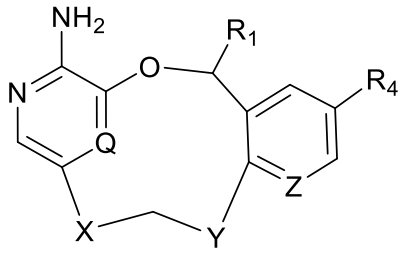
CLAIMS

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;

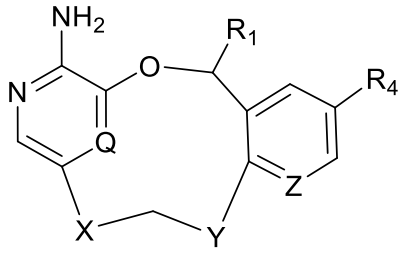
each R_2 is independently selected from the group consisting of H, halo, CN, C_{1-4} alkoxy, C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{3-4} cycloalkylmethyl, C_{3-6} cycloalkyl, and C_{3-6} heterocycloalkyl;

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;

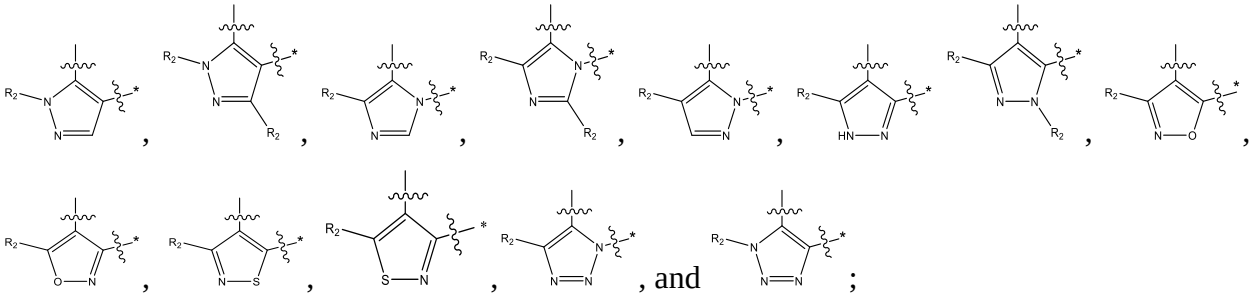
each R_2 is independently selected from the group consisting of H, halo, CN, C_{1-4} alkoxy, C_{1-4} alkyl, halo-C_{1-4} alkyl, C_{3-4} cycloalkylmethyl, C_{3-6} cycloalkyl, and C_{3-6} heterocycloalkyl;

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.

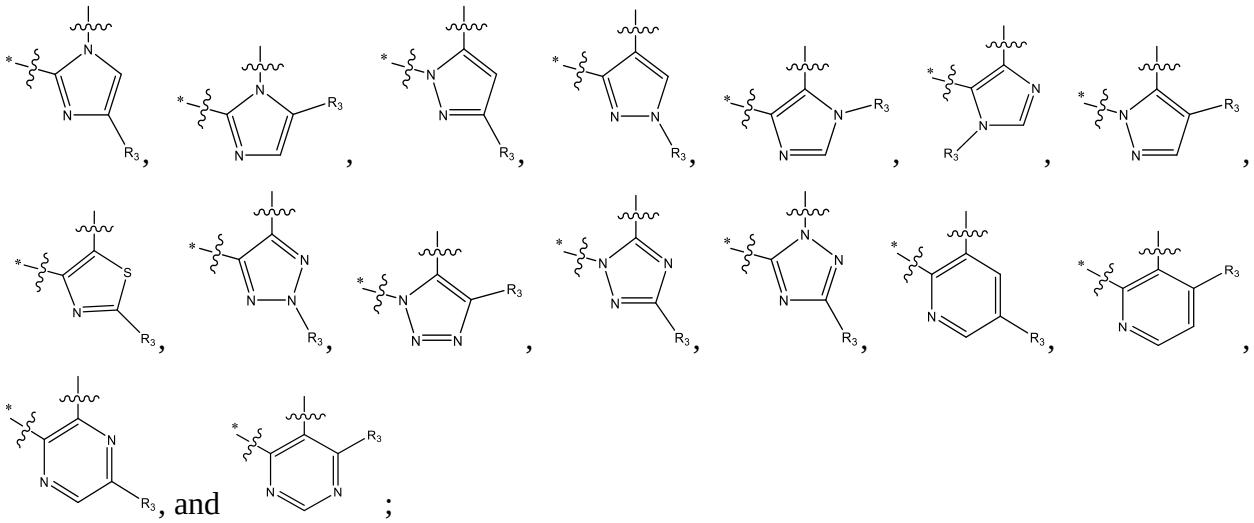
4. The compound of claim 1 or 2, wherein X is a 5-membered heteroarylene selected from the group consisting of:



* 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.

5. The compound of any one of claims 1-4, 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. The compound of any one of claims 1-5, wherein Q is CH.

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

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

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

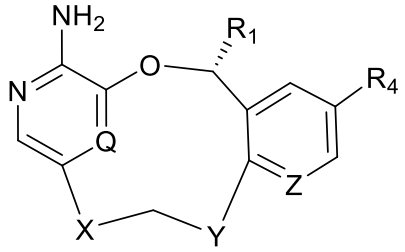
10. The compound of any one of claims 1-8, wherein R_5 is F.

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

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

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

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

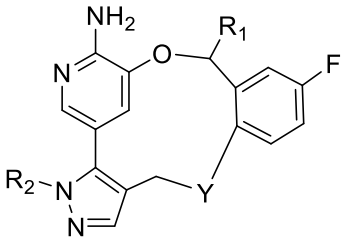
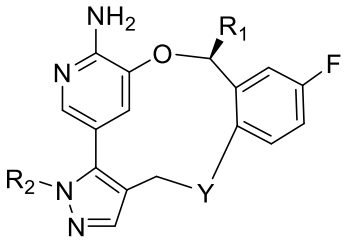
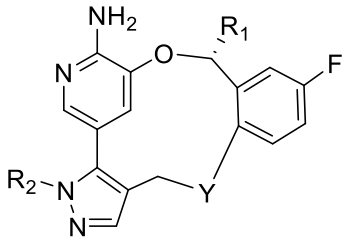
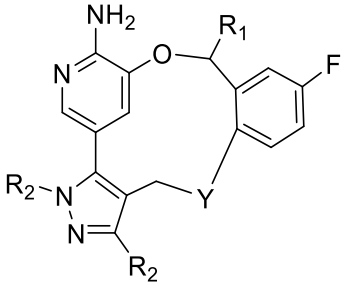
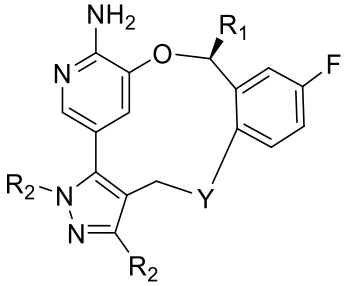
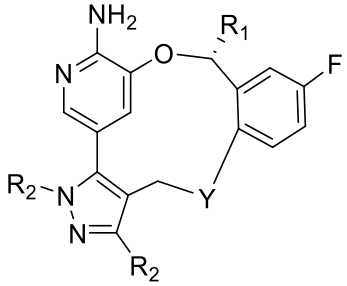
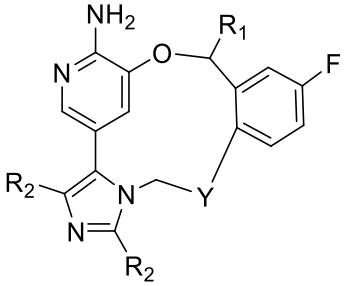
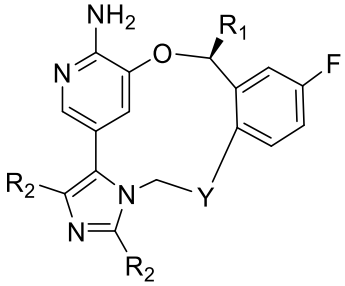
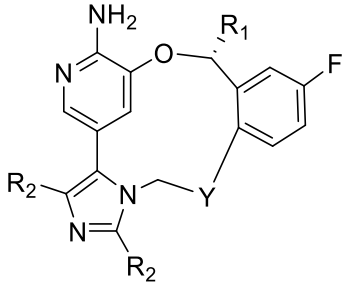
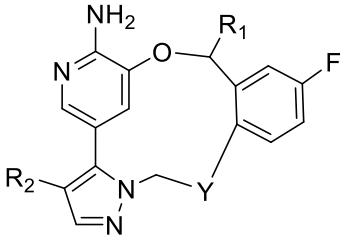
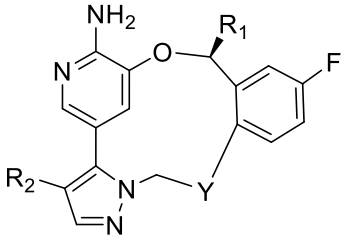
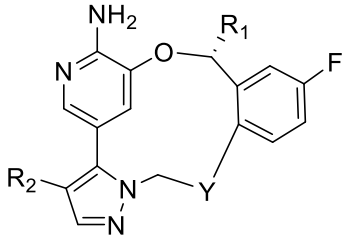


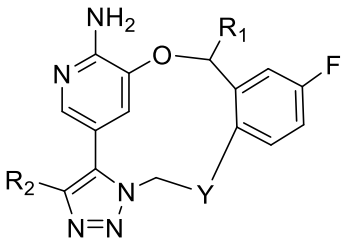
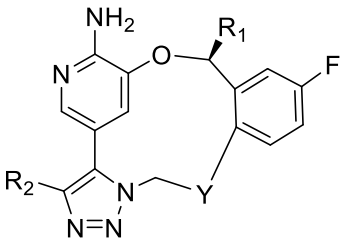
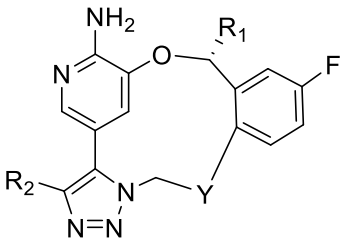
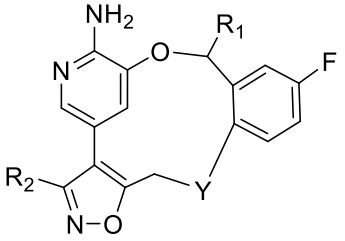
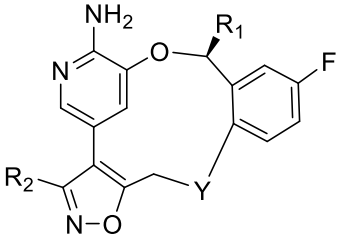
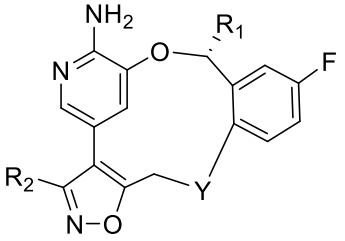
(I-B).

15. The compound of any one of claims 1-14, 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. The compound of any one of claims 1-15, wherein R_3 is each independently selected from the group consisting of H, fluoro, chloro, CN, methyl, and ethyl.

17. 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. A compound in Table 1, or a pharmaceutically acceptable salt thereof.

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

20. 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 treating cancer in a subject.

21. The use of claim 20, wherein the cancer is a solid tumor or a hematologic malignancy.

22. The use of claim 21, wherein the cancer is a solid tumor; and 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.

23. The use of claim 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.

24. The use of any one of claims 20 to 23, wherein the cancer is an ALK positive or ROS1 positive cancer.

25. The use of claim 20, wherein the cancer is non-small cell lung cancer.

26. The use of any one of claims 20-25, wherein the cancer comprises expression of an oncogenic *ROS1* gene or oncogenic *ROS1* gene-fusion.

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

28. The use of claim 26, 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. The use of any one of claims 20-25, wherein the cancer comprises expression of an oncogenic *ALK* gene or oncogenic *ALK* gene-fusion.

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

31. The use of claim 29, 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.

32. 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 selectively inhibiting ROS1 or ALK over TRK, wherein the inhibition takes place in a subject suffering from cancer.

33. The use of any one of claims 20-32, wherein the medicament is manufactured to be administered in combination with one or more additional therapeutic agents.

34. The use of claim 33, 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.

35. 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 1-18 or a pharmaceutical composition of claim 19.