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(54) Titre : MUTATIONS PONCTUELLES DANS LE CANCER RESISTANT AUX INHIBITEURS DE TRK ET METHODES ASSOCIEES

(54) Title: POINT MUTATIONS IN TRK INHIBITOR-RESISTANT CANCER AND METHODS RELATING TO THE SAME

(57) Abrégé/Abstract:
Provided herein are methods of treating a subject having a cancer, methods of selecting a treatment for a subject having a cancer, methods of selecting a subject having a cancer for a treatment that does not include a Trk inhibitor, methods of determining the likelihood that a subject having a cancer will have a positive response to a treatment with a Trk inhibitor, methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer, and methods of determining the presence of a Trk inhibitor-resistant cancer in a subject, based on the detection of a cell from a sample from the subject that has at least one of the the point mutations in NTRK1 and/or NTRK2 and/or NTRK3.

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(54) Title: POINT MUTATIONS IN TRK INHIBITOR-RESISTANT CANCER AND METHODS RELATING TO THE SAME

(57) Abstract: Provided herein are methods of treating a subject having a cancer, methods of selecting a treatment for a subject having a cancer, methods of selecting a subject having a cancer for a treatment that does not include a Trk inhibitor, methods of determining the likelihood that a subject having a cancer will have a positive response to a treatment with a Trk inhibitor, methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer, and methods of determining the presence of a Trk inhibitor-resistant cancer in a subject, based on the detection of a cell from a sample from the subject that has at least one of the the point mutations in NTRK1 and/or NTRK2 and/or NTRK3.

POINT MUTATIONS IN TRK INHIBITOR-RESISTANT CANCER AND METHODS RELATING TO THE SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Serial Nos. 62/246,580, filed on October 26, 2015, 62/287,778, filed on January 27, 2016, and 62/323,586, filed on April 15, 2016, each of which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

This invention relates to methods of genetics, pharmacogenetics, and cancer biology.

BACKGROUND

Tropomyosin-related kinase (TRK) is a receptor tyrosine kinase family of neurotrophin receptors that are found in multiple tissues types. Three members of the TRK proto-oncogene family have been described: TrkA, TrkB, and TrkC, encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively. The TRK receptor family is involved in neuronal development, including the growth and function of neuronal synapses, memory development, and maintenance, and the protection of neurons after ischemia or other types of injury (Nakagawara, *Cancer Lett.* 169:107-114, 2001).

TRK was originally identified from a colorectal cancer cell line as an oncogene fusion containing 5' sequences from tropomyosin-3 (TPM3) gene and the kinase domain encoded by the 3' region of the neurotrophic tyrosine kinase, receptor, type 1 gene (NTRK1) (Pulciani et al., *Nature* 300:539-542, 1982; Martin-Zanca et al., *Nature* 319:743-748, 1986). TRK gene fusions follow the well-established paradigm of other oncogenic fusions, such as those involving ALK and ROS1, which have been shown to drive the growth of tumors and can be successfully inhibited in the clinic by targeted drugs (Shaw et al., *New Engl. J. Med.* 371:1963-1971, 2014; Shaw et al., *New Engl. J. Med.* 370:1189-1197, 2014). Oncogenic TRK fusions induce cancer cell proliferation and engage critical cancer-related downstream signaling pathways such as mitogen activated protein kinase (MAPK) and AKT (Vaishnavi et al., *Cancer Discov.* 5:25-34, 2015). Numerous oncogenic rearrangements involving

NTRK1 and its related TRK family members *NTRK2* and *NTRK3* have been described (Vaishnavi et al., *Cancer Disc.* 5:25-34, 2015; Vaishnavi et al., *Nature Med.* 19:1469-1472, 2013). Although there are numerous different 5' gene fusion partners identified, all share an in-frame, intact TRK kinase domain. A variety of different Trk inhibitors have been developed to treat cancer (see, e.g., U.S. Patent Application Publication No. 62/080,374, International Application Publication Nos. WO 11/006074, WO 11/146336, WO 10/033941, and WO 10/048314, and U.S. Patent Nos. 8,933,084, 8,791,123, 8,637,516, 8,513,263, 8,450,322, 7,615,383, 7,384,632, 6,153,189, 6,027,927, 6,025,166, 5,910,574, 5,877,016, and 5,844,092).

SUMMARY

The present invention is based on the discovery of Trk inhibitor-resistance NTRK1, NTRK2, and NTRK3 mutations. In view of this discovery, provided herein are methods of treating a subject having a cancer, methods of selecting a treatment for a subject having a cancer, methods of selecting a subject having a cancer for a treatment that does not include a Trk inhibitor, methods of determining the likelihood that a subject having a cancer will have a positive response to a treatment with a Trk inhibitor, methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer, and methods of determining the presence of a Trk inhibitor-resistant cancer in a subject. In some embodiments, the methods provided herein are based, in part, on a determination of whether the subject has a cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705. Also provided are kits

that allow for the detection of at least one of the point mutations in NTRK1 and/or NTRK2 and/or NTRK3.

Detection and identification of a subject having cells having a Trk inhibitor-resistant mutation as described herein (e.g., (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705) can improve treatment of the subject by, for example, changing the treatment regimen (e.g., changing the Trk inhibitor administered to the subject or adding an additional anticancer agent or anticancer therapy) or by administering a Trk inhibitor that is effective in the presence of a Trk inhibitor-resistant mutation (e.g., one or more of the compounds of Table 5, or a pharmaceutically acceptable salt thereof).

Provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and administering to the identified subject a treatment that does not include a first Trk inhibitor as a monotherapy.

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and administering to the identified subject a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and administering to the identified subject a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy.

Also provided herein are methods of treating a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3) that include: administering to the subject a treatment that does not include a first Trk inhibitor as a monotherapy.

Also provided herein are methods of treating a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3) that include administering to the subject a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of treating a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3) that include administering to the subject a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy.

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of a treatment that does not include a first Trk inhibitor as a monotherapy, to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy, to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) administering a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) administering additional doses of the first Trk inhibitor of step (a) to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a

mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) administering a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) administering a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (b) administering a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a

subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering additional doses of the Trk inhibitor of step (a) to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Some embodiments of these methods include administering a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3). Some embodiments of these methods include administering additional doses of the first Trk inhibitor of step (a) to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) administering a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) administering a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting a treatment that does not include a first Trk inhibitor as a monotherapy for the identified subject.

Also provided herein are methods of selecting a treatment for a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, for the identified subject.

Also provided herein are methods of selecting a treatment for a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the

expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy for the identified subject.

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that does not include a first Trk inhibitor as a monotherapy for a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, for a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy for a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a subject having a cancer for a treatment that does not include a first Trk inhibitor as a monotherapy, that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting the identified subject for a treatment that does not include a first Trk inhibitor as a monotherapy.

Also provided herein are methods of selecting a subject having a cancer for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: identifying a subject having a cancer cell that has at least one point

mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting the identified subject for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of selecting a subject having a cancer for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting the identified subject for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy.

Also provided herein are methods of selecting a subject having a cancer for a treatment that does not include a first Trk inhibitor as a monotherapy, that include: selecting a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), for a treatment that does not include a first Trk inhibitor as a monotherapy.

Also provided herein are methods of selecting a subject having a cancer for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: selecting a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of selecting a subject having a cancer for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy that include: selecting a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a

mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and selecting the identified subject for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy.

Some embodiments of these methods further include administering the selected treatment to the identified subject.

Some embodiments of these methods further include recording the selected treatment in the identified subject's clinical record (e.g., a computer readable medium). For example, recording that the subject is selected for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof. In some embodiments, these methods further include recording that the subject is selected for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy in the subject's clinical record (e.g., a computer readable medium). In some embodiments, these methods further include recording that the subject is selected for a treatment that does not include a first Trk inhibitor as a monotherapy in the subject's clinical record (e.g., a computer readable medium).

Also provided herein are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment with a first Trk inhibitor as a monotherapy, that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3) has a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy.

Also provided herein are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more

amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3) has an increased likelihood of having a positive response to treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of determining the likelihood that a subject having cancer will have a positive response to treatment with a first Trk inhibitor as a monotherapy, that include: determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3) has a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy.

Also provided herein are methods of determining the likelihood that a subject having cancer will have a positive response to treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), has an increased likelihood of having a positive response to treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Some embodiments of these methods further include: administering a treatment not including a first Trk inhibitor as a monotherapy to the subject determined to have a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy. Some embodiments of these methods further include: administering a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to the subject determined to have an increased likelihood of having a positive response to treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of predicting the efficacy of treatment with a first Trk inhibitor as a monotherapy in a subject having cancer, that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and determining that treatment with a first Trk inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of predicting the efficacy of treatment with a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, in a subject having cancer, that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and determining that treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of predicting the efficacy of treatment with a first Trk inhibitor as a monotherapy in a subject having cancer, that include: determining that treatment with a first Trk inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3). Some embodiments of these methods further include administering a treatment not including a first Trk inhibitor as a monotherapy to the subject.

Also provided herein are methods of predicting the efficacy of treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, in a subject having

cancer, that include: determining that treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3). Some embodiments of these methods further include administering one or more compound of Table 5, or a pharmaceutically acceptable salt thereof, to the subject.

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) selecting a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) selecting additional doses of the first Trk inhibitor of step (a) for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) selecting a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a

mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) selecting a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer that includes: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) selecting a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) selecting additional doses of the first Trk inhibitor of step (a) to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene

that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Some embodiments of these methods include selecting a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3). Some embodiments of these methods include selecting additional doses of the first Trk inhibitor of step (a) for a subject having a cancer cell that does not have (at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a

mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Some embodiments of any of the methods described herein further include recording the selected treatment in the subject's clinical record (e.g., a computer readable medium). Some embodiments of any of the methods described herein further include administering selected treatment to the subject.

In some embodiments of any of the methods described herein, the subject is previously identified or diagnosed as having the cancer.

In some embodiments of the methods described herein, the treatment that does not include a first Trk inhibitor as a monotherapy is selected from a treatment that includes one or more of: surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant. In some embodiments of the methods described herein, the treatment that does not include a first Trk inhibitor as a monotherapy includes: one or more of surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant; and one or more Trk inhibitors. In some embodiments of the methods described herein, the treatment that does not include a first Trk inhibitor as a monotherapy includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, as a monotherapy.

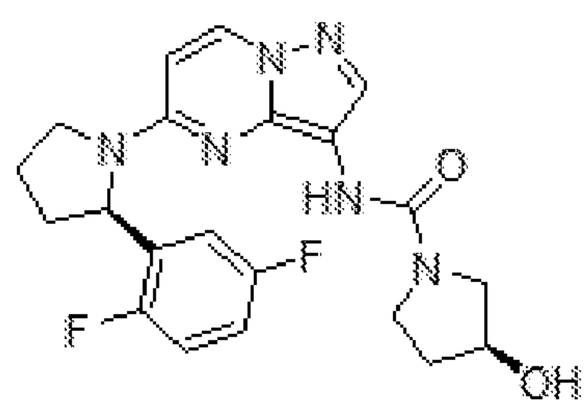
Also provided herein are methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer that include: determining whether a cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the

expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and identifying a subject having a cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), as having an increased likelihood of developing a Trk inhibitor-resistant cancer. Also provided herein are methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer that include: identifying a subject having a cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), as having an increased likelihood of developing a Trk inhibitor-resistant cancer. Some embodiments of these methods further include confirming a diagnosis of a Trk inhibitor-resistant cancer in a subject determined to have an increased likelihood of developing a Trk inhibitor-resistant cancer.

Also provided herein are methods of determining the presence of a Trk inhibitor-resistant cancer in a subject that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), has an a Trk inhibitor-resistant cancer. Also provided herein are methods of determining the presence of a Trk inhibitor-resistant cancer in a subject that include: determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

In some embodiments of any of the methods described herein, the first Trk inhibitor (e.g., the first Trk inhibitor in step (a)) is selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-

pyran-4-ylamino)-benzamide); (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; cabozantinib ((N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide)); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); belizatinib (4-fluoro-N-(6-((4-(2-hydroxypropan-2-yl)piperidin-1-yl)methyl)-1-((1s,4s)-4-(isopropylcarbamoyl)cyclohexyl)-1H-benzo[d]imidazol-2-yl)benzamide); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); PLX7486; altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); AZD7451 ((S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine). In some embodiments, the first Trk inhibitor (e.g., the first Trk inhibitor in step (a)) is entrectinib. In some embodiments, the first Trk inhibitor (e.g., the first Trk inhibitor in step (a)) is the compound of Formula I:



or a hydrogen sulfate salt thereof. In some embodiments, the first Trk inhibitor (e.g., the first Trk inhibitor in step (a)) is a crystalline form of the compound of Formula I or a hydrogen sulfate salt thereof (e.g., a compound of Formula I-HS).

In some embodiments of any of the methods described herein, the second Trk inhibitor is selected from the group consisting of: a (R)-2-phenylpyrrolidine substituted imadazopyridazine, AZD6918, GNF-4256, GTx-186, GNF-5837, AZ623, AG-879, altiratinib, CT327, ARRY-470, AR-772, AR-523, AR-786, AR-256, AR-618, AZ-23, AZD7451, cabozantinib, CEP-701, CEP-751, PHA-739358, dovitinib, entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-l-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide), PLX7486, Gö 6976, GW441756, MGCD516, ONO-5390556, PHA-848125AC, regorafenib, sorafenib, sunitinib, TSR-011, VM-902A, K252a, a 4-

aminopyrazolylpyrimidine, and a substituted pyrazolo[1,5-a] pyrimidine compound. In some embodiments of any of the methods described herein, the second Trk inhibitor is selected from the compounds of Table 5, or a pharmaceutically acceptable salt thereof.

In some embodiments of any of the methods described herein, the subject is suspected of having a cancer. In some embodiments of any of the methods described herein, the subject has one or more symptoms of cancer. In some embodiments of any of the methods described herein, the subject is previously identified or diagnosed as having a cancer.

In some embodiments of any of the methods described herein, the step of determining whether a cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or a NTRK2 gene and/or a NTRK3 gene in a cell in the sample. In some embodiments of any of the methods described herein, the step of determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or a NTRK2 gene and/or a NTRK3 gene in a cancer cell in the sample. In some embodiments of any of the methods described herein, the assay is selected from the group consisting of: denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), temperature gradient capillary electrophoresis, a single strand conformational polymorphism assay, a molecular beacon assay, a dynamic hybridization assay, a PCR-based assay, denaturing high performance liquid chromatography. In some embodiments of any of the methods described herein, the assay includes sequencing a segment of the NTRK1 gene and/or the NTRK2 gene and/or the NTRK3 gene including the at least one point mutation.

In some embodiments of any of the methods described herein, the cancer is selected from the group consisting of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder

urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, non-Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine

adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epitheliod cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

In some of embodiments of any of the methods described herein, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions can be selected from (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705. In some embodiments of any of the methods described herein, the TrkA protein includes one or more of the following amino acid substitutions: G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S. In some embodiments of any of the methods described herein, the TrkB protein includes one or more of the following amino acid substitutions: G545R, A570V, Q596E, Q596P, V601G,

F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S. In some embodiments of any of the methods described herein, the TrkC protein includes one or more of the following amino acid substitutions: G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A.

Also provided are kits that include: one or more probes that each specifically hybridize to a segment of a NTRK1 gene that encodes a mutation at one of amino acid positions 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 in TrkA protein; and/or one or more probes that each specifically hybridize to a segment of a NTRK2 gene that encodes a mutation at one of amino acid positions 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 in TrkB protein; and/or one or more probes that each specifically hybridize to a segment of a NTRK3 gene that encodes a mutation at one or amino acid positions 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 in TrkC protein. Some embodiments of these kits include: one or more probes that each specifically hybridize to a segment of a NTRK1 gene that encodes a mutation selected from the group consisting of: G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S in TrkA protein; and/or one or more probes that each specifically hybridize to a segment of a NTRK2 gene that encodes a mutation selected from the group consisting of: G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S in TrkB protein; and/or one or more probes that each specifically hybridize to a segment of a NTRK3 gene that encodes a mutation selected from the group consisting of: G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A in TrkC protein. In some embodiments of any of the kits described herein, the one or more probes are labeled with a detectable probe. In some embodiments of any of the kits described herein, the one or more probes are covalently attached to a substrate (e.g., a film, a plate, or a bead).

As used herein, the word “a” before a noun represents one or more of the particular noun. For example, the phrase “a cell” represents “one or more cells.”

The term “subject” means a vertebrate, including any member of the class mammalia, including humans, sports or pet animals, such as horse (e.g., race horse) or dog (e.g., race dogs), and higher primates. In some embodiments, the subject is a human.

The term “treating” or “positive response to treatment” means an improvement in the condition of a subject having a cancer, e.g., one or more of a decrease in the size of one or more tumor(s) in a subject, a decrease or no substantial change in the growth rate of one or more tumor(s) in a subject, a decrease in metastasis in a subject, and an increase in the period of remission for a subject (e.g., as compared to the one or more metric(s) in a subject having a similar cancer receiving no treatment or a different treatment, or as compared to the one or more metric(s) in the same subject prior to treatment). Additional metrics for assessing response to a treatment in a subject having a cancer are known in the art.

The term “point mutation” means a change in the nucleotide sequence of a gene that results in a single amino acid change in a protein encoded by the gene. For example, a point mutation in a gene can result in the deletion of a single amino acid in a protein encoded by the gene or can result in the substitution of an amino acid in a wildtype version of the encoded protein with a different amino acid. Non-limiting examples of point mutations in a NTRK1 genes, NTRK2 genes, and NTRK3 genes are described herein.

The phrase “significant level of carcinogen” is meant a level of exposure to a carcinogen that is known to increase (e.g., a statistically significant increase) the likelihood of a subject to develop a cancer (e.g., as compared to a subject that has not been exposed to the same level of exposure or has been exposed to a non-detectable amount of the carcinogen).

As used herein, a “first Trk kinase inhibitor” or “first Trk inhibitor” is a Trk inhibitor as described herein but does not include compounds of Table 5, or a pharmaceutically acceptable salt thereof, as defined herein. As used herein, a “second Trk kinase inhibitor” or a “second Trk inhibitor” is a Trk inhibitor as described herein and includes the compounds of Table 5, or a pharmaceutically acceptable salt thereof, as described herein. When both a first and a second Trk inhibitor are present in a method provided herein, the first and second Trk kinase inhibitors are different.

The term “monotherapy” means the use of a single drug to treat a particular disorder or disease.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other,

suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 is a flow chart of the experimental methods used in Example 1.

Figure 2 is a crystal structure of TrkA showing the location of some of the Trk inhibitor-resistance amino acid substitutions.

Figure 3 is a diagram showing the position of some of the Trk inhibitor-resistance amino acid substitutions.

Figure 4 is a graph of the POC of cells expressing a MPRIP-NTRK1 fusion protein including one of the Trk inhibitor resistance mutations at different concentrations of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A).

Figure 5 is a flow chart of the experimental methods used in Example 3.

Figure 6A is a graph representing the frequency of mutations and the dose of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A) from which they were isolated.

Figure 6B is a schematic of RIP-TRKA (encoded by MPRIP-NTRK1) with selected protein domains and resistance mutations that were identified.

Figure 6C is a ribbon representation of the crystallographic structure of the TRKA kinase domain in complex with the TRK inhibitor AZ-23 (PDB 4AOJ) showing localization of mutations that were identified.

Figure 7 is a graph of the percent of control of cells expressing a MPRIP-NTRK1 fusion protein including certain of the identified TrkA inhibitor resistance mutations at different concentrations of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A).

Figure 8 is a photograph of a Western blot analysis of NIH3T3 cells treated with the indicated concentrations of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A) for 2 hours.

Figure 9A is a graph representing the frequency of mutations and the dose of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A) they were isolated from.

Figure 9B is a schematic of TRIM24-TRKB (encoded by TRIIM24-NTRK1) with selected protein domains and resistance mutations that were identified.

Figure 9C is a ribbon representation of the crystallographic structure of the TRKB kinase domain in complex with the TRK inhibitor AZ-23 (PDB 4AOJ) showing localization of mutations that were identified.

Figure 10 is a graph of the percent of control of cells expressing a TRIM24-NTRK2 fusion protein including certain of the identified TrkB inhibitor resistance mutations at different concentrations of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A).

Figure 11 is a photograph of a Western blot analysis of NIH3T3 cells treated with the indicated concentrations of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Cmpd A) for 2 hours.

Figure 12 is a table showing the IC_{50} of certain TrkA and TrkB mutations that were identified.

Figure 13 is an alignment of kinase domains from selected oncogenes with known resistance mutations. In vitro- (green) or patient-derived (yellow) resistance mutations are shown for other drug-targeted kinases for comparison.

DETAILED DESCRIPTION

Trk inhibitor-resistance mutations in a NTRK1 gene, a NTRK2 gene, and a NTRK3 gene were discovered. In view of this discovery, provided herein are methods of treating a subject having a cancer, methods of selecting a treatment for a subject having a cancer, methods of selecting a subject having a cancer for a treatment that does not include a Trk

inhibitor, methods of determining the likelihood that a subject having a cancer will have a positive response to a treatment with a Trk inhibitor, methods of predicting the efficacy of a Trk inhibitor in a subject having cancer, methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer, and methods of determining the presence of a Trk inhibitor-resistant cancer in a subject, based on a determination as to whether the subject has a cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705. Also provided are kits that allow for the detection of at least one of the point mutations in NTRK1 and/or NTRK2 and/or NTRK3.

Detection and identification of a subject having cells having a Trk inhibitor-resistant mutation as described herein (e.g., (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705) can improve treatment of the subject by, for example, changing the treatment regimen (e.g., changing the Trk inhibitor administered to the subject or adding an additional anticancer agent or anticancer therapy) or by administering a Trk inhibitor that is effective in the presence of a Trk inhibitor-resistant

mutation (e.g., one or more of the compounds of Table 5, or a pharmaceutically acceptable salt thereof).

As can be appreciated in the art, the various aspects described below can be used in any combination without limitation.

Tropomyosin Receptor Kinases (Trks)

Three different NTRK genes have been implicated as having a role in cancer (e.g., through discovery of chromosome translocations resulting in constitutively active Trk fusion proteins): NTRK1, NTRK2, and NTRK3. The NTRK1, NTRK2, and NTRK3 genes encode TrkA, TrkB, and TrkC, respectively.

Non-limiting exemplary amino acid and cDNA sequences for wildtype TrkA are provided below. The exemplary wildtype protein and cDNA sequences provided below can be used to identify a point mutation in a NTRK1 gene or can be used to determine mutation in a TrkA protein caused by a point mutation in a NTRK1 gene, respectively. Additional wildtype protein and cDNA sequences for TrkA are known in the art.

The amino acid positions used to describe the TrkA substitutions herein are based on the wildtype sequence of TrkA of SEQ ID NO: 1. The corresponding amino acid position in the wildtype sequence of another isoform of TrkA (SEQ ID NO: 3) can be identified by performing a sequence alignment between SEQ ID NO: 1 and SEQ ID NO: 3. A similar method (e.g., alignment of SEQ ID NO: 1 to the amino acid sequence of any other isoform of TrkA) can be used to match the amino acid positions of the substitutions in TrkA described herein to the corresponding amino acid position in other isoforms of TrkA known in the art.

Wildtype Human TrkA Protein Isoform A (NP_002520) (SEQ ID NO: 1)
Wildtype Human TrkA cDNA Isoform A (NM_002529) (SEQ ID NO: 2)
Wildtype Human TrkA Protein Isoform B (NP_001007793) (SEQ ID NO: 3)
Wildtype Human TrkA cDNA Isoform B (NM_001007792) (SEQ ID NO: 4)

Alignment of TrkA isoforms (SEQ ID NO: 1 and SEQ ID NO: 3)

```
S1  68 LTELYIENQQHLQHLELRDLRGLGELRNLTIVKSGLRFVAPDAFHFTPRLSRLNLSFNAL 127
       L   YIENQQHLQHLELRDLRGLGELRNLTIVKSGLRFVAPDAFHFTPRLSRLNLSFNAL
S3  38 LAASYIENQQHLQHLELRDLRGLGELRNLTIVKSGLRFVAPDAFHFTPRLSRLNLSFNAL  97
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S1 128 ESLSWKTVQGLSLQELVLSGNPLHCSCALRWLQRWEEEGLGGVPEQKLQCHGQGPLAHMP 187
       ESLSWKTVQGLSLQELVLSGNPLHCSCALRWLQRWEEEGLGGVPEQKLQCHGQGPLAHMP
S3  98 ESLSWKTVQGLSLQELVLSGNPLHCSCALRWLQRWEEEGLGGVPEQKLQCHGQGPLAHMP 157

S1 188 NASCGVPTLKVQVPNASVDVGDDVLLRCQVEGRGLEQAGWILTELEQSATVMKSGGLPSL 247
       NASCGVPTLKVQVPNASVDVGDDVLLRCQVEGRGLEQAGWILTELEQSATVMKSGGLPSL
S3 158 NASCGVPTLKVQVPNASVDVGDDVLLRCQVEGRGLEQAGWILTELEQSATVMKSGGLPSL 217

S1 248 GLTLANVTSDLNRKNVTCWAENDVGRAEVSVQVNVSFPASVQLHTAVEMHHWCIPFSVDG 307
       GLTLANVTSDLNRKNVTCWAENDVGRAEVSVQVNVSFPASVQLHTAVEMHHWCIPFSVDG
S3 218 GLTLANVTSDLNRKNVTCWAENDVGRAEVSVQVNVSFPASVQLHTAVEMHHWCIPFSVDG 277

S1 308 QPAPSLRWLFNGSVLNETSFIFTEFLEPAANETVRHGCLRLNQPTHVNNGNYTLLAANPF 367
       QPAPSLRWLFNGSVLNETSFIFTEFLEPAANETVRHGCLRLNQPTHVNNGNYTLLAANPF
S3 278 QPAPSLRWLFNGSVLNETSFIFTEFLEPAANETVRHGCLRLNQPTHVNNGNYTLLAANPF 337

S1 368 GQASASIMAAFMDNPFEFNPEDPIPVSFSPVDTNSTSGDPVEKKDETPFGVSVAVGLAVF 427
       GQASASIMAAFMDNPFEFNPEDPIP      DTNSTSGDPVEKKDETPFGVSVAVGLAVF
S3 338 GQASASIMAAFMDNPFEFNPEDPIP------DTNSTSGDPVEKKDETPFGVSVAVGLAVF 391

S1 428 ACLFLSTLLLVLNKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGGSSLSPTEGKGSGLQ 487
       ACLFLSTLLLVLNKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGGSSLSPTEGKGSGLQ
S3 392 ACLFLSTLLLVLNKCGRRNKFGINRPAVLAPEDGLAMSLHFMTLGGSSLSPTEGKGSGLQ 451

S1 488 GHIIENPQYFSDACVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVAVKALK 547
       GHIIENPQYFSDACVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVAVKALK
S3 452 GHIIENPQYFSDACVHHIKRRDIVLKWELGEGAFGKVFLAECHNLLPEQDKMLVAVKALK 511

S1 548 EASESARQDFQREAELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLRSHGPD 607
       EASESARQDFQREAELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLRSHGPD
S3 512 EASESARQDFQREAELLTMLQHQHIVRFFGVCTEGRPLLMVFEYMRHGDLNRFLRSHGPD 571

S1 608 AKLLAGGEDVAPGPLGLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIG 667
       AKLLAGGEDVAPGPLGLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIG
S3 572 AKLLAGGEDVAPGPLGLGQLLAVASQVAAGMVYLAGLHFVHRDLATRNCLVGQGLVVKIG 631

S1 668 DFGMSRDIYSTDYYRVGGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQP 727
       DFGMSRDIYSTDYYRVGGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQP
S3 632 DFGMSRDIYSTDYYRVGGRTMLPIRWMPPESILYRKFTTESDVWSFGVVLWEIFTYGKQP 691

S1 728 WYQLSNTEAIDCITQGRELERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQA 787
       WYQLSNTEAIDCITQGRELERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQA
S3 692 WYQLSNTEAIDCITQGRELERPRACPPEVYAIMRGCWQREPQQRHSIKDVHARLQALAQA 751

S1 788 PPVYLDVLG  796
       PPVYLDVLG
S3 752 PPVYLDVLG  760
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Non-limiting exemplary amino acid and cDNA sequences for wildtype TrkB are provided below. The exemplary wildtype protein and cDNA sequences provided below can be used to identify a point mutation in a NTRK2 gene or can be used to determine mutation

in a TrkB protein caused by a point mutation in a NTRK2 gene, respectively. Additional wildtype protein and cDNA sequences for TrkB are known in the art.

The amino acid positions used to describe the TrkB substitutions herein are based on the wildtype sequence of TrkB of SEQ ID NO: 5. The corresponding amino acid position in the wildtype sequence of another isoform of TrkB can be identified by performing a sequence alignment between SEQ ID NO: 5 and the amino acid sequence of the other isoform of TrkB.

Wildtype Human TrkB Protein Isoform A (AAB33109.1) (SEQ ID NO: 5)
Wildtype Human TrkB cDNA Isoform A (S76473.1) (SEQ ID NO: 6)

Non-limiting exemplary amino acid and cDNA sequences for wildtype TrkC are provided below. The exemplary wildtype protein and cDNA sequences provided below can be used to identify a point mutation in a NTRK3 gene or can be used to determine mutation in a TrkC protein caused by a point mutation in a NTRK3 gene, respectively. Additional wildtype protein and cDNA sequences for TrkC are known in the art.

The amino acid positions used to describe the TrkC substitutions herein are based on the wildtype sequence of TrkC of SEQ ID NO: 7. The corresponding amino acid position in the wildtype sequence of another isoform of TrkC can be identified by performing a sequence alignment between SEQ ID NO: 7 and the amino acid sequence of the other isoform of TrkC.

Wildtype Human TrkC Protein (AAB33111.1) (SEQ ID NO: 7)
Wildtype Human TrkC cDNA (S76475.1) (SEQ ID NO: 8)

NTRK Point Mutations

Point mutations in a NTRK1 gene, a NTRK2 gene, and a NTRK3 gene were discovered in Trk inhibitor-resistant cancer cells. A point mutation in a NTRK1 gene can result in a TrkA protein that includes a substitution of an amino acid in a wildtype version of the TrkA protein with a different amino acid. In other examples, a point mutation in a NTRK1 gene can result in a TrkA protein with a deletion of an amino acid in a wildtype

version of the TrkA protein. Exemplary Trk inhibitor-resistance point mutations in TrkA protein are listed in Table 1.

Table 1. Exemplary Trk Inhibitor-Resistance Point Mutations in TrkA Protein

Amino acid position 517 (e.g., G517R)
Amino acid position 542 (e.g., A542V)
Amino acid position 568 (e.g., Q568x)
Amino acid position 573 (e.g., V573M)
Amino acid position 589 (e.g., F589L, F589C)
Amino acid position 595 (e.g., G595S, G595R[1])
Amino acid position 599 (e.g., D596V)
Amino acid position 600 (e.g., F600L)
Amino acid position 602 (e.g., R602x)
Amino acid position 646 (e.g., F646V)
Amino acid position 656 (e.g., C656Y, C656F)
Amino acid position 657 (e.g., L657V)
Amino acid position 667 (e.g., G667C[1], G667S)
Amino acid position 676 (e.g., Y676S)

The letter “x” when used to describe a mutation of an amino acid at a specific amino acid position means (i) a substitution of the amino acid present at the same amino acid position in the corresponding wildtype protein with a different naturally-occurring amino acid, or (ii) a deletion of the amino acid present at the same amino acid position in the corresponding wildtype protein.

A point mutation in a NTRK2 gene can result in a TrkB protein that includes a substitution of an amino acid in a wildtype version of the TrkB protein with a different amino acid. In other examples, a point mutation in a NTRK2 gene can result in a TrkB protein with a deletion of an amino acid in a wildtype version of the TrkB protein. Exemplary Trk inhibitor-resistance point mutations in TrkB protein are listed in Table 2.

Table 2. Exemplary Trk Inhibitor-Resistance Point Mutations in TrkB Protein

Amino acid position 545 (e.g., G545R)
Amino acid position 570 (e.g., A570V)
Amino acid position 596 (e.g., Q596E, Q596P)

Amino acid position 601 (e.g., V601G)
Amino acid position 617 (e.g., F617L, F617C, F617I)
Amino acid position 623 (e.g., G623S, G623R)
Amino acid position 624 (e.g., D624V)
Amino acid position 628 (e.g., F628x)
Amino acid position 630 (e.g., R630K)
Amino acid position 672 (e.g., F672x)
Amino acid position 682 (e.g., C682Y, C682F)
Amino acid position 683 (e.g., L683V)
Amino acid position 693 (e.g., G693S)
Amino acid position 702 (e.g., Y702x)

The letter "x" when used to describe a mutation of an amino acid at a specific amino acid position means (i) a substitution of the amino acid present at the same amino acid position in the corresponding wildtype protein with a different naturally-occurring amino acid, or (ii) a deletion of the amino acid present at the same amino acid position in the corresponding wildtype protein.

A point mutation in a NTRK3 gene can result in a TrkC protein that includes a substitution of an amino acid in a wildtype version of the TrkC protein with a different amino acid. In other examples, a point mutation in a NTRK3 gene can result in a TrkC protein with a deletion of an amino acid in a wildtype version of the TrkC protein. Exemplary Trk inhibitor-resistance NTRK3 mutations are listed in Table 3.

Table 3. Exemplary Trk Inhibitor-Resistance Point Mutations in TrkC Protein

Amino acid position 545 (e.g., G545R)
Amino acid position 570 (e.g., A570V)
Amino acid position 596 (e.g., Q596x)
Amino acid position 601 (e.g., V601)
Amino acid position 617 (e.g., F617x) F617L
Amino acid position 623 (e.g., G623R[1])
Amino acid position 624 (e.g., D624V)
Amino acid position 628 (e.g., F628x)
Amino acid position 630 (e.g., R630x)
Amino acid position 675 (e.g., F675x)
Amino acid position 685 (e.g., C685Y, C684F)
Amino acid position 686 (e.g., L686V)
Amino acid position 696 (e.g., G696x) G696A

Amino acid position 705 (e.g., Y705x)

The letter “x” when used to describe a mutation of an amino acid at a specific amino acid position means (i) a substitution of the amino acid present at the same amino acid position in the corresponding wildtype protein with a different naturally-occurring amino acid, or (ii) a deletion of the amino acid present at the same amino acid position in the corresponding wildtype protein.

Non-limiting examples of the specific amino acid positions discovered to have mutations (e.g., substitutions or deletions) in TrkA in Trk inhibitor-resistant cancer cells having a NTRK1 point mutation are listed below. Also listed below are the different specific amino acid mutations (e.g., substitutions) present in TrkA proteins present in Trk inhibitor-resistant cancer cells having a NTRK1 point mutation.

Trk inhibitor-resistant cancer cells were discovered to have point mutations in a NTRK1 gene that result in a TrkA protein that includes one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid substitutions or deletions at amino acid positions: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., amino acid positions corresponding to those in wildtype sequence NP_002520 (SEQ ID NO: 1)). Different specific amino acid substitutions present in a TrkA protein generated in a Trk inhibitor-resistant cancer cell include one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve) of the following: G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S (e.g., as compared to the wildtype sequence NP_002520 (SEQ ID NO: 1)).

Trk inhibitor-resistant cancer cells were discovered to have point mutations in a NTRK2 gene that result in a TrkB protein that includes one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid substitutions or deletions at amino acid positions: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., amino acid positions corresponding to those in wildtype sequence AAB33109.1 (SEQ ID NO: 5)). Different specific amino acid substitutions present in a TrkB protein generated in a Trk inhibitor-resistant cancer cell

include one or more (e.g., two, three, four, five, six, seven, eight, nine, eleven, or twelve) of the following: G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S (e.g., as compared to the wildtype sequence AAB33109.1 (SEQ ID NO: 5)).

Trk inhibitor-resistant cancer cells were discovered to have point mutations in a NTRK3 gene that result in a TrkC protein that includes one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid substitutions or deletions at amino acid positions: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., amino acid positions corresponding to those in a wildtype sequence (SEQ ID NO: 7)). Different specific amino acid substitutions present in a TrkC protein generated in a Trk inhibitor-resistant cancer cell include one or more (e.g., two, three, four, five, six, or seven, or eight) of the following: G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A (e.g., as compared to the wildtype sequence (SEQ ID NO: 7)).

As one skilled in the art can appreciate, the specific substitutions listed above are exemplary. For example, when a naturally-occurring amino acid at an amino acid position is substituted with a different amino acid, it is understood that an amino acid having a chemically-related amino acid side chain may also be substituted (and detected in a cancer cell). Amino acids that have chemically-related amino acid side chains are listed in Table 4.

Table 4. Chemically Related Amino Acid Side Chains

Positively-Charged Side Chains	Lysine, Arginine, Histidine
Negatively-Charged Side Chains	Glutamate and Aspartate
Nonpolar and/or Aliphatic Side Groups	Glycine, Alanine, Valine, Leucine, Isoleucine, and Proline
Polar, Uncharged Side Groups	Serine, Threonine, Cysteine, Methionine, Asparagine, Glutamine
Aromatic Side Chains	Phenylalanine, Tyrosine, and Tryptophan

Any of the point mutations described herein may result in, e.g., increased catalytic activity of a TrkA kinase or a TrkB kinase or a TrkC kinase. Any of the point mutations

described herein may result in, e.g., a decrease in the auto-inhibited conformation of a Trk kinase (e.g., a TrkA kinase or a TrkB kinase or a TrkC kinase). Any of the point mutations described herein may result in, e.g., an increase in the activated conformation of a Trk kinase (e.g., a TrkA kinase or a TrkB kinase or a TrkC kinase). Any of the point mutations described herein may result in, e.g., an altered tertiary structure of a TrkA kinase (as compared to a wildtype TrkA kinase) that decreases binding of a Trk inhibitor to the TrkA kinase, or an altered tertiary structure of a TrkB kinase (as compared to a wildtype TrkB kinase) that decreases binding of a Trk inhibitor to the TrkB kinase, or an altered tertiary structure of a TrkC kinase (as compared to a wildtype TrkC kinase) that decreases binding of a Trk inhibitor to the TrkC kinase. Any of the point mutations described herein may result in, e.g., an increase in the K_{off} rate and/or a decrease in the K_{on} rate of a Trk inhibitor when it interacts with the TrkA protein (as compared to a wildtype TrkA kinase) or the TrkB protein (as compared to a wildtype TrkB kinase) or the TrkC protein (as compared to a wildtype TrkC kinase).

Isolating Genomic DNA from a Biopsy Sample

Methods of isolating genomic DNA from biopsy sample are well known in the art. For example, a number of commercially available kits can be used to isolate genomic DNA from a sample containing mammalian cells (e.g., a biopsy sample). Non-limiting examples of commercially available kits for the isolation of genomic DNA from a sample containing mammalian cells include: ChargeSwitch® gDNA Tissue Kit (Life Technologies), Genomic DNA Isolation Kit (Norgen Biotek Corp., Ontario, Canada), QIAmp DNA FFPE (Qiagen), QIAsymphony DSP DNA kits (Qiagen), REPLI-g Mini Kit (Qiagen), Generation Capture Plate Kit (Qiagen), QI Amp 96 DNA Blood Kit (Qiagen), QIAmp DNA Mini kit (Qiagen), Biosprint 15 DNA Bloot Kit (Qiagen), Biosprint 96 DNA Blood Kit (Qiagen), MagAttract DNA Mini M48 Kit (Qiagen), QIAmp DNA Blood BioRobot 9604 Kit (Qiagen), QIAmp DNA Investigator Kit (Qiagen), QIAmp DNA Micro Kit, Xtreme DNA Isolation Kit (Isohelix; Harrietsham, Kent, UK), DDK DNA Isolation Kit (Isohelix), and XtraClean DNA kit (Isohelix). Genomic DNA can be isolated from a sample (e.g., a biopsy sample) using these and other commercially available genomic DNA isolation kits by following the manufacturer's instructions.

An exemplary method for isolating genomic DNA from a sample (e.g., a biopsy sample) include the steps of: lysing mammalian cells present in the sample, precipitating proteins in the lysate, removing the supernatant, precipitating genomic DNA out of the supernatant, washing the genomic DNA pellet with ethanol, and rehydrating the genomic DNA pellet in a pharmaceutically acceptable buffer (e.g., sterile or filtered water, or a buffered solution).

Assays for Determining the Presence of a Point Mutation

Some of the methods provided herein include a step of performing an assay to determine the presence of (i) at least one (e.g., two, three, four, five, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene (e.g., any of the point mutations in NTRK1 described herein), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene, and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene (e.g., any of the point mutations in a NTRK3 gene described herein), in a cell (e.g., cancer cell) in a sample from the subject (e.g., a biopsy sample).

A variety of assays for determining the presence of one or more point mutations in a cell (e.g., a cancer cell) are known in the art. Non-limiting examples of such assays (which can be used in any of the methods described herein) include: denaturing gradient gel electrophoresis (DGGE) (Nollau et al., *Clin. Chem.* 43:1114-1128, 1997), temperature gradient gel electrophoresis (TGGE) (Nollau et al., *Clin. Chem.* 43:1114-1128, 1997), temperature gradient capillary electrophoresis, single strand conformational polymorphism assays (see, e.g., Tahira et al., *Human Mutat.* 26:69-77, 2005), molecular beacon assays (see, e.g., Totowa, NJ, Vol. 212, pp. 111-128, 2003), dynamic hybridization (see, e.g., Howell et al., *Nature Biotechnol.* 17:87-88, 1999), PCR-based assays (e.g., tetraprimer ARMS-PCR (see, e.g., Zhang et al., *Plos One* 8:e62126, 2013), real-time PCR, allele-specific PCR (see, e.g., Gaudet et al., *Methods Mol. Biol.* 578:415-424, 2009), and TaqMan Assay Genotyping (see, e.g., Woodward, *Methods Mol. Biol.* 1145:67-74, 2014, and TaqMan®OpenArray® Genotyping Plates from Life Technologies)), Flap endonuclease assays (also called Invader assays) (see, e.g., Olivier et al., *Mutat. Res.* 573:103-110, 2005), oligonucleotide ligation

assays (see, e.g., Bruse et al., *Biotechniques* 45:559-571, 2008), or, denaturing high performance liquid chromatography (see, e.g., Yu et al., *J. Clin. Pathol.* 58:479-485, 2005), high-resolution melting of an amplified sequence containing the point mutation (see, e.g., Wittwer et al., *Clinical Chemistry* 49:853-860, 2003), or sequencing (e.g., Maxam-Gilbert sequencing, chain-termination methods, shotgun sequencing, bridge PCR, and next-generation sequencing methods (e.g., massively parallel signature sequencing, polony sequencing, 454 pyrosequencing, Illumina (Solexa) sequencing, SOLiD sequencing, Ion Torrent semiconductor sequence, DNA nanoball sequencing, heliscope single molecule sequencing, and single molecule real-time sequencing)). Additional details and a summary of various next-generation sequencing methods are described in Koboldt et al., *Cell* 155:27-38, 2013.

In some embodiments, the assay used to determine the presence of the (i) at least one point mutation in NTRK1, and/or (ii) at least one point mutation in NTRK2, and/or (iii) at least one point mutation in a NTRK3, includes a PCR assay (e.g., a real-time PCR-assay, e.g., a real-time PCR-based genotyping assay) (with or without a prior pre-amplification step). In some embodiments of any of the methods described herein the assay used to determine the presence of (i) at least one point mutation in NTRK1, and/or (ii) at least one point mutation in NTRK2, and/or (iii) at least one point mutation in NTRK3, is performed using TaqMan®-based sequencing (e.g., TaqMan®-based OpenArray® sequencing, e.g., high throughput TaqMan®-based Open Array® sequencing) (with or without a prior pre-amplification step). Methods for designing primers for use in the assays described herein are well-known in the art. For example, several vendors provide free software for designing forward and reverse primers for use in any of the assays described herein. A forward or reverse primer for use in any of the assays described herein can contain at least 10 (e.g., 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides). In some examples, a forward or reverse primer used in any of the assays described herein can include a label (e.g., any of the exemplary labels described herein) or can include a contiguous tag sequence (e.g., between about 5 nucleotides and about 25 nucleotides, between about 10 nucleotides and about 25 nucleotides, between about 10 nucleotides and 20 nucleotides, between about 5

nucleotides and about 20 nucleotides) that does not hybridize to a sequence within the subject's genome (e.g., the human genome).

In some embodiments, the assay includes the use of: one or more probes (e.g., detectably labeled probes) that specifically hybridize to one or more segments of a NTRK1 gene that include a point mutation (e.g., any of the point mutations in NTRK1 described herein); and/or one or more probes (e.g., detectable labeled probes) that specifically hybridize to one or more segments of a NTRK2 gene that include a point mutation (e.g., any of the point mutations in NTRK2 described herein); and/or one or more probes (e.g., a detectable labeled probe) that specifically hybridizes to one or more segments of a NTRK3 gene that include a point mutation (e.g., any of the point mutations in NTRK3 described herein). For example, the one or more probes can have 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 nucleotides. Additional description of the probes that can be used in exemplary assays are described herein.

Subjects

In various embodiments of the methods described herein, the subject can be previously identified or diagnosed as having a cancer (e.g., any of the cancers described herein). A subject can, e.g., be previously identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions. For example, (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene (e.g., any of the NTRK1 point mutations described herein), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene (e.g., any of the NTRK2 point mutations described herein), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene (e.g., any of the NTRK3 point mutations described herein). In some embodiments, a subject can be previously identified as having (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation (e.g., substitution) at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven,

twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., a TrkA protein including one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve) of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S); and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB including a mutation (e.g., substitution) at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., a TrkB protein including one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve) of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S; and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., a TrkC protein including one or more (e.g., two, three, four, five, six, seven, or eight) of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A).

In the methods of determining a subject's risk of developing a Trk inhibitor-resistant cancer and the methods of determining the presence of a Trk inhibitor-resistant cancer in a subject, the subject can be an undiagnosed subject, the subject can be identified as having been exposed to a significant level of carcinogen(s), the subject can be suspected of having a cancer (e.g., any of the cancers described herein), the subject can present with one or more (e.g., two, three, four, or five) symptoms of cancer (e.g., any of the symptoms of cancer described herein), and/or the subject is known to an elevated risk of developing a cancer (e.g., a family history of cancer).

In some embodiments, the subject is a pediatric subject.

The term "pediatric subject" as used herein refers to a patient under the age of 21

years at the time of diagnosis or treatment. The term "pediatric" can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman RE, Kliegman R, Arvin AM, Nelson WE. Nelson *Textbook of Pediatrics*, 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph AM, et al. *Rudolph's Pediatrics*, 21st Ed. New York: McGraw-Hill, 2002; and Avery MD, First LR. *Pediatric Medicine*, 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric subject is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

Cancers

Methods of treating a cancer are provided herein. Point mutations in NTRK1, NTRK2, and NTRK3 were found in Trk inhibitor-resistant cancer cells. Non-limiting examples of cancer (e.g., a Trk-associated cancer) include adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal

carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, lymphoma, non-Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epitheliod cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach

adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

Additional examples of cancers (e.g., Trk inhibitor-resistant cancer) include: adrenocortical carcinoma, anal cancer, appendix cancer, atypical teratoid/rhabdoid tumor (e.g., central nervous system atypical teratoid/rhabdoid tumor), B-cell cancer, bile duct cancer, bladder cancer, bone cancer (e.g., osteosarcoma and malignant fibrous histiocytoma), brain cancer (e.g., brain and spinal cord tumor, brain stem glioma, central nervous system embryonal tumors, central nervous system germ cell tumors, craniopharyngioma, and ependymoma), breast cancer, bronchogenic carcinoma, bronchus cancer, cancer of hematological tissues, cancer of the oral cavity or pharynx, carcinoid tumor, cervical cancer, childhood cancers, chordoma, chronic lymphocytic leukemia, chronic myeloproliferative neoplasms, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, ductal carcinoma in situ, embryonal tumor, endometrial cancer, esophageal cancer, esthesioneuroblastoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer (e.g., retinoblastoma), fallopian tube cancer, fibrosarcoma, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, germ cell tumor, gestational trophoblastic disease, glioblastoma multiforme, glioma (e.g., lower-grade glioma), head and neck cancer, heart cancer, histiocytosis, hypopharyngeal cancer, inflammatory myofibroblastic tumors, intrahepatic cholangiocarcinoma, islet cell tumor, kidney cancer (e.g., renal cell cancer), Langerhans cell histiocytosis, large cell neuroendocrine cancer, laryngeal cancer, leukemia (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, chronic myelogenous leukemia, and hairy cell leukemia), lip cancer, liver cancer, lung cancer, Burkitt lymphoma, Hodgkin's lymphoma, and primary central nervous system lymphoma), medulloblastoma, mesothelioma, mouth cancer, multiple myeloma, myelodysplastic syndromes, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer,

neoplasm (e.g., a melanocystic neoplasm), nephroma, neuroblastoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, paraganglioma, parathyroid cancer, pediatric glioma, penile cancer, pharyngeal cancer, pheochromocytoma, pilocytic astrocytoma, pituitary tumor, plasma cell neoplasm, primary peritoneal cancer, prostate cancer, rectum carcinoma, salivary gland cancer, sarcoma (e.g., Ewing sarcoma, rhabdomyosarcoma, uterine sarcoma, and undifferentiated sarcoma), secretory breast carcinoma, Sezary syndrome, skin cancer, small bowel cancer, small cell lung cancer, small intestine cancer, Spitz nevi, Spitz tumors, spitzoid melanoma, stomach cancer, squamous cell carcinoma, squamous neck cancer, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid carcinoma, urethral cancer, uterine cancer, urinary bladder cancer, vaginal cancer, vulvar cancer, and Wilms tumor.

In some embodiments, the cancer is a pediatric cancer. In some embodiments, the pediatric cancer is a mesenchymal cancer. For example, the mesenchymal cancer can be selected from the group consisting of: pediatric nephroma, congenital fibrosarcoma (CFS), pediatric high-grade glioma (HGG), mesenchymal cancers (infant fibrosarcoma (IF), congenital mesoblastic nephroma, congenital infantile fibrosarcoma (CIFS); pilocytic astrocytoma, brain tumors, pediatic acute leukemia, Ph-like acute lymphoblastic leukemia, cellular congenital mesoblastic nephroma (CMN); infantile fibrosarcoma, pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), non-brainstem HGGs (NBS-HGGs), anaplastic large cell lymphoma (ALCL), non-Hodgkin's lymphoma (NHL), pediatric papillary thyroid carcinoma, soft tissue sarcoma, spitzoid melanoma, pediatric hemangiopericytoma-like sarcoma, spindle cell sarcoma, NOS with myo/haemangiopericytic growth pattern, lung cancer, advanced pediatric solid tumors, neuroectodermal-derived tumors, pediatric colorectal cancer, adrenal neuroblastoma, and central nervous system tumors.

In some embodiments, the pediatric cancer is a fibrosarcoma such as infantile fibrosarcoma.

In some embodiments, the pediatric cancer is a glioma. For example, the pediatric cancer is selected from the group consisting of: pediatric high-grade glioma (HGG), diffuse intrinsic pontine gliomas (DIPGs), and on-brainstem HGGs (NBS-HGGs).

Methods of diagnosing a cancer (e.g., any of the cancers described herein) are known in the art. For example, a health care professional (e.g., a physician) can diagnose a subject as having a cancer by observing one or more symptoms of a cancer in the subject. Non-limiting examples of symptoms of a cancer include fever, fatigue, pain, hyperpigmentation, jaundice, erythema, pruritis, excessive hair growth, long-term constipation, diarrhea, change in the size of stool, pain when urinating, blood in urine, change in bladder function, sore that do not heal, white patches inside the mouth or on tongue, unusual bleeding or discharge, indigestion, trouble swallowing, changes in warts, moles, or freckles, nagging cough, hoarseness, lump or area of thickening that can be felt under skin, weight changes, trouble breathing, discomfort after eating, persistent, unexplained muscle or joint pain, persistent, unexplained fevers and night sweats, and unexplained bruising. The diagnosis of a cancer by a health care profession (e.g., a physician) can also include performing laboratory tests (e.g., urine or blood tests, e.g., complete blood count), imaging tests (e.g., computerized tomography (CT), bone scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, ultrasound, and X-ray), and obtaining and/or examining a biopsy sample from the subject.

A Trk inhibitor-resistant cancer cell can have, e.g., an increased rate of growth in the presence of at least one Trk inhibitor (e.g., any of the Trk inhibitors described herein or known in the art) as compared to the rate of growth of a control cell from a control subject having the same type of cancer and not having one or more of the point mutations in a NTRK1 gene described herein or one or more of the point mutations in a NTRK2 gene described herein or a point mutation in a NTRK3 gene described herein, when it is contacted with the at least one Trk inhibitor (e.g., a first Trk inhibitor). One of skill in the art will appreciate that the Trk inhibitor-resistant cancer cell and the control cell are contacted with the same concentration of the at least one Trk inhibitor. For example, rate of growth of the Trk inhibitor-resistant cancer cell is increased about 1% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15, about 10%, or about 5%; about 5% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15, or about 10%; about

10% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, or about 15%; about 15% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, or about 20%; about 20% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, or about 25%; about 25% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, or about 30%; about 30% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, or about 35%; about 35% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, or about 40%; about 40% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, or about 45%; about 45% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, to about 50%; about 50% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, to about 55%; about 55% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, or about 60%; about 60% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, or about 65%; about 65% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, or about 70%; about 70% to about 100%, about 95%, about 90%, about 85%, about 80%, to about 75%; about 75% to about 100%, about 95%, about 90%, about 85%, or about 80%; about 80% to about 100%, about 95%, about 90%, or about 85%; about 85% to about 100%, about 95%, or about 90%; about 90% to about 100% or about 95%; or about 95% to about 100% (as compared to the rate of growth of a control cell from a control subject having the same type of cancer and not having one or more of the point mutations in a NTRK1 gene described herein or one or more of the point mutations in a NTRK2 gene described herein or one or more of the point mutations in a NTRK3 gene described herein, when it is contacted with the at least one Trk inhibitor).

In some embodiments, a Trk inhibitor-resistant cancer can be resistant to treatment with (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (or a polymorph thereof), but the Trk inhibitor-resistant cancer is still sensitive to a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof. In some embodiments, a Trk inhibitor-resistant cancer can be resistant to treatment with entrectinib, but the Trk inhibitor-resistant cancer is still sensitive to a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

A Trk inhibitor-resistant cancer in a subject can have, e.g., an increased rate of growth of a solid tumor when the subject is treated with at least one Trk inhibitor (e.g., a first Trk inhibitor) as compared to the rate of growth of a control solid tumor in a control subject treated with the at least one Trk inhibitor and having the same type of cancer and not having one or more of the point mutations in a NTRK1 gene described herein or one or more of the point mutations in a NTRK2 gene described herein or a point mutation in a NTRK3 gene described herein). One of skill in the art will appreciate that the subject and the control subject are administered the same concentration of the at least one Trk inhibitor. For example, rate of growth of the solid tumor in a subject having a Trk inhibitor-resistant cancer and administered at least one Trk inhibitor is increased about 1% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15, about 10%, or about 5%; about 5% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15, or about 10%; about 10% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, or about 15%; about 15% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, or about 20%; about 20% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, or about 25%; about 25% to about 100%, about 95%, about 90%, about

85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, or about 30%; about 30% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, or about 35%; about 35% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, or about 40%; about 40% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, or about 45%; about 45% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, to about 50%; about 50% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, to about 55%; about 55% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, or about 60%; about 60% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, or about 65%; about 65% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, or about 70%; about 70% to about 100%, about 95%, about 90%, about 85%, about 80%, to about 75%; about 75% to about 100%, about 95%, about 90%, about 85%, or about 80%; about 80% to about 100%, about 95%, about 90%, or about 85%; about 85% to about 100%, about 95%, or about 90%; about 90% to about 100% or about 95%; or about 95% to about 100% (as compared to the rate of growth of a solid tumor in a control subject having the same type of cancer and not having one or more of the point mutations in a NTRK1 gene described herein or one or more of the point mutations in a NTRK2 gene described herein or a point mutation in a NTRK3 gene described herein, and administered the same at least one Trk inhibitor).

A Trk inhibitor-resistant cancer in a subject can have, e.g., a decreased rate of apoptosis in a solid tumor when the subject is treated with at least one Trk inhibitor (e.g., a first Trk inhibitor) as compared to the rate of apoptosis of a control solid tumor in a control subject treated with the at least one Trk inhibitor and having the same type of cancer and not having one or more of the point mutations in a NTRK1 gene described herein or one or more of the point mutations in a NTRK2 gene described herein or one or more point mutations in a NTRK3 gene described herein). One of skill in the art will appreciate that the subject and the control subject are administered the same concentration of the at least one Trk inhibitor. For

example, rate of apoptosis of the solid tumor in a subject having a Trk inhibitor-resistant cancer and administered at least one Trk inhibitor is decreased about 1% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15, about 10%, or about 5%; about 5% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15, or about 10%; about 10% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, or about 15%; about 15% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, or about 20%; about 20% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, or about 25%; about 25% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, about 35%, or about 30%; about 30% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, about 40%, or about 35%; about 35% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, about 45%, or about 40%; about 40% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, about 50%, or about 45%; about 45% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, to about 50%; about 50% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, to about 55%; about 55% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, or about 60%; about 60% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, or about 65%; about 65% to about 100%, about 95%, about 90%, about 85%, about 80%, about 75%, or about 70%; about 70% to about 100%, about 95%, about 90%, about 85%, about 80%, to about 75%; about 75% to about 100%, about 95%, about

90%, about 85%, or about 80%; about 80% to about 100%, about 95%, about 90%, or about 85%; about 85% to about 100%, about 95%, or about 90%; about 90% to about 100% or about 95%; or about 95% to about 100% (as compared to the rate of apoptosis in a solid tumor in a control subject having the same type of cancer and not having one or more of the point mutations in a NTRK1 gene described herein or one or more of the point mutations in a NTRK2 gene described herein or one or more point mutations in a NTRK3 gene described herein, and administered the same at least one Trk inhibitor).

Exemplary methods of determining the presence of a Trk inhibitor-resistant cancer in a subject are provided herein.

Trk Inhibitors

A variety of Trk inhibitors are known in the art. The ability of a Trk inhibitor to act as a Trk inhibitor may be tested using one or both of the assays described in Examples A and B in U.S. Patent No. 8,513,263, which is incorporated herein by reference.

A Trk inhibitor can have an IC_{50} of about 0.1 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, about 80 nM, about 60 nM, about 40 nM, about 20 nM, about 10 nM, or about 5 nM; about 1 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, about 80 nM, about 60 nM, about 40 nM, about 20 nM, about 10 nM, or about 5 nM; about 5 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, about

80 nM, about 60 nM, about 40 nM, about 20 nM, or about 10 nM; about 10 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, about 80 nM, about 60 nM, about 40 nM, or about 20 nM; about 20 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, about 80 nM, or about 40 nM; about 40 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, about 80 nM, or about 60 nM; about 60 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, about 100 nM, or about 80 nM; about 80 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, about 200 nM, about 150 nM, to about 100 nM; about 100 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about

250 nM, about 200 nM, or about 150 nM; about 150 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, about 250 nM, or about 200 nM; about 200 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, about 300 nM, or about 250 nM; about 250 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, about 350 nM, or about 300 nM; about 300 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, about 450 nM, about 400 nM, or about 350 nM; about 350 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, about 500 nM, or about 450 nM; about 450 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, about 550 nM, or about 500 nM; about 500 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about

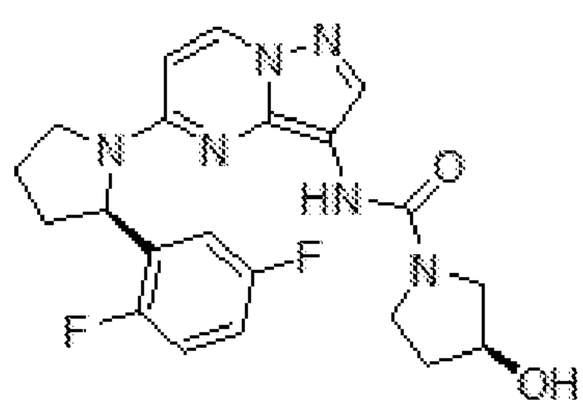
950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, about 600 nM, or about 550 nM; about 550 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, about 650 nM, or about 600 nM; about 600 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, about 700 nM, or about 650 nM; about 650 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, about 750 nM, or about 700 nM; about 700 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, about 800 nM, or about 750 nM; about 750 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, about 850 nM, or about 800 nM; about 800 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, about 900 nM, or about 850 nM; about 850 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, about 950 nM, or about 900 nM; about 900 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, about 1 μM, or about 950 nM; about 950 nM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, about 5 μM, or about 1 μM; about 1 μM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, about 10 μM, or about 5 μM; about 5 μM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, about 15 μM, or about 10 μM; about 10 μM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, about 20 μM, or about 15 μM; about 15 μM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, about 30 μM, about 25 μM, or about 20 μM; about 20 μM to about 50 μM,

about 45 μM, about 40 μM, about 35 μM, about 30 μM, or about 25 μM; about 25 μM to about 50 μM, about 45 μM, about 40 μM, about 35 μM, or about 30 μM; about 30 μM to about 50 μM, about 45 μM, about 40 μM, or about 35 μM; about 35 μM to about 50 μM, about 45 μM, or about 40 μM; about 40 μM to about 50 μM or about 45 μM; or about 45 μM to about 50 μM. In some embodiments, the Trk inhibitor also inhibits one or both of TrkB and TrkC, in addition to TrkA.

A Trk inhibitor can bind to one or more of the sites on TrkA: the extracellular cysteine-rich region (domain 1), the extracellular leucine rich region (domain 2), the extracellular cysteine-rich region (domain 3), the extracellular immunoglobulin-like region (domain 4), the extracellular immunoglobulin-like region (domain 5), the transmembrane region, the intracellular kinase domain, an amino acid in the active site, the ATP-binding pocket, the tyrosine substrate binding site, the activation loop (e.g., the DFG motif of the activation loop), the kinase insert domain (KID) region (e.g., amino acids 603 to 623), the hinge region of the kinase, the α-C helix in the catalytic domain, the N-lobe lysine responsible for the stabilization of the α phosphate of the ATP substrate, the C-terminus (see, e.g., Bertrand et al., *J. Mol. Biol.* 423:439-453, 2012), the α-D helix in the C-terminus, the α-E helix in the C-terminus, an amino acid in the kinase domain that interacts with a ligand in the ATP binding site (see, e.g., Cherry et al., *Curr. Med. Chem.* 11:663-673, 2004). For example, a Trk inhibitor can bind to domain 5 or the intracellular kinase domain of a TrkA.

Non-limiting examples of Trk inhibitors are described below.

An example of a Trk inhibitor is a (e.g., crystalline form of, a liquid formulation including) the compound of Formula I:



I

or a pharmaceutically acceptable salt thereof. Another example of a Trk inhibitor is a crystalline form including the hydrogen sulfate salt of the compound of Formula I in a stable polymorph form, referred to as crystalline form (Formula I-HS), which may be

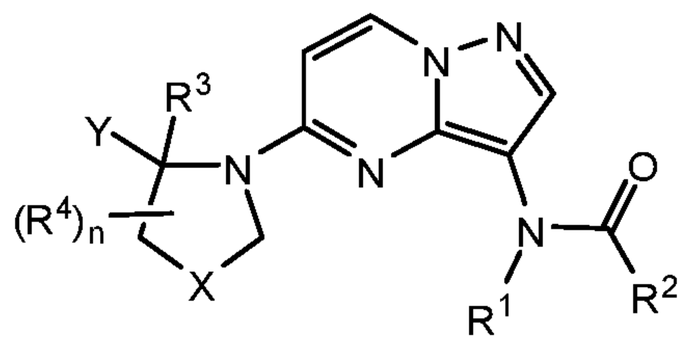
characterized, for example, by its X-ray diffraction pattern (see, U.S. Patent Application Serial Nos. 62/080,374 and 14/943,014, both of which are herein incorporated by reference in their entirety). Additional physical properties of a Trk inhibitor of Formula I and methods of making a Trk inhibitor of Formula I are described in U.S. Patent Application Serial Nos. 62/080,374 and 14/943,014 (both of which are herein incorporated by reference in its their entirety). In some embodiments, the compound of Formula I is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate or a polymorph thereof.

In some embodiments, crystalline form (I-HS) is characterized by having XRPD diffraction peaks (2θ degrees) at 18.4±0.2, 20.7±0.2, 23.1±0.2, and 24.0±0.2. In some embodiments, crystalline form (I-HS) is characterized by having XRPD diffraction peaks (2θ degrees) at 10.7±0.2, 18.4±0.2, 20.7±0.2, 23.1±0.2, and 24.0±0.2. In some embodiments, crystalline form (I-HS) is characterized by having XRPD diffraction peaks (2θ degrees) at 10.7±0.2, 18.4±0.2, 19.2±0.2, 20.2±0.2, 20.7±0.2, 21.5±0.2, 23.1±0.2, and 24.0±0.2. In some embodiments, crystalline form (I-HS) is characterized by having XRPD diffraction peaks (2θ degrees) at 10.7±0.2, 15.3±0.2, 16.5±0.2, 18.4±0.2, 19.2±0.2, 19.9±0.2, 20.2±0.2, 20.7±0.2, 21.5±0.2, 22.1±0.2, 23.1±0.2, 24.0±0.2. 24.4±0.2, 25.6±0.2, 26.5±0.2, 27.6±0.2, 28.2±0.2, 28.7±0.2, 30.8±0.2, and 38.5±0.2.

In some embodiments, the crystalline form exhibits an onset to maximum of about 193 to about 205 ° Celsius, as measured by differential scanning calorimetry. In some embodiments, the crystalline form (I-HS) exhibits a heat of melting of about 2.415 mW, as measured by differential scanning calorimetry.

In some embodiments, the Trk inhibitor is selected from the group consisting of: (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[l,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-l-carboxamide sulfate; (R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[l ,5-a]pyrimidine-3-carboxamide; (6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.17,11.02,6.020,24]pentacosa-1(23),7,9, 17(24), 18,21-hexaene-16,25-dione; and (6R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo [16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one.

Non-limiting examples of Trk inhibitors are described in U.S. Patent No. 8,513,263 and International Publication No. WO 2010/048314 both of which are incorporated by reference in their entireties herein, and include a compound of Formula I:



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or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or (1-6C alkyl);

R^2 is NR^bR^c, (1-4C)alkyl, (1-4C)fluoroalkyl, CF_3, (1-4C)hydroxyalkyl, -(1-4C alkyl)hetAr^1, -(1-4C alkyl)NH_2, -(1-4C alkyl)NH(1-4C alkyl), -(1-4C alkyl)N(1-4C alkyl)$_2$, hetAr^2, hetCyc^1, hetCyc^2, phenyl which is optionally substituted with $NHSO_2$(1-4C alkyl), or (3-6C)^{e}cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, OMe, NH_2, NHMe, $N(CH_3)_2$, F, CF_3, CO_2(1-4C alkyl), CO_2H, C(=O)NR^eR^f or C(=O)OR^g;

R^b is H or (1-6C alkyl);

R^c is H, (1-4C)alkyl, (1-4C)hydroxyalkyl, hetAr^3, or phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from halogen, CN, CF_3 and -O(1-4C alkyl),

or NR^bR^c forms a 4 membered heterocyclic ring having a ring nitrogen atom wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 C)alkoxy, -OC(=O)(1-4C alkyl), NH_2, -NHC(=O)O(1-4C alkyl) and (1-4C)hydroxyalkyl,

or NR^bR^c forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O and SO_2, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF_3, (1-4C)alkyl, CO_2(1-4C alkyl), CO_2H, NH_2, NHC(=O)O(1-4C alkyl) and oxo,

or NR^bR^c forms a 7-8 membered bridged heterocyclic ring having a ring nitrogen atom and optionally having a second ring heteroatom selected from N and O, wherein said ring is optionally substituted with CO_2(1-4C alkyl);

$hetAr^1$ is a 5-membered heteroaryl ring having 1-3 ring nitrogen atoms;

$hetAr^2$ is 5-6 membered heteroaryl ring having at least one nitrogen ring atom and optionally having a second ring heteroatom independently selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from (1-4C alkyl), halogen, -(1-4 C)alkoxy, and NH(1-4C alkyl);

$hetCyc^1$ is a carbon-linked 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-4C alkyl), and CO_2(1-4C alkyl);

$hetCyc^2$ is a pyridinone or pyridazinone ring which is optionally substituted with a substituent selected from (1-4C)alkyl;

$hetAr^3$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from (1-4C)alkyl;

R^e is H or (1-4C)alkyl;

R^f is H, (1-4C)alkyl, or (3-6C)cycloalkyl;

or NR^eR^f forms a 5-6-membered azacyclic ring optionally having an additional ring heteroatom selected from N and O, wherein the azacyclic ring is optionally substituted with OH;

R^g is H or (1-6C)alkyl;

Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF_3 and CHF_2, or (ii) a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms;

X is null, $-CH_2-$, $-CH_2CH_2-$, $-CH_2O-$ or $-CH_2NR^d-$;

R^d is H or (1-4C alkyl);

R^3 is H or (1-4C alkyl);

each R^4 is independently selected from halogen, (1-4C)alkyl, OH, (1-4C)alkoxy, NH_2, NH(1-4C alkyl) and CH_2OH; and

n is 0, 1, 2, 3, 4, 5 or 6.

For example, a Trk inhibitor can include one or more compounds selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

N-(5-(2-(3-fluorophenyl)-2-methylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-phenylurea;

(R)-N-(5-(2-(2-(difluoromethyl)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1-methyl-6-oxo-1,6-dihydropyridazine-3-carboxamide;

(S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide;

(3R,4R)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3,4-dihydroxypyrrolidine-1-carboxamide;

(S)-N-(5-((R)-2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-methylpiperazine-1-carboxamide;

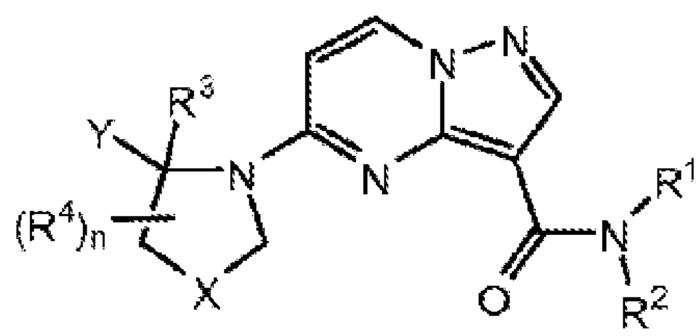
(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide; and

(R)-1-(4-chlorophenyl)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)urea,

or a pharmaceutically acceptable salt thereof.

Additional examples of Trk inhibitors are the substituted pyrazolo[1,5-a] pyrimidine compounds described in U.S. Patent No. 8,791,123 and International Publication No. WO 2011/006074, both of which are herein incorporated by reference in their entireties. For example, Trk inhibitors that are substituted pyrazolo[1,5-a]pyrimidine compounds can have the general formula II:



II

or a salt thereof, wherein:

R^1 is H or (1-6C alkyl);

R^2 is H, (1-6C)alkyl, -(1-6C)fluoroalkyl, -(1-6C)difluoroalkyl, -(1-6C)trifluoroalkyl, -(1-6C)chloroalkyl, -(2-6C)chlorofluoroalkyl, -(2-6C)difluorochloroalkyl, -(2-6C)chlorohydroxyalkyl, -(1-6C)hydroxyalkyl, -(2-6C)dihydroxyalkyl, -(1-6C alkyl)CN, -(1-6C alkyl)SO_2NH_2, -(1-6C alkyl)$NHSO_2$(1-3C alkyl), -(1-6C alkyl)NH_2, -(1-6C alkyl)NH(1-4C alkyl), -(1-6C alkyl)N(1-4C alkyl)$_2$, -(1-6C alkyl)NHC(=O)O(1-4C alkyl), -(1-6C alkyl)hetCyc^1, -(1-6C alkyl)hetAr^1, hetAr^2, hetCyc^2, -O(1-6C alkyl) which is optionally substituted with halogen, OH or (1-4C)alkoxy, -O(3-6C cycloalkyl) , Cyc^1, -(1-6C alkyl)(3-6C cycloalkyl) , -(1-6C alkyl)(1-4C alkoxy), -(1-6C hydroxyalkyl)(1-4C alkoxy), a bridged 7 -membered cycloalkyl ring optionally substituted with (1-6C)hydroxyalkyl, or a bridged 7-8 membered heterocyclic ring having 1-2 ring nitrogen atoms;

or NR^1R^2 forms a 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, OH, CO_2H, (1-3C alkyl)CO_2H, -O(1-6C alkyl), and (1-6C)hydroxyalkyl;

hetCyc^1 is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein hetCyc^1 is optionally substituted with oxo, OH, halogen, or (1-6C)alkyl;

hetCyc^2 is a 6 membered carbon-linked heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O, wherein hetCyc^2 is optionally substituted with F, SO_2NH_2, SO_2(1-3C alkyl), or halogen;

hetAr^1 is a 5-membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-4C)alkyl;

hetAr^2 is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms and optionally substituted with one or more substituents independently selected from (1-4C)alkyl, (3-6C)cycloalkyl, halogen, and OH;

Cyc^1 is a 3-6 membered cycloalkyl ring which is optionally substituted with one or

more substituents independently selected from -(1-4C alkyl), -OH, -OMe, $-CO_2H$, -(1-4C alkyl)OH, halogen, and CF_3;

Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, $-CF_3$, $-CHF_2$, -O(1-4C alkyl)$hetCyc^3$, -(l-4C alkyl)$hetCyc^3$, -O(1-4C alkyl)O(1-3C alkyl) and -O(3-6C dihydroxyalkyl), or (ii) a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein the heteroaryl ring is optionally substituted with one or more substituents independently selected from halogen, -O(1-4C alkyl), (1-4C)alkyl, and NH_2, or (iii) a pyrid-2-on-3-yl ring optionally substituted with one or more substituents independently selected from halogen and (1-4C)alkyl;

$hetCyc^3$ is a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with (1-6C)alkyl;

X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2O-$, or $-CH_2NR^d-$;

R^d is H or -(l-4C alkyl);

R^3 is H or -(l-4C alkyl);

each R^4 is independently selected from halogen, -(1-4C)alkyl, -OH, -(1-4C)alkoxy, -NH2, -NH(1-4C alkyl), and $-CH_2OH$; and

n is 0, 1, 2, 3, 4, 5, or 6.

For example, a Trk inhibitor can include one or more compounds selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((2S)-bicyclo[2.2.1]heptan-2-yl)-5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(2-oxoimidazolidin-1-yl)ethyl)pyrazole[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N—((R)-2,3-dihydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

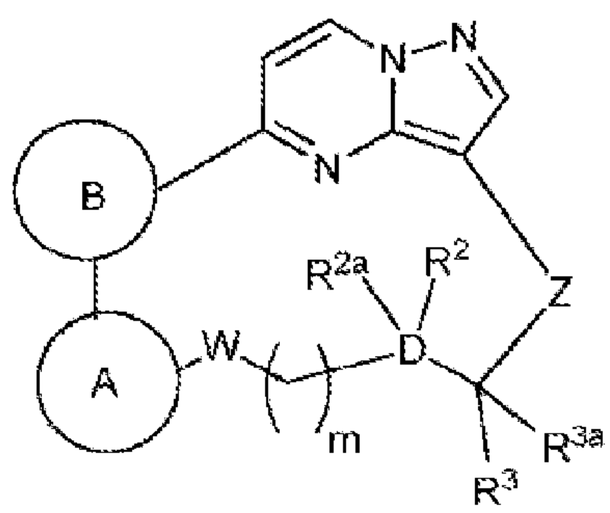
(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclobutyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide; and

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N—((S)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

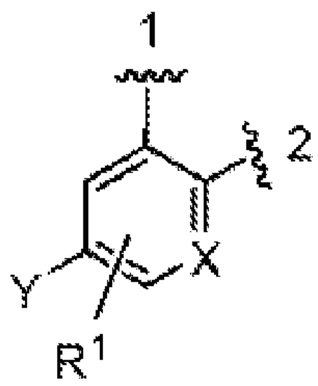
Additional examples of Trk inhibitors are the macrocyclic compounds described in U.S. Patent No. 8,933,084 and International Publication No. WO 2011/146336, both of which are herein incorporated by reference in their entireties. For example, Trk inhibitors that are macrocyclic compounds can have the general formula III:



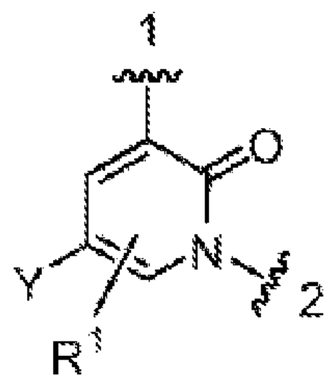
III ,

or a pharmaceutically acceptable salt thereof, wherein:

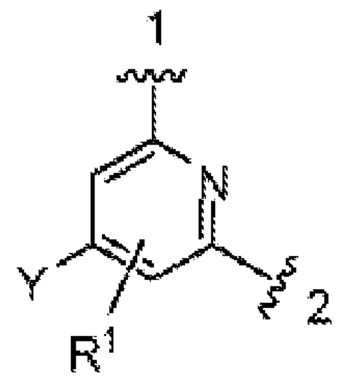
ring A is selected from rings A-I, A-2, and A-3 having the structures:



A-1



A-2



A-3

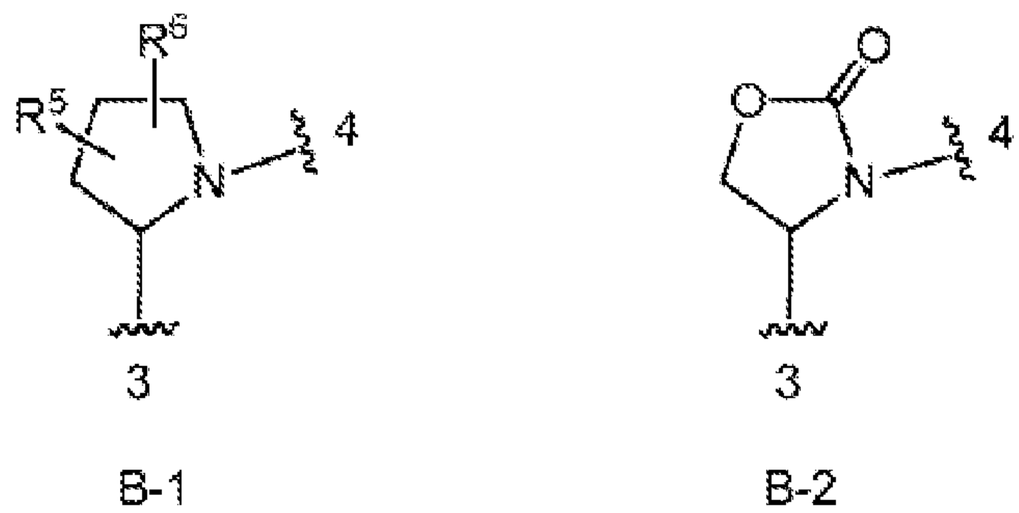
wherein the wavy line labeled 1 indicates the point of attachment of ring A to ring B and the wavy line labeled 2 indicates the point of attachment of ring A to W;

X is N or CH;

Y is H or F;

R^1 is H, (1-3C)alkoxy, or halogen;

ring B is selected from rings B-1 and B-2 having the structures:



wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy line labeled 4 indicates the point of attachment to the pyrazolo[I,5-a]pyrimidine ring of Formula III;

W is O, NH, or CH_2, wherein when ring A is A-2, then W is CH_2;

m is 0, 1, or 2;

D is carbon, R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH (provided that R^2 and R^{2a} are not both OH), and R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl, or

D is carbon or nitrogen, R^2 and R^3 are absent, and R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms;

Z is *-NR^{4a}C(=O)-, *-ONHC(=O)-, *-$NR^{4b}CH_2$- or *-OC(=O)-, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R^3;

R^{4a} is H, (I-6C)alkyl, fluoro(I-6C)alkyl, difluoro(I-6C)alkyl, trifluoro(I-6C)alkyl, hydroxy(1-6C alkyl), or dihydroxy(2-6C alkyl);

R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl), dihydroxy(2-6C alkyl), (1-6C alkyl)C(O)-, (3-6C cycloalkyl)C(O)-, Ar^1C(O)-, $HOCH_2$C(O)-, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$-, HO_2CCH_2-, or (1-6C alkyl)NH(CO)-;

Ar^1 is phenyl optionally substituted with one or more substituents independently

selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy;

Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl, or hydroxy(1-6C)alkyl.

For example, a Trk inhibitor can include one or more compounds selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*,15*R*)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-13-oxa-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7, 9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6*R*,13*S*)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo [15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-9-fluoro-2,11,13,16,20,21,24-heptaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-2,11,13,17,21,22,25-heptaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-17-methyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9-fluoro-(15R)-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

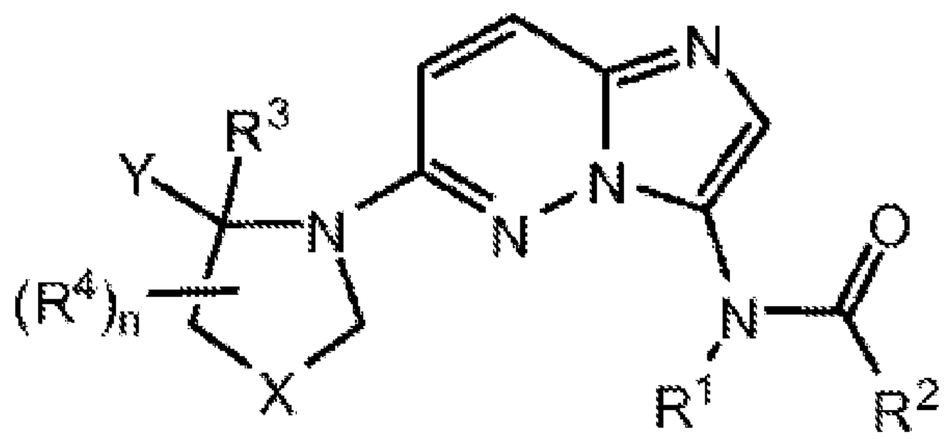
(6*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo [17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one; and

(6*R*)-9-fluoro-15,15-dimethyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

Additional examples of Trk inhibitors are the substituted imidazo[1,2-b]pyridazine compounds described in U.S. Patent No. 8,450,322 and International Publication No. WO 2010/033941, both of which are herein incorporated by reference in their entireties. For example, Trk inhibitors that are substituted imidazo[1,2B]pyridazine compounds can have the general formu



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IV

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or (1-6C alkyl);

R^2 is NR^bR^c, (1-4C)alkyl, (1-4C)fluoroalkyl, CF_3, (1-4C)hydroxyalkyl, -(l-4C alkyl)$hetAr^1$, -(1-4C alkyl)NH(1-4C alkyl), $hetAr^2$, $hetCyc^1$, $hetCyc^2$, phenyl which is optionally substituted with $NHSO_2$(1-4C alkyl), or (3-6C)cycloalkyl which is optionally substituted with (1-4C alkyl), CN, OH, CF_3, CO_2(1-4C alkyl) or CO_2H;

R^b is H or (1-6C alkyl);

R^c is H, (1-4C)alkyl, (1-4C)hydroxyalkyl, $hetAr^3$, or phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from halogen, CN, CF_3 and -O(1-4C alkyl),

or NR^bR^c forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 C)alkoxy, -OC(=O)(1-4C alkyl), NH_2, -NHC(=O)O(1-4C alkyl), and (1-4C)hydroxyalkyl,

or NR^bR^c forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O, and SO_2, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF_3, (1-4C)alkyl, CO_2(1-4C alkyl), CO_2H, NH_2, NHC(=O)O(1-4C alkyl), and oxo,

or NR^bR^c forms a 7-8 membered bridged heterocyclic ring having 1-2 ring nitrogen atoms and optionally substituted with CO_2(1-4C alkyl);

$hetAr^1$ is a 5-membered heteroaryl ring having 1-3 ring nitrogen atoms;

$hetAr^2$ is 5-6 membered heteroaryl ring having at least one nitrogen ring atom and optionally having a second ring heteroatom independently selected from Nand S, wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from (1-4C alkyl), halogen, -(1-4 C)alkoxy, and NH(1-4C alkyl);

$hetCyc^1$ is a carbon-linked 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-4C alkyl), CO_2H and CO_2(1-4C alkyl);

$hetCyc^2$ is a pyridinone or pyridazinone ring substituted with a substituent selected from (1-4C)alkyl;

$hetAr^3$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms

independently selected from N and O and optionally substituted with one or more substituents independently selected from (1-4C)alkyl;

Y is a phenyl ring optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF_3 and CHF_2, or a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S;

X is null, $-CH_2-$, $-CH_2CH_2-$, $-CH_2O-$, or $-CH_2NR^d-$;

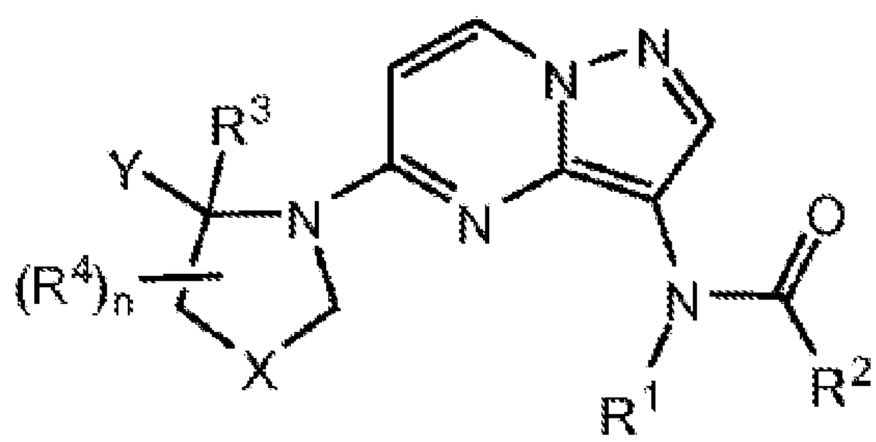
R^d is H or (1-4C alkyl);

R^3 is H or (1-4C alkyl);

each R^4 is independently selected from halogen, (1-4C)alkyl, OH, (1-4 C)alkoxy, NH_2, NH(1-4C alkyl), and CH_2OH; and

n is 0, 1, 2, 3, 4, 5, or 6.

Additional examples of Trk inhibitors are the substituted pyrazolo[1,5-a]pyrimidine compounds described in WO 10/048314, herein incorporated by reference in its entirety. For example, Trk inhibitors that are substituted pyrazolo[1,5-a]pyrimidine compounds can have the general formula V:



,

V

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or (1-6C alkyl);

R^2 is NR^bR^c, (1-4C)alkyl, (1-4C)fluoroalkyl, CF_3, (1-4C)hydroxyalkyl, -(l-4C alkyl)$hetAr^1$, -(1-4C alkyl)NH_2, -(l-4C alkyl)NH(1-4C alkyl), -(1-4C alkyl)N(1-4C alkyl)$_2$, $hetAr^2$, $hetCyc^1$, $hetCyc^2$, phenyl which is optionally substituted with $NHSO_2$(1-4C alkyl), or (3-6C)cycloalkyl which is optionally substituted with (l-4C alkyl), CN, OH, OMe, NH_2, NHMe, $N(CH_3)_2$, F, CF_3, CO_2(1-4C alkyl), CO_2H, $C(=O)NR^eR^f$ or $C(=O)OR^g$;

R^b is H or (1-6C alkyl);

R^c is H, (1-4C)alkyl, (1-4C)hydroxyalkyl, $hetAr^3$, or phenyl, wherein said phenyl is optionally substituted with one or more substituents independently selected from halogen, CN, CF_3, and -O(1-4C alkyl),

or NR^bR^c forms a 4 membered heterocyclic ring having a ring nitrogen atom, wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from halogen, OH, (1-4C alkyl), (1-4 C)alkoxy, -OC(=O)(1-4C alkyl), NH_2, -NHC(=O)O(1-4C alkyl), and (1-4C)hydroxyalkyl,

or NR^bR^c forms a 5-6 membered heterocyclic ring having a ring heteroatom which is nitrogen and optionally having a second ring heteroatom or group selected from N, O, and SO_2, wherein the heterocyclic ring is optionally substituted with one or more substituents independently selected from OH, halogen, CF_3, (1-4C)alkyl, CO_2(1-4C alkyl), CO_2H, NH_2, NHC(=O)O(1-4C alkyl), and oxo,

or NR^bR^c forms a 7-8 membered bridged heterocyclic ring having a ring nitrogen atom and optionally having a second ring heteroatom selected from N and O, wherein the ring is optionally substituted with CO_2(1-4C alkyl);

$hetAr^1$ is a 5-membered heteroaryl ring having 1-3 ring nitrogen atoms;

$hetAr^2$ is 5-6 membered heteroaryl ring having at least one nitrogen ring atom and optionally having a second ring heteroatom independently selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more substituents independently selected from (1-4C alkyl), halogen, -(1-4 C)alkoxy and NH(1-4C alkyl);

$hetCyc^1$ is a carbon-linked 4-6 membered azacyclic ring optionally substituted with one or more substituents independently selected from (1-4C alkyl) and CO_2(1-4C alkyl);

$hetCyc^2$ is a pyridinone or pyridazinone ring which is optionally substituted with a substituent selected from (1-4C)alkyl;

$hetAr^3$ is a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from (1-4C)alkyl;

R^e is H or (1-4C)alkyl;

R^f is H, (1-4C)alkyl, or (3-6C)cycloalkyl;

or NR^eR^f forms a 4-6-membered azacyclic ring optionally having an additional ring heteroatom selected from N and O, wherein the azacyclic ring is optionally substituted with OH;

R^g is H or (1-6C)alkyl;

Y is (i) phenyl optionally substituted with one or more substituents independently selected from halogen, (1-4C)alkoxy, CF_3, and CHF_2, or (ii) a 5-6 membered heteroaryl ring having a ring heteroatom selected from N and S, wherein said heteroaryl ring is optionally substituted with one or more halogen atoms;

X is null, $-CH_2-$, $-CH_2CH_2-$, $-CH_2O-$, or $-CH_2NR^d-$;

R^d is H or (1-4C alkyl);

R^3 is H or (1-4C alkyl);

each R^4 is independently selected from halogen, (1-4C)alkyl, OH, (1-4 C)alkoxy, NH_2, NH(1-4C alkyl), and CH_2OH; and

n is 0, 1, 2, 3, 4, 5, or 6.

For example, a Trk inhibitor can include one or more compounds selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((2S)-bicyclo[2.2.1]heptan-2-yl)-5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(2-oxoimidazolidin-1-yl)ethyl)pyrazole[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N—((R)-2,3-dihydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

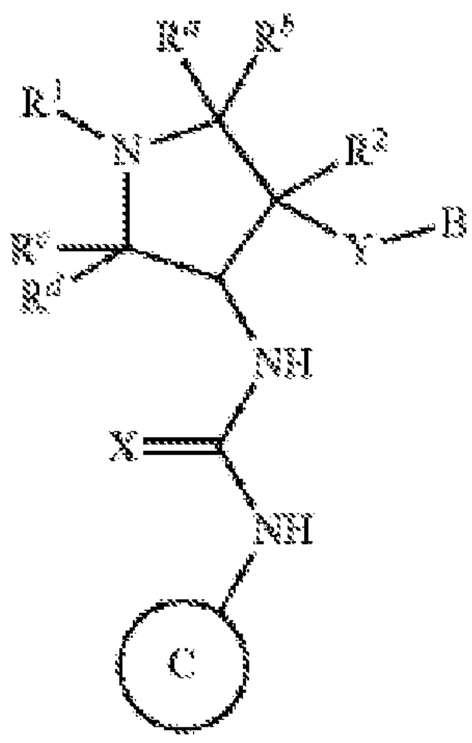
(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclobutyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide; and

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N—((S)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

Additional Trk inhibitors can be found in U.S. Publication No. 2015/0166564 and WO 2012/158413, both of which are incorporated by reference in their entireties herein. For example, a Trk inhibitor can be a compound of Formula I:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

the Y—B moiety and the NH—C(=X)—NH moiety are in the trans configuration;

R^a, R^b, R^c and R^d are independently selected from H and (1-3C)alkyl;

X is O, S or NH;

R^1 is (1-3C alkoxy)(1-6C)alkyl, (trifluoromethoxy)(1-6C)alkyl, (1-3C sulfanyl)(1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-6C)alkyl, (1-3Calkylamino)(1-3C)alkyl, (1-4C alkoxycarbonyl)(1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-3C alkoxy)(1-6C)alkyl, di(1-3C

alkoxy)(1-6C)alkyl, (1-3C alkoxy)trifluoro(1-6C)alkyl, hydroxytrifluoro(1-6C)alkyl, (1-4C alkoxycarbonyl)(1-3C alkoxy)(1-6C)alkyl, hydroxycarbonyl(1-3C alkoxy)(1-6C)alkyl, $hetAr^5(CH_2)_{0-1}$, or $Ar^5(CH_2)_{0-1}$;

R^2 is H, F, or OH;

Y is a bond, —O— or —OCH_2—;

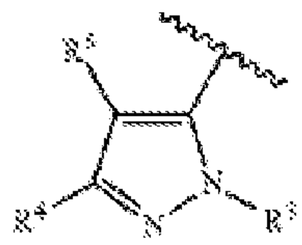
B is Ar^1, $hetAr^1$, 1-6C alkyl or (1-6C)alkoxy;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, CF_3, CF_3O—, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-6C)alkyl and CN;

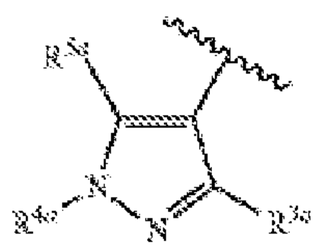
$hetAr^1$ is a 5-6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, S and O, and optionally substituted with 1-2 groups independently selected form (1-6C)alkyl, halogen, OH, CF_3, NH_2 and hydroxy(1-2C)alkyl;

Ring C is formula C-1, C-2, or C-3

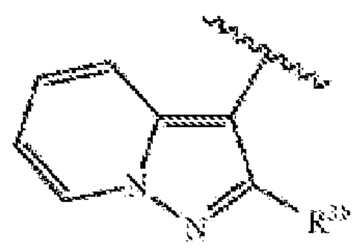
C-1



C-3



C-3



R^3 is H, (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, or $hetAr^2$;

Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and hydroxymethyl;

$hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

R^4 is H, OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, amino-carbonyl(1-6C)alkyl, (1-3C)alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl, hydroxyl-carbonyl(1-6C)alkyl, $hetAr^3$(1-6C)alkyl, Ar^3(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, $hetCyc^2$(1-6C)alkoxy, $hetAr^3$(1-6C)alkoxy, Ar^3(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], $hetAr^4$, Ar^4, $hetCyc^2(O)CH_2$—, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, $hetCyc^2C(=O)$(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)aminocarboxy, $hetCyc^2C(=O)O$—, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxycarbonyl, hydroxycarbonyl, aminocarbonyl, (1-3C alkoxy)amino-carbonyl, $hetCyc^3$, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)pyridinonyl, N-(1-3C trifluoroalkyl)pyridinonyl, (1-4C alkylsiloxy)(1-6C)alkoxy, isoindoline-1,3-dionyl(1-6C)alkoxy or N-(1-3C alkyl)oxadiazolonyl;

$hetCyc^2$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, and (1-6C)acyl;

$hetCyc^3$ is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, CF_3, (1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)acyl-, (1-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

$hetAr^3$ is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (1-6C)alkyl;

Ar^3 is phenyl optionally substituted with (1-4C)alkoxy;

$hetAr^4$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2— (3-6C cycloalkyl)C(=O)—, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), (1-3C)trifluoroalkyl, and methoxybenzyl; or a 9-10 membered bicyclic heteroaryl having 1-3 ring nitrogen atoms;

Ar^4 is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF_3, CF_3O—, (1-6C)alkoxy, (1-6Calkyl)OC(=O)—, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO_2—, HOC(=O)— and (1-3C alkoxy)(1-3C alkyl)OC(=O)—;

R^5 is H, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)—, (1-6C)alkylthio, phenyl [optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy], (3-4C)cycloalkyl, amino, aminocarbonyl, or trifluoro(1-3C alky)amido; or

R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or

R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)O—, (1-6)acyl, (1-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2;

$hetAr^5$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O or S, wherein the ring is optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, (1-6C)alkoxy and CF_3;

Ar^5 is phenyl optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl, (1-6C)alkoxy, CF_3O—, (1-4C)alkoxycarbonyl and aminocarbonyl;

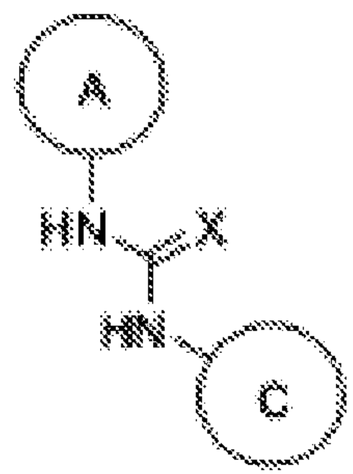
R^{3a} is hydrogen, halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl and hydroxymethyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

R^{3b} is hydrogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl and hydroxymethyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

R^{4a} is hydrogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF_3, CF_3O—, (1-6C)alkoxy, (1-6Calkyl)OC(=O)—, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO_2—, HOC(=O)— and (1-3C alkoxy)(1-3C alkyl)OC(=O)—], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (1-6C)alkyl, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2— (3-6C cycloalkyl)C(=O)—, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy)(1-3C)trifluoroalkyl, and methoxybenzyl; and

R^{5a} is hydrogen, halogen, (1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl and hydroxymethyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen.

Further examples of Trk inhibitors can be found in International Publication No. WO 2014078454, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I:

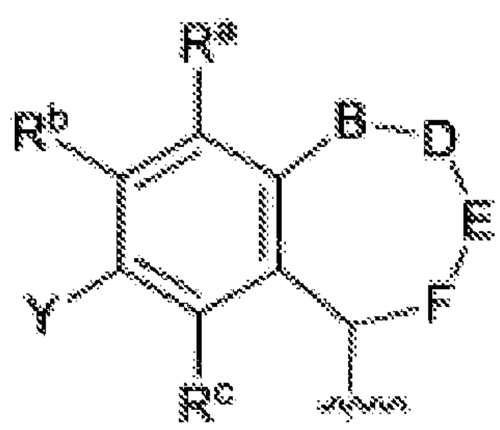


I

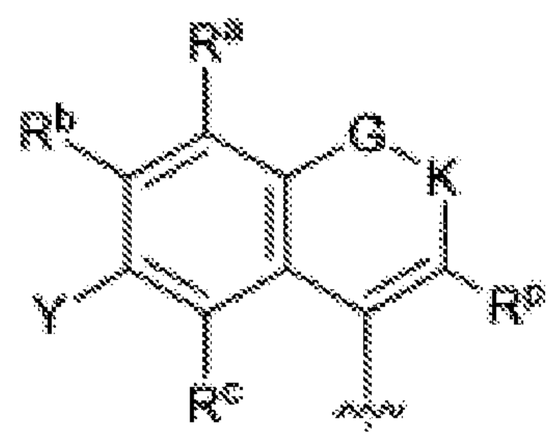
or stereoisomers, tautomers, or pharmaceutically acceptable salts, or solvates thereof, wherein:

X is O, S, NH or N-CN;

Ring A is formula A-1 or A-2



A-1



A-2

Y is H, halogen, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkyl [optionally substituted with 1-5 fluoros], cyano(l-6C)alkyl, hydroxy(l-6C)alkyl, dihydroxy(2-6C)alkyl, aminocarbonyl(l- 6C)alkyl, (l-6C)alkoxy [optionally substituted with 1-5 fluoros], CN, aminocarbonyl or (1-4C alkoxy)carbonyl ;

R^a, R^b and R^c are independently selected from H, halogen, (l-3C)alkyl, (l-3C)alkoxy and CN;

B is NR^1, O, a bond, CR^dR^e, S or SO_2;

D is NR^1, O, a bond, CR^fR^8, S or SO_2;

E is NR^1, O, a bond, or CR^hR\ S or SO_2;

F is CR^jR^k;

provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and zero or one of B, D or E is NR^1 or O;

G is CR^mR^n;

K is NR^1; R^1 is (l-6C)alkyl [optionally substituted with one to five fluoros], (l-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (l-6C)alkylC(=O)- or (1-6C alkoxy)C=O-;

R^d, R^e, R^f, R^g, R^h, R\ R^j and R^k are independently H, OH, (l-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2- 6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (l-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

or one of a pair of R^d and R^e, or R^f and R^8, or R^h and R^1, or R* and R^k, together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidinyl ring, or one of a pair of R^d and R^e, or $R^f$and R^8, or R^h and R^1, or R^j and R^k form an oxo group,

and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^8 can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R' can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

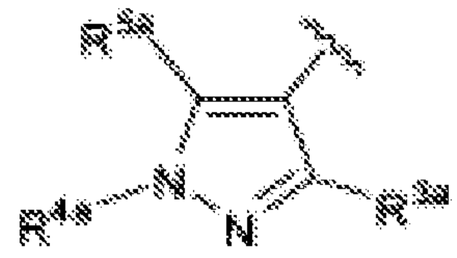
R^m is H, (l-3C)alkyl [optionally substituted with 1-5 fluoros], cyclopropyl or cyclobutyl, and R" is H or (l-3C)alkyl [optionally substituted with 1-5 fluoros], or

R^m and R^n together form an oxo group;

R^p is H, (l-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl;

Ring C is formula C-l or C-2

C-1



C-2

R^3 is (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, or $hetAr^2$;

Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen and (1-6C)alkyl; $hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1- 2 ring heteroatoms independently selected from N and O;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

R^4 is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3 C)alkylsulfonamido(1 -6C)alkyl, sulfamido(1 -6C)alkyl, hydroxycarbonyl(1 -6C)alkyl, $hetAr^3$(1-6C)alkyl, Ar^3(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1- 6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(1- 6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl- carbonyl(1-6C)alkoxy, $hetCyc^2$(1-6C)alkoxy, $hetAr^3$(1-6C)alkoxy, Ar^3(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], $hetAr^4$, $hetAr^4$-0-, Ar^4, $hetCyc^2(O)CH_2$-, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1- 6C)alkoxy, aminocarbonyl(1-6C)alkoxy, $hetCyc^2C(=O)$(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1- 6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1- 3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, $hetCyc^2C(=O)$0-, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, $hetCyc^3$, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, $hetAr^5$ or $hetCyc^4$-0-;

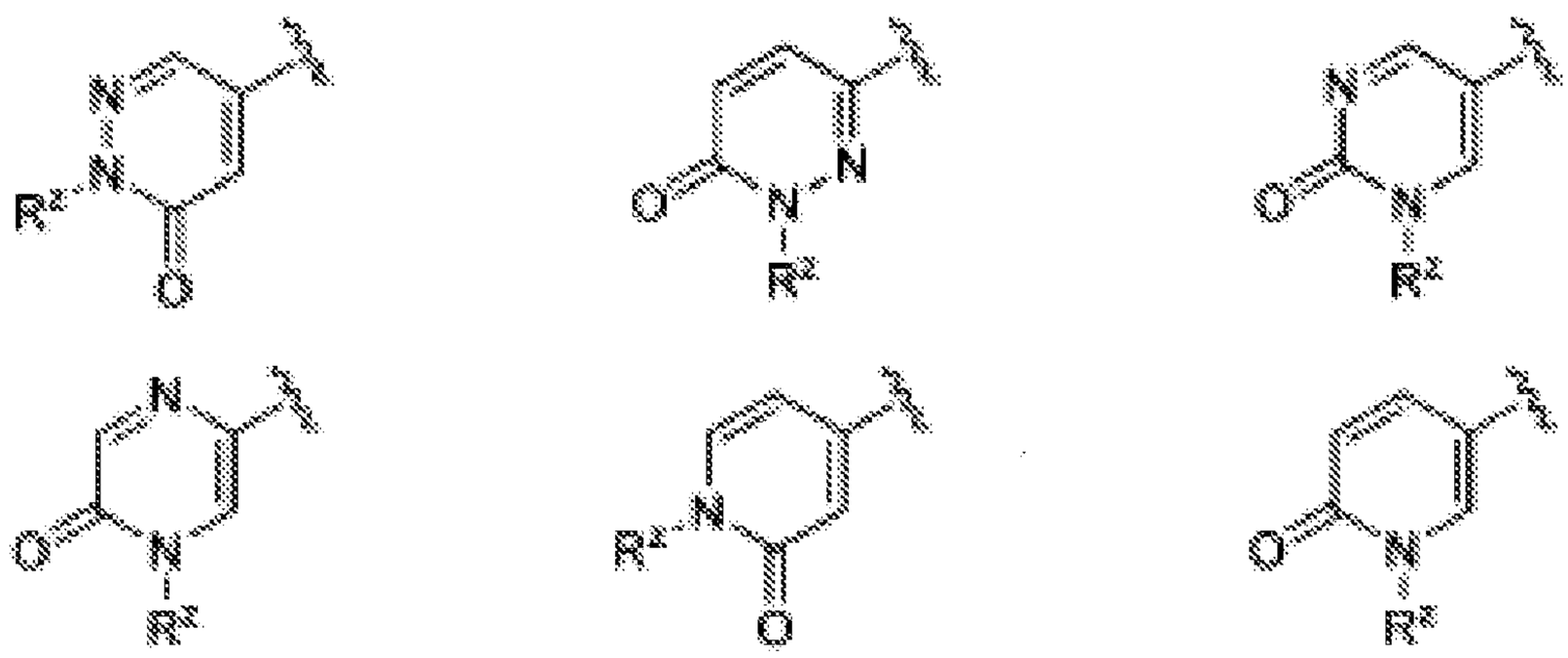
hetCyc is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, and (l-6C)acyl;

hetCyc^3 is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (l-6C)alkyl, trifluoro(l-6C)alkyl, hydroxy(l-6C)alkyl, (1-3C alkoxy)(l- 6C)alkyl, (l-6C)acyl-, (l-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl; hetAr^{3}is a 5 -membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (l-6C)alkyl;

Ar^3 is phenyl optionally substituted with (l-4C)alkoxy;

hetAr^4 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, difluoro(l- 6C)alkyl, fluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(l-6C alkyl)amino, difluoro(l-6C alkyl)amino, trifluoro(l-6C alkyl)amino, and (3-4C cycloalkyl)amino;

hetAr^5 is a group selected from the structures:



where R^z is (3-4C)cycloalkyl or (l-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr^5 groups is optionally further substituted with one or more groups independently selected from F and (l-3C)alkyl optionally substituted with 1-3 fluoros;

hetCyc^4 is a 7-8 membered bridged heterocycle having a ring nitrogen atom and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

Ar^4 is phenyl optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, $CF_3$0-, (l-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-;

R^5 is (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (l-4C)alkoxy, hydroxy(l- 4C)alkyl, (1-3C alkoxy)(l-4C)alkyl, (1-4C alkyl)OC(=O)-, (l-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(l-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (l-6C)alkyl and (l-6C)alkoxy); or

R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (l-6C)alkyl, or

R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)0-, (l-6C)acyl, (l-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2;

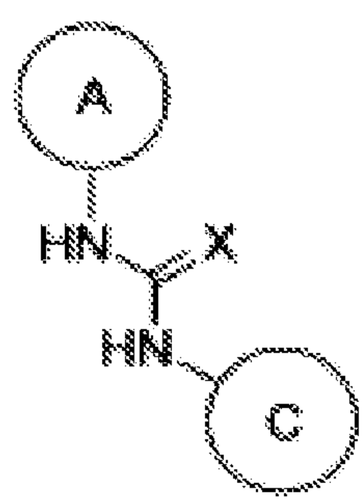
R^{3a} is halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1- 6C)alkyl and halogen;

R^{4a} is hydrogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, $CF_3$0-, (1-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from

N, S and O and optionally substituted with 1-2 substituents independently selected from (l-6C)alkyl, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino and (1-3C trifluoroalkoxy)(l-3C)trifluoroalkyl; and

R^{5a} is halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1- 6C)alkyl and halogen.

Further examples of Trk inhibitors can be found in International Publication No. WO 2014078417, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I:

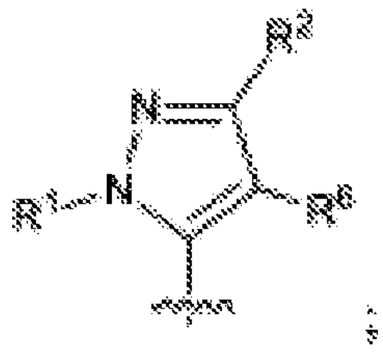


I

or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

X is O, S, NH or N-CN;

Ring A is

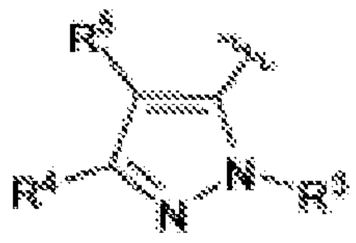


R^1 is phenyl optionally substituted with one or more substituents independently selected from halogen and (l-3C)alkyl;

R^2 is (l-3C)alkyl [optionally substituted with 1 to 5 fluoros] or (3-4C)cycloalkyl [optionally substituted with one or two fluoros];

R^6 is H or CH_3;

Ring C is formula C-l or C-2



C-1

C-2

R^3 is (l-6C)alkyl, hydroxy(l-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, or $hetAr^2$;

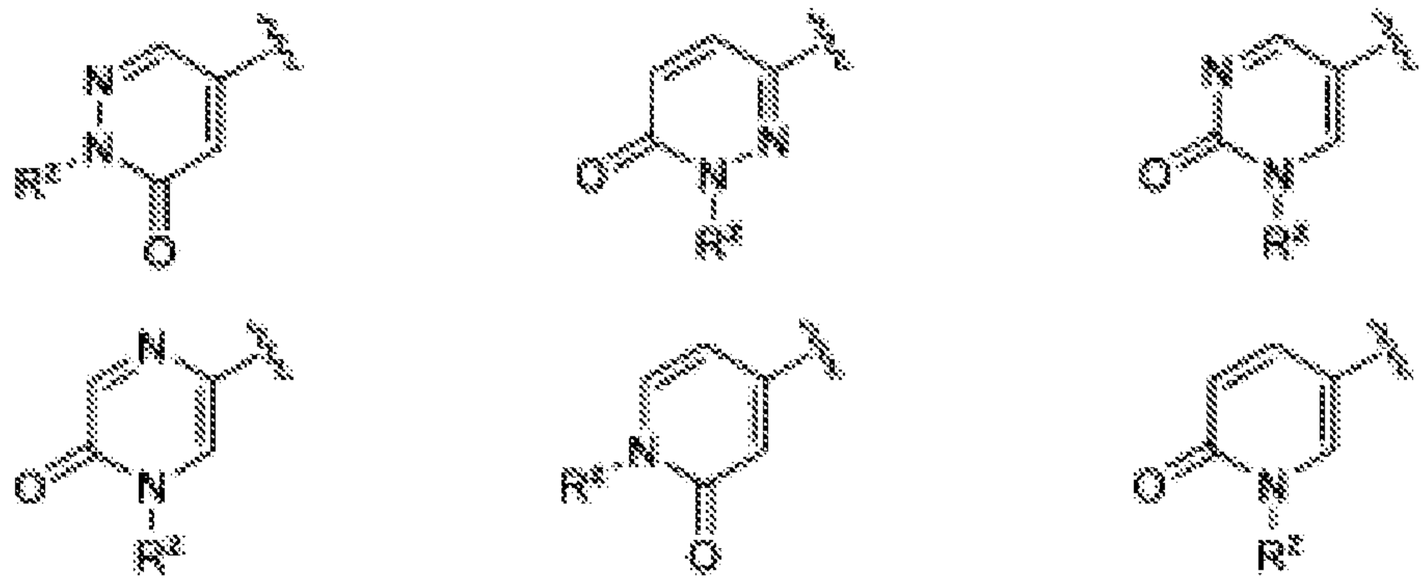
Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl;

$hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from (l-6C)alkyl and halogen; R^4 is $hetAr^4$, $hetAr^5$ or hydroxy(l-6C)alkoxy;

$hetAr^4$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, difluoro(l-6C)alkyl, fluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1- 6C alkyl)amino, di(l-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(l-6C alkyl)amino, difluoro(l-6C alkyl)amino, trifluoro(l-6C alkyl)amino, and (3-4C cycloalkyl)amino;

$hetAr^5$ is a group selected from the structures:



where R^z is (3-4C)cycloalkyl or (l-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said $hetAr^5$ groups is optionally further substituted with one or more substituents independently selected from F and (l-3C)alkyl optionally substituted with 1-3 fluoros;

R^5 is (l-6C)alkyl, monofiuoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (l-4C)alkoxy, hydroxy(l-4C)alkyl, (1-3C alkoxy)(l-4C)alkyl, (1-4C alkyl)OC(=O)-, (l-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(l-3C alkyl)amido, or phenyl (optionally substituted with one or more substituents independently selected from halogen, (l-6C)alkyl and (l-6C)alkoxy); or

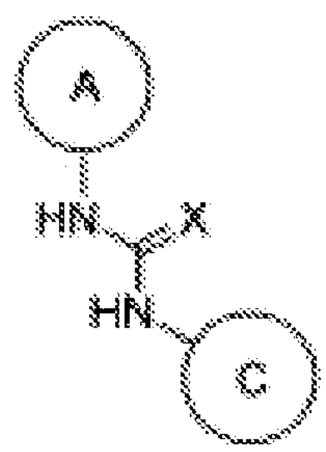
R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (l-6C)alkyl, or

R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)0-, (l-6C)acyl, (l-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2; R is hydrogen, halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from (l-6C)alkyl and halogen;

R^{4a} is hydrogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, phenyl [optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF3O-, (l-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)a!kylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (l-6C)alkyl, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1- 6C alkyl)amino, di(l-6C alkyl)amino and (1-3C trifluoroalkoxy)(l-3C)trifluoroalkyl; and

R^{5a} is hydrogen, halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from (l-6C)alkyl and halogen.

Additional examples of Trk inhibitors can be found in International Publication No. WO 2014078408, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I:

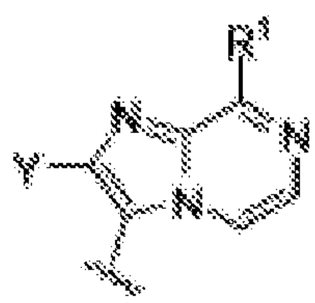


I

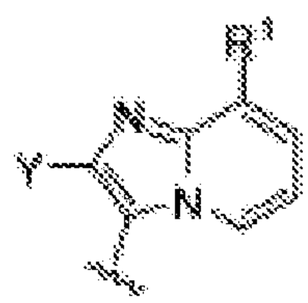
or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

X is O, S, NH or -N-CN;

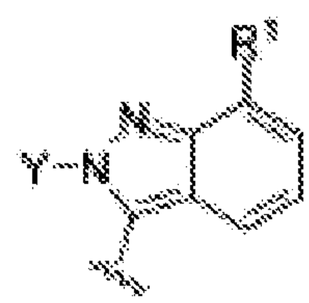
Ring A is formula A-1 A-2, A-3 or A-4



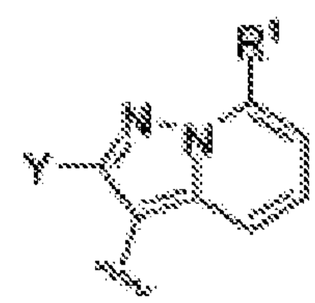
A-1



A-2



A-3



A-4

R^1 is H, halogen, (l-3C)alkyl [optionally substituted with 1-5 fluoros], (1- 3C)alkoxy [optionally substituted with 1-5 fluoros], or (3-5C)cycloalkyl;

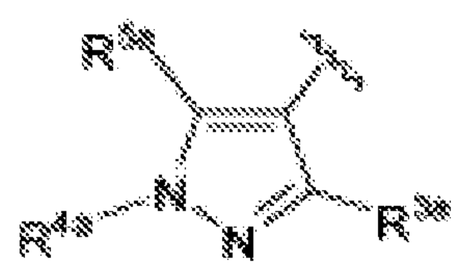
Y is Ar^1 or $hetAr^1$;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, (l-3C)alkyl [optionally substituted with 1-5 fluoros], and (1-3C)alkoxy [optionally substituted with 1-5 fluoros];

$hetAr^1$ is pyridyl optionally substituted with one or more substituents independently selected from halogen, (l-3C)alkyl [optionally substituted with 1-5 fluoros], and (l-3C)alkoxy [optionally substituted with 1-5 fluoros];

Ring C is formula C-l or C-2

C-1



C-2

R^3 is (l-6C)alkyl, hydroxy(l-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, or $hetAr^2$; Ar is phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl; $hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from (l-6C)alkyl and halogen;

R^4 is OH, (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(l-6C)alkyl, hydroxy(l-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, amino(l-6C)alkyl,

aminocarbonyl(l -6C)alkyl, (1 -3C)alkylsulfonamido(l -6C)alkyl, sulfamido(l -6C)alkyl, hydroxycarbonyl(l-6C)alkyl, hetAr^3(l-6C)alkyl, Ar^3(l-6C)alkyl, (l-6C)alkoxy, monofluoro(l-6C)alkoxy, difluoro(l-6C)alkoxy, trifluoro(l-6C)alkoxy, tetrafluoro(2- 6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(l-6C)alkoxy, hydroxy(l-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(1 -6C)alkoxy, hetCyc^2(l-6C)alkoxy, hetAr^3(l-6C)alkoxy, Ar^3(l-6C)alkoxy, (1-4C alkoxy)(l-6C)alkoxy, (1-3C alkylsulfonyl)(l-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(l-6C)alkyl], hetAr^4, hetAr^4-0-, Ar^4, hetCyc^2(O)CH_2-, (1-4C alkoxycarbonyl)(l-6C)alkoxy, hydroxycarbonyl(l-6C)alkoxy, aminocarbonyl(l-6C)alkoxy, hetCyc^{2}C(=O)(l-6C)alkoxy, hydroxy(l-3C alkoxy)(l- 6C)alkoxy, hydroxytrifluoro(l-6C)alkoxy, (l-3C)alkylsulfonamido(l-6C)alkoxy, (1- 3C)alkylamido(l-6C)alkoxy, di(l-3C alkyl)amino-carboxy, hetCyc^{2}C(=O)0-, hydroxydifluoro(l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, (l-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc^3, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or hetAr^5;

hetCyc is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, and (1- 6C)acyl;

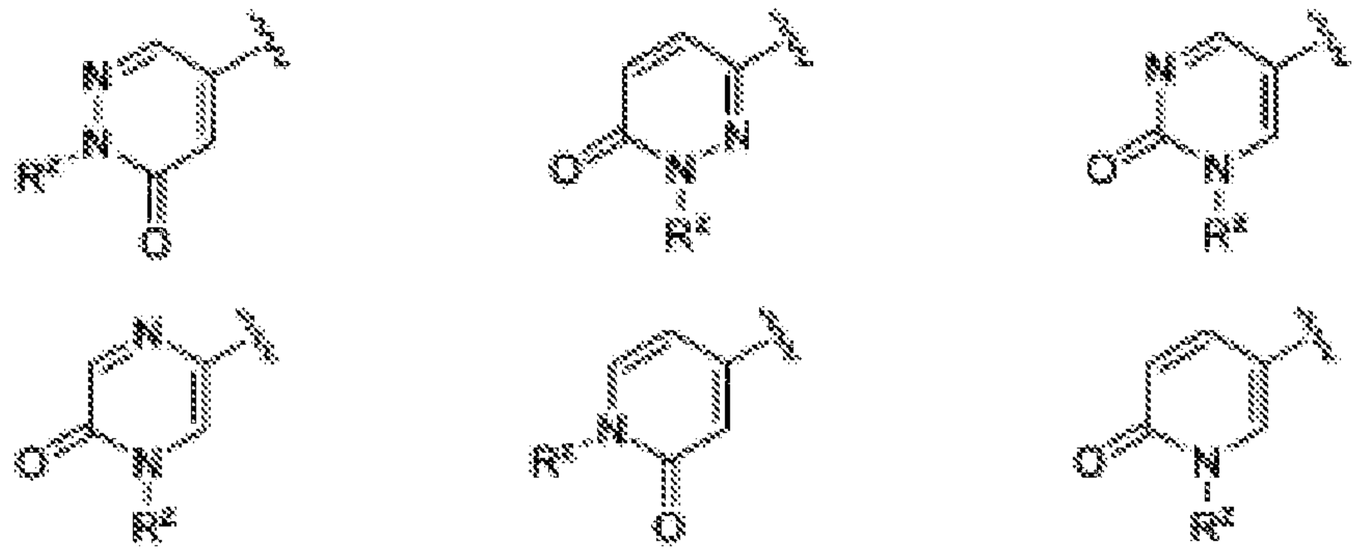
hetCyc is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (l-6C)alkyl, trifluoro(l-6C)alkyl, hydroxy(l-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, (l-6C)acyl-, (l-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

hetAr^3 is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (l-6C)alkyl; AT^3 is phenyl optionally substituted with (l-4C)alkoxy;

hetAr^4 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, difluoro(l-6C)alkyl, fluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2-(3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (1- 6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(l-6C

alkyl)amino, difluoro(l-6C alkyl)amino, trifluoro(l-6C alkyl)amino, and (3- 4C cycloalkyl)amino;

hetAr^5 is a group selected from the structures:



where R^z is (3-4C)cycloalkyl or (l-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr^5 groups is optionally further substituted with one or more substituents independently selected from F and (l-3C)alkyl optionally substituted with 1-3 fluoros;

Ar^4 is phenyl optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, CF_3, $CF_3$0-, (l-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-;

R^5 is (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l- 6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (l-4C)alkoxy, hydroxy(l-4C)alkyl, (1-3C alkoxy)(l-4C)alkyl, (1-4C alkyl)OC(=O)-, (l-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(l-3C alkyl)amido, or phenyl (optionally substituted with one or more substituents independently selected from halogen, (l-6C)alkyl and (l-6C)alkoxy); or

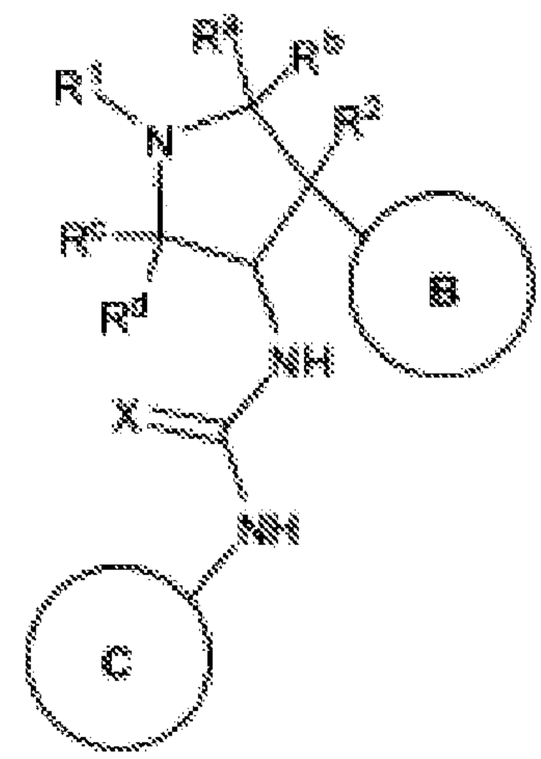
R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (l-6C)alkyl, or R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)0-, (l-6C)acyl, (1- 6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2;

R^{3a} is hydrogen, halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from (l-6C)alkyl and halogen;

R^{4a} is hydrogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, phenyl [optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF_30-, (l-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyI)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (l-6C)alkyl, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, (3- 6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l- 6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino and (1-3C trifluoroalkoxy)(l-3C)trifluoroalkyl; and

R^{5a} is hydrogen, halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from (l-6C)alkyl and halogen.

Further examples of Trk inhibitors can be found in International Publication No. WO 2014078378, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

Ring B and the NH-C(=X)-NH moiety are in the trans configuration;

R^a, R^b, R^c and R^d are independently selected from H and (1-3C)alkyl, or R^c and R^d are independently selected from H and (1-3C)alkyl, and R^a and R^b together with the atom to which they are attached form a cyclopropyl ring;

X is O, S, NH or N-CN;

R^1 is (1-3C alkoxy)(1-6C)alkyl, (trifluoromethoxy)(1-6C)alkyl, (1-3C sulfanyl)(1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-6C)alkyl, (1-3Calkylamino)(1-3C)alkyl, (1-4C alkoxycarbonyl)(1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-3C alkoxy)(1-6C)alkyl, di(1-3C alkoxy)(1-6C)alkyl, (1-3C alkoxy)trifluoro(1-6C)alkyl, hydroxytrifluoro(1-6C)alkyl, (1-4C alkoxycarbonyl)(1-3C alkoxy)(1-6C)alkyl, or hydroxycarbonyl(1-3C alkoxy)(1-6C)alkyl;

R^2 is H, F, or OH;

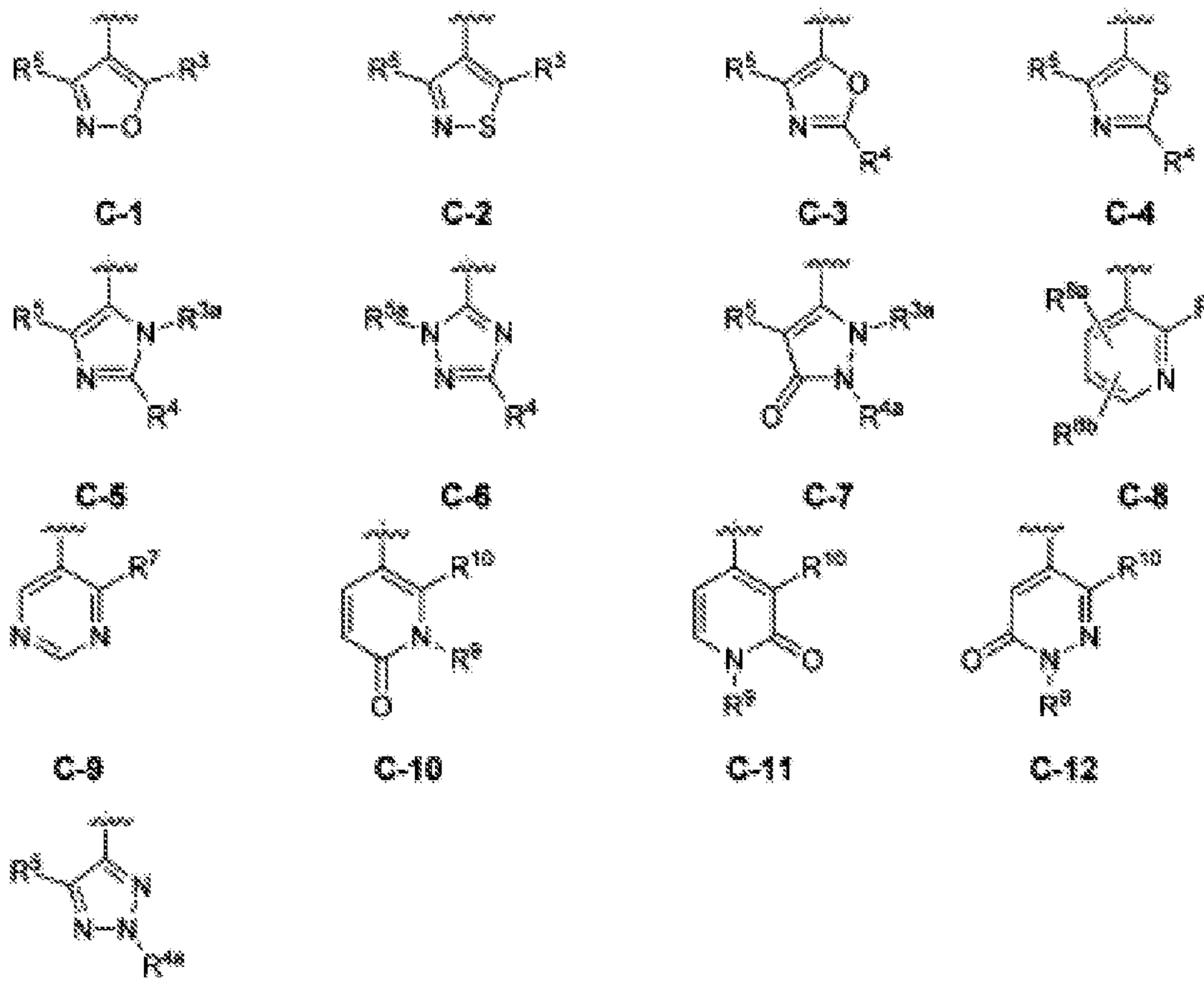
Ring B is Ar^1 or $hetAr^1$;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, CF_3, CF_30-, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-6C)alkyl and CN;

$hetAr^1$ is a 5-6 membered heteroaryl having 1-3 ring heteroatoms independently selected

from N, S and O, and optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, OH, CF_3, NH_2 and hydroxy(l-2C)alkyl;

Ring C is selected from formulas C-l through C-13:



R is H, NH_2, CN, halogen, (l-3C)alkyl [optionally substituted with 1 to 3 fluoros], $H_2NC(=O)$-, (l-3Calkyl)NHC(=O)-, di(l-3Calkyl)NHC(=OK hydroxy(l-3C)alkyl, CH3OCH2CH2, (3-4C)cycloalkyl or (l-3C)alkoxy;

R^{3a} is H, (l-3C)alkyl, $CF_3CH_2CH_2$, $HCF_2CH_2CH_2$, $H_2FCCH_2CH_2$, CF_3CH_2, $HOCH_2CH_2$, $MeOCH_2CH_2$, or (3-4C)cycloalkyl;

R^4 is H, OH, (l-6C)alkyl [optionally substituted with 1-5 fluoros], cyano(l-6C)alkyl, hydroxy(l-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, amino(l-6C)alkyl, aminocarbonyl(1 -6C)alkyl, (1 -3C)alkylsulfonamido(1 -6C)alkyl, sulfamido(1 -6C)alkyl, hydroxycarbonyl(l-6C)alkyl, $hetAr^3$(l-6C)alkyl, Ar^3(l-6C)alkyl, (l-6C)alkoxy [optionally substituted with 1-5 fluoros], cyano(l-6C)alkoxy, hydroxy(l-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(l-6C)alkoxy, hetCyc (l-6C)alkoxy,

hetAr^3(l-6C)alkoxy, Ar^3(l-6C)alkoxy, (1-4C alkoxy)(l-6C)alkoxy, (1-3C alkylsulfonyl)(l-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(l-6C)alkyl], hetAr^4, hetAr^4-0-, Ar^4, hetCyc^2(O)CH$_2$-, (1-4C alkoxycarbonyl)(1 -6C)alkoxy, hydroxycarbonyl(1 -6C)alkoxy, aminocarbonyl(1 -6C)alkoxy, hetCyc^{2}C(=O)(1 -6C)alkoxy, hydroxy(1 -3 C alkoxy)(1 -6C)alkoxy, hydroxytrifluoro(1 - 6C)alkoxy, (l-3C)alkylsulfonamido(l-6C)alkoxy, (l-3C)alkylamido(l-6C)alkoxy, di(l-3C alkyl)amino-carboxy, hetCyc C(=O)0-, hydroxydifluoro(l-6C)alkyl, (1-4C alkylcarboxy)(l- 6C)alkyl, (l-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc , halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or hetAr^5;

R^{4a} is H, (l-6C)alkyl, CF$_3$CH$_2$CH$_2$, HCF$_2$CH$_2$CH$_2$, H$_2$FCCH$_2$CH$_2$, CF$_3$CH$_2$,, cyano(l-6C)alkyl, hydroxy(l-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, amino(l-6C)alkyl, aminocarbonyl(l-6C)alkyl, (l-3C)alkylsulfonamido(l-6C)alkyl, sulfamido(l-6C)alkyl, hydroxycarbonyl(l-6C)alkyl, hetAr^3(l-6C)alkyl, Ar^3(l-6C)alkyl, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3 C alkoxy)(l-6C)alkyl], hetAr^4, Ar^4, hydroxydifluoro(l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, hetCyc^3, N-(1-3C alkyl)oxadiazolonyl, or hetAr^5;

hetCyc is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, and (l-6C)acyl;

hetCyc is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (l-6C)alkyl, trifluoro(l-6C)alkyl, hydroxy(l-6C)alkyl, (1-3C alkoxy)(l- 6C)alkyl, (l-6C)acyl-, (l-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

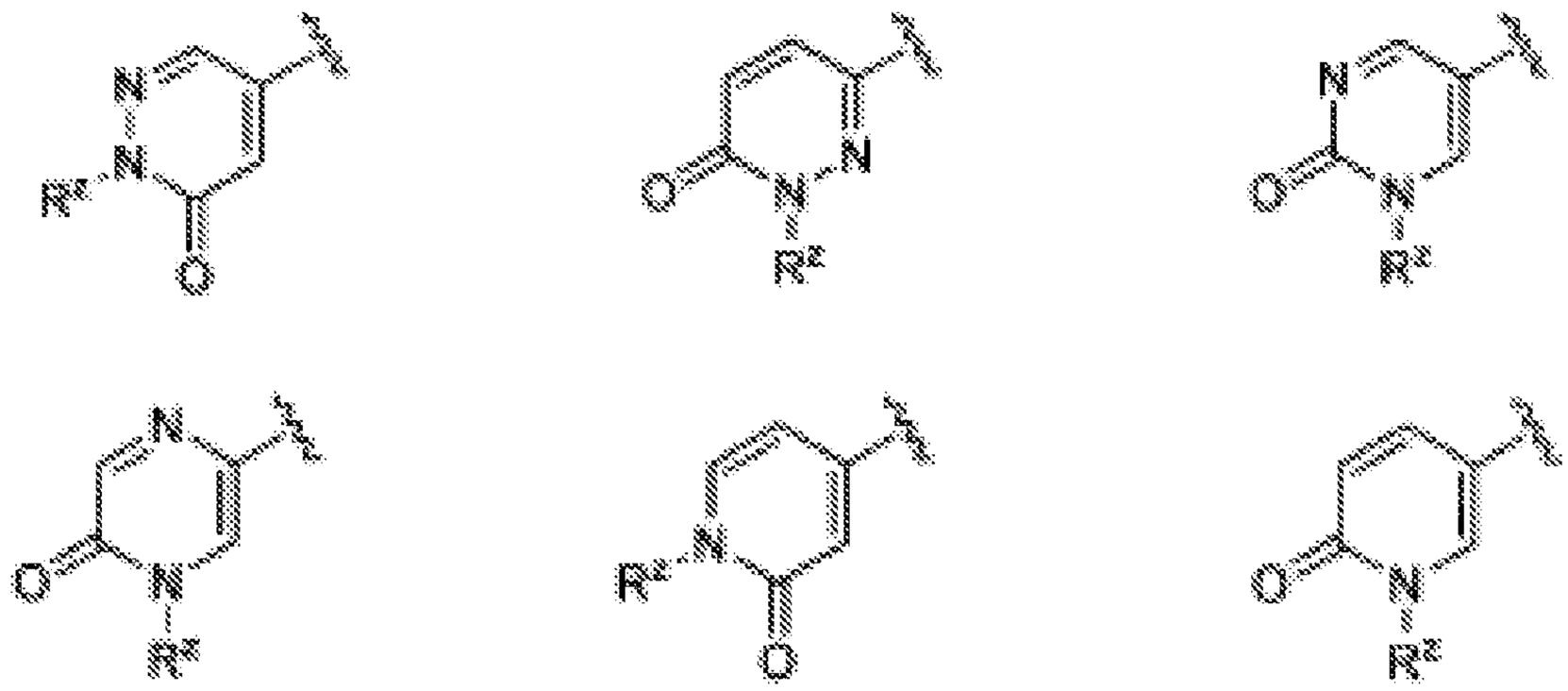
hetAr is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (l-6C)alkyl;

Ar is phenyl optionally substituted with (l-4C)alkoxy;

hetAr^4 is independently a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (l-6C)alkyl [optionally substituted with 1-3

fluoros], halogen, CN, hydroxy(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3-4C cycloalkyl)amino;

hetAr^5 is a group selected from the structures:



where R^z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr^5 groups is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros;

Ar^4 is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF_3, CF_3O-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-;

R^5 is H, (1-6C)alkyl [optionally substituted with 1-5 fluoros], halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl [optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy];

R^{5a} is H, (1-6C)alkyl, $CF_3CH_2CH_2$, $HCF_2CH_2CH_2$, $H_2FCCH_2CH_2$, CF_3CH_2, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (3-4C)cycloalkyl, or phenyl [optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1- 6C)alkoxy];

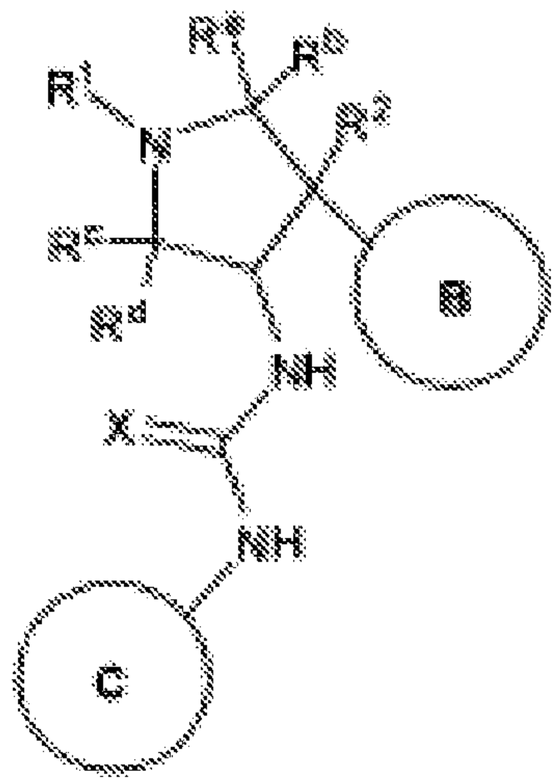
R is (1-6C)alkyl, (3-6C)cycloalkyl, or phenyl [optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl, (1-6C)alkoxy, (3- 4C)cycloalkyl, amino, aminocarbonyl, and trifluoro(1-3C)alkylamido];

R^{8a} and R^{8b} are independently H, halogen, CN, NH_2, (1-6C)alkyl [optionally substituted with 1-5 fluoros], (1-6C)alkoxy, (1-3C alkoxy)(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkoxy, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, (3-4C)cycloalkyl, amino, (1-6Calkyl)NH-, phenyl [optionally substituted with (1-6C alkyl)SO_2-] or $hetAr^4$, wherein only one of R^{8a} and R^{8b} can be phenyl [optionally substituted with (1-6C alkyl)SO_2-] or $hetAr^4$;

R^9 is H, (1-6C)alkyl, CF_3CH_2-, $CF_3CH_2CH_2$-, (1-3Calkoxy)(1-6C)alkyl or (3-4C)cycloalkyl; and

R^{10} is (3-6C)cycloalkyl or phenyl [optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, (1-6C)alkoxy, (3-4C)cycloalkyl, amino, aminocarbonyl and trifluoro(1-3C alkyl)amido].

Additional examples of Trk inhibitors can be found in International Publication No. WO 2014078372, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

Ring B and the NH-C(=X)-NH moiety are in the trans configuration;

R^a, R^b, R^c and R^d are independently selected from H and (1-3C)alkyl,

or R^c and R^d are independently selected from H and (1-3C)alkyl, and R^a and R^b together with the atom to which they are attached form a cyclopropyl ring;

X is O, S, NH or N-CN;

R^1 is (1-3C alkoxy)(1-6C)alkyl, (trifluoromethoxy)(1-6C)alkyl, (1-3C sulfanyl)(1-6C)alkyl, monofiuoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-6C)alkyl, (1-3C)alkylamino(1-3C)alkyl, (1-4C) alkoxycarbonyl(1-6C)alkyl, amino(1-6C)alkyl, hydroxy(1-3C alkoxy)(1-6C)alkyl, di(1-3C alkoxy)(1-6C)alkyl, (1-3C alkoxy)trifluoro(1-6C)alkyl, hydroxytrifluoro(1-6C)alkyl, (1-4C alkoxycarbonyl)(1-3C alkoxy)(1-6C)alkyl, or hydroxycarbonyl(1-3C alkoxy)(1-6C)alkyl;

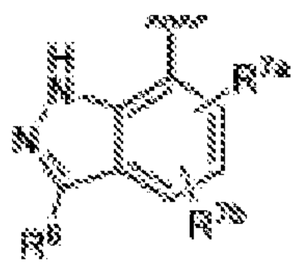
R^2 is H, F, or OH;

Ring B is Ar^1 or $hetAr^1$;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, CF_3, CF_30-, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-6C)alkyl and CN;

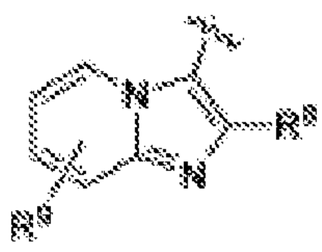
$hetAr^1$ is a 5-6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, S and O, and optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, OH, CF_3, NH_2 and hydroxy(1-2C)alkyl;

Ring C is selected from formulas C-l through C-9

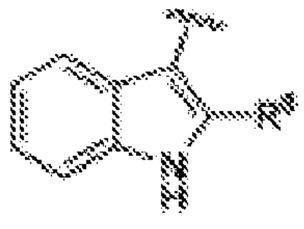


C-1

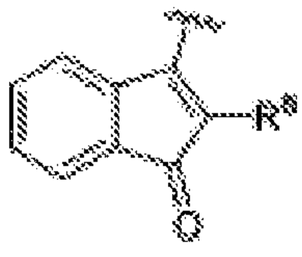
C-2



C-3

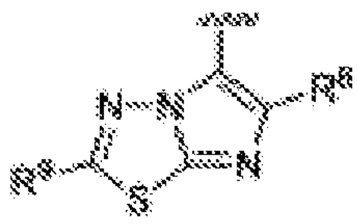


C-4

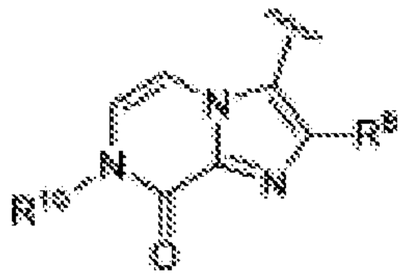


C-5

C-6



C-7



C-8

C-9

R is H, halogen, or phenyl [optionally substituted with one or more substituents independently selected from halogen and (1-3C)alkyl];

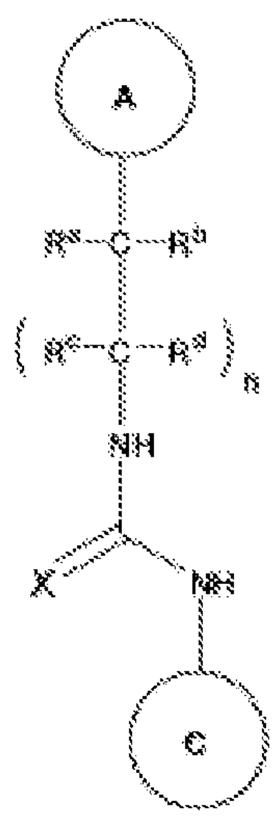
R^{7a} and R^{7b} are independently H, (1-6C)alkyl, or phenyl [optionally substituted with one or more substituents independently selected from halogen and (1-3C)alkyl], wherein only one of R^{7a} and R^{7b} can be phenyl optionally substituted with one or more substituents independently selected from halogen and (1-3C)alkyl;

R^8 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-3C)alkyl and (3-6C)cycloalkyl;

R^9 is H, halogen, (1-6C)alkyl [optionally substituted with one to five fluoros] or (1-6C)alkoxy; and

R^{10} is H or (1-6C)alkyl.

Further examples of Trk inhibitors can be found in International Publication No. WO 2014078331, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I-C:

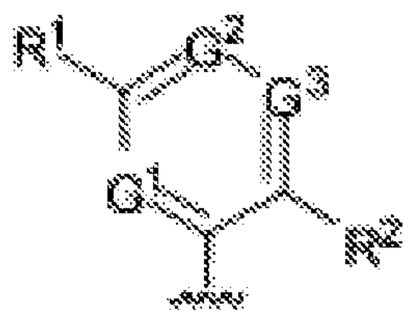


I-C

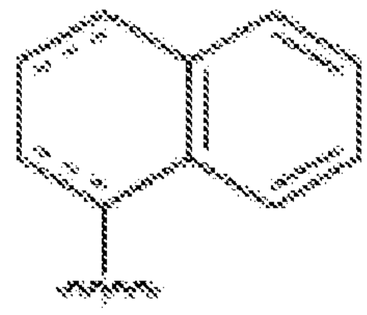
or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

X is O, S, NH or N-CN;

Ring A is formula A-1 or A-2



A-1



A-2

wherein the dashed lines are optional double bonds;

n is 0 or 1 when Ring A is formula A-1, and n is 0 when Ring A is formula A-2;

G^1, G^2 and G^3 are independently CR^X or N, wherein no more than 2 of G^1, G^2 and G^3 can be N;

each R^x is independently H, halogen, (l-4C)alkyl or (l-4C)alkoxy;

R^1 is H, halogen, (l-3C)alkoxy(l-3C)alkyl (optionally substituted with 1-5 fluoros), (1-3C alkyl)sulfanyl(l-3C)alkyl (optionally substituted with 1-5 fluoros), (l-3C)alkyl (optionally substituted with 1-5 fluoros), (l-3C)alkoxy (optionally substituted with 1-5 fluoros), (1-3C alkyl)sulfanyl (optionally substituted with 1-5 fluoros), cyano(l-3C)alkyl (optionally substituted with 1-5 fluoros), hydroxy(l-3C)alkyl (optionally substituted with 1-5 fluoros), (l-4C)alkyl (optionally substituted with 1-5 fluoros), $CH_3CH_2NR^y$, $CF_3CH_2NR^y$, $HCF_2CH_2NR^y$, $H_2CFCH_2NR^y$, $CH_3NR^yCH_2$, $R^yR^yNCH_2CH_2$, $R^yR^yNCH_2CFH$, or $R^yR^yNCH_2CF_2$;

each R^y is independently H or methyl;

when n is 0, R is selected from the group consisting of H, halogen, (l-6C)alkyl [optionally substituted with 1-5 fluoros], (l-6C)alkoxy [optionally substituted with 1-5 fluoros], (1-3C alkoxy)(l-4C)alkyl, (3-6C cycloalkyl)$CH_2$0-, amino(l-3C)alkyl, $CF_3CH_2NHCH_2$, $HCF_2CH_2NHCH_2$, a C5-C8 bridged cycloalkyl, $hetCyc^3$, $hetCyc^aCH_2$, Cyc^a, $hetAr^1$ and Ar^1, and

when n is 1, R is selected from the group consisting of H, halogen, CF_3, F_2CH, FCH_2, methyl and methoxy.

$hetCyc^3$ is a 4-6 membered heterocyclic ring having a ring heteroatom selected from N, O and S and optionally substituted with 1-3 groups independently selected from OH, F, (1- 6C)alkoxy or (l-6C)alkyl [optionally substituted with 1-3 fluoros];

Cyc^a is a (3-6C)cycloalkyl optionally substituted with (l-4C)alkoxy, (l-4C)alkyl, F or

OH;

$hetAr^1$ is a 5-6 membered heteroaryl having 1-3 ring heteroatoms independently selected from N, S and O, and optionally substituted with 1 -2 groups independently selected from (l-6C)alkyl, halogen, OH, CF_3, NH_2 and hydroxy(l-2C)alkyl;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, CF_3, CF_30-, (l-4C)alkoxy, (l-4C)sulfanyl, hydroxy(l-4C)alkyl, (1-6C)alkyl and CN;

R^a is H, (l-3C)alkyl, cyclopropyl, cyclobutyl, or CF_3, and

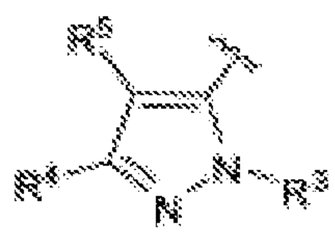
R^b is H, methyl or ethyl,

or R^a and R^b together with the carbon atom to which they are attached form a 3-6 membered cycloalkyl ring;

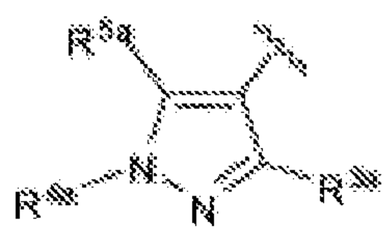
R^c is H, methyl or ethyl

R^d is $CF_3CH_2CH_2$, phenyl or phenylCH_2- wherein each phenyl ring is optionally substituted with one or more substituents independently selected from halogen, methoxy and methoxymethyl;

Ring C is formula C-l or C-2



C-1



C-2 ;

R^3 is (l-6C)alkyl, hydroxy(l-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, a C5-C8 bridged cycloalkyl, or $hetAr^2$;

Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen and (l-6C)alkyl;

$hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

R^4 is OH, (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(l-6C)alkyl, hydroxy(l-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, amino(l-6C)alkyl, aminocarbonyl(l -6C)alkyl, (1 -3C)alkylsulfonamido(l -6C)alkyl, sulfamido(l -6C)alkyl, hydroxycarbonyl(l-6C)alkyl, $hetAr^3$(l-6C)alkyl, Ar^3(l-6C)alkyl, (l-6C)alkoxy, monofluoro(l-6C)alkoxy, difluoro(l-6C)alkoxy, trifluoro(l-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(l-6C)alkoxy, hydroxy(l-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(l-6C)alkoxy, $hetCyc^2$(l- 6C)alkoxy, $hetAr^3$(l-6C)alkoxy, Ar^3(l-6C)alkoxy, (1-4C alkoxy)(l-6C)alkoxy, (1-3C alkylsulfonyl)(l-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(l-6C)alkyl], $hetAr^4$, $hetAr^4$-0-, Ar^4, $hetCyc^2(O)CH_2$-, (1-4C alkoxycarbonyl)(l-6C)alkoxy, hydroxycarbonyl(l-6C)alkoxy, aminocarbonyl(l-6C)alkoxy, $hetCyc^2C(=O)$(l-6C)alkoxy, hydroxy(l-3C alkoxy)(l-6C)alkoxy, hydroxytrifluoro(l -6C)alkoxy, (1 -3C)alkylsulfonamido(1 -6C)alkoxy, (1-3 C)alkylamido(1 - 6C)alkoxy, di(l-3C alkyl)amino-carboxy, $hetCyc^2C(=O)0$-, hydroxydifluoro(l-6C)alkyl, (1 - 4C alkylcarboxy)(l-6C)alkyl, (l-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1- 3C alkoxy)aminocarbonyl, $hetCyc^3$, halogen, CN, trifiuoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, $hetAr^5$, Ar^4-0-, $hetCyc^4$-0-, Cyc'-O-, or aminohydroxy(l-6C)alkoxy; $hetCyc^2$ is a 4-6 membered heterocyclic ring having 1 -2 ring heteroatoms

independently selected from N and O and optionally substituted with 1-2 groups independently selected from (l-6C)alkyl, 1-4C alkoxy)carbonyl, (l-6C)acyl, halogen and oxo;

hetCyc is a 4-7 membered heterocycle having 1 -2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents

independently selected from F, CN, (l-6C)alkyl, trifluoro(l-6C)alkyl, hydroxy(l-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, (l-6C)acyl-, (l-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1- 4C alkoxy)carbonyl;

$hetCyc^4$ is a 5-8 membered monocyclic, spirocyclic or bridged heterocycle having a ring nitrogen atom and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

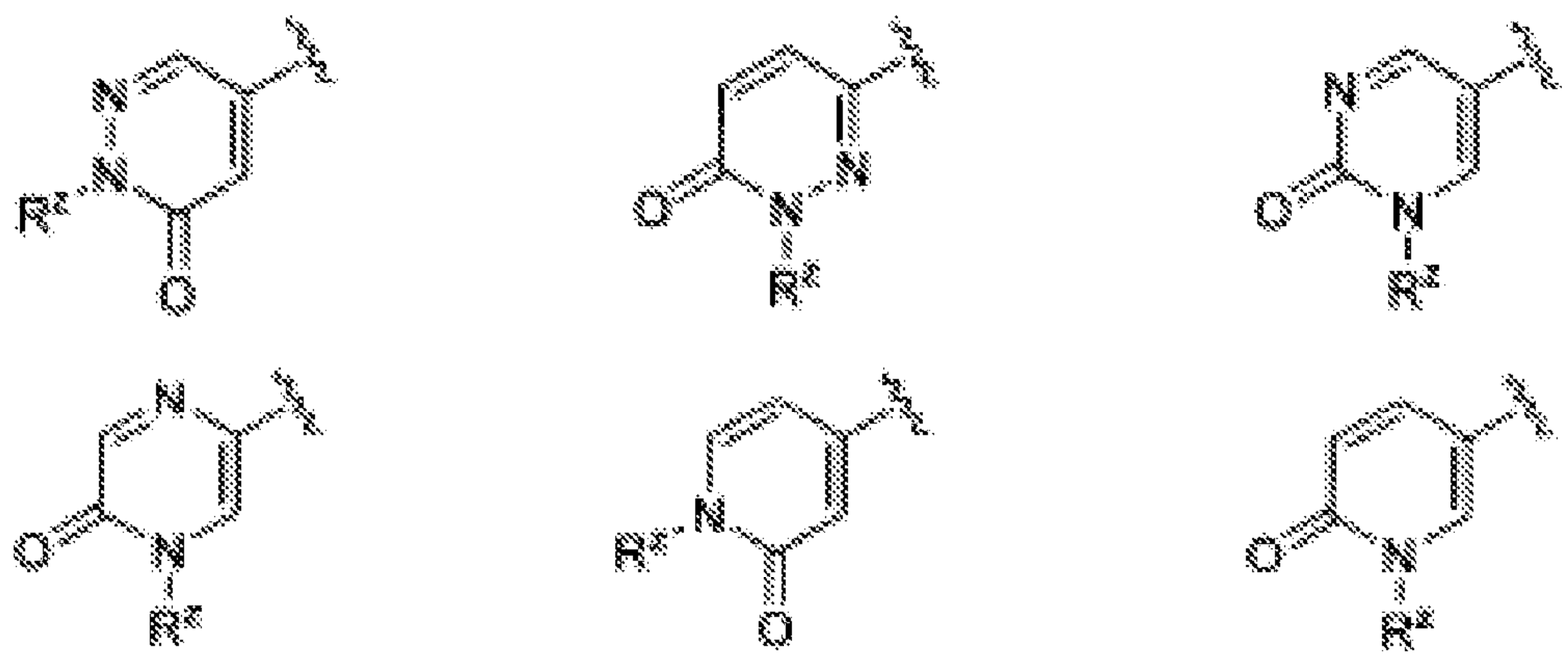
Cyc^1 is a 3-6 membered carbocycle optionally substituted with an amino group;

$hetAr^3$ is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (l-6C)alkyl;

Ar is phenyl optionally substituted with (l-4C)alkoxy;

$hetAr^4$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, difluoro(l-6C)alkyl, fluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2-(3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(l-6C alkyl)amino, difluoro(l-6C alkyl)amino, trifluoro(l-6C alkyl)amino, and (3-4C cycloalkyl)amino ;

$hetAr^5$ is a group selected from the structures:



where R^z is (3-4C)cycloalkyl or (l-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said $hetAr^5$ groups is optionally further substituted with one or more groups independently selected from F and (l-3C)alkyl optionally substituted with 1-3 fluoros;

Ar^4 is phenyl optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF_30-, (l-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-;

R^5 is (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (l-4C)alkoxy, hydroxy(l-4C)alkyl, (1-3C alkoxy)(l-4C)alkyl, (1-4C alkyl)OC(=O)-, (l-6C)alkylthio, (3-

4C)cycloalkyl, amino, aminocarbonyl, trifluoro(l-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (l-6C)alkyl and (l-6C)alkoxy); or

R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (l-6C)alkyl, or

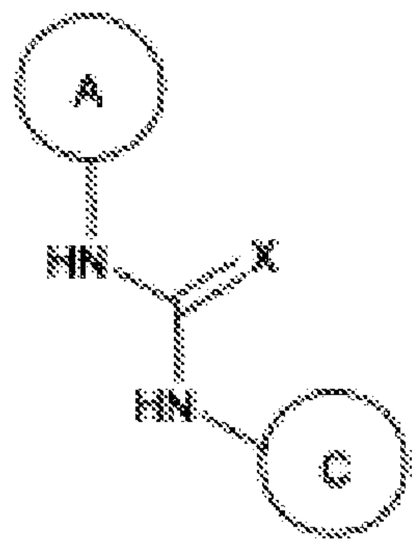
R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)0-, (l-6C)acyl, (l-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2;

R^{3a} is halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

R^{4a} is hydrogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF_30-, (1-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (l-6C)alkyl, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1- 6C alkyl)amino, di(l-6C alkyl)amino and (1-3C trifluoroalkoxy)(l-3C)trifluoroalkyl; and

R^{5a} is halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen.

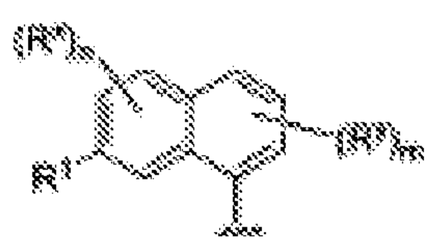
Additional examples of Trk inhibitors can be found in International Publication No. WO 2014078328, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I-1:



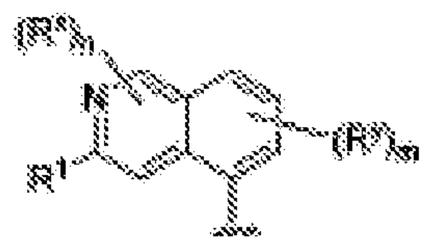
I-1

or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

Ring A is selected from formulas A-l, A-2, A-3 or A-4:

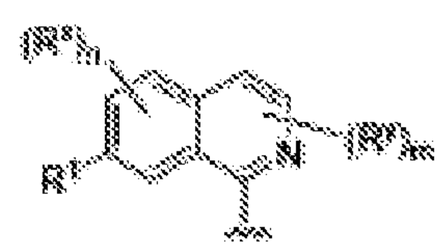


A-1



A-2

A-3



A-4

R^1 is H, halogen, (l-3C)alkoxy(l-3C)alkyl [optionally substituted with 1-5 fluoros], (1-3C alkyl)sulfanyl(l-3C)alkyl [optionally substituted with 1-5 fluoros], (l-3C)alkoxy [optionally substituted with 1-5 fluoros], (1-3C alkyl)sulfanyl [optionally substituted with 1-5 fluoros], cyano(l-3C)alkyl [optionally substituted with 1-5 fluoros], hydroxy(l-3C)alkyl [optionally substituted with 1-5 fluoros], (l-4C)alkyl [optionally substituted with 1-5 fluoros], $CH_3CH_2NR^a$, $CF_3CH_2NR^a$, $HCF_2CH_2NR^a$, $H_2CFCH_2NR^a$, $CH_3NR^aCH_2$, R^^CHzCHs or R^^CHzCFz;

each R^a is independently H or methyl;

R^x and R^y are independently selected from H, halogen, (l-3C)alkyl [optionally substituted with 1-5 fluoros] or (l-3C)alkoxy [optionally substituted with 1-5 fluoros];

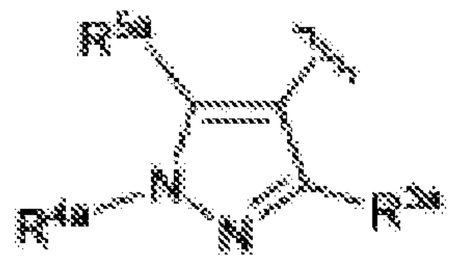
n is 0, 1 or 2;

m is 0, 1 or 2;

X is O, S, NH or N-CN;

Ring C is formula C-1 or C-2

C-1



C-2

R^3 is (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, or $hetAr^2$;

Ar is phenyl optionally substituted with one or more groups independently selected from halogen and (1-6C)alkyl;

$hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

R^4 is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1 -6C)alkyl, (1 -3C)alkylsulfonamido(1 -6C)alkyl, sulfamido(1 -6C)alkyl, hydroxycarbonyl(1-6C)alkyl, $hetAr^3$(1-6C)alkyl, Ar^3(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy trifluoro(1-6C)alkoxy, tetrafluoro(2- 6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(1-6C)alkoxy, $hetCyc^2$(1- 6C)alkoxy, $hetAr^3$(1-6C)alkoxy, Ar^3(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], $hetAr^4$, $hetAr^4$-0-, Ar^4, $hetCyc^2(O)CH_2$-, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1- 6C)alkoxy, $hetCyc^2C(=O)$(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1 -6C)alkoxy, (1 -3C)alkylsulfonamido(1 -6C)alkoxy, (1 -3C)alkylamido(1 - 6C)alkoxy, di(1-3C alkyl)amino-carboxy, $hetCyc^2C(=O)$0-, hydroxydifluoro(1-6C)alkyl, (1- 4C alkylcarboxy)(1-

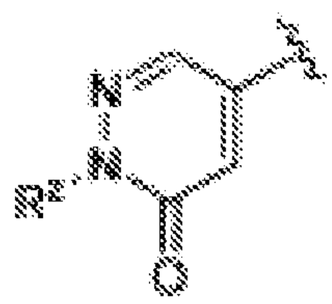
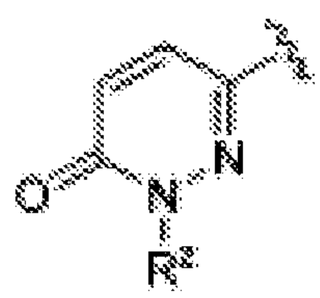
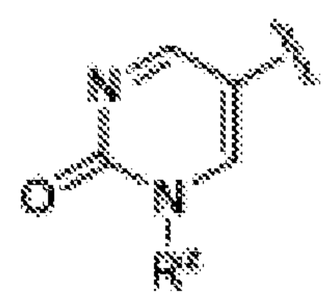
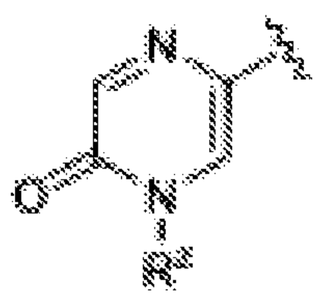
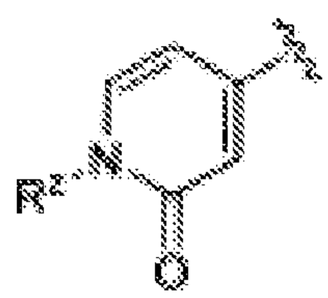
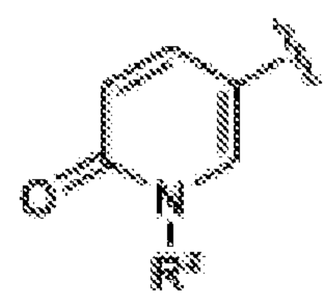
6C)alkyl, (l-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1- 3C alkoxy)aminocarbonyl, hetCyc^3, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or hetAr^5;

hetCyc is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, and (l-6C)acyl; hetCyc is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (l-6C)alkyl, trifluoro(l-6C)alkyl, hydroxy(l-6C)aikyl, (1-3C alkoxy)(l-6C)alkyl, (l-6C)acyl-, (l-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1- 4C alkoxy)carbonyl; hetAr^3 is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (l-6C)alkyl;

Ar^3 is phenyl optionally substituted with (l-4C)alkoxy;

hetAr^4 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, difluoro(l-6C)alkyl, fluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2-(3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(l-6C alkyl)amino, difluoro(l-6C alkyl)amino, trifluoro(l-6C alkyl)amino, and (3-4C cycloalkyl)amino;

hetAr^5 is a group selected from the structures:

where R^z is (3-4C)cycloalkyl or (l-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said $hetAr^5$ groups is optionally further substituted with one or more groups independently selected from F and (l-3C)alkyl optionally substituted with 1-3 fluoros;

Ar^4 is phenyl optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF_30-, (l-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-;

R^5 is (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (l-4C)alkoxy, hydroxy(l-4C)alkyl, (1-3C alkoxy)(l-4C)alkyl, (1-4C alkyl)OC(=O)-, (l-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(l-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (l-6C)alkyl and (l-6C)alkoxy); or

R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (l-6C)alkyl, or R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(-0)0-, (l-6C)acyl, (l-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2;

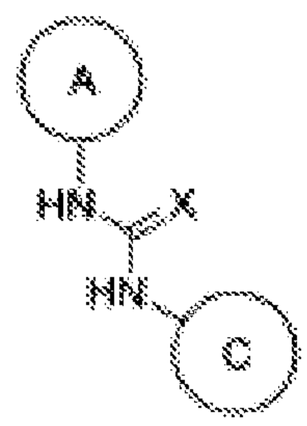
R^{3a} is halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

R^{4a} is (l-6C)alkyl, trifluoro(l-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF3O-, (1-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and

optionally substituted with 1-2 substituents independently selected from (l-6C)alkyl, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1- 6C alkyl)amino, di(l-6C alkyl)amino and (1-3C trifluoroalkoxy)(l-3C)trifluoroalkyl; and

R^{5a} is halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen.

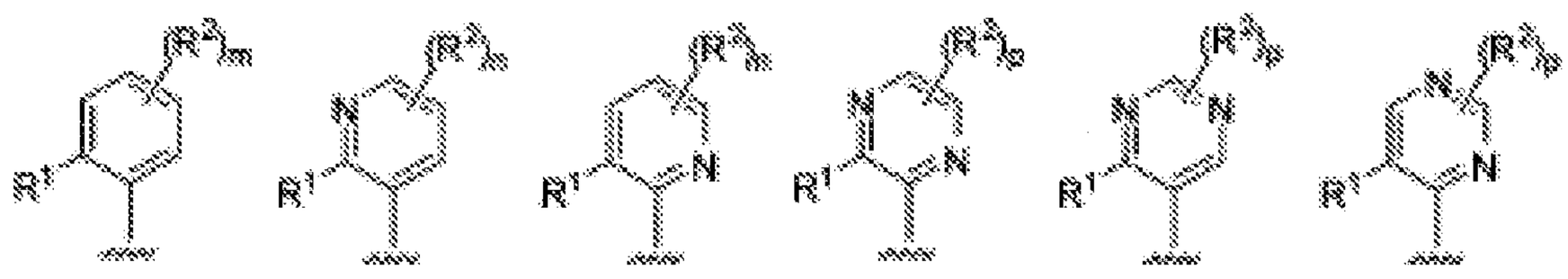
Further examples of Trk inhibitors can be found in International Publication No. WO 2014078325, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I:



I-2

or a stereoisomer, tautomer, or pharmaceutically acceptable salt, solvate or prodrug thereof, wherein:

Ring A is formula A-l, A-2, A-3, A-4, A-5 or A-6



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

n is 0, 1, 2 or 3;

p is 0, 1 or 2 ;

R^1 is formula R^1-1, R^1-2 or R^1-3

R^{L1}

R^{L2}

R^{L3} ;

Y^1 is CH_3CH_2-, CF_3CH_2-, CH_30-, F_3CO-, F_2CHO-, FCH_20-, CH_3S-, F_3CS-, F_2CHS-, or FCH_2S-;

Y^2 is O, S, NH, MeN- or CH_2;

Y^3 is CH3O-, CH3S-, MeNH- or Me_2N-;

Y^4 is CH_2 and Y^5 is S or O, or Y^4 is S or O and Y^5 is CH_2;

R^2 is halogen, (l-3C)alkyl (optionally substituted with 1-3 fluoros), (l-3C)alkoxy (optionally substituted with 1-3 fluoros), CH_3OCH_2- (optionally substituted with 1-3 fluoros), (1-3C alkyl)sulfanyl, di(l-3C)alkylamino, cyclopropyl, cyclobutyl or azetidinyl, wherein each of said cyclopropyl, cyclobutyl and azetidinyl is optionally substituted with 1 to 2 fluoros;

X is O, S, NH or N-CN;

Ring C is formula C-1 or C-2

C-1

C-2

R^3 is (l-6C)alkyl, hydroxy(l-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, or $hetAr^2$;

Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen and (l-6C)alkyl;

$hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

R^4 is H, OH, (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(l-6C)alkyl, hydroxy(l-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, amino(l-6C)alkyl, aminocarbonyl(l -6C)alkyl, (1 -3C)alkylsulfonamido(l -6C)alkyl, sulfamido(l -6C)alkyl, hydroxycarbonyl(l-6C)alkyl, $hetAr^3$(l-6C)alkyl, Ar^3(l-6C)alkyl, (l-6C)alkoxy, monofluoro(l-6C)alkoxy, difluoro(l-6C)alkoxy trifluoro(l-6C)alkoxy, tetrafluoro(2- 6C)alkoxy, pentafluoro(2-6C)alkoxy cyano(l-6C)alkoxy, hydroxy(l-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(l-6C)alkoxy, $hetCyc^2$(l - 6C)alkoxy, $hetAr^3$(l-6C)alkoxy, Ar^3(l-6C)alkoxy, (1-4C alkoxy)(l-6C)alkoxy, (1-3C alkylsulfonyl)(l-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(l-6C)alkyl], $hetAr^4$, $hetAr^4$-0-, Ar^4, $hetCyc^2(O)CH_2$-, (1-4C alkoxycarbonyl)(l -6C)alkoxy, hydroxycarbonyl(l-6C)alkoxy, aminocarbonyl(l-6C)alkoxy, $hetCyc^2C(=O)$(l-6C)alkoxy, hydroxy(l-3C alkoxy)(l- 6C)alkoxy, hydroxytrifluoro(l-6C)alkoxy, (l-3C)alkylsulfonamido(l-6C)alkoxy, (1- 3C)alkylamido(l-6C)alkoxy, di(l-3C alkyl)amino-carboxy, hetCyc C(=O)0-, hydroxydifluoro(l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, (l-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, hetCyc , halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or $hetAr^5$;

$hetCyc^2$ is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, (l-6C)acyl and halogen;

$hetCyc^3$ is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (l-6C)alkyl, trifluoro(l-6C)alkyl, hydroxy(l-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, (l-6C)acyl-, (l-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

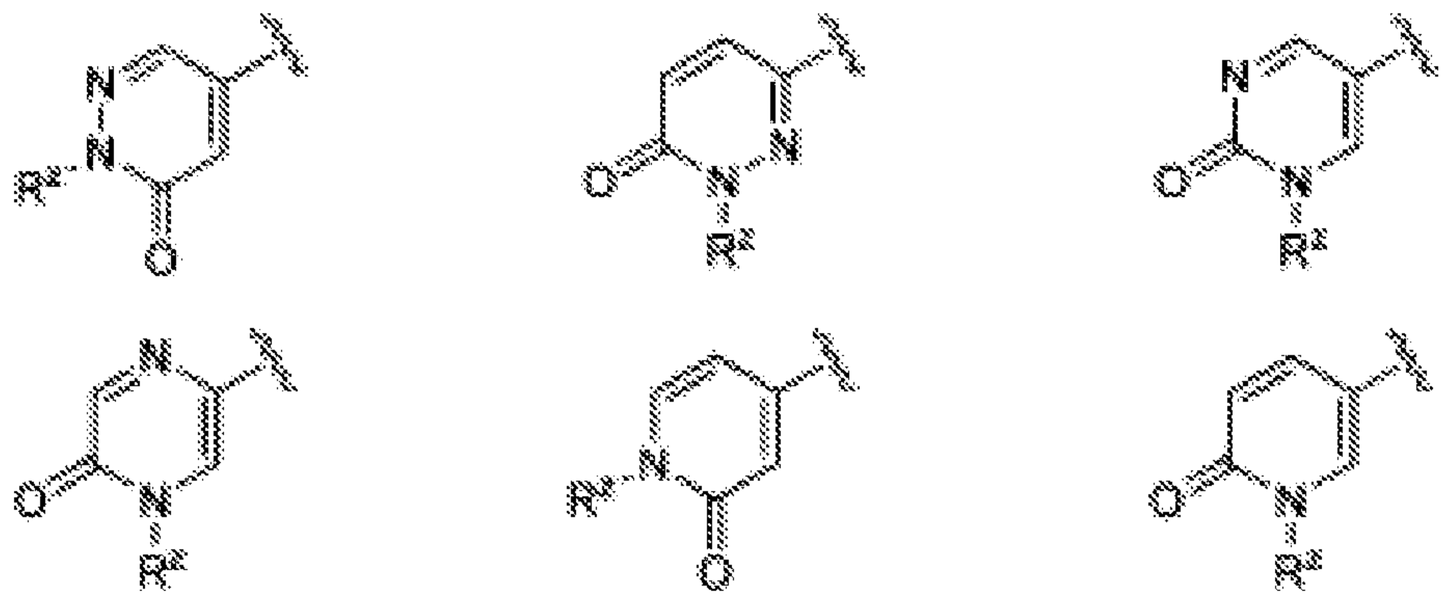
$hetAr^3$ is a 5 -membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (l-6C)alkyl;

Ar is phenyl optionally substituted with (l-4C)alkoxy;

$hetAr^4$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents

independently selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, difluoro(1-6C)alkyl, fluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2-(3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1- 6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3- 4C cycloalkyl)amino;

$hetAr^5$ is a group selected from the structures:



where R^z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said $hetAr^5$ groups is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1- 3 fluoros;

AT^4 is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF_3, CF_30-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-;

R^5 is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1- 6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (1- 6C)alkyl and (1-6C)alkoxy); or

R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (1-6C)alkyl, or

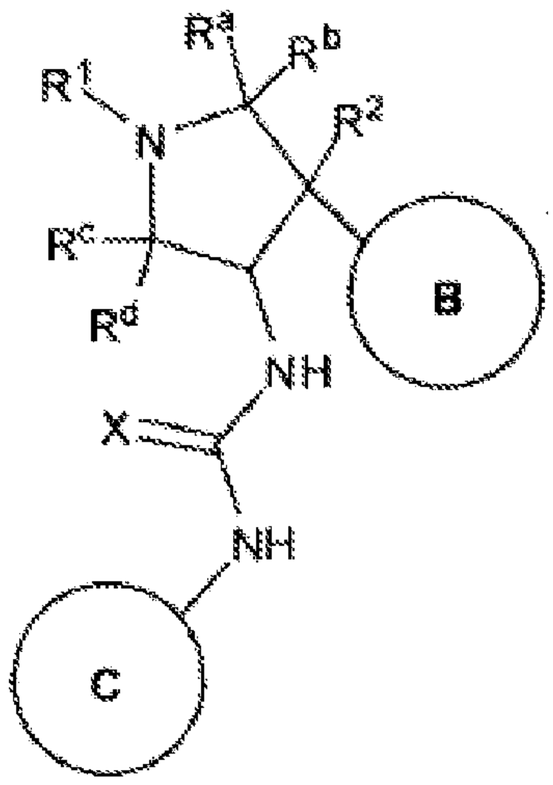
R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom

selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)0-, (l-6C)acyl, (1- 6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2;

R^{3a} is halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

R^{4a} is (l-6C)alkyl, trifluoro(l-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF_30-, (1-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with 1-2 substituents independently selected from (1- 6C)alkyl, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l-6C)alkoxy, (1- 6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino and (1-3C trifluoroalkoxy(1-3 C)trifluoroalkyl; and R^{5a} is (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (1-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen.

Additional examples of Trk inhibitors can be found in International Publication No. WO 2014078323, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

Ring B and the NH-C(=X)-NH moiety are in the trans configuration;

R^a, R^b, R^c and R^d are independently selected from H and (l-3C)alkyl, or R° and R^d are independently selected from H and (l-3C)alkyl, and R^a and R^b together with the atom to which they are attached form a cyclopropyl ring;

X is O, S, NH, or N-CN;

R^1 is (1-3C alkoxy)(l-6C)alkyl, (trifluoromethoxy)(l-6C)alkyl, (1-3C sulfanyl)(l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(l-6C)alkyl, aminocarbonyl(l-6C)alkyl, hydroxy(l-6C)alkyl, dihydroxy(2-6C)alkyl, (l-6C)alkyl, (l-3Calkylamino)(l-3C)alkyl, (1-4C alkoxycarbonyl)(l-6C)alkyl, amino(l-6C)alkyl, hydroxy(l-3C alkoxy)(l-6C)alkyl, di(l-3C alkoxy)(l-6C)alkyl, (1-3C alkoxy)trifluoro(l-6C)alkyl, hydroxytrifluoro(l-6C)alkyl, (1-4C alkoxycarbonyl)(l-3C alkoxy)(l-6C)alkyl or hydroxycarbonyl(l-3C alkoxy)(l-6C)alkyl;

R^2 is H, F, or OH;

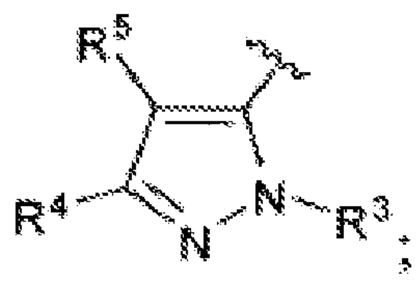
Ring B is Ar^1 or $hetAr^1$;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, CF_3, CF_30-, (l-4C)alkoxy, hydroxy(l-4C)alkyl, (l-6C)alkyl and CN;

$hetAr^1$ is a 5-6 membered heteroaryl having 1-3 ring heteroatoms independently selected

from N, S and O, and optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, OH, CF_3, NH_2 and hydroxy(l-2C)alkyl;

Ring C is



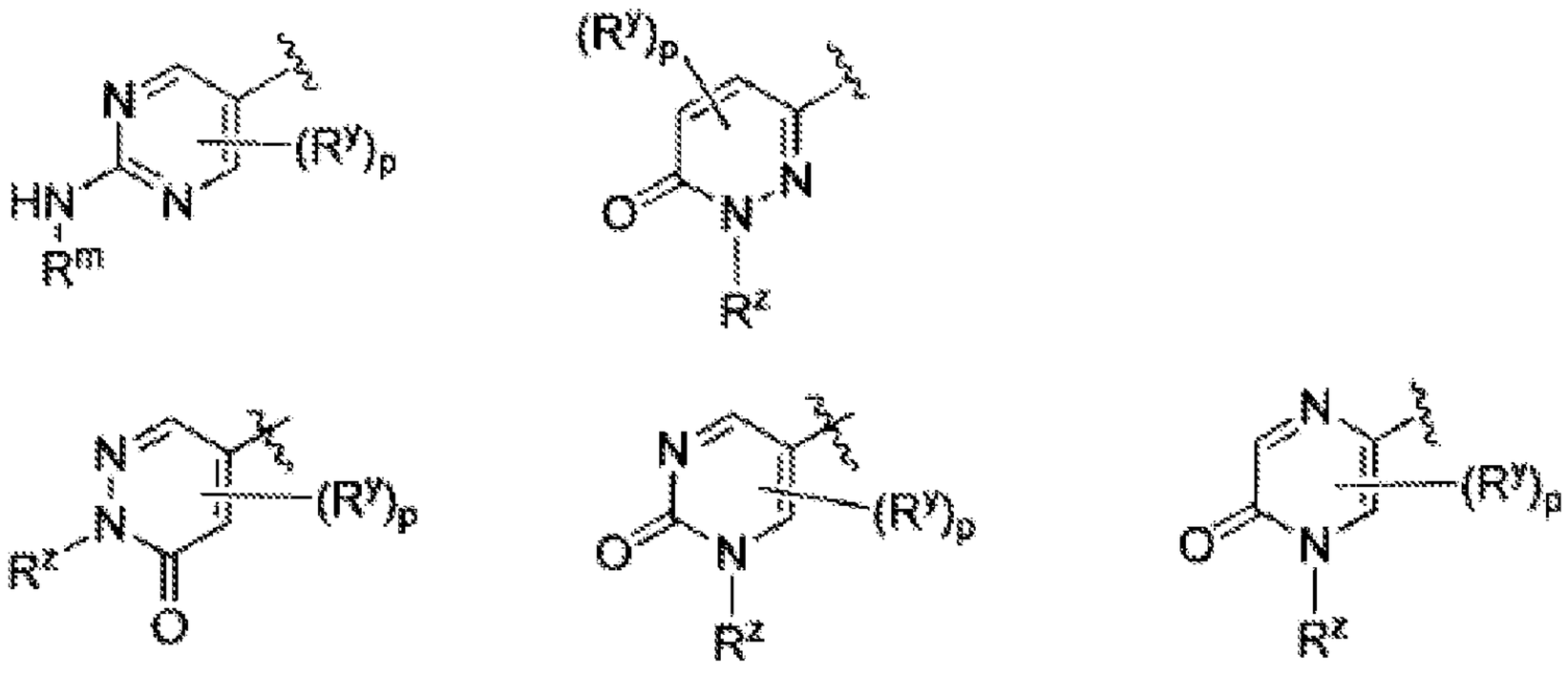
R^3 is H, (l-6C)alkyl, hydroxy(l-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, $hetAr^2$, or a C5-C8 bridged carbocyclic ring;

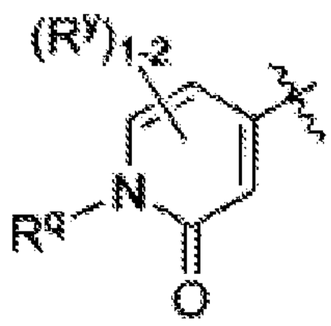
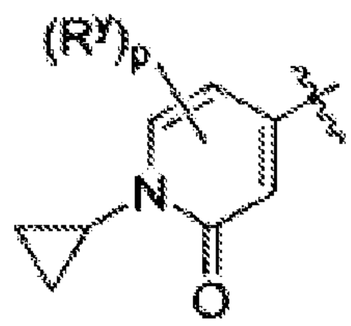
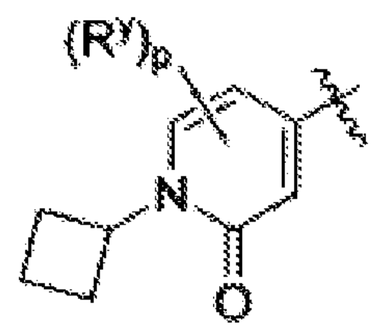
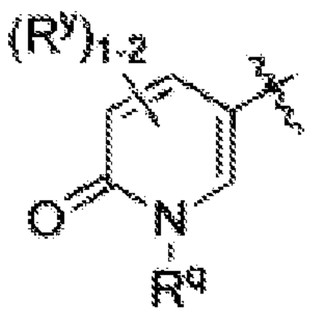
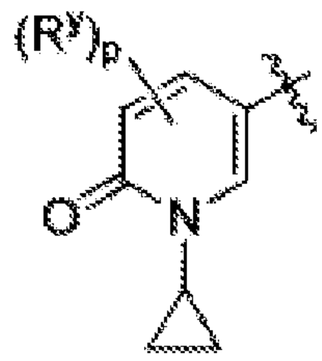
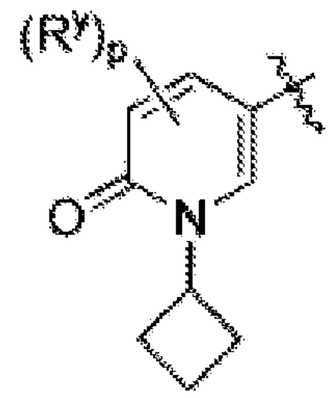
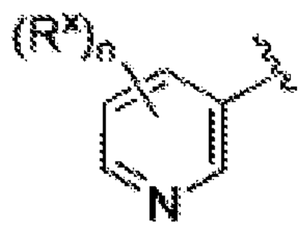
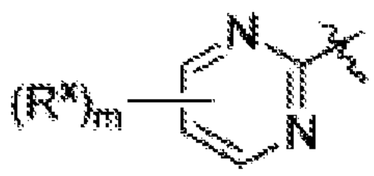
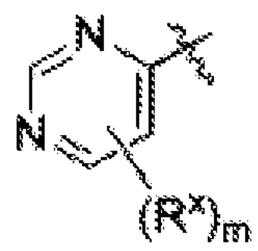
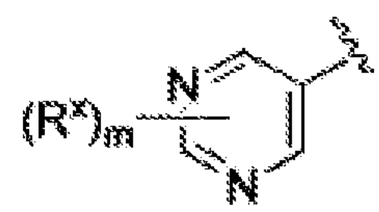
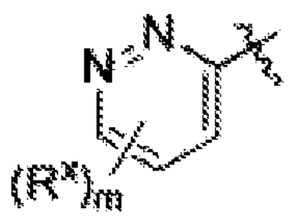
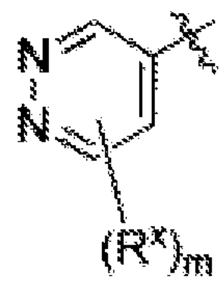
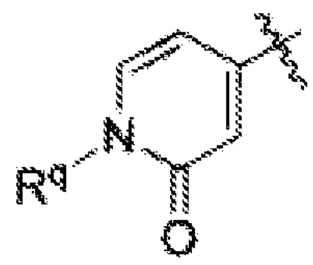
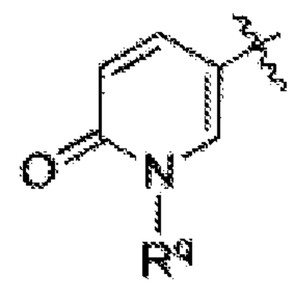
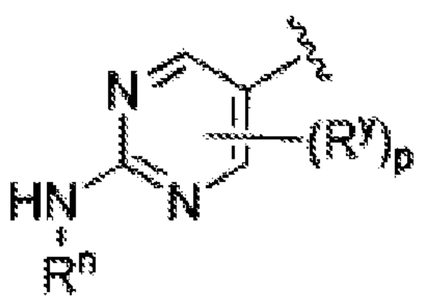
Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl;

$hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more substituents independently selected from (l-6C)alkyl and halogen;

R^4 is selected fro -6C alkyl)SO_2-, (1-6C alkyl)C(=O)- and from the structures:



R^m is (1-3C)alkyl substituted with 1-3 fluoros, or (3-4C)cycloalkyl;

R^n is (1-3C)alkyl;

R^q is (1-3C)alkyl optionally substituted with 1-3 fluoros;

R^x is (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2-, (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(1-6C alkyl)amino, trifluoro(1-3C)alkoxy or trifluoro(1-6C)alkyl;

n is 0, 1, 2, 3 or 4;

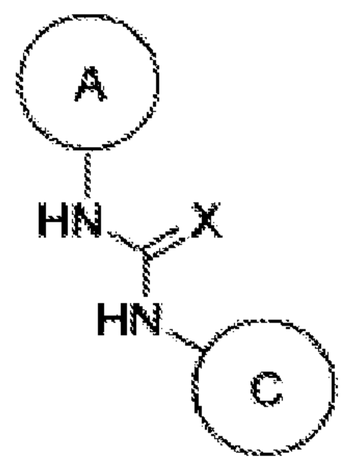
m is 0, 1, 2 or 3;

R^y is F or (1-3C)alkyl optionally substituted with 1-3 fluoros;

p is 0, 1 or 2;

R^z is (3-4C)cycloalkyl, or (l-3C)alkyl optionally substituted with 1-3 fluoros; and R^5 is H, (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l- 6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (l-4C)alkoxy, hydroxy(l-4C)alkyl, (1-3C alkoxy)(l-4C)alkyl, (1-4C alkyl)OC(=O)-, (l-6C)alkylsulfanyl, phenyl [optionally substituted with one or more substituents independently selected from halogen, (l-6C)alkyl and (l-6C)alkoxy], (3-4C)cycloalkyl, amino, aminocarbonyl, or trifluoro(1 -3 C alkyl)amido.

Additional examples of Trk inhibitors can be found in International Publication No. WO 2014078322, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound of Formula I:

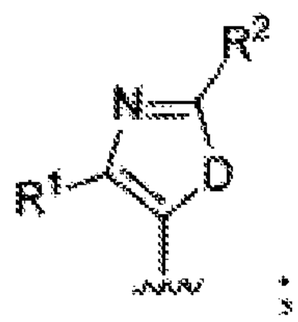


I

or stereoisomers, tautomers, or pharmaceutically acceptable salts, solvates or prodrugs thereof, wherein:

X is O, S, NH or N-CN;

Ring A is

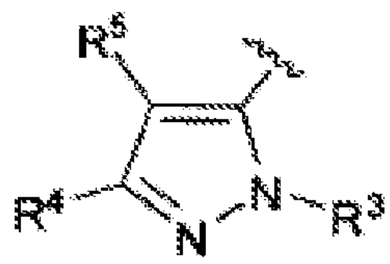


D is O or S;

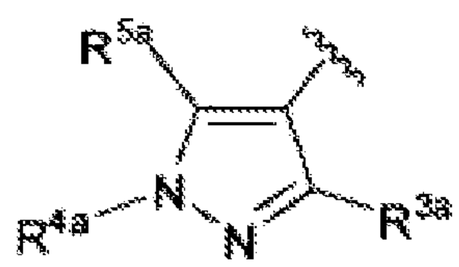
R^1 is phenyl optionally substituted with one or more substituents independently selected from halogen and (l-3C)alkyl;

R is (l-6C)alkyl [optionally substituted with 1 to 5 fluoros] or (3-6C)cycloalkyl [optionally substituted with one or two fluoros];

Ring C is formula C-l or C-2



C-1



C-2 ;

R^3 is (l-6C)alkyl, hydroxy(l-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, or $hetAr^2$;

Ar is phenyl optionally substituted with one or more groups independently selected from halogen and (l-6C)alkyl;

$hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O; $hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

R^4 is H, OH, (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(l-6C)alkyl, hydroxy(l-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, amino(l-6C)alkyl, aminocarbonyl(l-6C)alkyl, (l-3C)alkylsulfonamido(l-6C)alkyl, sulfamido(l-6C)alkyl, hydroxycarbonyl(l-6C)alkyl, $hetAr^3$(l-6C)alkyl, Ar^3(l-6C)alkyl, (l-6C)alkoxy, monofluoro(l-6C)alkoxy, difluoro(l-6C)alkoxy, trifluoro(l-6C)alkoxy, tetrafluoro(2- 6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(l-6C)alkoxy, hydroxy(l-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(l-6C)alkoxy, $hetCyc^2$(l- 6C)alkoxy, $hetAr^3$(l-6C)alkoxy, Ar^3(l-6C)alkoxy, (1-4C alkoxy)(l-6C)alkoxy, (1-3C alkylsulfonyl)(l-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(l-6C)alkyl], $hetAr^4$, $hetAr^4$-0-, Ar^4, $hetCyc^2(O)CH_2$-, (1-4C alkoxycarbonyl)(l-6C)alkoxy, hydroxycarbonyl(l-6C)alkoxy, aminocarbonyl(l- 6C)alkoxy, $hetCyc^2C(=O)$(l-6C)alkoxy, hydroxy(l-3C alkoxy)(l-6C)alkoxy, hydroxytrifluoro(1 -6C)alkoxy, (1-3 C)alkylsulfonamido(1 -6C)alkoxy, (1-3 C)alkylamido(1 - 6C)alkoxy, di(l-3C alkyl)amino-

carboxy, hetCyc^{2}C(=O)0-, hydroxydifluoro(l-6C)alkyl, (1- 4C alkylcarboxy)(l-6C)alkyl, (l-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1- 3C alkoxy)aminocarbonyl, hetCyc , halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or hetAr^5;

hetCyc^2 is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (l-6C)alkyl, (1-4C alkylcarboxy)(l-6C)alkyl, and (l-6C)acyl;

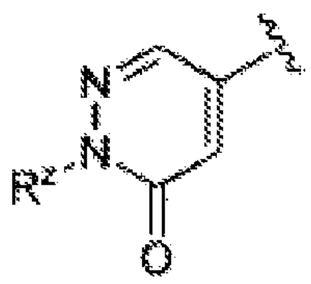
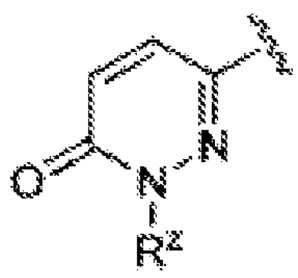
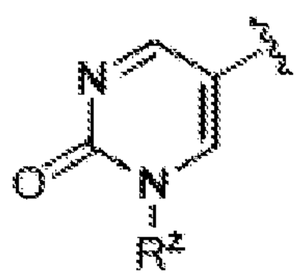
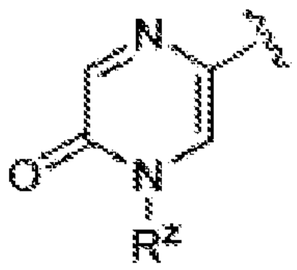
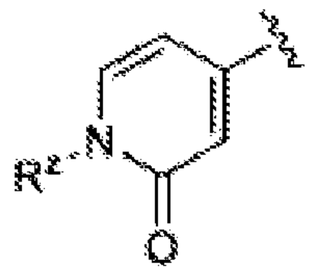
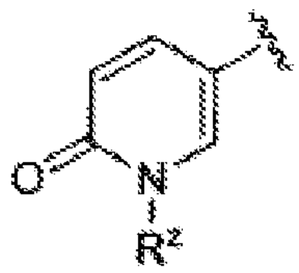
hetCyc is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (l-6C)alkyl, trifluoro(l-6C)alkyl, hydroxy(l-6C)alkyl, (1-3C alkoxy)(l-6C)alkyl, (l-6C)acyl-, (l-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1- 4C alkoxy)carbonyl;

hetAr is a 5 -membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (l-6C)alkyl;

Ar is phenyl optionally substituted with (l-4C)alkoxy;

hetAr^4 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (l-6C)alkyl, halogen, CN, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, difluoro(l-6C)alkyl, fluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2-(3-6C cycloalkyl)C(O)-, (1-3C alkoxy)(l -6C)alkyl, (l-6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(l-6C alkyl)amino, difluoro(l-6C alkyl)amino, trifluoro(l-6C alkyl)amino, and (3-4C cycloalkyl)amino;

hetAr^5 is a group selected from the structures:

where R^z is (3-4C)cycloalkyl or (l-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said $hetAr^5$ groups is optionally further substituted with one or more groups independently selected from F and (l-3C)alkyl optionally substituted with 1-3 fluoros;

Ar^4 is phenyl optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF_30-, (l-6C)alkoxy, (1-6C alkyl)OC(O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(O)- and (1- 3C alkoxy)(l-3C alkyl)OC(=O)-;

R^5 is (l-6C)alkyl, monofluoro(l-6C)alkyl, difluoro(l-6C)alkyl, trifluoro(l-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (l-4C)alkoxy, hydroxy(l-4C)alkyl, (1-3C alkoxy)(l-4C)alkyl, (1-4C alkyl)OC(=O)-, (l-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(l-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (l-6C)alkyl and (l-6C)alkoxy); or

R^4 and R^5 together with the atoms to which they are attached form a 5-6 membered saturated, partially unsaturated or unsaturated carbocyclic ring optionally substituted with one or more substituents independently selected from (l-6C)alkyl, or

R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)0-, (l-6C)acyl, (l-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2; ^{3a} is hydrogen, halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen;

R^{4a} is hydrogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, phenyl [optionally substituted with one or more groups independently selected from (l-6C)alkyl, halogen, CN, CF_3, CF_30-, (1-6C)alkoxy, (l-6Calkyl)OC(=O)-, aminocarbonyl, (l-6C)alkylthio, hydroxy(l-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(l-3C alkyl)OC(=O)-], or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and

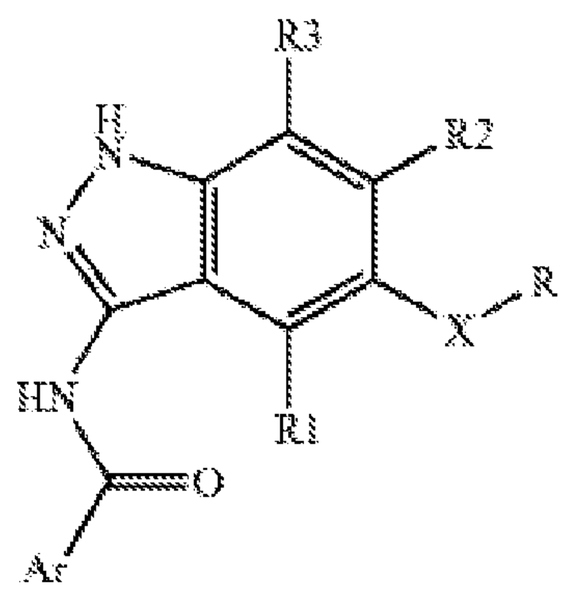
optionally substituted with 1-2 substituents independently selected from (l-6C)alkyl, hydroxy(l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(l-6C)alkyl, (l -6C)alkoxy, (l-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(l-6C alkyl)amino and (1-3C trifluoroalkoxy)(l-3C)trifluoroalkyl; and

R^{5a} is hydrogen, halogen, (l-6C)alkyl, trifluoro(l-6C)alkyl, (3-6C)cycloalkyl, phenyl optionally substituted with one or more substituents independently selected from halogen and (l-6C)alkyl, or a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (l-6C)alkyl and halogen.

Further examples of Trk inhibitors can be found in International Publication No. WO 2015175788, which is incorporated by reference in its entirety herein. For example, a Trk inhibitor can be a compound l-((3S,4R)-4-(3-fluorophenyl)-l-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(2- methylpyrimidin-5-yl)-l -phenyl- lH-pyrazol-5-yl)urea, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is a chloride salt.

Exemplary Trk inhibitors include AR-772, AR-786, AR-256, and AR-618.

Non-limiting examples of Trk inhibitors can be found in U.S. Patent No. 8,299,057 and International Publication No. WO 2009/013126 both of which are incorporated by reference in their entireties. For example, a Trk inhibitor can be a compound of Formula (I):



wherein:

X is —CH_2—, —CH(OH)—, —CH(OR′)— or —C(R′R″)—, wherein:

R′ is C_1-C_6 alkyl and R″ is hydrogen;

Ar is phenyl, pyrazolyl or pyridyl optionally substituted with one or more substituents independently selected from halogen, nitro, COR4, OR7, NR5R6, $NHSO_2R10$, a straight or branched C_1-C_6 alkyl optionally substituted by a heterocyclyl, in its turn optionally substituted by a straight or branched C_1-C_6 alkyl or an heterocyclylalkyl, or

a heterocyclyl optionally substituted by a straight or branched C_1-C_6 alkyl, in its turn optionally substituted by a heterocyclyl or a C_1-C_6 alkoxycarbonyl, or a C_1-C_6 dialkylamino:

R4 is NR5R6, or a heterocyclyl, optionally further substituted by a straight or branched C_1-C_6 alkyl, heterocyclylalkyl, heterocyclyl or a C_1-C_6 dialkylamino;

R5 and R6 are independently hydrogen, R8R9N—C_2-C_6 alkyl, R8O—C_2-C_6alkyl, a straight or branched C_1-C_6 alkyl optionally further substituted by C_1-C_6 alkoxy, C_1-C_6 dialkylamino, halogen, phenyl, hydroxyl or heterocyclyl in its turn optionally substituted by alkyl, C_3-C_6 cycloalkyl optionally substituted by hydroxyl or trifluoro C_1-C_6 alkyl, heterocyclyl optionally substituted by C_1-C_6 alkyl in its turn optionally substituted by halogen or heterocyclyl, C_1-C_6alkoxycarbonyl, C_1-C_6 dialkylamino, heterocyclyl, or phenyl,

or R5 and R6, taken together with the nitrogen atom to which they are bonded, may form a heterocyclyl group optionally substituted by a straight or branched C_1-C_6 alkyl, in its turn optionally substituted by a heterocyclyl or a C_1-C_6 alkoxycarbonyl, a C_1-C_6 dialkylamino or a heterocyclyl;

R7 is straight or branched C_1-C_6 alkyl, optionally substituted by C_1-C_6dialkylamino or heterocyclyl in its turn substituted by C_1-C_6 alkyl;

R8 and R9 are independently an optionally further substituted straight or branched C_1-C_6 alkyl;

R10 is an optionally further substituted straight or branched C_1-C_6 alkyl;

R is phenyl or pyridyl optionally substituted halogen or straight or branched C_1-C_6 alkyl;

R1, R2 and R3 are hydrogen;

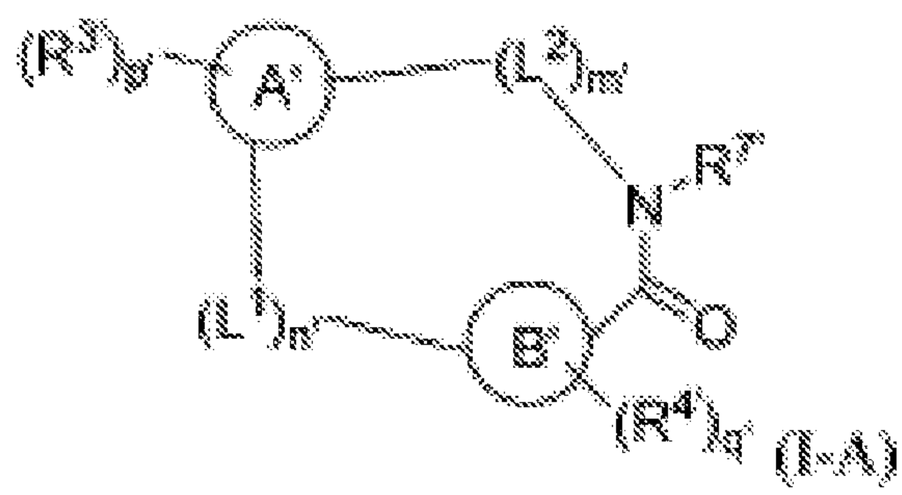
or optical isomers, tautomers or pharmaceutically acceptable salt thereof.

For example, a Trk inhibitor can be entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methyl-piperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide), or a pharmaceutically acceptable salt thereof. For example, a Trk inhibitor can be a polymorph such as those described in U.S. Publication No. 2015/0051222 or International Publication

No. WO 2013/174876, both of which are incorporated by reference in their entireties herein. In some embodiments, a Trk inhibitor can be any disclosed in U.S. Publication No. 2015/0283132, International Publication No. WO 2015/124697, U.S. Patent No. 8,946,226, International Publication No. WO 2010/012733, U.S. Patent No. 8,912,194, and International Publication No. WO 2010/058006, all of which are incorporated by reference in their entireties herein.

Additional examples of Trk inhibitors can be found in U.S. Publication No. International Publication No. WO 2015/017533, which is incorporated by reference in its entirety herein.

Further examples of Trk inhibitors can be found in U.S. Publication No. 2016/0272725 and International Publication No. WO 2015/112806, both of which are incorporated by reference in their entirety herein. For example, a Trk inhibitor can be a compound of Formula (I-A):



or a pharmaceutically acceptable salt thereof,

wherein

Ring A' and Ring B' are each independently a monocyclic or bicyclic aryl or heteroaryl; wherein one of Ring A' and Ring B' is a monocyclic aryl or heteroaryl and the other is a bicyclic heteroaryl; and at least one of Ring A' and Ring B' comprises at least one nitrogen ring member;

each L^1 and L^2 is independently $-C(R^{1'})(R^{2'})-$, -O-, $-N(R^{k'})-$, -S-, -S(O)- or $-S(O)_2$;

each R^1 and R^2 are independently H, deuterium, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or mono- or bicyclic heteroaryl, $-OR^{a'}$, $-OC(O)R^{a'}$, $-OC(O)NR^{a'}R^{b'}$, $-OS(O)R^{a'}$, $-OS(O)_2R^{a'}$, $-SR^{a'}$, $-S(O)R^{a'}$, $-S(O)_2R^{a'}$, $-S(O)NR^{a'}R^{b'}$, $-S(O)_2NR^{a'}R^{b'}$, $-OS(O)NR^{a'}R^{b'}$, $-OS(O)_2NR^{a'}R^{b'}$, $-NR^{a'}R^{b'}$, -

$NR^{a'}C(O)R^{b'}$, $-NR^{a'}C(O)OR^{b'}$, $-NR^{a'}C(O)NR^{a'}R^{b'}$, $-NR^{a'}S(O)R^{b'}$, $-NR^{a'}S(O)_2R^{b'}$, $-NR^{a'}S(O)NR^{a'}R^{b'}$, $-NR^{a'}S(O)_2NR^{a'}R^{b'}$, $-C(O)R^{a'}$, $-C(O)OR^{a'}$, $-C(O)NR^{a'}R^{b'}$, $-PR^{a'}R^{b'}$, $-P(O)R^{a'}R^{b'}$, $-P(O)_2R^{a'}R^{b'}$, $-P(O)NR^{a'}R^{b'}$, $-P(O)_2NR^{a'}R^{b'}$, $-P(O)OR^{a'}$, $-P(O)_2OR^{a'}$, -CN, or $-N0_2$, or $R^{1'}$ and $R^{2'}$ taken together with the carbon or carbons to which they are attached form a C_{3-6}cycloalkyl or a 4- to 6-membered heterocycloalkyl, wherein each hydrogen atom in C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, mono- or bicyclic heteroaryl, 4- to 6-membered heterocycloalkyl is independently optionally substituted by deuterium, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR^{e'}$, $-OC(O)R^{e'}$, $-OC(O)NR^{e'}R^{f'}$, $-OS(O)R^{e'}$, $-OS(O)_2R^{e'}$, $-OS(O)NR^{e'}R^{f'}$, $-OS(O)_2NR^{e}R^{f}$, $-SR^{e'}$, $-S(O)R^{e'}$, $-S(O)_2R^{e'}$, $-S(O)NR^{e'}R^{f'}$, $-S(O)_2NR^{e'}R^{f'}$, $-NR^{e'}R^{f'}$, $-NR^{e'}C(O)R^{f'}$, $-NR^{e'}C(O)OR^{f'}$, $-NR^{e'}C(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)R^{f'}$, $-NR^{e'}S(O)_2R^{f'}$, $-NR^{e'}S(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)_2NR^{e'}R^{f'}$, $-C(O)R^{e''}$, $-C(O)OR^{e'}$, $-C(O)NR^{e'}R^{f'}$, $-PR^{e'}R^{f'}$, $-P(O)R^{e'}R^{f'}$, $-P(O)_2R^{e'}R^{f'}$, $-P(O)NR^{e'}R^{f'}$, $-P(O)_2NR^{e'}R^{f'}$, $-P(O)OR^{e'}$, $-P(O)_2OR^{e'}$, -CN, or $-NO_2$;

each $R^{k'}$ is independently H, deuterium, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or mono- or bicyclic heteroaryl, wherein each hydrogen atom in C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-Or^{e'}$, $-OC(O)R^{e'}$, $-OC(O)NR^{e'}R^{f'}$, $-OS(O)R^{e'}$, $-OS(O)_2R^{e'}$, $-OS(O)NR^{e'}R^{f'}$, $-OS(O)_2NR^{e'}R^{f'}$, $-SR^{e'}$, $-S(O)R^{e'}$, $-S(O)_2R^{e'}$, $-S(O)NR^{e'}R^{f'}$, $-S(O)_2NR^{e'}R^{f'}$, $-NR^{e'}R^{f'}$, $-NR^{e'}C(O)R^{f'}$, $-NR^{e'}C(O)OR^{f'}$, $-NR^{e'}C(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)R^{f'}$, $-NR^{e'}S(O)_2R^{f'}$, $-NR^{e'}S(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)_2NR^{e'}R^{f'}$, $-C(O)R^{e'}$, $-C(O)OR^{e'}$, $-C(O)NR^{e'}R^{f'}$, $-PR^{e'}R^{f'}$, $-P(O)R^{e'}R^{f'}$, $-P(O)_2R^{e'}R^{f'}$, $-P(O)NR^{e'}R^{f'}$, $-P(O)_2NR^{e'}R^{f'}$, $-P(O)OR^{e'}$, $-P(O)_2OR^{e'}$, -CN, or $-NO_2$;

each $R^{3'}$ and $R^{4'}$ is independently deuterium, halogen, $-OR^{c'}$, $-OC(O)R^{c'}$, $-OC(O)NR^{c'}R^{d'}$, $-OC(=N)NR^{c'}R^{d'}$, $-OS(O)R^{c'}$, $-OS(O)_2R^{c'}$, $-OS(O)NR^{c'}R^{d'}$, $-OS(O)_2NR^{c'}R^{d'}$, $-SR^{c'}$, $-S(O)R^{c'}$, $-S(O)_2R^{c'}$, $-S(O)NR^{c'}R^{d'}$, $-S(O)_2NR^{c'}R^{d'}$, $-NR^{c'}R^{d'}$, $-NR^{c'}C(O)R^{d'}$, $-NR^{c'}C(O)OR^{d'}$, $-NR^{c'}C(O)NR^{c'}R^{d'}$, $-NR^{c'}C(=N)NR^{c'}R^{d'}$, $-NR^{c'}S(O)R^{d'}$, $-NR^{c'}S(O)_2R^{d'}$, $-NR^{c'}S(O)NR^{c'}R^{d'}$, $-NR^{c'}S(O)_2NR^{c'}R^{d'}$, $-C(O)R^{c'}$, $-C(O)OR^{c'}$, $-C(O)NR^{c'}R^{d'}$, $-C(=N)NR^{c'}R^{d'}$, $-PR^{c'}R^{d'}$, $-P(O)R^{c'}R^{d'}$, $-P(O)_2R^{c'}R^{d'}$, $-P(O)NR^{c'}R^{d'}$, $-P(O)_2NR^{c'}R^{d'}$, $-P(O)OR^{c'}$, $-P(O)_2OR^{c'}$, -CN, $-NO_2$, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or mono- or bicyclic heteroaryl, or any two $R^{3'}$ groups or any

two $R^{4'}$ groups taken together with the ring to which they are attached form a C_{5-8}cycloalkyl or a 5- to 8-membered heterocycloalkyl, wherein each hydrogen atom in C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, mono- or bicyclic heteroaryl C_{5-8}cycloalkyl or a 5- to 8-membered heterocycloalkyl is independently optionally substituted by deuterium, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, $-OR^{e'}$, $-OC(O)R^{e'}$, $-OC(O)NR^{e'}R^{f'}$, $-OS(O)R^{e'}$, $-OS(O)_2R^{e'}$, $-OS(O)NR^{e'}R^{f'}$, $-OS(O)_2NR^{e'}R^{f'}$, $-SR^{e'}$, $-S(O)R^{e'}$, $-S(O)_2R^{e'}$, $-S(O)NR^{e'}R^{f'}$, $-S(O)_2NR^{e'}R^{f'}$, $-NR^{e'}R^{f'}$, $-NR^{e'}C(O)R^{f'}$, $-NR^{e'}C(O)OR^{f'}$, $-NR^{e'}C(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)R^{f'}$, $-NR^{e'}S(O)_2R^{f'}$, $-NR^{e'}S(O)NR^{e'}R^{f'}$, $-NR^{e'}S(O)_2NR^{e'}R^{f'}$, $-C(O)R^{e'}$, $-C(O)OR^{e'}$, $-C(O)NR^{e'}R^{f'}$, $-PR^{e'}R^{f'}$, $-P(O)R^{e'}R^{f'}$, $-P(O)_2R^{e'}R^{f'}$, $-P(O)NR^{e'}R^{f'}$, $-P(O)_2NR^{e'}R^{f'}$, $-P(O)OR^{E'}$, $-P(O)_2OR^{e'}$, -CN, or $-NO_2$;

$R^{7'}$ is H, deuterium, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or mono- or bicyclic heteroaryl, wherein each hydrogen atom in C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, $-OR^{i'}$, $-OC(O)R^{i'}$, $-OC(O)NR^{i'}R^{j'}$, $-OS(O)R^{i'}$, $-OS(O)_2R^{i'}$, $-OS(O)NR^{i'}R^{j'}$, $-OS(O)_2NR^{i'}R^{j'}$, $-SR^{i'}$, $-S(O)R^{i'}$, $-S(O)_2R^{i'}$, $-S(O)NR^{i'}R^{j'}$, $-S(O)_2NR^{i'}R^{j'}$, $-NR^{i'}R^{j'}$, $-NR^{i'}C(O)R^{j'}$, $-NR^{i'}C(O)OR^{j'}$, $-NR^{i'}C(O)NR^{i'}R^{j'}$, $-NR^{i'}S(O)R^{j'}$, $-NR^{i'}S(O)_2R^{j'}$, $-NR^{i'}S(O)NR^{i'}R^{j'}$, $-NR^{i'}S(O)_2NR^{i'}R^{j'}$, $-C(O)R^{i'}$, $-C(O)OR^{i'}$, $-C(O)NR^{i'}R^{j'}$, $-PR^{i'}R^{j'}$, $-P(O)R^{i'}R^{j'}$, $-P(O)_2R^{i'}R^{j'}$, $-P(O)NR^{i'}R^{j'}$, $-P(O)_2NR^{i'}R^{j'}$, $-P(O)OR^{i'}$, $-P(O)_2OR^{i'}$, -CN, or $-NO_2$;

each $R^{a'}$, $R^{b'}$, $R^{c'}$, $R^{d'}$, $R^{e'}$, $R^{f'}$, $R^{i'}$ and $R^{j'}$ is independently selected from the group consisting of H, deuterium, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, 3- to 7-membered heterocycloalkyl, C_{6-10} aryl, and heteroaryl;

m' is 2, 3, 4, or 5;

n' is 2, 3, or 4;

p' is 0, 1, 2, 3, or 4; and

q' is 0, 1, 2, 3, or 4; or a pharmaceutically acceptable salt thereof. Exemplary Trk inhibitors include TPX-0005.

A Trk inhibitor can be one found in U.S. Patent No. 9,187,489 and International Publication No. WO 2013/183578, both of which are incorporated by reference in their entireties herein. Exemplary Trk inhibitors include PLX7486 and DS-6051.

Non-limiting examples of Trk inhibitors can be found in U.S. Publication No. 2015/0306086 and International Publication No. WO 2013/074518, both of which are incorporated by reference in their entireties herein. Exemplary Trk inhibitors include TSR-011.

Further examples of Trk inhibitors can be found in U.S. Patent No. 8,637,516, International Publication No. WO 2012/034091, U.S. Patent No. 9,102,671, International Publication No. WO 2012/116217, U.S. Publication No. 2010/0297115, International Publication No. WO 2009/053442, U.S. Patent No. 8,642,035, International Publication No. WO 2009092049, U.S. Patent No. 8,691,221, International Publication No. WO2006131952, all of which are incorporated by reference in their entireties herein. Exemplary Trk inhibitors include GNF-4256, described in *Cancer Chemother. Pharmacol.* 75(1):131-141, 2015; and GNF-5837 (N-[3-[[2,3-dihydro-2-oxo-3-(1H-pyrrol-2-ylmethylene)-1H-indol-6-yl]amino]-4-methylphenyl]-N′-[2-fluoro-5-(trifluoromethyl)phenyl]-urea), described in *ACS Med. Chem. Lett.* 3(2):140-145, 2012, each of which is incorporated by reference in its entirety herein.

Additional examples of Trk inhibitors include those disclosed in U.S. Publication No. 2010/0152219, U.S. Patent No. 8,114,989, and International Publication No. WO 2006/123113, all of which are incorporated by reference in their entireties herein. Exemplary Trk inhibitors include AZ623, described in *Cancer* 117(6):1321-1391, 2011; AZD6918, described in *Cancer Biol. Ther.* 16(3):477-483, 2015; AZ64, described in *Cancer Chemother. Pharmacol.* 70:477-486, 2012; AZ-23 ((S)-5-Chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine), described in *Mol. Cancer Ther.* 8:1818-1827, 2009; and AZD7451; each of which is incorporated by reference in its entirety.

A Trk inhibitor can include those described in U.S. Patent Nos. 7,615,383; 7,384,632; 6,153,189; 6,027,927; 6,025,166; 5,910,574; 5,877,016; and 5,844,092, each of which is incorporated by reference in its entirety.

Further examples of Trk inhibitors include CEP-751, described in *Int. J. Cancer* 72:672-679, 1997; CT327, described in *Acta Derm. Venereol.* 95:542-548, 2015; compounds described in International Publication No. WO 2012/034095; compounds described in U.S. Patent No. 8,673,347 and International Publication No. WO 2007/022999; compounds described in U.S. Patent No. 8,338,417; compounds described in International Publication

No. WO 2016/027754; compounds described in U.S. Patent No. 9,242,977; compounds described in U.S. Publication No. 2016/0000783; sunitinib (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide), as described in *PLoS One* 9:e95628, 2014; compounds described in International Publication No. WO 2011/133637; compounds described in U.S. Patent No. 8,637,256; compounds described in *Expert. Opin. Ther. Pat.* 24(7):731-744, 2014; compounds described in *Expert Opin. Ther. Pat.* 19(3):305-319, 2009; (R)-2-phenylpyrrolidine substituted imadizopyridazines, e.g., (4-((5-chloro-4-(methylamino)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)amino)-3-methoxyphenyl)(morpholino)methanone as described in ACS Med. Chem. Lett. 6(5):562-567, 2015; GTx-186 and others, as described in *PLoS One* 8(12):e83380, 2013; K252a ((9S-(9α,10β,12α))-2,3,9,10,11,12-hexahydro-10-hydroxy-10-(methoxycarbonyl)-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one), as described in *Mol. Cell Biochem.* 339(1-2):201-213, 2010; 4-aminopyrazolylpyrimidines, e.g., AZ-23 (((S)-5-chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine)), as described in *J. Med. Chem.* 51(15):4672-4684, 2008; PHA-739358 (danusertib), as described in *Mol. Cancer Ther.* 6:3158, 2007; Gö 6976 (5,6,7,13-tetrahydro-13-methyl-5-oxo-12H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-12-propanenitrile), as described in *J. Neurochem.* 72:919-924, 1999; GW441756 ((3Z)-3-[(1-methylindol-3-yl)methylidene]-1H-pyrrolo[3,2-b]pyridin-2-one), as described in *IJAE* 115:117, 2010; milciclib (PHA-848125AC), described in *J. Carcinog.* 12:22, 2013; AG-879 ((2E)-3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-cyano-2-propenethioamide); altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); cabozantinib (N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); lestaurtinib ((5S,6S,8R)-6-Hydroxy-6-(hydroxymethyl)-5-methyl-7,8,14,15-tetrahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[b,h]cycloocta[jkl]cyclopenta[e]-as-indacen-13(6H)-one); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); ONO-5390556; regorafenib (4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-

methylpyridine-2-carboxamide hydrate); VSR-902A; all of the references above are incorporated by reference in their entireties herein.

In some embodiments, a Trk inhibitor is selected from the group consisting of:

(6*R*)-9-fluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.$1^{7,11}$.$0^{2,6}$.$0^{21,25}$]hexacosa-1(24),7(26),8,10, 18(25),19,22-heptaen-17-one;

(6R)-9-fluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*,13*S*)-9-fluoro-13-hydroxy-2,11,15,19,20,23-hexaazapentacyclo-[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$] pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*,15*R*)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*,13*R*)-9-fluoro-13-hydroxy-2,11,15,19,20,23-hexaazapentacyclo-[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$] pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-9-fluoro-13-oxa-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7, 9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6*R*)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$1^{7,11}$.$0^{2,6}$.$0^{21,25}$]hexacosa-1(24),7,9,18(25),19,22-hexaene-17,26-dione;

(6*R*)-9-fluoro-2,11,13,16,20,21,24-heptaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-2,11,13,17,21,22,25-heptaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-14-oxa-2,11,18,19,22-pentaazapentacyclo[14.5.2.$1^{7,11}$.$0^{2,6}$.$0^{19,23}$]tetracosa-1(22),7,9, 16(23),17,20-hexaene-15,24-dione;

(6*R*)-9-fluoro-13,16-dioxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa- 1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*,13*R*)-9,13-difluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23), 7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-9-fluoro-17-methyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa- 1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9, 11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9, 11,18(25),19,22-heptaene;

1-[(6*R*)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

1-[(6*R*)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]-2-hydroxyethan-1-one;

(6*R*)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9, 11,19(26),20,23-heptaene;

(6*R*)-9-fluoro-16-methanesulfonyl-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$] pentacosa-1(24),7,9,11,18(25),19,22-heptaene;

2-[(6*R*)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]acetic acid;

(6*R*)-9-fluoro-17-methanesulfonyl-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaene;

(6*R*)-N-ethyl-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa- 1(25),7,9,11,19(26),20,23-heptaene-17-carboxamide;

(6*R*)-N-ethyl-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo-[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa- 1(24),7,9,11,18(25),19,22-heptaene-16-carboxamide;

(6*S*)-9-fluoro-4,13-dioxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa- 1(25),7(12),8,10,19(26),20,23-heptaene-3,18-dione;

(6*S*)-9-fluoro-4,13-dioxa-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa- 1(24),7(12),8,10,18(25),19,22-heptaene-3,17-dione;

(6*R*)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11, 18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*,13*R*)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa- 1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*,13*S*)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$]pentacosa- 1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6*R*)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6*R*)-9-fluoro-15,15-dimethyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa- 1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6*R*)-9-fluoro-13-oxa-2,11,16,17,21,25,26,29-octaazahexacyclo[21.5.2.$0^{2,6}$.$0^{7,12}$.$0^{16,20}$.$0^{26,30}$]triaconta-1(29),7,9,11,17,19,23(30),24,27-nonaen-22-one;

(6*R*)-9-fluoro-13-oxa-2,11,19,21,25,26,29-heptaazahexacyclo[21.5.2.$0^{2,6}$.$0^{7,12}$.$0^{15,20}$.$0^{26,30}$]triaconta-1(29),7,9,11,15(20),16,18,23(30),24,27-decaen-22-one;

(6R)-9-fluoro-13,13-dimethyl-2,11,15,19,20,23-hexaazapentacyclo [15.5.2.$1^{7,11}$.$0^{2,6}$.$0^{20,24}$] pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(4R,6R,15S)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4R,6S,15S)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*R*)-9-fluoro-4-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*S*)-9-fluoro-4-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$] hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*R*)-9-fluoro-4-hydroxy-13-oxa-2,16,20,21,24-pentaazapentacyclo [16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$] pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(4*R*,6*S*)-9-fluoro-4-hydroxy-13-oxa-2,16,20,21,24-pentaazapentacyclo [16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$] pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(4*R*,6*R*,15*R*)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(4*R*,6*S*,15*R*)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one; and

(15*S*)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

In some embodiments, a Trk inhibitor is selected from the group consisting of:

(R)-N-tert-butyl-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(3-methylpyridin-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((5-methylfuran-2-yl)methyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-hydroxy-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-methyl-1-morpholinopropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonyl)piperidine-4-carboxylic acid;

(R)-2-(1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carbonyl)piperidin-4-yl)acetic acid;

(R)-N-cyclopropyl-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclobutyl-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((2S)-bicyclo[2.2.1]heptan-2-yl)-5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-(hydroxymethyl)cyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-hydroxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)((S)-3-hydroxypyrrolidin-1-yl)methanone;

(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)((R)-3-hydroxypyrrolidin-1-yl)methanone;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(tetrahydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((1-methyl-1H-imidazol-4-yl)methyl) pyrazole[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((1-methyl-1H-pyrazol-4-yl)methyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(1-methyl-1H-imidazol-5-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(2-oxoimidazolidin-1-yl)ethyl) pyrazole[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-(1H-imidazol-4-yl)ethyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazole [1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((R)-2,3-dihydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N,N-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-(1H-imidazol-1-yl)ethyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-2,3-dihydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxyazetidin-1-yl)methanone;

(R)-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxy-3-methylazetidin-1-yl)methanone;

Trans-4-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)cyclohexanecarboxylic acid;

5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)-N-((*trans*)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(3-fluorophenyl)pyrrolidin-1-yl)-N-((*trans*)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-cyanopropan-2-yl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(cyanomethyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-fluoro-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-cyclopropyl-5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-tert-butyl-5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R,4R)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1-sulfamoylpiperidin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(methylsulfonamido)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-sulfamoylethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)-N-(2-hydroxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(4-hydroxy-4-methyl cyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Diastereomer 1);

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(4-hydroxy-4-methylcyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (Diasteromer 2);

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)-N-(2-morpholinoethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((S)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((R)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxyphenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-methyl-1-(methylsulfonamido)propan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-amino-2-methylpropyl)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(4,4-difluoro-2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1,3-dihydroxy-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((3S,4R)-3-fluoropiperidin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((S)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((R)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-(trifluoromethyl)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-(trifluoromethyl)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(5-(2,5-difluorophenyl)-2,2-dimethylpyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-cyanopropan-2-yl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(1-fluoro-2-methylpropan-2-yl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(tetrahydro-2H-pyran-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

((R)-5-(2-(3-fluorophenyl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(3-fluoro-5-(2-morpholinoethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(3-fluoro-5-(2-methoxyethoxy)phenyl)pyrrolidin-1-yl)pyrazole [1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(3-fluoro-5-(2-methoxyethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(1-fluoro-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-1-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)cyclopropanecarboxylic acid;

(R)-N-cyclopropyl-5-(2-(3-fluoro-5-(2-morpholinoethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-(2-morpholinoethoxy) phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoro-2-(2-morpholinoethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-2,3-dihydroxypropoxy)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoro-2-(2-methoxyethoxy)phenyl) pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxy-3-methylazetidin-1-yl)methanone;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(pyrrolidin-1-yl)methanone;

(R)-N-(5-fluoropyridin-2-yl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-methoxyazetidin-1-yl)methanone;

N-(3-chloro-2-fluoropropyl)-5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-(trifluoromethyl)cyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((cis)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclobutyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclobutyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((1S,2S)-2-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((1S,2R)-2-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((1S,3S)-3-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(cyclopropylmethyl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-(hydroxymethyl)cyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxyazetidin-1-yl)methanone;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((S)-2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((R)-2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-(1-cyclopropylethyl)-5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((R)-1-hydroxypropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((S)-1-hydroxypropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methoxypropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxy-3-methoxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((trans)-2-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((S)-1-hydroxy-3-methylbutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((R)-1-hydroxy-3-methylbutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((R)-1-cyclopropylethyl)-5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((S)-1-cyclopropylethyl)-5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(3-hydroxy-2,2-dimethylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-azetidin-1-yl(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)methanone;

(R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-(hydroxymethyl)azetidin-1-yl)methanone;

(5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)((S)-3-hydroxypyrrolidin-1-yl)methanone;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((R)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((S)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2,2,2-trifluoroethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-hydroxy-2-methylpropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((1R,2R)-2-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2,2-difluoroethyl)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((1R,2S)-2-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((1R,2R)-2-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(piperidin-1-yl)methanone;

5-((R)-2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((2R,3S,4S)-3-(hydroxymethyl)bicyclo[2.2.1]heptan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxyazetidin-1-yl)methanone;

5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-tert-butyl 3-(5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)propylcarbamate;

(R)-N-(3-aminopropyl)-5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((S)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((S)-3-chloro-2-hydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((R)-3-chloro-2-hydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-chloroethoxy)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxy-3-methylazetidin-1-yl)methanone;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(3-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-(2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((R)-2,3-dihydroxypropyl)-5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(4-hydroxybutyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-tert-butoxyethoxy)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-((1S,3S)-3-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-((S)-2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-((R)-2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(1,3-dihydroxypropan-2-yl)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(6-oxo-1,6-dihydropyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(1-(methylsulfonyl)piperidin-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-chloroethyl)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-bromoethoxy)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-hydroxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(3-hydroxy-2,2-dimethylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((1S,3S)-3-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(4-hydroxypiperidin-1-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-(4-methylpiperazin-1-yl)ethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(2-methoxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-(1,3-dihydroxypropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((2S,3R)-1,3-dihydroxybutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((2S,3S)-1,3-dihydroxybutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((2R,3S)-1,3-dihydroxybutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-1-hydroxypropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-1-hydroxybutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-1-hydroxy-3-methylbutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-N-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-cyclopropyl-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-cyclopropyl-5-(2-(2-ethyl-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclobutyl-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-((R)-2-hydroxypropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-(2-methoxyethyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(3-hydroxyazetidin-1-yl)methanone;

(R)-5-(2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-(1-(hydroxymethyl)cyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-((cis)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-((1S,3S)-3-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-((1R,2R)-2-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-2-methylpyridin-3-yl)pyrrolidin-1-yl)-N-((R)-quinuclidin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2-ethyl-5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(2-ethyl-5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-((1S,3S)-3-hydroxycyclopentyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2-ethyl-5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxy-2-methylpropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-chloroethyl)-5-(2-(5-fluoro-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-cyclopropyl-5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R)-2-(2-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-cyclopropyl-5-((2R)-2-(3-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R)-2-(3-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-cyclopropyl-5-((2R)-2-(3-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R)-2-(3-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-cyclopropyl-5-((2R)-2-(2-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R)-2-(2-(2,3-dihydroxypropoxy)-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-N-((R)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-N-((S)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R,5S)-2-(5-fluoropyridin-3-yl)-5-(hydroxymethyl)pyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-((S)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2R,4S)-2-(3-fluorophenyl)-4-hydroxypyrrolidin-1-yl)-N-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((2S,5R)-5-(5-fluoropyridin-3-yl)-2-(hydroxymethyl)-2-methylpyrrolidin-1-yl)-N-((S)-1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-(5-(2-(2-amino-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)(azetidin-1-yl)methanone;

(R)-tert-butyl 3-(5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamido)propylcarbamate;

(R)-N-(3-aminopropyl)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(2-tert-butoxyethoxy)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(2-chloro-5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(2-hydroxyethoxy)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-tert-butyl-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-isopropylpyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-(6-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclobutyl-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(cyclopropylmethyl)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-((S)-1-hydroxy-3,3-dimethylbutan-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-((1R,2R)-2-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((R)-1-cyclopropylethyl)-5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

N-((S)-1-cyclopropylethyl)-5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

5-((R)-2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-((trans)-4-hydroxycyclohexyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)pyrrolidin-1-yl)-N-(5-fluoropyridin-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(3-methyl-1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(1-methyl-1H-pyrazol-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(3-cyclopropyl-1H-pyrazol-5-yl)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-(3-ethyl-1H-pyrazol-5-yl)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide; and

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-(1-isopropyl-1H-pyrazol-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide, or a pharmaceutically acceptable salt thereof.

In some embodiments, a Trk inhibitor is selected from the group consisting of:

5-fluoro-2-[[(l S)-1-(5-fluoro-2-pyridyl)ethyl]amino]-6-[(5-isopropoxy- lH-pyrazol-3- yl)amino]pyridine-3-carbonitrile; ((2E)-3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-cyano-2-propenethioamide);

2,2-dichloro-N-[3-[(7-chloroquinolin-4-yl)amino]propyl]-N-methylacetamide;

N-[3-[[2,3-dihydro-2-oxo-3-(1H-pyrrol-2-ylmethylene)-1H-indol-6-yl]amino]-4-methylphenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]-urea;

(S)-5-chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-(S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine,4-diamine;

5,6,7,13-tetrahydro-13-methyl-5-oxo-12H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-12-propanenitrile;

1,3-dihydro-3-[(1-methyl-1H-indol-3-yl)methylene]-2H-pyrrolo[3,2-b]pyridin-2-one;

or a pharmaceutically acceptable salt thereof.

In some embodiments, a Trk inhibitor is selected from the group consisting of:

(2R)-2-({4-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-5-fluoropyrimidin-2-yl}amino)-2-(4-fluorophenyl)ethanol;

5-bromo-N^4-(3-cyclopropyl-1H-pyrazol-5-yl)-N^2-[(1S)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine;

(2R)-2-({5-chloro-4-[(3-cyclopropyl-1H-pyrazol-5-yl)amino]pyrimidin-2-yl}amino)-2-(4-fluorophenyl)ethanol;

(2R)-2-({5-chloro-4-[(3-isopropoxy-1H-pyrazol-5-yl)amino]pyrimidin-2-yl}amino)-2-(4-fluorophenyl)ethanol;

(3S)-3-({5-chloro-4-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]pyrimidin-2-yl}amino)-3-(4-fluorophenyl)-N-methylpropanamide;

2-({5-chloro-2-{[(1S)-1-(4-fluorophenyl)ethyl]amino}-6-[(5-isopropoxy-1H-pyrazol-3-yl)amino]pyrimidin-4-yl}amino)propane-1,3-diol;

2-[(5-chloro-6-[(3-cyclopropyl-1H-pyrazol-5-yl)amino]-2-{[(1S)-1-(4-fluorophenyl)ethyl]amino]pyrimidin-4-yl)amino}propane-1,3-diol;

5-chloro-N^4-(5-cyclopropyl-1H-pyrazol-3-yl)-N^2-[(1S)-(4-fluoro-phenyl)-ethyl]-6-(4-methyl-piperazin-1-yl)-pyrimidine-2,4-diamine;

(2R)-2-({4-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-7-fluoroquinazolin-2-yl}amino)-2-(4-fluorophenyl)ethanol; and

2-[(5-chloro-6-[(5-cyclopropyl-1H-pyrazol-3-yl)amino]-2-{[(1R)-1-(4-fluorophenyl)-2-hydroxyethyl]amino}pyrimidin-4-yl)amino]propane-1,3-diol;

or a pharmaceutically acceptable salt thereof.

In some embodiments, a Trk inhibitor is selected from the group consisting of:

1-(3-tert-butyl-1-phenyl-1H-pyrazol-5-yl)-3-(trans-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-tert-butyl-1-p-tolyl-1H- pyrazol-5-yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea hydrochloride;

trans-1-(4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(2-phenyl-2,4,5,6- tetrahydrocyclopenta[c]pyra- zol-3-yl)urea;

trans-1-(4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(3-isopropyl-1-phenyl- 1H-pyrazol-5-yl)urea;

1-(3-tert-butyl-1-methyl-1H- pyrazol-5-yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(1,3-dimethyl-1H-pyrazol-5- yl)-3-(trans-1-(2- methoxyethyl)-4- phenylpyrrolidin-3-yl)urea;

1-(3-tert-butyl-1-(pyridin-3- yl)-1H-pyrazol-5-yl)-3- (trans-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-tert-butyl-1-(4- fluorophenyl)-1H-pyrazol-5- yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-cyclopropyl-1-phenyl- 1H-pyrazol-5-yl)-3-(trans-1- (2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(1,3-diphenyl-1H-pyrazol- 5-yl)-3-(trans-1-(2- methoxyethyl)-4- phenylpyrrolidin-3-yl)urea;

1-(trans-1-(2-methoxyethyl)- 4-phenylpyrrolidin-3-yl)-3- (3-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-isopropyl-1-phenyl-1H- pyrazol-5-yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(trans-1-(2-methoxyethyl)- 4-phenylpyrrolidin-3-yl)-3- (1-methyl-3-phenyl-1H-pyrazol-5-yl)urea;

1-(trans-1-(2-methoxyethyl)- 4-phenylpyrrolidin-3-yl)-3- (2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyra- zol-3-yl)urea;

1-(trans-1-(2-methoxyethyl)- 4-phenylpyrrolidin-3-yl)-3- (1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-tert-butyl-1-(2- fluorophenyl)-1H-pyrazol-5- yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-tert-butyl-1-(3- fluorophenyl)-1H-pyrazol-5- yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3,4-dimethyl-1-phenyl-1H- pyrazol-5-yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(trans-1-(2-methoxyethyl)- 4-phenylpyrrolidin-3-yl)-3- (2-(pyridin-3-yl)-2,4,5,6-tetrahydrocyclopenta[c]pyra- zol-3-yl)urea;

1-(trans-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)-3-(1-methyl-1H-pyrazol-5-yl)urea;

1-(trans-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)thiourea;

1-(2-(3-fluorophenyl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-(trans-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(2-(4-fluorophenyl)-2,4,5,6- tetrahydrocyclopenta[c]pyrazol- 3-yl)-3-(trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)urea;

1-(3-cyclopentyl-1-phenyl-1H- pyrazol-5-yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(1-ethyl-3-phenyl-1H-pyrazol- 5-yl)-3-(trans-1-(2- methoxyethyl)-4- phenylpyrrolidin-3-yl)urea;

1-(trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(2- phenyl-4,5,6,7-tetrahydro-2H- indazol-3-yl)urea;

1-(trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(2- methyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol- 3-yl)urea;

1-(1,3-dimethyl-4-phenyl-1H- pyrazol-5-yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-tert-butyl-1-o-tolyl-1H- pyrazol-5-yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-tert-butyl-1-m-tolyl-1H- pyrazol-5-yl)-3-(trans-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(1- methyl-4-phenyl-1H-pyrazol- 5-yl)urea;

1-(4-cyano-3-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-(trans-1- (2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(2-(1- methyl-1H-pyrazol-4-yl)-2,4,5,6- tetrahydrocyclopenta[c]pyrazol- 3-yl)urea;

1-(3-tert-butyl-1-(tetrahyro- 2H-pyran-4-yl)-1H-pyrazol-5- yl)-3-(trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)urea;

1-(trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(2- (pyridin-2-yl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol- 3-yl)urea;

1-(6,6-dimethyl-2-phenyl- 2,4,5,6-tetrahydro-yclopenta [c]pyrazol-3-yl)-3-(trans-1-(2-methoxyethyl)-4-phenyl- pyrrolidin-3-yl)urea;

1-(7,7-dimethyl-2-phenyl- 4,5,6,7-tetrahydro-2H-indazol- 3-yl)-3-(trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)urea;

1-(trans-1-(2-methoxyethyl)-4-(pyridin-4-yl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

trans-1-(4-(3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

trans-1-(-4-(3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea;

trans-1-(4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea;

trans-1-(4-(3-chlorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea;

trans-1-(4-(2-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)urea;

trans-1-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)-3-(1-(2-methoxyethyl)-4-(thiophen-2-yl)pyrrolidin-3-yl)urea;

1-((3,4-trans)-4-(2,4-dimethylthiazol-5-yl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(trans-1-(2-methoxyethyl)-4-(oxazol-5-yl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(trans-4-(isoxazol-5-yl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3,4-trans)-1-(2-methoxyethyl)-4-(3-methoxyphenyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(1-(2-methoxyethyl)-4-(thiazol-2-yl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(1,3-diphenyl-1H-pyrazol-5-yl)-3-((3S,4R)-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)-3-(1-methyl-3-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-1-(2- methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(1- phenyl-3-(trifluoromethyl)- 1H-pyrazol-5-yl)urea;

1-(1,4-dimethyl-3-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)- 1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-cyclopropyl-1-methyl- 1H-pyrazol-5-yl)-3-((3S,4R)- 4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(1-methyl-3-(pyridin-2- yl)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(1-methyl-3-(pyridin-3- yl)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(1,1′-dimethyl-1H,1′H- 3,4′-bipyrazol-5-yl)urea;

1-(3-(3-cyanophenyl)-1- methyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(3-(4-cyanophenyl)-1- methyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(3-(imidazo[1,2- a]pyridin-5-yl)-1-methyl-1H- pyrazol-5-yl)urea;

1-(4-chloro-1,3-diphenyl- 1H-pyrazol-5-yl)-3-((3S,4R)- 4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-1,3-diphenyl- 1H-pyrazol-5-yl)-3-((3S,4R)- 4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(1,3-dimethyl-4- phenyl-1H-pyrazol-5-yl)urea;

1-(4-cyano-3-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-1-methyl-3- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-1-methyl-3- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-cyano-3-(cyanomethyl)- 1-phenyl-1H-pyrazol-5-yl)- 3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(3-(2-cyanopropan-2-yl)-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(3-ethyl-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(1′-methyl-1-phenyl- 1H,1′H-3,4′-bipyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(4-methyl-3-(oxetan-3- ylmethoxy)-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(4-methyl-3-((3- methyloxetan-3- yl)methoxy)-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(3-(((S)-2,2-dimethyl- 1,3-dioxolan-4-yl)methoxy)- 4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(3-(((R)-2,2-dimethyl- 1,3-dioxolan-4-yl)methoxy)- 4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-(3,4-dimethyl-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

tert-butyl 3-(3-((3S,4R)-1-(2- methoxyethyl)-4- phenylpyrrolidin-3-yl)ureido)-2- phenyl-4,6-dihydropyrrolo[3,4- c]pyrazole-5(2H)-carboxylate;

1-(3-isopropyl-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(2- phenyl-4,6-dihydro-2H-furo[3,4- c]pyrazol-3-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(2- phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(3,4-dimethyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(2-phenyl-2,4,5,6- tetrahydrocyclopenta[c]pyrazol-3- yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(3-isopropyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(3-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(2-phenyl-2,4,5,6- tetrahydrocyclopenta[c]pyrazol-3- yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(2-phenyl-4,6-dihydro-2H- furo[3,4-c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(2-phenyl-4,6-dihydro-2H- thieno[3,4-c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(2-phenyl-4,6-dihydro-2H- furo[3,4-c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(2-phenyl-4,6-dihydro-2H- thieno[3,4-c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(3,4-dimethyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(1-methyl-3-phenyl-1H- pyrazol-5-yl)urea;

1-(3-(1-hydroxy-2-methylpropan- 2-yl)-1-phenyl-1H-pyrazol-5-yl)- 3-((3S,4R)-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(5- oxido-2-phenyl-4,6-dihydro-2H- thieno[3,4-c]pyrazol-3-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(1- methyl-3-(pyridin-4-yl)-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-(pyridin-4-yl)-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-(thiophen-2-yl)-1H- pyrazol-5-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(3- (methoxymethyl)-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(3- (methoxymethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-p-tolyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-m-tolyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-o-tolyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(3-methoxyphenyl)-1-methyl- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(2-methoxyphenyl)-1-methyl- 1H-pyrazol-5-yl)urea;

1-(3-(4-fluorophenyl)-1-methyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(3-(4- methoxyphenyl)-1-methyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- (3- (trifluoromethyl)phenyl)pyrrolidin- 3-yl)-3-(1-methyl-3-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)-1- (2-methoxyethyl)pyrrolidin-3-yl)- 3-(1-methyl-3-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(2,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)-1- (2-methoxyethyl)pyrrolidin-3-yl)- 3-(3-(4-fluorophenyl)-1-methyl- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(4-fluorophenyl)-1-methyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(3-fluorophenyl)-1-methyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(2-fluorophenyl)-1-methyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)-1- (2-methoxyethyl)pyrrolidin-3-yl)- 3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3- yl)urea;

1-(3-(1-hydroxy-2-methylpropan- 2-yl)-4-methyl-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-1-(2- methoxyethyl)-4- phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(1-hydroxy-2-methylpropan-2- yl)-4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-(3-(4-chlorophenyl)-1-methyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(2,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(4-fluorophenyl)-1-methyl-1H- pyrazol-5-yl)urea;

methyl 4-(5-(3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)ureido)-1-methyl-1H-pyrazol- 3-yl)benzoate;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-(2-hydroxyethyl)-3-phenyl- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(methoxymethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(methoxymethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-(4- (methylthio)phenyl)-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1,3-diphenyl-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(3-methoxypropyl)-4-methyl- 1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1- (2-methoxyethyl)pyrrolidin-3-yl)- 3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3- yl)urea;

1-(3,4-dimethyl-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(4- fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(4-(2-methoxyethoxy)phenyl)- 1-methyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (4-methoxy-3-methyl-1-phenyl- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(hydroxymethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(2-hydroxyethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(2-methoxyethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-ethoxy-4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-(3-(benzyloxy)-1-methyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(2-methoxyethoxy)-4-methyl- 1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-ethoxy-4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

trans-1-(3-ethoxy-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3-1-(2- methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-methoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)urea;

1-(3-(cyanomethoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4-difluoro- phenyl)-1-(2-methoxyethyl) pyrrolidin-3-yl)-3-(3-(4-methoxybenzyloxy)-4-methyl- 1-phenyl-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(3-methoxy-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(3-(2-fluoroethoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)-3-(3-(2-hydroxy-2- methylpropoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-ethoxy-1-phenyl-1H-pyrazol- 5-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(2-hydroxyethoxy)-4-methyl- l-phenyl-1H-pyrazol-5-yl)urea;

1-(2-cyclohexyl-2,4,5,6- tetrahydrocyclopenta[c]pyrazol- 3-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)-3-(2-(pyridin-4-yl)-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1-methyl-3-(5- methylpyrazin-2-yl)-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1,4-dimethyl-3-(5- methylpyrazin-2-yl)-1H- pyrazol-5-yl)urea;

ethyl 5-(3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)ureido)-1-phenyl-1H- pyrazole-4-carboxylate;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1-methyl-3-(pyrazin-2-yl)- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-methoxy-1-methyl-4- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-ethoxy-1-methyl-4-phenyl- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl)urea dihydrochloride;

1-(5-acetyl-2-phenyl-2,4,5,6-tetrahydropyrrolo[3,4-c]pyrazol-3-yl)-3-((3S,4R)-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-(hydroxymethyl)-3-(methoxymethyl)-1-phenyl-1H-pyrazol-5-yl)urea;

4-(5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-methyl-1H-pyrazol-3-yl)benzoic acid;

4-(5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-methyl-1H-pyrazol-3-yl)benzamide;

4-(5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-methyl-1H-pyrazol-3-yl)-N-methylbenzamide;

4-(5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-methyl-1H-pyrazol-3-yl)-N,N-dimethylbenzamide;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(4-(hydroxymethyl)phenyl)-1-methyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1-methyl-3-(4-(methylsulfonyl)phenyl)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-fluoro-3-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-fluoro-1-methyl-3-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-fluoro-1,3-diphenyl-1H-pyrazol-5-yl)urea;

2-methoxyethyl 4-(5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-methyl-1H-pyrazol-3-yl)benzoate;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(5,5-dioxido-2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-yl)urea;

1-(5,5-dioxido-2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-yl)-3-((3S,4R)-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(5,5-dioxido-2-phenyl-4,6-dihydro-2H-thieno[3,4-c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(2-(methylsulfonyl)ethoxy)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-(hydroxymethyl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-((R)-2,3-dihydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-((S)-2,3-dihydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(2-hydroxyethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea hydrochloride;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-((S)-2-hydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea hydrochloride;

1-((3R,4S)-4-hydroxy-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3R,4S)-4-fluoro-1-(2-methoxyethyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(trans-4-phenyl-1-(2-(trifluoromethoxy)ethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(trans-1-(2-(methylthio)ethyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-1-((S)-2-methoxypropyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3,4-trans)-4-phenyl-1-(4,4,4-trifluorobutyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-1-(cyanomethyl)-4-(3,4-difluorophenyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-1-(cyanomethyl)-4-(3,4-difluorophenyl)pyrrolidin-3-yl)-3-(3-(2-methoxyethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3,4-trans)-1-(cyanomethyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-1-(cyanomethyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

2-((3R,4S)-3-phenyl-4-(3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)ureido)pyrrolidin-1-yl)acetamide;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-hydroxyethyl)pyrrolidin-3-yl)-3-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((trans)-1-(3,3,4,4,4-pentafluorobutyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((trans)-1-ethyl-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((trans)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)-3-((trans)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(3-(2-methoxyethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((trans)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-((trans)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(3-(2-methoxyethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(3-(2-methoxyethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(1-methyl-3-phenyl-1H-pyrazol-5-yl)urea;

1-((3R,4S)-4-(3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3R,3S)-4-(3-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-((trans)-1-(1,3-difluoropropan-2-yl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

(trans)-tert-butyl 3-(3-methoxyphenyl)-4-(3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)ureido)pyrrolidine-1-carboxylate;

1-((trans)-4-(3-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-((trans)-4-(pyridin-2-yl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-((trans)-4-(4-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((trans)-4-(4-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((trans)-4-(2-chlorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)-3-((trans)-4-(pyridin-3-yl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-((trans)-4-(2-fluorophenyl)-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((trans)-4-(4-fluorophenyl)-1-(2,2-difluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(1H-pyrazol-4-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(1H-pyrazol-4-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(1H-pyrazol-3-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(3-methyl-1H-pyrazol-4-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(3-(trifluoromethyl)-1H-pyrazol-4-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(1H-pyrazol-4-yl)pyrrolidin-3-yl)-3-(3-((S)-2-hydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(1H-pyrazol-4-yl)pyrrolidin-3-yl)-3-(3-((R)-2,3-dihydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluoro- phenyl)-1-(1H-pyrazol-4- yl)pyrrolidin-3-yl)-3-(3,4-dimethyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(1H-pyrazol- 4-yl)pyrrolidin-3-yl)-3-(3,4-dimethyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(1H-pyrazol- 4-yl)pyrrolidin-3-yl)-3-(3-(3-methoxypropyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(1H-pyrazol- 4-yl)pyrrolidin-3-yl)-3-(3-(2-methoxyethoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(1H-pyrazol- 4-yl)pyrrolidin-3-yl)-3-(3-(2-hydroxy-2-methylpropoxy)-4- methyl-1-phenyl-1H-pyrazol-5- yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (1-methyl-1H-pyrazol-5-yl)-4- phenylpyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3R,4S)-1- (1-methyl-1H-pyrazol-5-yl)-4- phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(1-methyl-1H- pyrazol-5-yl)pyrrolidin-3-yl)-3- (3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)urea;

1-((3R,4S)-4-(3,5- difluorophenyl)-1-(1-methyl-1H- pyrazol-5-yl)pyrrolidin-3-yl)-3- (3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1- phenylpyrrolidin-3-yl)-3-(3- ethoxy-4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyphenyl)pyrrolidin-3-yl)- 3-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (2-fluorophenyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (4-fluorophenyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (2-methylphenyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (2-methoxyphenyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (2-chlorophenyl)-4-phenylpyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- phenyl-1-(2-(trifluoromethoxy)phenyl)pyrroli- din-3-yl)urea;

1-((3S,4R)-1-(2,6- difluorophenyl)-4- phenylpyrrolidin-3-yl)-3-(3- ethoxy-4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (2-methoxypyridin-4-yl)-4- phenylpyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (2-methoxypyridin-3-yl)-4- phenylpyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-1- (2-ethoxypyridin-3-yl)-4- phenylpyrrolidin-3-yl)urea;

1-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)-3- ((3S,4R)-1-(2-methoxypyridin- 3-yl)-4-phenylpyrrolidin-3- yl)urea;

1-((3S,4R)-1-(2- methoxypyridin-3-yl)-4- phenylpyrrolidin-3-yl)-3-(4- methyl-1,3-diphenyl-1H- pyrazol-5-yl)urea;

1-(4-bromo-1′-methyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)-3- ((3S,4R)-1-(2-methoxypyridin- 3-yl)-4-phenylpyrrolidin-3- yl)urea;

1-(4-bromo-1,3-diphenyl-1H- pyrazol-5-yl)-3-((3S,4R)-1-(2- methoxypyridin-3-yl)-4-phenylpyrrolidin-3-yl)urea;

1-((3S,4R)-1-((1,2,3-thiadiazol-4-yl)methyl)-4-(3,4-difluorophenyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydro cyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-1-((1,2,3-thiadiazol-4-yl)methyl)-4-(3,4-difluorophenyl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-1-((1,2,3-thiadiazol-4-yl)methyl)-4-(3,4-difluorophenyl)pyrrolidin-3-yl)-3-(3-(cyanomethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-1-((1,2,3-thiadiazol-4-yl)methyl)-4-(3,4-difluorophenyl)pyrrolidin-3-yl)-3-(1′,4-dimethyl-1-phenyl-1H, 11′H-3,4′-bipyrazol-5-yl)urea;

1-((3S,4R)-1-((1,2,3-thiadiazol-4-yl)methyl)-4-(3,4-difluorophenyl)pyrrolidin-3-yl)-3-(4-methyl-3-(1-methyl-1H-imidazol-4-yl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-((1-methyl-1H-1,2,3-triazol-4-yl)methyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(1,3-dimethoxypropan-2-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(1-methoxypropan-2-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((trans)-4-(4-fluorophenyl)-1-(2-(methylamino)ethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((trans)-1-((1H-imidazol-2-yl)methyl)-4-phenylpyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

methyl 3-methoxy-2-((trans)-3-phenyl-4-(3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)ureido)pyrrolidin-1-yl)propanoate;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(1-methoxypropan-2-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(1-hydroxy-3-methoxypropan-2-yl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(3-hydroxy-1-methoxy-3-methylbutan-2-yl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

2-((3R,4S)-3-(3,4-difluorophenyl)-4-(3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)ureido)pyrrolidin-1-yl)-3-methoxypropanoic acid hydrochloride;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(1-hydroxy-3-methoxypropan-2-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-(4-chloro-1′-methyl-1-phenyl-1H, 1′H-3,4′-bipyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(1-hydroxy-3-methoxypropan-2-yl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-methoxy-1-phenyl-4-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-(3-(2-fluoroethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(3-(cyanomethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(1′,4-dimethyl-1-phenyl-1H, 1′H-3,4′-bipyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-1′-methyl-1-phenyl-1H,1′H-3,4′-bipyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(3-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(3-((R)-2,3-dihydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

(R,S)1-((2α,3β,4α)-2-methyl-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

(R,S)-1-((3 (3,4α,5α)-5-methyl-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)-3-(2-phenyl-2,4,5,6-tetrahydrocyclopenta[c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-((S)-1,1,1-trifluoro-3-hydroxypropan-2-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-((S)-1,1,1-trifluoro-3-methoxypropan-2-yl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-((S)-1,1,1-trifluoro-3-methoxypropan-2-yl)pyrrolidin-3-yl)-3-(3-((S)-2-hydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-(4-chloro-1′-methyl-1-phenyl-1H, 1′H-3,4′-bipyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-((R)-1,1,1-trifluoro-3-methoxypropan-2-yl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-((R)-1,1,1-trifluoro-3-methoxypropan-2-yl)pyrrolidin-3-yl)-3-(3-((S)-2-hydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1- (2-methoxyethyl) pyrrolidin-3-yl)-3- (3-methyl-4-(methylthio)-1- phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-(3-methoxypropyl)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-(3-(1,1-difluoro-2- hydroxyethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(3-(1,1-difluoro-2- hydroxyethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(3-(1,1-difluoro-2- hydroxyethyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(4-fluorophenyl)-1- (2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(3-(1,1-difluoro-2- hydroxyethyl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-(2-hydroxyethyl)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(3-(2-hydroxyethyl)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-(2-hydroxy-2- methylpropyl)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-((S)-2-hydroxypropyl)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-((R)-2-hydroxypropyl)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

ethyl 5-(3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)ureido)-4-methyl-1-phenyl- 1H-pyrazole-3-carboxylate;

5-(3-((3S,4R)-4-(4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)ureido)-N,4-dimethyl-1- phenyl-1H-pyrazole-3- carboxamide;

1-(trans-4-(3-chloro-4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5- yl)urea;

1-(trans-4-(4-chloro-3- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5- yl)urea;

1-(trans-4-(3-chloro-5- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5- yl)urea;

1-(trans-4-(3-chlorophenyl)-1- (2-methoxyethyl)pyrrolidin-3- yl)-3-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-(5-methyl-1,3,4- oxadiazol-2-yl)-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-(3-methyl-1,2,4- oxadiazol-5-yl)-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1-phenyl-3-(3- (trifluoromethyl)-1,2,4- oxadiazol-5-yl)-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(4-methyl-1-phenyl-3- (3-(trifluoromethyl)-1,2,4- oxadiazol-5-yl)-1H-pyrazol-5- yl)urea;

5-(3-(trans-4-(3-chloro-4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)ureido)-N,4-dimethyl-1- phenyl-1H-pyrazole-3- carboxamide;

5-(3-(trans-4-(4-chloro-3- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)ureido)-N,4-dimethyl-1- phenyl-1H-pyrazole-3- carboxamide;

1-(trans-4-(4-chloro-3- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-(1-methyl-2- oxo-1,2-dihydropyridin-4-yl)- 1-phenyl-1H-pyrazol-5-yl)urea;

1-(trans-4-(3-chloro-4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-(1-methyl-2- oxo-1,2-dihydropyridin-4-yl)- 1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1′,4,5′-trimethyl-1-phenyl- 1H,1′H-[3,3′-bipyrazol]-5- yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1′,4,5′-trimethyl-1-phenyl- 1H,1′H-[3,3′-bipyrazol]-5- yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(1′,4,5′-trimethyl-1- phenyl-1H,1′H-[3,3′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(2′,4,5′-trimethyl-1-phenyl- 1H,2′H-[3,3′-bipyrazol]-5- yl)urea;

1-(4-cyclopropyl-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-isopropyl-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-ethyl-1′-methyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1-(4-fluorophenyl)-1′,4- dimethyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1-(3-fluorophenyl)-1′,4- dimethyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1-(2-fluorophenyl)-1′,4- dimethyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1-(3-chlorophenyl)-1′,4- dimethyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-(1-(3-chloro-4- fluorophenyl)-1′,4-dimethyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(1-(3-chloro-2- fluorophenyl)-1′,4-dimethyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(1-(4-fluorophenyl)- 1′,4-dimethyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(1-(3-fluorophenyl)- 1′,4-dimethyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(1-(2-fluorophenyl)- 1′,4-dimethyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1-(3-chlorophenyl)-1′,4- dimethyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-(1-(3-chloro-4- fluorophenyl)-1′,4-dimethyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-((3S,4R)-4-(4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(1-(3-chloro-2- fluorophenyl)-1′,4-dimethyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-((3S,4R)-4-(4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(2,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5- yl)urea;

1-((3S,4R)-4-(3-cyanophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(4-cyanophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-((3S,4R)-1-(2-methoxyethyl)-4-(p- tolyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1,3-diphenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1,3-diphenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4,5- trifluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1,3-diphenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1,3-diphenyl-1H- pyrazol-5-yl)urea;

1-(4-bromo-3-methyl-1- phenyl-1H-pyrazol-5-yl)-3- trans-1-(2-methoxyethyl)-4-(1-methyl-1H-pyrazol-4- yl)pyrrolidin-3-yl)urea;

1-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-(trans-1-(2-methoxyethyl)-4- (1-methyl-1H-pyrazol-4- yl)pyrrolidin-3-yl)urea;

1-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-((trans-1-(2-methoxyethyl)-4-(1,2,3-thiadiazol-4- yl)pyrrolidin-3-yl)urea;

1-(3-ethoxy-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- (trans-1-(2-methoxyethyl)-4- (3-(trifluoromethyl)phenyl)pyrroli- din-3-yl)urea;

1-(3,4-dimethyl-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-1-(2- methoxyethyl)-4-(3-(trifluoromethyl)phenyl)pyrrol- idin-3-yl)urea;

1-((3S,4R)-4-(5-fluoropyridin- 3-yl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(2-phenyl-2,4,5,6- tetrahydrocyclopenta[c]pyrazol- 3-yl)urea;

1-((3R,4S)-4-(5-fluoropyridin- 3-yl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(2-phenyl-2,4,5,6- tetrahydrocyclopenta[c]pyrazol- 3-yl)urea;

1-(3-(2-fluoroethoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-4-(5-fluoropyridin-3-yl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(3-(2-fluoroethoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)-3-((3R,4S)-4-(5-fluoropyridin-3-yl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(trans-4-(5-fluoropyridin-3- yl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(2-phenyl-2,4,5,6- tetrahydrocyclopenta[c]pyrazol- 3-yl)urea;

1-(trans-4-(5-chloropyridin-3- yl)-1-(2-methoxyethyl) pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-(trans-4-(5-chloropyridin-3- yl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3,4-dimethyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-(trans-4-(5-fluoropyridin-3- yl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1,3-diphenyl-1H- pyrazol-5-yl)urea;

1-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-(trans-4-(5-fluoropyridin-2-yl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)- 3-((3S,4R)-4-(3-fluoropyridin-4-yl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-(1-methyl-1H- 1,2,4-triazol-3-yl)-1-phenyl- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1′-(2-methoxyethyl)-4- methyl-1-phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-(3-cyano-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1′-(2-hydroxyethyl)-4- methyl-1-phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-(2-methyl-2H- 1,2,3-triazol-4-yl)-1-phenyl- 1H-pyrazol-5-yl)urea;

1-(3-bromo-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(5-methyl-6-oxo-2-phenyl- 2,4,5,6-tetrahydropyrrolo[3,4- c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(5-methyl-6-oxo-2-phenyl- 2,4,5,6-tetrahydropyrrolo[3,4- c]pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-((5-methyl- 1,3,4-oxadiazol-2- yl)methoxy)-1-phenyl-1H- pyrazol-5-yl)urea;

1-(4-chloro-3-ethoxy-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-ethoxy-4-fluoro-1- phenyl-1H-pyrazol-5-yl)urea;

1-(4-bromo-3-(2-hydroxy-2- methylpropoxy)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(2-hydroxy-2- methylpropoxy)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-((S)-2-hydroxybutoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

ethyl 2-((5-(3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl- 1H-pyrazol-3-yl)oxy)acetate;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(3-(2-hydroxy-2-methylpropoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-(2-hydroxy-2- methylpropoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(3-((R)-2-hydroxypropoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-((R)-2-hydroxypropoxy)- 4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-((R)-2-hydroxypropoxy)- 4-methyl-1-phenyl-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1-phenyl-3-((R)- 3,3,3-trifluoro-2- hydroxypropoxy)-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(3-((S)-2-hydroxypropoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1-phenyl-3-((S)- 3,3,3-trifluoro-2- hydroxypropoxy)-1H-pyrazol- 5-yl)urea;

1-(4-chloro-3-(2-hydroxy-2- methylpropoxy)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(3,5-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(2-hydroxy-2- methylpropoxy)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-((R)-2- hydroxypropoxy)-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-((R)-2- hydroxypropoxy)-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (3,5-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-((R)-2- hydroxypropoxy)-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (4-fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-((R)-2- hydroxypropoxy)-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-((R)-2- hydroxypropoxy)-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (3,5-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-((R)-2- hydroxypropoxy)-1-phenyl- 1H-pyrazol-5-yl)-3-((3S,4R)-4- (4-fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-((R)-2-hydroxybutoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(3-((R)-2-hydroxybutoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-((R)-2-hydroxybutoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

ethyl 4-bromo-5-(3-((3S,4R)- 4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)ureido)-1-phenyl-1H- pyrazole-3-carboxylate;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(1′-(2-methoxyethyl)- 4-methyl-1-phenyl-1H,1′H- [3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(1′-(2-methoxyethyl)- 4-methyl-1-phenyl-1H,1′H- [3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(4-methyl-3-(2-methyl- 2H-1,2,3-triazol-4-yl)-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)-3-(4-methyl-3-(2-methyl- 2H-1,2,3-triazol-4-yl)-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-(2- morpholinoethoxy)-1-phenyl- 1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-(2-(1,3-dioxoisoindolin-2- yl)ethoxy)-4-methyl-1-phenyl- 1H-pyrazol-5-yl)urea;

tert-butyl 4-(2-((5-(3-((3S,4R)- 4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl- 1H-pyrazol-3- yl)oxy)ethyl)piperazine-1- carboxylate;

Trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(2- phenyl-2H-indazol-3-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(2-phenyl-2H-indazol-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-3-((1-methyl-1H- 1,2,4-triazol-3-yl)methoxy)-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-((R)-2,2-dimethyl-1,3- dioxolan-4-yl)methoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-(((S)-2,2-dimethyl-1,3- dioxolan-4-yl)methoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(3-ethoxy-4-methyl-1- (pyrazin-2-yl)-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(2-(pyridazin-4-yl)-2,4,5,6- tetrahydrocyclopenta[c]pyrazol- 3-yl)urea;

5-(3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)ureido)-4-methyl-1-phenyl- 1H-pyrazol-3-yl dimethylcarbamate;

5-(3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)ureido)-4-methyl-1-phenyl- 1H-pyrazol-3-yl morpholine-4- carboxylate;

1-(3-(((S)-2,2-dimethyl-1,3- dioxolan-4-yl)methoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-1-(2- methoxyethyl)-4-(3,4,5- trifluorophenyl)pyrrolidin-3- yl)urea;

1-(3-(((R)-2,2-dimethyl-1,3- dioxolan-4-yl)methoxy)-4- methyl-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-1-(2- methoxyethyl)-4-(3,4,5- trifluorophenyl)pyrrolidin-3- yl)urea;

1-(3-((S)-2-(tert- butyldimethylsilyloxy)propoxy)- 4-methyl-1-phenyl-1- pyrazol-5-yl)-3-((3S,4R)-1-(2- methoxyethyl)-4-(3,4,5- trifluorophenyl)pyrrolidin-3- yl)urea;

1-(3-(2-hydroxy-2- methylpropoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-1-(2-methoxyethyl)- 4-(3,4,5- trifluorophenyl)pyrrolidin-3- yl)urea;

1-(3-((S)-2-(tert- butyldimethylsilyloxy)-3- methoxypropoxy)-4-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(methoxy- methyl)-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-(methoxy- methyl)-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(methoxy- methyl)-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-4-(3,5-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-(methoxy- methyl)-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-4-(3,5-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(methoxy- methyl)-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-(methoxy- methyl)-1-phenyl-1H-pyrazol- 5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(1,1-difluoro-2- hydroxyethyl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(1,1-difluoro-2- hydroxyethyl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(3,5-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(1,1-difluoro-2- hydroxyethyl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-((S)-2- hydroxypropyl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-((R)-2- hydroxypropyl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-((R)-2- hydroxypropyl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(2-hydroxy-2- methylpropyl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(3-methyl-1,2,4- oxadiazol-5-yl)-1-phenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-(2-cyanopropan- 2-yl)-1-phenyl-1H-pyrazol-5- yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(2-cyanopropan- 2-yl)-1-phenyl-1H-pyrazol-5- yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (3,5-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3-4- (4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (3,5-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (4-fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- phenyl-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-1,3-diphenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4- (3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-1,3-diphenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4- (3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-1,3-diphenyl-1H- pyrazol-5-yl)-3-((3S,4R)-4-(4- fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-methyl-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (5-fluoropyridin-3-yl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-fluoro-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (5-fluoropyridin-3-yl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-methyl-1- phenyl-1H-pyrazol-5-yl)-3- trans-4-(5-fluoropyridin-3-yl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)urea;

1-(4-bromo-3-methyl-1- phenyl-1H-pyrazol-5-yl)-3- trans-4-(5-fluoropyridin-3-yl)- 1-(2-methoxyethyl)pyrrolidin- 3-yl)urea;

1-(4-bromo-1,3-diphenyl-1H- pyrazol-5-yl)-3-(trans-4-(5- fluoropyridin-3-yl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-1,3-diphenyl-1H- pyrazol-5-yl)-3-(trans-4-(5- fluoropyridin-3-yl)-1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-methyl-1- phenyl-1H-pyrazol-5-yl)-3- (trans-4-(5-fluoropyridin-2- yl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-fluoro-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-fluoro-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)urea;

1-(4-bromo-1′-methyl-1- phenyl-1H,1′H-[3,4′- bipyrazol]-5-yl)-3-((3S,4R)-4- (5-fluoropyridin-3-yl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,4,5-trifluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′-(4-methoxybenzyl)-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′-(4-methoxybenzyl)-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)urea trifluoroacetate;

2-(4-chloro-5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-phenyl-1H-pyrazol-3-yl)ethyl acetate;

1-(4-chloro-3-(2-hydroxyethyl)-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(cis-3-hydroxycyclobutyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(trans-3-hydroxycyclobutyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-(4-chloro-3-(cis-3-hydroxycyclobutyl)-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-3-((1r,3S)-3-hydroxycyclobutyl)-1-phenyl-1H-pyrazol-5-yl)-3-(trans-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(cis-3-hydroxycyclobutyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(trans-3-hydroxycyclobutyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(cis-3-hydroxycyclobutyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(trans-3-hydroxycyclobutyl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl-1H-pyrazole-3-carboxylic acid;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-N,4-dimethyl-1-phenyl-1H-pyrazole-3-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-N,N,4-trimethyl-1-phenyl-1H-pyrazole-3-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-N-ethyl-4-methyl-1-phenyl-1H-pyrazole-3-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-N-isopropyl-4-methyl-1-phenyl-1H-pyrazole-3-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl-1H-pyrazole-3-carboxamide;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-ethoxy-4-(hydroxymethyl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3-chloro-4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′,4-dimethyl-1-phenyl-1H,1′H-3,4′-bipyrazol-5-yl)urea;

1-((3S,4R)-4-(4-chloro-3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′,4-dimethyl-1-phenyl-1H,1′H-3,4′-bipyrazol-5-yl)urea;

1-((3S,4R)-4-(3-chloro-5-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′,4-dimethyl-1-phenyl-1H,1′H-3,4′-bipyrazol-5-yl)urea;

2-((3R,4S)-3-(3,4-difluorophenyl)-4-(3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)ureido)pyrrolidin-1-yl)acetate;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(3,3,3-trifluoro-2-hydroxypropyl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-hydroxypropyl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-1-(2-cyanoethyl)-4-(3,4-difluorophenyl)pyrrolidin-3-yl)-3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

2-((3R,4S)-3-(3,4-difluorophenyl)-4-(3-(3-ethoxy-4-methyl-1-phenyl-1H-pyrazol-5-yl)ureido)pyrrolidin-1-yl)-N-methylacetamide;

1-(1-cyclohexyl-3,4-dimethyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(3-hydroxy-2-(hydroxymethyl)propoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1-phenyl-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1-phenyl-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1-phenyl-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl)urea;

1-(3-(2,2-difluoroethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-1-phenyl-3-(2,2,2-trifluoroethoxy)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-1-phenyl-3-(pyridin-2-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-1-phenyl-3-(pyridin-4-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-bromo-1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-bromo-1-phenyl-3-(pyridin-2-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-3-phenyl-1-(pyridin-3-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1-phenyl-3-(pyridin-3-yl)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(4-methyl-1-phenyl-3- (pyridin-4-yl)-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(4-methyl-1-phenyl-3- (pyridin-2-yl)-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(3-(5-fluoropyridin-3-yl)-4- methyl-1-phenyl-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(3-(5-fluoropyridin-3-yl)-4- methyl-1-(pyridin-3-yl)-1H- pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)-3-(1′,4-dimethyl-1-phenyl- 1H,1′H-[3,3 ′-bipyrazol]-5-yl)urea;

1-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,3′-bipyrazol]-5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′,4-dimethyl-1-phenyl-1H,1′H-[3,3′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(2′,4-dimethyl-1-phenyl-1H,2′H-[3,3′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1-(5-fluoropyridin-3-yl)-1′,4-dimethyl-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′,4-dimethyl-1-(5-methylpyridin-3-yl)-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-(1-(5-chloropyridin-3-yl)-1′,4-dimethyl-1H, 1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1-phenyl-1′-(2,2,2-trifluoro-1-(2,2,2-trifluoroethoxy)ethyl)-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1-phenyl-1′-(2,2,2-trifluoroethyl)-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-(1′-(cyclopropylmethyl)-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(1′-(cyclopropanecarbonyl)-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1′-(methylsulfonyl)-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′-isopropyl-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (4-methyl-1-phenyl-3- (pyrimidin-5-yl)-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (4-methyl-3-(1-methyl-2-oxo- 1,2-dihydropyridin-4-yl)-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (4-methyl-3-(1-methyl-6-oxo- 1,6-dihydropyridin-3-yl)-1- phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1′,4,5′-trimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1′,3′,4-trimethyl-1-phenyl- 1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-(1′-cyclopropyl-4-methyl-1- phenyl-1H,1′H-[3,4′-bipyrazol]- 5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (4-methyl-3-(2-methylthiazol-5- yl)-1-phenyl-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (4-methyl-3-(2-methylpyrimidin- 5-yl)-1-phenyl-1H-pyrazol-5- yl)urea;

1-(3-(2-aminopyrimidin-5-yl)-4- methyl-1-phenyl-1H-pyrazol-5- yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(2,4-dimethylthiazol-5-yl)-4- methyl-1-phenyl-1H-pyrazol-5- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (3-(2,6-dimethylpyridin-4-yl)-4- methyl-1-phenyl-1H-pyrazol-5- yl)urea;

1-(3-(6-aminopyridin-3-yl)-4- methyl-1-phenyl-1H-pyrazol-5- yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(3-bromo-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′-isopropyl-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-bromo-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea;

1-(3-(2-aminopyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3R,4S)-4-phenyl-1-(2,2,2-trifluoroethyl)pyrrolidin-3-yl)urea bis(2,2,2-trifluoroacetate;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′-ethyl-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)urea;

1-(1′-ethyl-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl trifluoromethanesulfonate;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(2-methoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(2-(dimethylamino)pyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(2-methoxypyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-(2-(dimethylamino)pyrimidin-5-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(1′-ethyl-4-methyl-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-cyclopropyl-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(3-cyclopropyl-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-((S)-2-hydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea dihydrochloride;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1-phenyl-3-(2-(piperazin-1-yl)ethoxy)-1H-pyrazol-5-yl)urea trihydrochloride;

1-(3-(benzyloxy)-4-chloro-1-methyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

2-((5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)acetic acid;

2-((5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)-N-ethylacetamide;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-ethyl-3-(2-hydroxy-2-methylpropoxy)-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-(2-aminoethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

N-(2-((5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)ethyl)methanesulfonamide;

N-(2-((5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)ethyl)acetamide;

1-(3-(2-(4-acetylpiperazin-1-yl)ethoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

2-((5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-4-methyl-1-phenyl-1H-pyrazol-3-yl)oxy)acetamide;

N-(5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-3-ethoxy-1-phenyl-1H-pyrazol-4-yl)-2,2,2-trifluoroacetamide;

1-(4-amino-3-ethoxy-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-ethoxy-4-(2-hydroxyethyl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(2-(4-methylpiperazin-1-yl)ethoxy)-1-phenyl-1H-pyrazol-5-yl)urea trihydrochloride;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(2-morpholino-2-oxoethoxy)-1-phenyl-1H-pyrazol-5-yl)urea;

4-bromo-5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-phenyl-1H-pyrazole-3-carboxylic acid;

4-bromo-5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-N-methyl-1-phenyl-1H-pyrazole-3-carboxamide;

4-bromo-5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-N-methoxy-1-phenyl-1H-pyrazole-3-carboxamide;

1-(4-chloro-1′-(2-methoxyethyl)-1-phenyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-((S)-2,3-dihydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-((R)-2,3-dihydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-((R)-2,3-dihydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-1-(2-methoxyethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-3-yl)urea;

1-(3-((S)-2,3-dihydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-1-(2-methoxyethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-3-yl)urea;

1-(3-((S)-2-hydroxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-1-(2-methoxyethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-((S)-2-hydroxy-3-methoxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-((R)-2-hydroxy-3-methoxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-((S)-2-hydroxy-3-methoxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-1-(2-methoxyethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-3-yl)urea;

1-(3-((R)-2-hydroxy-3-methoxypropoxy)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-1-(2-methoxyethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-3-yl)urea;

1-(4-bromo-1,1′-dimethyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-1,1′-dimethyl-1H,1′H-[3,4′-bipyrazol]-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-1-phenyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

Tert-butyl 4-(4-chloro-5-(3- ((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-1-phenyl-1H-pyrazol- 3-yl)piperidine-1-carboxylate;

1-(4-chloro-1-phenyl-3- (tetrahydro-2H-pyran-4-yl)-1H- pyrazol-5-yl)-3-((3S,4R)-4-(4-fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-chloro-3-(3,5- dimethylisoxazol-4-yl)-1- phenyl-1H-pyrazol-5-yl)-3- ((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)urea;

(R)-tert-butyl 2-(4-chloro-5-(3- ((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-1-phenyl-1H-pyrazol- 3-yl)pyrrolidine-1-carboxylate;

(S)-tert-butyl 2-(4-chloro-5-(3- ((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-1-phenyl-1H-pyrazol- 3-yl)pyrrolidine-1-carboxylate;

1-(4-bromo-1-phenyl-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

Tert-butyl 4-(4-bromo-5-(3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-1-phenyl-1H- pyrazol-3-yl)piperidine-1- carboxylate;

1-(4-bromo-1-phenyl-3- (tetrahydro-2H-pyran-4-yl)- 1H-pyrazol-5-yl)-3- ((3S,4R)-4-(4-fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

1-(4-bromo-3-(3,5- dimethylisoxazol-4-yl)-1- phenyl-1H-pyrazol-5-yl)-3-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea;

(R)-tert-butyl 2-(4-bromo- 5-(3-((3S,4R)-4-(3,4- difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-1-phenyl-1H- pyrazol-3-yl)pyrrolidine-1- carboxylate;

tert-butyl 4-((4-bromo-5-(3- ((3S,4R)-4-(3,4- difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-1-phenyl-1H- pyrazol-3- yl)methoxy)piperidine-1-carboxylate;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1-phenyl-3-(piperidin-4-yl)-1H-pyrazol-5-yl)urea dihydrochloride;

1-(4-chloro-1-phenyl-3- (piperidin-4-yl)-1H-pyrazol-5- yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea dihydrochloride;

1-(4-bromo-1-phenyl-3- (piperidin-4-yl)-1H-pyrazol-5- yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea dihydrochloride;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1-phenyl-3-((R)- pyrrolidin-2-yl)-1H-pyrazol-5- yl)urea dihydrochloride;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1-phenyl-3-((S)- pyrrolidin-2-yl)-1H-pyrazol-5- yl)urea dihydrochloride;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-chloro-1-phenyl-3-((R)- pyrrolidin-2-yl)-1H-pyrazol-5- yl)urea dihydrochloride;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-1-phenyl-3-((S)- pyrrolidin-2-yl)-1H-pyrazol-5- yl)urea dihydrochloride;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(4-chloro-1-phenyl-3-((S)- pyrrolidin-2-yl)-1H-pyrazol-5- yl)urea dihydrochloride;

1-(4-bromo-1-phenyl-3-((R)- pyrrolidin-2-yl)-1H-pyrazol-5- yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea dihydrochloride;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(1-phenyl-3-((piperidin-4- yloxy)methyl)-1H-pyrazol-5- yl)urea dihydrochloride;

1-(4-chloro-1-phenyl-3- ((piperidin-4-yloxy)methyl)- 1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea dihydrochloride;

1-(4-bromo-1-phenyl-3- ((piperidin-4-yloxy)methyl)- 1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3- yl)urea dihydrochloride;

1-(4-bromo-3-(1-(methylsulfonyl)piperidin-4-yl)-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(3-(1-acetylpiperidin-4-yl)-4-bromo-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-chloro-1-phenyl-3-(1-(trifluoromethylsulfonyl)piperidin-4-yl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea hydrochloride;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-((R)-1-(methylsulfonyl)pyrrolidin-2-yl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-(3-((R)-1-acetylpyrrolidin-2-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-((R)-1-methylpyrrolidin-2-yl)-1-phenyl-1H-pyrazol-5-yl)urea dihydrochloride;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-((S)-1-methylpyrrolidin-2-yl)-1-phenyl-1H-pyrazol-5-yl)urea dihydrochloride;

1-(4-bromo-3-((1-(methylsulfonyl)piperidin-4-yloxy)methyl)-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(3-((1-acetylpiperidin-4-yloxy)methyl)-4-bromo-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-(4-isopropyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methyl-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-1-phenyl-3-(pyrazin-2-yloxy)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4-(3,4,5-trifluorophenyl)pyrrolidin-3-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-methoxy-1-phenyl-4-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,5-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-methoxy-1-phenyl-4-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-methoxy-1-phenyl-4-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-methoxy-1-phenyl-4-(trifluoromethyl)-1H-pyrazol-5-yl)urea;

1-((trans)-4-(4-chloro-3-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-5-oxo-2-phenyl-2,5-dihydro-1H-pyrazol-3-yl)urea;

1-((trans)-4-(3-chloro-4- fluorophenyl)-1-(2-methoxyethyl) pyrrolidin-3-yl)-3-(4-methyl-5- oxo-2-phenyl-2,5-dihydro-1H- pyrazol-3-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (4-methyl-5-oxo-2-phenyl-2,5- dihydro-1H-pyrazol-3-yl)urea;

1-((3S,4R)-1-(2-methoxyethyl)-4- (3,4,5-trifluorophenyl)pyrrolidin- 3-yl)-3-(4-methyl-5-oxo-2-phenyl- 2,5-dihydro-1H-pyrazol-3-yl)urea;

1-((3S,4R)-4-(3-fluorophenyl)-1- (2-methoxyethyl)pyrrolidin-3-yl)- 3-(4-methyl-5-oxo-2-phenyl-2,5- dihydro-1H-pyrazol-3-yl)urea;

1-((trans)-4-(3-chloro-5- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (4-methyl-5-oxo-2-phenyl-2,5- dihydro-1H-pyrazol-3-yl)urea;

1-(4-cyano-3-methoxy-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-((3S,4R)-4-(3-chloro-5-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-5-oxo-2-phenyl-2,5-dihydro-1H-pyrazol-3-yl)urea;

1-(4-cyano-1-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

1-(4-cyano-5-oxo-2-phenyl-2,5-dihydro-1H-pyrazol-3-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)urea;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-3-methoxy-1-phenyl-1H-pyrazole-4-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluoro-phenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-3-methyl-1-phenyl-1H- pyrazole-4-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-3-ethyl-1-phenyl-1H- pyrazole-4-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-1-phenyl-3- (trifluoromethyl)-1H-pyrazole-4- carboxamide;

5-(3-((trans)-4-(3-chloro-4- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)ureido)- 3-methyl-1-phenyl-1H-pyrazole-4- carboxamide;

5-(3-((trans)-4-(4-chloro-3- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)ureido)- 3-methyl-1-phenyl-1H-pyrazole-4- carboxamide;

5-(3-((trans)-4-(3-chloro-5- fluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)ureido)- 3-methyl-1-phenyl-1H-pyrazole-4- carboxamide;

5-(3-((3S,4R)-4-(3,5-difluorophenyl)- 1-(2-methoxyethyl)pyrrolidin-3- yl)ureido)-3-methyl-1-phenyl-1H- pyrazole-4-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-phenyl-1H-pyrazole-4-carboxamide;

5-(3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)ureido)-1-phenyl-1H-pyrazole-4-carboxamide;

1-(4-bromo-3-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)guanidine dihydrochloride;

1-(4-bromo-3-methyl-1-phenyl-1H-pyrazol-5-yl)-3-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)thiourea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(4-methyl-3-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)-1-phenyl-1H-pyrazol-5-yl)thiourea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′,4-dimethyl-1-phenyl-1H,1′H-3,4′-bipyrazol-5-yl)thiourea;

1-((3S,4R)-4-(4-fluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1′,4-dimethyl-1-phenyl-1H,1′H-3,4′-bipyrazol-5-yl)thiourea;

Trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3-(2- phenylpyrazolo[1,5-a]pyridin-3-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(2-phenylpyrazolo[1,5- a]pyridin-3-yl)urea;

Trans-1-(2-methoxyethyl)-4- phenylpyrrolidin-3-yl)-3- (pyrazolo[1,5-a]pyridin-3-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(pyrazolo[1,5-a]pyridin-3- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)- 3-(5-methyl-3-phenyl-1- (pyrazin-2-yl)-1H-pyrazol-4- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1,5-dimethyl-3-phenyl-1H- pyrazol-4-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1,5-dimethyl-3-phenyl-1H- pyrazol-4-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-isopropyl-5-methyl-3-phenyl- 1H-pyrazol-4-yl)urea;

1-((3S,4R)-4-(3,5- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-isopropyl-5-methyl-3-phenyl- 1H-pyrazol-4-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (5-methyl-3-phenyl-1-(2,2,2- trifluoroethyl)-1H-pyrazol-4- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-ethyl-5-methyl-3-phenyl-1H- pyrazol-4-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-ethyl-3-methyl-5-phenyl-1H- pyrazol-4-yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-5-phenyl-3- (trifluoromethyl)-1H-pyrazol-4- yl)urea;

1-((3S,4R)-4-(3,4- difluorophenyl)-1-(2- methoxyethyl)pyrrolidin-3-yl)-3- (1-methyl-3-phenyl-5- (trifluoromethyl)-1H-pyrazol-4- yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(3-methyl-1-phenyl-1H-pyrazol-4-yl)urea;

1-((3S,4R)-4-(3,4-difluorophenyl)-1-(2-methoxyethyl)pyrrolidin-3-yl)-3-(1-phenyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)urea;

or a pharmaceutically acceptable salt thereof.

In some embodiments, a Trk inhibitor is selected from the group consisting of:

5-Chloro-N^4-(5-cyclopropyl-1H-pyrazol-3-yl)-N^2-(1-phenylethyl)pyrimidine-2,4-diamine;

5-Bromo-N^4-(3-ethyl-1H-pyrazol-5-yl)-N^2-(1-phenylethyl) pyrimidine-2,4-diamine;

N^4-(3-tert-Butyl-1H-pyrazol-5-yl)-5-chloro-N^2-(1-phenylethyl)pyrimidine-2,4-diamine;

N^4-(3-Cyclopropyl-1H-pyrazol-5-yl)-N^2-(1-phenylethyl)- 5-(trifluoromethyl)pyrimidine-2,4-diamine;

5-Bromo-N^4-(3-cyclopropyl-1H-pyrazol-5-yl)-N^2-[(1S)-1-(4-fluorophenyl)ethyl]pyrimidine-2,4-diamine;

5-Bromo-N^4-(3-cyclopropyl-1H-pyrazol-5-yl)-N^2-[(1S)-1-phenylpropyl]pyrimidine-2,4-diamine;

5-Bromo-N^4-(3-cyclopropyl-1H-pyrazol-5-yl)-N^2-[(1S)-1-(4-nitrophenyl)ethyl]pyrimidine-2,4-diamine;

(2R)-2-({5-Bromo-4-[(3-cyclopropyl-1H-pyrazol-5-yl)amino]pyrimidin-2yl}amino)-2-phenylethanol;

5-Bromo-N^4-(5-cyclopropyl-1H-pyrazol-3-yl)-N^2-(1-phenylethyl)pyrimidine-2,4-diamine;

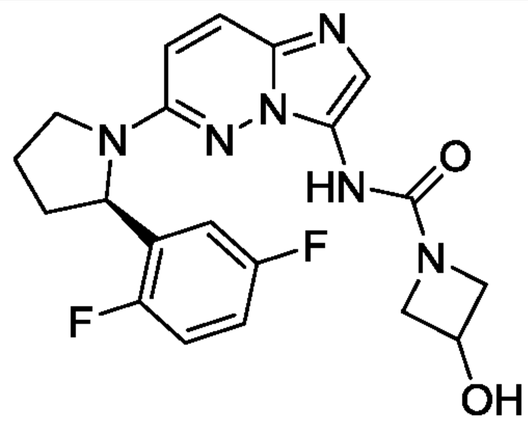
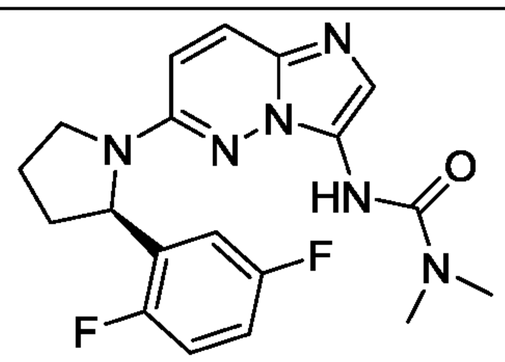
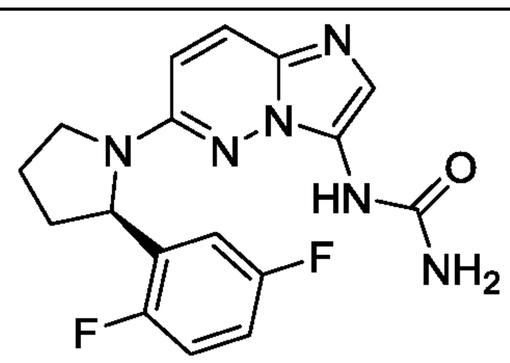
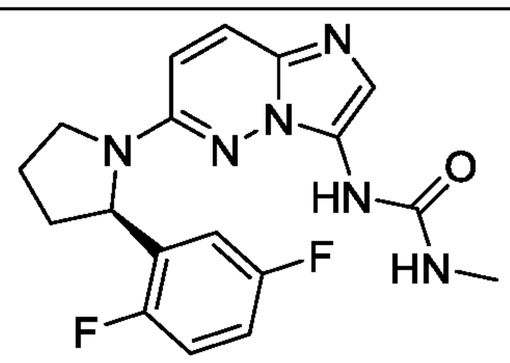
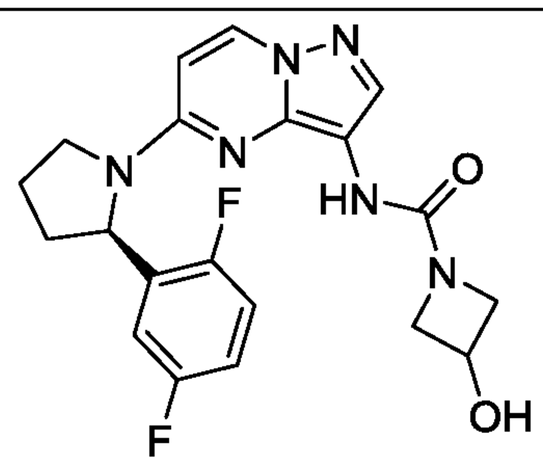
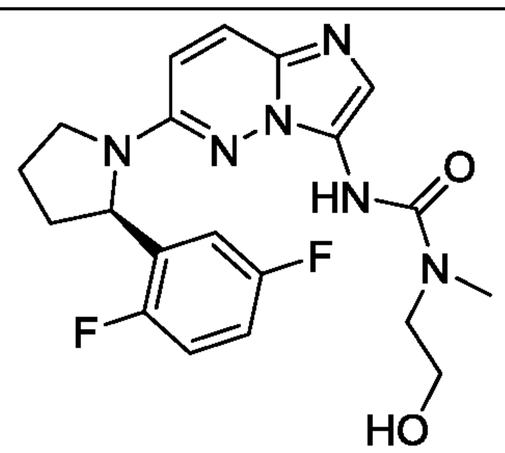
5-Chloro-N^4-(5-cyclopropyl-1H-pyrazol-3-yl)-N^2-(1-phenylpropyl)pyrimidine-2,4-diamine;

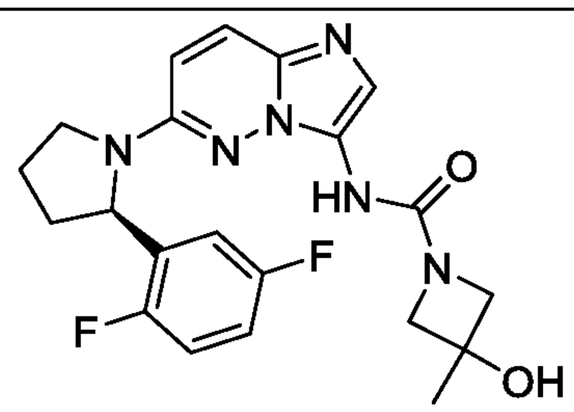
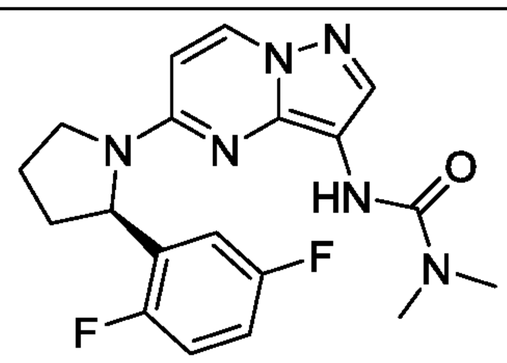
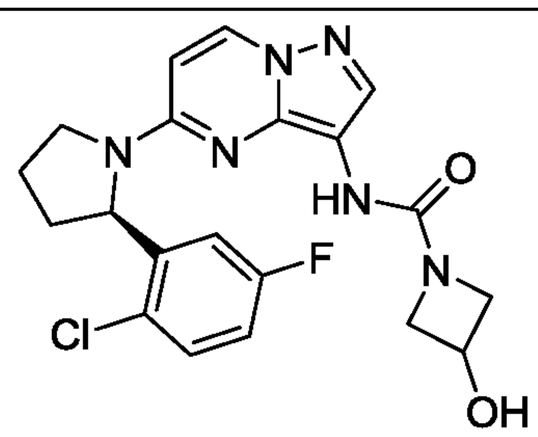
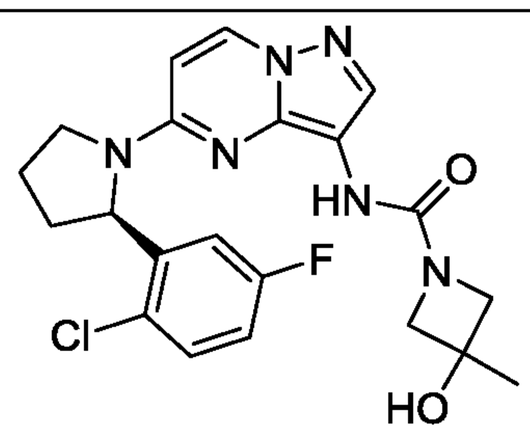
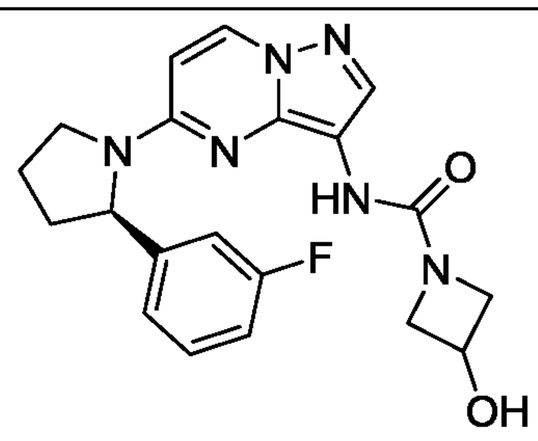
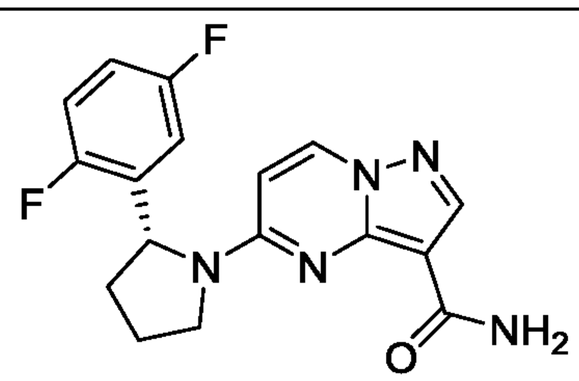
or a pharmaceutically acceptable salt thereof.

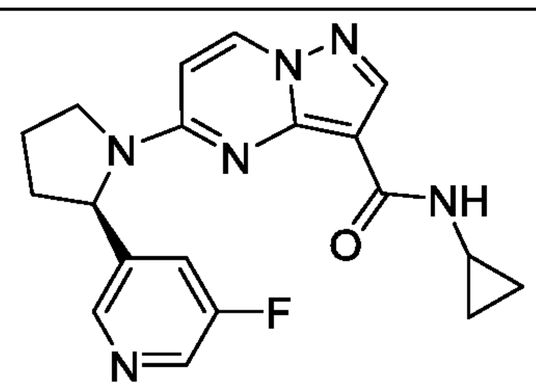
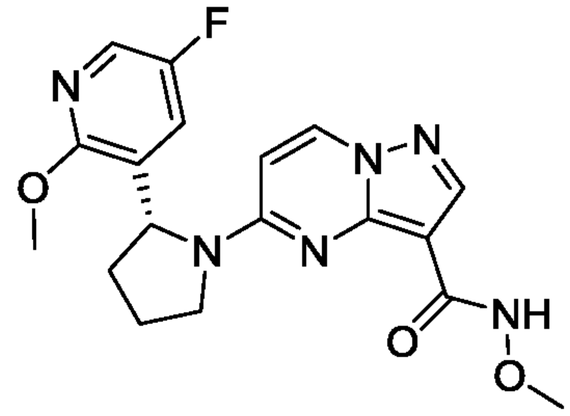
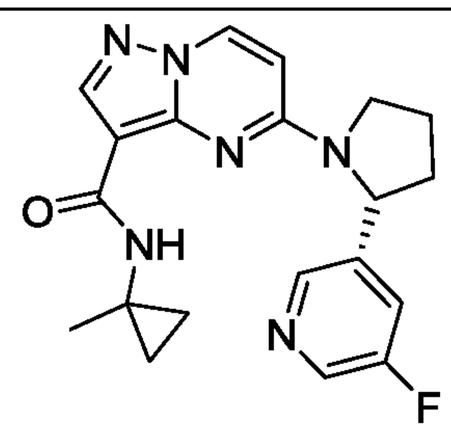
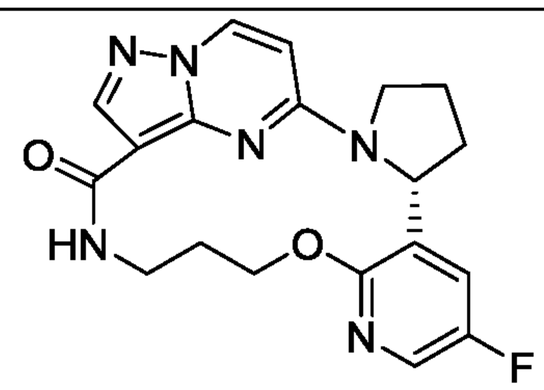
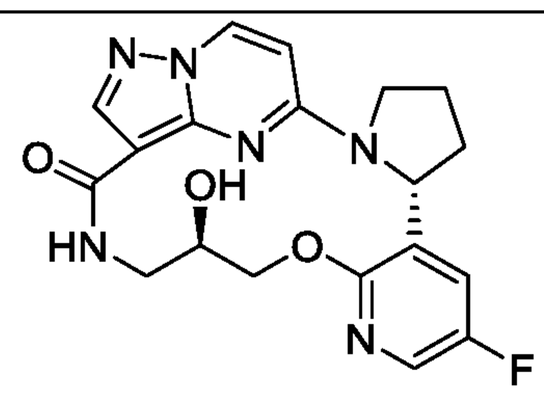
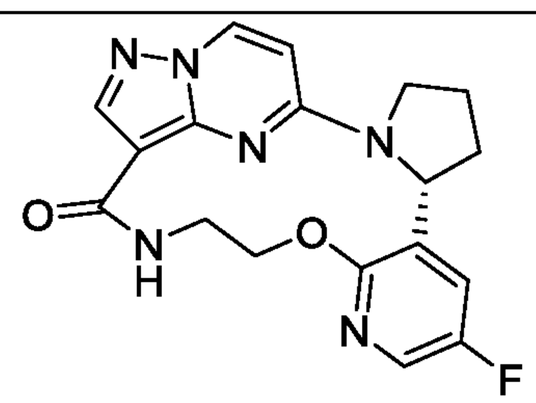
In some embodiments, a Trk inhibitor is one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

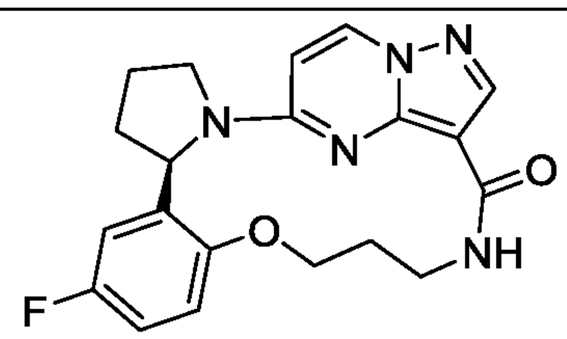
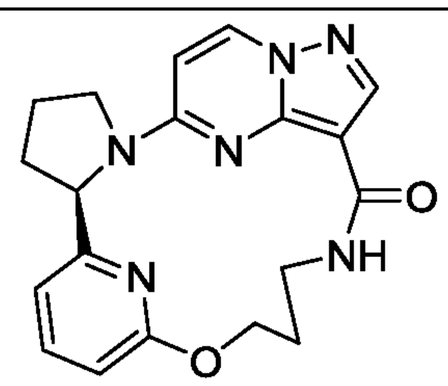
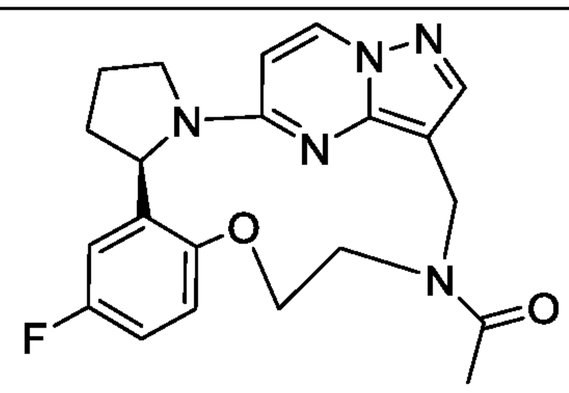
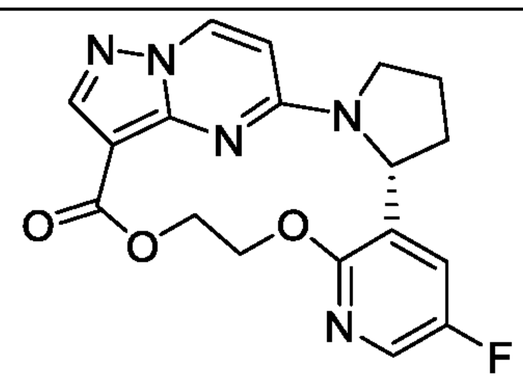
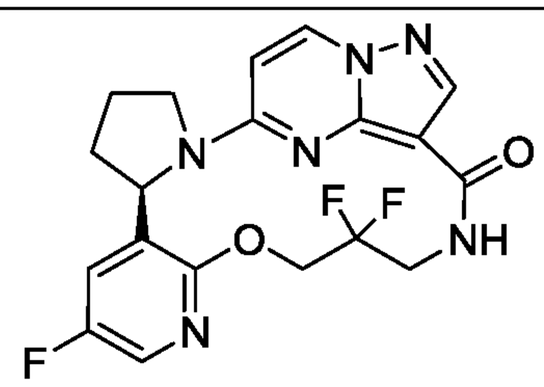
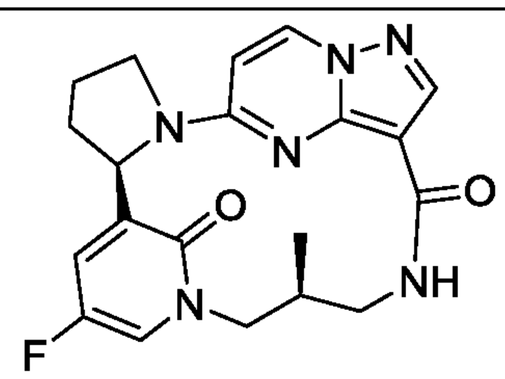
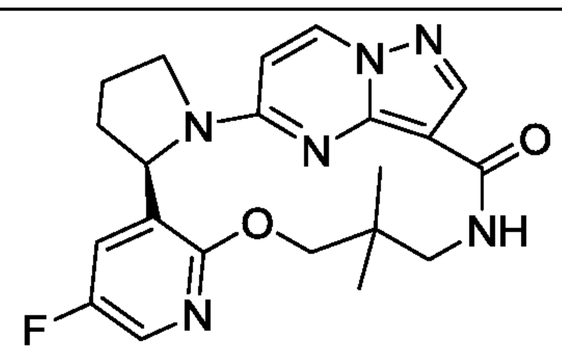
Table 5. Exemplary Trk inhibitors

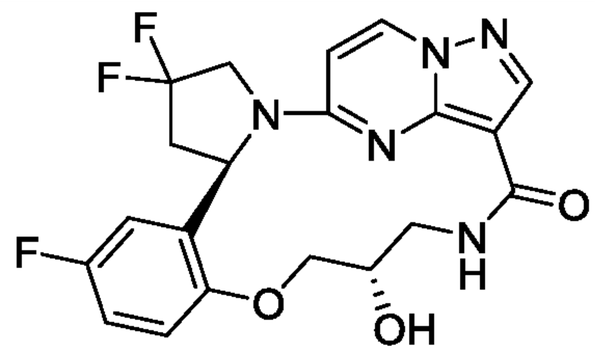
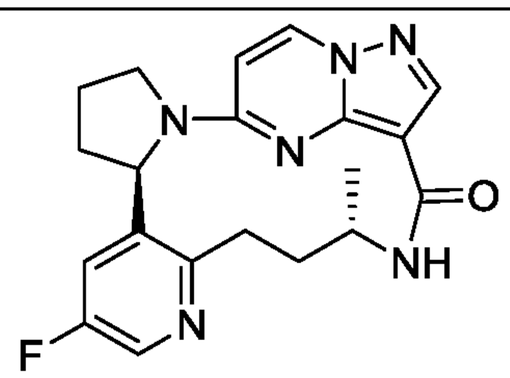
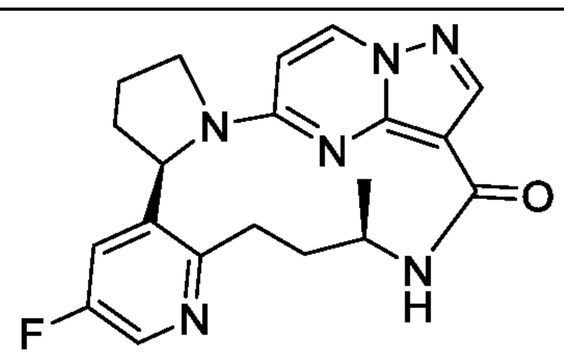
Compound No.	Compound Structure	Compound Name

1		(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide
2		(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea
3		(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea
4		(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea
5		(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide
6		(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea

7		(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide
8		(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea
9		(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide
10		(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide
11		(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide
12		(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide

13		(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
14		(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide
15		(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
16		(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
17		(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one
18		(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one

19		(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
20		(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one
21		1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one
22		(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
23		(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
24		(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
25		(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one

26		(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one
27		(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
28		(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one

Additional examples of Trk inhibitors are described in U.S. Patent Application Serial No. 62/080,374, International Application Publication Nos. WO 11/006074, WO 11/146336, WO 10/033941, and WO 10/048314, and U.S. Patent Nos. 8,933,084, 8,791,123, 8,637,516, 8,513,263, 8,450,322, 7,615,383, 7,384,632, 6,153,189, 6,027,927, 6,025,166, 5,910,574, 5,877,016, and 5,844,092, each of which is herein incorporated by reference in its entirety. Additional Trk inhibitors are known in the art.

In some embodiments, a first Trk inhibitor is selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; cabozantinib ((N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide)); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); belizatinib (4-fluoro-N-(6-((4-(2-hydroxypropan-2-yl)piperidin-1-yl)methyl)-1-((1s,4s)-4-(isopropylcarbamoyl)cyclohexyl)-1H-benzo[d]imidazol-2-yl)benzamide); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); PLX7486; altiratinib

(N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); and AZD7451 ((S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine)). For example, a first Trk inhibitor can be entrectinib or S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (or a polymorph thereof).

In some embodiments, a second Trk inhibitor is a compound of Table 5, or a pharmaceutically acceptable salt thereof.

In some embodiments, a second Trk inhibitor does not include a compound selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; cabozantinib ((N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide)); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); belizatinib (4-fluoro-N-(6-((4-(2-hydroxypropan-2-yl)piperidin-1-yl)methyl)-1-((1s,4s)-4-(isopropylcarbamoyl)cyclohexyl)-1H-benzo[d]imidazol-2-yl)benzamide); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); PLX7486; altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); and AZD7451 ((S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine)).

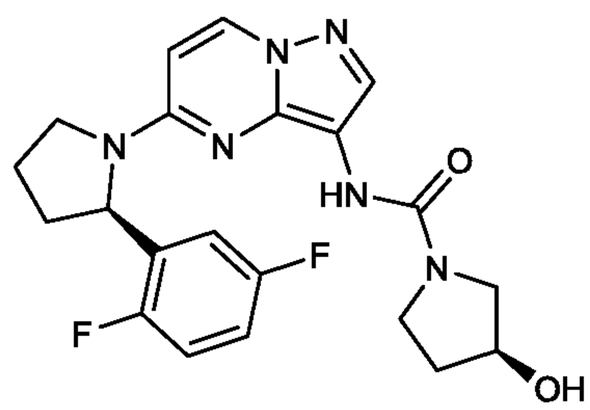
Further provided herein are pharmaceutical compositions containing one or more Trk inhibitors as provided herein with a pharmaceutically acceptable carrier. Pharmaceutical compositions containing one or more Trk inhibitors as the active ingredient can be prepared by mixing the Trk inhibitor with a pharmaceutical carrier according to conventional pharmaceutical techniques. The carrier may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral). Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols,

oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations may also be coated with substances such as sugars or be enteric-coated so as to modulate major site of absorption. For parenteral administration, the carrier will usually consist of sterile water and other ingredients may be added to increase solubility or preservation. Injectable suspensions or solutions may also be prepared.

In some embodiments, a Trk inhibitor as provided herein can be administered as a tablet or capsule.

In some embodiments, a Trk inhibitor provided herein can be administered as a liquid formulation. For example, provided herein is a liquid formulation including:

(a) (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)-pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide having the Formula I:



(I)

a pharmaceutically acceptable salt thereof, or a combination thereof;

(b) a solubilizing agent (e.g., a cyclodextrin such as a hydroxypropyl-β-cyclodextrin) present in an amount of about 5 wt.% to about 35 wt.%; and

(c) a buffer (e.g., a citrate buffer such as sodium citrate) present in an amount of about 0.1 wt.% to about 5 wt.%;

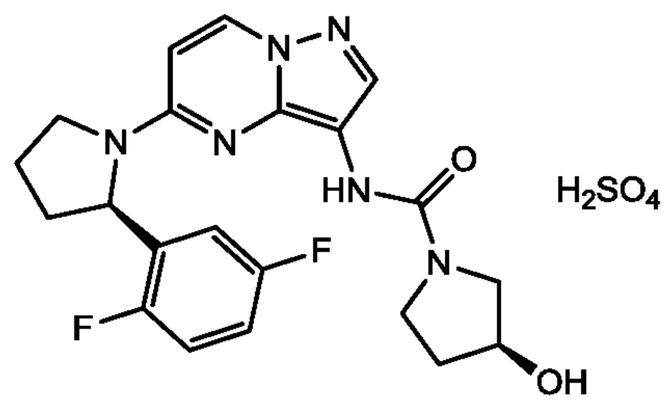
(d) a sweetener (e.g., a sweetener comprising sucrose or an intense sweetener) present in an amount of about 30 wt.% to about 70 wt.%;

(e) a bitterness masking agent present in an amount of about 0.2 wt.% to about 0.5 wt.%.; and

(f) a flavoring agent present in an amount of about 0.01 wt.% to about 2 wt.%. In some embodiments, the formulation has a pH of about 3 to about 4. In some embodiments,

the compound of Formula I has a concentration of about 20 mg/mL to about 30 mg/mL in the liquid formulation. Further examples of a liquid formulation can be found in U.S. Provisional Serial Nos. 62/380,773 and 62/329,561, both of which are incorporated by reference in their entireties herein.

In some embodiments, the liquid formulation is prepared from a pharmaceutically acceptable salt of the compound of Formula I. For example, the pharmaceutically acceptable salt is a hydrogen sulfate salt. In some embodiments, the liquid formulation is prepared from a crystalline form of the compound of Formula I. For example, the crystalline form of the compound of Formula I can have the Formula I-HS:



I-HS

In the methods provided herein, a Trk inhibitor can be orally, subcutaneously, intraperitoneally, intravenously, or intramuscularly administered. In some examples, a Trk inhibitor can be administered in one or more doses including between about 1 mg and about 250 mg, between about 1 mg and about 200 mg, between about 1 mg and about 180 mg, between about 1 mg and about 160 mg, between about 1 mg and about 140 mg, between about 1 mg and about 120 mg, between about 1 mg and about 100 mg, between about 1 mg and about 80 mg, between about 1 mg and about 60 mg, between about 1 mg and about 40 mg, between about 1 mg and about 40 mg, between about 10 mg and about 200 mg, between about 10 mg and about 180 mg, between about 10 mg and about 160 mg, between about 10 mg and about 140 mg, between about 10 mg and about 120 mg, between about 10 mg and about 100 mg, between about 10 mg and about 80 mg, between about 10 mg and about 60 mg, between about 10 mg and about 40 mg, between about 10 mg and about 20 mg, between about 20 mg and about 200 mg, between about 20 mg and about 180 mg, between about 20 mg and about 160 mg, between about 20 mg and about 140 mg, between about 20 mg and about 120 mg, between about 20 mg and about 100 mg, between about 20 mg and about 80 mg, between about 20 mg and about 60 mg, between about 20 mg and about 40 mg, between

about 40 mg and about 200 mg, between about 40 mg and about 180 mg, between about 40 mg and about 160 mg, between about 40 mg and about 140 mg, between about 40 mg and about 120 mg, between about 40 mg and about 100 mg, between about 40 mg and about 80 mg, between about 40 mg and about 60 mg, between about 60 mg and about 200 mg, between about 60 mg and about 180 mg, between about 60 mg and about 140 mg, between about 60 mg and about 120 mg, between about 60 mg and about 100 mg, between about 60 mg and about 80 mg, between about 80 mg and about 200 mg, between about 80 mg and about 180 mg, between about 80 mg and about 160 mg, between about 80 mg and about 140 mg, between about 80 mg and about 120 mg, between about 80 mg and about 100 mg, between about 90 mg and about 110 mg, between about 95 mg and about 105 mg, between about 100 mg and about 200 mg, between about 100 mg and about 180 mg, between about 100 mg and about 160 mg, between about 100 mg and about 140 mg, between about 100 mg and about 120 mg, between about 120 mg and about 200 mg, between about 120 mg and about 180 mg, between about 120 mg and about 160 mg, between about 120 mg and about 140 mg, between about 140 mg and about 200 mg, between about 140 mg and about 180 mg, between about 140 mg and about 160 mg, between about 160 mg and about 200 mg, between about 160 mg and about 180 mg, or between about 180 mg and about 200 mg of the Trk inhibitor. The appropriate dose of a Trk inhibitor to be administered to a subject can be determined by a medical professional, e.g., based upon one or more of the subject's mass, the subject's condition, subject's gender, and the other diseases that the subject may have.

Multiple doses of the Trk inhibitor (e.g., any of the doses described herein) can be administered once every six months, once every five months, once every four months, once every three months, once every two months, once every six weeks, once a month, once every three weeks, once every two weeks, once a week, twice a week, three times a week, four times a week, three times a week, every other day, once a day, twice a day, or three times a day as part of a treatment. The Trk inhibitor can be self-administered (e.g., by the subject having a cancer) or can be administered by a health care professional (e.g., a physician, a nurse, a physician's assistance, or a pharmacist) as part of a treatment as described herein.

Treatments That Do Not Include a Trk Inhibitor as a Monotherapy and Additional Anticancer Agents and Therapies

In any of the methods described herein, a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor as described herein) (e.g., entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy can be, e.g., a treatment that includes another anticancer agent or anticancer therapy. In some embodiments, a treatment that does not include a Trk inhibitor as a monotherapy can be, for example, a treatment that includes one or more of: surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant. In some embodiments, an additional anticancer agent is selected from the group consisting of: chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, and recombinant antibodies. In some embodiments, an anticancer therapy is selected from the group consisting of: surgery, radiation therapy, and stem cell transplant.

In some embodiments, a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor) as a monotherapy can be, e.g., a combination treatment that includes (i) one or more of surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant, and (ii) one or more Trk inhibitors (e.g., any of the Trk inhibitors described herein). In some embodiments, a treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes two or more Trk inhibitors (e.g., any of the Trk inhibitors described herein).

In some embodiments, a treatment that does not include a first Trk inhibitor as a monotherapy can be, e.g., a treatment that includes a second Trk inhibitor as a monotherapy. In some embodiments, a treatment that does not include a first Trk inhibitor as a monotherapy can be, e.g., a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Non-limiting examples of surgery include, e.g., open surgery or minimally invasive surgery. Surgery can include, e.g., removing an entire tumor, debulking of a tumor, or removing a tumor that is causing pain or pressure in the subject. Methods for performing

open surgery and minimally invasive surgery on a subject having a cancer are known in the art.

Non-limiting examples of radiation therapy include external radiation beam therapy (e.g., external beam therapy using kilovoltage X-rays or megavoltage X-rays) or internal radiation therapy. Internal radiation therapy (also called brachytherapy) can include the use of, e.g., low-dose internal radiation therapy or high-dose internal radiation therapy. Low-dose internal radiation therapy includes, e.g., inserting small radioactive pellets (also called seeds) into or proximal to a cancer tissue in the subject. High-dose internal radiation therapy includes, e.g., inserting a thin tube (e.g., a catheter) or an implant into or proximal to a cancer tissue in the subject, and delivering a high dose of radiation to the thin tube or implant using a radiation machine. Methods for performing radiation therapy on a subject having a cancer are known in the art.

In some embodiments provided herein, an additional anticancer agent is administered. Non-limiting examples of such additional anticancer agents are as follows.

Non-liming examples of chemotherapy include, e.g., an alkylating agent, an antimetabolite, an anti-microtubule agent, a topoisomerase inhibitor, and a cytotoxic antibiotic. Examples of alkylating agents include, e.g., nitrogen mustards (e.g., cyclophosphamide, mechlorethamine or mustine, uramustine or uracil mustard, melphalan, chlorambucil, ifosfamide, and bendamustine), nitrosoureas (e.g., carmustine, lomustine, and streptozocin), and alkyl suflonates (e.g., busulfan). Additional examples of alkylating agents include, e.g., cisplatin, carboplatin, nedaplatin, oxaliplatin, satraplatin, triplatin tetranitrate, procarbazine, altretamine, dacarbazine, mitozolomide, and temozolomide. Non-limiting examples of anti-metabolites include fluorouracil, cladribine, capecitabine, mercaptopurine, pemetrexed, fludarabine, gemcitabine, hydroxyurea, methotrexate, nelarabine, clofarabine, cytarabine, decitabine, pralatrexate, floxuridine, and thioguanine. Non-limiting examples of anti-microtubule agents include colchicine, dolastatin 15, nocodazole, paclitaxel, podophyllotoxin, rhizoxin, vinblastine, vincristine, vindesine, and vinorelbine. Non-limiting examples of topoisomerase inhibitors include camptosar, hycamtin, irinotecan, topotecan, voreloxin, camptothecin, SN-38, gimatecan, belotecan, lurtotecan, exatecan, diflometecan, S 39625, NSC 314622, NSC 706744, NSC 725776, NSC 724998, topovale (ARC-111), endotecarin (ED-709), BMS-250749, and indenoisoquinoline. Non-limiting examples of

cytotoxic antibiotics include bleomycin, dactinomycin, daunorubicin, plicamycin, mitomycin, mitoxantrone, daunorubicin, doxorubicin, epirubicin, idarubicin, and mitoxantrone. Additional examples of chemotherapy are known in the art.

Non-limiting examples of immunotherapy include adoptive cell transfer, a cytokine, a cancer vaccine, bispecific T cell engagers (e.g., Huehls et al., *Immunol. Cell Biol.* 93:290-296, 2015), and Bacillus Calmette-Guérom. Non-limiting examples of adoptive cell transfer include tumor infiltrating lymphocytes (Demaria et al., *Clin. Cancer Res.* 7:3025-3030, 2001), sensitized B cells (Li et al., *J. Immunol.* 183:3195-3203, 2009), sensitized T cells (Wang et al., *Breast Cancer Res. Treatment* 134:61-70, 2012), antigen-loaded dendritic cells (Ponsaerts et al., *Clin. Exp. Immunol.* 134:378-384, 2003), chimeric antigen receptor-T cells (CAR-T cells) (Hinrichs et al., *Immunol. Rev.* 257:56-71, 2014), artificial antigen presenting cells (aAPCs) (e.g., Turtle et al., *Cancer J.* 16:374-381, 2010), immunomodulated NK cells (e.g., Flannery et al., *Eur. J. Cancer Clin. Oncol.* 20:791-798, 1984), and T cells genetically engineered with T cell receptors (e.g., Essand et al., *J. Intern Med.* 273:166-181, 2013). Additional examples of immunotherapy are known in the art.

Non-limiting examples of hormone therapy include drugs that block estrogen, drugs that lower estrogen levels, progesterone-like drugs, and anti-androgen drugs. Examples of drugs that block estrogen include, e.g., vorozole, testolactone, formestane, tamoxifen, clomifene, arzooxifene, clomiphene, anastrozole, lentrozole, exemestane, raloxifene, toremifene, and fulvestrant. Examples of anti-progestrone agent of mifepristone and aglepristone. Examples of drugs that are anti-androgen drugs include, e.g., bicalutamide, flutamide, nilutamide, and enzalutamide. Additional examples of hormone therapy are known in the art.

Non-limiting examples of small molecule drugs targeting other kinases in a Trk-signaling pathway including inhibitors of PI3K, Akt, Ras, Raf, MEK, and ERK. Examples of a PI3K include A-769662, acalisib (GS-9820 or CAL-120), afuresertib (GSK-2110183), AMG-319, ARQ-092, AS-252424, AS-604850, AS-605240, AZD6482, BAY 80-6940, BEZ235 (NVP-BEZ235), BGT-226, buparlisib (BKM120), BYL719, CAL-101, CAY10505, CC-115, CC-223, CH5132799, copanlisib (BAY 80-6946), CUDC-907, CZC24832, D-106669, D-116883, D-87503, deguelin, DS-3078a, duvelisib (IPI-145), everolimus (RAD001), GDC-0032, GDC-0349 (RG7603), GDC-0980 (RG7422), GSK1059615,

GSK2126458, GSK-2141795, HS-173, IC-87114, idelalisib (CAL-101 or GS-1101), INCB040093, INK1117, LY2780301, LY294002 (SF1101), MK-2206, MLN0128, NU7441, OSI-027, panulisib, PF-04691502, PF376304, phenformin hydrochloride, PI-103, pictilisib (GDC-0941 or RG7321), PIK-124, PIK-294, PIK-39, PIK-90, PIK-93, PIK-402, PKI-587, PP121, PWT33597, PX-866, quercetin (sophoretin), ridaforolimus, rigosertib (ON 01910.Na), RP-6539, SAR245408 (XL147), SAR260301, SF1126, SF1326, sirolimus, staurosporine, TASP0415914, temsirolimus, TG100-115, TGR-1202, TGX221, theophylline, triciribine, VS-5584, wortmannin, XL-765 (SAR245409), and ZSTK474.

Non-limiting examples of Akt inhibitors include A-443654, A-674563, afuresertib (GSK-2110183), API-1, ARQ-094, AT7867, AZ7328, AZD-5363, CCT128930, DC120, deguelin, GDC-0068, GSK-2141795, GSK-690693, ISC-4, KP372-1, LY2780301, LY294002, Y294005, MK-2206, oleandrin (PBI-05204), palomid 529, perifosine, PF-AKT400, PHT-427, PX-316, SC66, semaxanib, SH-5, SR13668, temsirolimus, trametinib, and triciribine.

Non-limiting examples of Ras inhibitors include Kobe2602, manumycin A, L-744,832 dihydrochloride, farnesyl thiosalicylic acid, FTI-276 trifluoroacetate salt, SCH 51344, tipifarnib, and K-ras(G12C) inhibitor 12, and K-ras(G12C) inhibitor 6. Non-limiting examples of Raf inhibitors include sorafenib (Nexavar or BAY 43-9006), GDC0879, RAF265, dabrafenib (GSK2118436), vemurafenib (PLX-4032), SB590885, PLX-4720, encorafenib (LGX818), LY3009120, AZ 628, CEP-32496, TAK-632, ZM 336372, NVP-BHG712, and GW5074.

Non-limiting examples of MEK inhibitors include CI-1040, trametinib (GSK1120212), selumetinib (AZD6244), binimetinib (MEK162, ARRY-162, or ARRY-438162), PD-325901, cobimetinib (XL518), CI-1040, PD035901, U0126, PD184352 (CI-1040), PD98059, BIX 02189, pimasertib (AS-703026), BIX 02188, TAK-733, AZD8330, PD318088, honokiol, SL-327, refametinib (RDEA119 or Bay 86-9766), GDC-0623, and BI-847325.

Non-limiting examples of ERK inhibitors include SCH772984, XMD8-92, FR 180204, GDC-0994, ERK5-IN-1, ulixertinib (BVD-523 or VRT752271), FR180204, BIX 02189, pluripotin, TCS ERK 11e, TMCB, XMD 8-92, U0126, trametinib, and selumetinib.

Non-limiting examples of recombinant antibodies include monoclonal antibodies, bispecific antibodies (e.g., BiTE® antibodies), Fab, Fab_2, Fab_3, scFv, Bis-scFv, minibody, triabody, diabody, tetrabody, VhH domain, V-NAR domain, IgNAR, and camel Ig. Additional examples of a recombinant antibody (e.g., a recombinant human antibody) are IgG (e.g., IgG1, IgG2, IgG3, or IgG4), IgM, IgE, IgD, and IgA. Non-limiting examples of recombinant antibodies include human antibodies, humanized antibodies, or chimeric antibodies. Non-limiting examples of recombinant antibodies include antibodies that specifically bind to NGF.

Non-limiting examples of recombinant antibodies that bind specifically to NGF include tanezumab, futuximab, MNAC13, fasinumab (REGN475), mAb NGF30 (e.g., Saragovi et al., *J. Biol. Chem.* 273:34933-34940, 1998), ME20.4, and ME82.11. Additional antibodies that bind specifically to NGF are described, e.g., in US Patent No. 8,106,167; 8,148,107; and 8,911,734; U.S. Patent Application Publication Nos. 2009/0041717, 2011/0268725, and 2014/0227287; International Patent Application Publication Nos. WO 06/131051 and WO 12/024650; and European Patent No. 18646451.

Additional examples of recombinant antibodies include, e.g., 3F8, 8H9, abagovomab, abituzumab, adecatumumab, afutuzumab, alacizumab pegol, alemtuzumab, altumomab pentetate, amatuximab, anatumomab mefanetox, anetumab ravtansine, apolizumab, arcitumomab, ascrinvacumab, atezolizumab, bavituximab, bectumomab, belimumab, besilesomab, bevacizumab, bivatuzumab mertansine, blinatumomab, brentuximab, brontictuzumab, cantuzumab mertansine, cantuzumab ravansine, capromab pendetide, carlumab, catumaxomab, cBR96-doxorubicin immunoconjugate, CC49, cetuximab, Ch.14.18, citatuzumab bogatox, cixutumumab, clivatuzumab tetraxetan, codrituzumab, coltuximab ravtansine, conatumumab, dacetuzumab, dalotuzumab, daratumumab, demcizumab, denintuzumab mafodotin, denosumab, derlotuximab biotin, detumomab, dinutuximab, drozitumab, durvalumab, dusigitumab, ecromeximab, edrecolomab, elgemtumab, elotuzumab, emactuzumab, emibetuzumab, enavatuzumab, enfortunmab vedotin, enoblituzumab, ensituximab, epratuzumab, ertumaxomab, etaracizumab, farletuzumab, FBTA05, ficlatuzumab, figitumumab, flanvotumab, galiximab, ganitumab, gemtuzumab ozogamicin, girentuximab, glembatumumab vedotin, ibritumomab, icrucumab, igovomab, IMAB362, imalumab, imgatuzumab, indatuzimab ravtansine, indusatumab

vedotin, intetumumab, inotuzumab ozogamicin, ipilimumab, iratumumab, isatuzimab, labetuzumab, lambrolizumab, lexatumumab, lifastuzumab vedotin, lilotomab satetraxetan, lintuzumab, lorvotuzumab mertansine, lucatumumab, lumiliximab, lumretuzumab, mapatumumab, margetuximab, matuzumab, milatuzumab, mirvetuximab soravtansine, mitumomab, mogamulizumab, moxetumomab pasudotox, nacolomab tafenatox, naptumomab estafenatox, narnatumab, necitumumab, nesvacumab, nimotuzumab, nivolumab, nofetumomab merpentan, obinutuzumab, ocaratuzumab, ofatumumab, olaratumab, onartuzumab, ontuxizumab, oportuzumab monatox, oregovomab, otlertuzumab, panitumumab, pankomab, parsatuzumab, pasotuxizumab, patritumab, pembrolizumab, pemtumomab, pertuzumab, pidilizumab, pinatuzumab vedotin, pintumomab, polatuzumab vedotin, pritumumab, racotumomab, radretumab, ramucirumab, rilotumumab, rituximab, robatumumab, sacituzumab govitecan, samalizumab, satumomab pendetide, seribantumab, sibrotuzumab, SGN-CD19A, SGN-CD33A, siltuximab, sofituzumab vedotin, tabalumab, tacatuzumab tetraxetan, taplitumomab paptox, tarextumab, tenatumomab, teprotumumab, TGN1412, ticilimumab (tremelimumab), tigatuzumab, TNX-650, tositumomab, tovetumab, trastuzumab, TRBS07, tremelimumab, tucotuzumab celmoleukin, ublituximab, ulocuplumab, urelumab, vandortuzumab vedotin, vantictumab, vanucizumab, veltuzumab, volociximab, vorsetuzumab mafodotin, votumumab, zalutumamab, zanolimumab, and zatuximab.

Non-limiting examples of stem cell transplant include autologous stem cell transplant, allogeneic stem cell transplant, and syngeneic stem cell transplant. Methods for performing autologous stem cell transplant are described in, e.g., Perales et al., *Biol. Blood Marrow Transplant.*, e-published ahead of print, 2015; and Isdori et al., *World J. Stem Cells* 7:1039-1046, 2015. Methods for performing allogeneic stem cell transplant is described in, e.g., Imamura et al., *Exp. Hematol. Oncol.* 4:20, 2015; Hobbs et al., *J. Clin. Med.* 19:488-503, 2015; and Bensinger et al., *Stem Cells* 14:90-105, 1996. Methods for performing syngeneic stem cell transplant are described in, e.g., Engman et al., *Clin. Adv. Heamtol. Oncol.* 7:321-323, 2009; and Richard et al., *Br. J. Haematol.* 117:245-246, 2002. Additional methods for isolating stem cells and administering stem cells to a subject are known in the art.

In some examples, the subject is hospitalized or receives a treatment not including a Trk inhibitor as a monotherapy on in inpatient basis. In other examples, the subject is treated or receives a treatment not including a Trk inhibitor as a monotherapy on an outpatient basis.

In some examples, the subject is hospitalized or receives a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and an additional anticancer agent or anticancer therapy including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, on an inpatient basis. In other examples, the subject is treated or receives a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and an additional anticancer agent or a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, on an outpatient basis.

Methods of Treating a Subject Having a Cancer

Provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein) that include identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3, and administering to the identified subject a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy (e.g., any of treatments that do not include a Trk inhibitor as a monotherapy described herein).

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein) and identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3) that include administering to the identified subject a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy (e.g., any of treatments that do not include a Trk inhibitor as a monotherapy described herein).

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor) as a monotherapy, to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and administering to the identified subject a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and administering to the identified subject a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent (e.g., any one or more of the anticancer agents described herein) or anticancer therapy (e.g., any one or more of the anticancer therapies provided herein.

Also provided herein are methods of treating a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), that include administering to the subject a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of treating a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one

or more of the amino acid positions shown in Tables 1, 2, or 3), that include administering to the subject a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent (e.g., any one or more of the another anticancer agents described herein) or anticancer therapies (e.g., any one or more of the anticancer therapies described herein).

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject that include administering a therapeutically effective amount of a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent (e.g., any one or more of the anticancer agents described herein) or anticancer therapies (e.g., any one or more of the anticancer therapies described herein), to a subject having a clinical record that indicates that the subject has a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer that include (a) administering one or more doses Trk inhibitor (e.g., a first Trk inhibitor, such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), and (c) administering a different Trk inhibitor or a treatment that does not include the Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the

expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) administering additional doses of the Trk inhibitor of step (a) to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate), has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) administering a different Trk inhibitor than that administered in step (a) or a treatment that does not include the Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering additional doses of the Trk inhibitor of step (a) to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3). In some embodiments, the different Trk inhibitor is a second Trk inhibitor (e.g., a compound of Table 5 or a pharmaceutically acceptable salt thereof).

Also provided herein are methods of treating a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) administering a treatment including one or more doses of a second Trk inhibitor to a subject having a cancer cell that

has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) administering a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) administering a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in

Tables 1, 2, or 3); or (d) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) administering a treatment that includes one or more doses of a second Trk inhibitor to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) administering a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

Also provided herein are methods of treating a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); (b) administering a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

In some embodiments, the first Trk inhibitor of step (a) is selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; cabozantinib ((N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide)); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); belizatinib (4-fluoro-N-(6-((4-(2-hydroxypropan-2-yl)piperidin-1-yl)methyl)-1-((1s,4s)-4-(isopropylcarbamoyl)cyclohexyl)-1H-benzo[d]imidazol-2-yl)benzamide); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); PLX7486; altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); AZD7451 ((S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine). For example, the first Trk inhibitor can be entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-

yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (or a polymorph thereof).

In some embodiments, a second Trk inhibitor is a compound of Table 5, or a pharmaceutically acceptable salt thereof. For example, the second Trk inhibitor can be selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments, the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments, the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments, the second Trk inhibitor is selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

In some embodiments of the methods provided herein, the first Trk inhibitor is entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments of the methods provided herein, the first Trk inhibitor is entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments of the methods provided herein, the first Trk inhibitor is entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments of the methods provided herein, the first Trk inhibitor is entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

In some embodiments of the methods provided herein, the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments of the methods provided herein, the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments of the methods provided herein, the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof. In some embodiments of the methods provided herein, the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

Some examples of these methods further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject should be administered a treatment that does not include the Trk inhibitor in step (a) as a monotherapy or a different Trk inhibitor in the future.

Provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein) that include identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), and administering to the identified subject a treatment that includes an increased dosage of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) (e.g., as compared to control dosage of a Trk inhibitor). As used anywhere herein, a control dosage of a Trk inhibitor is a dosage of the Trk inhibitor sufficient to treat a subject having a cancer that is not a Trk inhibitor-resistant cancer (e.g., a cancer that does not include at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3)).

Also provided herein are methods of treating a subject having a cancer (e.g., any of the cancers described herein) and identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3), that include administering to the identified subject a treatment that includes an increased dosage of a Trk inhibitor (e.g., a first Trk inhibitor such

as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) (e.g., as compared to control dosage of a Trk inhibitor).

In some examples, the step of identifying a subject having a cancer cell that has the at least one point mutation (e.g., any of the point mutations described herein) in a NTRK1 gene that results in the expression of a TrkA including a mutation at one or more amino acid position(s) and/or the at least one point mutation (e.g., any of the point mutations described herein) in a NTRK2 gene that results in the expression of a TrkB including a mutation at one or more amino acid position(s), and/or the at least one point mutation (e.g., any of the point mutations described herein) in a NTRK3 gene that results in the expression of a TrkC including a mutation at one or more amino acid position(s), comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene in a cancer cell in a sample (e.g., a biopsy sample) from the subject. Any of the assays described herein can be used to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene. In addition, any of the kits provided herein can be used in an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene. In some examples, the assay includes sequencing a segment of a NTRK1 including the at least one point mutation and/or a segment of a NTRK2 gene including the at least one point mutation and/or a segment of a NTRK3 gene including the at least one point mutation.

Also provided herein are methods of treating a subject having a cancer that include (a) administering a control dosage of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (c) administering an increased dosage of the

Trk inhibitor to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (d) administering a control dosage of the Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3). As used anywhere herein, a control dosage of a Trk inhibitor is a dosage of the Trk inhibitor sufficient to treat a subject having a cancer that is not a Trk inhibitor-resistant cancer (e.g., a cancer that does not include at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3)).

Also provided herein are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a control dosage of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate), has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); and (b) administering an increased dosage of the Trk inhibitor to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3); or (c) administering a control dosage of the Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3).

The cancer can be any of the exemplary cancers described herein. In some embodiments, the subject has previously been identified or diagnosed as having a cancer. In

some examples, the subject has previously been administered a treatment for cancer, and the treatment for cancer has been unsuccessful (e.g., high toxicity in the subject or no positive response to the previously administered treatment for cancer).

Some examples of these methods further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject should be administered a treatment that includes an increased dosage of a Trk inhibitor in the future.

Some embodiments of these methods include administering an increased dosage of the Trk inhibitor in step (b). Some embodiments of these methods include administering a control dosage of a Trk inhibitor in step (c).

Some examples of these methods further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject should be administered an elevated dosage of the Trk inhibitor in the future. Some examples of these methods further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject should be administered a treatment that does not include a Trk inhibitor as a monotherapy in the future.

In some of the embodiments provided herein, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions includes (i) at least one (e.g., one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I,

G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A). In some embodiments, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions is selected from a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3.

Methods of Selecting a Treatment for a Subject Having a Cancer

Also provided herein are methods of selecting a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy for a subject having a cancer (e.g., any of the cancers described herein) that include identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), and selecting a treatment that does not include a Trk inhibitor as a monotherapy (e.g., any of the treatments that do not include a Trk inhibitor as a monotherapy described herein) for the identified subject.

Also provided herein are methods of selecting a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy for a subject having a cancer (e.g., any of the treatments that do not include a Trk inhibitor as a monotherapy described herein) that include selecting a treatment that does not include a Trk inhibitor as a monotherapy (e.g., any of the treatments that do not include a Trk inhibitor as a monotherapy described herein) for a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene

that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Some of these methods include selecting a different Trk inhibitor (e.g., a second Trk inhibitor) or a treatment that does not include the Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3). In some embodiments, the different Trk inhibitor is a compound of Table 5, or a

Also provided herein are methods of selecting a treatment for a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, for the identified subject.

Also provided herein are methods of selecting a treatment for a subject having a cancer (e.g., any of the cancers described herein or known in the art) that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent (e.g., any one or more of the anticancer agents described herein or known in the art) or anticancer therapy (e.g., any one or more of the anticancer therapies described herein or known in the art) for the identified subject.

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, for a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent (e.g., any one or more of the anticancer agents described herein or known in the art) or anticancer therapy (e.g., any one or more of the anticancer therapies described herein or known in the art) for a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: (a) administering one or more doses Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and (c) selecting a different Trk inhibitor or a treatment that does not include the Trk inhibitor of step (a) (e.g., (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (d) selecting additional doses of the Trk inhibitor of step (a) (e.g., (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-

difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate), has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); (b) selecting a different Trk inhibitor or a treatment that does not include the Trk inhibitor of step (a) as a monotherapy for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (c) selecting additional doses of the Trk inhibitor of step (a) for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and (c) selecting a treatment including one or more doses of a second Trk inhibitor for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a

mutation at one or more amino acid positions shown in Table 1, 2, or 3); and (c) selecting a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) administering one or more doses of a first Trk inhibitor to the subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and (c) selecting a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); (b) selecting a treatment that includes one or more doses of a second Trk inhibitor to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more

amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); (b) selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment for a subject having a cancer, that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); (b) selecting a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and an another anticancer agent or anticancer therapy to a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression

of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of selecting a treatment that includes an increased dosage of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) (e.g., as compared to control dosage of a Trk inhibitor) for a subject having a cancer (e.g., any of the cancers described herein) that include identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), and selecting an increased dosage of a Trk inhibitor (e.g., as compared to control dosage of a Trk inhibitor) for the identified subject. As used anywhere herein, a control dosage of a Trk inhibitor is a dosage of the Trk inhibitor sufficient to treat a subject having a cancer that is not a Trk inhibitor-resistant cancer (e.g., a cancer that does not include at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3)).

Also provided herein are methods of selecting a treatment that includes an increased dosage of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) (e.g., as compared to control dosage of a Trk inhibitor) for a subject having a cancer (e.g., any of the cancers described herein) that include selecting a treatment that includes an increased dosage of a Trk inhibitor (e.g., as compared to control dosage of a Trk inhibitor) for a subject identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3)).

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: (a) administering a control dosage of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) to the

subject for a period of time; (b) after (a), determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and (c) selecting an increased dosage of the Trk inhibitor for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (d) selecting a control dosage of the Trk inhibitor for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3). As used anywhere herein, a control dosage of a Trk inhibitor is a dosage of the Trk inhibitor sufficient to treat a subject having a cancer that is not a Trk inhibitor-resistant cancer (e.g., a cancer that does not include at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3)).

Also provided herein are methods of selecting a treatment for a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a control dosage of a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate), has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); (b) selecting an increased dosage of the Trk inhibitor for a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); or (c) selecting a control dosage of the Trk inhibitor for a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Some examples of these methods further include administering the selected treatment to the identified subject. In some examples, the selected treatment is self-administered. In other examples, the selected treatment is administered by a medical professional (e.g., any of the medical professionals described herein). Some examples of these methods further include recording the selected treatment in the identified subject's clinical record (e.g., a computer readable medium).

In some of the embodiments provided herein, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions includes (i) at least one (e.g., one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A). In some embodiments, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or

more amino acid positions is selected from a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3.

Methods of Selecting a Subject Having a Cancer for Treatment

Also provided herein are methods of selecting a subject having a cancer for a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy that include identifying a subject as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), and selecting the identified subject for a treatment that does not include a Trk inhibitor as a monotherapy (e.g., any of the treatments that do not include a Trk inhibitor as a monotherapy described herein).

Also provided herein are methods of selecting a subject having a cancer for a treatment that does not include a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy that include selecting a subject having a cancer (e.g., any of the cancers described herein) and identified as having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), for a treatment that does not include a Trk inhibitor as a monotherapy (e.g., any of the treatments that do not include a Trk inhibitor as a monotherapy described herein).

In some examples, the treatment that does not include a Trk inhibitor as a monotherapy includes one or more of: surgery (e.g., open surgery or minimally invasive surgery), radiation therapy (e.g., external beam radiation therapy or internal radiation therapy), chemotherapy (e.g., an alkylating agent, antimetabolites, anti-microtubule agents, topoisomerase inhibitors, and cytotoxic antibiotics), immunotherapy (e.g., adoptive cell transfer, a cytokine, a cancer vaccine, and Bacillus Calmette-Guérom), hormone therapy (e.g., a drug that blocks estrogen, a drug that lowers estrogen levels, a progesterone-like

drug, or an anti-androgen drug), small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies (e.g., any of exemplary recombinant antibodies described herein, e.g., anti-NGF antibodies), and stem cell transplant. In some examples, the treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes (i) one or more of surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant, and (ii) one or more Trk inhibitors (e.g., any of the Trk inhibitors described herein). In some embodiments, the treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes two or more Trk inhibitors (e.g., any of the Trk inhibitors described herein). Additional examples of treatments that do not include a Trk inhibitor as a monotherapy, and doses and routes of administration of the same, are described herein or known in the art.

Some examples of these methods further include administering a treatment that does not include a Trk inhibitor as a monotherapy (e.g., using any of the treatments that do not include a Trk inhibitor as a monotherapy, any of the routes of administration, any of the doses, and/or any of the frequencies of administration described herein) to the selected subject. In some examples, the treatment that does not include a Trk inhibitor as a monotherapy is self-administered. In other examples, the treatment that does not include a Trk inhibitor as a monotherapy is administered to the selected subject by a medical professional. In some examples, the selected subject is hospitalized. In other examples, the subject is administered the treatment that does not include a Trk inhibitor as a monotherapy, on an outpatient basis. Some methods further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject is selected for a treatment that does not include a Trk inhibitor as a monotherapy.

Also provided herein are methods of selecting a subject having a cancer for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and selecting the identified subject for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of selecting a subject having a cancer for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent (e.g., any one or more of the another anticancer agents described herein or known in the art) or another anticancer therapy that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and selecting the identified subject for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy.

Also provided herein are methods of selecting a subject having a cancer for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and selecting the identified subject for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of selecting a subject having a cancer for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy that include: identifying a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and selecting the identified subject for a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy.

Some examples of these methods further include administering a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, or a treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, and another anticancer agent or anticancer therapy to the selected subject.

In some of the embodiments provided herein, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions includes (i) at least one (e.g., one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A). In some embodiments, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions is selected from a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3.

Methods of Determining the Likelihood that a Subject Having a Cancer will have a Positive Response to a Treatment with a Trk Inhibitor as a Monotherapy

Also provided herein are methods of determining the likelihood that a subject having a cancer (e.g., any of the cancers described herein) will have a positive response to a treatment with a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy that include determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), has a decreased likelihood of having a positive response to a treatment with a Trk inhibitor as a monotherapy (e.g., as compared to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3)).

Also provided herein are methods of determining the likelihood that a subject having cancer (e.g., any of the cancers described herein) will have a positive response to a treatment with a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy that include determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), has a decreased likelihood of having a positive response to treatment with a Trk inhibitor as a monotherapy (e.g., as compared to a subject having a cancer cell that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3)).

Some examples of these methods include administering a treatment that does not include a Trk inhibitor as a monotherapy (e.g., any of the treatments that do not include a Trk inhibitor as a monotherapy described herein) to a subject determined to have a decreased likelihood of having a positive response to treatment with a Trk inhibitor as a monotherapy.

In some examples, the treatment that does not include a Trk inhibitor as a monotherapy includes one or more of: surgery (e.g., open surgery or minimally invasive surgery), radiation therapy (e.g., external beam radiation therapy or internal radiation therapy), chemotherapy (e.g., an alkylating agent, antimetabolites, anti-microtubule agents, topoisomerase inhibitors, and cytotoxic antibiotics), immunotherapy (e.g., adoptive cell transfer, a cytokine, a cancer vaccine, and Bacillus Calmette-Guérom), hormone therapy (e.g., a drug that blocks estrogen, a drug that lowers estrogen levels, a progesterone-like drug, or an anti-androgen drug), small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies (e.g., any of exemplary recombinant antibodies described herein, e.g., anti-NGF antibodies), and stem cell transplant. In some examples, the treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes (i) one or more of surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant, and (ii) one or more Trk inhibitors (e.g., any of the Trk inhibitors described herein). In some embodiments, the treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes two or more Trk inhibitors (e.g., any of the Trk inhibitors described herein). Additional examples of treatments that do not include a Trk inhibitor as a monotherapy, and doses and routes of administration of the same, are described herein or known in the art.

In some examples, the treatment that does not include a Trk inhibitor as a monotherapy is self-administered. In other examples, the treatment that does not include a Trk inhibitor as a monotherapy is administered to the subject by a medical professional. In some examples, the subject is hospitalized. In other examples, the subject is administered the treatment that does not include a Trk inhibitor as a monotherapy, on an outpatient basis. Some methods further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject has a decreased likelihood of having a positive response to treatment with a Trk inhibitor as a monotherapy.

Also provided herein are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK

gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), has an increased likelihood of having a positive response to treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

Also provided herein are methods of determining the likelihood that a subject having cancer will have a positive response to treatment that includes one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, that include: determining that a subject having a cancer cell that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), has an increased likelihood of having a positive response to treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof.

In some of the embodiments provided herein, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions includes (i) at least one (e.g., one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC

protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A). In some embodiments, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions is selected from a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3.

Methods of Predicting the Efficacy of Treatment with a Trk inhibitor as a Monotherapy in a Subject Having Cancer

Also provided herein are methods of predicting the efficacy of treatment with a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy in a subject having cancer (e.g., any of the cancers described herein) that include determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3), and determining that a treatment with a Trk inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3) (e.g., as compared to a subject having a cancer cell in a sample obtained from the subject that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3)).

Also provided herein are methods of predicting the efficacy of a treatment with a Trk inhibitor (e.g., a first Trk inhibitor such as entrectinib or (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate) as a monotherapy in a subject having a cancer (e.g., any of the cancers

described herein) that include determining that treatment with a Trk inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3) (e.g., as compared to a subject having a cancer cell in a sample obtained from the subject that does not have at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3)).

Some methods further include recording in the subject's clinical record (e.g., a computer readable medium) the predicted efficacy of a treatment with a Trk inhibitor as a monotherapy, in the subject having a cancer. Some examples of these methods further include selecting a treatment that does not include a Trk inhibitor as a monotherapy for the subject. Some examples further include administering the selected treatment to the subject (e.g., using any of the treatments that do not include a Trk inhibitor as a monotherapy, any of the routes of administration, any of the doses, and/or any of the frequencies of administration described herein).

In some examples, the treatment that does not include a Trk inhibitor as a monotherapy includes one or more of: surgery (e.g., open surgery or minimally invasive surgery), radiation therapy (e.g., external beam radiation therapy or internal radiation therapy), chemotherapy (e.g., an alkylating agent, antimetabolites, anti-microtubule agents, topoisomerase inhibitors, and cytotoxic antibiotics), immunotherapy (e.g., adoptive cell transfer, a cytokine, a cancer vaccine, and Bacillus Calmette-Guérom), hormone therapy (e.g., a drug that blocks estrogen, a drug that lowers estrogen levels, a progesterone-like drug, or an anti-androgen drug), small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies (e.g., any of exemplary recombinant antibodies described herein, e.g., anti-NGF antibodies), and stem cell transplant. In some examples, the treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes (i) one or more of surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant, and (ii) one or more Trk inhibitors (e.g.,

any of the Trk inhibitors described herein). In some embodiments, the treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes two or more Trk inhibitors (e.g., any of the Trk inhibitors described herein). Additional examples of treatments that do not include a Trk inhibitor as a monotherapy, and doses and routes of administration of the same, are described herein or known in the art.

In some examples, the treatment that does not include a Trk inhibitor as a monotherapy is self-administered. In other examples, the treatment that does not include a Trk inhibitor as a monotherapy is administered to the subject by a medical professional. In some examples, the subject is hospitalized. In other examples, the subject is administered the treatment that does not include a Trk inhibitor as a monotherapy, on an outpatient basis.

Also provided herein are methods of predicting the efficacy of treatment with a treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, in a subject having cancer, that include: determining whether a cancer cell in a sample obtained from the subject has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3); and determining that treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

Also provided herein are methods of predicting the efficacy of treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, in a subject having cancer, that include: determining that treatment including one or more compounds of Table 5, or a pharmaceutically acceptable salt thereof, is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions (e.g., a mutation at one or more amino acid positions shown in Table 1, 2, or 3).

In some of the embodiments provided herein, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions includes (i) at least one (e.g., one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A). In some embodiments, the at least one point mutation in a NTRK gene that results in the expression of a Trk protein including a mutation at one or more amino acid positions is selected from a mutation at one or more of the amino acid positions shown in Tables 1, 2, or 3.

Methods of Predicting a Subject's Risk for Developing a Trk Inhibitor-Resistant Cancer

Also provided herein are methods of identifying a determining a subject's risk for developing a Trk inhibitor-resistant cancer (e.g., any of the cancers described herein) that include determining whether a cell in a sample obtained from the subject has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S) and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A), and identifying a subject having a cell that has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V,

G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A), as having an increased likelihood of developing a Trk inhibitor-resistant cancer (e.g., as compared to a subject not having (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A)).

Also provided herein are methods of determining a subject's risk for developing a Trk inhibitor-resistant cancer (e.g., any of the cancers described herein) that include identifying a subject having a cell that has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation(s) in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A), as having an increased likelihood of developing a Trk inhibitor-resistant cancer (e.g., as compared to a subject having a cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or

more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A)).

Some methods further include recording in the subject's clinical record (e.g., a computer readable medium) the subject's risk of developing a Trk inhibitor-resistant cancer. The Trk inhibitor-resistant cancer can be any of the exemplary cancers described herein. Some methods further include periodic testing for the presence of a Trk inhibitor-resistant cancer in the subject.

In some examples, the subject is identified as having been exposed to a significant level of carcinogen(s) (e.g., tobacco smoke, UVB radiation, and gamma irradiation). In some examples, the subject is suspected of having cancer, presents with one or more symptoms of cancer (e.g., any of the symptoms of cancer described herein), and/or has a family history of cancer.

In some examples, the step of determining whether a cancer cell in a sample obtained from the subject has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) mutations (e.g., any of the mutations in TrkA described herein), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) mutations (e.g., any of the mutations in TrkB described herein), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen)

point mutation in a NTRK3 gene that results in the expression of a TrkC protein including one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) mutations (e.g., any of the mutations in TrkC described herein), comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene in a cancer cell in the sample (e.g., a biopsy sample) from the subject. Any of the assays described herein can be used to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene. In addition, any of the kits provided herein can be used in an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene. In some examples, the assay includes sequencing a segment of a NTRK1 gene including the at least one point mutation and/or a segment of a NTRK2 gene including the at least one point mutation and/or a segment of a NTRK3 gene including the at least one point mutation.

Methods of Determining the Presence of a Trk Inhibitor-Resistant Cancer in a Subject

Also provided herein are methods of determining the presence of a Trk inhibitor-resistant cancer (e.g., any of the cancers described herein) in a subject that include determining whether a cell in a sample obtained from the subject has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the

group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A), and determining that a subject having a cell that has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g.,

one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A), has a Trk inhibitor-resistant cancer.

Also provided herein are methods of determining the presence of a Trk inhibitor-resistant cancer (e.g., any of the cancers described herein) in a subject that include determining that a subject having a cell that has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A), has a Trk inhibitor-resistant cancer (e.g., as compared to a subject having a cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V,

G667S, G667C, and Y676S), or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A)).

Some embodiments further include confirming a diagnosis of a Trk inhibitor-resistant cancer in the subject. Confirming the diagnosis of a Trk inhibitor-resistant cancer in a subject can include, e.g., performing additional laboratory tests (e.g., urine or blood tests, e.g., complete blood count), imaging tests (e.g., computerized tomography (CT), bone scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, ultrasound, and X-ray), and/or physical examination, e.g., before and after administration of a treatment with a Trk inhibitor as a monotherapy.

Some methods further include recording in the subject's clinical record (e.g., a computer readable medium) that the subject has a Trk inhibitor-resistant cancer. The cancer can be any of the exemplary cancers described herein.

Some examples further includes administering a treatment that does not include a Trk inhibitor as a monotherapy (e.g., any of the treatments that do not include a Trk inhibitor as a monotherapy described herein). In some examples, the treatment that does not include a Trk inhibitor as a monotherapy includes one or more of: surgery (e.g., open surgery or minimally invasive surgery), radiation therapy (e.g., external beam radiation therapy or internal radiation therapy), chemotherapy (e.g., an alkylating agent, antimetabolites, anti-microtubule agents, topoisomerase inhibitors, and cytotoxic antibiotics), immunotherapy (e.g., adoptive cell transfer, a cytokine, a cancer vaccine, and Bacillus Calmette-Guérom), hormone therapy (e.g., a drug that blocks estrogen, a drug that lowers estrogen levels, a progesterone-like

drug, or an anti-androgen drug), small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies (e.g., any of exemplary recombinant antibodies described herein, e.g., anti-NGF antibodies), and stem cell transplant. In some examples, the treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes (i) one or more of surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, small molecule drugs targeting other kinases in a Trk-signaling pathway, recombinant antibodies, and stem cell transplant, and (ii) one or more Trk inhibitors (e.g., any of the Trk inhibitors described herein). In some embodiments, the treatment that does not include a Trk inhibitor as a monotherapy can be, e.g., a treatment that includes two or more Trk inhibitors (e.g., any of the Trk inhibitors described herein). Additional examples of treatments that do not include a Trk inhibitor as a monotherapy, and doses and routes of administration of the same, are described herein or known in the art.

In some examples, the treatment that does not include a Trk inhibitor as a monotherapy is self-administered. In other examples, the treatment that does not include a Trk inhibitor as a monotherapy is administered to the subject by a medical professional. In some examples, the subject is hospitalized. In other examples, the subject is administered the treatment that does not include a Trk inhibitor as a monotherapy, on an outpatient basis.

In some examples, the subject is identified as having been exposed to a significant level of carcinogen(s) (e.g., tobacco smoke, UVB radiation, and gamma irradiation). In some examples, the subject is suspected of having cancer, presents with one or more symptoms of cancer (e.g., any of the symptoms of cancer described herein), and/or has a family history of cancer.

In some examples, the step of determining whether a cancer cell in a sample obtained from the subject has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) mutations (e.g., any of the mutations in TrkA described herein) and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen)

mutations (e.g., any of the TrkB mutations described herein), and/or (iii) at least one (e.g., two, three, four, five, six, or seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including one or more (e.g., two, three, four, five, six, or seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) mutations (e.g., any of the mutations in TrkC described herein), comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene in a cancer cell in the sample (e.g., a biopsy sample) from the subject. Any of the assays described herein can be used to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene. In addition, any of the kits provided herein can be used in an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene. In some examples, the assay includes sequencing a segment of a NTRK1 gene including the at least one point mutation and/or a segment of a NTRK2 gene including the at least one point mutation and/or a segment of a NTRK3 gene including the at least one point mutation.

Methods of Selecting a Subject Having a Cancer for Participation in a Clinical Study

Also provided herein are methods of selecting a subject having a cancer for participation in a clinical study that includes administration of treatment for a cancer that include (a) determining whether a cancer cell in a sample obtained from the subject has (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S) and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression

of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A); and (b) selecting a subject having a cancer cell having (i) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group

consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A), for participation in a clinical study that includes administration of a treatment for a cancer.

Also provided herein are methods of selecting a subject having a cancer for participation in a clinical study that includes administration of a Trk inhibitor that include (a) determining whether a cancer cell in a sample obtained from the subject has (i) at least one point (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), and/or (ii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), and/or (iii) at least one (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A); and (b) selecting a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen)

amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 (e.g., one or more of the substitutions of G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S), or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid positions selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 (e.g., one or more of the substitutions of G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S), or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein including a mutation at one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 (e.g., one or more of the substitutions of G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A), for participation in a clinical study that includes administration of a Trk inhibitor.

The cancer can be any of the exemplary cancers described herein. In some embodiments, the subject has previously been identified or diagnosed as having a cancer. In some examples, the subject has previously been administered a treatment for cancer, and the treatment for cancer has been unsuccessful (e.g., high toxicity in the subject or no positive response to the previously administered treatment for cancer).

In some examples, the step of determining whether a cancer cell in a sample obtained from the subject has the at least one point mutation (e.g., any of the point mutations described herein) in a NTRK1 gene that results in the expression of a TrkA including a mutation at one or more amino acid position(s) and/or the at least one point mutation (e.g., any of the point mutations described herein) in a NTRK2 gene that results in the expression of a TrkB including a mutation at one or more amino acid position(s) and/or the at least one point mutation (e.g., any of the point mutations described herein) in a NTRK3 gene that results in the expression of a TrkC including a mutation at one or more amino acid position(s), comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or

the at least one point mutation in a NTRK3 gene in a cancer cell in a sample (e.g., a biopsy sample) from the subject. Any of the assays described herein can be used to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene. In addition, any of the kits provided herein can be used in an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene. In some examples, the assay includes sequencing a segment of a NTRK1 including the at least one point mutation and/or a segment of a NTRK2 including the at least one point mutation and/or a segment of a NTRK3 including the at least one point mutation.

Kits

Also provided herein are kits that include one or more (e.g., two, three, four, five, six, or seven) probes that specifically hybridize to a segment of a NTRK1 gene that comprises one of the point mutations described herein (e.g., any point mutation that results in an amino acid substitution at amino acid position 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 in TrkA); and/or one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) probes that specifically hybridize to a segment of a NTRK2 gene that comprises one of the point mutations described herein (e.g., any point mutation that results in an amino acid substitution at amino acid position 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, 702, or 713; and/or one or more (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen) probes that specifically hybridizes to a segment of a NTRK3 gene that comprises one of the point mutations described herein (e.g., any point mutation that results in an amino acid substitution at amino acid position 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, 705, or 730 in TrkC). For example, the kits provided herein can include one or more probes that specifically hybridize to a segment of a NTRK1 gene that encodes a mutation selected from the group consisting of: G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S in a TrkA protein); and/or one or more probes that specifically hybridize to a segment of a NTRK2 gene that encodes a mutation selected from the group consisting of: G545R,

A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S; and/or one or more probes that specifically hybridizes to a segment of a NTRK3 gene that encodes a mutation selected from the group consisting of: G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A.

Each of the one or more probes can have a length of 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35 nucleotides. In some embodiments, the one or more probes include a detectable label (e.g., a fluorophore, a quencher, a radioisotope, or a metal). In some embodiments, the one or more probes can be covalently attached to a substrate (e.g., a film, a plate, or a bead).

The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

Example 1. Identification of Trk Inhibitor-Resistance Point Mutations

A genetic screen was performed to determine if resistance mutations arise in cancer subjects having $NTRK^+$ tumors treated with Trk inhibitors. In the genetic screen cDNAs harboring the MPRIP-NTRK1 oncogene were introduced into Ba/F3 cells. The Ba/F3 cells were treated with the mutagen, 100 μg/mL N-ethyl-N-nitrosourea (ENU; Sigma Aldrich, St. Louis, MO), overnight. The ENU-treated Ba/F3 cells were plated into 96-well plates in media supplemented with different concentrations of (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (25 nM, 50 nM, 100 nM, 250 nM, 500 nM, or 1 μM). The wells were observed for media color change and cell growth. The contents of the outgrown wells were expanded in 12-well plates in media supplemented with (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate at the same concentration as in the initial 96-well plate. At confluence, the cells were collected and genomic DNA was extracted. The NTRK1 kinase region was amplified and the PCR products were purified and sequenced. A plasmids encoding MPRIP-NTRK1 mutations were generated with QuickChange site-directed mutagenesis according to the manufacturer's instructions using a sequence encoding a wildtype MPRIP-NTRK1 fusion

protein as a template. Each mutation was confirmed by DNA sequencing. The Ba/F3 cells and NIH353 cells expressing MPRIP-NTRK1 mutants were generated by infecting Ba/F3 and NIH353 parental cells with lentivirus encoding the mutation MPRIP-NTRK1 fusion proteins, followed by selection with puromycin. A flow chart showing the steps in the experimental methods is shown in Figure 1.

The identified (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate resistance point mutations resulted in the following amino acid substitutions in TrkA: V573M, F589L, F600L, G667S, and Y676S. The location of three substitutions in TrkA resulting from (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate resistance point mutations were mapped onto the crystal structure of TrkA: V573, F589, and G667 (Figure 2) and a diagram of the domain structure of TrkA (Figure 3). Cancer cells having a MPRIP-NTRK1 point mutation have increased resistance to (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Figure 4).

These experiments show that the presence of one or more of the V573M, F589L, F600L, G667S, and Y676S substitutions in TrkA (or one or more of the corresponding point mutations in a NTRK1 gene) in a cancer cell can be used to predict the resistance of the cancer cell to (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate and other Trk inhibitors, and indicate that the cancer cell will not be sensitive to treatment with (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate and other Trk inhibitors.

Example 2. Identification of Trk Inhibitor-Resistance Point Mutations

N-ethyl-N-nitrosourea (ENU)-exposed Ba/F3-MPRIP-NTRK1 and Ba/F3-TRIM24-NTRK2 cells were used to generate mutations permitting growth of Ba/F3 cells in the absence of IL-3 despite the presence of 100, 250, or 500 nM (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate. The Mutations identified by genomic DNA sequencing in the initial screen were validated by cloning the mutation-bearing cDNAs back into Ba/F3 cells to

evaluate their sensitivity to (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE using both proliferation assays and TRK phosphorylation by immunoblot analyses. Modeling of the mutations was performed by mapping of the amino acid substitutions onto a drug-bound TRK kinase domain crystal structure.

Mutations at 6 amino acid positions in the TRKA protein and 3 amino acid positions in the TRKB protein that induce resistance to (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate were identified. In the TRKA kinase domain, the (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate resistance mutations of V573M, and F589L/C, G595S, F600L, F646V, and G667S were identified. In the TRKB kinase domain, the (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate resistance mutations of Q596E/P, F617L/C/I, and G623S were identified. These TRK mutations reduce target inhibition by (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate as measured by TRK tyrosine phosphorylation and resultant downstream signaling through the MAPK or other critical pathways.

Example 3. Identification of TRKA and TRKB Kinase Domain Mutations that Induce Resistance to a Pan-TRK Inhibitor

A mutagenesis and genetic screening approach to identify candidate mutations in TRKA and TRKB that mediate resistance to (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE was performed. A flow chart showing the steps in the experimental methods is shown in Figure 5.

Ba/F3 cells stably expressing *MPRIP-NTRK1* or *TRIM24-NTRK2* were treated overnight with 100mg/ml N-Ethyl-N-nitrosourea (ENU), pelleted, resuspended in fresh media, and distributed in 96-well plates in 200 μL media supplemented with (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE (100, 250, and 500

nM). The wells were observed for media color change and cell growth. The contents of outgrown wells were expanded in 12-well plates in media supplemented with (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE at the same concentration as in the initial 96-well plate. At confluence, cells were collected and genomic DNA was extracted. The *NTRK1* and *NTRK2* kinase region was PCR-amplified and sequenced. Plasmids encoding *MPRIP-NTRK1* and *TRIM24-NTRK2* mutations were generated with QuickChange site-directed mutagenesis and confirmed by DNA sequencing. Ba/F3 cells and NIH3T3 cells expressing *MPRIP-NTRK1* mutants were generated by infecting Ba/F3 and NIH3T3 parental cells with lentivirus encoding *MPRIP-NTRK1* mutation followed by selection with puromycin.

The identified (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate resistance point mutations resulted in the following amino acid substitutions in RIP-TrkA: V573M, F589L, F589C, G595R, F600L, F646V, G667S, and Y676S (Figure 6A). The location of selected substitutions in TrkA resulting from (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate resistance point mutations were mapped onto a diagram of the domain structure of TrkA (Figure 6B) and the crystal structure of TrkA (Figure 6C). Cancer cells having a MPRIP-NTRK1 point mutation resulting in amino acid substitutions V573M, F589L, and G667S exhibit increased resistance to (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Figure 7). TRKA and downstream signaling is not inhibited in NIH3T3 cells expressing these TRKA kinase domain mutations: TRKA, and ERK1/2 activation are sensitive to (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE inhibition in NIH3T3 cells expressing MPRIP-NTRK1$^{[WT]}$ fusion, whereas NIH3T3 cells expressing MPRIP-NTRK1$^{[V573M]}$, MPRIP-NTRK1$^{[F589L]}$ or MPRIP-NTRK1$^{[G667S]}$ fusions are resistant (Figure 8).

The identified (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate resistance point mutations

resulted in the following amino acid substitutions in TRIM24-TrkB: Q596E, Q596P, V601G, F617C, F617I, F617l, G623S, R630K, and G713S (Figure 9A). The location of selected substitutions in TrkB resulting from (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate resistance point mutations were mapped onto a diagram of the domain structure of TrkB (Figure 9B) and the crystal structure of TrkB (Figure 9C). Cancer cells having a TRIM24-NTRK2 point mutation resulting in amino acid substitutions V601G, G623S, and R630K exhibit increased resistance to (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate (Figure 10). TRKB and downstream signaling is not inhibited in NIH3T3 cells expressing these TRKB kinase domain mutations: TRKB, and ERK1/2 activation are sensitive to (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE inhibition in NIH3T3 cells expressing *TRIM24-NTRK2*[WT] fusion, whereas NIH3T3 cells expressing *TRIM24-NTRK2* [V601G], *TRIM24-NTRK2*[G623S] or *TRIM24-NTRK2* [R630K] fusions are resistant. (Figure 11).

Figure 12 shows the IC_{50} of certain Ba/F3 (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE-resistant clones that were identified. The IC_{50} measurements for the mutations shown were determined by an average of 3 experiments. Clones are ordered by conserved amino acids residues between TRKA and TRKB.

An alignment of kinase domains from selected oncogenes with known resistance mutations is shown in Figure 13.

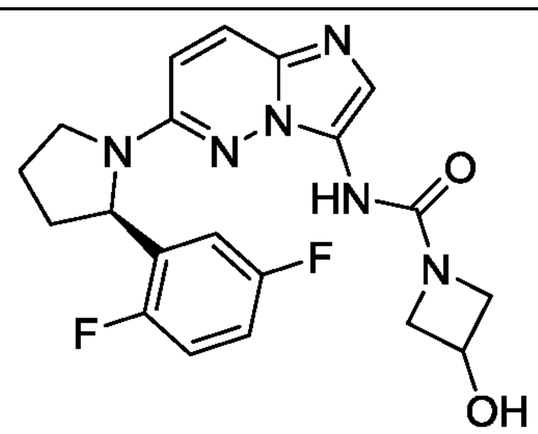
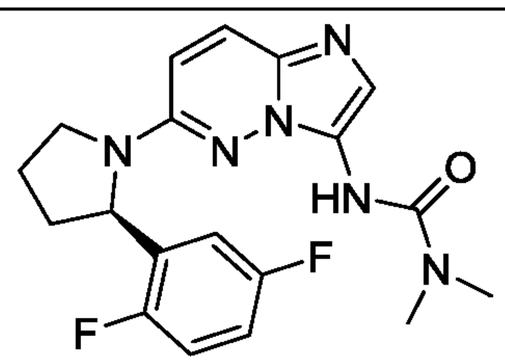
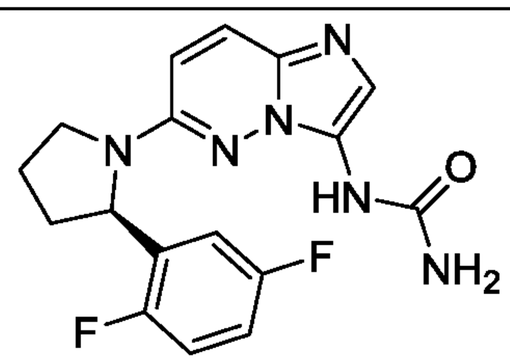
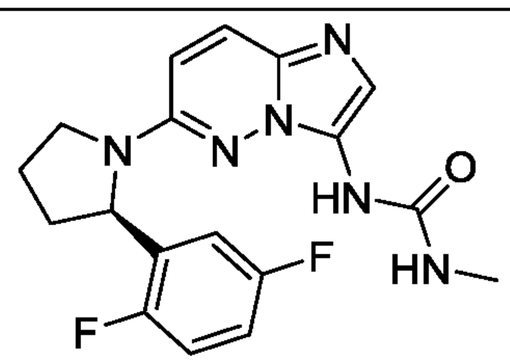
Novel mutations in the TRKA kinase domain of the MPRIP-NTRK1 oncogene and in the TRKB kinase domain of TRIM24-NTRK2 were identified using a combined mutagenesis/genetic screen. All mutations identified confer resistance to the pan-TRK inhibitor (S)-N-(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE as assessed by cellular proliferation assays and measurement of cell signaling. The majority of the mutations cluster to the back of the ATP/drug-binding pocket, possibly functioning by altering the topology of this pocket, thereby inhibiting (S)-N-

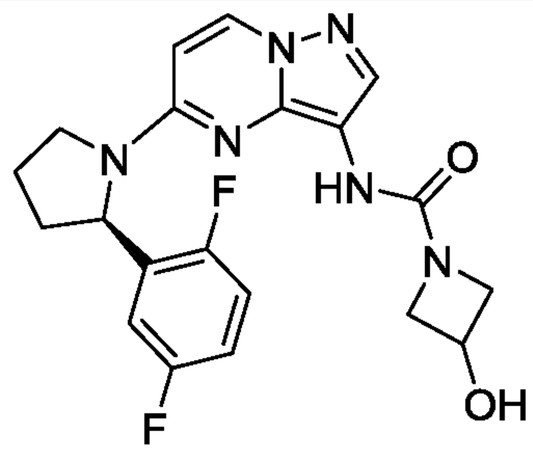
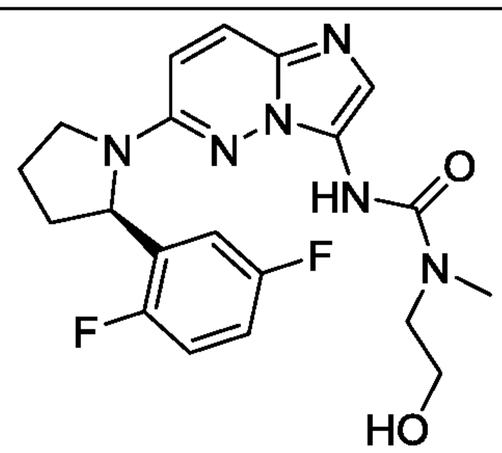
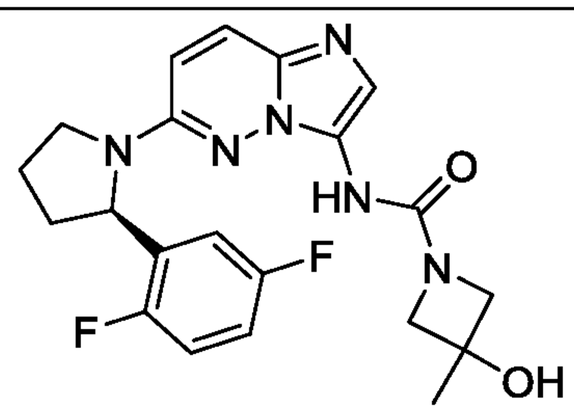
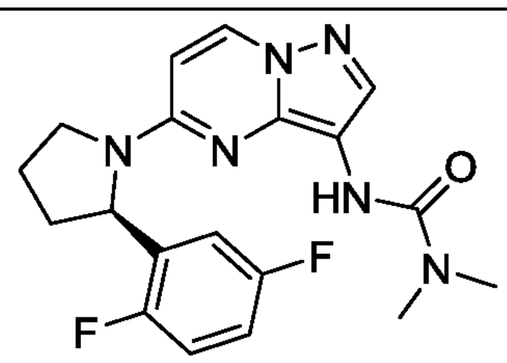
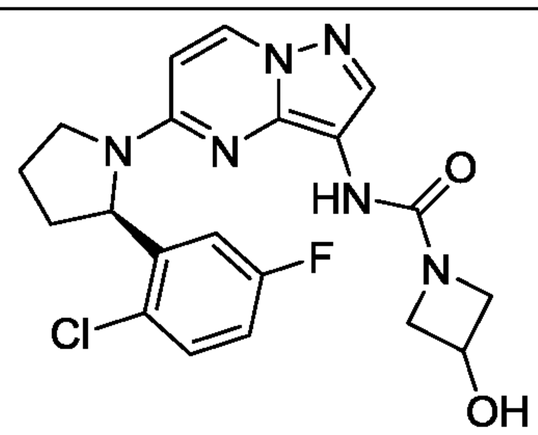
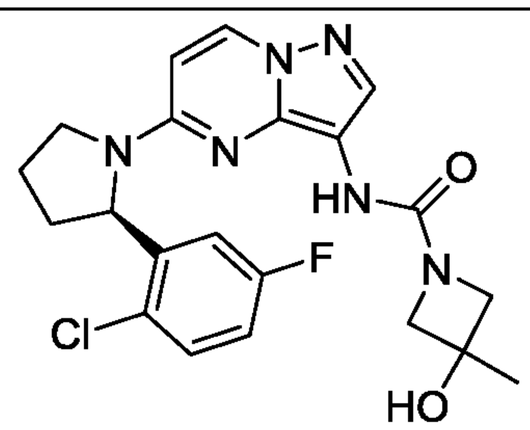
(5-((R)-2-(2,5-DIFLUOROPHENYL)PYRROLIDIN-1-YL)PYRAZOLO[1,5-A]PYRIMIDIN-3-YL)-3-HYDROXYPYRROLIDINE-1-CARBOXAMIDE SULFATE binding. Evaluation of tumors or circulating free DNA at disease progression for these and other resistance mutations permits the use of structurally distinct TRK inhibitors to overcome drug resistance.

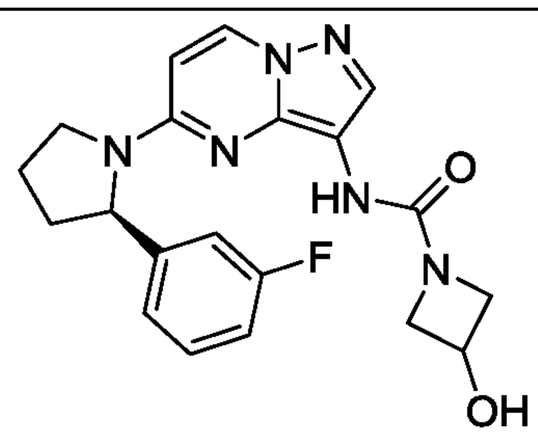
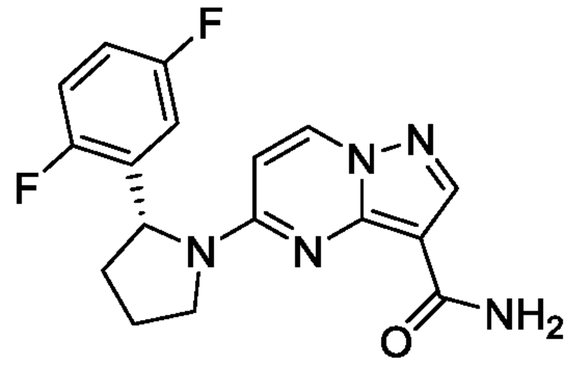
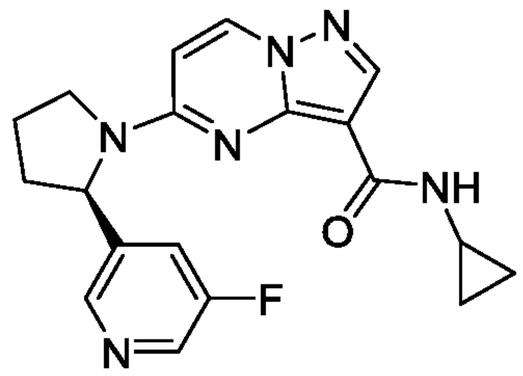
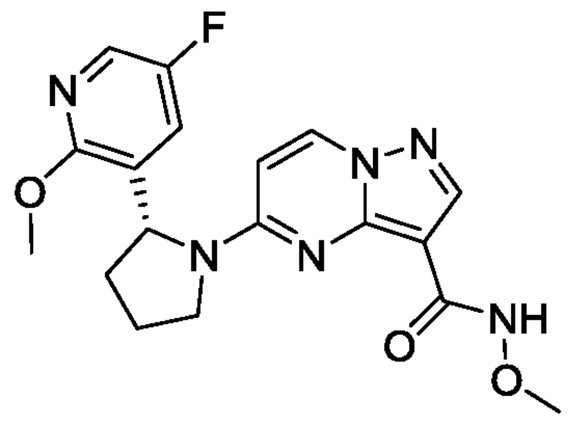
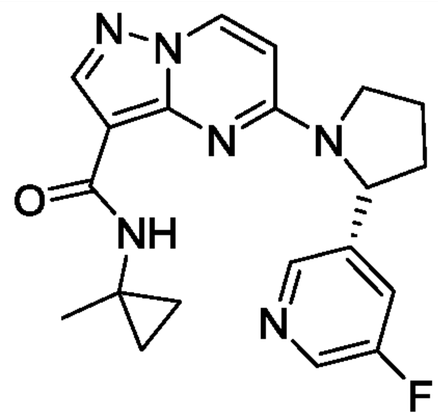
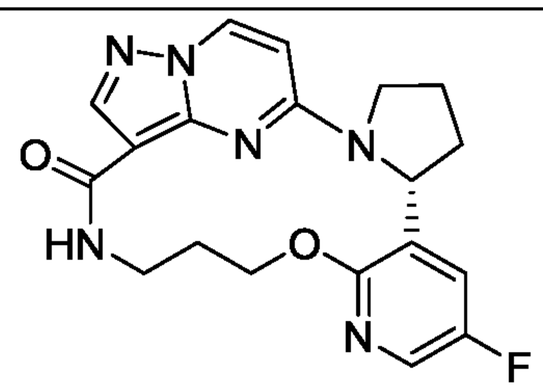
Example 4. Trk Enzyme Assay

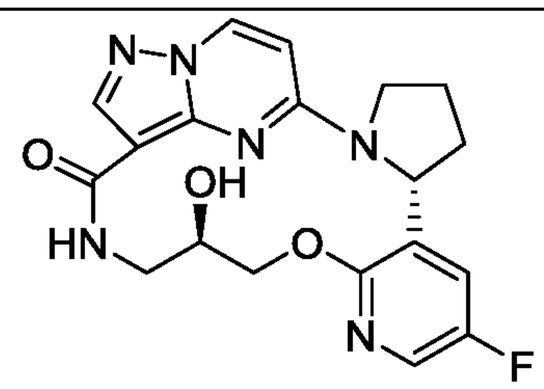
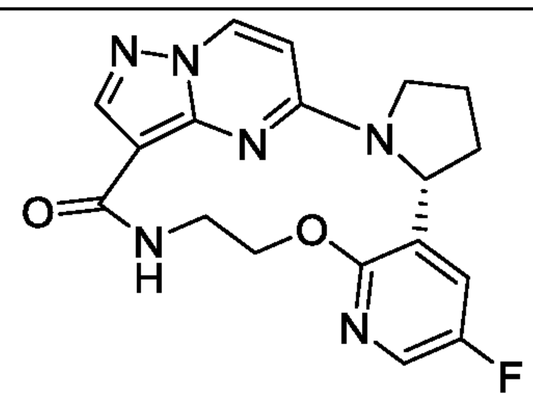
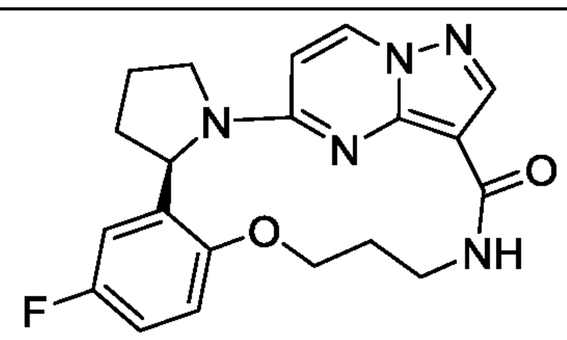
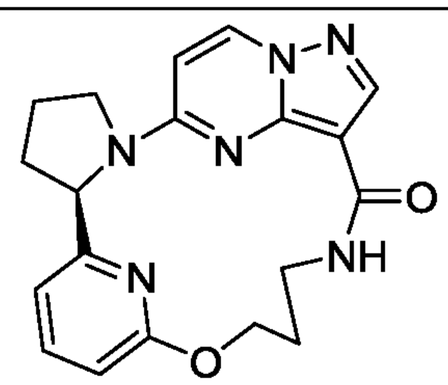
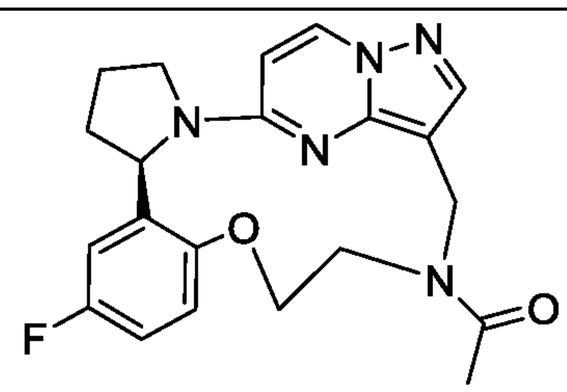
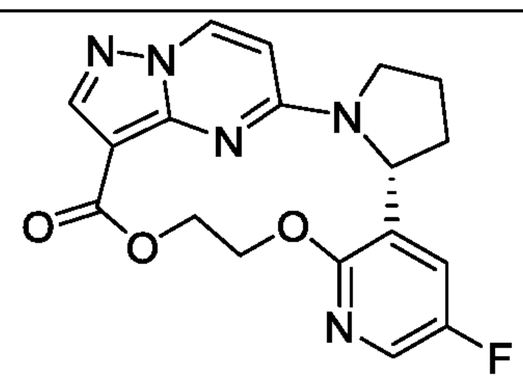
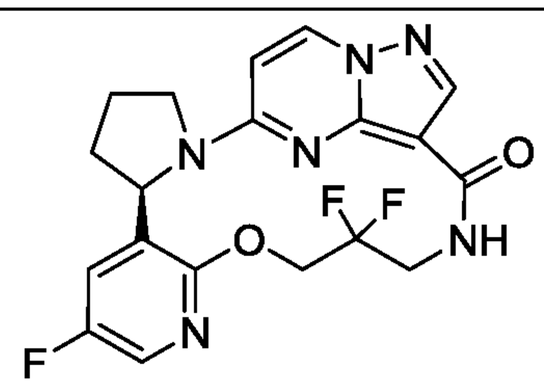
The activity of the various Trk compounds exemplified in Table 6 was determined by monitoring the incorporation of [^{33}P]PO_4 from [γ-^{33}P]ATP into poly-EAY (Sigma-Aldrich, P3899).

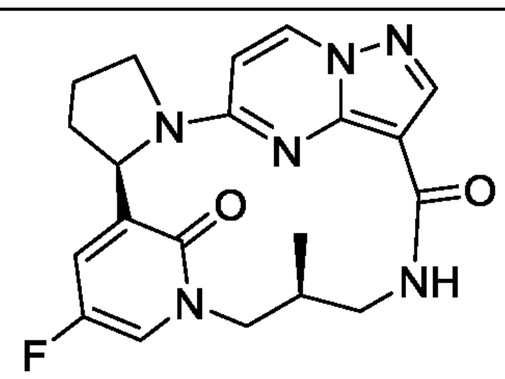
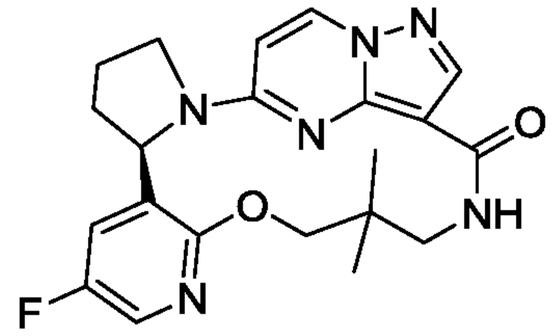
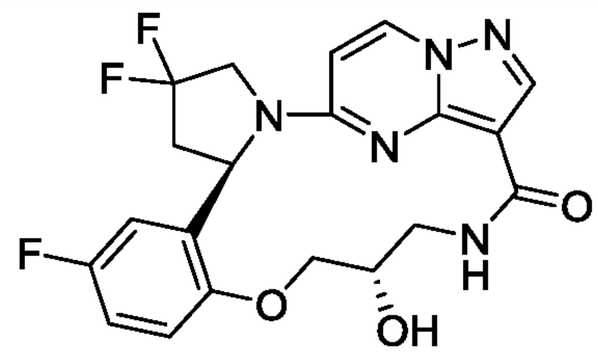
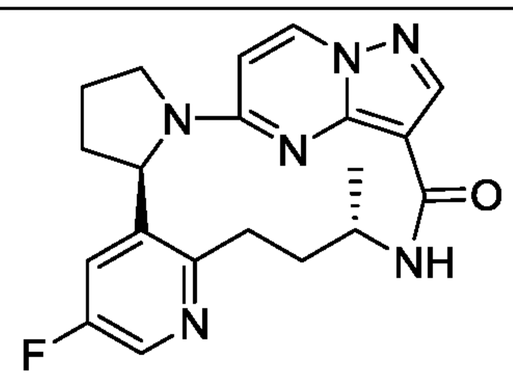
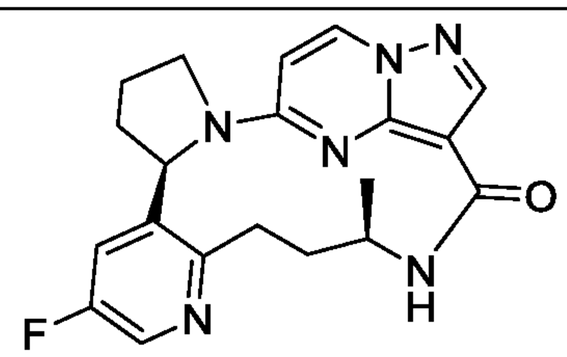
Table 6. Compounds tested in the Trk Enzyme Assay

Compound No.	Compound Structure	Compound Name
1		(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide
2		(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea
3		(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea
4		(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea

5		(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide
6		(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea
7		(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide
8		(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea
9		(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide
10		(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide

11		(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide
12		(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
13		(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
14		(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide
15		(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide
16		(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one

17		(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one
18		(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one
19		(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
20		(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one
21		1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one
22		(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
23		(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one

24		(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
25		(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
26		(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one
27		(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
28		(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one

The assays were conducted in 96-well polypropylene v-bottom microtitre plates (Corning, Costar® 3363) in a total volume of 50 µL. Reaction mixtures typically contained 25 mM Na^+MOPS, pH 7.4, 5 mM $MgCl_2$, 0.005% Triton X-100, 2% DMSO, 1 mM DTT, 5 µM [^{33}P]ATP (50 µCi/mL), 100 µg/mL poly-EAY, Trk enzyme (Trk A, B or C, wild-type or mutant at an appropriate concentration ranging from 0.1-10 nM, depending on the compound) and compound varying over a 10-point, three-fold dilution series ranging from 2000 to 0.1 nM. Incubations were conducted at 22 °C for 60 minutes and quenched by the addition of 100 µL aliquots of 25% trichloroacetic acid. The radiolabeled product was then captured on glass fiber filter plates (PerkinElmer, Unifilter®-96, GF/B®) and washed with

5% phosphoric acid to remove unbound radiolabel using a Tomtec MACH III Harvester 96®. After adding 35 µL/well of Bio-Safe II™ liquid scintillation cocktail (Research Products International), the plates were counted in a TopCount NXT (PerkinElmer) using a counting time of 30 s/well. The activity at each concentration of compound was expressed as percent of control (POC) and plotted versus compound concentration. An IC_{50} was estimated using a 4-parameter logistic model fit to the dose-response plots, with IC_{50} being defined as the concentration of compound where the best-fit curve crosses 50 POC. The IC_{50} values for the compounds tested in this assay are provided in Table 7.

Table 7. IC_{50} values of compounds tested in the assay of Example 4.

Compound Number	IC_{50} (nM)										
	TrkA WT	TrkA V573M	TrkA F589L	TrkA G595R	TrkA G667C	TrkA G667S	TrkB WT	TrkB G623R	TrkC WT	TrkC G623R	TrkC F617L
1	1.0	94.9	124.0	24.8	91.3	30.1	5.7	59.7	<2.5	29.3	58.0
2	0.8	76.4	61.5	19.4	46.3	21.3	4.5	34.1	<2.5	23.1	37.6
3	2.8	627.6	577.5	61.0	295.7	91.1	11.9	90.0	4.5	55.7	273.0
4	2.5	547.4	384.8	57.0	298.1	108.5	10.6	132.3	3.1	70.8	177.0
5	1.1	151.6	231.6	84.6	141.2	38.5	5.9	131.9	<2.5	95.0	153.7

6	0.8	74.9	78.5	25.3	55.1	23.3	5.0	27.5	<2.5	24.1	49.7
7	<0.5	67.1	83.1	30.5	52.5	26.4	7.0	47.9	<2.5	22.7	42.5
8	0.9	129.3	153.5	49.6	84.2	19.7	5.0	64.6	<2.5	54.9	67.1
9	0.8	106.4	90.7	91.9	76.5	21.6	4.6	104.3	<2.5	92.6	66.5
10	0.9	104.8	102.6	107.3	89.2	27.0	6.5	149.8	<2.5	100.5	80.1
11	6.9	1198.9	1084.1	560.6	830.4	274.6	19.0	671.4	4.4	445.7	476.2
12	<0.5	14.9	21.0	1.0	15.6	3.6	3.3	1.3	<2.5	1.6	9.9
13	<0.5	20.9	37.2	3.3	32.4	4.1	3.5	2.7	<2.5	3.1	8.7
14	<0.5	12.1	14.8	1.5	9.0	2.8	4.4	1.5	<2.5	2.7	12.4

15	<0.5	6.3	7.3	1.6	8.1	1.4	<2.5	1.6	<2.5	1.7	<5.0
16	<0.5	<5.0	<1.0	0.9	1.1	0.4	2.9	0.9	<2.5	1.3	<5.0
17	<0.5	<5.0	2.1	1.5	2.6	0.7	3.6	1.1	<2.5	1.8	<5.0
18	<0.5	<5.0	3.9	1.3	2.6	0.6	4.1	1.0	<2.5	1.4	5.5
19	0.5	<5.0	1.1	1.2	0.9	0.3	4.4	1.0	<2.5	1.8	5.1
20	<0.5	36.5	48.3	2.7	13.3	3.2	3.1	3.1	<2.5	3.1	18.3
21	0.6	29.1	66.3	7.3	22.2	8.4	5.6	12.4	<2.5	7.8	48.5
22	0.5	<5.0	8.4	1.5	5.7	0.9	2.9	1.3	<2.5	1.5	5.4
23	0.7	<5.0	<1.0	1.6	0.8	0.3	6.1	1.1	2.7	2.1	5.8

24	0.5	38.3	86.8	3.3	22.3	4.7	4.7	4.2	<2.5	4.5	61.9
25	1.0	<5.0	1.1	3.0	1.0	0.5	8.7	2.3	4.0	4.7	8.1
26	0.6	<5.0	3.9	2.1	1.0	0.5	3.3	1.8	<2.5	2.6	9.6
27	<0.5	9.3	21.0	1.5	5.6	2.1	3.4	1.7	<2.5	2.2	9.5
28	0.5	<5.0	3.3	2.0	9.8	2.3	3.2	1.9	<2.5	2.8	<5.0

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method of treating a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at amino acid position 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) administering a treatment including one or more doses of a second Trk inhibitor or a pharmaceutically acceptable salt thereof, to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) administering additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or

more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

2. The method of claim 1 or 2, wherein the first Trk inhibitor is selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; cabozantinib ((N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide)); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); belizatinib (4-fluoro-N-(6-((4-(2-hydroxypropan-2-yl)piperidin-1-yl)methyl)-1-((1s,4s)-4-(isopropylcarbamoyl)cyclohexyl)-1H-benzo[d]imidazol-2-yl)benzamide); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); PLX7486; altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); and AZD7451 ((S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine)).

3. The method of claim 1, wherein the first Trk inhibitor is selected from the group consisting of: entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate.

4. The method of any one of claims 1-3, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

5. The method of any one of claims 1-4, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

6. The method of any one of claims 1-4, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

7. The method of any one of claims 1-4, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

8. The method of any one of claims 1-4, wherein the second Trk inhibitor is selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof

9. The method of claim 1, wherein the first Trk inhibitor is entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

10. The method of claim 1, wherein the first Trk inhibitor is entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

11. The method of claim 1, wherein the first Trk inhibitor is entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

12. The method of claim 1, wherein the first Trk inhibitor is entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); and the second Trk inhibitor is selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17 .5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

13. The method of claim 1, wherein the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

14. The method of claim 1, wherein the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

or a pharmaceutically acceptable salt thereof.

15. The method of claim 1, wherein the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

or a pharmaceutically acceptable salt thereof.

16. The method of claim 1, wherein the first Trk inhibitor is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; and the second Trk inhibitor is selected from the group consisting of:

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

17. The method of any one of claims 1-16, wherein step (c) further comprises administration of another anticancer agent or anticancer therapy.

18. A method of treating a subject having a cancer, the method comprising:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542,

568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

(b) administering a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(c) administering additional doses of the first Trk inhibitor of step (a) to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

19. The method of claim 18, wherein step (b) comprises administering one or more doses of a second Trk inhibitor, wherein the second Trk inhibitor is selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17 .5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

20. The method of claim 18 or 19, wherein step (b) further comprises administering another anticancer agent or anticancer therapy.

21. A method of treating a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

administering to the identified subject a treatment that does not include a first Trk inhibitor as a monotherapy.

22. A method of treating a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

administering to the identified subject a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

23. The method of claim 22, wherein the method further comprises administration of another anticancer agent or anticancer therapy.

24. A method of treating a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, the method comprising administering to the subject a treatment that does not include a first Trk inhibitor as a monotherapy.

25. A method of treating a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623,

624, 628, 630, 675, 685, 686, 696, and 705, the method comprising administering to the subject a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

26. The method of claim 25, wherein the method further comprises administration of another anticancer agent or anticancer therapy.

27. A method of treating a subject, the method comprising administering a therapeutically effective amount of a treatment that does not include a first Trk inhibitor as a monotherapy, to a subject having a clinical record that indicates that the subject has a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

28. A method of treating a subject, the method comprising administering a therapeutically effective amount of one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

to a subject having a clinical record that indicates that the subject has a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting

of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

29. The method of claim 28, wherein the method further comprises administering another anticancer agent or anticancer therapy.

30. A method of selecting a treatment for a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting a treatment for the identified subject that does not include a first Trk inhibitor as a monotherapy.

31. A method of selecting a treatment for a subject having a cancer, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino

acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting a treatment for the identified subject that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

32. The method of claim 31, wherein the selected treatment further comprises administering another anticancer agent or anticancer therapy.

33. A method of selecting a treatment for a subject having a cancer, the method comprising:

selecting a treatment that does not include a first Trk inhibitor as a monotherapy for a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

34. A method of selecting a treatment for a subject having a cancer, the method comprising:

selecting a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17 .5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

for a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

35. The method of claim 34, wherein the selected treatment further comprises administering another anticancer agent or anticancer therapy.

36. A method of selecting a subject having a cancer for a treatment that does not include a first Trk inhibitor as a monotherapy, the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting the identified subject for a treatment that does not include a first Trk inhibitor as a monotherapy.

37. A method of selecting a subject having a cancer for a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

the method comprising:

identifying a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

selecting the identified subject for a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

38. The method of claim 37, wherein the selected treatment further comprises administration of another anticancer agent or anticancer therapy.

39. A method of selecting a subject having a cancer for a treatment that does not include a first Trk inhibitor as a monotherapy, the method comprising:

selecting a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a

mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, for a treatment that does not include a first Trk inhibitor as a monotherapy.

40. A method of selecting a subject having a cancer for a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

the method comprising:

selecting a subject identified as having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, for a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

41. The method of claim 40, wherein the treatment further comprises administration of another anticancer agent or anticancer therapy.

42. A method of determining the likelihood that a subject having a cancer will have a positive response to treatment with a first Trk inhibitor as a monotherapy, the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy.

43. A method of determining the likelihood that a subject having a cancer will have a positive response to treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has a increased likelihood of having a positive response to treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

44. A method of determining the likelihood that a subject having cancer will have a positive response to treatment with a first Trk inhibitor as a monotherapy, the method comprising:

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2

gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has a decreased likelihood of having a positive response to treatment with a first Trk inhibitor as a monotherapy.

45. A method of determining the likelihood that a subject having cancer will have a positive response to treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

the method comprising:

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has an increased likelihood of having a positive response to treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

46. A method of predicting the efficacy of treatment with a first Trk inhibitor as a monotherapy in a subject having cancer, the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that treatment with a first Trk inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

47. A method of predicting the efficacy of treatment with a treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

in a subject having cancer, the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising

a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

48. A method of predicting the efficacy of treatment with a first Trk inhibitor as a monotherapy in a subject having cancer, the method comprising:

determining that treatment with a first Trk inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting

of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

49. A method of predicting the efficacy of treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

in a subject having cancer, the method comprising:

determining that treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

is more likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein

comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

50. A method of treating a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) administering a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) administering additional doses of the Trk inhibitor of step (a) to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570,

596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

51. The method of claim 50, wherein the first Trk inhibitor of step (a) is selected from the group consisting of entrectinib (N-[5-(3,5-difluoro-benzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-pyran-4-ylamino)-benzamide); (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide sulfate; cabozantinib ((N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide)); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); belizatinib (4-fluoro-N-(6-((4-(2-hydroxypropan-2-yl)piperidin-1-yl)methyl)-1-((1s,4s)-4-(isopropylcarbamoyl)cyclohexyl)-1H-benzo[d]imidazol-2-yl)benzamide); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); PLX7486; altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); and AZD7451 ((S)-N-(1-(5-fluoropyrimidin-2-yl)ethyl)-3-(5-isopropoxy-1H-pyrazol-3-yl)-3H-imidazo[4,5-b]pyridin-5-amine)).

52. A method of selecting a treatment for a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation

at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) selecting a second Trk inhibitor or a treatment that does not include the Trk inhibitor of step (a) as a monotherapy for a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) selecting additional doses of the first Trk inhibitor of step (a) for a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

53. A method of selecting a treatment for a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising

a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) selecting a treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

for a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

54. A method of selecting a treatment for a subject having a cancer, the method comprising:

(a) administering one or more doses of a first Trk inhibitor to the subject for a period of time;

(b) after (a), determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

(c) selecting a treatment including one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

and another anticancer agent or anticancer therapy for a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(d) selecting additional doses of the first Trk inhibitor for a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group

consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

55. A method of selecting a treatment for a subject having a cancer, the method comprises:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

(b) selecting a second Trk inhibitor or a treatment that does not include the first Trk inhibitor of step (a) as a monotherapy to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(c) selecting additional doses of the first Trk inhibitor of step (a) to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

56. A method of selecting a treatment for a subject having a cancer, the method comprises:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

(b) selecting a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602,

646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

57. A method of selecting a treatment for a subject having a cancer, the method comprises:

(a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered one or more doses of a first Trk inhibitor, has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705;

(b) selecting a treatment that includes one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17 .5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof;

and an another anticancer agent or anticancer therapy to a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; or

(c) selecting additional doses of the first Trk inhibitor to a subject having a cancer cell that does not have (i) a point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, or (ii) a point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, or (iii) a point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705.

58. The method of any one of claims 1-57, wherein the cancer is selected from the group consisting of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal

carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, non-Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epitheliod cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell

carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

59. The method of any one of claims 1-58, wherein the subject is previously identified or diagnosed as having the cancer.

60. A method of determining a subject's risk for developing a Trk inhibitor-resistant cancer, the method comprising:

determining whether a cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

identifying a subject having a cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, as having an increased likelihood of developing a Trk inhibitor-resistant cancer.

61. A method of determining a subject's risk for developing a Trk inhibitor-resistant cancer, the method comprising:

identifying a subject having a cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, as having an increased likelihood of developing a Trk inhibitor-resistant cancer.

62. A method of determining the presence of a Trk inhibitor-resistant cancer in a subject, the method comprising:

determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that

results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has an a Trk inhibitor-resistant cancer.

63. A method of determining the presence of a Trk inhibitor-resistant cancer in a subject, the method comprising:

determining that a subject having a cancer cell that has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, has a Trk inhibitor-resistant cancer.

64. The method of any one of claims 60-63, wherein the subject is suspected of having a cancer.

65. The methods of any one of claims 60-63, wherein the subject has one or more symptoms of cancer.

66. The methods of any one of claims 60-63, wherein the subject is previously identified or diagnosed as having a cancer.

67. The method of any one of claims 60-66, wherein the cancer is selected from the group consisting of: adenocarcinoma, adrenal gland cortical carcinoma, adrenal gland neuroblastoma, anus squamous cell carcinoma, appendix adenocarcinoma, bladder urothelial carcinoma, bile duct adenocarcinoma, bladder carcinoma, bladder urothelial carcinoma, bone chordoma, bone marrow leukemia lymphocytic chronic, bone marrow leukemia non-lymphocytic acute myelocytic, bone marrow lymph proliferative disease, bone marrow multiple myeloma, bone sarcoma, brain astrocytoma, brain glioblastoma, brain medulloblastoma, brain

meningioma, brain oligodendroglioma, breast adenoid cystic carcinoma, breast carcinoma, breast ductal carcinoma in situ, breast invasive ductal carcinoma, breast invasive lobular carcinoma, breast metaplastic carcinoma, cervix neuroendocrine carcinoma, cervix squamous cell carcinoma, colon adenocarcinoma, colon carcinoid tumor, duodenum adenocarcinoma, endometrioid tumor, esophagus adenocarcinoma, eye intraocular melanoma, eye intraocular squamous cell carcinoma, eye lacrimal duct carcinoma, fallopian tube serous carcinoma, gallbladder adenocarcinoma, gallbladder glomus tumor, gastroesophageal junction adenocarcinoma, head and neck adenoid cystic carcinoma, head and neck carcinoma, head and neck neuroblastoma, head and neck squamous cell carcinoma, kidney chromophore carcinoma, kidney medullary carcinoma, kidney renal cell carcinoma, kidney renal papillary carcinoma, kidney sarcomatoid carcinoma, kidney urothelial carcinoma, leukemia lymphocytic, liver cholangiocarcinoma, liver hepatocellular carcinoma, lung adenocarcinoma, lung adenosquamous carcinoma, lung atypical carcinoid, lung carcinosarcoma, lung large cell neuroendocrine carcinoma, lung non-small cell lung carcinoma, lung sarcoma, lung sarcomatoid carcinoma, lung small cell carcinoma, lung small cell undifferentiated carcinoma, lung squamous cell carcinoma, lymph node lymphoma diffuse large B cell, lymph node lymphoma follicular lymphoma, lymph node lymphoma mediastinal B-cell, lymph node lymphoma plasmablastic lung adenocarcinoma, lymphoma follicular lymphoma, non-Hodgkin's lymphoma, nasopharynx and paranasal sinuses undifferentiated carcinoma, ovary carcinoma, ovary carcinosarcoma, ovary clear cell carcinoma, ovary epithelial carcinoma, ovary granulosa cell tumor, ovary serous carcinoma, pancreas carcinoma, pancreas ductal adenocarcinoma, pancreas neuroendocrine carcinoma, peritoneum mesothelioma, peritoneum serous carcinoma, placenta choriocarcinoma, pleura mesothelioma, prostate acinar adenocarcinoma, prostate carcinoma, rectum adenocarcinoma, rectum squamous cell carcinoma, skin adnexal carcinoma, skin basal cell carcinoma, skin melanoma, skin Merkel cell carcinoma, skin squamous cell carcinoma, small intestine adenocarcinoma, small intestine gastrointestinal stromal tumors (GISTs), soft tissue angiosarcoma, soft tissue Ewing sarcoma, soft tissue hemangioendothelioma, soft tissue inflammatory myofibroblastic tumor, soft tissue leiomyosarcoma, soft tissue liposarcoma, soft tissue neuroblastoma, soft tissue paraganglioma, soft tissue perivascular epitheliod cell tumor, soft tissue sarcoma, soft tissue synovial sarcoma, stomach adenocarcinoma, stomach adenocarcinoma diffuse-type, stomach adenocarcinoma intestinal type, stomach adenocarcinoma intestinal type, stomach leiomyosarcoma, thymus carcinoma, thymus thymoma lymphocytic, thyroid papillary carcinoma, unknown primary adenocarcinoma, unknown primary carcinoma, unknown primary malignant neoplasm, unknown

primary melanoma, unknown primary sarcomatoid carcinoma, unknown primary squamous cell carcinoma, unknown undifferentiated neuroendocrine carcinoma, unknown primary undifferentiated small cell carcinoma, uterus carcinosarcoma, uterus endometrial adenocarcinoma, uterus endometrial adenocarcinoma endometrioid, uterus endometrial adenocarcinoma papillary serous, and uterus leiomyosarcoma.

68. The method of claim 60, wherein the step of determining whether a cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene in a cell in the sample.

69. The method of claim 62, wherein the step of determining whether a cancer cell in a sample obtained from the subject has (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705, comprises performing an assay to determine the presence of the at least one point mutation in a NTRK1 gene and/or the at least one point mutation in a NTRK2 gene and/or the at least one point mutation in a NTRK3 gene in a cancer cell in the sample.

70. The method of claim 68 or 69, wherein the assay is selected from the group consisting of: denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), temperature gradient capillary electrophoresis, a single strand conformational polymorphism assay, a molecular beacon assay, a dynamic hybridization assay, a PCR-based assay, denaturing high performance liquid chromatography.

71. The method of claim 68 or 69, wherein the assay comprises sequencing a segment of the NTRK1 gene comprising the at least one point mutation.

72. The method of claim 60 or 61, further comprising confirming a diagnosis of a Trk inhibitor-resistant cancer in a subject determined to have an increased likelihood of developing a Trk inhibitor-resistant cancer.

73. The method of any one of claims 1-72, wherein the TrkA protein comprises one or more of the following amino acid substitutions: G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S, and/or the TrkB protein comprises one or more of the following amino acid substitutions: G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S, and/or the TrkC protein comprises one or more of the following amino acid substitution G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A.

74. A method for inhibiting a Trk kinase activity in a mammalian cell, the method comprising:

determining that the mammalian cell comprises (i) at least one point mutation in a NTRK1 gene that results in the expression of a TrkA protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676, and/or (ii) at least one point mutation in a NTRK2 gene that results in the expression of a TrkB protein comprising a mutation at one or more amino acid position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702, and/or (iii) at least one point mutation in a NTRK3 gene that results in the expression of a TrkC protein comprising a mutation at one or more amino acid

position(s) selected from the group consisting of: 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705; and

contacting the mammalian cell with one or more compounds selected from the group consisting of:

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1,1-dimethylurea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)urea;

(R)-1-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-methylurea;

(R)-N-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-3-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-1-(2-hydroxyethyl)-1-methylurea;

(R)-N-(6-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-3-(5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,1-dimethylurea;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-N-(5-(2-(2-chloro-5-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxy-3-methylazetidine-1-carboxamide;

(R)-N-(5-(2-(3-fluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxyazetidine-1-carboxamide;

(R)-5-(2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-N-cyclopropyl-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoro-2-methoxypyridin-3-yl)pyrrolidin-1-yl)-N-methoxypyrazolo[1,5-a]pyrimidine-3-carboxamide;

(R)-5-(2-(5-fluoropyridin-3-yl)pyrrolidin-1-yl)-N-(1-methylcyclopropyl)pyrazolo[1,5-a]pyrimidine-3-carboxamide;

(6R)-9-fluoro-13-oxa-2, 11, 17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]-hexacosa-1(25),7,9,11, 19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.$0^{2,6}$.$0^{7,12}$.$0^{23,27}$]-heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.^{17,11}.$0^{2,6}$.$0^{21,25}$]-hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one;

1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one;

(6R)-9-fluoro-13,16-dioxa-2,11,20,21,24-pentaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.^{17,11}.$0^{2,6}$.$0^{20,24}$]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22.25-pentaazapentacyclo[17.5.2.$0^{2,6}$.$0^{7,12}$.$0^{22,26}$]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one;

(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one; and

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.$0^{2,6}$.$0^{7,12}$.$0^{21,25}$]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one;

or a pharmaceutically acceptable salt thereof.

75. A kit comprising:

one or more probes that each specifically hybridize to a segment of a NTRK1 gene that encodes a mutation at one of amino acid positions 517, 542, 568, 573, 589, 595, 599, 600, 602, 646, 656, 657, 667, and 676 in TrkA protein; and/or

one or more probes that each specifically hybridize to a segment of a NTRK2 gene that encodes a mutation at one of amino acid positions 545, 570, 596, 601, 617, 623, 624, 628, 630, 672, 682, 683, 693, and 702 in a TrkB protein; and/or

one or more probes that each specifically hybridizes to a segment of a NTRK3 gene that encodes a mutation at one of amino acid positions 545, 570, 596, 601, 617, 623, 624, 628, 630, 675, 685, 686, 696, and 705 in a TrkC protein.

76. The kit of claim 75, wherein the kit comprises:

one or more probes that each specifically hybridize to a segment of a NTRK1 gene that encodes a mutation selected from the group consisting of: G517R, A542V, V573M, F589L, F589C, G595S, G595R, D596V, F600L, F646V, C656Y, C656F, L657V, G667S, G667C, and Y676S in TrkA protein; and/or

one or more probes that each specifically hybridize to a segment of a NTRK2 gene that encodes a mutation selected from the group consisting of: G545R, A570V, Q596E, Q596P, V601G, F617L, F617C, F617I, G623S, G623R, D624V, R630K, C682Y, C682F, L683V, G693S, and G713S in a TrkB protein; and/or

one or more probes that each specifically hybridizes to a segment of a NTRK3 gene that encodes a mutation selected from the group consisting of: G545R, A570V, F617L, G623R, D624V, C685Y, C685F, L686V, and G696A in a TrkC protein.

77. The kit of claim 75 or 76, wherein the one or more probes are labeled with a detectable probe.

78. The kit of claims 75-77, wherein the one or more probes are covalently attached to a substrate.

79. The kit of claim 78, wherein the substrate is a film, a plate, or a bead.

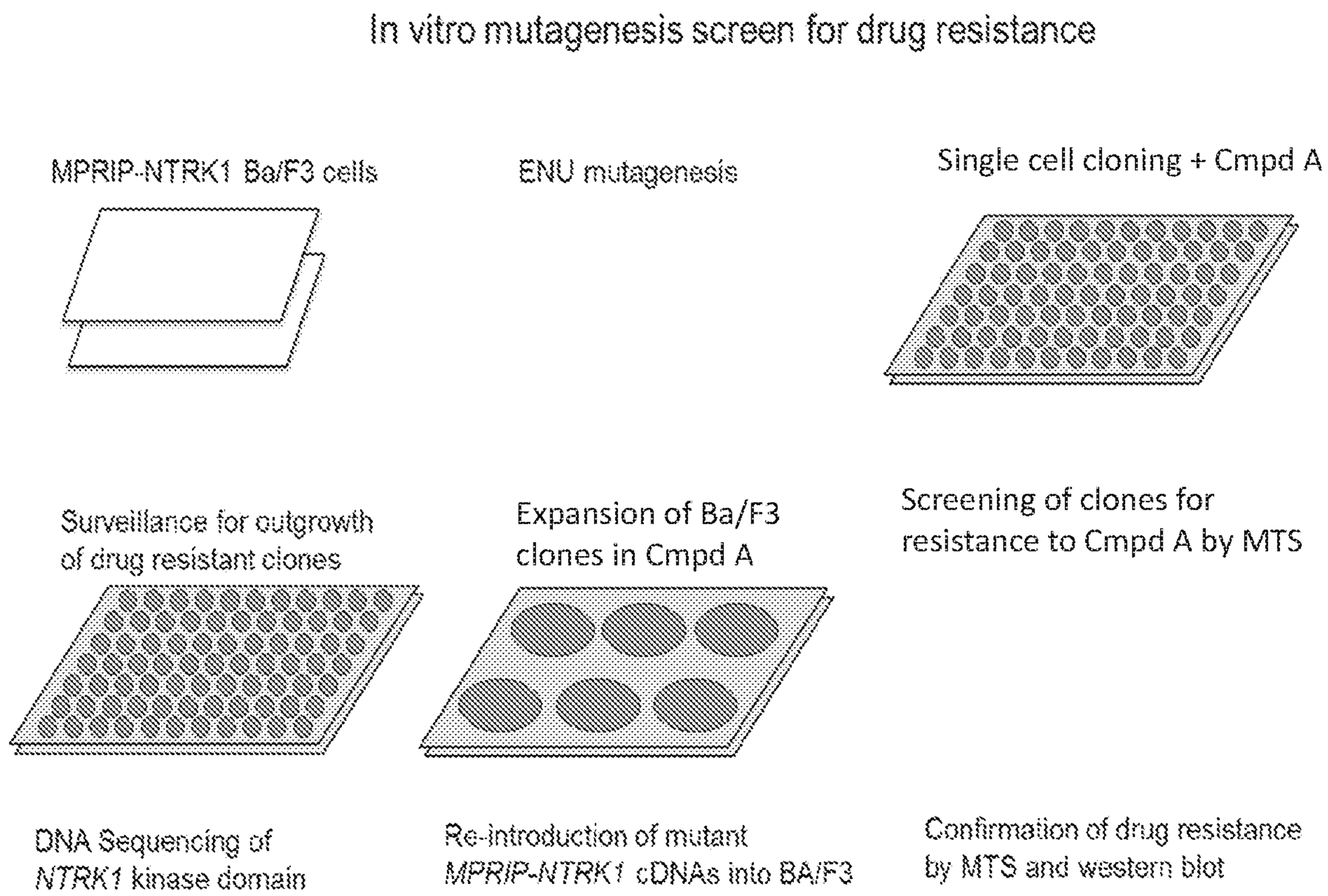

In vitro mutagenesis screen for drug resistance
MPRIP-NTRK1 Ba/F3 cells
ENU mutagenesis
Single cell cloning + Cmpd A
Surveillance for outgrowth of drug resistant clones
Expansion of Ba/F3 clones in Cmpd A
Screening of clones for resistance to Cmpd A by MTS
DNA Sequencing of NTRK1 kinase domain
Re-introduction of mutant MPRIP-NTRK1 cDNAs into BA/F3
Confirmation of drug resistance by MTS and western blot

Figure 1

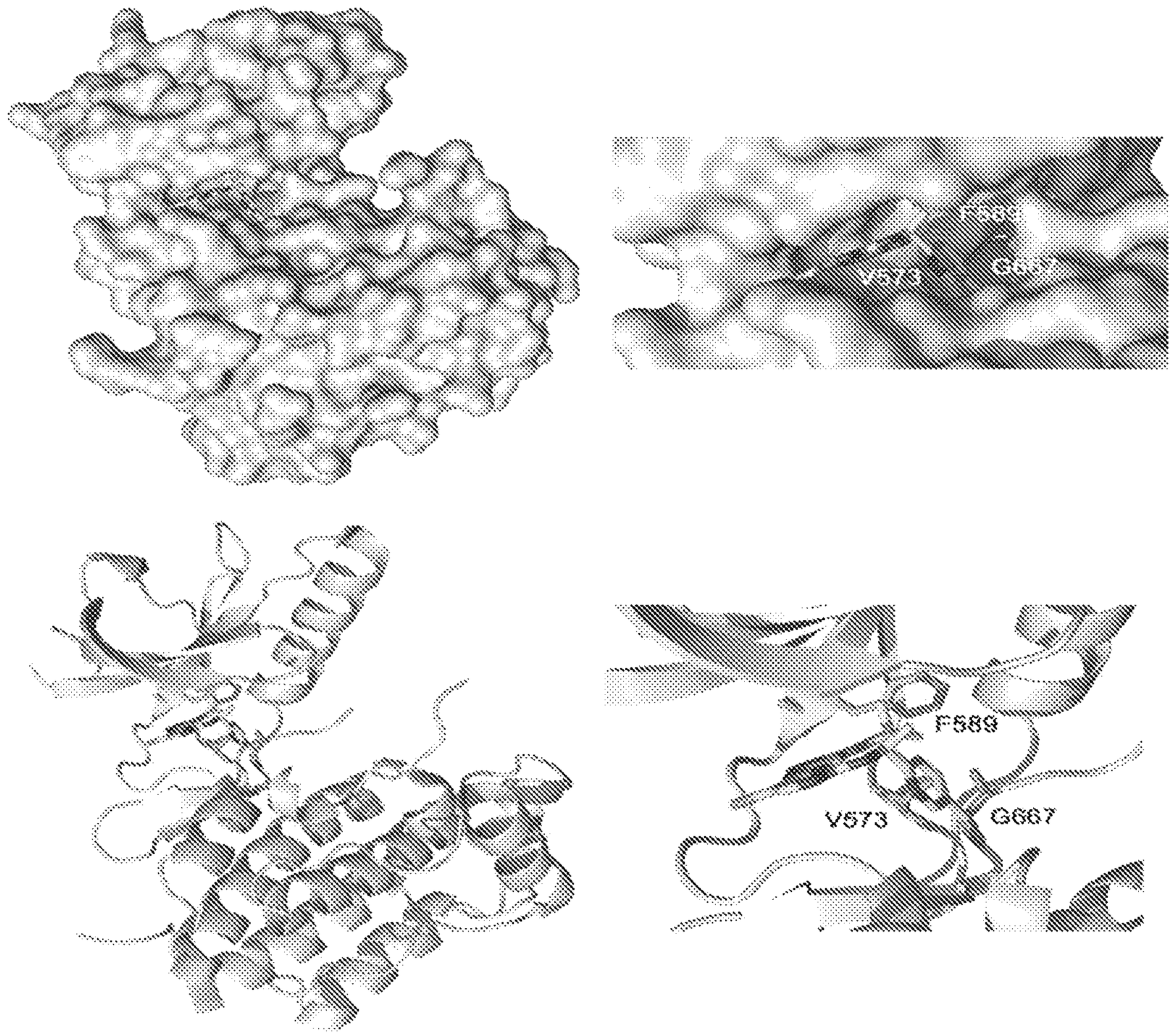


Figure 2

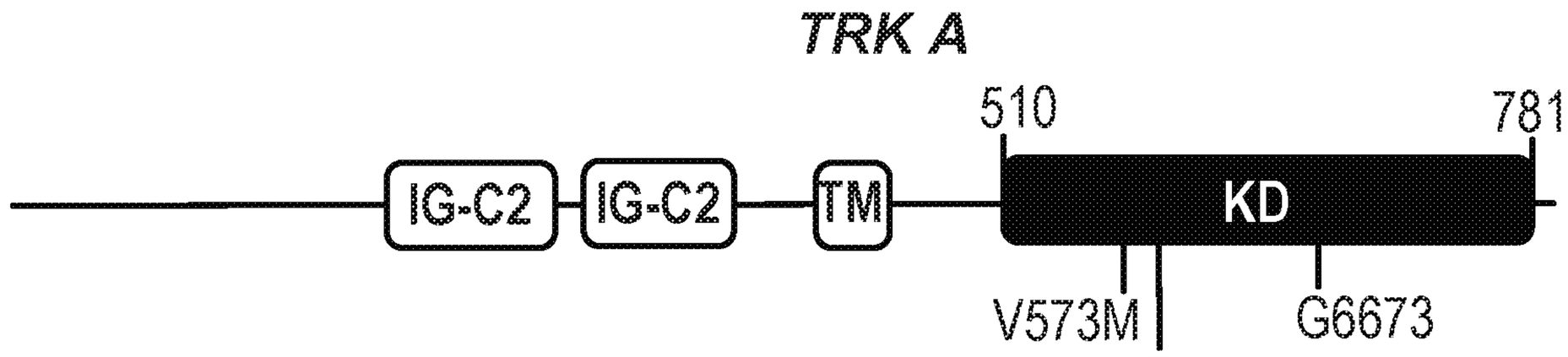


Figure 3

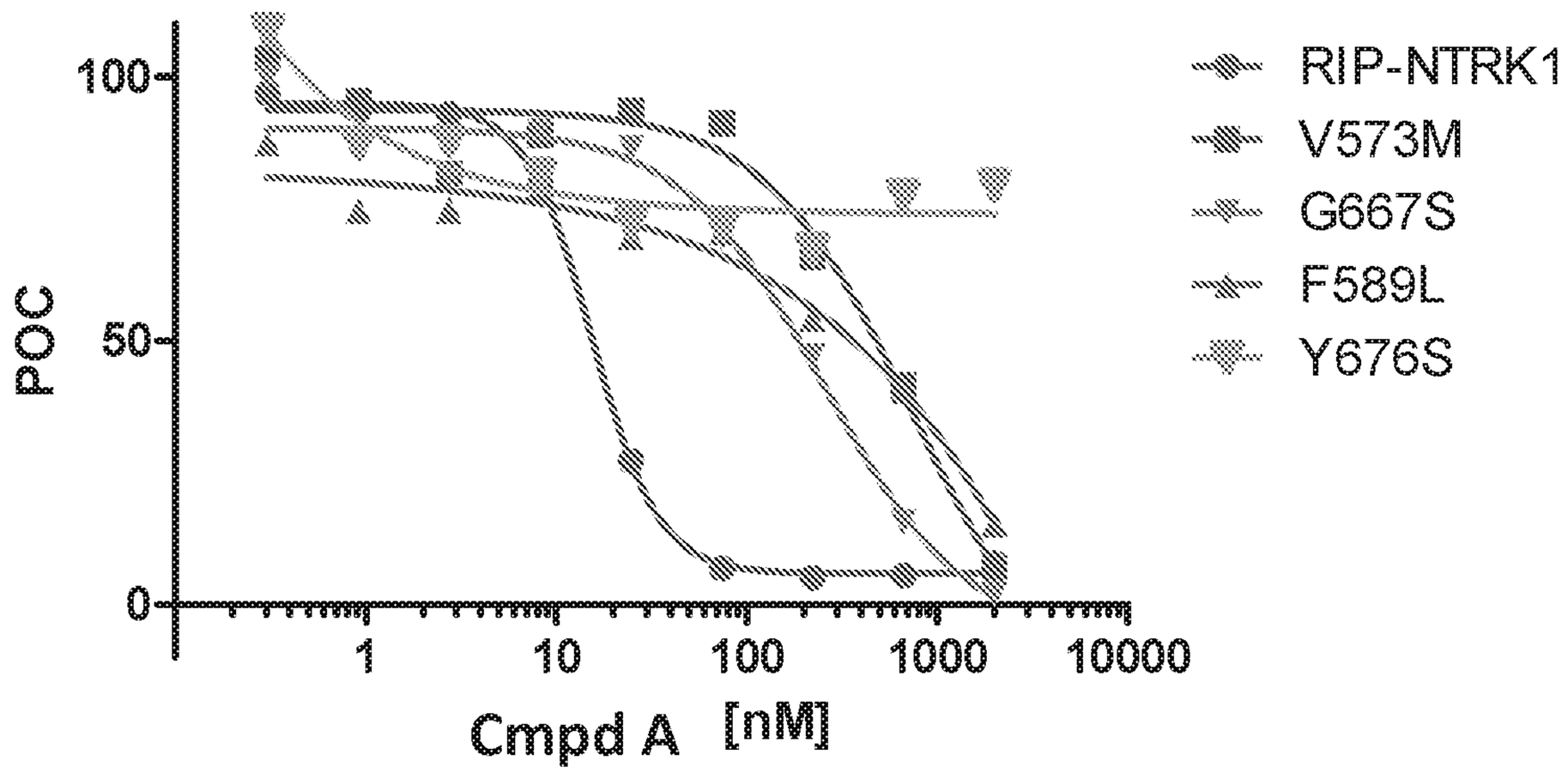

100
50
0
POC
1
10
100
1000
10000
Cmpd A [nM]
RIP-NTRK1
V573M
G667S
F589L
Y676S

Figure 4

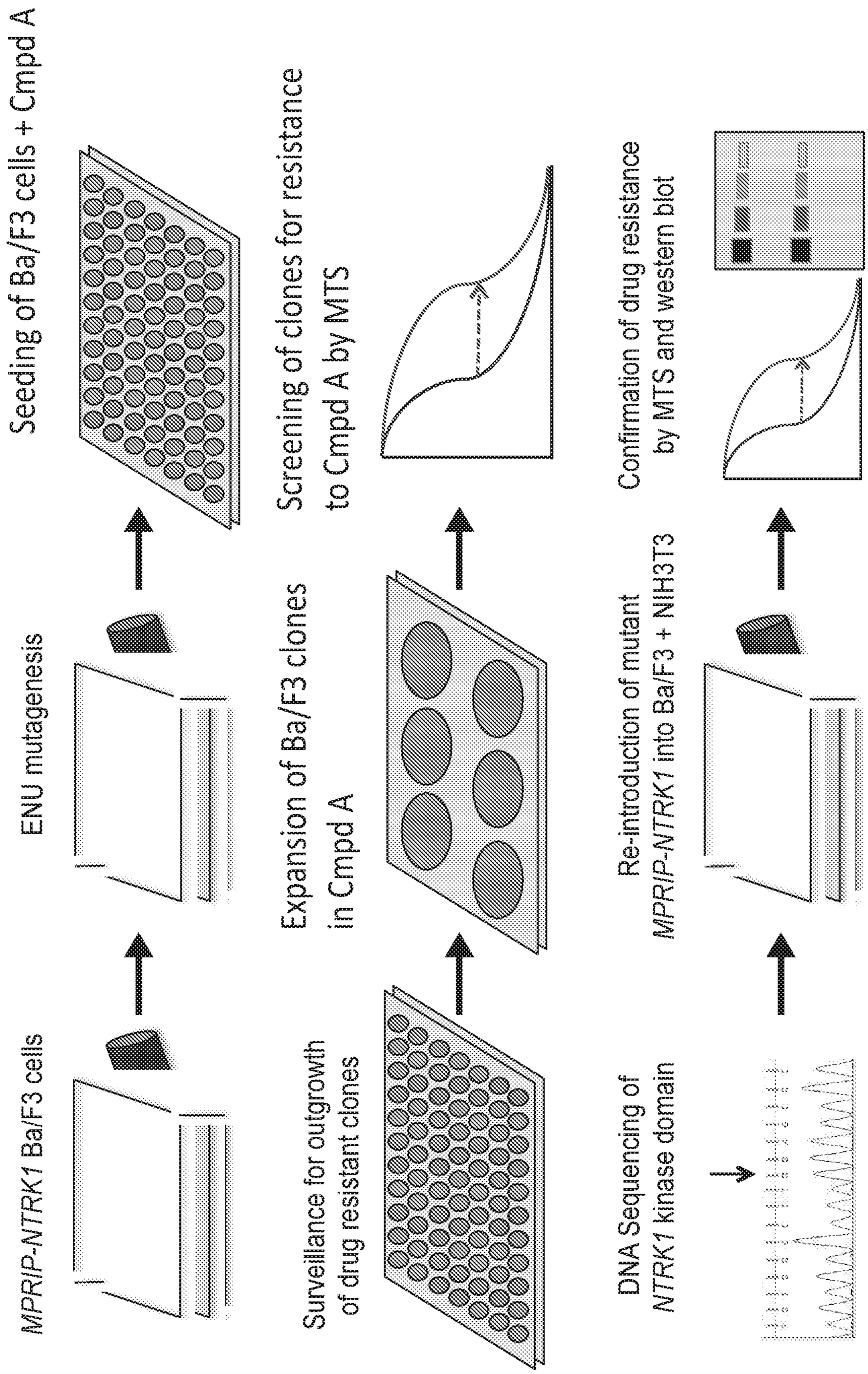

MPRIP-NTRK1 Ba/F3 cells
ENU mutagenesis
Seeding of Ba/F3 cells + Cmpd A
Surveillance for outgrowth of drug resistant clones
Expansion of Ba/F3 clones in Cmpd A
Screening of clones for resistance to Cmpd A by MTS
DNA Sequencing of NTRK1 kinase domain
Re-introduction of mutant MPRIP-NTRK1 into Ba/F3 + NIH3T3
Confirmation of drug resistance by MTS and western blot

Figure 5

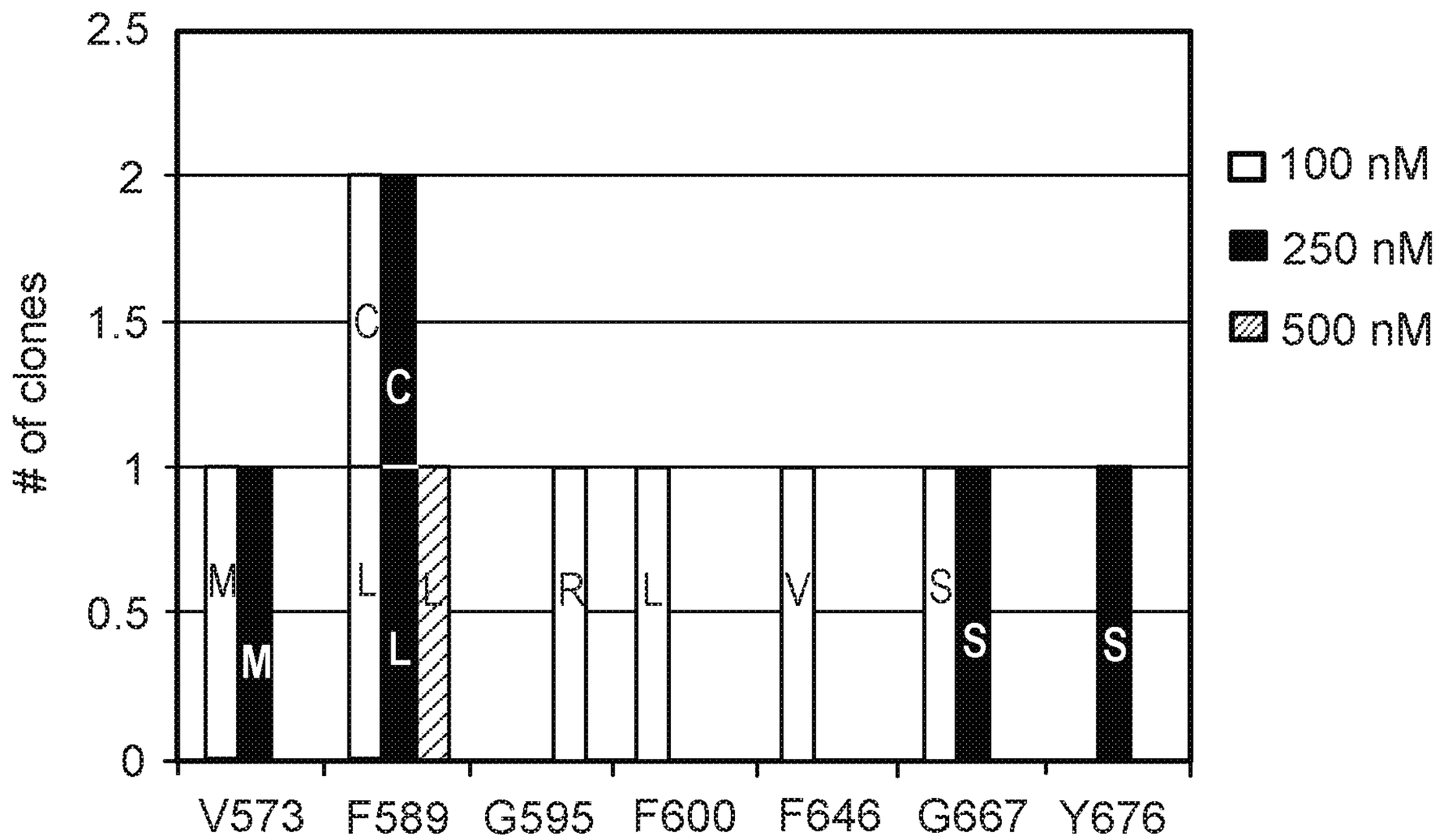


Figure 6A

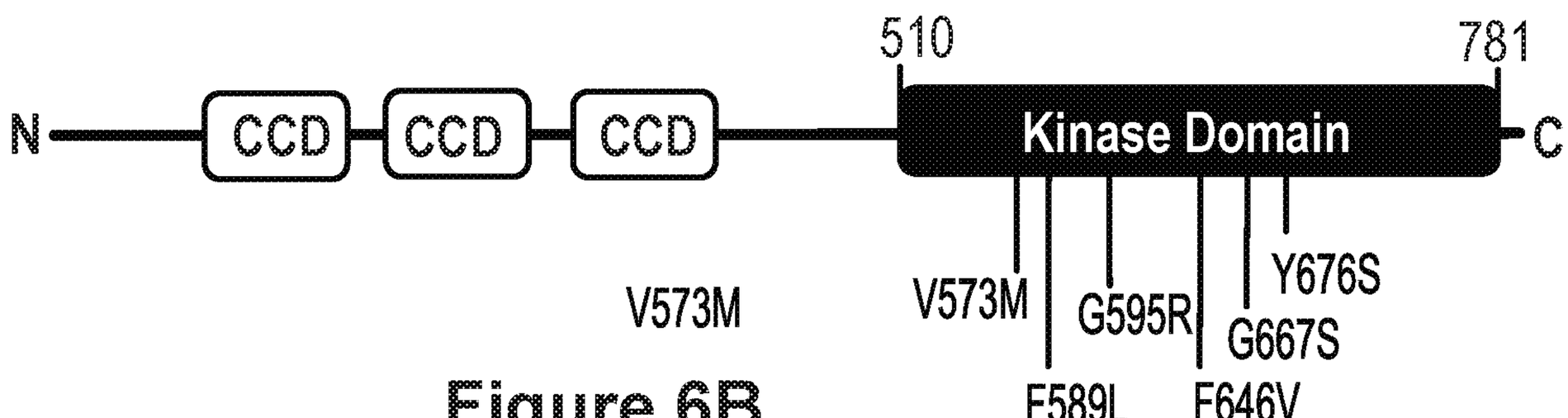


Figure 6B

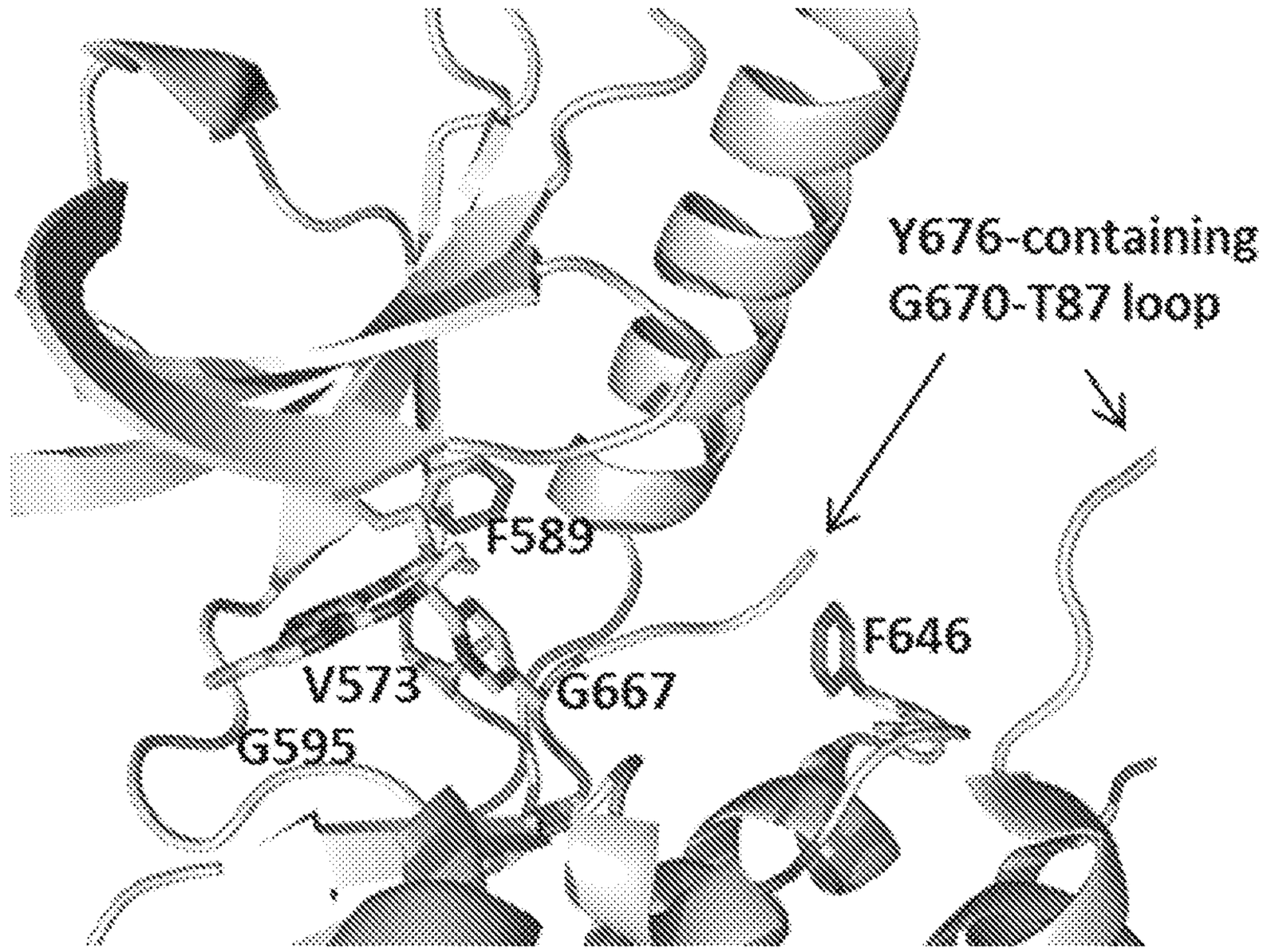


Figure 6C

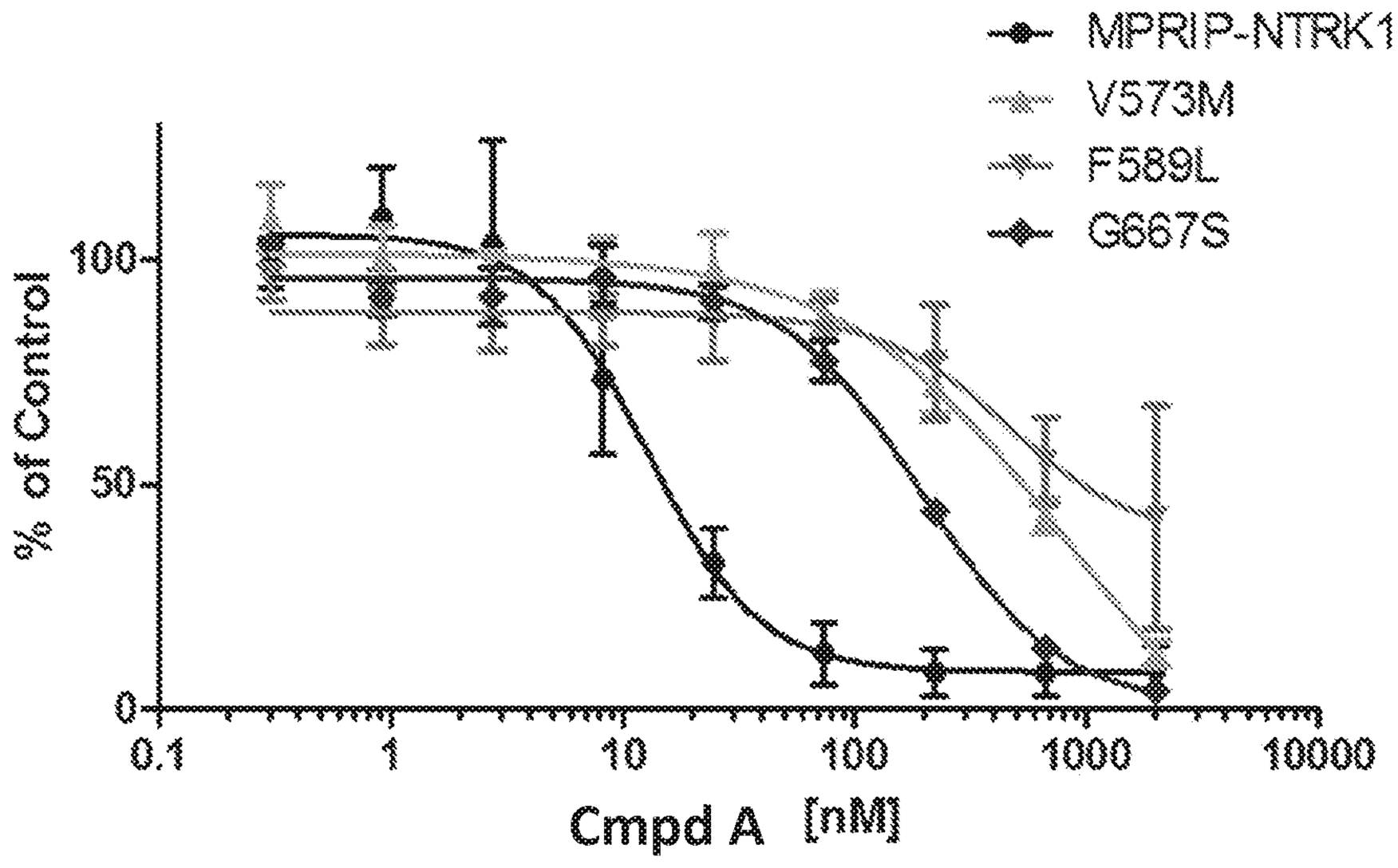

MPRIP-NTRK1
V573M
F589L
G667S
% of Control
100
50
0
0.1
1
10
100
1000
10000
Cmpd A [nM]

Figure 7

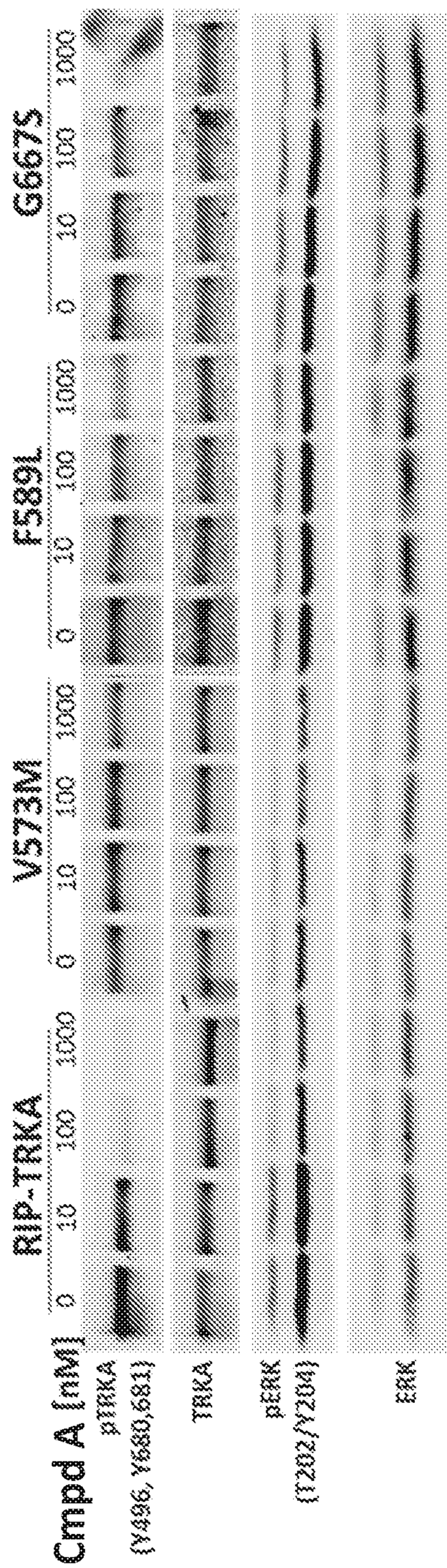

RIP-TRKA
V573M
F589L
G667S
Cmpd A [nM]
0
10
100
1000
pTRKA
(Y490,Y681)
TRKA
pERK
(T202/Y204)
ERK

Figure 8

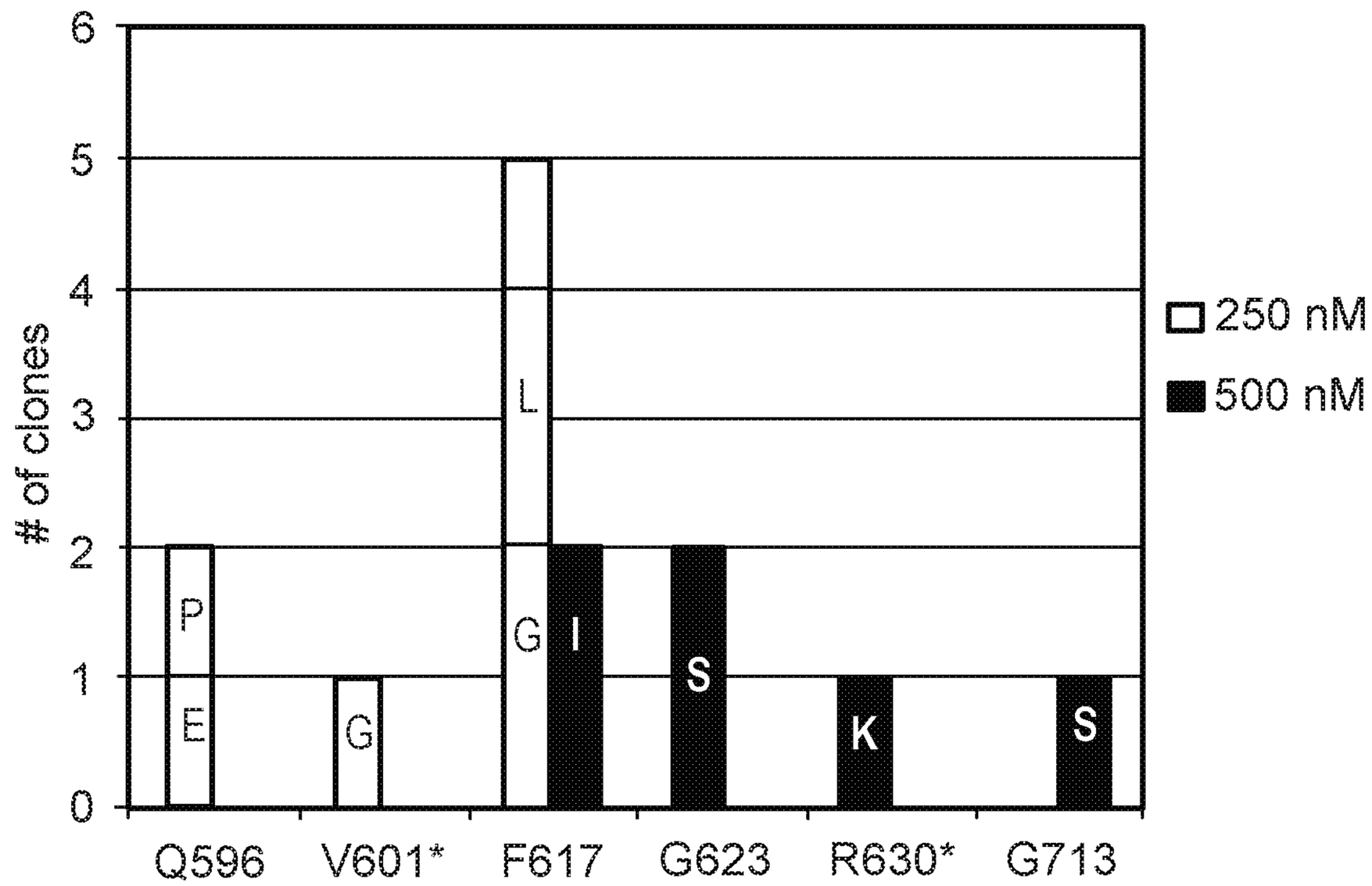


Figure 9A

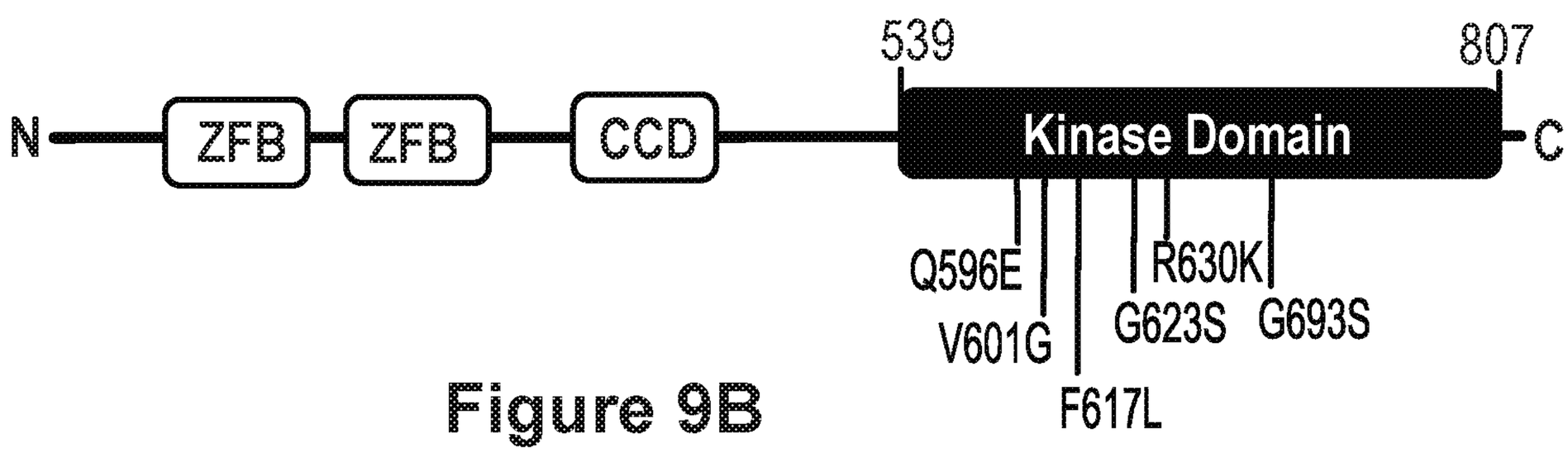


Figure 9B

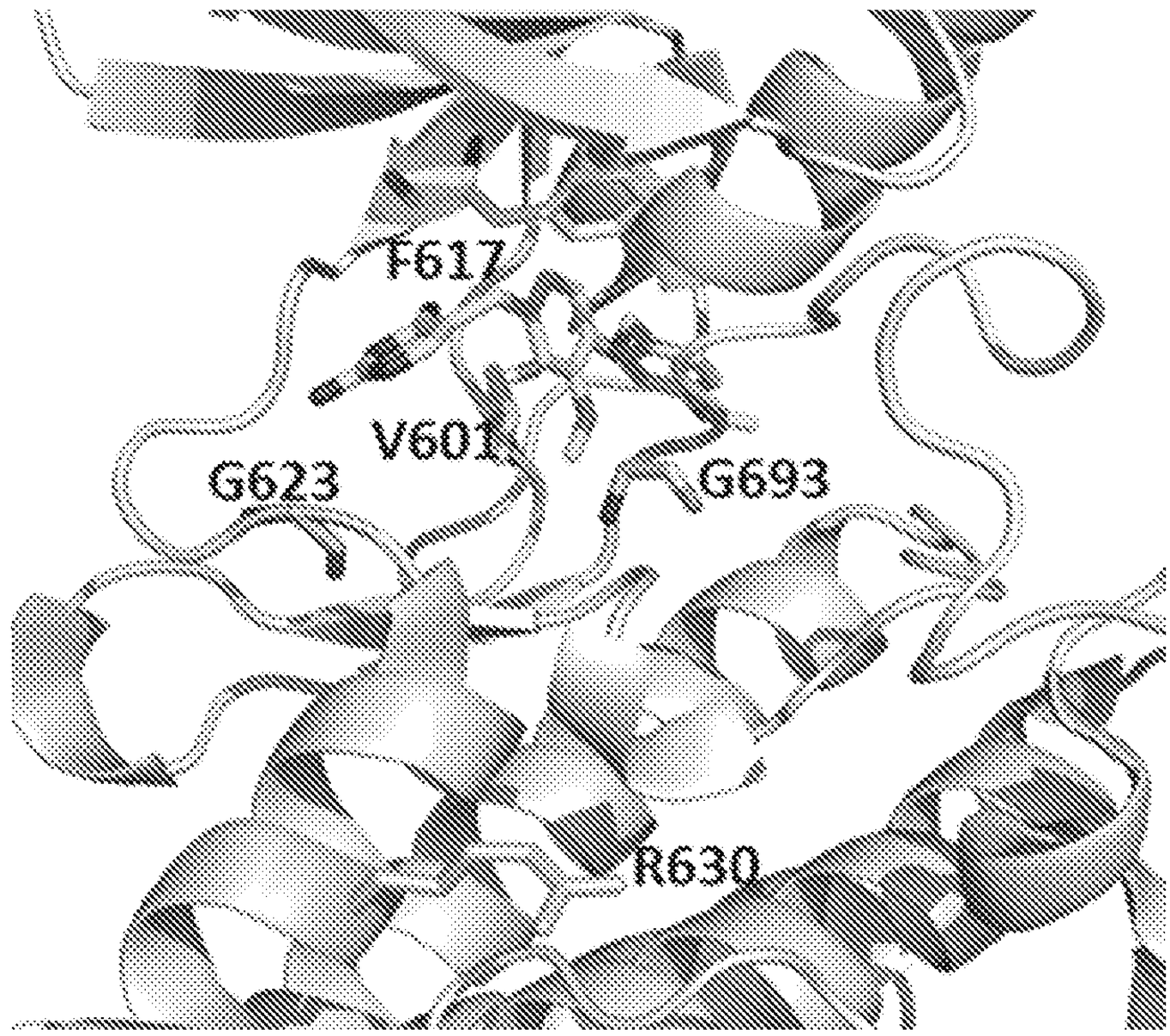


Figure 9C

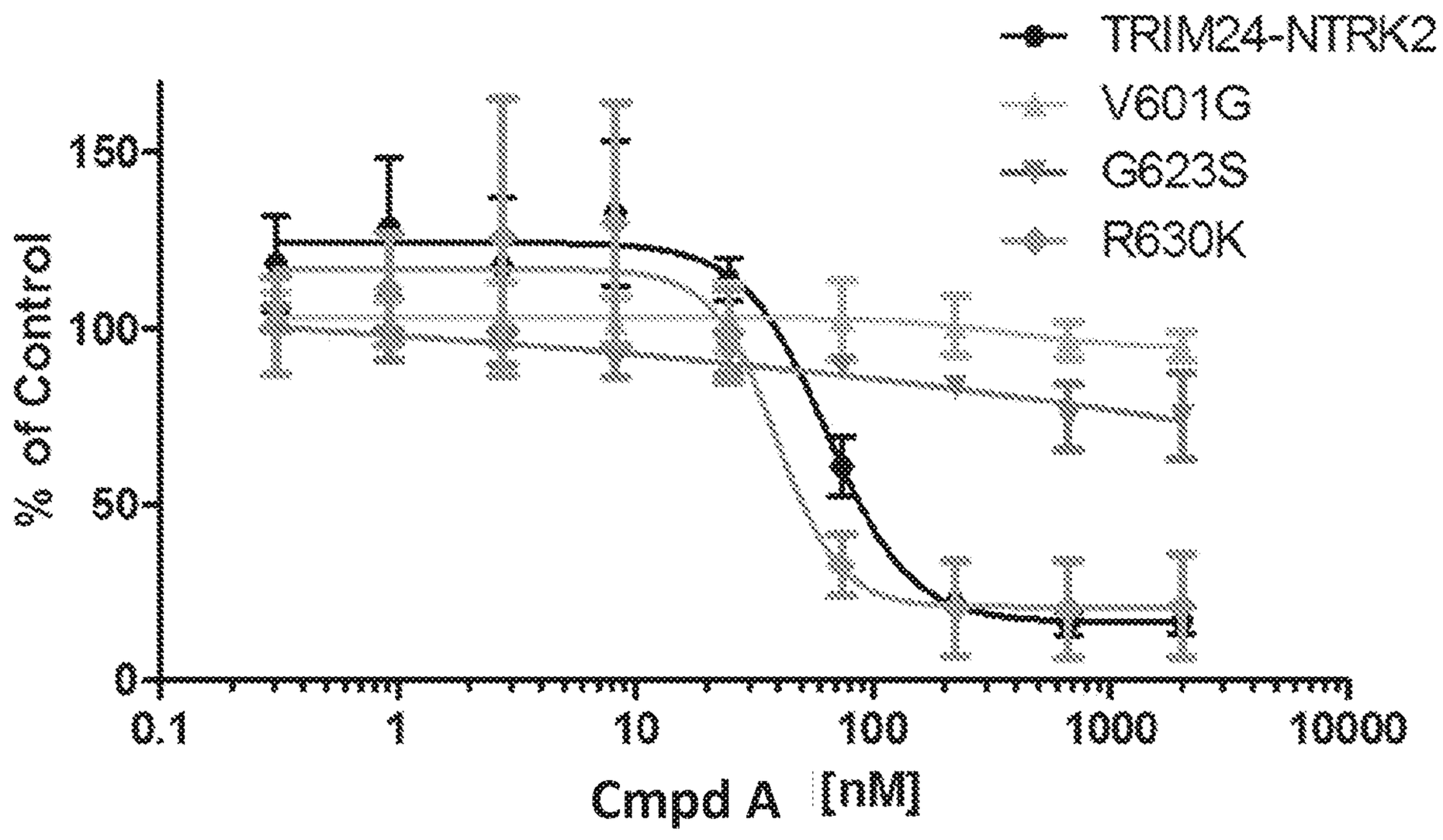

TRIM24-NTRK2
V601G
G623S
R630K
% of Control
150
100
50
0
0.1
1
10
100
1000
10000
Cmpd A [nM]

Figure 10

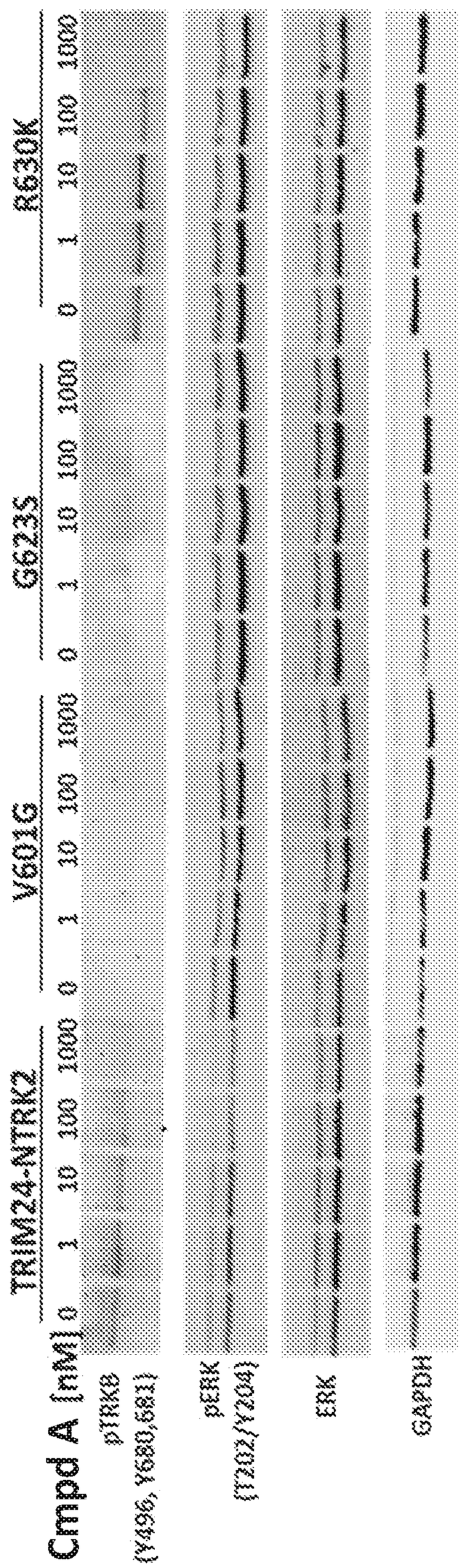

TRIM24-NTRK2
V601G
G623S
R630K
Cmpd A (nM)
0 1 10 100 1000 0 1 10 100 1000 0 1 10 100 1000
pTRK
(Y496, Y680,681)
pERK
(T202/Y204)
ERK
GAPDH

Figure 11

IC_{50} (nM)			
MPRIP-NTRK1	15	TRIM24-NTRK2	88.3
V573M	534.5	V601G	>2000
F589L	1999.8	F617	--
G595R		G623S	>2000
G667S	217.2	G693S	
		R630K	45.7
		Q596E	

Figure 12

```
NTRK1 486   -----------LQGHIIENPQYFS--------DACVHHIKRRDIVLKWELGEGAFGKVFL 526
NTRK2 490   ------VIIGMTKIPVIENPQYFGITNSQLKPDTFVQHIKRHNIVLKRELGEGAFGKVFL 554
ALK   1083  --------LRTSTIMTDYNPNYCFAGK--TSSISDLKEVPRKNITLIRGLGHGAFGEVYE 1132
ROS1  1908  ------ELRGLAAGVGLANACYAIHTLPTQEEIENLPAFPREKLTLRLLLGSGAFGEVYE 1961
ABL1  199   VHHHSTVADGLITTLHYPAPKRNKPTVYGVSPNYDKWEMERTDITMKHKLGGGQYGEVYE 258
EGFR  680   --------RRLLQERELVEPLTPSGEAPN---QALLRILKETEFKKIKVLGSGAFGTVYK 728
                                                      596 573/601
NTRK1 527   AECHNLLP-EQDKMLVAVKALKEA-SESARQDFQREAELLTMLQHQHIVRFFGVCTEGRP 584
NTRK2 555   AECYNLCP-EQDKILVAVKTLKDA-SDNARKDFHREAELLTNLQHEHIVKFYGVCVEGDP 612
ALK   1133  GQVSGMPN-DPSPLQVAVKTLPEVCSEQDELDFLMEALIISKFNHQNIVRCIGVSLQSLP 1191
ROS1  1962  GTAVDILGVGSGEIKVAVKTLKKGSTDQEKIEFLKEAHLMSKFNHPNILKQLGVCLLNEP 2021
ABL1  259   GVWKK------YSLTVAVKTLKEDTM--EVEEFLKEAAVMKEIKHPNLVQLLGVCTREPP 310
EGFR  729   GLWI--PEGEKVKIPVAIKELREATSPKANKEILDEAYVMASVDNPHVCRLLGICLTSTV 786
              589/617595/623 639
NTRK1 585   LLMVFEYMRHGDLNRFLRSHGPDAKLLAGGEDVAPGPLGLGQLLAVASQVAAGMVYLAGL 644
NTRK2 613   LIMVFEYMKHGDLNKFLRAHGPDAVLMAEGN--PPTELTQSQMLHIAQQIAAGMVYLASQ 670
ALK   1192  RFILLEMAGGDLKSFLRETRPRPS--------QPSSLAMLDLLHVARDIACGCQYLEEN 1243
ROS1  2022  QYIILELMEGGDLLTYLRKARMATF--------YGPLLTLVDLVDLCVDISKGCVYLERM 2073
ABL1  311   FYIITEFMTYGNLLDYLRECNRQEV-------------NAVVLLYMATQISSAMEYLEKK 357
EGFR  787   QL-ITQLMPFGCLLDYVREHKDNI--------------GSQYLLNWCVQIAKGMNYLEDR 831
            646                         667/693
NTRK1 645   NFVHRDLATRNCLV-----GQGLVVKIGDFGMSRDIYSTDYYRVGGRTMLPIRWMPPESI 699
NTRK2 671   NFVHRDLATRNCLV-----GENLLVKIGDFGMSRDVYSTDYYRVGGHTMLPIRWMPPESI 725
ALK   1244  NFIHRDIAARNCLLTCP--GPGRVAKIGDFGMARDIYRASYYRKGGCAMLPVKWMPPEAF 1301
ROS1  2074  NFIHRDLAARNCLVSVKDYTSPRIVKIGDFGLARDIYKNDYYRKRGEGLLPVRWMAPESL 2133
ABL1  358   NFIHRDLAARNCLV-----GENHLVKVADFGLSRLMTGDTYTAH-AGAKFPIKWTAPESL 411
EGFR  832   SLVHRDLAARNVLV-----KTPQHVKITDFGLAKLLGAEEKEYHAEGGKVPIKWMALESI 886

NTRK1 700   LYRKFTTESDVWSFGVVLWEIFTYGKQPWYQLSNTEAIDCITQGRELERPRACPPEVYAI 759
NTRK2 726   MYRKFTTESDVWSLGVVLWEIFTYGKQPWYQLSNNEVIECITQGRVLQRPRTCPQEVYEL 785
ALK   1302  MEGIFTSKTDTWSFGVLLWEIFSLGYMPYPSKSNQEVLEFVTSGGRMDPPKNCPGPVYRI 1361
ROS1  2134  MDGIFTTQSDVWSFGILIWEILTFGHQPYPAHSNLDVLNYVQTGGRLEPPRNCPDDLWNL 2193
ABL1  412   AYNKFSIKSDVWAFGVLLWEIATYGMSPYPGIDLSQVYELLEKDYRMERPEGCPEKVYEL 471
EGFR  887   LHRIYTHQSDVWSYGVTVWELMTFGSKPYDGIPASEISSILEKGERLPQPPICTIDVYMI 946
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Figure 13