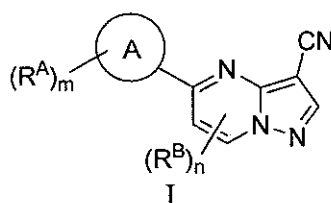


compositions thereof, to inhibit the activity of NTRK or its mutants in a cell or patient. The present disclosure further provides methods for using the compounds of the invention, and pharmaceutically acceptable salts and compositions thereof, to treat a subject suffering from a condition mediated by aberrant NTRK activity, *e.g.*, cancer.

5 The present disclosure features a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:



10 Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, - $N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2N(R^2)(R^2)$, $-(C_1-C_6$
 15 $alkylene)-S(O)_2N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6$ $alkylene)-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^a ;

20 each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently
 25 substituted with 0-5 occurrences of R^b ;

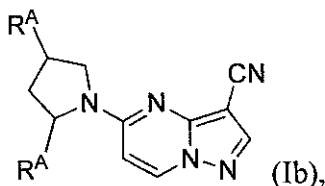
each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^b ;

each R^a and R^b is independently selected from halo, cyano, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -(C₁-C₆ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and C₁-C₆ alkyl or C₁-C₆ hydroxyalkyl;
m is 0, 1, 2, 3, 4 or 5; and
n is 0, 1 or 2;

provided that the compound is not (R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile.

In one aspect, the present disclosure provides a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof,



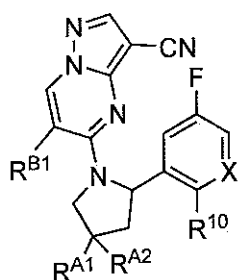
wherein:

one R^A is halo and one R^A is aryl or heteroaryl, wherein each of aryl, or heteroaryl is independently substituted with 0-5 occurrences of R^a;

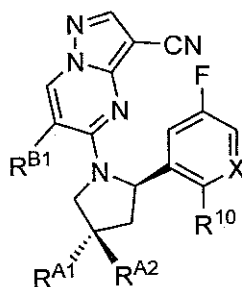
each R^a is independently selected from halo, cyano, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')-C(O)R', and -(C₁-C₆ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen, C₁-C₆ alkyl and C₁-C₆ hydroxyalkyl.

In another aspect, the present disclosure provides compound of Formula (Ic) or (Ic-1):



(Ic),



(Ic-1), or a

pharmaceutically acceptable salt thereof, wherein:

X is N or C(R⁹);

R^{A1} is fluoro or -CN;

5 R^{A2} is fluoro or hydrogen;

R^{B1} is hydrogen or fluoro;

R⁹ is selected from hydrogen, halo, -CN, -C₁-C₄ alkyl, -C(O)N(R¹¹)(R¹¹), and -S(O)₂N(R¹¹)(R¹¹), wherein any alkyl portion of R⁹ is optionally substituted with one or more substituents selected from -OH and -F;

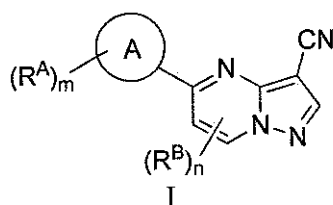
10 R¹⁰ is selected from hydrogen, halo, -O-(C₁-C₄ alkyl) optionally substituted with one or more halo, and -C(O)N(R¹¹)(R¹¹); and

each R¹¹ is independently selected from hydrogen, and C₁-C₄ alkyl optionally substituted with one or more substituents selected from -OH and cyclopropyl.

The present disclosure relates to pharmaceutical compositions comprising a compound of structural formula (I) as described herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as disclosed herein or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier

The present disclosure provides a method for inhibiting NTRK activity in a cell or in a patient. In some embodiments, said method comprises the step of contacting the cell or administering to the patient a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

The present disclosure relates to a method for inhibiting NTRK activity in a cell, said method comprising the step of contacting the cell with a compound of structural Formula I or a pharmaceutically acceptable salt or composition thereof, wherein:



Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

each R^A is independently selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic cycloalkyl, monocyclic or bicyclic heterocyclyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)OR^1$, $-SR^1$, $-S(O)_2R^1$, $-S(O)_2N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^1$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^1$, $-NR^2S(O)_2R^1$, $-P(O)(R^1)(R^1)$, and $-OR^1$; wherein each of aryl, heteroaryl, cycloalkyl, heterocyclyl, alkyl, alkoxy, haloalkyl, hydroxyalkyl, heteroalkyl is independently substituted with 0-5 occurrences of R^A ;

each R^B is independently selected from C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, $-N(R^1)(R^1)$, nitro, cyano, and $-OR^1$;

each R^1 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl, wherein each of C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 heteroalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl is independently substituted with 0-5 occurrences of R^B ;

each R^2 is independently selected from hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl; or 2 R^2 together with the nitrogen to which they are attached form a heterocyclyl ring substituted with 0-5 occurrences of R^B ;

each R^a and R^b is independently selected from halo, cyano, hydroxyl, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -N(R'')(R''), -C(O)-N(R'')(R''), -N(R'')(R'')-C(O)R', and -(C₁-C₆ alkylene)-N(R'')-C(O)R';

each R' and R'' is independently selected from hydrogen and C₁-C₆ alkyl or C₁-C₆ hydroxyalkyl;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1 or 2.

In another aspect, the present disclosure provides a use of a compound as disclosed herein or a pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament for inhibiting NTRK activity in a patient, wherein the patient has non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, or spitzoid neoplasms.

The present disclosure also provides a method for treating a subject suffering from a condition mediated by aberrant NTRK activity. In some embodiments, said method comprises
5 administering to the subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

In another aspect, the present disclosure provides a use of a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament, for treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity, wherein the condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity is selected from non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, and spitzoid neoplasms.

The present disclosure further provides a method for treating a subject who has developed resistance to a cancer treatment. In some embodiments, said method comprises administering to the

subject a therapeutically effective amount of a compound of structural formula (I) or a pharmaceutically acceptable salt or composition thereof.

In another aspect, the present disclosure provides a use of a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament for treating a subject who has developed resistance to a cancer treatment.

In a further aspect, the present disclosure provides a compound as disclosed herein or a pharmaceutically acceptable salt or composition thereof for use in inhibiting NTRK activity in a cell or in a patient, wherein the patient has non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, or spitzoid neoplasms.

In yet another aspect, the present disclosure provides a compound as disclosed herein or a pharmaceutically acceptable salt or composition thereof for use in treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity, wherein the condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity is selected from non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, and spitzoid neoplasms.

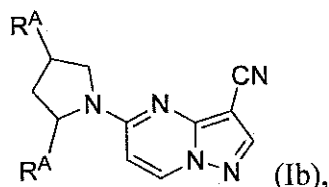
In another aspect, the present disclosure provides a compound as disclosed herein or a pharmaceutically acceptable salt or composition thereof for use in treating a subject who has developed resistance to a cancer treatment.

EMBODIMENTS OF THE INVENTION

In one aspect, the invention features a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:

We claim:

1. A compound of Formula (Ib) or a pharmaceutically acceptable salt thereof,



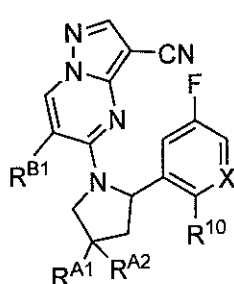
wherein:

one R^A is halo and one R^A is aryl or heteroaryl, wherein each of aryl, or heteroaryl is independently substituted with 0-5 occurrences of R^a ;

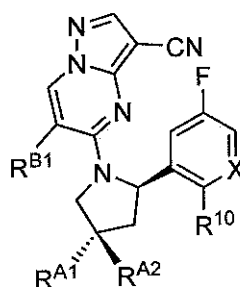
each R^a is independently selected from halo, cyano, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-N(R'')(R'')$, $-C(O)-N(R'')(R'')$, $-N(R'')-C(O)R'$, and $-(C_1-C_6 \text{ alkylene})-N(R'')-C(O)R'$;

each R' and R'' is independently selected from hydrogen, C_1 - C_6 alkyl and C_1 - C_6 hydroxyalkyl.

2. A compound of Formula (Ic) or (Ic-1):



(Ic),



(Ic-1), or a

pharmaceutically acceptable salt thereof, wherein:

X is N or $C(R^9)$;

R^{A1} is fluoro or $-CN$;

R^{A2} is fluoro or hydrogen;

R^{B1} is hydrogen or fluoro;

R^9 is selected from hydrogen, halo, -CN, -C₁-C₄ alkyl, -C(O)N(R¹¹)(R¹¹), and -S(O)₂N(R¹¹)(R¹¹), wherein any alkyl portion of R⁹ is optionally substituted with one or more substituents selected from -OH and -F;

R^{10} is selected from hydrogen, halo, -O-(C₁-C₄ alkyl) optionally substituted with one or more halo, and -C(O)N(R¹¹)(R¹¹); and

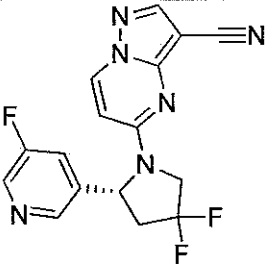
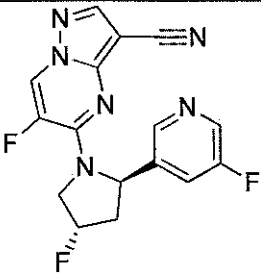
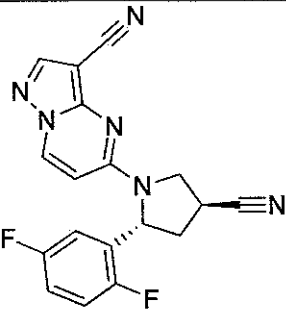
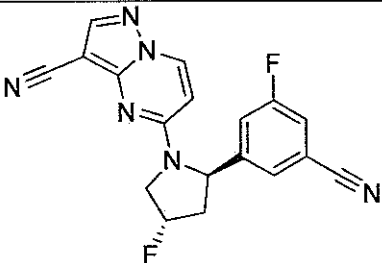
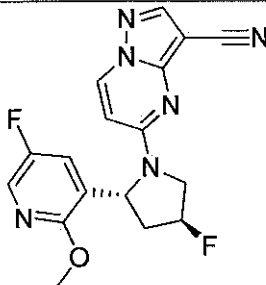
each R¹¹ is independently selected from hydrogen, and C₁-C₄ alkyl optionally substituted with one or more substituents selected from -OH and cyclopropyl.

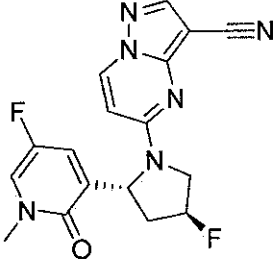
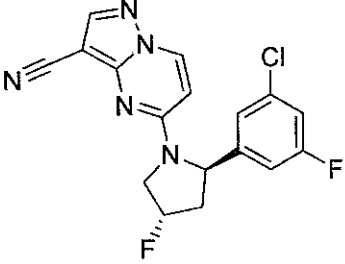
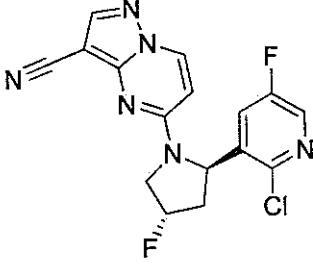
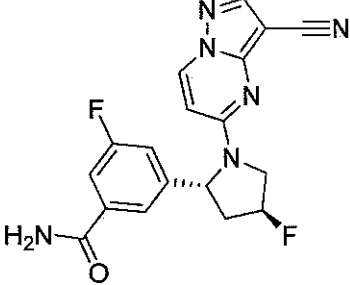
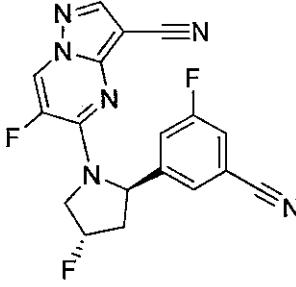
3. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein R⁹ is selected from hydrogen, fluoro, chloro, -CN, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, -C(O)NHCH₂CH₂OH, -C(OH)(CH₃)₂, -S(O)₂NH₂, and N-(cyclopropylmethyl)carbonyl.

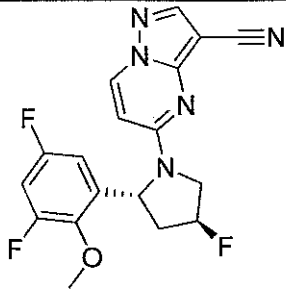
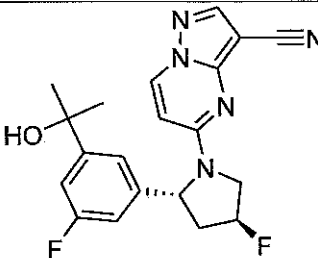
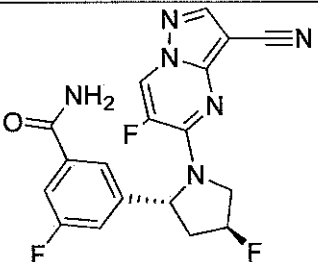
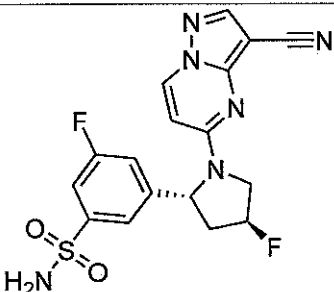
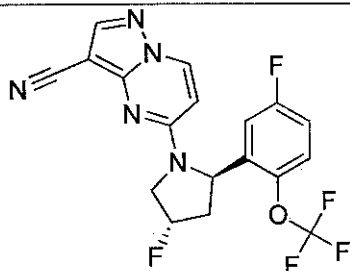
4. The compound of claim 2 or 3, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is selected from hydrogen, fluoro, chloro, -OCH₃, -OCF₃ and -C(O)NH₂.

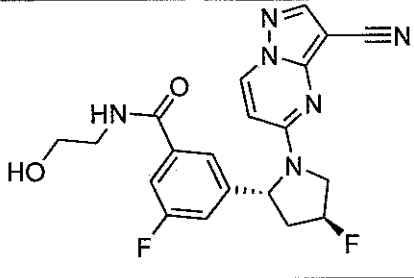
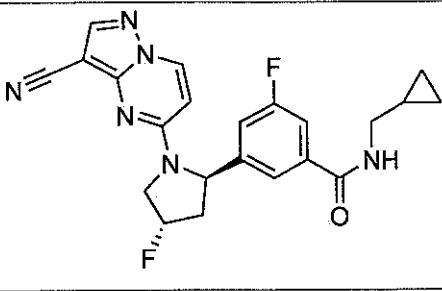
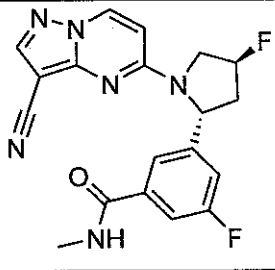
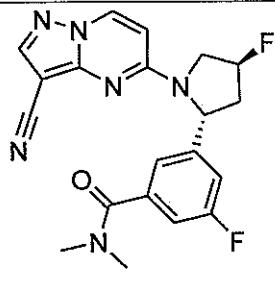
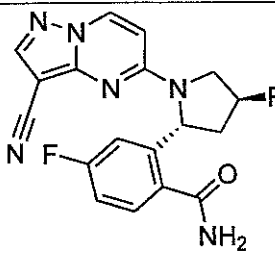
5. A compound selected from any one of the compounds in the table below and a pharmaceutically acceptable salt thereof:

Compound Number	Structure
1	
2	

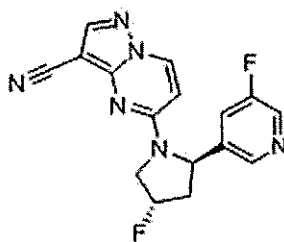
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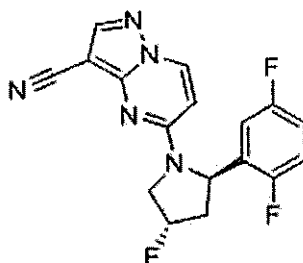
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6. A compound selected from



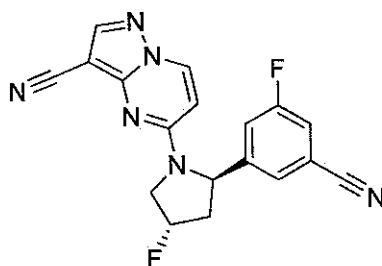
and a pharmaceutically acceptable salt thereof.

7. A compound selected from



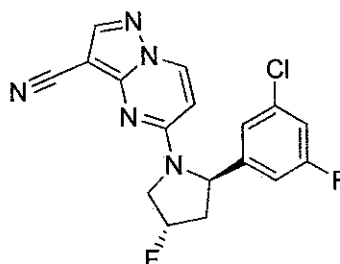
and a pharmaceutically acceptable salt thereof.

8. A compound selected from



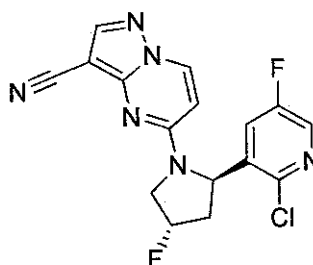
and a pharmaceutically acceptable salt thereof.

9. A compound selected from



and a pharmaceutically acceptable salt thereof.

10. A compound selected from



and a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a compound of any one of claims 1-10 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

12. Use of a therapeutically effective amount of a compound of any one of claims 1-10 or a pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament, for treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity,

wherein the condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity is selected from non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, and spitzoid neoplasms.

13. Use of a therapeutically effective amount of a compound of any one of claims 1-10 or a pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament for treating a subject who has developed resistance to a cancer treatment.

14. A compound of any one of claims 1-10 or a pharmaceutically acceptable salt or composition thereof for use in inhibiting NTRK activity in a cell or in a patient,

wherein the patient has non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, or spitzoid neoplasms.

15. A compound of any one of claims 1-10 or a pharmaceutically acceptable salt or composition thereof for use in treating a subject suffering from a condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity,

wherein the condition mediated by aberrant neurotrophic tyrosine receptor kinase (NTRK) activity is selected from non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, and spitzoid neoplasms.

16. A compound of any one of claims 1-10 or a pharmaceutically acceptable salt or composition thereof for use in treating a subject who has developed resistance to a cancer treatment.

17. Use of a compound of any one of claims 1-10 or a pharmaceutically acceptable salt or composition thereof in the manufacture of a medicament for inhibiting NTRK activity in a patient,

wherein the patient has non-small cell lung cancer, breast cancer, melanoma, low and high grade glioma, glioblastoma, pediatric astrocytoma, colorectal cancer, thyroid cancer, pancreatic cancer, biliary cancer, head and neck cancer, primary CNS tumors, cholangiocarcinoma, acute myelogenous leukemia, breast cancer, salivary gland cancer, sarcoma, or spitzoid neoplasms.