented by:



or a pharmaceutically acceptable salt thereof.

10 [0005d] In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein and a pharmaceutically acceptable carrier.

[0005] The present disclosure also provides, for example, pharmaceutical compositions containing the compounds described herein. Further, the disclosure provides a method of inhibiting SHP2 phosphatase activity in a subject by administering a therapeutically effective amount of a compound or composition described herein, to a subject, *e.g.*, a human, in need.

5 [0006] The present disclosure further provides, for example, a method of treating a disorder in a subject by administering a therapeutically effective amount of a compound or composition described herein, to a subject in need thereof. Examples of disorders include Noonan syndrome, neutropenia, diabetes, neuroblastoma, melanoma, acute myeloid leukemia, juvenile leukemia, juvenile myelomonocytic leukemia, breast cancer, lung cancer,
10 and colorectal cancer. In addition to the compound or composition described herein, such method may include administration of a therapeutically effective amount of an antibody, an antibody-drug conjugate, an immunomodulator, or a histone deacetylase inhibitor.

[0007] The present disclosure is based, in part, on certain discoveries which are described more fully in the Examples section of the present application. For example, the present
15 disclosure is based, in part, on the discovery of compounds disclosed herein, and the SHP2 phosphatase inhibition exhibited by such compounds.

[0008] These and other ~~embodiments~~examples of the disclosure are further described in the following sections of the application, including the Detailed Description, Examples, and Claims. Still other objects and advantages of the disclosure will become apparent by those of
20 skill in the art from the disclosure herein, which are simply illustrative and not restrictive. Thus, other examples ~~embodiments~~ will be recognized by the ordinarily skilled artisan without departing from the spirit and scope of the disclosure.

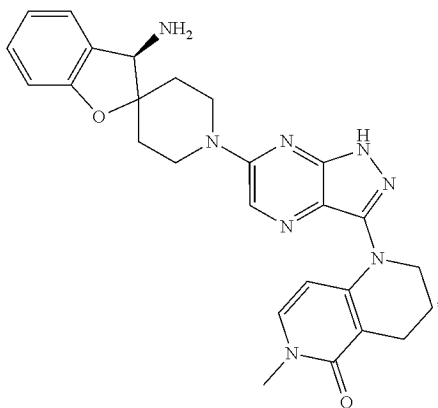
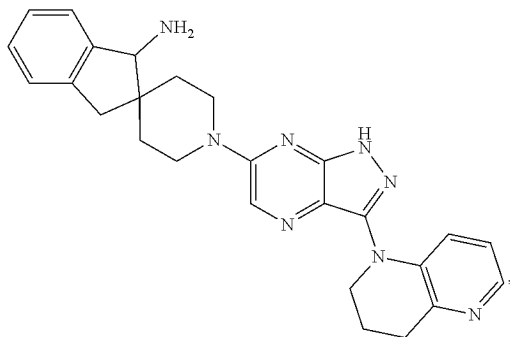
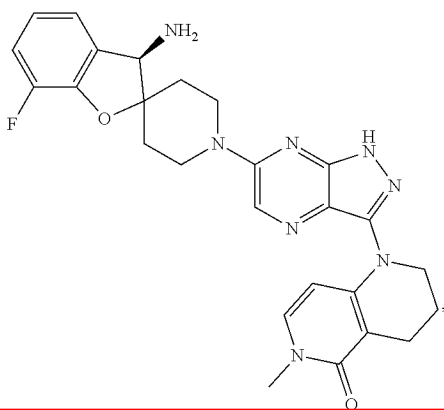
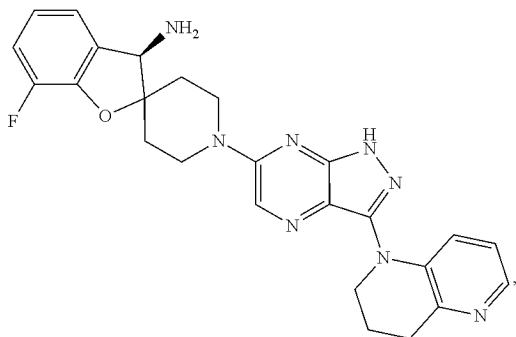
BRIEF DESCRIPTION OF THE DRAWINGS

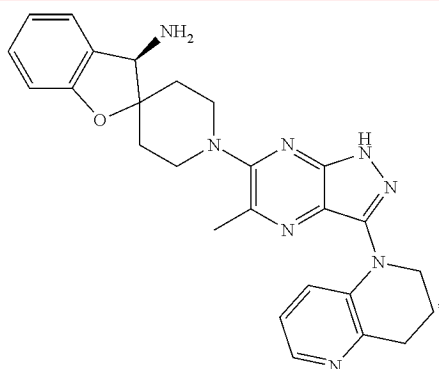
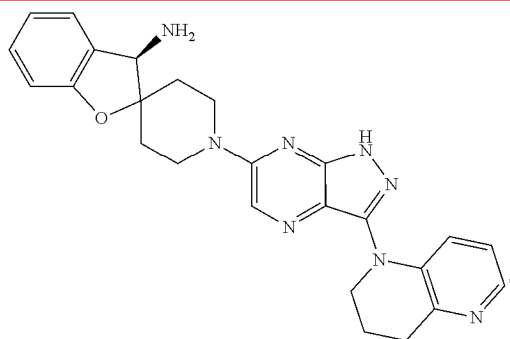
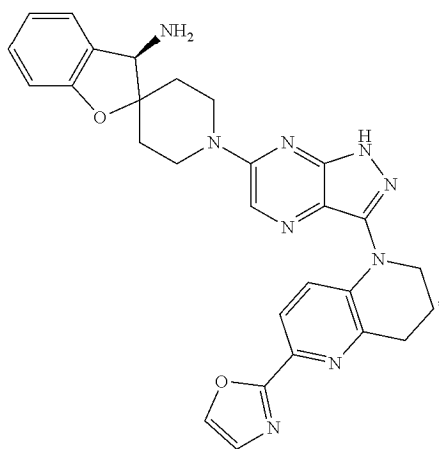
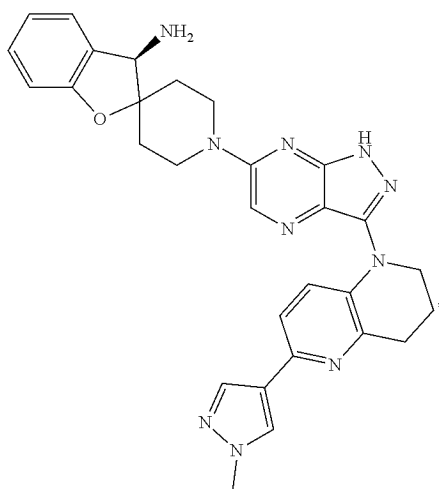
FIG. 1A depicts an isobologram illustrating synergistic growth inhibition of KYSE520
25 (squamous-cell carcinoma of the head and neck cells) using erlotinib (EGFR inhibitor) and a SHP2 inhibitor of the instant disclosure.

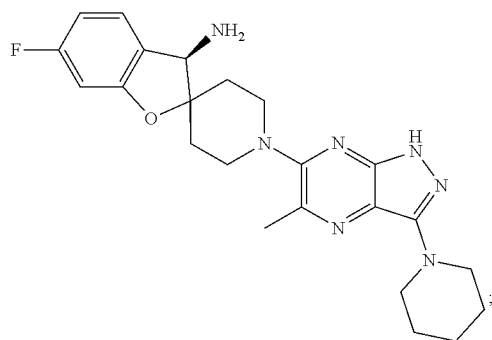
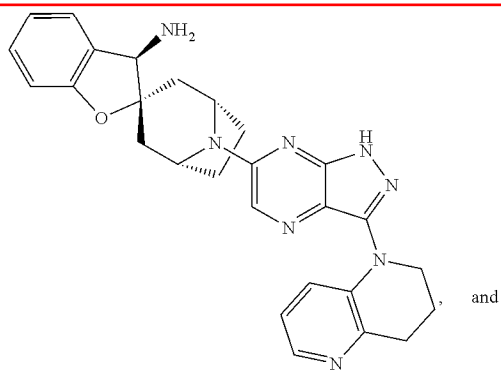
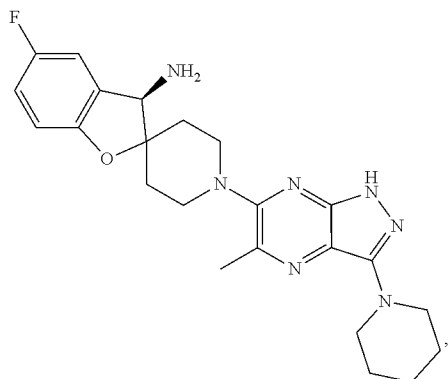
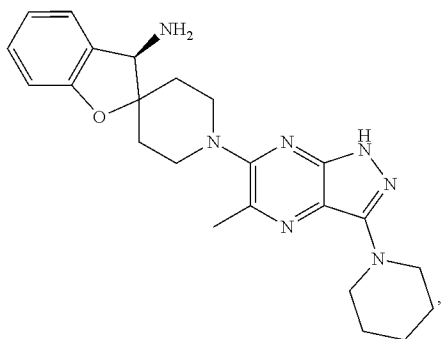
FIG. 1B. depicts an isobologram illustrating synergistic growth inhibition of NCI-H3122 (non-small cell lung cancer cells) using crizotinib (ALK inhibitor) and a SHP2 inhibitor of the instant disclosure.

CLAIMS

1. A compound selected from the group consisting of:

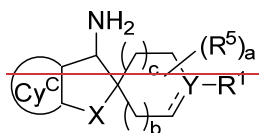






or a pharmaceutically acceptable salt thereof.

1. A compound of Formula X:



~~X~~

or a pharmaceutically acceptable salt thereof, wherein;

~~X is CH_2 , $\text{CH}(\text{R}^{\text{X}})$, $\text{C}(\text{R}^{\text{X}})_2$, $\text{C}(\text{O})$, NH , $\text{N}(\text{R}^{\text{X}})$, or O ;~~

~~Y is C, CH, $\text{C}(\text{R}^{\text{Y}})$, or N;~~

~~== is a single bond when Y is CH, $\text{C}(\text{R}^{\text{Y}})$, or N; or == is a double bond when Y is C;~~

~~R^1 is $\text{L}^1\text{-Cy}^{\text{B}}\text{-L}^2\text{-R}^2$;~~

~~Cy^{B} is phenyl, a monocyclic 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a bicyclic 8-10 membered heteroaryl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein Cy^{B} is substituted by m instances of R^2 ;~~

~~Cy^{C} is benzo; 5-6 membered heteroaryl; or 3-7 membered saturated or partially unsaturated cycloaliphatic fused; or 3-7 membered saturated or partially unsaturated heterocyclo having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein when Cy^{C} is heterocyclo or heteroaryl, said heteroatoms may occur at any position within Cy^{C} ; and wherein in each case Cy^{C} is substituted by n instances of R^4 ;~~

~~L^1 is a covalent bond or $\text{C}(\text{O})$;~~

~~L^2 is a covalent bond, or a C_{1-4} bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $\text{CH}(\text{R}^1)$, $\text{C}(\text{R}^1)_2$, C_{3-5} cycloalkylene, $\text{N}(\text{R})$, $\text{N}(\text{R})\text{C}(\text{O})$, $\text{C}(\text{O})\text{N}(\text{R})$, $\text{N}(\text{R})\text{S}(\text{O})_2$, $\text{S}(\text{O})_2\text{N}(\text{R})$, O , $\text{C}(\text{O})$, $\text{OC}(\text{O})$, $\text{C}(\text{O})\text{O}$, S , $\text{S}(\text{O})$, or $\text{S}(\text{O})_2$;~~

- ~~—————R² is hydrogen, R^A, or R^B, and when R² is R^B, R² is substituted by q instances of R^C;~~
- ~~—————each instance of R³, R⁴, R^X, R^Y, and R¹ is independently R^A or R^B, and is substituted by r instances of R^C;~~
- ~~—————each instance of R⁵ is independently R^A or R^B, and is substituted by r instances of R^C; or two instances of R⁵ are taken together with their intervening atoms to form a 3-6 membered carbocyclic fused ring or a 3-6 membered heterocyclic fused ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~
- ~~—————each instance of R^A is independently oxo, halogen, CN, NO₂, OR, SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, C(O)R, C(O)OR, C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, or N(R)S(O)₂R;~~
- ~~—————each instance of R^B is independently C₁₋₆ aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~
- ~~—————each instance of R^C is independently oxo, halogen, CN, NO₂, OR, SR, NR₂, S(O)₂R, S(O)₂NR₂, S(O)R, S(O)NR₂, OS(O)₂F, C(O)R, C(O)OR, C(O)NR₂, C(O)N(R)OR, OC(O)R, OC(O)NR₂, N(R)C(O)OR, N(R)C(O)R, N(R)C(O)NR₂, N(R)C(NR)NR₂, N(R)S(O)₂NR₂, N(R)S(O)₂R, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;~~

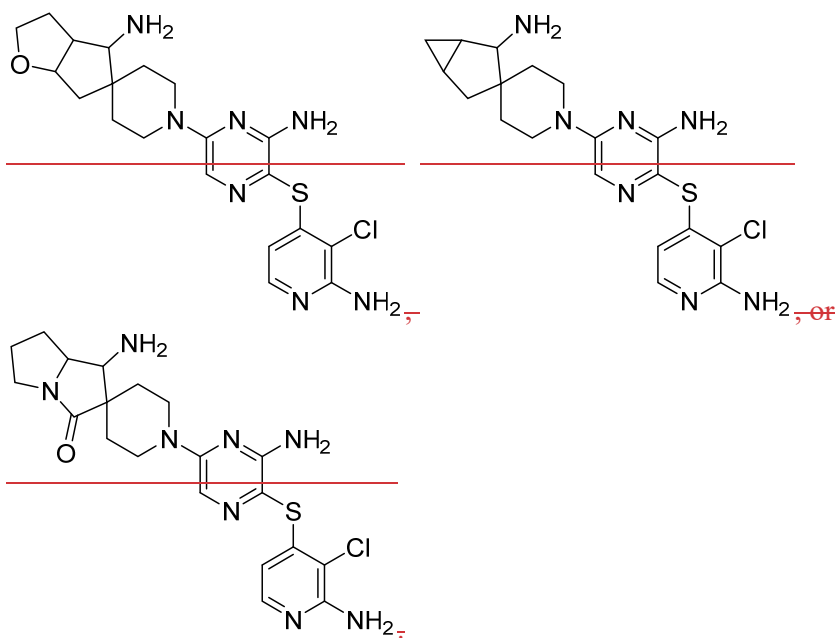
~~each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or;~~

~~two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;~~

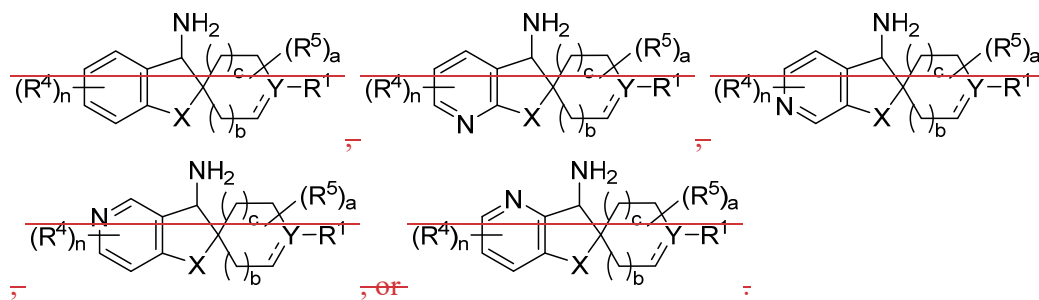
~~each of b and c is independently 0 or 1; and~~

~~each of a, m, n, q, and r is independently 0, 1, 2, 3, or 4;~~

~~wherein the compound is not~~

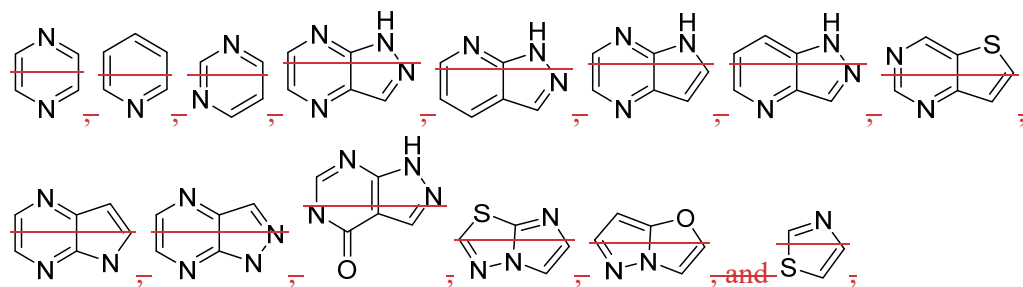


~~2. The compound of claim 1 wherein the compound is of the one of formulas:~~



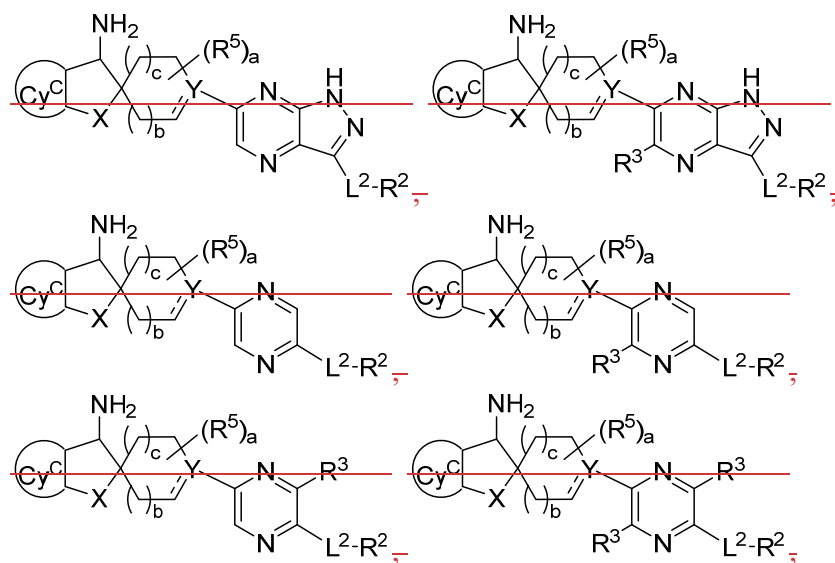
or a pharmaceutically acceptable salt thereof.

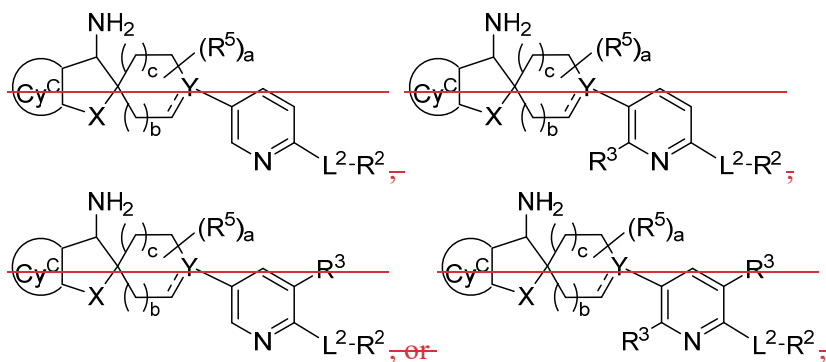
3. The compound of claim 1 wherein Cy^B is selected from the group consisting of:



wherein Cy^B is substituted by m instances of R³.

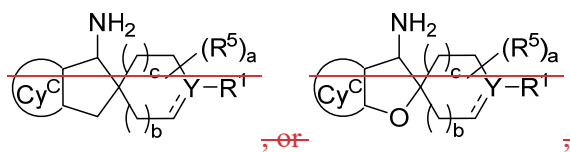
4. The compound of claim 1 wherein the compound is of one of formulas:





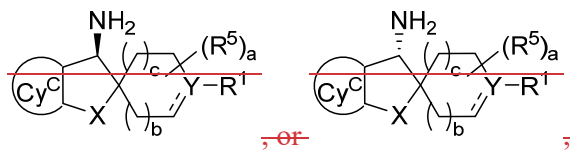
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 wherein the compound is of one of formulas:



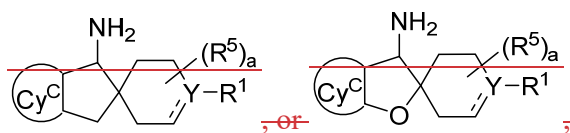
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1 wherein the compound is of one of formulas:



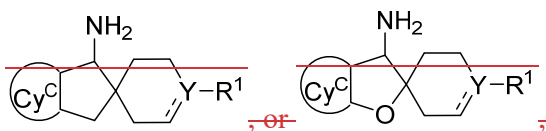
or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1 wherein the compound is of one of formulas:



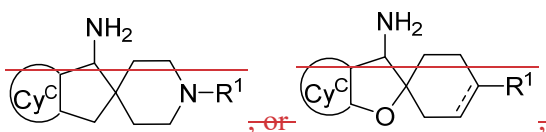
or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1 wherein the compound is of one of formulas:



~~or a pharmaceutically acceptable salt thereof.~~

~~9. The compound of claim 1 wherein the compound is of one of formulas:~~

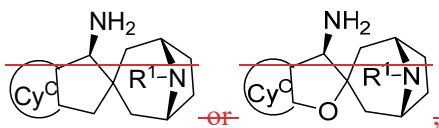


~~or a pharmaceutically acceptable salt thereof.~~

~~10. The compound of claim 1 wherein variable a is 2, or a pharmaceutically acceptable salt thereof.~~

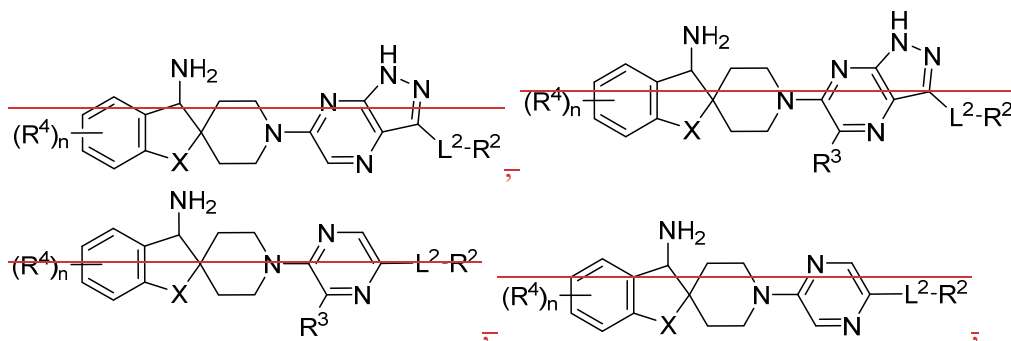
~~11. The compound of claim 1 wherein two instances of R⁵ are taken together with their intervening atoms to form a 3-6 membered carbocyclic fused ring or a 3-6 membered heterocyclic fused ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a pharmaceutically acceptable salt thereof.~~

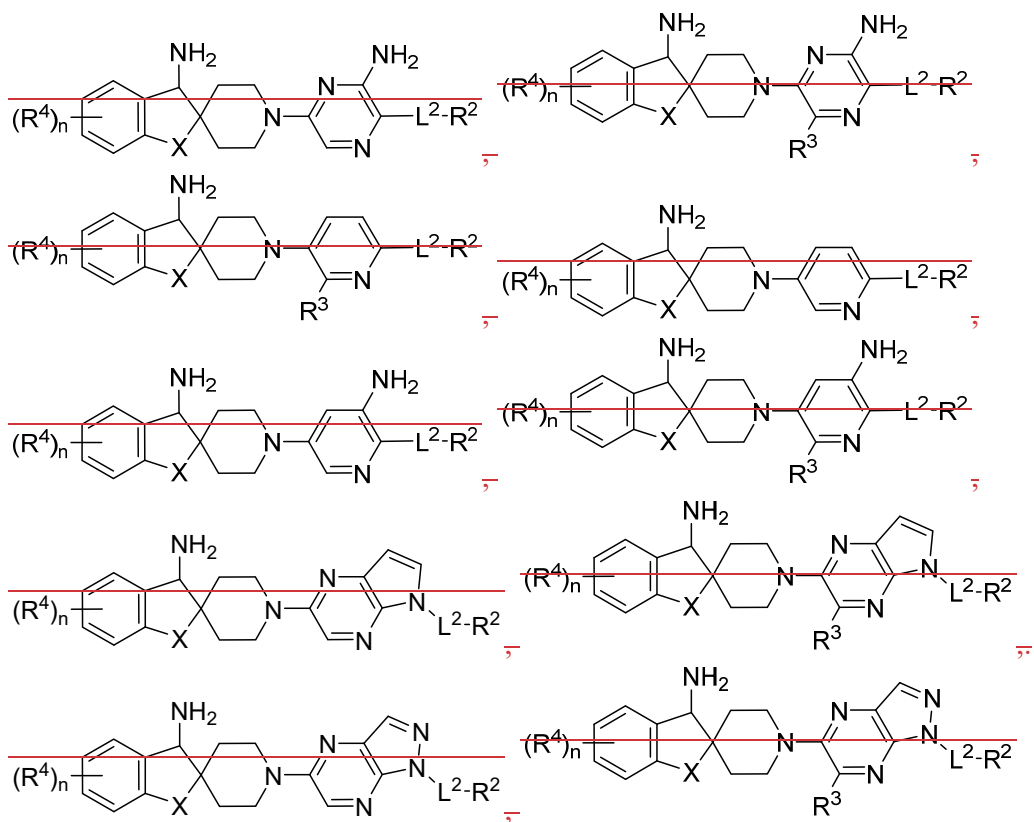
~~12. The compound of claim 11 of one of formulas:~~



~~or a pharmaceutically acceptable salt thereof.~~

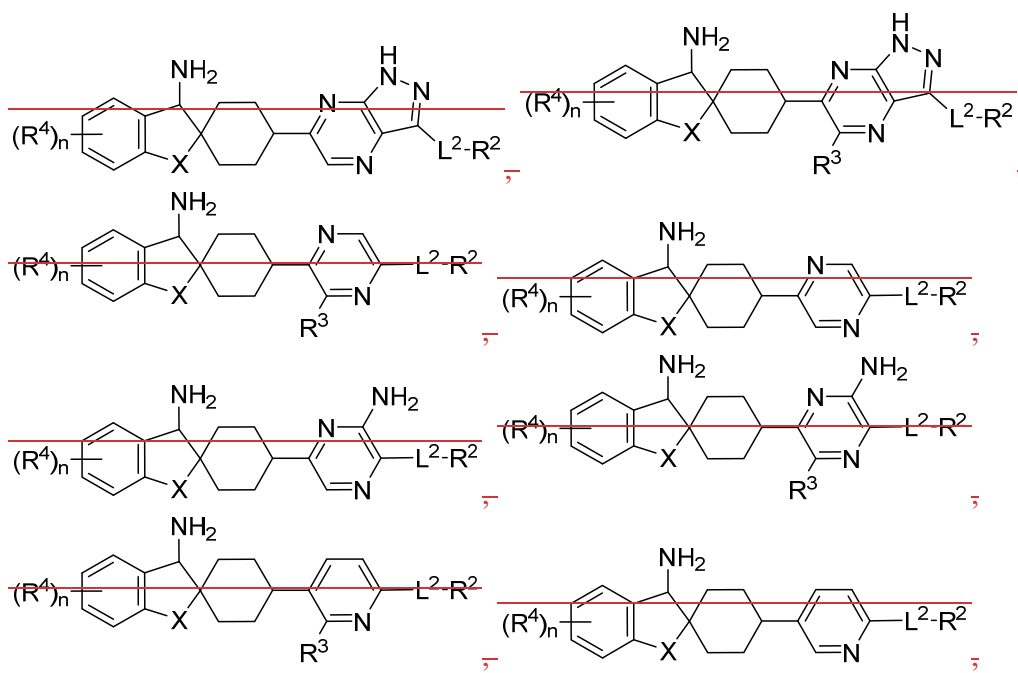
~~13. The compound of claim 1 of the formula:~~

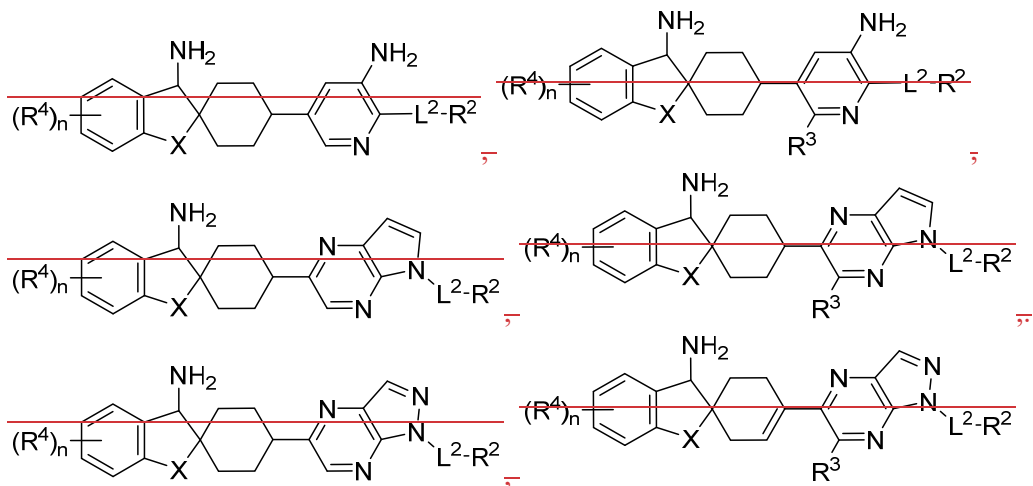




or a pharmaceutically acceptable salt thereof.

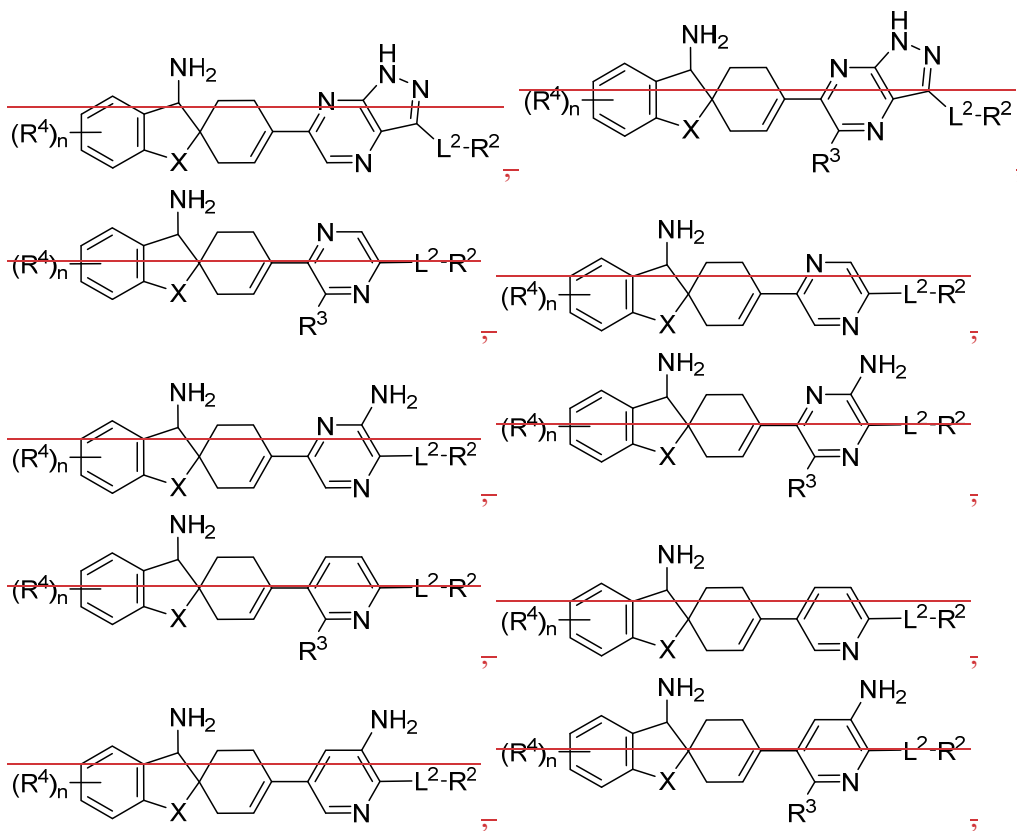
14. The compound of claim 1 of the formula:

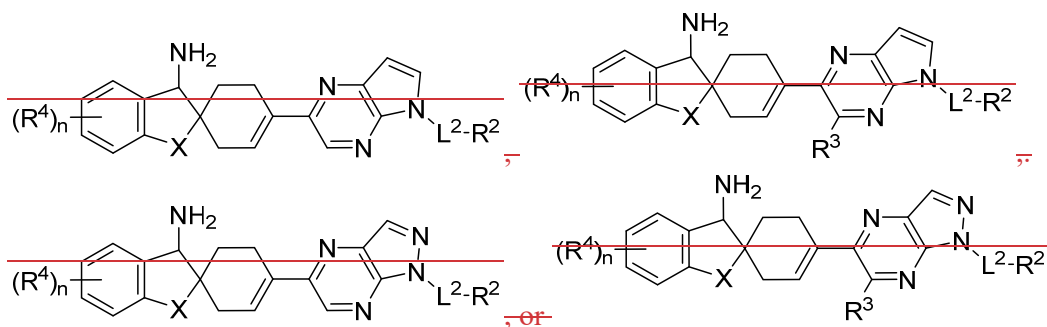




or a pharmaceutically acceptable salt thereof.

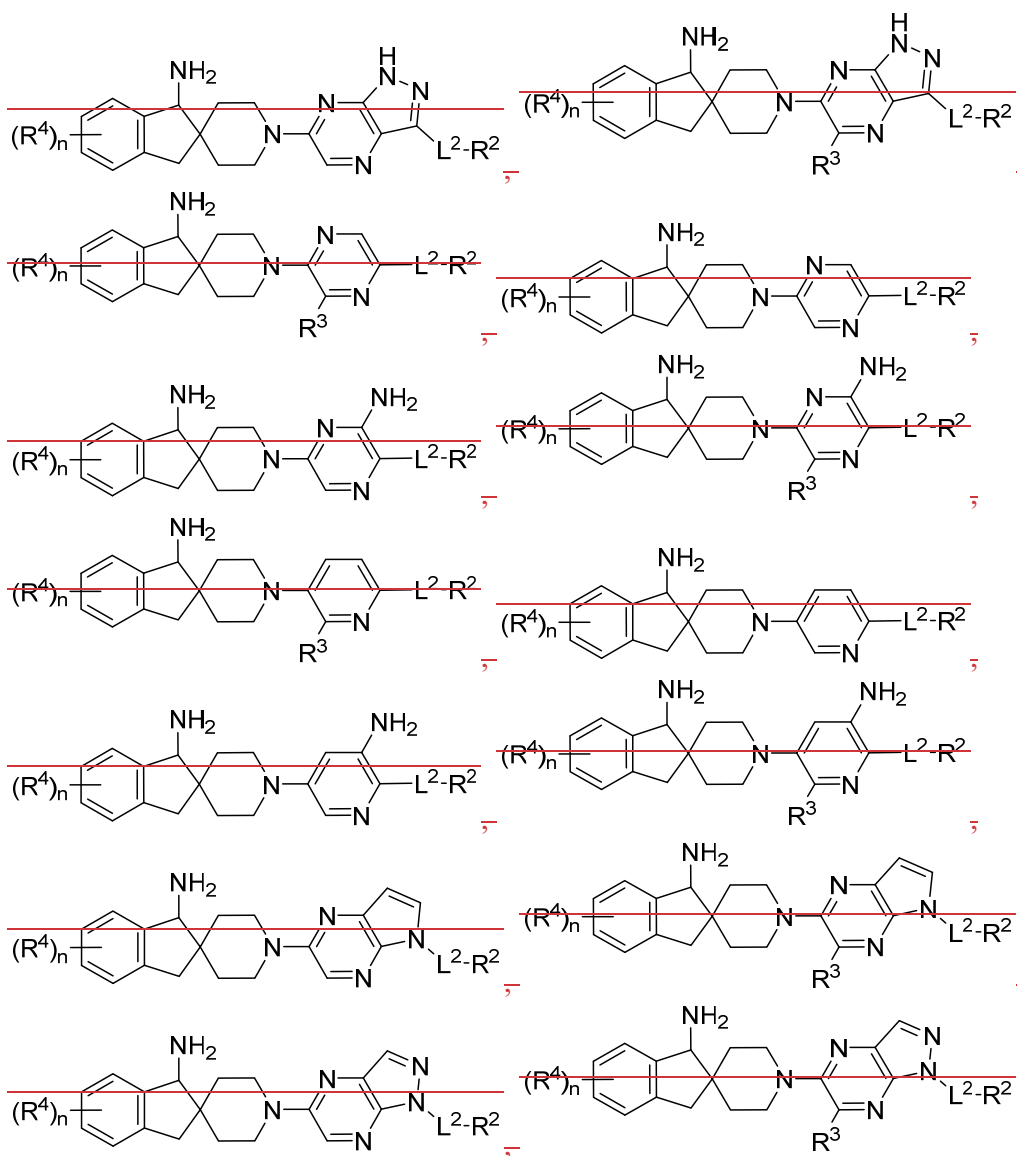
15. The compound of claim 1 of the formula:





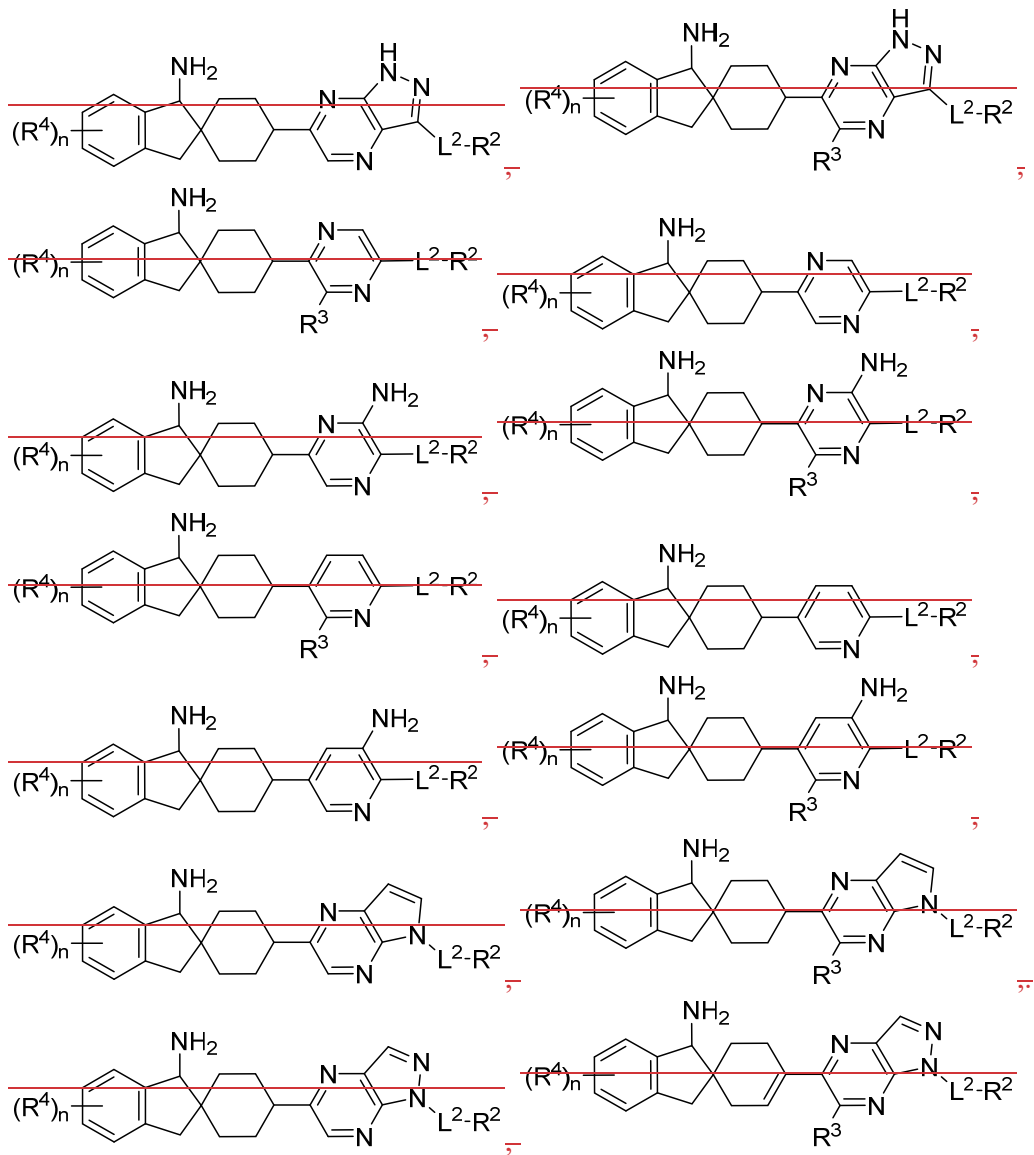
or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1 of the formula:



or a pharmaceutically acceptable salt thereof.

~~17. The compound of claim 1 of the formula:~~

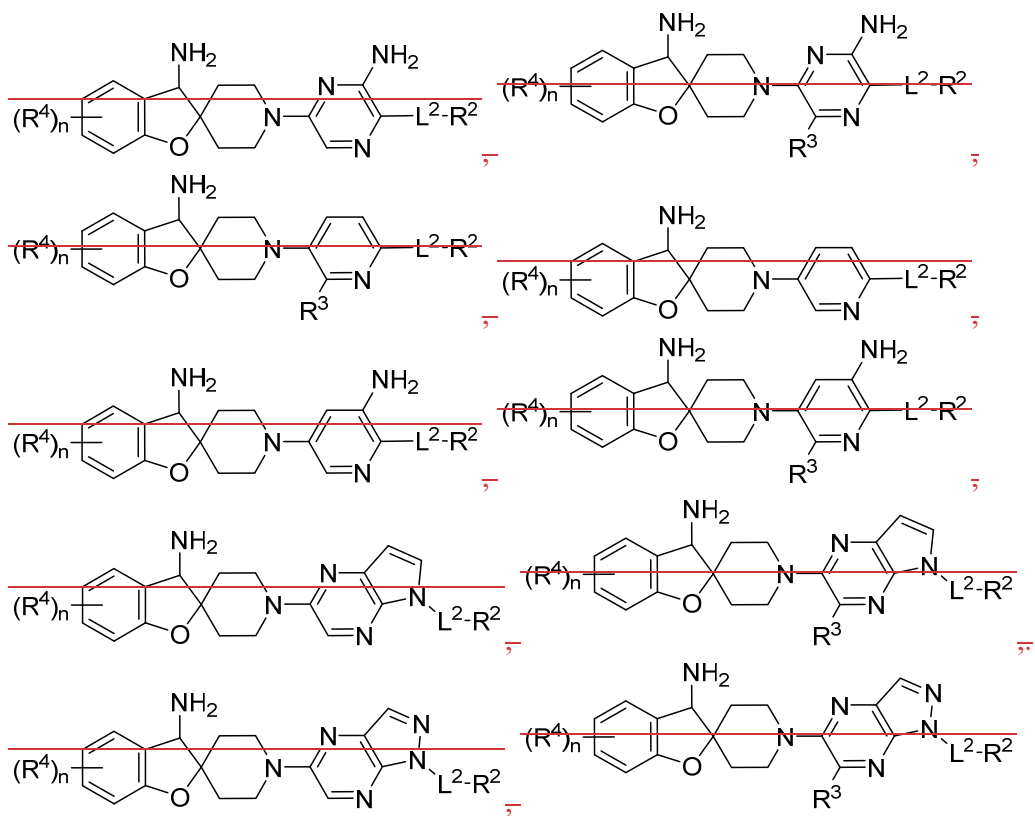


~~or a pharmaceutically acceptable salt thereof.~~

~~18. The compound of claim 1 of the formula:~~

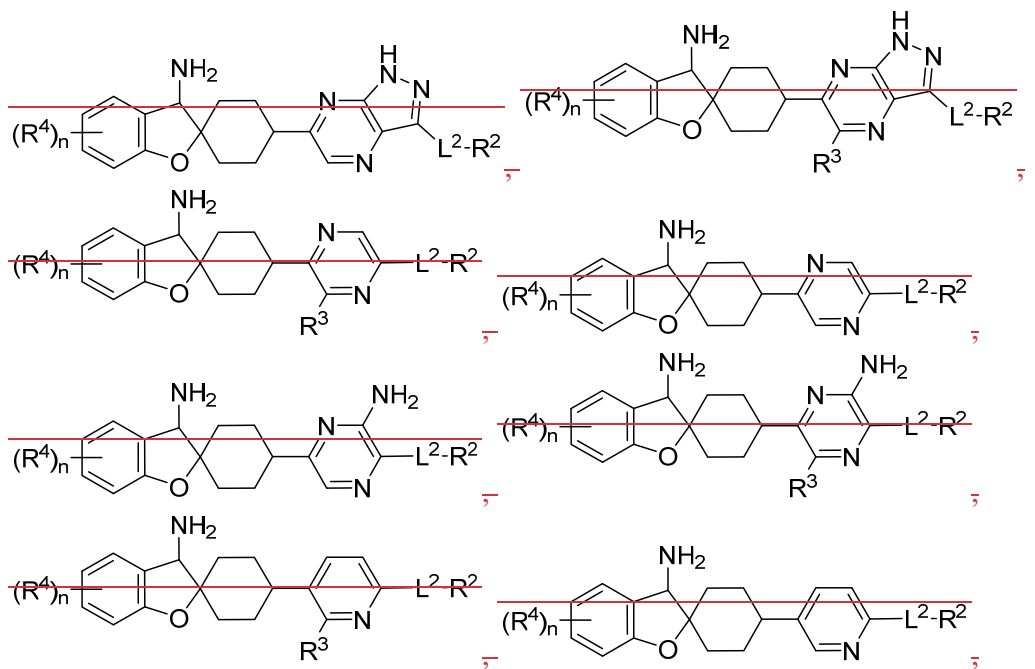


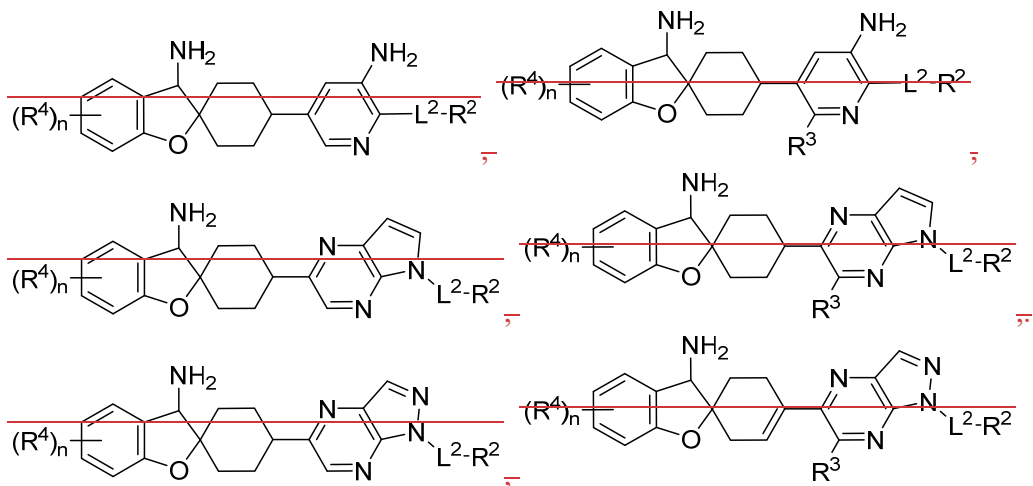
Chemical structures 5a, 5b, 5c, and 5d are shown. Each structure features a 6-amino-2,3-dihydro-1H-indolo[2,3-b]pyridine core. The indole ring is substituted at the 6-position with an amino group (NH₂) and at the 3-position with a (R⁴)_n group. The pyridine ring is substituted at the 2-position with an amino group (NH₂) and at the 4-position with an L²-R² group. The structures are labeled 5a, 5b, 5c, and 5d.



or a pharmaceutically acceptable salt thereof.

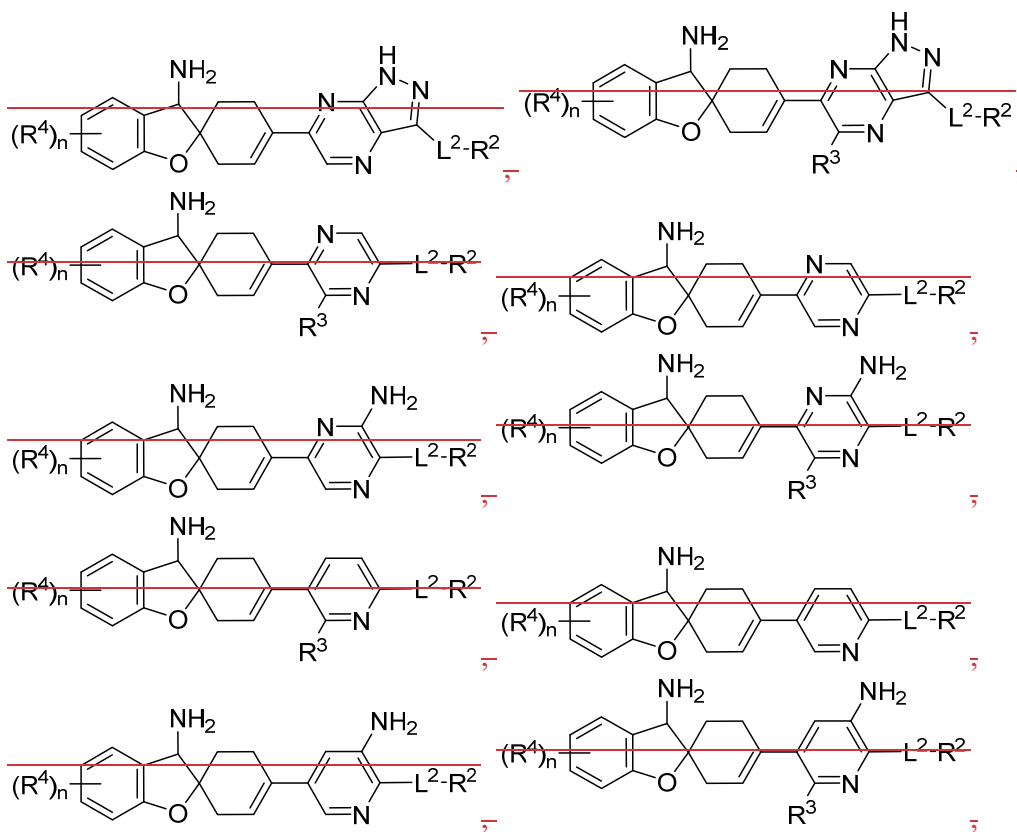
20. The compound of claim 1 of the formula:

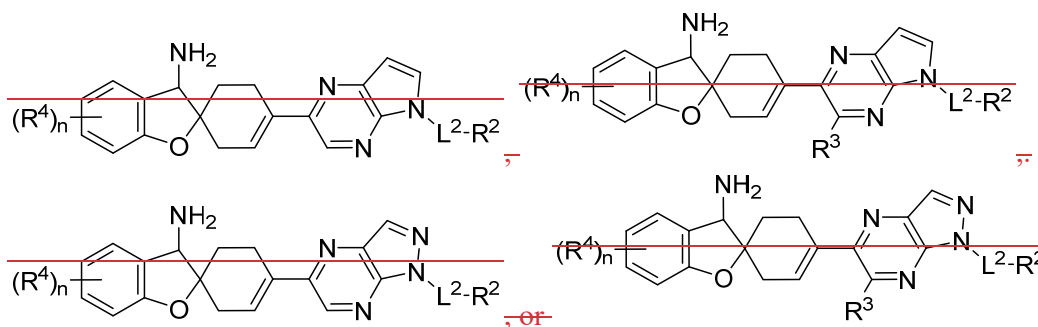




— or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1 of the formula:





~~or a pharmaceutically acceptable salt thereof.~~

~~22. The compound according to any one of the preceding claims wherein at least one instance of R^3 is CH_3 , CHF_2 , CH_2OH , $\text{CH}(\text{CH}_3)\text{OH}$, or cyclopropyl.~~

~~23. The compound according to any one of the preceding claims wherein X is CH_2 , or a pharmaceutically acceptable salt thereof.~~

~~24. The compound according to any one of the preceding claims wherein X is O, or a pharmaceutically acceptable salt thereof.~~

~~25. The compound according to any one of the preceding claims wherein Cy^E is benzo, or a pharmaceutically acceptable salt thereof.~~

~~26. The compound according to any one of the preceding claims wherein Cy^E is 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a pharmaceutically acceptable salt thereof.~~

~~27. The compound according to any one of the preceding claims wherein Y is N, or a pharmaceutically acceptable salt thereof.~~

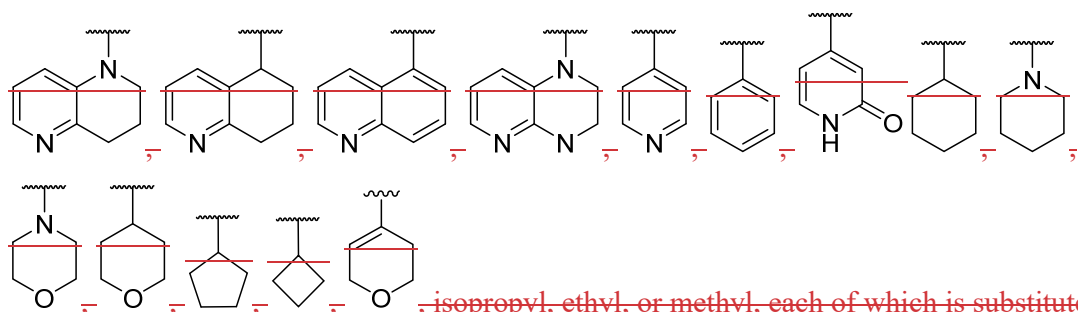
~~28. The compound according to any one of the preceding claims wherein Y is CH_2 , or a pharmaceutically acceptable salt thereof.~~

~~29. The compound according to any one of the preceding claims wherein L^1 is a covalent bond, or a pharmaceutically acceptable salt thereof.~~

~~30. The compound according to any one of the preceding claims wherein L^1 is $\text{C}(\text{O})$, or a pharmaceutically acceptable salt thereof.~~

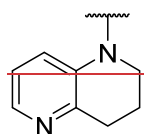
- ~~31. The compound according to any one of the preceding claims wherein L^2 is a covalent bond, or a pharmaceutically acceptable salt thereof.~~
- ~~32. The compound according to any one of the preceding claims wherein L^2 is S, or a pharmaceutically acceptable salt thereof.~~
- ~~33. The compound according to any one of the preceding claims wherein L^2 is O, or a pharmaceutically acceptable salt thereof.~~
- ~~34. The compound according to any one of the preceding claims wherein L^2 is C(O), or a pharmaceutically acceptable salt thereof.~~
- ~~35. The compound according to any one of the preceding claims wherein L^2 is C₁₋₃-aliphatic, or a pharmaceutically acceptable salt thereof.~~
- ~~36. The compound according to any one of the preceding claims wherein n is 1, 2, 3, or 4, or a pharmaceutically acceptable salt thereof.~~
- ~~37. The compound according to any one of the preceding claims wherein n is 0, or a pharmaceutically acceptable salt thereof.~~
- ~~38. The compound according to any one of the preceding claims, wherein at least one instance of R^4 is fluoro, or a pharmaceutically acceptable salt thereof.~~
- ~~39. The compound according to any one of the preceding claims wherein R^2 is C₁₋₆-aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein R^2 is substituted by q instances of R^C , or a pharmaceutically acceptable salt thereof.~~
- ~~40. The compound according to any one of the preceding claims wherein R^2 is C₁₋₆-aliphatic substituted with q instances of R^C , or a pharmaceutically acceptable salt thereof.~~

41. ~~The compound according to any one of the preceding claims wherein R^2 is phenyl substituted with q instances of R^C , or a pharmaceutically acceptable salt thereof.~~
42. ~~The compound according to any one of the preceding claims wherein R^2 is an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur substituted with q instances of R^C , or a pharmaceutically acceptable salt thereof.; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.~~
43. ~~The compound according to any one of the preceding claims wherein R^2 is a 3-7 membered saturated or partially unsaturated carbocyclic ring substituted with q instances of R^C , or a pharmaceutically acceptable salt thereof.~~
44. ~~The compound according to any one of the preceding claims wherein R^2 is a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, substituted with q instances of R^C , or a pharmaceutically acceptable salt thereof.~~
45. ~~The compound according to any one of the preceding claims wherein R^2 is 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, substituted with q instances of R^C , or a pharmaceutically acceptable salt thereof.~~
46. ~~The compound according to any one of the preceding claims wherein R^2 is:~~



~~, isopropyl, ethyl, or methyl, each of which is substituted with q instances of R^C , or a pharmaceutically acceptable salt thereof.~~

47. ~~The compound according to any one of the preceding claims wherein R^2 is:~~

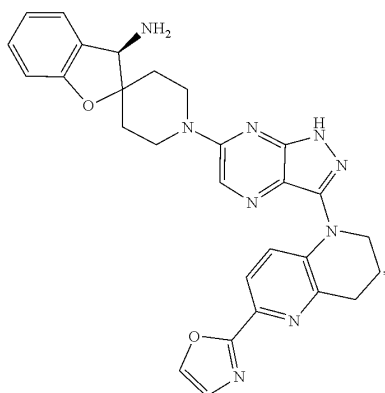
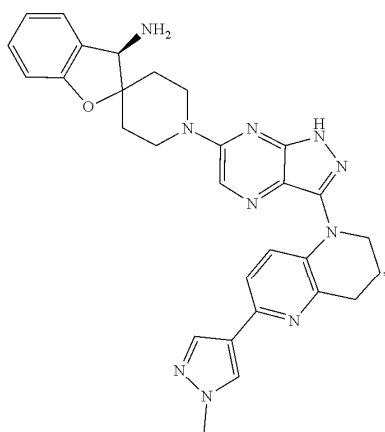
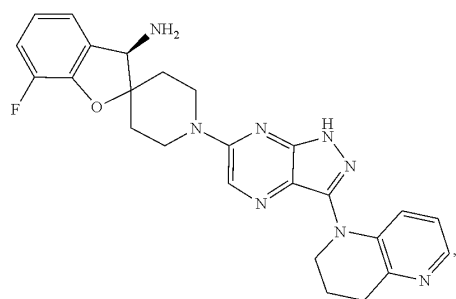


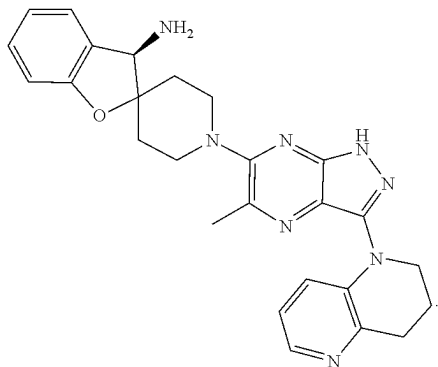
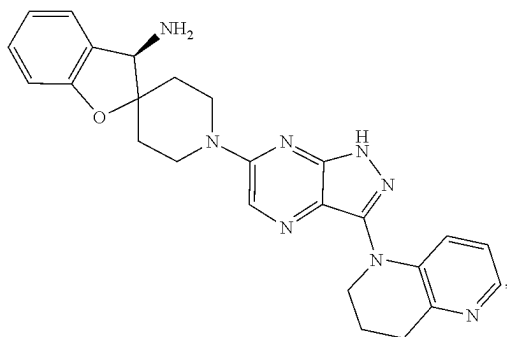
, or a pharmaceutically acceptable salt thereof.

~~48. A compound selected from the group consisting of the compounds depicted in Table 1, and a pharmaceutically acceptable salt, stereoisomer, or mixture of stereoisomers thereof.~~

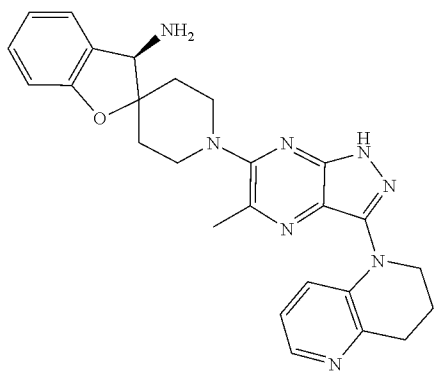
~~492. A pharmaceutical composition comprising a compound of claim 1 any of claims 1-48 and a pharmaceutically acceptable carrier.~~

3. The compound of claim 1, wherein the compound is selected from the group consisting of:





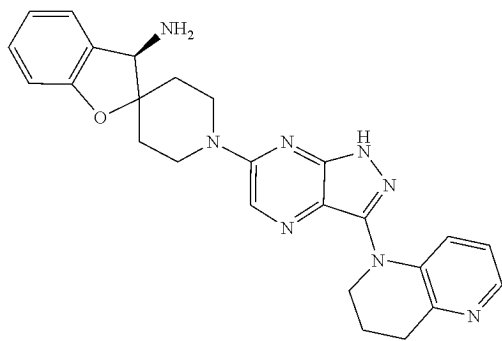
4. A compound represented by:



or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a compound of claim 4 and a pharmaceutically acceptable carrier.

6. A compound represented by:



or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a compound of claim 6 and a pharmaceutically acceptable carrier.

~~50. A method of inhibiting SHP2 phosphatase activity in a subject comprising administration of a therapeutically effective amount of the compound of any of claims 1-48, or the composition of claim 49, to a subject in need thereof.~~

~~51. The method of claim 50, further comprising administration of a therapeutically effective amount of an antibody, an antibody drug conjugate, an immunomodulator, or a histone deacetylase inhibitor.~~

~~52. The method of claim 50 or 51, wherein the subject is a human.~~

~~53. A method of treating a disorder in a subject comprising administration of a therapeutically effective amount of the compound of any of claims 1-48, or the composition of claim 49, to a subject in need thereof.~~

~~54. The method of claim 53, further comprising administration of a therapeutically effective amount of an antibody, an antibody drug conjugate, an immunomodulator, or a histone deacetylase inhibitor.~~

~~55. The method of claim 53 or 54, wherein the disorder is Noonan syndrome.~~

~~56. The method of claim 53 or 54, wherein the disorder is neutropenia.~~

~~57. The method of claim 53 or 54, wherein the disorder is diabetes.~~

~~58. The method of claim 53 or 54, wherein the disorder is neuroblastoma.~~

~~59. The method of claim 53 or 54, wherein the disorder is melanoma.~~

~~60. The method of claim 53 or 54, wherein the disorder is acute myeloid leukemia.~~

~~61. The method of claim 53 or 54, wherein the disorder is juvenile leukemia.~~

~~62. The method of claim 53 or 54, wherein the disorder is juvenile myelomonocytic leukemia.~~

~~63. The method of claim 53 or 54, wherein the disorder is breast cancer.~~

~~64. The method of claim 53 or 54, wherein the disorder is lung cancer.~~

~~65. The method of claim 53 or 54, wherein the disorder is colorectal cancer.~~