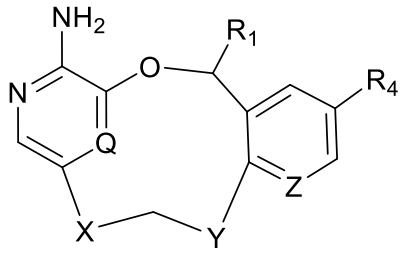
CLAIMS

1. A compound of Formula (I), or an enantiomer, a mixture of enantiomers, or a tautomer thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein

Q is CH or N;

Z is CR_5 or N;

X is a 5-membered heteroarylene, comprising 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; 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, 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 the 5- to 6-membered heteroarylene ring atom alpha to the point of attachment to the methylene group and 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;

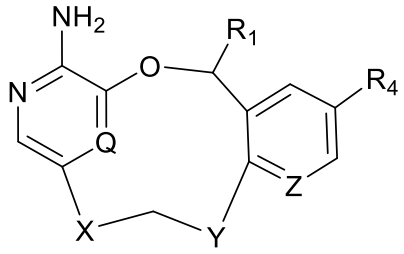
each R_2 is independently selected from the group consisting of H, halo, CN, C_{1-4} alkoxy, C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{3-4} cycloalkylmethyl, C_{3-6} cycloalkyl, and C_{3-6} heterocycloalkyl;

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

each of R_4 and R_5 is independently H or F;

provided that X is not 3*,4-substituted-pyrazolylene, where * indicates the point of attachment of X or Y to the methylene group bonded to X and Y.

2. A compound of Formula (I), or an enantiomer, a mixture of enantiomers, or a tautomer thereof, or a pharmaceutically acceptable salt thereof:



(I)

wherein

Q is CH or N;

Z is CR_5 or N;

X is a 5-membered heteroarylene, comprising 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; 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, 5*,6-substituted-1,2,3,4-tetrazinylene, 1*,5-substituted-1,2,3,4-tetrazolylene, 1,5*-substituted-1,2,3,4-tetrazolylene, 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;

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

in Y the heteroarylene ring atom alpha to the point of attachment to the methylene group and 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 R_2 is independently selected from the group consisting of H, halo, CN, C_{1-4} alkoxy, C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{3-4} cycloalkylmethyl, C_{3-6} cycloalkyl, and C_{3-6} heterocycloalkyl;

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

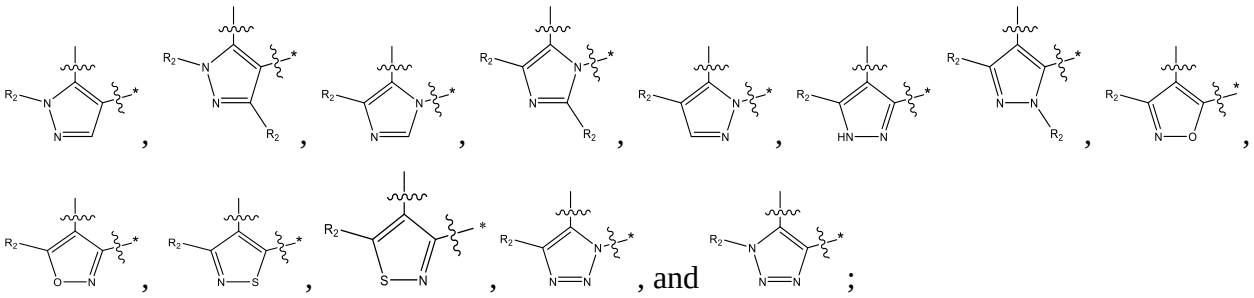
each of R_4 and R_5 is independently H or F.

3. The compound of claim 1 or 2, wherein X is a 5-membered heteroarylene selected from the group consisting of pyrazolylene, isoxazolylene, imidazolylene, isothiazolylene, and triazolylene.

~~4. The compound of claim 1 or 2, wherein X is a 5-membered heteroarylene selected from the group consisting of 4*,5-substituted-pyrazolylene, 4,5*-substituted-pyrazolylene, 1*,5-substituted-pyrazolylene, 4*,5-substituted-isoxazolylene, 4,5*-substituted-isoxazolylene, 3*,4-substituted-isoxazolylene, 3*,4-substituted-isothiazolylene, 4*,5-substituted-isothiazolylene,~~

~~4,5* substituted isothiazolylene, 4*,5 substituted imidazolylene, 1*,5 substituted imidazolylene, 1*,5 substituted triazolylene, and 4*,5 substituted triazolylene.~~

4.~~5.~~ The compound of claim 1 or 2, wherein X is a 5-membered heteroarylene selected from the group consisting of:

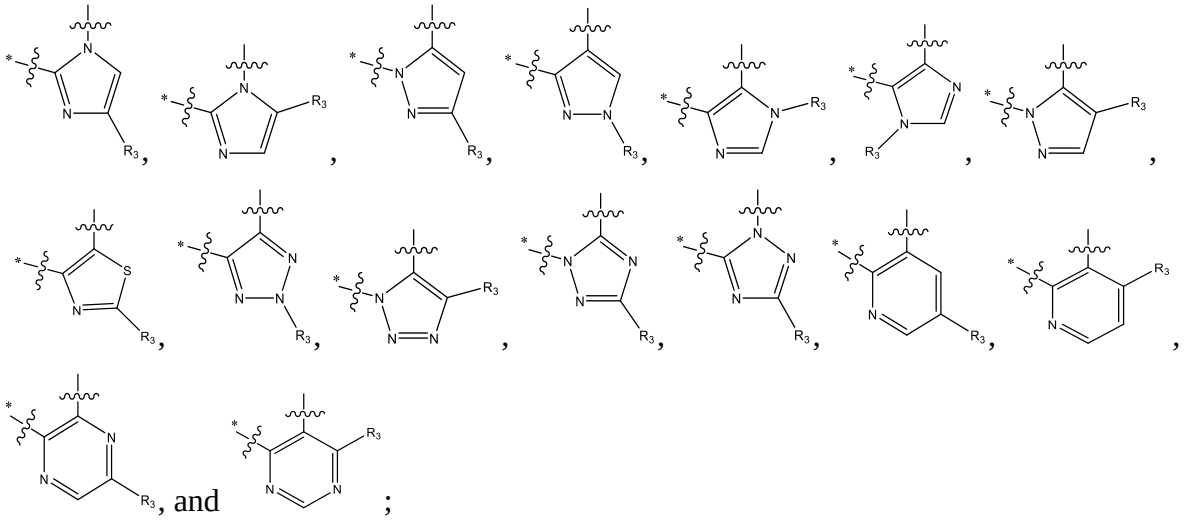


* indicates the point of attachment of X to the methylene group bonded to X and Y; and

R_2 is independently selected from the group consisting of H, halo, CN, C_{1-4} alkoxy, C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{3-4} cycloalkylmethyl, C_{3-6} cycloalkyl, and C_{3-6} heterocycloalkyl.

~~6. The compound of any one of claims 1-5, wherein Y is a heteroarylene selected from the group consisting of 1*,5 substituted pyrazolylene, 3*,4 substituted pyrazolylene, 1,2* substituted imidazolylene, 4*,5 substituted imidazolylene, 4,5* substituted imidazolylene, 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, 4*,5 substituted 1,3 thiazolylene, 2*,3 substituted pyridinylene, 4*,5 substituted pyrimidinylene, and 2*,3 substituted pyrazinylene.~~

5.~~7.~~ The compound of any one of claims 1-4~~5~~, 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

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

6.~~8.~~ The compound of any one of claims 1-5~~7~~, wherein Q is CH.

7.~~9.~~ The compound of any one of claims 1-5~~7~~, wherein Q is N.

8.~~10.~~ The compound of any one of claims 1-7~~9~~, wherein Z is CR_5.

9.~~11.~~ The compound of any one of claims 1-8~~10~~, wherein R_5 is H.

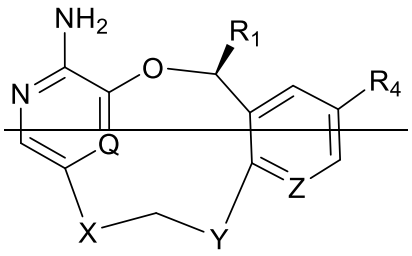
10.~~12.~~ The compound of any one of claims 1-8~~10~~, wherein R_5 is F.

11.~~13.~~ The compound of any one of claims 1-10~~2~~, wherein Z is N.

12.~~14.~~ The compound of any one of claims 1-11~~3~~, wherein R_4 is H.

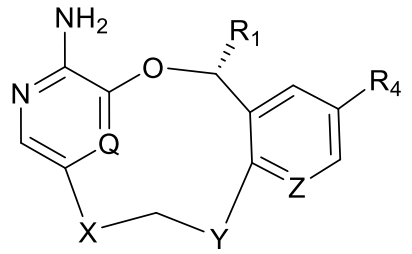
13.~~15.~~ The compound of any one of claims 1-11~~3~~, wherein R_4 is F.

~~16. The compound of any one of claims 1-15, wherein the compound of Formula (I) has the structure (I-A):~~



~~(I-A).~~

~~17.~~14. ~~The~~ The compound of any one of claims 1-13~~5~~, wherein the compound of Formula (I) has the structure (I-B):

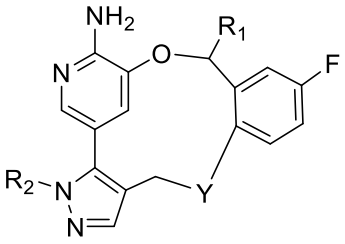
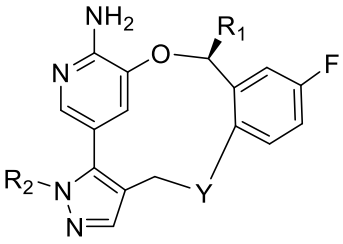
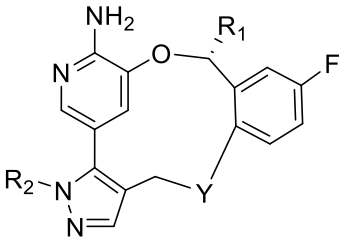
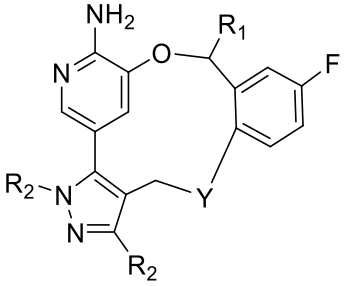
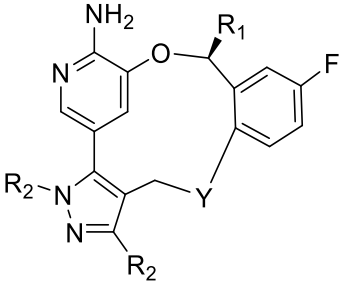
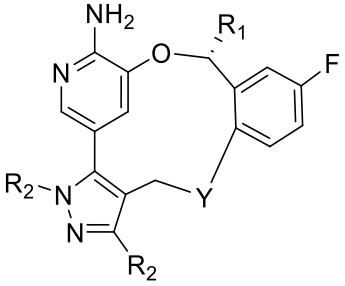
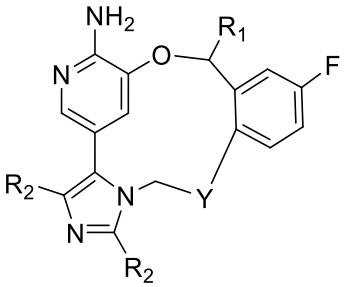
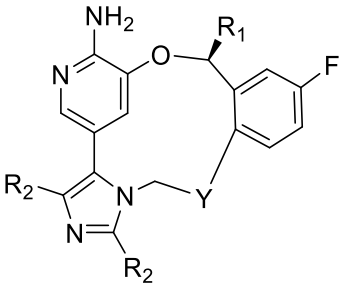
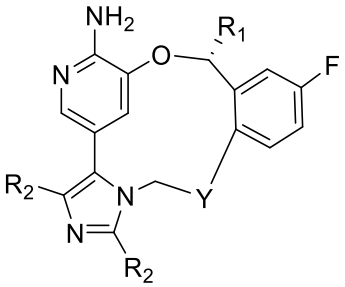
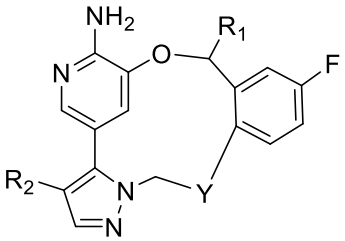
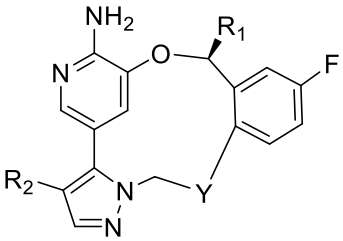
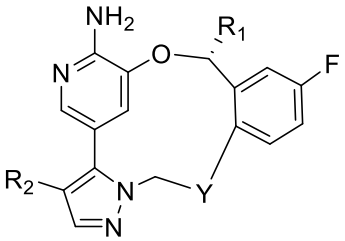


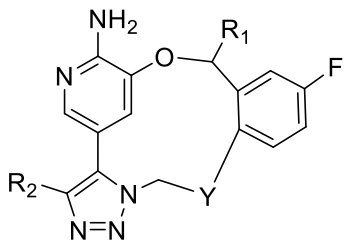
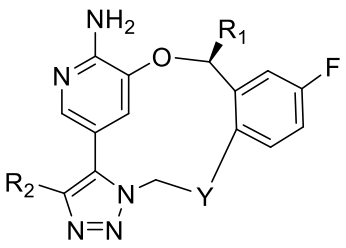
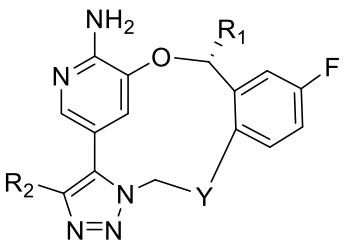
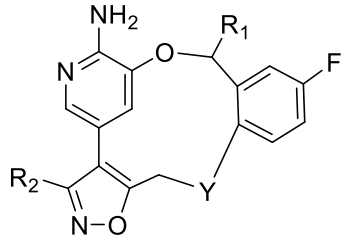
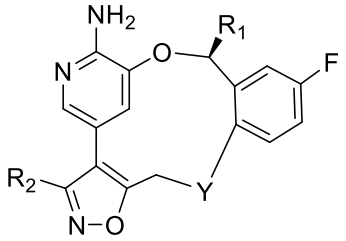
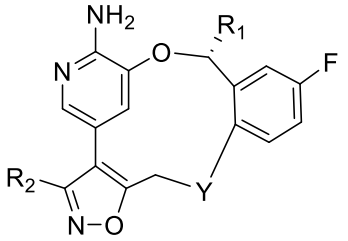
(I-B).

15.~~18.~~ The compound of any one of claims 1-14~~7~~, wherein R_2 is each 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.

16.~~19.~~ The compound of any one of claims 1-15~~8~~, wherein R_3 is each independently selected from the group consisting of H, fluoro, chloro, CN, methyl, and ethyl.

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

 (II),	 (II-A),	 (II-B),
 (III),	 (III-A),	 (III-B),
 (IV),	 (IV-A)	 (IV-B),
 (V),	 (V-A),	 (V-B),

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

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

18.~~21.~~ A compound in Table 1, or a pharmaceutically acceptable salt thereof.

~~22. The compound of any one of claims 1-21, wherein the compound is in the form of a pharmaceutically acceptable salt; and the salt is selected from the group consisting of alkyl ammonium salts, dialkyl ammonium salts, trialkyl ammonium salts, tetra-alkyl ammonium salts, L-arginine salts, benenthamine salts, benzathine salts, betaine salts, calcium hydroxide salts, choline salts, deanol salts, diethanolamine salts, diethylamine salts, 2-(diethylamino)ethanol salts, ethanolamine salts, ethylenediamine salts, N-methylglucamine salts, hydrabamine salts, 1H-imidazole salts, lithium salts, L-lysine salts, magnesium salts, 4-(2-hydroxyethyl)morpholine salts, piperazine salts, potassium salts, 1-(2-hydroxyethyl)pyrrolidine salts, sodium salts, triethanolamine salts, tromethamine salts, Na salts, Ca salts, K salts, Mg salts, and Zn salts.~~

~~23. The compound of claim 22, wherein the pharmaceutically acceptable salt is a solvate comprising a solvent molecule selected from the group consisting of water, methanol, ethanol, and dimethylformamide.~~

19.~~24.~~ A pharmaceutical composition, comprising the compound or pharmaceutically acceptable salt of any one of claims 1-18~~23~~; and a pharmaceutically acceptable carrier or excipient.

~~25. The pharmaceutical composition of claim 24, wherein the composition is a tablet, a capsule, a granule, a lyophile for reconstitution, a powder, a solution, a syrup, a suppository, an injection, a transdermal delivery system, or a solution suitable for topical administration.~~

20.~~26.~~ Use of a therapeutically effective amount of the compound or pharmaceutically acceptable salt of any one of claims 1-18, or the pharmaceutical composition of claim 19, in the manufacture of a medicament for ~~A method of~~ treating cancer in a subject~~, comprising administering to a subject in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt of any one of claims 1-23~~.

~~27. The method of claim 26, wherein the subject is a human.~~

21.~~28.~~ The ~~method~~ use of claim ~~26 or 27~~20, wherein the cancer is a solid tumor or a hematologic malignancy.

22.~~29.~~ The ~~method~~ use of claim 21~~28~~, wherein the cancer is a solid tumor; and the solid tumor is ~~selected from~~ 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, ~~and~~ or neuroblastoma.

23.~~30.~~ The ~~method~~ use of claim ~~28~~21, wherein the cancer is a hematologic malignancy; and the hematologic malignancy is anaplastic large cell lymphoma (ALCL), diffuse large B-cell lymphoma (DLBCL), or large B-cell lymphoma.

~~31.~~24. The ~~method~~ use of any one of claims 2~~0~~6 to 23~~30~~, wherein the cancer is an ALK positive or ROS1 positive cancer.

~~32. The method of claim 26 or 27, wherein the compound or salt thereof is an inhibitor of ROS1 and ALK.~~

25.~~33.~~ The use ~~method~~ of ~~any one of claims 26-27 and 32~~claim 20, wherein the cancer is non-small cell lung cancer.

~~34. The method of any one of claims 26-27 and 32, wherein the cancer is inflammatory myofibroblastic tumor.~~

~~35. The method of any one of claims 26-27 and 32, wherein the cancer is ovarian cancer.~~

~~36. The method of any one of claims 26-27 and 32, wherein the cancer is spitzoid melanoma.~~

~~37. The method of claim 26 or 27, wherein the compound is an inhibitor of ROS1.~~

~~38. The method of any one of claims 26-27 and 37, wherein the cancer is glioblastoma.~~

~~39. The method of any one of claims 26-27 and 37, wherein the cancer is cholangiocarcinoma.~~

~~40. The method of any one of claims 26-27 and 37, wherein the cancer is gastric cancer.~~

~~41. The method of any one of claims 26-27 and 37, wherein the cancer is colorectal cancer.~~

~~42. The method of any one of claims 26-27 and 37, wherein the cancer is angiosarcoma.~~

~~43. The method of claim 26 or 27, wherein the compound is an inhibitor of ALK.~~

~~44. The method of any one of claims 26-27 and 43, wherein the cancer is anaplastic large cell lymphoma.~~

~~45. The method of any one of claims 26-27 and 43, wherein the cancer is diffuse large B-cell lymphoma.~~

~~46. The method of any one of claims 26-27 and 43, wherein the cancer is esophageal squamous cell carcinoma.~~

~~47. The method of any one of claims 26-27 and 43, wherein the cancer is renal medullary carcinoma.~~

~~48. The method of any one of claims 26-27 and 43, wherein the cancer is renal cell carcinoma.~~

~~49. The method of any one of claims 26-27 and 43, wherein the cancer is breast cancer.~~

~~50. The method of any one of claims 26-27 and 43, wherein the cancer is papillary thyroid cancer.~~

~~51. The method of any one of claims 26-27 and 43, wherein the cancer is neuroblastoma.~~

26.~~52.~~ The ~~method~~ use of any one of claims ~~26-27 and 32-42~~20-25, wherein the cancer comprises expression of an oncogenic *ROS1* gene or oncogenic *ROS1* gene-fusion.

27.~~53.~~ The ~~method~~ use of claim ~~52~~26, wherein the oncogenic *ROS1* gene or oncogenic *ROS1* gene-fusion contains one or more mutations of the human *ROS1* gene.

28.~~54.~~ The ~~method~~ use of claim 26~~52~~, wherein the mutations in the oncogenic *ROS1* gene or oncogenic *ROS1* gene-fusion results in expression of a ROS1 protein with a G2032R mutation.

29.~~55.~~ The ~~method~~ use of any one of claims ~~26-27, 32-36, and 43-51~~20-25, wherein the cancer comprises expression of an oncogenic *ALK* gene or oncogenic *ALK* gene-fusion.

30.~~56.~~ The ~~method~~ use of claim 29~~55~~, wherein the oncogenic *ALK* gene or the oncogenic *ALK* gene-fusion contains one or more mutations of the human *ALK* gene.

31.~~57.~~ The ~~method~~ use of claim 29~~56~~, wherein the mutations in the oncogenic *ALK* gene or the oncogenic *ALK* gene-fusion results in expression of an ALK protein with one or more mutations selected from the group consisting of G1202R, L1196M, G1269A, D1203N, and I1171N.

~~58. The method of any one of claims 26-57, wherein the subject has received one prior cancer therapy.~~

~~59. The method of any one of claims 26-57, wherein the subject has received at least two prior cancer therapies.~~

~~60. The method of any one of claims 26-59, wherein the compound is an inhibitor of human tropomyosin receptor kinase A, B, or C.~~

~~61. The method claim 60, wherein the IC_{50} of the compound for inhibition of mutant or non-mutant ROS1 or ALK is no more than one-fifth of the IC_{50} of the compound for inhibition of wild-type tropomyosin receptor kinase A, B, or C.~~

32~~62~~. Use of a therapeutically effective amount of the compound or pharmaceutically acceptable salt of any one of claims 1-18, or the pharmaceutical composition of claim 19, in the manufacture of a medicament for ~~A method for~~ selectively inhibiting ROS1 or ALK over TRK, wherein the inhibition takes place in a subject suffering from cancer, ~~said method comprising administering an effective amount of a compound of any one of claims 1 to 23 or a pharmaceutical composition of claim 24 or 25 to said subject~~.

~~63. A method for selectively inhibiting ALK over TRK, wherein the inhibition takes place in a subject suffering from cancer, said method comprising administering an effective amount of a compound of any one of claims 1 to 23 or a pharmaceutical composition of claim 24 or 25 to said subject.~~

33~~64~~. The ~~method~~ use of any one of claims ~~26 to 63~~20-32, wherein the medicament is manufactured to be administered in combination with ~~further comprising administering to the subject an effective amount of~~ one or more additional therapeutic agents.

34~~65~~. The ~~method~~ use of claim 33~~64~~, wherein the additional therapeutic agent is a TKI, optionally selected from crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, entrectinib, repotrectinib, cabozantinib, foretinib, taletrectinib, merestinib, masitinib, or ensartinib.

~~66. The method of claim 65, wherein the TKI is crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, entrectinib, repotrectinib, cabozantinib, foretinib, taletrectinib, merestinib, masitinib, or ensartinib.~~

3657. A method of decreasing a level of ROS1 or ALK in a cell, comprising contacting the cell with a compound of any one of claims 1-1823 or a pharmaceutical composition of claim 24 or 2519.

68. The method of claim 67, further comprising contacting the cell with one or more additional therapeutic agents.

69. The method of claim 68, wherein the additional therapeutic agent is a TKI.

70. The method of claim 69, wherein the TKI is crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, entrectinib, repotrectinib, cabozantinib, foretinib, taletrectinib, merestinib, masitinib, or ensartinib.