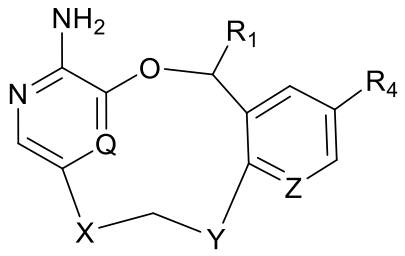
CLAIMS

1. A compound of Formula (I):



(I),

or an enantiomer, a mixture of enantiomers, or a tautomer thereof, or a pharmaceutically acceptable salt thereof,

wherein

Q is CH or N;

Z is CR_5 or N;

X is a 5-membered heteroarylene selected from the group consisting of pyrazolylene, isoxazolylene, imidazolylene, isothiazolylene, triazolylene, and pyrrolylene; wherein the 5-membered heteroarylene is substituted with 0, 1, or 2 occurrences of R_2;

Y is a 5- or 6-membered heteroarylene, comprising 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the 5- or 6-membered heteroarylene is substituted with 0, 1, or 2 occurrences of R_3;

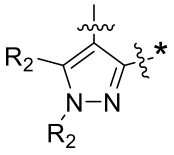
in Y, (a) the point of attachment to the methylene group bonded to X and Y and the point of attachment to the aromatic ring comprising Z are on adjacent atoms, and (b) the 5- or 6-membered heteroarylene ring atom which is (i) alpha to the point of attachment to the methylene group and (ii) beta to the point of attachment to the aromatic ring comprising Z is nitrogen;

R_1 is selected from the group consisting of H, methyl, and hydroxymethyl;

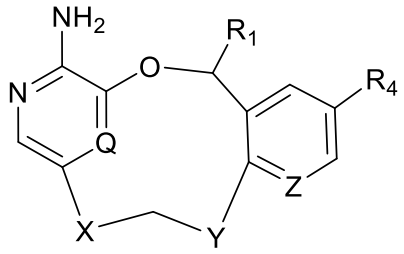
each instance of R_2 is independently selected from the group consisting of H, halo, CN, O-C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} haloalkyl, CH_2-C_{3-4} cycloalkyl, C_{3-6} cycloalkyl, and three- to six-membered heterocycloalkyl;

each instance of R_3 is independently selected from the group consisting of H, halo, CN, O-C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkyl; and

each of R_4 and R_5 is independently H or F;

provided that X is not  wherein R_2 is not H, where * indicates the point of attachment of X to the methylene group bonded to X and Y.

2. A compound of Formula (I):



(I),

or an enantiomer, a mixture of enantiomers, or a tautomer thereof, or a pharmaceutically acceptable salt thereof,

wherein

Q is CH or N;

Z is CR_5 or N;

X is a 5-membered heteroarylene selected from the group consisting of pyrazolylene, isoxazolylene, imidazolylene, isothiazolylene, triazolylene, and pyrrolylene; wherein the 5-membered heteroarylene is substituted with 0, 1, or 2 occurrences of R_2;

Y is a heteroarylene selected from the group consisting of 1,2*-substituted-imidazolylene, 4*,5-substituted-imidazolylene, 4,5*-substituted-imidazolylene, 4*,5-substituted-1,2,3-oxadiazolylene, 3*,4-substituted-1,2,5-oxadiazolylene, 3*,4-substituted-1,2-oxazolylene, 4*,5-substituted-1,3-oxazolylene, 2*,3-substituted-pyrazinylene, 1*,5-substituted-pyrazolylene, 3*,4-substituted-pyrazolylene, 3*,4-substituted-pyridazinylene, 2*,3-substituted-pyridinylene, 4*,5-substituted-pyrimidinylene, 2*,3-substituted-pyrrolylene, 4*,5-substituted-1,2,3-thiadiazolylene, 3*,4-substituted-1,2,5-thiadiazolylene, 3*,4-substituted-1,2-thiazolylene, 4*,5-substituted-1,3-thiazolylene, 4*,5-substituted-1,2,3-triazinylene, 5*,6-substituted-1,2,4-triazinylene, 5,6*-substituted-1,2,4-triazinylene, 1*,5-substituted-1,2,3-triazolylene, 4*,5-substituted-1,2,3-triazolylene, 1*,5-substituted-1,2,4-triazolylene, 1,5*-substituted-1,2,4-triazolylene, and 3*,4-substituted-1,2,4-triazolylene; wherein the heteroarylene is substituted with 0, 1, or 2 occurrences of R_3; wherein * indicates the point of attachment of Y to the methylene group bonded to X and Y;

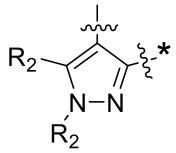
in Y the heteroarylene ring atom which is (i) alpha to the point of attachment to the methylene group and (ii) beta to the point of attachment to the aromatic ring comprising Z is nitrogen;

R_1 is selected from the group consisting of H, methyl, and hydroxymethyl;

each instance of R_2 is independently selected from the group consisting of H, halo, CN, O-C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} haloalkyl, CH_2-C_{3-4} cycloalkyl, C_{3-6} cycloalkyl, and three- to six-membered heterocycloalkyl;

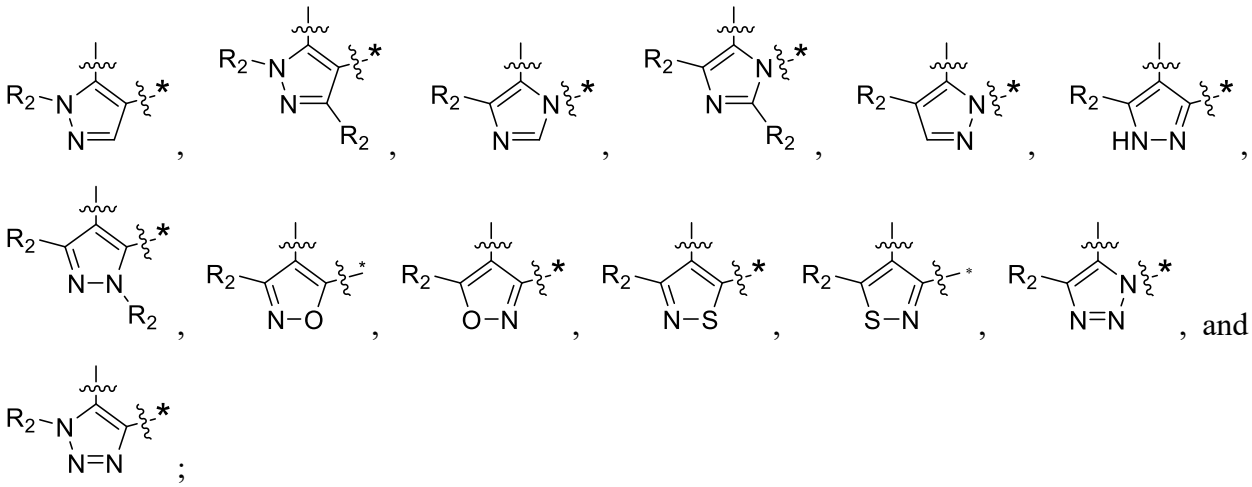
each instance of R_3 is independently selected from the group consisting of H, halo, CN, O-C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkyl; and

each of R_4 and R_5 is independently H or F,

provided that X is not 

wherein R_2 is not H, wherein * indicates the point of attachment of X to the methylene group bonded to X and Y.

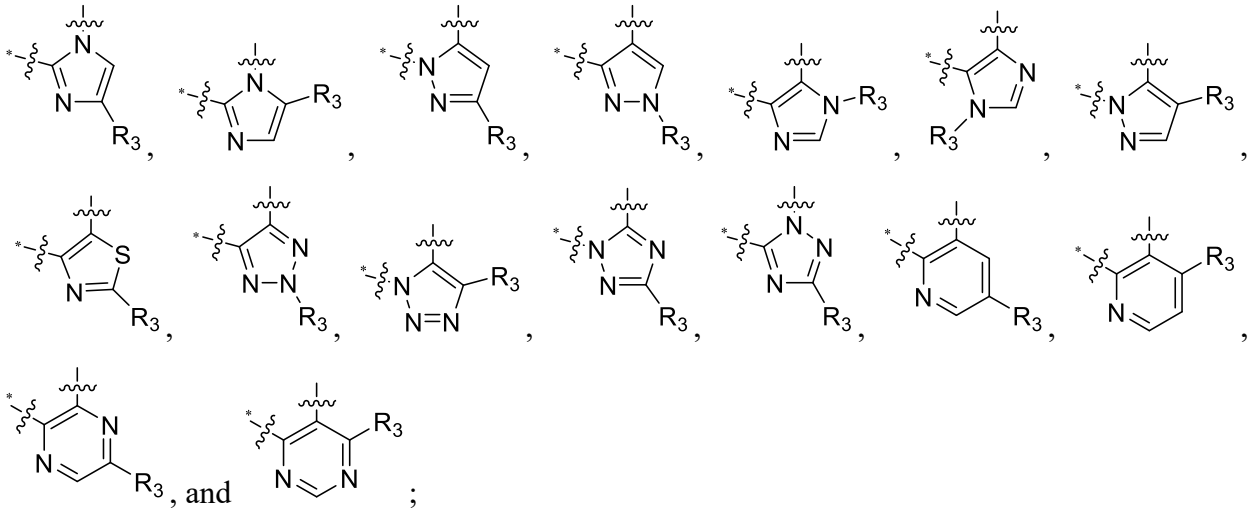
3. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of claim 1 or 2, wherein X is a 5-membered heteroarylene selected from the group consisting of:



* indicates the point of attachment of X to the methylene group bonded to X and Y; and

each instance of R_2 is independently selected from the group consisting of H, halo, CN, O-C_{1-4} alkyl, C_{1-4} alkyl, C_{1-4} haloalkyl, CH_2-C_{3-4} cycloalkyl, C_{3-6} cycloalkyl, and three- to six-membered heterocycloalkyl.

4. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-3, wherein Y is a heteroarylene selected from the group consisting of:



* indicates the point of attachment of Y to the methylene group bonded to X and Y; and

each instance of R_3 is selected from the group consisting of H, halo, CN, O-C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{1-4} alkyl.

5. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-4, wherein Q is CH.

6. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-4, wherein Q is N.

7. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-6, wherein Z is CR_5.

8. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-7, wherein R_5 is H.

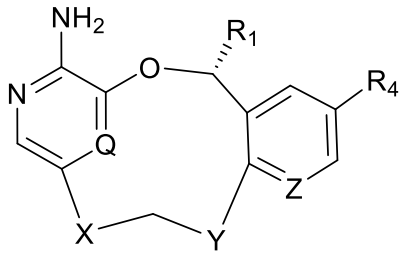
9. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-7, wherein R_5 is F.

10. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-6, wherein Z is N.

11. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-10, wherein R_4 is H.

12. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-10, wherein R_4 is F.

13. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-12, which has the structure (I-B):



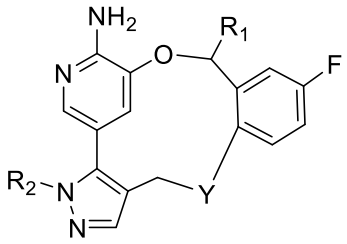
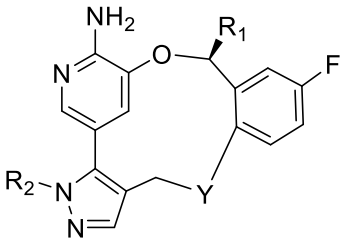
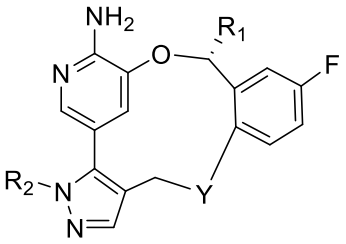
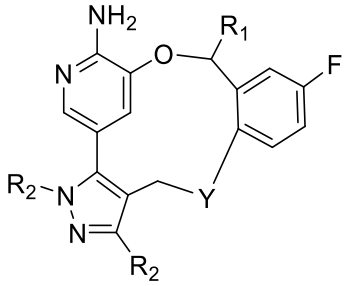
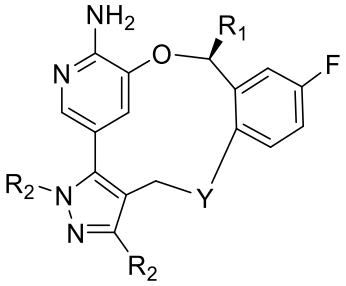
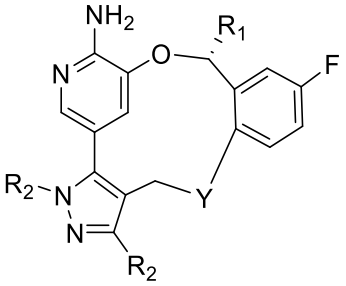
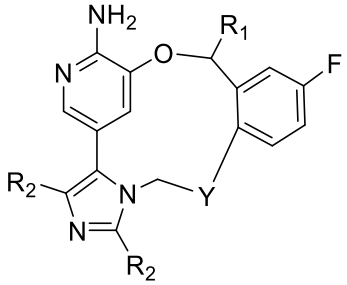
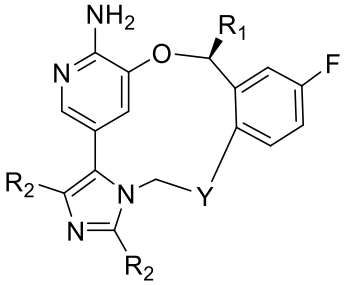
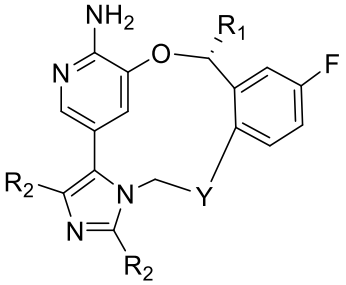
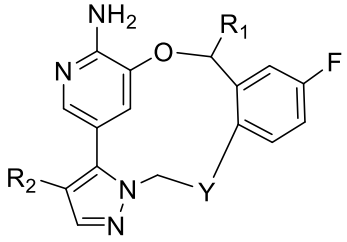
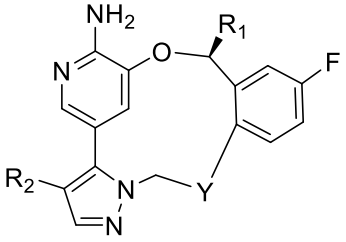
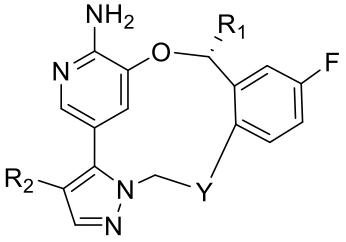
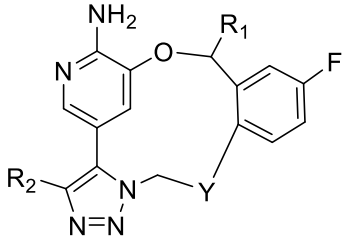
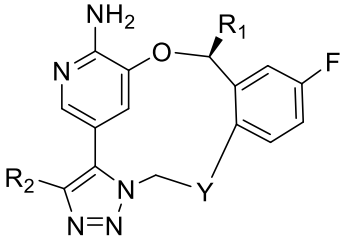
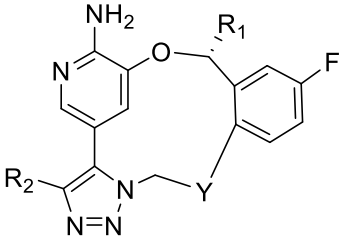
(I-B),

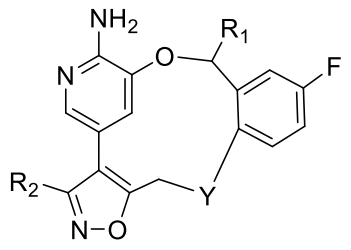
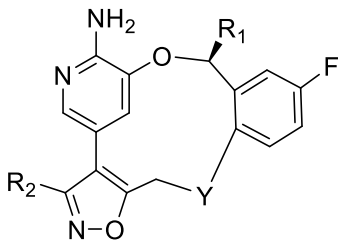
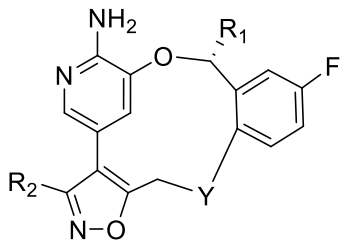
or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

14. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-13, wherein each instance of R_2 is independently selected from the group consisting of H, chloro, CN, methyl, ethyl, isobutyl, methoxy, trifluoromethyl, cyclopropylmethyl, 2-fluoroethyl, difluoromethyl, 2,2-difluoroethyl, cyclopropyl, cyclobutyl, and oxetanyl.

15. The compound, or the enantiomer, mixture of enantiomers, tautomer or pharmaceutically acceptable salt thereof, of any one of claims 1-14, wherein each instance of R_3 is independently selected from the group consisting of H, fluoro, chloro, CN, methyl, and ethyl.

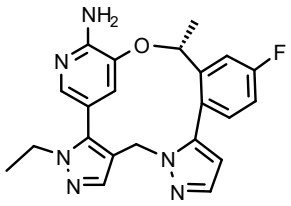
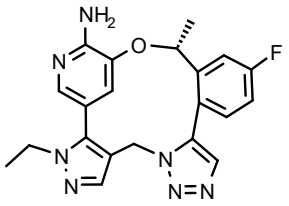
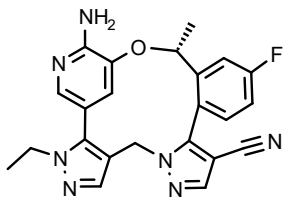
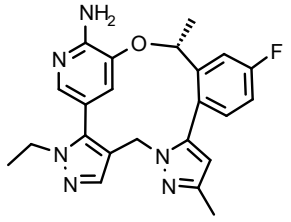
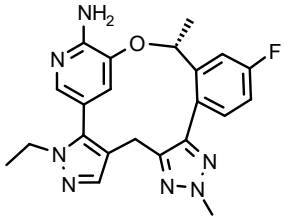
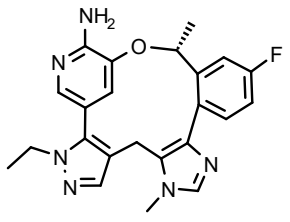
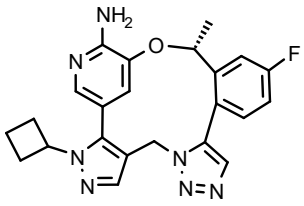
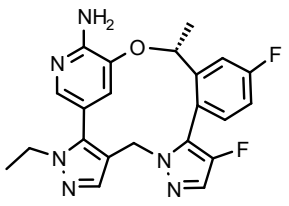
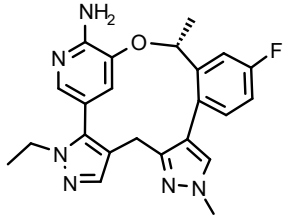
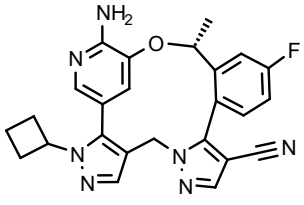
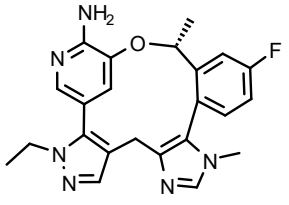
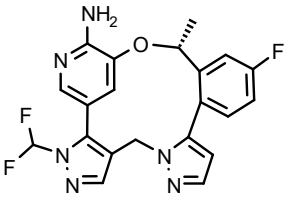
16. The compound of claim 1 or 2, which is a compound of any of the following formula:

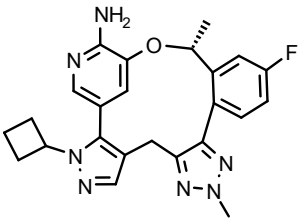
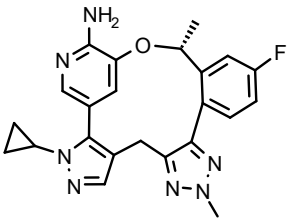
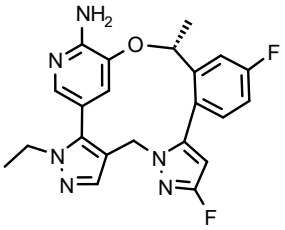
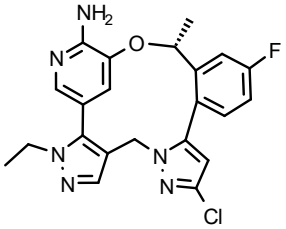
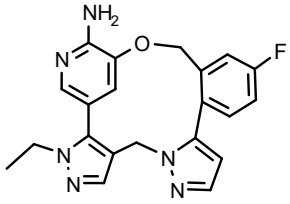
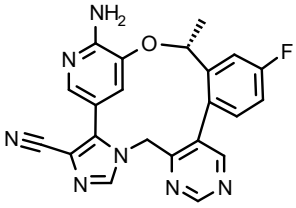
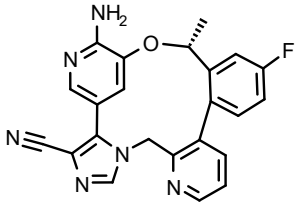
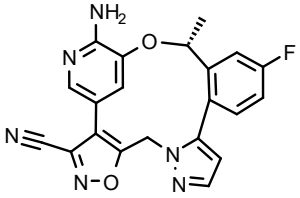
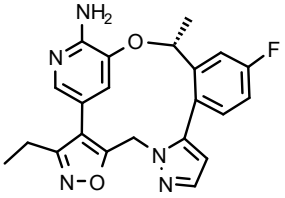
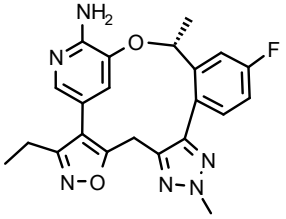
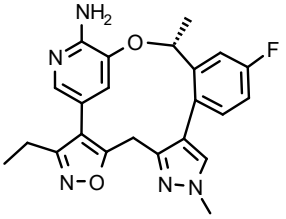
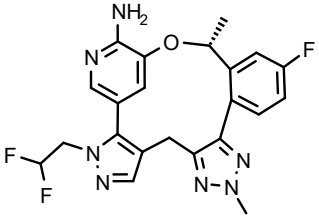
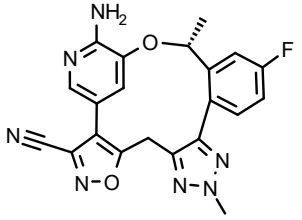
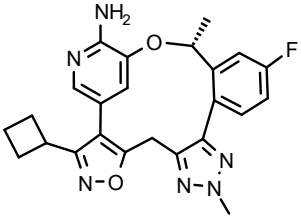
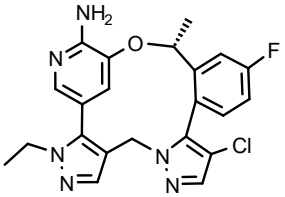
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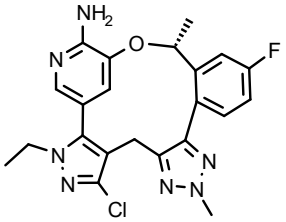
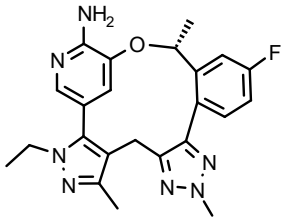
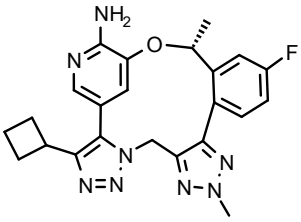
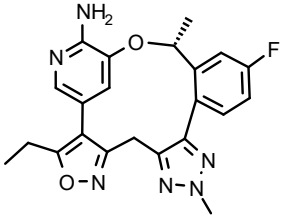
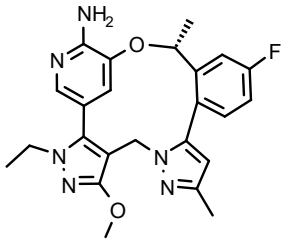
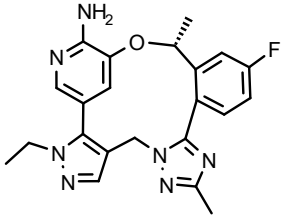
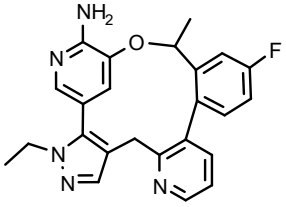
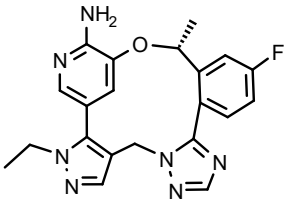
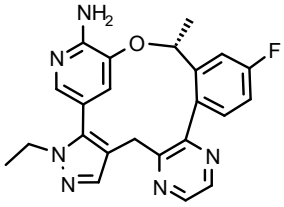
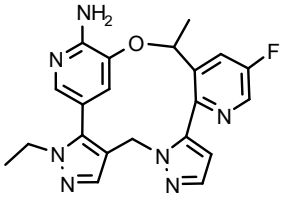
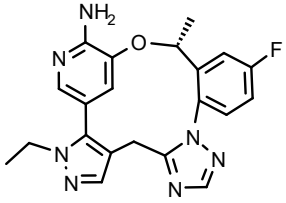
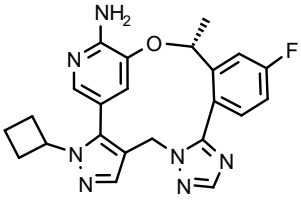
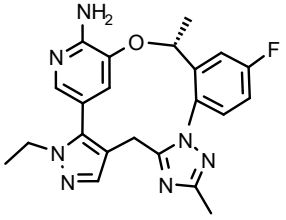
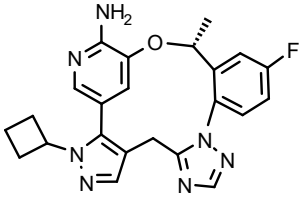
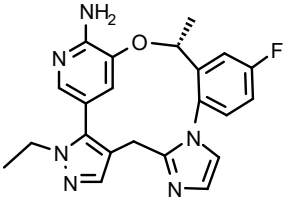
		
(VII),	(VII-A), or	(VII-B),

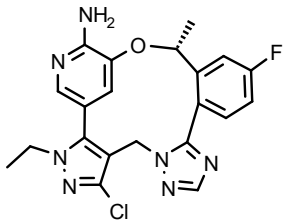
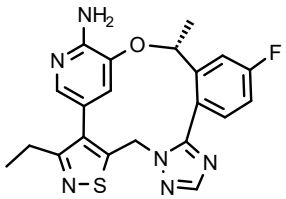
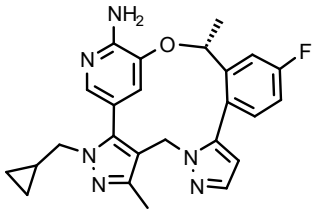
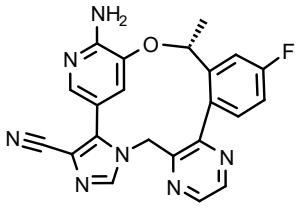
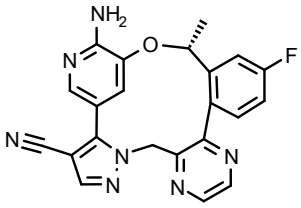
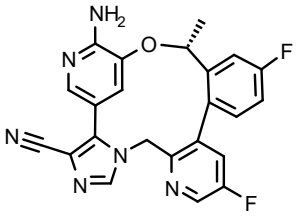
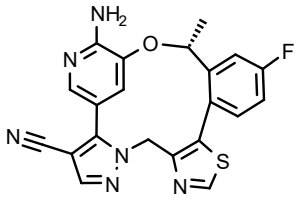
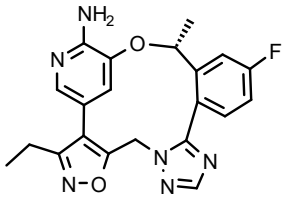
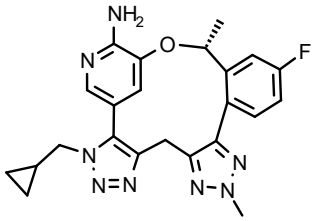
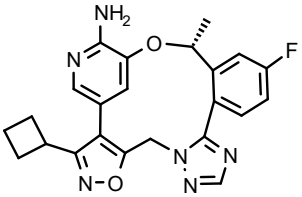
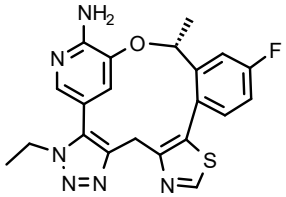
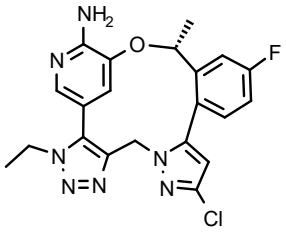
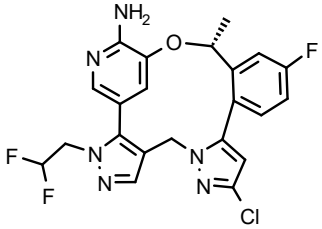
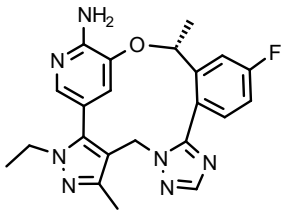
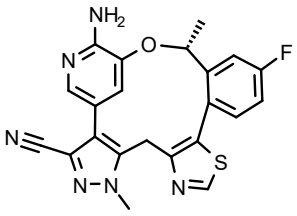
or an enantiomer, a mixture of enantiomers, or a tautomer thereof, or a pharmaceutically acceptable salt thereof.

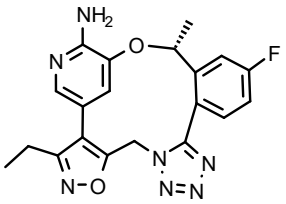
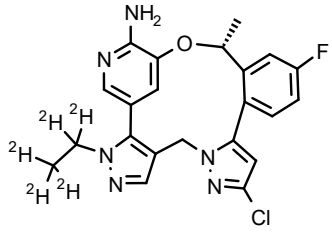
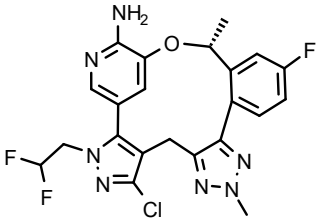
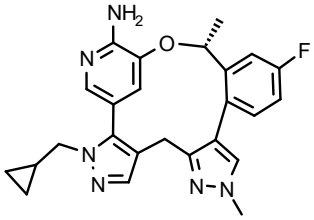
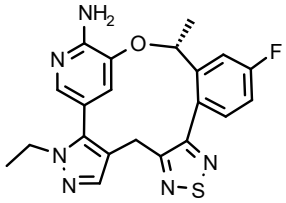
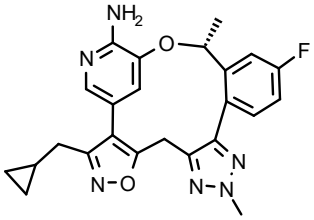
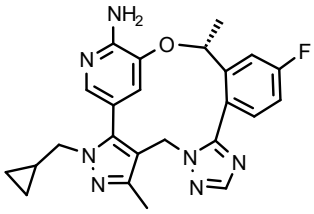
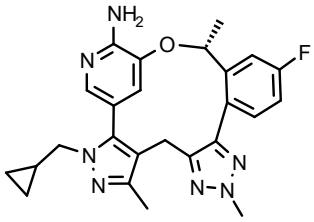
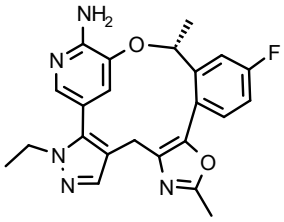
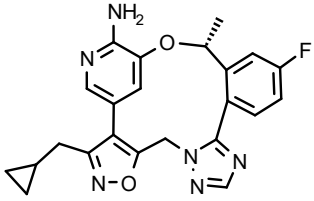
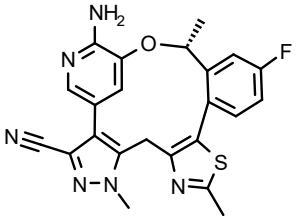
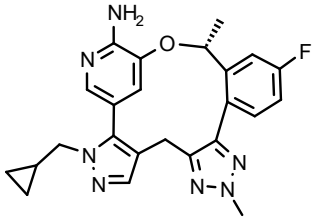
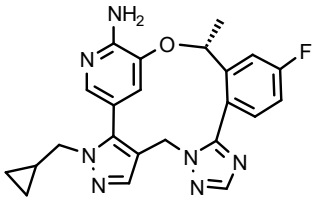
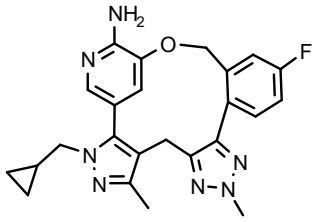
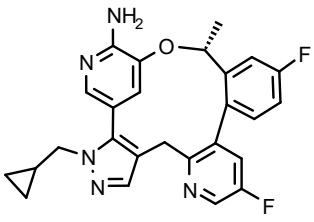
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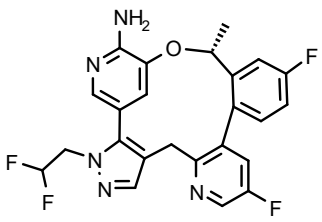
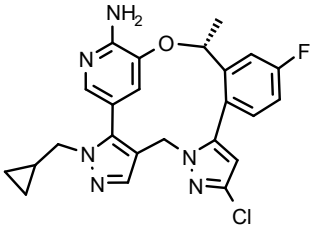
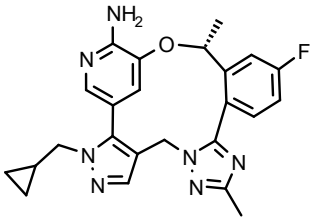
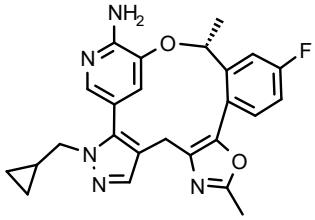
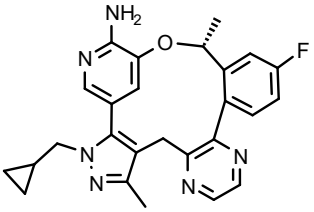
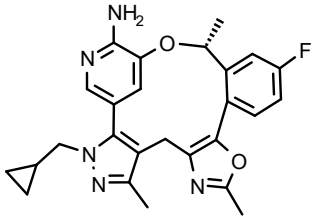
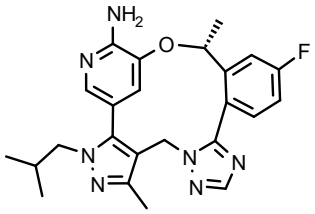
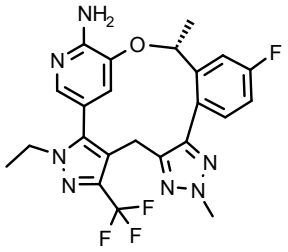
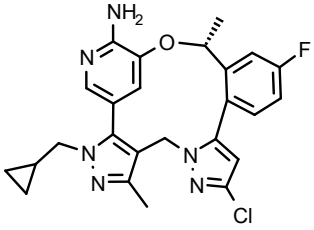
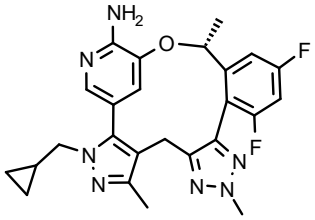
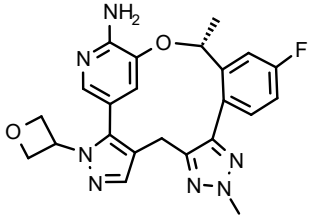
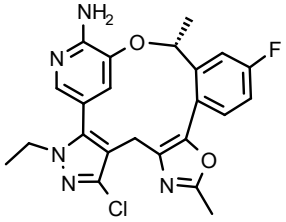
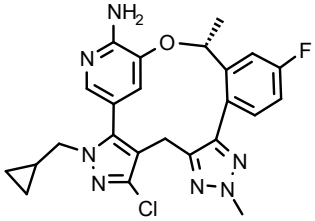
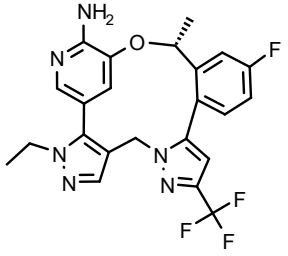
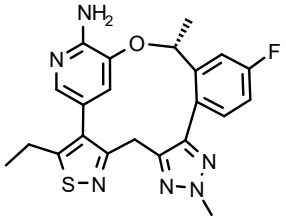
		
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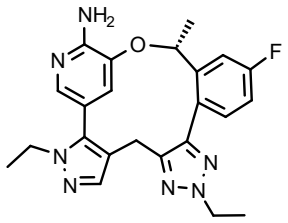
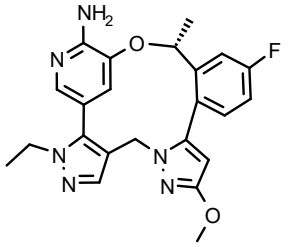
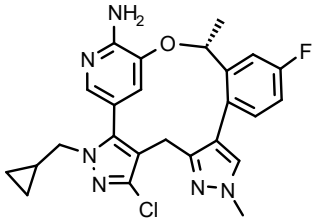
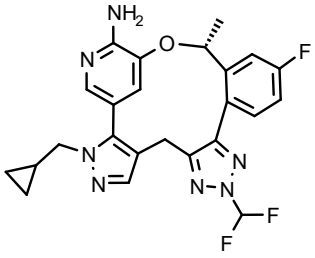
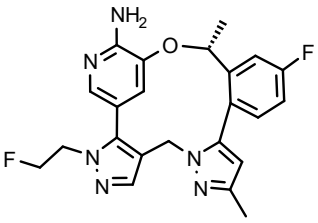
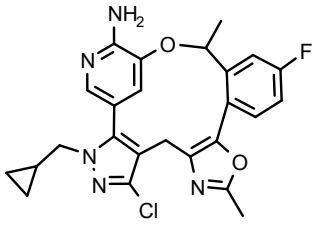
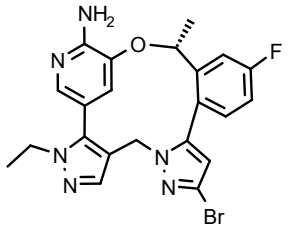
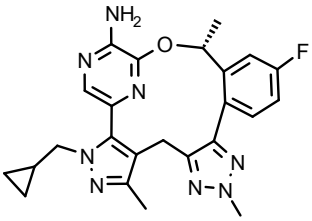
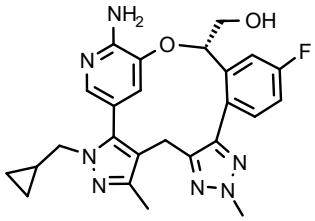
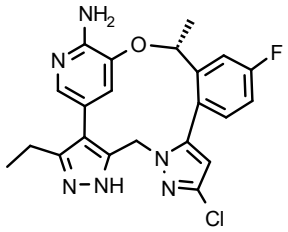
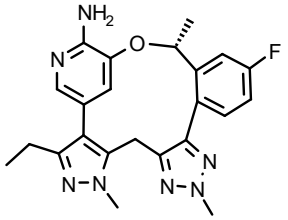
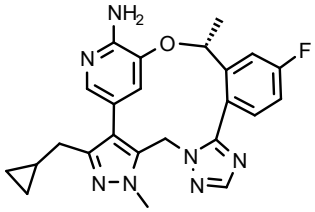
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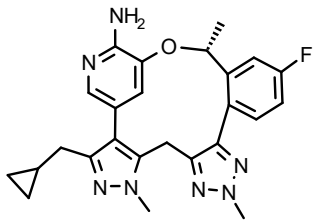
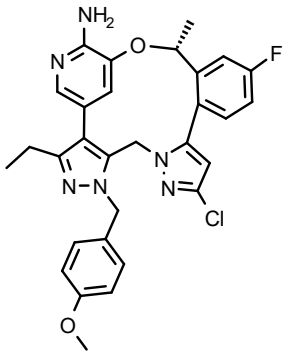
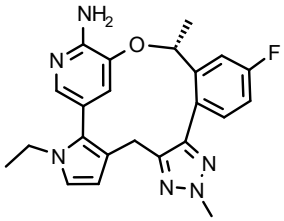
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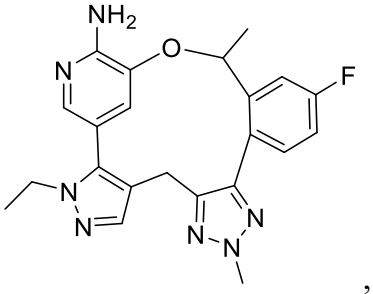
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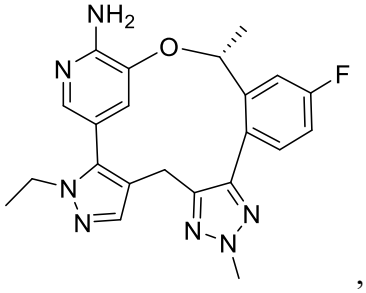
or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1, which is:


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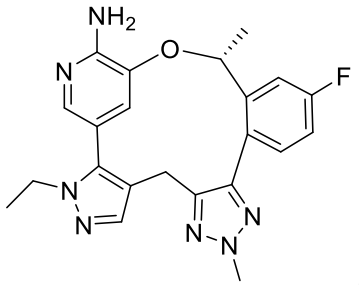
or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, which is


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or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1, which is



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21. A pharmaceutical composition, comprising the compound or pharmaceutically acceptable salt of any one of claims 1-20; and a pharmaceutically acceptable carrier or excipient.

22. Use of the compound or pharmaceutically acceptable salt of any one of claims 1-20, or the pharmaceutical composition of claim 21, in the manufacture of a medicament for treating cancer in a subject.

23. The use of claim 22, wherein the cancer is a solid tumor.

24. The use of claim 23, wherein the solid tumor is lung cancer, glioblastoma, inflammatory myofibroblastic tumor (IMT), bile duct cancer, ovarian cancer, gastric cancer, colorectal cancer, angiosarcoma, melanoma, epithelioid hemangioendothelioma, esophageal cancer, kidney cancer, breast cancer, colon cancer, thyroid cancer, spitzoid tumor, cholangiocarcinoma, or neuroblastoma.

25. The use of claim 22, wherein the cancer is a hematologic malignancy.

26. The use of claim 25, wherein the hematologic malignancy is anaplastic large cell lymphoma (ALCL), diffuse large B-cell lymphoma (DLBCL), or large B-cell lymphoma.

27. The use of claim 22, wherein the cancer is lung cancer.

28. The use of claim 27, wherein the cancer is non-small cell lung cancer.

29. The use of claim 22, wherein the cancer is spitzoid melanoma, esophageal squamous cell carcinoma, renal medullary carcinoma, renal cell carcinoma, papillary thyroid cancer, or serous ovarian carcinoma.

30. The use of any one of claims 22-29, wherein the cancer is a ROS1 (ROS proto-oncogene 1, receptor tyrosine kinase) positive cancer.

31. The use of any one of claims 22-30, wherein the cancer comprises expression of an oncogenic *ROS1* gene or oncogenic *ROS1* gene-fusion.

32. The use of claim 31, wherein the oncogenic *ROS1* gene or oncogenic *ROS1* gene-fusion contains one or more mutations of the human *ROS1* gene.

33. The use of claim 32, wherein the one or more mutations in the oncogenic *ROS1* gene or oncogenic *ROS1* gene-fusion results in:
(a) expression of a ROS1 protein comprising a mutation at L1951, L1982, S1986, F2004, L2026, G2032, D1033, F2075, or G2101, or a combination thereof;
(b) expression of a ROS1 protein comprising a L1951R, L1982F, S1986F, F2004C, F2004V, L2026M, G2032R, G2032K, D2033N, F2075V, or G2101A mutation, or a combination thereof;
(c) expression of a ROS1 protein comprising a ROS1 fusion protein selected from the group consisting of CD74-ROS1, EZR-ROS1, SLC34A2-ROS1, GOPC-ROS1, CEP85L-ROS1, SDC4-ROS1, TFG-ROS1, and TPM3-ROS1; or
(d) expression of a ROS1 protein comprising (i) a ROS1 fusion protein selected from the group consisting of CD74-ROS1, EZR-ROS1, SLC34A2-ROS1, GOPC-ROS1, and CEP85L-ROS1 and (ii) a L1982F, S1986F, F2004C, F2004V, L2026M, G2032R, D2033N, or G2101A mutation, or a combination thereof.

34. The use of claim 32, wherein the one or more mutations in the oncogenic *ROS1* gene or oncogenic *ROS1* gene-fusion results in expression of a ROS1 protein with a G2032R mutation.

35. The use of any one of claims 22-29, wherein the cancer is an ALK (anaplastic lymphoma kinase) positive cancer.

36. The use of any one of claims 22-29 and 35, wherein the cancer comprises expression of an oncogenic *ALK* gene or oncogenic *ALK* gene-fusion.

37. The use of claim 36, wherein the oncogenic *ALK* gene or the oncogenic *ALK* gene-fusion contains one or more mutations of the human *ALK* gene.

38. The use of claim 37, wherein the mutations in the oncogenic *ALK* gene or the oncogenic *ALK* gene-fusion results in:
(a) expression of an ALK protein with one or more mutations at I1171, L1196, L1198, G1202, D1203, G1269, F1174, V1180, C1156, S1206, E1210, or R1275, or a combination thereof;
(b) expression of an ALK protein with one or more mutations selected from the group consisting of G1202R, G1202del, L1196M, L1196Q, L1198F, G1269A, D1203N, I1171N, I1171S, I1171T, F1174C, F1174L, V1180L, C1156Y, S1206Y, E1210K, and R1275Q, or wherein the one or more mutations in the oncogenic ALK gene or the oncogenic ALK gene-fusion results in expression of an ALK protein with a co-mutation of G1202R and one or more mutations selected from L1196M, G1269A, and L1198F; or
(c) expression of an ALK protein comprising (i) an ALK fusion protein selected from the group consisting of EML4-ALK and NPM1-ALK, and (ii) a G1202R, L1196M, L1198F, G1269A, D1203N, or I1171N mutation, or a combination thereof.

39. Use of the compound or pharmaceutically acceptable salt of any one of claims 1-20, or the pharmaceutical composition of claim 21, in the manufacture of a medicament for selectively inhibiting ROS1 or ALK over tropomyosin receptor kinase (TRK), wherein the inhibition takes place in a subject suffering from cancer.

40. The use of any one of claims 22 to 39, wherein:

(a) the cancer is metastatic, relapsed, or refractory to a prior treatment; and/or
(b) the cancer is metastatic, relapsed, or refractory to a prior TKI treatment; and/or
(c) the cancer comprises brain metastases.

41. The use of any one of claims 22-40, wherein the medicament is manufactured to be administered in combination with one or more additional therapeutic agents.

42. The use of claim 41, wherein:
(a) the additional therapeutic agent is a TKI, wherein the TKI is crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, entrectinib, repotrectinib, cabozantinib, foretinib, taletrectinib, merestinib, masitinib, or ensartinib; or
(b) the additional therapeutic agent is a chemotherapeutic agent, an immuno-oncology agent, a SH2 inhibitor, a MEK inhibitor, a MET inhibitor, a SHP2 inhibitor, an anti-PD-1 agent, or a RAS inhibitor.

43. Use of the compound or pharmaceutically acceptable salt of any one of claims 1-20, or the pharmaceutical composition of claim 21, in the manufacture of a medicament for decreasing a level of ROS1 or ALK in a cell in a subject suffering from cancer.