

INDAZOLE COMPOUNDS FOR THE TREATMENT OF CANCER**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Application No. 63/610,500 filed on December 15, 2023, and U.S. Provisional Application No. 63/679,751 filed on August 6, 2024. Each of these applications is incorporated by reference in its entirety herein.

TECHNICAL FIELD

[0002] The disclosure pertains to indazole compounds that are useful in treating cancer, pharmaceutical compositions that include one or more such indazole compounds, and methods of using such indazole compounds in treating cancer.

BACKGROUND

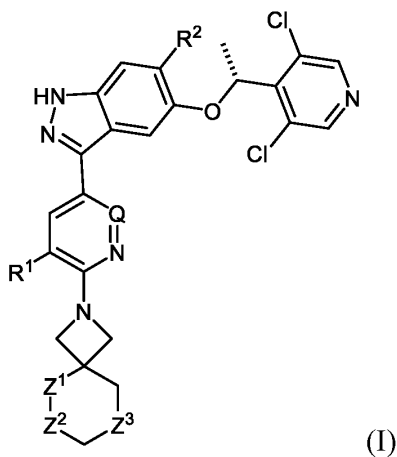
[0003] Kinase inhibitors have been used to block the activity of kinases and thereby treat cancer (e.g., by inhibiting mitotic processes). These kinase inhibitors are often small molecules that target kinases to block the development, growth or spread of cancer.

[0004] However, although various inhibitors of kinases are known, there remains a need for selective inhibitors to be used for the treatment of diseases such as hyper-proliferative diseases, which offer one or more advantages over current compounds. Those advantages include: improved activity and/or efficacy; beneficial kinase selectivity profile according to the respective therapeutic need; improved side effect profile, such as fewer undesired side effects, lower intensity of side effects, or reduced (cyto)toxicity; improved targeting of mutant receptors in diseased cells; improved physicochemical properties, such as solubility/stability in water, body fluids, and/or pharmaceutical formulations; improved pharmacokinetic properties, allowing e.g. for dose reduction or an easier dosing scheme; easier drug substance manufacturing, e.g. by shorter synthetic routes or easier purification.

SUMMARY OF THE INVENTION

[0005] The compounds disclosed herein provide small molecule kinase inhibitors that are both efficacious and selective.

[0006] In some aspects, the disclosure provides compounds of formula (I):



or pharmaceutically acceptable salts thereof, wherein

Q is CH or N;

R¹ is H, F, or CN;

R² is H or OCH₃;

Z¹ is absent, CH₂, NR³, or O;

Z² is absent, CH₂, NR³, or O;

Z³ is absent, CH₂, NR³, or O;

wherein at least one of Z¹, Z², and Z³ is NR³ or O;

wherein if R¹ is H or CN and Q is CH, then Z¹ is NR³, Z² is absent or CH₂, and Z³ is CH₂, NR³, or O;

wherein if R¹ is F or CN and R² is OCH₃, then Z¹ is NR³, Z² is absent or CH₂, and Z³ is CH₂, NR³, or O;

and

each R³ is independently H or SO₂CH₃.

[0007] Stereoisomers of the compounds of formula (I), and the pharmaceutical salts and solvates thereof, are also described. Methods of using compounds of formula (I) are described, as well as pharmaceutical compositions including the compounds of formula (I).

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0008] The disclosure may be more fully appreciated by reference to the following description, including the following definitions and examples. Certain features of the disclosed compositions and methods which are described herein in the context of separate aspects, may also be provided in combination in a single aspect. Alternatively, various features of the disclosed compositions and methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any subcombination.

[0009] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In several embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic, trifluoroacetic acid, or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine.

[0010] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition, it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. It is understood that, in any compound described herein having one or more chiral centers, all possible diastereomers are also envisioned. It is understood that, in any compound described herein all tautomers are envisioned. It is also understood that, in any compound described herein, all isotopes of the included atoms are envisioned. For example, any instance of hydrogen, may include hydrogen-1 (protium), hydrogen-2 (deuterium), hydrogen-3 (tritium) or other isotopes; any instance of carbon may include carbon-12, carbon-13, carbon-14, or other isotopes; any instance of oxygen may include oxygen-16, oxygen-17, oxygen-18, or other isotopes; any instance of fluorine may include one or more of fluorine-18, fluorine-19, or other isotopes; any instance of sulfur may include one or more of sulfur-32, sulfur-34, sulfur-35, sulfur-36, or other isotopes.

[0011] As used herein, the term “kinase inhibitor” means any compound, molecule or composition that inhibits or reduces the activity of a kinase. The inhibition can be achieved by, for example, blocking phosphorylation of the kinase (e.g., competing with adenosine triphosphate (ATP), a phosphorylating entity), by binding to a site outside the active site, affecting its activity by a conformational change, or by depriving kinases of access to the molecular chaperoning systems on which they depend for their cellular stability, leading to their ubiquitylation and degradation.

[0012] As used herein, “subject,” “host,” “patient,” and “individual” are used interchangeably and shall be given its ordinary meaning and shall also refer to an organism that has FGFR proteins. This includes mammals, e.g., a human, a non-

human primate, ungulates, canines, felines, equines, mice, rats, and the like. The term “mammal” includes both human and non-human mammals.

[0013] The term “sample” or “biological sample” shall be given its ordinary meaning and also encompasses a variety of sample types obtained from an organism and can be used in an imaging, a diagnostic, a prognostic, or a monitoring assay. The term encompasses blood and other liquid samples of biological origin, solid tissue samples, such as a biopsy specimen or tissue cultures or cells derived therefrom and the progeny thereof. The term encompasses samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components. The term encompasses a clinical sample, and also includes cells in cell culture, cell supernatants, cell lysates, serum, plasma, biological fluids, and tissue samples.

[0014] The terms “treatment,” “treating,” “treat” and the like shall be given its ordinary meaning and shall also include herein to generally refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete stabilization or cure for a disease and/or adverse effect attributable to the disease. “Treatment” as used herein shall be given its ordinary meaning and shall also cover any treatment of a disease in a mammal, particularly a human, and includes: (a) preventing the disease or symptom from occurring in a subject which may be predisposed to the disease or symptom but has not yet been diagnosed as having it; (b) inhibiting the disease symptom, e.g., arresting its development; and/or (c) relieving the disease symptom, e.g., causing regression of the disease or symptom.

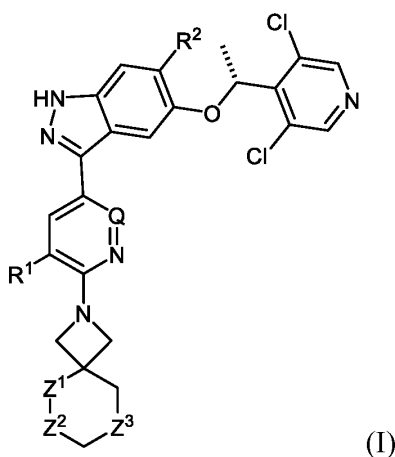
[0015] The terms “cancer,” “neoplasm,” and “tumor” are used interchangeably herein, shall be given its ordinary meaning and shall also refer to cells which exhibit relatively autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In general, cells of interest for detection or treatment in the present application include precursors, precancerous (*e.g.*, benign), malignant, pre-metastatic, metastatic, and

non-metastatic cells. As used herein, “FGFR related cancer” denotes those cancers that involve an increased activity in a mutant FGFR kinase, for example, the continued activation of FGFR.

[0016] The term “control” refers shall be given its ordinary meaning and shall also include a sample or standard used for comparison with a sample which is being examined, processed, characterized, analyzed, etc. In several embodiments, the control is a sample obtained from a healthy patient or a non-tumor tissue sample obtained from a patient diagnosed with a tumor. In several embodiments, the control is a historical control or standard reference value or range of values. In several embodiments, the control is a comparison to a wild-type FGFR arrangement or scenario.

[0017] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article “a” or “an” does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[0018] In some aspects, the disclosure is directed to compounds of formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

Q is CH or N;

R¹ is H, F, or CN;

R² is H or OCH₃;

Z¹ is absent, CH₂, NR³, or O;

Z² is absent, CH₂, NR³, or O;

Z³ is absent, CH₂, NR³, or O;

wherein at least one of Z¹, Z², and Z³ is NR³ or O;

wherein if R¹ is H or CN and Q is CH, then Z¹ is NR³, Z² is absent or CH₂, and Z³ is CH₂, NR³, or O;

wherein if R¹ is F or CN and R² is OCH₃, then Z¹ is NR³, Z² is absent or CH₂, and Z³ is CH₂, NR³, or O;

and

each R³ is independently H or SO₂CH₃.

[0019] In some embodiments of Formula (I), Q is CH.

[0020] In other embodiments of Formula (I), Q is N.

[0021] In some embodiments of Formula (I), R¹ is H.

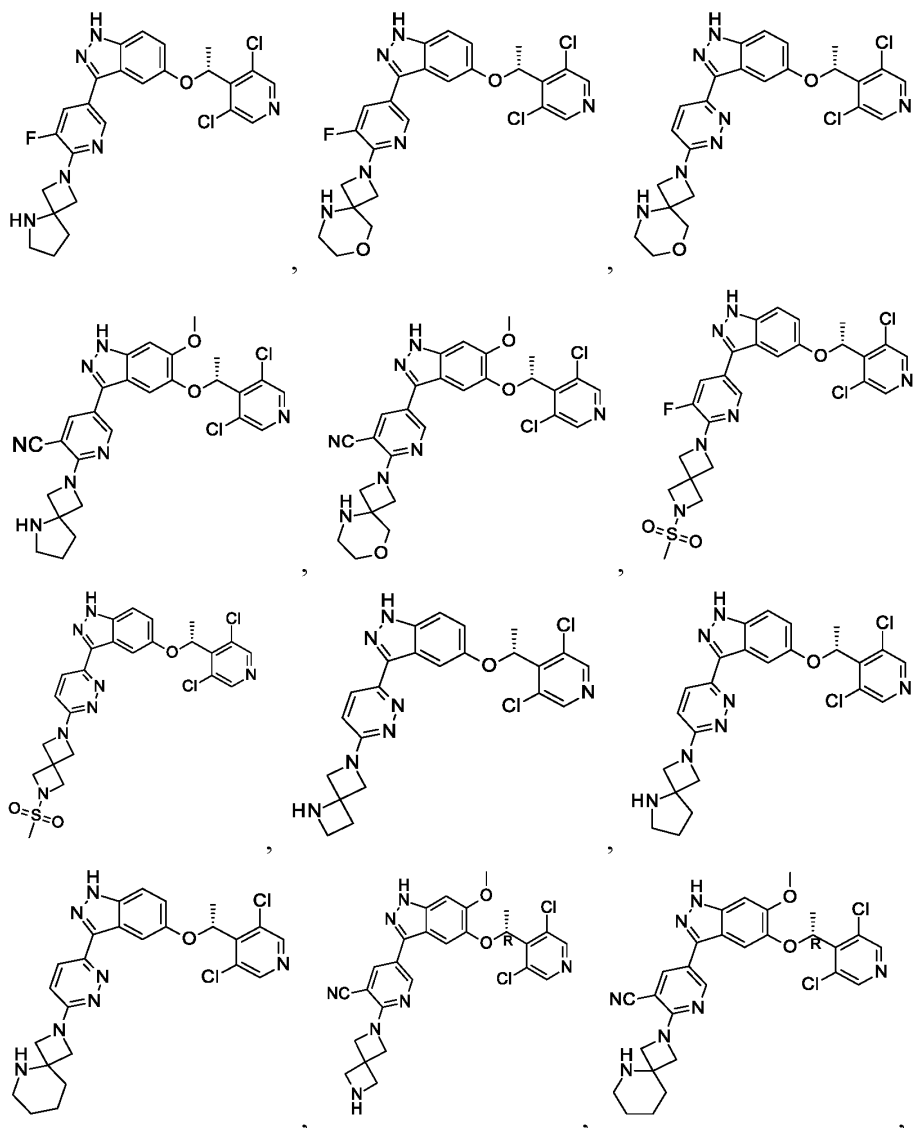
[0022] In other embodiments of Formula (I), R¹ is F.

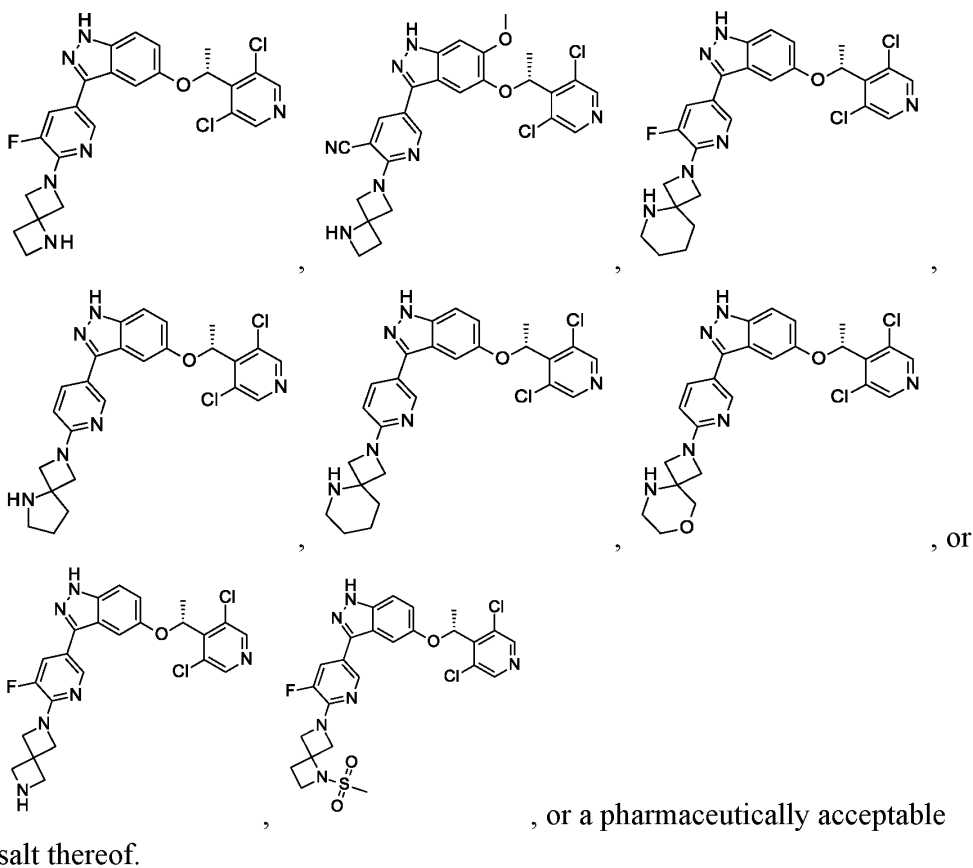
- [0023] In some embodiments of Formula (I), R^1 is CN.
- [0024] In some embodiments of Formula (I), R^2 is H.
- [0025] In other embodiments of Formula (I), R^2 is OCH_3 .
- [0026] In some embodiments of Formula (I), Z^1 is absent.
- [0027] In some embodiments of Formula (I), Z^1 is CH_2 .
- [0028] In some embodiments of Formula (I), Z^1 is NR^3 .
- [0029] In some embodiments of Formula (I), Z^1 is O.
- [0030] In some embodiments of Formula (I), Z^2 is absent.
- [0031] In some embodiments of Formula (I), Z^2 is CH_2 .
- [0032] In some embodiments of Formula (I), Z^2 is NR^3 .
- [0033] In some embodiments of Formula (I), Z^2 is O.
- [0034] In some embodiments of Formula (I), Z^3 is absent.
- [0035] In some embodiments of Formula (I), Z^3 is CH_2 .
- [0036] In some embodiments of Formula (I), Z^3 is NR^3 .
- [0037] In some embodiments of Formula (I), Z^3 is O.
- [0038] In some embodiments of Formula (I), Z^1 is NR^3 ; Z^2 is CH_2 ; and Z^3 is CH_2 .
- [0039] In some embodiments of Formula (I), Z^1 is NR^3 ; Z^2 is absent; and Z^3 is CH_2 .
- [0040] In some embodiments of Formula (I), Z^1 is absent; Z^2 is absent; and Z^3 is NR^3 .
- [0041] In some embodiments of Formula (I), Z^1 is NR^3 ; Z^2 is absent; and Z^3 is absent.
- [0042] In some embodiments of Formula (I), Z^1 is NR^3 ; Z^2 is CH_2 ; and Z^3 is O.
- [0043] In some embodiments of Formula (I), R^3 is H.
- [0044] In some embodiments of Formula (I), R^3 is SO_2CH_3 .
- [0045] In some aspects of the compounds of Formula (I), at least one of Z^1 , Z^2 , and Z^3 is NR^3 or O.

[0046] In other aspects of the compounds of Formula (I), if R^1 is H or CN and Q is CH, then Z^1 is NR^3 , Z^2 is absent or CH_2 , and Z^3 is CH_2 , NR^3 , or O.

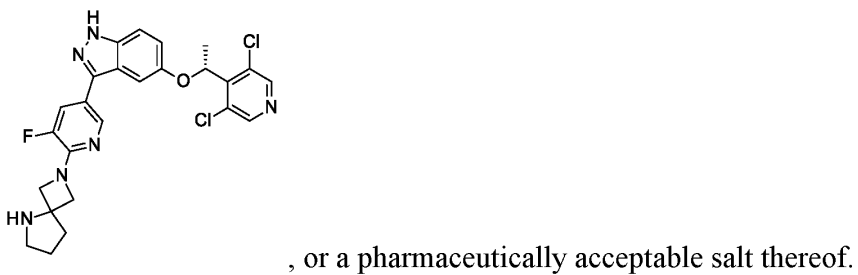
[0047] In yet other aspects of the compounds of Formula (I), if R^1 is F or CN and R^2 is OCH_3 , then Z^1 is NR^3 , Z^2 is absent or CH_2 , and Z^3 is CH_2 , NR^3 , or O.

[0048] In some embodiments, the compound of Formula (I) is:

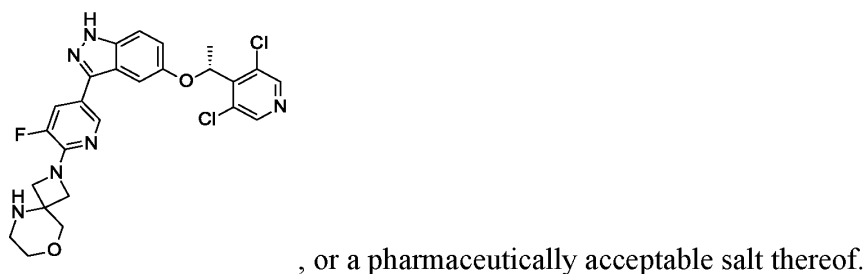




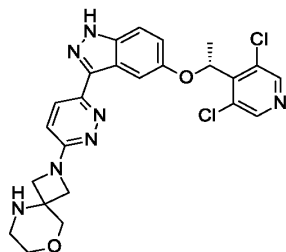
[0049] In some embodiments, the compound of Formula (I) is:



[0050] In other embodiments, the compound of Formula (I) is:

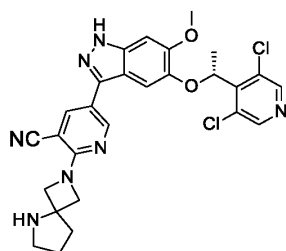


[0051] In other embodiments, the compound of Formula (I) is:



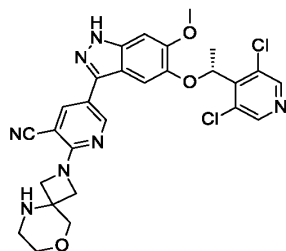
, or a pharmaceutically acceptable salt thereof.

[0052] In some embodiments, the compound of Formula (I) is:



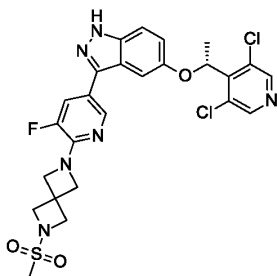
, or a pharmaceutically acceptable salt thereof.

[0053] In some embodiments, the compound of Formula (I) is:



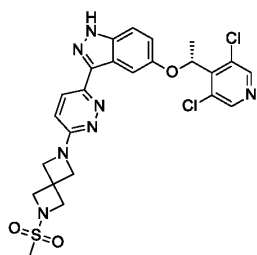
, or a pharmaceutically acceptable salt thereof.

[0054] In some embodiments, the compound of Formula (I) is:



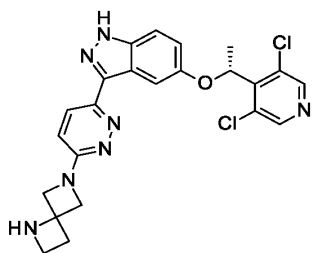
, or a pharmaceutically acceptable salt thereof.

[0055] In some embodiments, the compound of Formula (I) is:



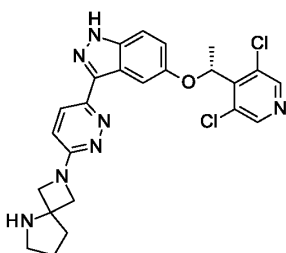
, or a pharmaceutically acceptable salt thereof.

[0056] In some embodiments, the compound of Formula (I) is:



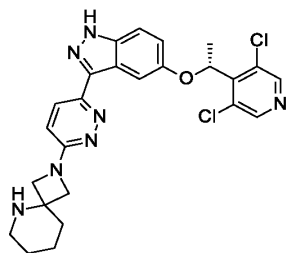
, or a pharmaceutically acceptable salt thereof.

[0057] In some embodiments, the compound of Formula (I) is:



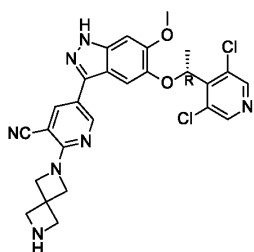
, or a pharmaceutically acceptable salt thereof.

[0058] In some embodiments, the compound of Formula (I) is:



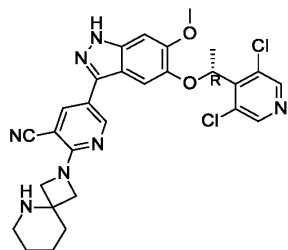
, or a pharmaceutically acceptable salt thereof.

[0059] In some embodiments, the compound of Formula (I) is:



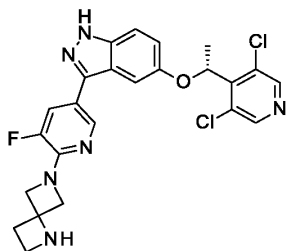
, or a pharmaceutically acceptable salt thereof.

[0060] In some embodiments, the compound of Formula (I) is:



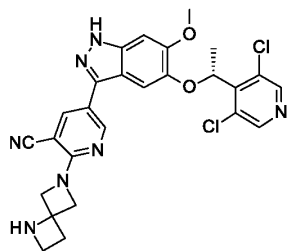
, or a pharmaceutically acceptable salt thereof.

[0061] In some embodiments, the compound of Formula (I) is:



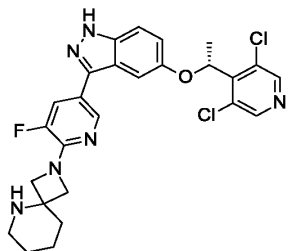
, or a pharmaceutically acceptable salt thereof.

[0062] In some embodiments, the compound of Formula (I) is:



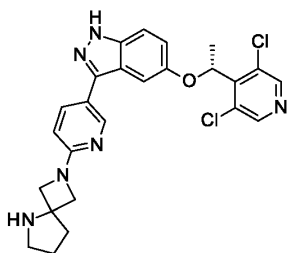
, or a pharmaceutically acceptable salt thereof.

[0063] In some embodiments, the compound of Formula (I) is:



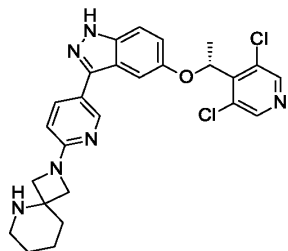
, or a pharmaceutically acceptable salt thereof.

[0064] In some embodiments, the compound of Formula (I) is:



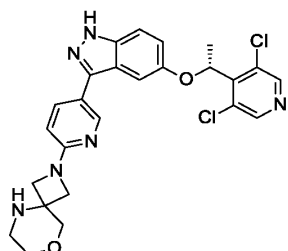
, or a pharmaceutically acceptable salt thereof.

[0065] In some embodiments, the compound of Formula (I) is:



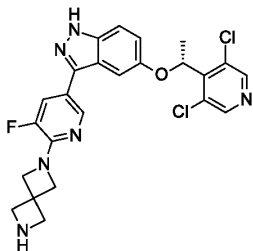
, or a pharmaceutically acceptable salt thereof.

[0066] In some embodiments, the compound of Formula (I) is:



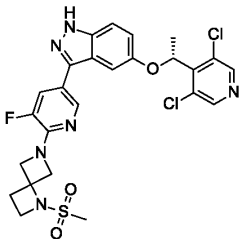
, or a pharmaceutically acceptable salt thereof.

[0067] In some embodiments, the compound of Formula (I) is:



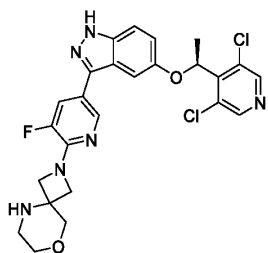
, or a pharmaceutically acceptable salt thereof.

[0068] In some embodiments, the compound of Formula (I) is:



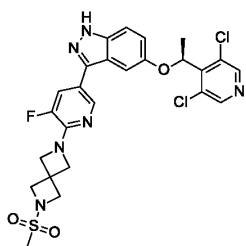
, or a pharmaceutically acceptable salt thereof.

[0069] In some aspects, the disclosure provides a compound of formula:



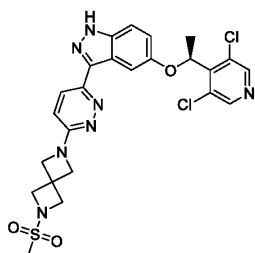
, or a pharmaceutically acceptable salt thereof.

[0070] In some aspects, the disclosure provides a compound of formula:



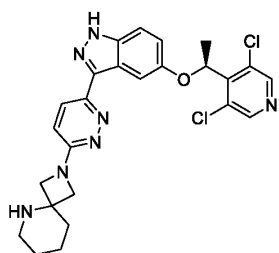
, or a pharmaceutically acceptable salt thereof.

[0071] In some aspects, the disclosure provides a compound of formula:



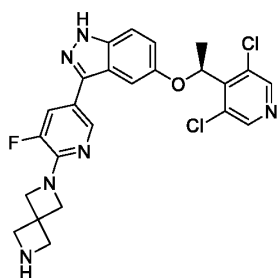
, or a pharmaceutically acceptable salt thereof.

[0072] In some aspects, the disclosure provides a compound of formula:



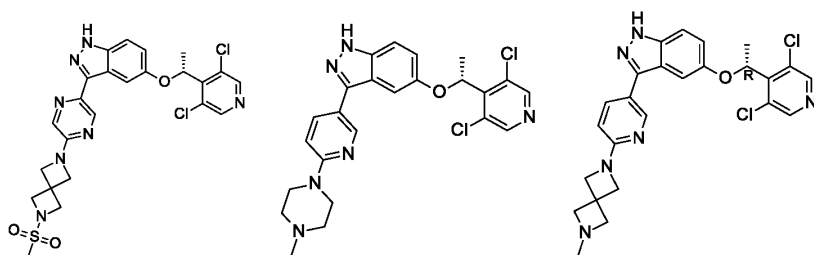
, or a pharmaceutically acceptable salt thereof.

[0073] In some aspects, the disclosure provides a compound of formula:

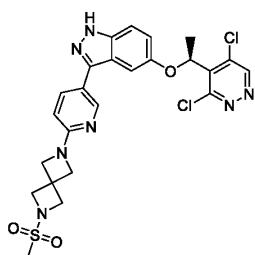


, or a pharmaceutically acceptable salt thereof.

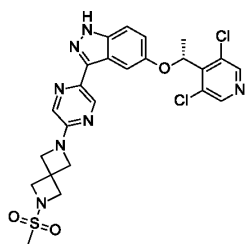
[0074] In other aspects, the disclosure provides the following compounds, or pharmaceutically acceptable salts thereof:



, or

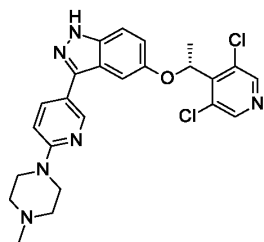


[0075] In some embodiments, the disclosure provides a compound of formula:



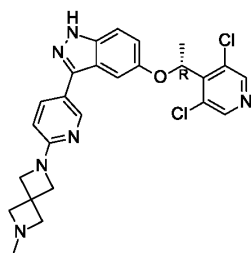
, or a pharmaceutically acceptable salt thereof.

[0076] In some embodiments, the disclosure provides a compound of formula:



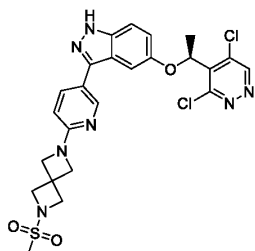
, or a pharmaceutically acceptable salt thereof.

[0077] In some embodiments, the disclosure provides a compound of formula:



, or a pharmaceutically acceptable salt thereof.

[0078] In some embodiments, the disclosure provides a compound of formula:



, or a pharmaceutically acceptable salt thereof.

[0079] Stereoisomers of compounds of the disclosure (*e.g.*, formula (I)) are also contemplated by the present disclosure. Thus, the disclosure encompasses all stereoisomers and constitutional isomers of any compound disclosed or claimed herein, including all enantiomers and diastereomers, or mixtures thereof.

[0080] Pharmaceutically acceptable salts and solvates of the compounds of the disclosure (*e.g.*, formula (I)) are also within the scope of the disclosure.

[0081] It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. That is, unless obviously incompatible or specifically excluded, each individual embodiment is deemed to be

combinable with any other embodiment(s) and such a combination is considered to be another embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination. While an embodiment may be described as part of a series of steps or part of a more general structure, each said step may also be considered an independent embodiment in itself, combinable with others.

Pharmaceutical compositions and methods of administration

[0082] In some aspects, the disclosure provides pharmaceutical compositions comprising a compounds of the disclosure (*e.g.*, formula (I)), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0083] The subject pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a compound of the present disclosure as the active ingredient, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. In some embodiments, the pharmaceutical compositions contain a compound of the present disclosure or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[0084] The subject pharmaceutical compositions can be administered alone or in combination with one or more other agents, which are also typically administered in the form of pharmaceutical compositions. Where desired, the one or more compounds of the invention and other agent(s) may be mixed into a preparation or both components may be formulated into separate preparations to use them in combination separately or at the same time.

[0085] In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions of the present invention is less than 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%,

0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% (or a number in the range defined by and including any two numbers above) w/w, w/v or v/v.

[0086] In some embodiments, the concentration of one or more compounds of the invention is greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25%, 19%, 18.75%, 18.50%, 18.25%, 18%, 17.75%, 17.50%, 17.25%, 17%, 16.75%, 16.50%, 16.25%, 16%, 15.75%, 15.50%, 15.25%, 15%, 14.75%, 14.50%, 14.25%, 14%, 13.75%, 13.50%, 13.25%, 13%, 12.75%, 12.50%, 12.25%, 12%, 11.75%, 11.50%, 11.25%, 11%, 10.75%, 10.50%, 10.25%, 10%, 9.75%, 9.50%, 9.25%, 9%, 8.75%, 8.50%, 8.25%, 8%, 7.75%, 7.50%, 7.25%, 7%, 6.75%, 6.50%, 6.25%, 6%, 5.75%, 5.50%, 5.25%, 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 1.25%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% (or a number in the range defined by and including any two numbers above) w/w, w/v, or v/v.

[0087] In some embodiments, the concentration of one or more compounds of the invention is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately

14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v.

[0088] In some embodiments, the concentration of one or more compounds of the invention is in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

[0089] In some embodiments, the amount of one or more compounds of the invention is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g (or a number in the range defined by and including any two numbers above).

[0090] In some embodiments, the amount of one or more compounds of the invention is more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, , 0.15 g, 0.2 g, , 0.25 g, 0.3 g, , 0.35 g, 0.4 g, , 0.45 g, 0.5 g, 0.55 g, 0.6 g, , 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5g, 7 g, 7.5g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g (or a number in the range defined by and including any two numbers above).

[0091] In some embodiments, the amount of one or more compounds of the invention is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

[0092] In some embodiments, the compounds according to the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. An exemplary dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

[0093] Unless otherwise noted, the amounts of the compounds described herein are set forth on a free base basis. That is, the amounts indicate that amount of the compound administered, exclusive of, for example, solvent (such as in solvates) or counterions (such as in pharmaceutically acceptable salts).

[0094] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

Pharmaceutical compositions for oral administration.

[0095] In some embodiments, the invention provides a pharmaceutical composition for oral administration containing a compound of the invention, and a pharmaceutical excipient suitable for oral administration.

[0096] In some embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of a compound of the invention; optionally (ii) an effective amount of a second agent; and (iii) a pharmaceutical excipient suitable for oral administration. In some embodiments, the composition further contains: (iv) an effective amount of a third agent.

[0097] In some embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as

discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0098] This invention further encompasses anhydrous pharmaceutical compositions and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water may be added (e.g., 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are

not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[0099] An active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[00100] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

[00101] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

[00102] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which may disintegrate in the bottle. Too little

may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other alginates, other celluloses, gums or mixtures thereof.

[00103] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[00104] When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[00105] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[00106] Surfactants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[00107] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions.

[00108] Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (i.e., hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[00109] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00110] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

[00111] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP -phosphatidylethanolamine, lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, choly sarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[00112] Hydrophilic non-ionic surfactants may include, but are not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers;

polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[00113] Other hydrophilic-non-ionic surfactants include, without limitation, PEG- 10 laurate, PEG- 12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG- 12 oleate, PEG- 15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG- 15 stearate, PEG-32 distearate, PEG-40 stearate, PEG- 100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG- 100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose mono laurate, sucrose

monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[00114] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[00115] In one embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use, e.g., compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[00116] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofuro) or methoxy PEG ; amides

and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, ϵ -caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, ϵ -caprolactone and isomers thereof, δ -valerolactone and isomers thereof, β -butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[00117] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcitol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[00118] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a subject using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[00119] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without

limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

[00120] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth metals, and the like. Example may include, but not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[00121] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid,

butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid and the like.

Pharmaceutical compositions for injection.

[00122] In some embodiments, the invention provides a pharmaceutical composition for injection containing a compound of the present invention and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

[00123] The forms in which the novel compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[00124] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, and the like (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like.

[00125] Sterile injectable solutions are prepared by incorporating the compound of the present invention in the required amount in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case

of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00126] Pharmaceutical compositions for topical (e.g. transdermal) delivery.

[00127] In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing a compound of the present invention and a pharmaceutical excipient suitable for transdermal delivery.

[00128] Compositions of the present invention can be formulated into preparations in solid, semisolid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation may provide more immediate exposure of the active ingredient to the chosen area.

[00129] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation.

[00130] Examples of such carriers and excipients include, but are not limited to, humectants (e.g., urea), glycols (e.g., propylene glycol), alcohols (e.g., ethanol), fatty acids (e.g., oleic acid), surfactants (e.g., isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (e.g., menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[00131] Another exemplary formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches

may be used to provide continuous or discontinuous infusion of a compound of the present invention in controlled amounts, either with or without another agent. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Pat. Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Pharmaceutical compositions for inhalation.

[00132] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices that deliver the formulation in an appropriate manner.

Other pharmaceutical compositions.

[00133] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, e.g., Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingstone, New York, 1990; Katzung, ed., Basic and Clinical Pharmacology, Ninth Edition, McGraw Hill, 2003; Goodman and Gilman, eds.,

The Pharmacological Basis of Therapeutics, Tenth Edition, McGraw Hill, 2001 ; Remingtons Pharmaceutical Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; Martindale, The Extra Pharmacopoeia, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety.

[00134] Administration of the compounds or pharmaceutical composition of the present invention can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (e.g. transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. Compounds can also be administered intraadiposally or intrathecally.

[00135] The amount of the compound administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, preferably about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, preferably about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, e.g. by dividing such larger doses into several small doses for administration throughout the day.

[00136] In some embodiments, a compound of the invention is administered in a single dose.

[00137] Typically, such administration will be by injection, e.g., intravenous injection, in order to introduce the agent quickly. However, other routes may be used as appropriate. A single dose of a compound of the invention may also be used for treatment of an acute condition.

[00138] In some embodiments, a compound of the invention is administered in multiple doses. Dosing may be about once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be about once a month, once every two weeks, once a week, or once every other day. In another embodiment a compound of the invention and another agent are administered together about once per day to about 6 times per day. In another embodiment the administration of a compound of the invention and an agent continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

[00139] Administration of the compounds of the invention may continue as long as necessary. In some embodiments, a compound of the invention is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, a compound of the invention is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, a compound of the invention is administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

[00140] An effective amount of a compound of the invention may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[00141] The compositions of the invention may also be delivered via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer. Such a method of administration may, for example, aid in the prevention or amelioration of restenosis following procedures such as balloon angioplasty. Without being bound by theory, compounds of the invention may slow or inhibit the migration and proliferation of smooth muscle cells in the arterial wall which contribute to restenosis. A compound of the invention may be administered, for example, by local delivery from the struts of a stent, from a stent graft, from grafts, or from the cover or sheath of a stent. In some embodiments, a compound of the

invention is admixed with a matrix. Such a matrix may be a polymeric matrix, and may serve to bond the compound to the stent. Polymeric matrices suitable for such use, include, for example, lactone-based polyesters or copolyesters such as polylactide, polycaprolactoneglycolide, polyorthoesters, polyanhydrides, polyaminoacids, polysaccharides, polyphosphazenes, poly (ether-ester) copolymers (e.g. PEO-PLLA); polydimethylsiloxane, poly(ethylene-vinylacetate), acrylate-based polymers or copolymers (e.g. polyhydroxyethyl methacrylate, polyvinyl pyrrolidinone), fluorinated polymers such as polytetrafluoroethylene and cellulose esters. Suitable matrices may be nondegrading or may degrade with time, releasing the compound or compounds. Compounds of the invention may be applied to the surface of the stent by various methods such as dip/spin coating, spray coating, dip-coating, and/or brush-coating. The compounds may be applied in a solvent and the solvent may be allowed to evaporate, thus forming a layer of compound onto the stent.

Alternatively, the compound may be located in the body of the stent or graft, for example in microchannels or micropores. When implanted, the compound diffuses out of the body of the stent to contact the arterial wall. Such stents may be prepared by dipping a stent manufactured to contain such micropores or microchannels into a solution of the compound of the invention in a suitable solvent, followed by evaporation of the solvent. Excess drug on the surface of the stent may be removed via an additional brief solvent wash. In yet other embodiments, compounds of the invention may be covalently linked to a stent or graft. A covalent linker may be used which degrades in vivo, leading to the release of the compound of the invention. Any bio-labile linkage may be used for such a purpose, such as ester, amide or anhydride linkages. Compounds of the invention may additionally be administered intravascularly from a balloon used during angioplasty. Extravascular administration of the compounds via the pericard or via adventitial application of formulations of the invention may also be performed to decrease restenosis.

[00142] A variety of stent devices which may be used as described are disclosed, for example, in the following references, all of which are hereby incorporated by reference: U.S. Pat. No. 5451233; U.S. Pat. No. 5040548; U.S. Pat.

No. 5061273; U.S. Pat. No. 5496346; U.S. Pat. No. 5292331; U.S. Pat. No. 5674278; U.S. Pat. No. 3657744; U.S. Pat. No. 4739762; U.S. Pat. No. 5195984; U.S. Pat. No. 5292331; U.S. Pat. No. 5674278; U.S. Pat. No. 5879382; U.S. Pat. No. 6344053.

[00143] The compounds of the invention may be administered in dosages. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. Dosing for a compound of the invention may be found by routine experimentation in light of the instant disclosure.

[00144] When a compound of the invention is administered in a composition that comprises one or more agents, and the agent has a shorter half-life than the compound of the invention unit dose forms of the agent and the compound of the invention may be adjusted accordingly.

[00145] The subject pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

[00146] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Methods of use

[00147] The FGFR receptors (FGFR1, FGFR2, FGFR3, and FGFR4) share several structural features in common, including three extracellular immunoglobulin-

like (Ig) domains, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain split by a kinase insert domain, followed by a cytoplasmic c-terminal tail (Johnson et al., *Adv. Cancer Res.* 60:1-40, 1993; and Wilkie et al., *Curr. Biol.* 5:500-507, 1995). In FGFR1, the kinase insert domain spans positions 582 to 595 of the alpha A1 isoform of FGFR1. In FGFR2, the kinase insert domain spans positions 585 to 598 of the FGFR2 Ille isoform. In FGFR3, the kinase insert domain spans positions 576 to 589 of the FGFR3 Ille isoform. In FGFR4, the kinase insert domain spans positions 571 to 584 of FGFR4 isoform 1. The c-terminal tail of FGFRs begins following the end of the tyrosine kinase domain and extends to the c-terminus of the protein. Several isoforms of each FGFR have been identified and are the result of alternative splicing of their mRNAs (Johnson et al., *Mol. Cell. Biol.* 11:4627-4634, 1995; and Chellaiah et al., *J. Biol. Chem.* 269:11620-11627, 1994).

[00148] A few of the receptor variants that result from this alternative splicing have different ligand binding specificities and affinities (Zimmer et al., *J. Biol. Chem.* 268:7899-7903, 1993; Cheon et al., *Proc. Natl. Acad. Sci. U.S.A.* 91:989-993, 1994; and Miki et al., *Proc. Natl. Acad. Sci. U.S.A.* 89:246-250, 1992). Protein sequences for FGFR proteins and nucleic acids encoding FGFR proteins are known in the art. Signaling by FGFRs regulates key biological processes including cell proliferation, survival, migration, and differentiation. Dysregulation of a FGFR gene, a FGFR protein, or expression or activity, or level of the same, has been associated with many types of cancer. For example, dysregulation of FGFRs can occur by multiple mechanisms, such as FGFR gene overexpression, FGFR gene amplification, activating mutations (e.g., point mutations or truncations), and chromosomal rearrangements that lead to FGFR fusion proteins. Dysregulation of a FGFR gene, a FGFR protein, or expression or activity, or level of the same, can result in (or cause in part) the development of a variety of different FGFR-associated cancers.

[00149] FGFR fusion proteins are known in the art. *See, e.g.,* Baroy et al., *PloS One*; 11(9):e0163859. doi: 10.1371/journal.pone.0163859, 2016; Ren et al., *Int. J. Cancer*, 139(4):836-40, 2016; Marchwicka et al., *Cell Biosci.*, 6:7. doi: 10.1186/s13578-016-0075-9, 2016; PCT Patent Application Publication No. WO

2014/071419A2; U.S. Patent Application Publication No. 2015/0366866A1; PCT Patent Application Publication No. WO 2016/084883A1; PCT Patent Application Publication No. WO 2016/030509A1; PCT Patent Application Publication No. WO 2015/150900A2; PCT Patent Application Publication No. WO 2015/120094A2; Kasaian et al., *BMC Cancer*, 15:984, 2015; Vakil et al., *Neuro-Oncology*, 18:Supp. Supplement 3, pp. iii93. Abstract Number: LG-64, 17th International Symposium on Pediatric Neuro-Oncology, Liverpool, United Kingdom, 2016; Astsaturov et al., *Journal of Clinical Oncology*, 34:Supp. Supplement 15, Abstract Number: 11504, 2016 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL; Heinrich et al., *Journal of Clinical Oncology*, 34:Supp. Supplement 15, Abstract Number: 11012, 2016 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL; Hall et al., *Molecular Cancer Therapeutics*, Vol. 14, No. 12, Supp.2, Abstract Number: B151, AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, 2015; Reuther et al., *Journal of Molecular Diagnostics*, Vol. 17, No. 6, pp. 813, Abstract Number: ST02, 2015 Annual Meeting of the Association for Molecular Pathology, Austin, TX; Moeini et al., *Clin. Cancer Res.*, 22(2):291-300, 2016; Schrock et al, *J Thorac. Oncol.* pii S1556-0864(18)30674-9, 2018. doi: 10.1016/j.jtho.2018.05.027; Pekmezci et al, *Acta Neuropathol. Commun.* 6(1):47. doi: 10.1186/s40478-018-0551-z; Lowery et al. *Clin Cancer Res.* pii: clincanres.0078.2018. doi: 10.1158/1078-0432.CCR-18-0078; Ryland et al. *J Clin Pathol*/ pii: jclinpath-2018-205195, 2018. doi: 10.1136/jclinpath-2018-205195; Ferguson et al. *J Neuropathol/ Exp Neurol* 77(6):437-442, 2018. doi: 10.1093/jnen/nly022; Wu et al, *BMC Cancer* 18(1):343, 2018. doi: 10.1186/s12885-018-4236-6; Shibata et al, *Cancer Sci* 109(5):1282-1291, 2018. doi: 10.1111/cas.13582; Papadopoulos et al, *Br J Cancer*, 117(11):1592-1599, 2017. doi: 10.1038/bjc.2017.330; Hall et al, *PLoS One*, 11(9):e1062594, 2016. doi: 10.1371/journal.pone.0162594; Johnson et al, *Oncologist*, 22(12):1478-1490, 2017. doi: 10.1634/theoncologist.2017-0242; Yang et al, *Am J Hum Genet*, 98(5):843-856, 2016. doi: 10.1016/j.ajhg.2016.03.017; U.S. Patent Application Publication No. 2013/009621; Babina and Turner, *Nat Rev Cancer* 17(5):318-332, 2017. doi:

10.1038/nrc.2017.8; Ryland et al, *J Clin Pathol*., 2018 May 14. pii: jclinpath-2018-205195. doi: 10.1136/jclinpath-2018-205195; Kumar et al, *Am J Clin Pathol*., 143(5):738-748, 2015. doi: 10.1309/AJCPUD6W1JLQQMNA; Grand et al, *Genes Chromosomes Cancer*40(1):78-83, 2004. doi: 10.1002/gcc.20023; Reeser, et al, *J Mol Diagn*, 19(5):682-696, 2017. doi: 10.1016/j.jmoldx.2017.05.006; Basturk, et al, *Mod Pathol*., 30(12):1760-1772, 2017. doi: 10.1038/modpathol.2017.60; Wang, et al, *Cancer* 123(20):3916-3924, 2017. doi: 10.1002/cncr.30837; Kim, et al, *Oncotarget*, 8(9):15014-15022, 2017. doi: 10.18632/oncotarget.14788; Busse, et al, *Genes Chromosomes Cancer*, 56(10):730-749, 2017. doi: 10.1002/gcc.22477; Shi, et al, *J Transl Med.*, 14(1):339, 2016. doi: 10.1186/s12967-016-1075-6, each of which is incorporated by reference herein.

[00150] FGFR point mutations are known in the art. See, e.g., UniParc entry UPI00000534B8; UniParc entry UPI0000001COF; UniParc entry UPI000002A99A; UniParc entry UPI000012A72A; UniParc entry UPI000059D1C2; UniParc entry UPI000002A9AC; Uniparc entry UPI000012A72C; Uniparc entry UPI000012A72D; Uniparc entry UPI000013EOB8; Uniparc entry UPI0001CE06A3; Gen bank entry BAD92868.1; Ang et al., *Diagn. Mol. Pathol.* Feb 24, 2014; U.S. Patent Application Publication No. 2011/0008347; Gallo et al., *Cytokine Growth Factor Rev.* 26:425-449, 2015; Davies et al., *J. Cancer Res.* 65:7591, 2005; Kelleher et al., *Carcinogenesis* 34:2198, 2013; Cazier et al., *Nat. Commun.* 5:3756, 2014; Liu et al., *Genet. Mol. Res.* 13:1109, 2014; Trudel et al., *Blood* 107:4039, 2006; Gallo et al., *Cytokine Growth Factor Rev.* 26:425, 2015; Liao et al., *Cancer Res.* 73:5195-5205, 2013; Martincorena et al., *Science* 348:880 (2015); U.S. Patent Application Publication No. US2016/0235744A1; U.S. Patent No. 9254288B2; U.S. Patent No. 9267176B2; U.S. Patent Application Publication No. S2016/0215350A1; European Patent Application Publication No. EP3023101A1; PCT Patent Application Publication No. WO2016105503A1; Rivera et al., *Acta. Neuropathol.*, 131(6):847-63, 2016; Lo Iacono et al., *Oncotarget*., 7(12):14394-404, 2016; Deeken et al., *Journal of Clinical Oncology*, 34:Supp. Supplement 15, pp. iii93. Abstract Number: e1 7520, 2016 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL; Sullivan et al.,

Journal of Clinical Oncology, 34:Supp. Supplement 15, pp. iii93. Abstract Number: 11596, 2016 Annual Meeting of the American Society of Clinical Oncology, Chicago, IL; Nguyen et al., *Molecular Cancer Therapeutics*, Vol. 14, No. 12, Supp.2, Abstract Number: C199, AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics, 2015; Li et al., *Hum. Pathol.*, 55:143-50, 2016; European Patent No. EP2203449B1; Yoza et al., *Genes Cells.*, (10):1049-1058, 2016; U.S. Patent No. 9,254,288B2; European Patent Application Publication No. 3023101A1; PCT Application Publication No. WO 2015/099127A1; European Patent No. EP2203449B1; Yoza et al., *Genes Cells.*, (10):1049-1058, 2016; Bunney et al., *EbioMedicine*, 2(3):194-204, 2015; Byron et al., *Neoplasia*, 15(8):975-88, 2013; European Patent Application Publication No. EP3023101A1; PCT Application Publication No. WO 2015/099127A1; Thussbs et al., *J. Clin. Oncol.*, 24(23):3747-55, 2006; Chell et al., *Oncogene*, 32(25):3059-70, 2013; Tanizaki et al., *Cancer Res.* 75(15):3149-3146 doi: 10.1158/0008-5472.CAN-14-3771; Yang et al., *EBioMedicine* pii S2352-3964(18)30218-4. doi: 10.1016/j.ebiom.2018.06.011; Jakobsen, et al *Oncotarget* 9(40):26195-26208, 2018. doi: 10.18632/oncotarget.25490; Stone, et al *Acta Neuropathol* 135(1):115-129, 2017. doi: 10.1007/s00401-017-1773-z; Pekmezci et al, *Acta Neurotrophol. Commun.* 6(1):47. doi: 10.1186/s40478-018-0551-z; De Mattos-Arruda et al, *Oncotarget* 9(29):20617-20630, 2018. doi:10.18632/oncotarget.25041; Oliveira et al, *J Exp Clin Cancer Res* 37(1):84, 2018. doi: 10.1186/s13046-018-0746-y; Cha et al, *Mo/ Oncol* 12(7):993-1003, 2018. doi: 10.1002/1878-0261.12194; Ikeda et al, *Oncologist*, 23(5):586-593, 2018. doi: 10.1634/theoncologist.2017-0479; Pelaez-Garda et al, *PLoS One*, 8(5):e63695, 2013. doi: 10.1371/journal.pone.0063695; Shimada et al, *Oncotarget*, 8(55):93567-93579, 2017. doi: 10.18632/oncotarget.20510; Welander et al, *World J Surg*, 42(2):482-489, 2018. doi: 10.1007/s00268-017-4320-0; Chandrani et al, *Ann Oncol*, 28(3):597-603, 2017. doi: 10.1093/annonc/mdw636; Dalin et al, *Nat Commun*, 8(1):1197, 2017. doi: 10.1038/s41467-017-01178-z; Taurin et al, *Intl Gynecol Cancer*, 28(1):152-160, 2018. doi: 10.1097/IGC.0000000000001129; Haugh et al, *J Invest Dermatol* 138(2):384-393, 2018. doi: 10.1016/j.jid.2017.08.022; Babina and Turner, *Nat Rev Cancer*

17(5):318-332, 2017. doi: 10.1038/nrc.2017.8; Greenman et al, *Nature* 446(7132):153-158, 2007. doi: 10.1038/nature05610; Helsten et al, *Clin Cancer Res*, 22(1):259-267, 2016. doi: 10.1158/1078-0432.CCR-14-3212; Kim et al, *BMC Urol*, 18:68, 2018. doi: 10.1186/s12894-018-0380-1; Goyal et al, *Cancer Discov*, 7(3):252-263, 2017. doi: 10.1158/2159-8290.CD-16-1000; Premov et al, *Oncogene*, 36(22):3168-3177, 2017. doi: 10.1038/onc.2016.464; Geelvink et al, *Int J Mo/ Sci*. 19(9): pii:E2548, 2018. doi: 10.3390/ijms19092548; Lee et al, *Exp Ther Med*. 16(2):1343-1349, 2018. doi: 10.3892/etm.2018.6323; Kas et al, *Cancer Res*, 78(19):5668-5679, 2018. doi: 10.1158/0008-5472.CAN-18-0757; Chesi et al, *Blood*, 97(3):729-736, 2001. PMID: 11157491. Note that the deletion of FGFR3 isoform Ille residues 795-808 also deletes the stop codon, elongating the protein by 99 amino acids
(ATGPQQCEGSLAAHPAAGAQLPLPGMRLSADGETATQSFGLCVVCVCVCVCVCTSA
CACVRAHLASRCRGTGVPAA
VQRSPDWCCSTEGPLFWGDPVQNVSGPTRWDPVGQAGPDMARPLPLHHGTSQ
GALGPSHTQS); Ge, et al, *Am J Cancer Res*. 7(7):1540-1553, 2017. PMID: 28744403; Jiao et al, *Nat Genet*, 45(12):1470-1473, 2013. doi: 10.1038/ng.2813; Jusakul et al, *Cancer Discov*. 7(10):1116-1135, 2017. doi: 10.1158/2159-8290.CD-17-0368; Guyard et al, *Respir Res.*, 18(1):120, 2018. doi: 10.1186/s12931-017-0605-y; Paik et al, *Clin Cancer Res.*, 23(18):5366-5373, 2017. doi: 10.1158/1078-0432.CCR-17-0645; Roy et al, *Mod Pathol.*, 30(8):1133-1143, 2017. doi: 10.1038/modpathol.2017.33; Chakrabarty et al, *Br J Cancer*, 117(1):136-143, 2017. doi: 10.1038/bjc.2017.148; Hoang et al, *Sci Transl Med.*, 5(197):197ra102. doi: 10.1126/scitranslmed.3006200; Kim et al, *Ann Oneal.*, 28(6):1250-1259. doi: 10.1093/annonc/mdx098, each of which is incorporated by reference herein.

[00151] Compounds of the disclosure have been found to inhibit FGFR1, FGFR2, FGFR3, and/or FGFR4 and are therefore believed to be useful for treating diseases and disorders which can be treated with an inhibitor of FGFR1, FGFR2, FGFR3 and/or FGFR4. For example, compounds of the disclosure can be useful in treating FGFR-associated diseases and disorders, e.g., proliferative disorders such as

cancers, including hematological cancers and solid tumor, and angiogenesis-related disorders. Compounds of the disclosure may also be useful in treating disorders arising from autosomal dominant mutations in FGFR, *e.g.*, FGFR3, including, for example, developmental disorders. Developmental disorders to be treated with compounds of the disclosure include Achondroplasia (Ach) and related chondrodysplasia syndromes, including Hypochondroplasia (Hch), Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans (SADDAN), and Thanatophoric dysplasia (TD). Compounds of the disclosure may also be useful in Double dominant ACH. Compounds of the disclosure may also be useful in Craniosynostosis, *e.g.*, Crouzon syndrome with acanthosis nigricans and Meunke syndrome. Compounds of the disclosure may also be useful in other genetic short stature conditions, *e.g.*, Leri-Weill dyschondrosteosis, Turner syndrome, Osteogenesis imperfecta, Mucopolysaccharidoses IVA, Mucopolysaccharidoses VI, and Laron syndrome (growth hormone insensitivity). Compounds of the disclosure may also be useful in pediatric short stature conditions, *e.g.*, Idiopathic short stature and Severe idiopathic short stature.

[00152] Non-limiting examples of FGFR-associated diseases and disorders include Acanthosis nigricans, Achondroplasia, Apert syndrome, Beare-Stevenson syndrome (BSS), Camptodactyly, tall stature, and hearing loss syndrome (CATSHL) syndrome, cleft lip and palate, congenital heart disease (*e.g.*, associated with ambiguous genitalia), craniosynostosis, Crouzon syndrome, ectrodactyly, encephalocraniocutaneous lipomatosis, Hartsfield syndrome, hypochondroplasia, hypogonadotropic hypogonadism (*e.g.*, hypogonadotropic hypogonadism 2 with or without anosmia, Kallman syndrome), ichthyosis vulgaris and/or atopic dermatitis, Jackson-Weiss syndrome, lethal pulmonary acinar dysplasia, microphthalmia, Muenke coronal craniosynostosis, osteoglophonic dysplasia, Pfeiffer syndrome, seborrheic keratosis, syndactyly, thanatophoric dysplasia (*e.g.*, type I or type II), trigonocephaly 1 (also called metopic craniosynostosis), tumor-induced osteomalacia, Crouzon syndrome with acanthosis nigricans, Meunke syndrome, Leri-Weill dyschondrosteosis, Turner syndrome, Osteogenesis imperfecta, Mucopolysaccharidoses

IVA, Mucopolysaccharidoses VI, Laron syndrome, Idiopathic short stature, Severe idiopathic short stature, and Camptodactyly, Tall Stature, and Hearing Loss (CATSHL).

[00153] Non-limiting examples of FGFR1 associated diseases and disorders include congenital heart disease (e.g., associated with ambiguous genitalia), craniosynostosis, encephalocraniocutaneous lipomatosis, Hartsfield syndrome, hypogonadotropic hypogonadism (e.g., hypogonadotropic hypogonadism 2 with or without anosmia, Kallman syndrome), ichthyosis vulgaris and/or atopic dermatitis, Jackson-Weiss syndrome, osteoglophonic dysplasia, Pfeiffer syndrome, trigonocephaly 1 (also called metopic craniosynostosis), and tumor-induced osteomalacia.

[00154] Non-limiting examples of FGFR2-associated diseases and disorders include Apert syndrome, Beare-Stevenson syndrome (BSS), Crouzon syndrome, ectrodactyly, Jackson-Weiss syndrome, lethal pulmonary acinar dysplasia, Pfeiffer syndrome, and syndactyly. Non-limiting examples of FGFR3-associated diseases and disorders include acanthosis nigricans, achondroplasia, Camptodactyly, tall stature, and hearing loss syndrome (CATSHL) syndrome, cleft lip and palate, craniosynostosis, hypochondroplasia, microphthalmia, Muenke coronal craniosynostosis, seborrhic keratosis, and thanatophoric dysplasia (e.g., type I or type II). *See also*, See UniParc entry UPI00000534B8; UniParc entry UPI0000001COF; Uni Pare entry UPI000002A99A; UniParc entry UPI000012A72A; Yong-Xing et al., Hum. Mol. Genet. 9(13):2001-2008, 2000; Eva-Maria Laitinen et al., PLoS One 7(6):e39450, 2012; Hart et al., Oncogene 19(29):3309-3320, 2000; Shiang et al., Cell 76:335-342, 1994; Rosseau et al., Nature 371:252-254, 1994; Tavormina et al., Nature Genet. 9:321-328, 1995; Bellus et al., Nature Genet. 10:357-359, 1995; Muenke et al., Nature Genet. 8:269-274, 1994; Rutland et al., Nature Genet. 9:173-176, 1995; Reardon et al., Nature Genet. 8:98-103, 1994; Wilkie et al., Nature Genet. 9:165-172, 1995; Jabs et al., Nature Genet. 8:275-279, 1994; Japanese Patent No. JP05868992B2; Ye et al., Plast. Reconstr. Surg., 137(3):952-61, 2016; U.S. Patent No. 9447098B2; Bellus et al., Am. J. Med. Genet.

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[00155] The term "angiogenesis-related disorder" means a disease characterized in part by an increased number or size of blood vessels in a tissue in a subject or patient, as compared to a similar tissue from a subject not having the disease. Non-limiting examples of angiogenesis-related disorders include: cancer (e.g., any of the exemplary cancers described herein, such as prostate cancer, lung cancer, breast cancer, bladder cancer, renal cancer, colon cancer, gastric cancer, pancreatic cancer, ovarian cancer, melanoma, hepatoma, sarcoma, and lymphoma), exudative macular degeneration, proliferative diabetic retinopathy, ischemic retinopathy, retinopathy of prematurity, neovascular glaucoma, iritis rubeosis, corneal neovascularization, cyclitis, sickle cell retinopathy, and pterygium.

[00156] Compounds of the disclosure inhibit wild-type FGFR1, FGFR2, FGFR3, and/or FGFR4. In other aspects, compounds of the disclosure inhibit a mutated FGFR1, FGFR2, FGFR3, and/or FGFR4. In other aspects, compounds of the disclosure inhibit FGFR1, FGFR2, FGFR3, and/or FGFR4 that includes an FGFR kinase inhibitor resistance mutation.

[00157] In some embodiments of any of the methods or uses described herein, the cancer (e.g., FGFR-associated cancer) is a hematological cancer. In some embodiments of any of the methods or uses described herein, the cancer (e.g., FGFR-associated cancer) is a solid tumor.

[00158] In some embodiments of any of the methods or uses described herein, the cancer (e.g., FGFR-associated cancer) is a lung cancer (e.g., small cell lung carcinoma, non-small cell lung carcinoma, squamous cell carcinoma, lung adenocarcinoma, large cell carcinoma, mesothelioma, lung neuroendocrine carcinoma, smoking-associated lung cancer), prostate cancer, colorectal cancer (e.g., rectal adenocarcinoma), endometrial cancer (e.g., endometrioid endometrial cancer, endometrial adenocarcinoma), breast cancer (e.g., hormone-receptor-positive breast cancer, triple-negative breast cancer, neuroendocrine carcinoma of the breast), skin cancer (e.g., melanoma, cutaneous squamous cell carcinoma, basal cell carcinoma, large squamous cell carcinoma), gallbladder cancer, liposarcoma (e.g., dedifferentiated liposarcoma, myxoid liposarcoma), pheochromocytoma,

myoepithelial carcinoma, urothelial carcinoma, spermatocytic seminoma, stomach cancer, head and neck cancer (e.g., head and neck (squamous) carcinoma, head and neck adenoid cystic adenocarcinoma), brain cancer (e.g., glialneural tumors, glioma, neuroblastoma, glioblastoma, pilocytic astrocytoma, Rosette forming glioneural tumor, dysembryoplastic neuroepithelial tumor, anaplastic astrocytoma, medulloblastoma, ganglioglioma, oligodendroglioma), malignant peripheral nerve sheath tumor, sarcoma (e.g., soft tissue sarcoma (e.g., leiomyosarcoma), osteosarcoma), esophageal cancer (e.g., esophageal adenocarcinoma), lymphoma, bladder cancer (e.g., bladder urothelial (transition cell) carcinoma), cervical cancer (e.g., cervical squamous cell carcinoma, cervical adenocarcinoma), fallopian tube cancer (e.g., fallopian tube carcinoma), ovarian cancer (e.g., ovarian serous cancer, ovarian mucinous carcinoma), cholangiocarcinoma, adenoid cystic carcinoma, pancreatic cancer (e.g., pancreatic exocrine carcinoma, pancreatic ductal adenocarcinoma, pancreatic cancer intraepithelial neoplasia), salivary gland cancer (e.g., pleomorphic salivary gland adenocarcinoma, salivary adenoid cystic cancer), oral cancer (e.g., oral squamous cell carcinoma), uterine cancer, gastric or stomach cancer (e.g., gastric adenocarcinoma), gastrointestinal stromal tumors, myeloma (e.g., multiple myeloma), lymphoepithelioma, anal cancer (e.g., anal squamous cell carcinoma), prostate cancer (e.g., prostate adenocarcinoma), renal cell carcinoma, thymic cancer, gastroesophageal junction adenocarcinoma, testicular cancer, rhabdomyosarcoma (e.g., alveolar rhabdomyosarcoma, embryonic rhabdomyosarcoma), renal papillary carcinoma, liver cancer (e.g., hepatocellular carcinoma, intrahepatic cholangiocarcinoma), carcinoid, myeloid proliferative disorders (also called myeloid proliferative neoplasms (MPN); e.g., 8p11 myeloproliferative syndrome (EMS, also called stem cell leukemia/lymphoma), acute myeloid leukemia (AML), chronic myeloid leukemia (CML)), lymphoma (e.g., T-cell lymphoma, T-lymphoblastic lymphoma, acute lymphoblastic leukemia (ALL), B-cell lymphoma), myeloid and lymphoid neoplasms, chronic neutrophilic leukemia, phosphaturic mesenchymal tumor, thyroid cancer (e.g. anaplastic thyroid carcinoma), or biliary duct cancer.

[00159] In some embodiments of any of the methods or uses described herein, the cancer (e.g., FGFR-associated cancer) is selected from the group of: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), cancer in adolescents, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumor, Burkitt lymphoma, carcinoid tumor, unknown primary carcinoma, cardiac tumors, cervical cancer, childhood cancers, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasms, neoplasms by site, neoplasms, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, cutaneous angiosarcoma, bile duct cancer, ductal carcinoma in situ, embryonal tumors, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic disease, glioma, hairy cell tumor, hairy cell leukemia, head and neck cancer, thoracic neoplasms, head and neck neoplasms, CNS tumor, primary CNS tumor, heart cancer, hepatocellular cancer, histiocytosis, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma of bone, osteocarcinoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, neoplasms by site, neoplasms, myelogenous leukemia, myeloid leukemia, multiple myeloma, myeloproliferative neoplasms, nasal cavity and para nasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung

cancer, lung neoplasm, pulmonary cancer, pulmonary neoplasms, respiratory tract neoplasms, bronchogenic carcinoma, bronchial neoplasms, oral cancer, oral cavity cancer, lip cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, para nasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromosytoma, pituitary cancer, plasma cell neoplasm, pleuropulmonary blastoma, pregnancy-associated breast cancer, primary central nervous system lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, colon cancer, colonic neoplasms, renal cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Sezary syndrome, skin cancer, Spitz tumors, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach cancer, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, unknown primary carcinoma, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms' tumor.

[00160] In some embodiments, a hematological cancer (e.g., hematological cancers that are FGFR associated cancers) is selected from the group consisting of leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocytic leukemia (JMML), adult Tcell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM).

[00161] Additional examples of hematological cancers include myeloproliferative disorders (MPD) such as polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic primary myelofibrosis (IMF/IPF/PMF). In

some embodiments, the hematological cancer (e.g., the hematological cancer that is a FGFR-associated cancer) is AML or CMML.

In some embodiments, the cancer (e.g., the FGFR-associated cancer) is a solid tumor. Examples of solid tumors (e.g., solid tumors that are FGFR-associated cancers) include, for example, lung cancer (e.g., lung adenocarcinoma, non-small-cell lung carcinoma, squamous cell lung cancer), bladder cancer, colorectal cancer, brain cancer, testicular cancer, bile duct cancer cervical cancer, prostate cancer, and spermatocytic seminomas. See, for example, Turner and Grose, *Nat. Rev. Cancer*, 10(2):116-129, 2010.

[00162] In some embodiments, the cancer is selected from the group consisting of bladder cancer, brain cancer, breast cancer, cholangiocarcinoma, head and neck cancer, lung cancer, multiple myeloma, rhabdomyosarcoma, urethral cancer, uterine cancer. In some embodiments, the cancer is selected from the group consisting of lung cancer, breast cancer, and brain cancer.

[00163] In some embodiments, the cancer is hepatocellular carcinoma.

[00164] In some embodiments, a FGFR1-associated cancer is selected from the group consisting of lung cancer, breast cancer, and brain cancer.

[00165] In some embodiments, the cancer is selected from the group consisting of breast cancer, uterine cancer, cholangiocarcinoma, and lung cancer.

[00166] In some embodiments, a FGFR2-associated cancer is selected from the group consisting of breast cancer, uterine cancer, cholangiocarcinoma, and lung cancer. In some embodiments, the cancer is selected from the group consisting of lung cancer, bladder cancer, urethral cancer, multiple myeloma, and head and neck cancer.

[00167] In some embodiments, a FGFR3-associated cancer is selected from the group consisting of lung cancer, bladder cancer, urethral cancer, multiple myeloma, and head and neck cancer.

[00168] In some embodiments, the cancer is selected from lung cancer, rhabdomyosarcoma, and breast cancer.

[00169] In some embodiments, a FGFR4-associated cancer is selected from hepatocellular carcinoma, lung cancer, rhabdomyosarcoma, and breast cancer.

[00170] In some aspects, the compounds of the disclosure are useful in treating cancers associated with amplification or overexpression of FGFR1, for example, Breast cancer or carcinoma (e.g., hormone receptor-positive breast cancer, ductal carcinoma in situ (breast)), pancreatic ductal adenocarcinoma, pancreatic exocrine carcinoma, smoking-associated lung cancer, small cell lung cancer, lung adenocarcinoma, non-small cell lung cancer, squamous cell lung cancer or carcinoma, prostate cancer or carcinoma, ovarian cancer, fallopian tube carcinoma, bladder cancer, rhabdomyosarcoma, head and neck carcinoma (e.g., head and neck squamous cell carcinoma), esophageal cancer (e.g., esophageal squamous cell carcinoma), sarcoma (e.g., osteosarcoma), hepatocellular carcinoma, renal cell carcinoma, colorectal cancer (e.g., colorectal adenocarcinoma), prostate cancer, salivary gland tumors, glioblastoma multiforme, urinary bladder cancer, urothelial carcinoma, carcinoma of unknown primary, squamous non-lung tumors, gastric cancer, gastroesophageal junction carcinoma, adenoid cystic carcinoma, anal squamous cell carcinoma, oral squamous cell carcinoma, cholangiocarcinoma, hemangioendothelioma, leiomyosarcoma, melanoma, neuroendocrine carcinoma, squamous cell carcinoma, uterine carcinosarcoma.

[00171] In some aspects, the compounds of the disclosure are useful in treating cancers associated with amplification of FGFR2, for example, Gastric cancer, gastroesophageal junction adenocarcinoma, breast cancer (e.g., triple negative breast cancer), colon cancer, colorectal cancer (e.g., colorectal adenocarcinoma), urothelial cancer, bladder adenocarcinoma, carcinoma of unknown primary, cholangiocarcinoma, endometrial adenocarcinoma, esophageal adenocarcinoma, gallbladder carcinoma, ovarian cancer, fallopian tube carcinoma, pancreatic exocrine carcinoma, sarcoma, squamous cell carcinoma.

[00172] In some aspects, the compounds of the disclosure are useful in treating cancers associated with overexpression of FGFR2, for example, Myxoid lipocarcinoma, rectal cancer, renal cell carcinoma, breast cancer.

[00173] In some aspects, the compounds of the disclosure are useful in treating cancers associated with upregulation of activity of FGFR3, for example,

Colorectal cancer, hepatocellular carcinoma, pancreatic exocrine carcinoma. In some aspects, the compounds of the disclosure are useful in treating cancers associated with overexpression of activity of FGFR3, for example, Multiple myeloma, thyroid carcinoma. In some aspects, the compounds of the disclosure are useful in treating cancers associated with amplification of activity of FGFR3, for example, Bladder cancer and salivary adenoid cystic cancer, urothelial cancer, breast cancer, carcinoid, carcinoma of unknown primary, colorectal cancer (e.g., colorectal adenocarcinoma), gallbladder carcinoma, gastric cancer, gastroesophageal junction adenocarcinoma, glioma, mesothelioma, non-small cell lung carcinoma, small cell lung cancer, ovarian cancer, fallopian tube carcinoma, pancreatic exocrine carcinoma.

[00174] In some aspects, the compounds of the disclosure are useful in treating cancers associated with amplification of FGFR4, for example, Rhabdomyosarcoma, prostate cancer or carcinoma, breast cancer, urothelial cancer, carcinoid, carcinoma of unknown primary, esophageal adenocarcinoma, head and neck carcinoma, hepatocellular carcinoma, non-small cell lung carcinoma, ovarian cancer, fallopian tube carcinoma, peritoneal carcinoma, renal cell carcinoma.

[00175] In some aspects, the compounds of the disclosure are useful in treating cancers associated with upregulation of activity of FGFR4, for example, Colorectal cancer, hepatocellular carcinoma, adrenal carcinoma, breast cancer.

[00176] In some aspects, the compounds of the disclosure are useful in treating cancers associated with overexpression of activity of FGFR4, for example, Pancreatic intraepithelial neoplasia, and pancreatic ductal adenocarcinoma.

[00177] In some aspects, the compounds of the disclosure are more selective for one FGFR than for another. As used herein, the "selectivity" of a compound for a first target over a second target means that the compound has more potent activity at the first target than the second target. A fold selectivity can be calculated by any method known in the art. For example, a fold selectivity can be calculated by dividing the IC₅₀ value (or K_d value) of a compound for the second target (e.g., FGFR1) by the IC₅₀ value (or K_d value) of the same compound for the first target (e.g., FGFR2 or FGFR3). An IC₅₀ value (or K_d value) can be determined by any method known in the

art. In some embodiments, a compound is first determined to have an activity of less than 500 nM for the first target. In some embodiments, a compound is first determined to have an activity of less than 500 nM for the second target.

[00178] For example, in some aspects, the compounds of the disclosure are more selective for FGFR3 than for FGFR1. In some aspects, the compounds are at least 3-fold more selective for FGFR3 than for FGFR1. In some aspects, the compounds are 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 200, 500, or 1000 fold more selective for FGFR3 than for FGFR1.

[00179] For example, in some aspects, the compounds of the disclosure are more selective for FGFR4 than for FGFR1. In some aspects, the compounds are at least 3-fold more selective for FGFR4 than for FGFR1. In some aspects, the compounds are 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 200, 500, or 1000 fold more selective for FGFR4 than for FGFR1.

[00180] In some aspects, the compounds of the disclosure are more selective for FGFR2 than for FGFR1. In some aspects, the compounds are at least 3-fold more selective for FGFR2 than for FGFR1. In some aspects, the compounds are 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 75, 100, 200, 500, or 1000 fold more selective for FGFR2 than for FGFR1.

[00181] In some aspects, the compounds of the disclosure are more selective for a first FGFR family member (*e.g.*, FGFR2 or FGFR3) over a second FGFR family member (*e.g.*, FGFR1 or FGFR4). In some aspects, the compounds of the disclosure are at least 3-fold more selective for a first FGFR family member over a second FGFR family member. In some aspects, the compounds are at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 200, 300, 400, 500, 600, 700, 800, 900, or at least 1000 fold more selective for a first FGFR family member over a second FGFR family member.

[00182] In some aspects, the compounds of the disclosure are more selective for a first FGFR family member (*e.g.*, FGFR4 or FGFR3) over a second FGFR family member (*e.g.*, FGFR1 or FGFR2). In some aspects, the compounds of the disclosure are at least 3-fold more selective for a first FGFR family member over a second FGFR family member. In some aspects, the compounds are at least 10, 20, 30, 40, 50, 60,

70, 80, 90, 200, 300, 400, 500, 600, 700, 800, 900, or at least 1000 fold more selective for a first FGFR family member over a second FGFR family member.

[00183] In some aspects, the compounds of the disclosure are more selective for an FGFR kinase over another kinase that is not an FGFR kinase. For example, the compounds of the disclosure are at least 3-fold more selective for an FGFR kinase over another kinase that is not an FGFR kinase. In some aspects, the compounds of the disclosure are at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 200, 300, 400, 500, 600, 700, 800, 900, or at least 1000 fold more selective for an FGFR kinase over another kinase that is not an FGFR kinase. Kinases that are not FGFR kinases include, for example, KDR kinase and Aurora B kinase.

[00184] In some embodiments, the compounds of the disclosure exhibit brain and/or central nervous system (CNS) penetrance. Such compounds are capable of crossing the blood brain barrier and inhibiting a FGFR kinase in the brain and/or other CNS structures. In some embodiments, the compounds provided herein are capable of crossing the blood brain barrier in a therapeutically effective amount. For example, treatment of a subject with cancer (e.g., a FGFR-associated cancer such as a FGFR-associated brain or CNS cancer) can include administration (e.g., oral administration) of the compound to the subject. In some such embodiments, the compounds provided herein are useful for treating a primary brain tumor or metastatic brain tumor. For example, a FGFR-associated primary brain tumor or metastatic brain tumor.

[00185] In some embodiments, the compounds of the disclosure, exhibit one or more of high GI absorption, low clearance, and low potential for drug-drug interactions.

[00186] In some aspects, compounds of the disclosure can be used for treating a subject diagnosed with (or identified as having) a FGFR-associated disease or disorder (e.g., a FGFR-associated cancer) that include administering to the subject a therapeutically effective amount of a compound of the disclosure. Also provided herein are methods for treating a subject identified or diagnosed as having a FGFR-associated disease or disorder (e.g., a FGFR-associated cancer) that include administering to the subject a therapeutically effective amount of a compound of the

disclosure. In some embodiments, the subject that has been identified or diagnosed as having a FGFR-associated disease or disorder (e.g., a FGFR-associated cancer) through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a FGFR gene, a FGFR kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the FGFR-associated disease or disorder is a FGFR-associated cancer. For example, the FGFR-associated cancer can be a cancer that includes one or more FGFR inhibitor resistance mutations.

[00187] Also provided are methods for treating a disease or disorder in a subject in need thereof, the method comprising: (a) detecting a FGFR-associated disease or disorder in the subject; and (b) administering to the subject a therapeutically effective amount of a compound of the disclosure. Some embodiments of these methods further include administering to the subject an additional therapy or therapeutic agent (e.g., a second FGFR inhibitor, a second compound of the disclosure, or an immunotherapy). In some embodiments, the subject was previously treated with a first FGFR inhibitor or previously treated with another treatment. In some embodiments, the subject is determined to have a FGFR-associated disease or disorder through the use of a regulatory agency-approved, e.g., FDA approved test or assay for identifying dysregulation of a FGFR gene, a FGFR kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit.

[00188] Also provided are methods for treating cancer in a subject in need thereof, the method comprising: (a) detecting a FGFR-associated cancer in the subject ; and (b) administering to the subject a therapeutically effective amount of a compound of the disclosure. Some embodiments of these methods further include administering to the subject an additional therapy or therapeutic agent (e.g., a second FGFR inhibitor, a second compound of the disclosure, or an immunotherapy). In some

embodiments, the subject was previously treated with a first FGFR inhibitor or previously treated with another anticancer treatment, e.g., at least partial resection of the tumor or radiation therapy. In some embodiments, the subject is determined to have a FGFR-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a FGFR gene, a FGFR kinase, or expression or activity or level of any of the same, in a subject or a biopsy sample from the subject or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the cancer is a FGFR associated cancer. For example, the FGFR-associated cancer can be a cancer that includes one or more FGFR inhibitor resistance mutations. In some embodiments, the cancer is a FGFR associated cancer. For example, the FGFR-associated cancer can be a cancer that includes one or more FGFR activating mutations.

[00189] Also provided are methods of treating a subject that include performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a FGFR gene, a FGFR kinase, or expression or activity or level of any of the same, and administering (e.g., specifically or selectively administering) a therapeutically effective amount of a compound of the disclosure or pharmaceutically acceptable salt or solvate thereof to the subject determined to have a dysregulation of a FGFR gene, a FGFR kinase, or expression or activity or level of any of the same. Some embodiments of these methods further include administering to the subject an additional therapy or therapeutic agent (e.g., a second FGFR inhibitor, a second compound of the disclosure, or immunotherapy). In some embodiments of these methods, the subject was previously treated with a first FGFR inhibitor or previously treated with another anticancer treatment, e.g., at least partial resection of a tumor or radiation therapy. In some embodiments, the subject is a subject suspected of having a FGFR-associated disease or disorder (e.g., a FGFR-associated cancer), a subject presenting with one or more symptoms of a FGFR-associated disease or disorder (e.g., a FGFR-associated cancer), or a subject having an elevated risk of developing a FGFR-associated disease or disorder (e.g., a FGFR-associated cancer).

In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. Additional, non-limiting assays that may be used in these methods are described herein. Additional assays are also known in the art. In some embodiments, the dysregulation of a FGFR gene, a FGFR kinase, or expression or activity or level of any of the same includes one or more FGFR inhibitor resistance mutations.

[00190] Also provided herein are methods of selecting a treatment for a subject, wherein the methods include a step of performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a FGFR gene, a FGFR kinase, or expression or activity or level of any of the same (e.g., one or more FGFR inhibitor resistance mutations), and identifying or diagnosing a subject determined to have a dysregulation of a FGFR gene, a FGFR kinase, or expression or activity or level of any of the same, as having a FGFR-associated cancer. Some embodiments further include administering the selected treatment to the subject identified or diagnosed as having a FGFR-associated cancer. For example, in some embodiments, the selected treatment can include administration of a therapeutically effective amount of a compound of the disclosure to the subject identified or diagnosed as having a FGFR-associated cancer. In some embodiments, the assay is an *in vitro* assay. For example, an assay that utilizes the next generation sequencing, immunohistochemistry, or break apart FISH analysis. In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy.

[00191] Also provided herein are methods of treating a FGFR-associated cancer in a subject that include (a) administering one or more (e.g., two or more, three or more, four or more, five or more, or ten or more) doses of a first FGFR kinase inhibitor to a subject identified or diagnosed as having a FGFR associated cancer (e.g., any of the types of FGFR-associated cancers described herein) (e.g., identified or diagnosed as having a FGFR-associated cancer using any of the exemplary methods

described herein or known in the art); (b) after step (a), determining a level of circulating tumor DNA in a biological sample (e.g., a biological sample comprising blood, serum, or plasma) obtained from the subject; (c) administering a therapeutically effective amount of a second FGFR inhibitor or a compound of the disclosure as a monotherapy or in conjunction with an additional therapy or therapeutic agent to a subject identified as having about the same or an elevated level of circulating tumor DNA as compared to a reference level of circulating tumor DNA (e.g., any of the reference levels of circulating tumor DNA described herein). In some examples of these methods, the reference level of circulating tumor DNA is a level of circulating tumor DNA in a biological sample obtained from the subject prior to step (a). Some embodiments of these methods further include determining the level of circulating tumor DNA in the biological sample obtained from the subject prior to step (a). In some examples of these methods, the reference level of circulating tumor DNA is a threshold level of circulating tumor DNA (e.g., an average level of circulating tumor DNA in a population of subjects having a similar FGFR-associated cancer and having a similar stage of the FGFR-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment, or a level of circulating tumor DNA in a subject having a similar FGFR-associated cancer and having a similar stage of the FGFR-associated cancer, but receiving a non-effective treatment or a placebo, or not yet receiving therapeutic treatment). In some examples of these methods, the first FGFR inhibitor is: ARQ-087, ASP5878, AZD4547, B-701, BAY1179470, BAY1187982, BGJ398, brivanib, Debio 1347, dovitinib, E7090, erdafitinib, FPA144, HMPL-453, INCB054828, lenvatinib, lucitanib, LY3076226, MAX-40279, nintedanib, orantinib, pemigatinib, ponatinib, PRN1371, rogaratinib, sulfatinib, roblitinib, ICP-105, BIO-1262, futibatinib, fisogatinib, LOXO-435, or RLY-4008.

[00192] Compounds of the disclosure can also be administered with additional therapy or therapeutic agents. In some aspects, the additional therapy or therapeutic agent includes one or more of radiation therapy, a chemotherapeutic agent (e.g., any of the exemplary chemotherapeutic agents described herein or known in the art), a checkpoint inhibitor (e.g., any of the exemplary checkpoint inhibitors described

herein or known in the art), surgery (e.g., at least partial resection of the tumor), and one or more other kinase inhibitors (e.g., any of the kinase inhibitors described herein or known in the art).

[00193] Compounds of the disclosure may also be useful as adjuvants to cancer treatment, that is, they can be used in combination with one or more additional therapies or therapeutic agents, for example a chemotherapeutic agent that works by the same or by a different mechanism of action. In some embodiments, a compound of the disclosure can be used prior to administration of an additional therapeutic agent or additional therapy. For example, a subject in need thereof can be administered one or more doses of a compound of the disclosure for a period of time and then undergo at least partial resection of the tumor. In some embodiments, the treatment with one or more doses of a compound of the disclosure reduces the size of the tumor (e.g., the tumor burden) prior to the at least partial resection of the tumor. In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to standard therapy (e.g., administration of a chemotherapeutic agent, such as a first FGFR inhibitor or a multikinase inhibitor, immunotherapy, radiation, or a platinum-based agent (e.g., cisplatin)). In some embodiments, a subject has a cancer (e.g., a locally advanced or metastatic tumor) that is refractory or intolerant to prior therapy (e.g., administration of a chemotherapeutic agent, such as a first FGFR inhibitor or a multikinase inhibitor, immunotherapy, radiation, or a platinum-based agent (e.g., cisplatin)).

[00194] In some embodiments of any the methods described herein, the compound of the disclosure is administered in combination with a therapeutically effective amount of at least one additional therapeutic agent selected from one or more additional therapies or therapeutic (e.g., chemotherapeutic) agents. Non-limiting examples of additional therapeutic agents include: other FGFR-targeted therapeutic agents (i.e. a first or second FGFR kinase inhibitor), other kinase inhibitors (e.g., receptor tyrosine kinase targeted therapeutic agents (e.g., Trk inhibitors or EGFR inhibitors)), signal transduction pathway inhibitors, checkpoint inhibitors, modulators of the apoptosis pathway (e.g. obataclax); cytotoxic chemotherapeutics, angiogenesis-

targeted therapies, immune-targeted agents, including immunotherapy, and radiotherapy.

[00195] Also provided herein are methods of treating a disease or disorder, comprising administering to a subject in need thereof a pharmaceutical combination for treating the disease or disorder which comprises (a) a compound of the disclosure, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of the disease or disorder, wherein the amounts of the compound of the disclosure and the additional therapeutic agent are together effective in treating the disease or disorder. In some embodiments, the compound of the disclosure, and the additional therapeutic agent are administered simultaneously as separate dosages. In some embodiments, the compound of the disclosure, and the additional therapeutic agent are administered as separate dosages sequentially in any order, in jointly therapeutically effective amounts, e.g. in daily or intermittently dosages. In some embodiments, the compound of the disclosure, and the additional therapeutic agent are administered simultaneously as a combined dosage. In some embodiments, the disease or disorder is a FGFR-associated disease or disorder. In some embodiments, the subject has been administered one or more doses of a compound of the disclosure, prior to administration of the pharmaceutical composition.

[00196] In some embodiments, the treatment period is at least 7 days (e.g., at least or about 8 days, at least or about 9 days, at least or about 10 days, at least or about 11 days, at least or about 12 days, at least or about 13 days, at least or about 14 days, at least or about 15 days, at least or about 16 days, at least or about 17 days, at least or about 18 days, at least or about 19 days, at least or about 20 days, at least or about 21 days, at least or about 22 days, at least or about 23 days, at least or about 24 days, at least or about 25 days, at least or about 26 days, at least or about 27 days, at least or about 28 days, at least or about 29 days, or at least or about 30 days).

[00197] In some embodiments, the treatment period is at least 21 days (e.g., at least or about 22 days, at least or about 23 days, at least or about 24 days, at least or about 25 days, at least or about 26 days, at least or about 27 days, at least or about 28

days, at least or about 29 days, at least or about 30 days, at least or about 31 days, at least or about 32 days, at least or about 33 days, at least or about 34 days, at least or about 35 days, at least or about 36 days, at least or about 37 days, at least or about 38 days, at least or about 39 days, or at least or about 40 days).

[00198] Also provided herein are pharmaceutical compositions that contain, as the active ingredient, a compound of the disclosure, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is formulated as a tablet or capsule.

[00199] The compositions comprising a compound of the disclosure can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units for human subjects and other subjects, each unit containing a predetermined quantity of active material (i.e., a compound of the disclosure) to produce the desired therapeutic effect, with a suitable pharmaceutical excipient.

[00200] In some embodiments, the compositions provided herein contain from about 5 mg to about 50 mg of the active ingredient, *i.e.*, the compound of the disclosure. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 mg to about 10 mg, about 10 mg to

about 15 mg, about 15 mg to about 20 mg, about 20 mg to about 25 mg, about 25 mg to about 30 mg, about 30 mg to about 35 mg, about 35 mg to about 40 mg, about 40 mg to about 45 mg, or about 45 mg to about 50 mg of the active ingredient. In some embodiments, the compositions provided herein contain from about 50 mg to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 mg to about 100 mg, about 100 mg to about 150 mg, about 150 mg to about 200 mg, about 200 mg to about 250 mg, about 250 mg to about 300 mg, about 350 mg to about 400 mg, or about 450 mg to about 500 mg of the active ingredient. In some embodiments, the compositions provided herein contain from about 500 mg to about 1,000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 mg to about 550 mg, about 550 mg to about 600 mg, about 600 mg to about 650 mg, about 650 mg to about 700 mg, about 700 mg to about 750 mg, about 750 mg to about 800 mg, about 800 mg to about 850 mg, about 850 mg to about 900 mg, about 900 mg to about 950 mg, or about 950 mg to about 1,000 mg of the active ingredient.

[00201] The active compound may be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual subject, the severity of the subject's symptoms, and the like.

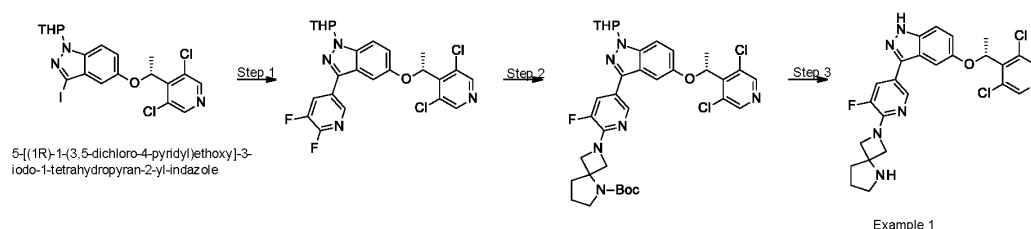
[00202] In some embodiments, the compounds provided herein can be administered in an amount ranging from about 1 mg/kg to about 100 mg/kg. In some embodiments, the compound provided herein can be administered in an amount of about 1 mg/kg to about 20 mg/kg, about 5 mg/kg to about 50 mg/kg, about 10 mg/kg to about 40 mg/kg, about 15 mg/kg to about 45 mg/kg, about 20 mg/kg to about 60 mg/kg, or about 40 mg/kg to about 70 mg/kg. For example, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 35

mg/kg, about 40 mg/kg, about 45 mg/kg, about 50 mg/kg, about 55 mg/kg, about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 95 mg/kg, or about 100 mg/kg. In some embodiments, such administration can be once-daily or twice-daily (BID) administration.

Examples

[00203] The examples and preparations provided below further illustrate and exemplify the compounds of the present invention and methods of preparing such compounds. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following examples and preparations.

[00204] In several embodiments, where single enantiomers are provided, the enantiomers may be separated by conventional means (chiral chromatography, preparing diastereomeric salts, chiral derivatization, crystallization, enzymatic reactions, etc.). In several embodiments, a chiral intermediate compound is purified to prepare an enantiomerically pure (or substantially enantiomerically pure, enantiomerically enriched, etc.) intermediate.



Example 1. 3-[6-(2,5-diazaspiro[3.4]octan-2-yl)-5-fluoro-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole

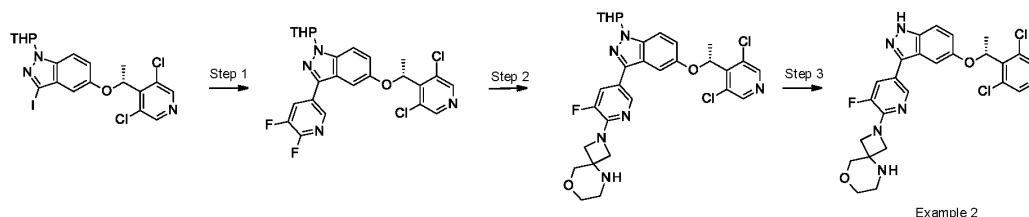
[00205] Step 1. 5-[(1R)-1-(3,5-Dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole. To a solution of 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-iodo-1-tetrahydropyran-2-yl-indazole (4.50 g, 8.68 mmol, 1.0 eq) and 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (3.14 g, 13.03 mmol, 1.5 eq) in dioxane (50 mL) and water (5 mL) was added K_2CO_3 (3.60 g, 26.05 mmol, 3.0 eq) and $Pd(dppf)Cl_2$ (708 mg, 0.87 mmol, 0.1 eq). The reaction mixture was stirred for 3 h at 90 °C under N_2 protection. After the reaction was completed, the solid was filtered out and the filtrate was concentrated in vacuum. The

crude product was purified by silica gel column (Petroleum Ether/EtOAc = 10/1) to give a white solid (2.3 g, 52%). LCMS m/z = 505.2 (M+H).

[00206] Step 2. tert-Butyl 2-(5-(5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-3-fluoropyridin-2-yl)-2,5-diazaspiro[3.4]octane-5-carboxylate. A solution of 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole (0.170 g, 0.33 mmol, 1 equiv), tert-butyl 2,5-diazaspiro[3.4]octane-5-carboxylate (0.346 g, 0.67 mmol, 2.0 equiv) and N,N-diisopropylethylamine (0.52 mL, 3.02 mmol, 9 equiv) in acetonitrile (3 mL) was heated at 80 °C for 16 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was diluted with water (40 mL). The resulting precipitate was filtered and dried at 40 °C for 16 hours to give a white solid (0.23 g, 98%). LCMS m/z = 697 (M+H).

[00207] Step 3. 3-[6-(2,5-diazaspiro[3.4]octan-2-yl)-5-fluoro-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole. 1-Dodecanethiol (146 mg, 0.72 mmol, 2.2 equiv) and trifluoroacetic acid (3 mL) were sequentially added to a solution of tert-Butyl 2-(5-(5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)-3-fluoropyridin-2-yl)-2,5-diazaspiro[3.4]octane-5-carboxylate (230 mg, 0.33 mmol, 1.0 equiv) in dichloromethane (3 mL). After stirring for 16 hours at room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane (15 mL) and saturated sodium carbonate (25 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 7 mL). The combined organics were washed with saturated brine (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on a Biotage automated chromatography system (RediSep Rf GOLD 100 g HP C18 column), eluting with a gradient of 0 to 100% acetonitrile in water to give a white solid (89 mg, 52%) after lyophilization of clean product containing fractions. LCMS m/z = 513.1 (M+H); ¹H NMR (400 MHz, DMSO-d₆) δ = 13.13 (br s, 1H), 8.57 (s, 2H), 8.36 (s, 1H), 7.69 (br d, J = 13.2 Hz, 1H), 7.50 - 7.45 (m, J = 8.8 Hz, 1H), 7.19 (s, 1H), 7.14 - 7.05 (m, J = 8.9 Hz, 1H),

6.14 (br d, J = 6.5 Hz, 1H), 4.10 - 3.98 (m, 4H), 2.96 (br s, 1H), 2.84 (br t, J = 6.4 Hz, 2H), 1.98 (br t, J = 7.1 Hz, 2H), 1.78 - 1.69 (m, 5H).

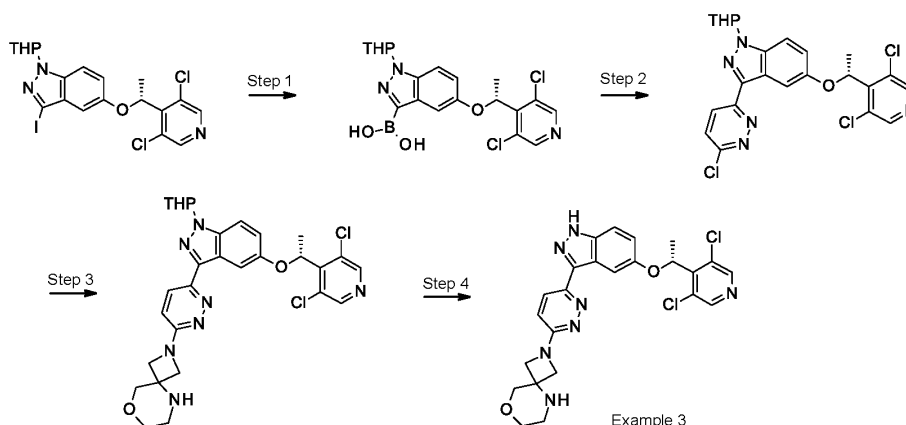


Example 2. (R)-2-(5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)-3-fluoropyridin-2-yl)-8-oxa-2,5-diazaspiro[3.5]nonane

[00208] Step 1. 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole. To a solution of 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-iodo-1-tetrahydropyran-2-yl-indazole (4.50 g, 8.68 mmol, 1.0 eq) and 2,3-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (3.14 g, 13.03 mmol, 1.5 eq) in dioxane (50 mL) and water (5 mL) was added K_2CO_3 (3.60 g, 26.05 mmol, 3.0 eq) and $Pd(dppf)Cl_2$ (708 mg, 0.87 mmol, 0.1 eq). The reaction mixture was stirred for 3 h at 90 °C under N_2 protection. After the reaction was completed, the solid was filtered out and the filtrate was concentrated in vacuum. The crude product was purified by silica gel column (Petroleum Ether/EtOAc = 10/1) to give a white solid (2.3 g, 52% yield). LCMS m/z = 505.2 (M+H).

[00209] Step 2. 2-[5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]-3-fluoro-2-pyridyl]-8-oxa-2,5-diazaspiro[3.5]nonane. To a solution of 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole (550 mg, 1.09 mmol, 1.0 eq) and 8-oxa-2,5-diazaspiro[3.5]nonane (1.39 g, TFA salt) in DMSO (12 mL) was added K_2CO_3 (751 mg, 5.44 mmol, 5.0 eq) at rt. The reaction solution was stirred at 100 °C for 3 h. After cooled to rt, the mixture was diluted with EtOAc (30 mL) and washed with water (30 mL x 2) and brine (30 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column (DCM/MeOH = 10/1) to give a yellow solid (600 mg, 90% yield). LCMS m/z = 613.3 (M+1).

[00210] Step 3. (R)-2-(5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)-3-fluoropyridin-2-yl)-8-oxa-2,5-diazaspiro[3.5]nonane. To a solution of 2-[5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]-3-fluoro-2-pyridyl]-8-oxa-2,5-diazaspiro[3.5]nonane (550 mg, 0.90 mmol, 1.0 eq) in DCM (12 mL) was added TFA (4 mL) at 0 °C. The reaction was stirred at rt for 4 h, and then concentrated in vacuum. The crude product was treated with DCM/MeOH (V:V= 5:1, 50 mL), and solid NaHCO₃ was added to adjust pH of the solution to 7~8. The solids were filtered out and the filtrate was concentrated. The crude product was purified by silica gel column chromatography (DCM/MeOH = 8/1) to give an off-white solid (355 mg, 75% yield). LCMS *m/z* = 529.2 (M+1); ¹H-NMR (400 MHz, DMSO-d₆) δ 13.12 (s, 1H), 8.57 (s, 2H), 8.38 (s, 1H), 7.71 (dd, *J* = 13.2 Hz, 1.6 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.20 (d, *J* = 1.6 Hz, 1H), 7.10 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.14 (q, *J* = 6.4 Hz, 1H), 4.00 (d, *J* = 7.2 Hz, 2H), 3.90 (d, *J* = 8.0 Hz, 2H), 3.69 (s, 2H), 3.56 (t, *J* = 4.4 Hz, 2H), 2.74 (t, *J* = 4.4 Hz, 2H), 1.76 (d, *J* = 6.4 Hz, 3H).



Example 3. (R)-2-(6-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)pyridazin-3-yl)-8-oxa-2,5-diazaspiro[3.5]nonane

[00211] Step 1. [5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]boronic acid. To a solution of bis(pinacolato)diboron (19.61 g, 77.2 mmol, 10.0 eq) in DMSO (100 mL) was added KOAc (1.51 g, 15.44 mmol, 2.0 eq) and Pd(dppf)Cl₂ (631 mg, 0.77 mmol, 0.1 eq). The reaction mixture was stirred at 100 °C for 10 min under N₂ protection. A solution of 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-iodo-1-tetrahydropyran-2-yl-indazole

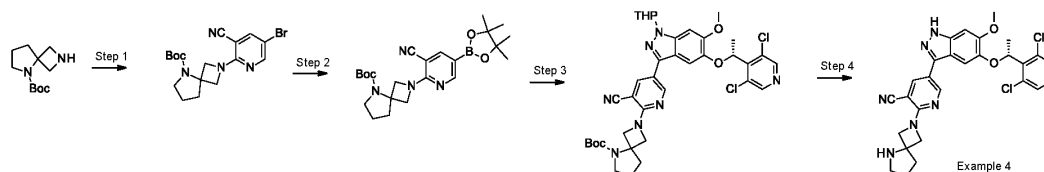
(4.0 g, 7.72 mmol, 1.0 eq) in DMSO (40 mL) was added. The reaction mixture was stirred at 100 °C for 4 h under N₂. After completion, the mixture was diluted with EtOAc (300 mL) and washed with water (100 mL x 2) and brine (100 mL x 2). The organic layer was dried over Na₂SO₄ and concentrated to give a crude brown solid (12.1 g) that was used directly in the next step. LCMS m/z = 436.2 (M+1).

[00212] Step 2. 3-(6-Chloropyridazin-3-yl)-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazole. To a solution of [5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]boronic acid from step 1 (12.1 g, crude) and 3,6-dichloropyridazine (8.21 g, 55.50 mmol, 5.0 eq) in dioxane (150 mL) and water (15 mL) was added K₂CO₃ (3.06 g, 22.20 mmol, 2.0 eq), Pd(dppf)Cl₂ (907 mg, 1.11 mmol, 0.1 eq). The reaction mixture was stirred at 100 °C for 4 h under N₂ protection. The reaction was cooled to room temperature, and the solvent was removed in vacuum. The crude product was purified by silica gel column (Petroleum Ether /EtOAc = 3/1) to give a yellow solid (1.0 g, 30%). LCMS m/z = 504.2 (M+1).

[00213] Step 3. 2-[6-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]pyridazin-3-yl]-8-oxa-2,5-diazaspiro[3.5]nonane. To a solution of 3-(6-chloropyridazin-3-yl)-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazole (1.0 g, 1.98 mmol, 1.0 eq) and 8-oxa-2,5-diazaspiro[3.5]nonane (2.4 g, TFA salt, crude) in DMSO (20 mL) was added K₂CO₃ (1.37 g, 9.91 mmol, 5.0 eq). The reaction mixture was stirred at 110 °C for 16 h. After cooled to rt, the mixture was diluted with EtOAc (50 mL), washed with water (50 mL x 2) and brine (50 mL x 2). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by silica gel column chromatography (DCM/MeOH = 15/1) to give a yellow solid (800 mg, 68%) a yellow solid. LCMS m/z = 596.3 (M+1).

[00214] Step 4. (R)-2-(6-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)pyridazin-3-yl)-8-oxa-2,5-diazaspiro[3.5]nonane. To a solution of 2-[6-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]pyridazin-3-yl]-8-oxa-2,5-diazaspiro[3.5]nonane (800 mg, 1.34 mmol, 1.0 eq) in DCM (16 mL)

was added TFA (4 mL) at 0 °C, the reaction mixture was stirred at rt for 4 h. After completion, the reaction mixture was concentrated in vacuum. The crude product was treated with DCM/MeOH (V:V = 5:1, 50 mL), and solid NaHCO₃ was added to the solution to adjust pH to 7~8. The solids were filtered off, and filtrate was concentrated. The crude product was purified by silica gel column (DCM/MeOH = 10/1) to give an off-white solid (503 mg, 73% yield). LCMS *m/z* = 512.2 (M+H); ¹HNMR (400 MHz, DMSO-d₆) δ 13.19 (s, 1H), 8.56 (s, 2H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.95 (d, *J* = 1.6 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.09 (dd, *J* = 9.2 Hz, 2.8 Hz, 1H), 6.93 (d, *J* = 9.6 Hz, 1H), 6.08 (q, *J* = 6.4 Hz, 1H), 4.01 (d, *J* = 8.4 Hz, 2H), 3.84 (d, *J* = 8.4 Hz, 2H), 3.70 (s, 2H), 3.57 (t, *J* = 4.4 Hz, 2H), 2.76 (t, *J* = 4.0 Hz, 2H), 1.77 (d, *J* = 6.4 Hz, 3H).



Example 4. 2-(2,5-diazaspiro[3.4]-octan-2-yl)-5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1H-indazol-3-yl]pyridine-3-carbonitrile.

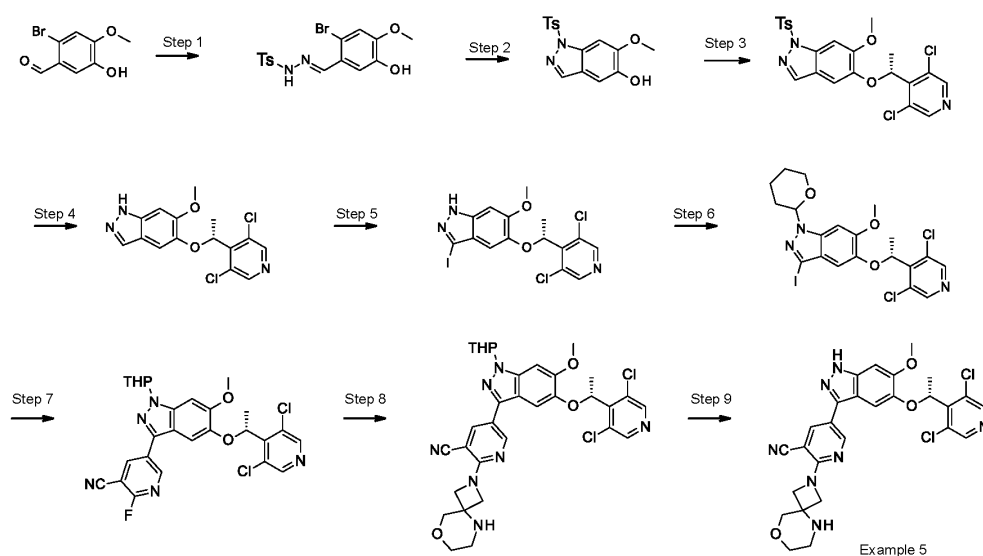
[00215] Step 1. tert-Butyl 2-(5-bromo-3-cyanopyridin-2-yl)-2,5-diazaspiro[3.4]octane-5-carboxylate. A solution of tert-butyl 2,5-diazaspiro[3.4]octane-5-carboxylate hemi-oxalate (0.35 g, 0.68 mmol, 1.00 equiv), 5-bromo-2-chloro-pyridine-3-carbonitrile (0.364 g, 1.67 mmol, 2.47 equiv) and N,N-diisopropylethylamine (1.2 mL, 6.8 mmol, 10 equiv) in acetonitrile (5 mL) was heated at 50 °C for 38 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (15 mL) and saturated sodium bicarbonate (15 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 7 mL). The combined organics were washed with saturated brine (15 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on a Biotage automated chromatography system (Biotage Sfär 25 g, 60 μm), eluting with a gradient of 0 to 20% ethyl acetate in hexanes to give an off-white solid (0.45 g, 89%). LCMS *m/z* = 393 (M+H).

[00216] Step 2. tert-Butyl 2-(3-cyano-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-2,5-diazaspiro[3.4]octane-5-carboxylate. A mixture of tert-butyl 2-(5-bromo-3-cyanopyridin-2-yl)-2,5-diazaspiro[3.4]octane-5-carboxylate (0.25 g, 0.64 mmol, 1.00 equiv), bis(pinacolato)diboron (0.18 g, 0.67 mmol, 1.10 equiv), [1,1' bis(diphenylphosphino)ferrocene]palladium(II) dichloride (46 mg, 0.06 mmol, 0.1 equiv) and potassium acetate (0.075 g, 0.77 mmol, 1.2 equiv) in 1,4-dioxane (5 mL) was sparged with argon at room temperature for 5 minutes and then heated in a sealed vial at 85 °C for 18 hours. The reaction mixture was cooled to room temperature and the solution used subsequently in the next step.

[00217] Step 3. tert-Butyl 2-(3-cyano-5-(5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyridin-2-yl)-2,5-diazaspiro[3.4]octane-5-carboxylate. tert-Butyl 2-(3-cyano-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-2,5-diazaspiro[3.4]octane-5-carboxylate (0.63 mmol, 1.00 equiv) 1,4-dioxane (5 mL) solution from step 2 was added 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-iodo-6-methoxy-1-tetrahydropyran-2-yl-indazole (0.347 g, 0.63 mmol, 1 equiv), [1,1' bis(diphenylphosphino) ferrocene]palladium(II) dichloride (60 mg, 0.1 mmol, 0.1 equiv), potassium carbonate (0.26 g, 1.89 mmol, 3.0 equiv) and water (2 mL), then sparged with argon at room temperature for 5 minutes. After heating in a sealed vial at 80 °C for 16 hours, the mixture was cooled to room temperature and diluted with aqueous saturated sodium carbonate (25 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 8 mL). The combined organics were washed with saturated brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on a Biotage automated chromatography system (Biotage Sfar 50 g, 20 µm), eluting with a gradient of 0 to 60% ethyl acetate in hexanes to give an off-white solid (0.30 g, 64%). LCMS m/z = 734 (M+H).

[00218] Step 4. 2-(2,5-diazaspiro[3.4]-octan-2-yl)-5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1H-indazol-3-yl]pyridine-3-carbonitrile. Trifluoroacetic acid (4 mL) was added to a solution of tert-butyl 2-(3-cyano-5-(5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-

indazol-3-yl)pyridin-2-yl)-2,5-diazaspiro[3.4]octane-5-carboxylate (300 mg, 0.49 mmol, 1.0 equiv) and 1-dodecanethiol (182 mg, 0.99 mmol, 2.00 equiv) in dichloromethane (4 mL) at room temperature. After stirring at room temperature for 20 hours, the volatiles were removed under reduced pressure, and the residue was neutralized with saturated sodium carbonate (20 mL) and 30% sodium hydroxide (10 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with saturated brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified on a Biotage automated chromatography system (RediSep Rf GOLD 100 g HP C18 column), eluting with a gradient of 0 to 100% acetonitrile in water to give a white solid (130 mg, 50% yield) after lyophilization of clean product containing fractions. LCMS m/z = 550.1 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ = 12.96 (br s, 1H), 8.71 (d, J = 2.3 Hz, 1H), 8.58 (s, 2H), 8.06 (d, J = 2.3 Hz, 1H), 7.04 (s, 1H), 7.00 (s, 1H), 5.99 (q, J = 6.7 Hz, 1H), 4.26 (d, J = 8.8 Hz, 2H), 4.17 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 2.86 (t, J = 6.9 Hz, 2H), 2.01 - 1.94 (m, 2H), 1.78 - 1.68 (m, 5H).



Example 5. (R)-5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazol-3-yl)-2-(8-oxa-2,5-diazaspiro[3.5]nonan-2-yl)nicotinonitrile

[00219] Step 1. (E)-N'-(2-Bromo-5-hydroxy-4-methoxybenzylidene)-4-methylbenzenesulfonohydrazide. p-Toluenesulfonyl hydrazide (0.56 g, 3.0 mmol, 1.0 equiv) was added to a solution of 2-bromo-5-hydroxy-4-methoxy-benzaldehyde (0.7 g, 3.0 mmol, 1.0 equiv) in methanol (7.0 mL) at rt. The resulting mixture was heated at 60 °C for 2 h. The reaction was cooled to rt and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (20 mL), then heptanes (80 mL) was added to give a light-yellow solid (1.21 g, 100%). LCMS m/z = 399.0 (M+H).

[00220] Step 2. 6-Methoxy-1-tosyl-1H-indazol-5-ol. Copper(I) oxide (0.22 g, 1.5 mmol, 0.5 equiv) was added to a solution of (E)-N'-(2-Bromo-5-hydroxy-4-methoxybenzylidene)-4-methylbenzenesulfonohydrazide (1.2 g, 3.0 mmol, 1.0 equiv) in isoamyl alcohol (30 mL) at room temperature. After heating at 132 °C for 2 hours, the mixture was cooled to room temperature and diluted with water (80 mL). The mixture was extract with ethyl acetate (4 x 50 mL). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated onto silica gel (8.0 g) and purified on a Biotage automated purification system (Biotage Sfär Silica, 50 g; 0% to 100% ethyl acetate in heptanes) to give a light yellow solid (0.66 g, 70% yield). LCMS m/z = 319.1 (M+H).

[00221] Step 3. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-6-methoxy-1-tosyl-1H-indazole. (1S)-1-(3,5-dichloro-4-pyridyl)ethyl] methanesulfonate (0.57 g, 2.1 mmol, 1.0 equiv) and cesium carbonate (1.03 g, 3.2 mmol, 1.5 equiv) were added to a solution of 6-methoxy-1-tosyl-1H-indazol-5-ol (0.67 g, 2.1 mmol, 1.0 equiv) in acetonitrile (21 mL) at room temperature. After heating at 90 °C overnight, the mixture was cooled to room temperature and concentrated onto silica gel (6.0 g) under reduced pressure. The product was purified on a Biotage automated purification system (Sorbtech silica, 40 g), eluting with a gradient of 0% to 60% ethyl acetate in heptanes to give a white solid (0.71 g, 70% yield). LCMS m/z = 492.1 (M+H).

[00222] Step 4. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazole. 1M Tetrabutylammonium fluoride in THF (7.2 mL, 7.2 mmol, 18.0 equiv) was added to a solution of (R)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1-

tosyl-1H-indazole (0.20 g, 0.4 mmol, 1.0 equiv) in tetrahydrofuran (4 mL) at room temperature. After heating at 50 °C for 4 days, the solvent was removed under reduced pressure. The residue was concentrated onto silica gel (2.0 g) and purified on a Biotage automated purification system (Sorbtech silica, 12 g), eluting with a gradient of 0% to 100% ethyl acetate in heptanes to give a white solid (74.7 mg, 54%). LCMS $m/z = 338.0$ (M+H).

[00223] Step 5. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-iodo-6-methoxy-1H-indazole. Potassium hydroxide (27.9 mg, 0.50 mmol, 2.25 equiv) and iodine (84.1 mg, 0.33 mmol, 1.5 equiv) were added to a solution of (R)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazole (74.7 mg, 0.22 mmol, 1.0 equiv) in N,N-dimethylformamide (2.2 mL) at 0 °C. The resulting mixture was allowed to warm up to room temperature and stirred overnight. The reaction was diluted with ethyl acetate (10 mL) and washed with water (4 x 5 mL). The organic layer was dried over sodium sulfate and concentrated onto silica gel (1.5 g) under reduced pressure. The product was purified on a Biotage automated purification system (Sorbtech silica, 12 g), eluting with a gradient of 0% to 100% ethyl acetate in heptanes to give an off-white solid (80 mg, 77%). LCMS $m/z = 463.9$ (M+H).

[00224] Step 6. 5-((R)-1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-iodo-6-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole. 5-[(1R)-1-(3,5-Dichloro-4-pyridyl)ethoxy]-3-iodo-6-methoxy-1H-indazole (0.5 g, 1.1 mmol, 1 equiv) was treated with 3,4-dihydro-2H-pyran (0.2 mL, 2.2 mmol, 2 equiv) and p-toluenesulfonic acid monohydrate (10 mg, 0.05 mmol, 0.05 equiv) in anhydrous dichloromethane (6 mL) at room temperature overnight. The mixture was diluted with dichloromethane (8 mL) and washed with water (8 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure onto silica gel (6 g). The residue was purified on a Biotage automated chromatography system (Sorbtech, 12 g silica gel column), eluting with a gradient of 0 to 20% ethyl acetate in heptanes to give a white solid (510 mg, 86% yield). $m/z = 548$ (M+H).

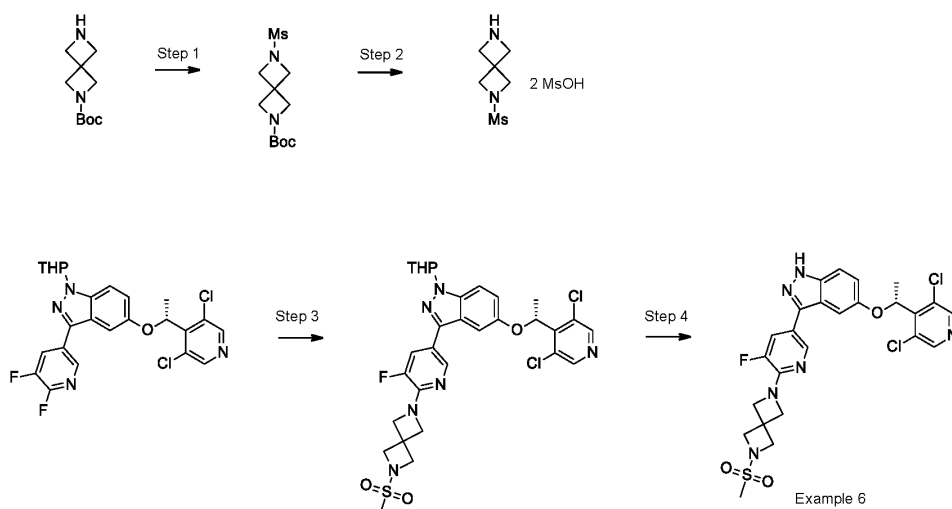
[00225] Step 7A. 2-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbonitrile. To a solution of 5-bromo-2-fluoro-pyridine-3-carbonitrile

(10 g, 49.8 mmol, 1.0 eq) and bis(pinacolato)diboron (25.3 g, 99.5 mmol, 2.0 eq) in dioxane (200 mL) was added KOAc (20.6 g, 149.3 mmol, 3.0 eq) and Pd(dppf)Cl₂ (2.0 g, 20wt%). The reaction mixture was stirred for 5 h at 90 °C under N₂ protection. After the reaction was completed, the solid was filtered out and the filtrate was concentrated in vacuum. The crude product was purified by silica gel column (Petroleum Ether/EtOAc = 10/1) to give a white solid (12 g, 59% yield). LCMS m/z = 249.2 (M+H); ¹H NMR (400 MHz, DMSO-d₆) δ 8.68 (d, J = 1.6 Hz, 1H), 8.63 (dd, J = 9.2 Hz, 1.6 Hz, 1H), 1.32 (s, 12H).

[00226] Step 7B. 5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1-tetrahydropyran-2-yl-indazol-3-yl]-2-fluoro-pyridine-3-carbonitrile. To a solution of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine-3-carbonitrile (1.0 g, 4.0 mmol, 2.2 eq) and 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-iodo-6-methoxy-1-tetrahydropyran-2-yl-indazole (1.0 g, 1.8 mmol, 1.0 eq) in dioxane (20 mL) and H₂O (2 mL) was added K₂CO₃ (745 mg, 5.4 mmol, 3.0 eq) and Pd(dppf)Cl₂ (100 mg, 10%wt) at rt. The mixture was stirred for 2 h at 90 °C under N₂ protection. After the reaction was completed, the solid was filtered out and the filtrate was concentrated in vacuum. The crude product was purified by silica gel column (Petroleum Ether/EtOAc = 1/1) to give an off-white solid (900 mg, 91% yield). LCMS m/z = 542.2 (M+H).

[00227] Step 8. 5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1-tetrahydropyran-2-yl-indazol-3-yl]-2-(8-oxa-2,5-diazaspiro[3.5]nonan-2-yl)pyridine-3-carbonitrile. To a solution of 5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1-tetrahydropyran-2-yl-indazol-3-yl]-2-fluoro-pyridine-3-carbonitrile (800 mg, 1.47 mmol, 1.0 eq) and 8-oxa-2,5-diazaspiro[3.5]nonane (1.88 g, TFA salt) in DMSO (15 mL) was added DIEA (951 mg, 7.37 mmol, 5.0 eq) at rt. The reaction solution was stirred at 100 °C for 3 h. After completion, the solution was diluted with EtOAc (50 mL) and washed with water (50 mL x 2). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by silica gel column chromatography (DCM/MeOH = 10/1) to give a yellow solid (760 mg, 79% yield). LCMS m/z = 650.3 (M+1).

[00228] Step 9. (R)-5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazol-3-yl)-2-(8-oxa-2,5-diazaspiro[3.5]nonan-2-yl)nicotinonitrile. To a solution of 5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1-tetrahydropyran-2-yl-indazol-3-yl]-2-(8-oxa-2,5-diazaspiro[3.5]nonan-2-yl)pyridine-3-carbonitrile (760 mg, 1.17 mmol, 1.0 eq) in DCM (15 mL) was added TFA (5 mL) at 0 °C. The reaction was stirred at rt for 4 h, and then was concentrated in vacuum. The crude product was treated with DCM/MeOH (V:V= 5:1, 50 mL), and solid NaHCO₃ was added to the solution to adjust pH to 7~8. The solid was filtered out and filtrate was concentrated. The crude product was purified by silica gel column chromatography (DCM/MeOH = 15/1) to give a white solid (505 mg, 76% yield). LCMS *m/z* = 566.2 (M+H); ¹HNMR (400 MHz, DMSO-d₆) δ 12.96 (brs, 1H), 8.73 (d, *J* = 2.0 Hz 1H), 8.59 (s, 2H), 8.08 (d, *J* = 2.0 Hz, 1H), 7.03-7.01 (m, 2H), 6.02 (q, *J* = 6.4 Hz, 1H), 4.17 (d, *J* = 8.8 Hz, 2H), 4.03 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.67 (s, 2H), 3.56-3.54 (m, 2H), 3.10 (s, 1H), 2.7-2.73 (m, 2H), 1.77 (d, *J* = 6.4 Hz, 3H).



Example 6. 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[5-fluoro-6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1H-indazole

[00229] Step 1. tert-Butyl 6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate. Saturated sodium bicarbonate (10 mL) was added dropwise to a suspension of tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate hemi-oxylate (1 g, 4.1 mmol, 1 equiv) in dichloromethane (70 mL) at 0 °C. After 10 minutes, a solution

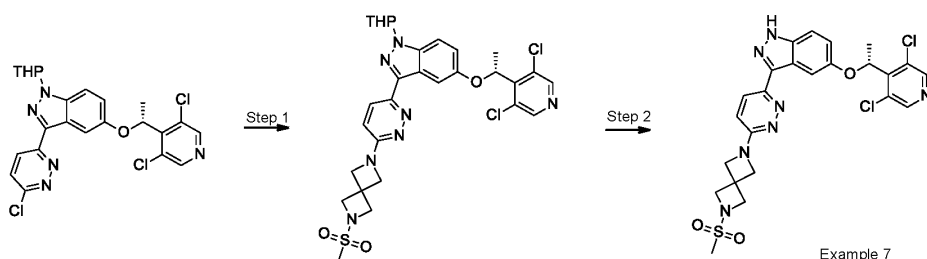
of methanesulfonyl chloride (0.94 g, 8.2 mmol, 2 equiv) in dichloromethane (5 mL) was added dropwise. The resulting mixture was stirred at room temperature for 16 hours. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a white solid (1.2 g). LCMS m/z = 553.2 (M+H).

[00230] Step 2. 2-(Methylsulfonyl)-2,6-diazaspiro[3.3]heptane bis(methanesulfonic acid) salt. Methanesulfonic acid (0.85 mL, 1.25 g, 13 mmol, 3 equiv) was added dropwise to a solution of tert-Butyl 6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (1.2 g, 4.3 mmol, 1 equiv) in a mixture of dichloromethane (36 mL) and 1,4-dioxane (4 mL) at 0 °C. After stirring at room temperature for 16 hours, methyl tert-butyl ether (50 mL) was added to precipitate the solids. The suspension was filtered and washed with methyl tert-butyl ether (50 mL) to give a white solid (1.34 g, 88% yield over 2 steps). LCMS m/z = 177.1 (M+H) (free base).

[00231] Step 3. 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[5-fluoro-6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1-tetrahydropyran-2-yl-indazole. 5-[(1R)-1-(3,5-Dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole (260 mg, 0.51 mmol, 1 equiv) in acetonitrile (10 mL) was treated with 2-(methylsulfonyl)-2,6-diazaspiro[3.3]heptane bis(methanesulfonic acid) salt (305 mg, 0.83 mmol, 1.6 equiv) and N,N-diisopropylethylamine (0.70 mL, 4.0 mmol, 7.8 equiv) at 80 °C for 12 hours. The mixture was cooled to room temperature, diluted with water (30 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a white solid (360 mg, 100%). LCMS m/z = 661 (M+H).

[00232] Step 4. (5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[5-fluoro-6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1H-indazole. A solution of concentrated sulfuric acid (2.4 mL, 42.85 mmol, 15 equiv) in water (81 mL) was stirred at room temperature for 5 minutes, and then a solution of 5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-3-(5-fluoro-6-(6-(methylsulfonyl)-2,6-

diazaspiro[3.3]heptan-2-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (1.89 g, 2.86 mmol, 1 equiv) in acetic acid (15.1 mL) was added. The reaction turned white and cloudy, forming a sticky solid. It was then heated at 36 °C for 48 hours. Methyl tert-butyl ether (10 mL) was added, and the reaction was stirred for an additional 10 minutes. The solids were collected by vacuum filtration, washed with isopropanol (20 mL) and dried at 40 °C under vacuum overnight to give a white solid. The solid was dissolved in tetrahydrofuran (20 mL) and 2M sodium hydroxide (7 mL) was added. The biphasic mixture was separated, and the aqueous layer extracted with tetrahydrofuran (2 x 15 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give a white solid (1.70 g, 100% yield). LCMS m/z = 577.1 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ = 13.12 (br s, 1H), 8.57 (s, 2H), 8.38 (s, 1H), 7.72 (dd, J = 1.7, 13.1 Hz, 1H), 7.47 (d, J = 8.9 Hz, 1H), 7.24 - 7.15 (m, 1H), 7.10 (dd, J = 2.2, 8.9 Hz, 1H), 6.14 (q, J = 6.6 Hz, 1H), 4.31 (d, J = 1.5 Hz, 4H), 4.12 (s, 4H), 3.02 (s, 3H), 1.76 (d, J = 6.6 Hz, 3H).

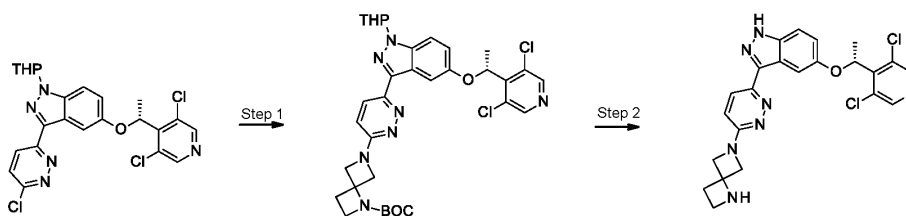


Example 7. 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[6-(2-methylsulfonyl)-2,6-diazaspiro[3.3]heptan-6-yl]pyridazin-3-yl]-1H-indazole

[00233] Step 1. 5-((R)-1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(6-(6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyridazin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole. A mixture of 3-(6-chloropyridazin-3-yl)-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazole (800 mg, 1.59 mmol, 1.0 equiv), 2-(methylsulfonyl)-2,6-diazaspiro[3.3]heptane bis(methanesulfonic acid) salt (1.17 g, 3.17 mmol, 2.0 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.9 mL, 12.7 mmol, 8 equiv) in 1-methoxy-2-propanol (8.2 mL) was stirred at 115 °C for 20 hours, then cooled to room temperature. The reaction mixture was diluted gradually with water (30 mL), then stirred for 7.5 hours. The resulting precipitate was filtered,

washed with water (50 mL), and then dried under vacuum at 40 °C for 15 hours to give an off-white solid (946 mg, 93% yield). LCMS m/z = 644, 646 (M+H).

[00234] Step 2. 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)pyridazin-3-yl]-1H-indazole. Concentrated sulfuric acid (2.0 mL, 35 mmol, 15 equiv) was added to water (50 mL), then stirred for 15 minutes. A mixture of 5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-3-(6-(6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyridazin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (1.5 g, 2.3 mmol, 1.0 equiv) in acetic acid (9.4 mL, 164 mmol, 70 equiv) was added in one portion. The reaction mixture was heated at 60 °C for 22 hours, then at 70 °C for 30 hours. After cooling to room temperature, the resulting solid was filtered, then washed with 2-propanol (3 x 10 mL) and air-dried for 5 minutes. The solid was suspended in tetrahydrofuran (12 mL), treated with a 2.5M sodium hydroxide solution (2.8 mL, 7.0 mmol, 3.0 equiv) and stirred for 20 minutes. The layers were separated, and the aqueous layer was extracted with tetrahydrofuran (3 x 10 mL). The combined organic layers were washed with saturated brine (12 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was dried under vacuum at 40 °C for 15 hours, then was absorbed onto Celite (20 g) with ethyl acetate (40 mL) and purified on a Biotage automated chromatography system (BiotageAmino Duo column, 55 g, 50 μ m) eluting with a gradient of 0 to 10% methanol in ethyl acetate to give a white solid (783 mg, 60% yield). LCMS m/z = 560 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ 1H NMR (400 MHz, METHANOL- d_4) δ = 8.43 (s, 2H), 8.05 (d, J = 9.3 Hz, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.15 (dd, J = 2.3, 9.0 Hz, 1H), 6.93 (d, J = 9.3 Hz, 1H), 6.21 (q, J = 6.7 Hz, 1H), 4.36 (s, 4H), 4.19 (s, 4H), 2.98 (s, 3H), 1.82 (d, J = 6.7 Hz, 3H).

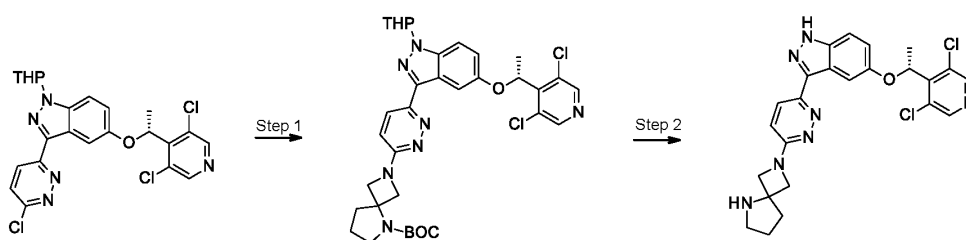


Example 8

Example 8. (R)-3-(6-(1,6-diazaspiro[3.3]heptan-6-yl)pyridazin-3-yl)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole

[00235] Step 1. tert-butyl 6-[6-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]pyridazin-3-yl]-1,6-diazaspiro[3.3]heptane-1-carboxylate. To a solution of 3-(6-chloropyridazin-3-yl)-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazole (130 mg, 0.26 mmol, 1.0 eq) and tert-butyl 1,6-diazaspiro[3.3]-heptane-1-carboxylate oxylate (188 mg, 0.39 mmol, 1.5 eq) in DMSO (5 mL) was added DIEA (99 mg, 0.77 mmol, 3.0 eq). The reaction mixture was stirred for 16 h at 120 °C. After the reaction was completed, the mixture was diluted with ethyl acetate (50 mL) and washed with brine (15 mL x 3). The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by silica gel chromatography, eluted with petroleum ether/ethyl acetate (1/1) to give a yellow solid (90 mg, 52% yield). LCMS m/z = 666.6 (M+1).

[00236] Step 2. (R)-3-(6-(1,6-diazaspiro[3.3]heptan-6-yl)pyridazin-3-yl)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole. A solution of tert-butyl 6-[6-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]pyridazin-3-yl]-1,6-diazaspiro[3.3]heptane-1-carboxylate (90 mg, 0.13 mmol, 1.0 eq) in DCM (5 mL) was added TFA (4 mL), and was stirred at rt for 5 h. The reaction mixture was then treated with aqueous NaHCO₃ solution to adjust pH to 7~8, and extracted with DCM (40 mL x 2). The combined organic layers were washed with brine (30 mL x 2), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by Prep-HPLC (Prep-C18, 5 μM Triart column, 19 × 150 mm, YMC-Actus; gradient elution of 17% MeCN in water to 42% MeCN in water over a 12 min period, where both solvents contain 0.05% NH₃.H₂O) to give a light-yellow solid (16 mg, 25% yield). LCMS m/z = 482.2 (M+H); ¹HNMR (400 MHz, DMSO-d₆) δ = 13.27 (s, 1H), 9.49 (brs, 1H), 8.56 (s, 2H), 8.06 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 1.6 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.11 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.06 (d, J = 9.6 Hz, 1H), 6.08 (q, J = 6.8 Hz, 1H), 4.66 (d, J = 10.8 Hz, 2H), 4.42 (d, J = 10.4 Hz, 2H), 3.90-3.83 (m, 2H), 2.78 (t, J = 8.0 Hz, 2H), 1.78 (d, J = 6.4 Hz, 3H).



Example 9

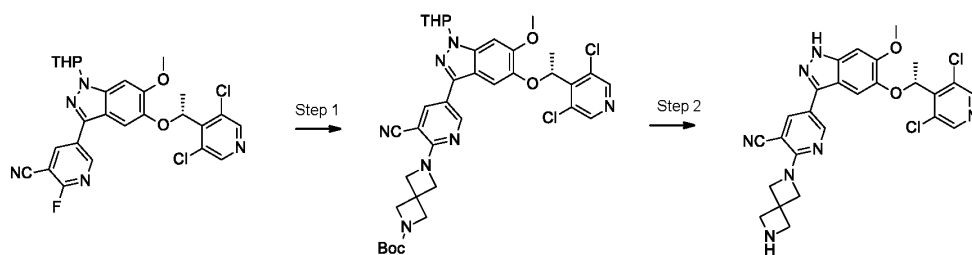
Example 9. (R)-3-(6-(2,5-diazaspiro[3.4]octan-2-yl)pyridazin-3-yl)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole

[00237] Step 1. tert-butyl 2-[6-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]pyridazin-3-yl]-2,5-diazaspiro[3.4]octane-5-carboxylate. To a solution of 3-(6-chloropyridazin-3-yl)-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazole (120 mg, 0.24 mmol, 1.0 eq) and tert-butyl 2,5-diazaspiro[3.4]octane-5-carboxylate (151 mg, 0.71 mmol, 3.0 eq) in DMSO (3 mL) was added K_2CO_3 (164 mg, 1.19 mmol, 5.0 eq) at rt. The reaction solution was stirred at 80 °C for 16 h. After cooled to rt, the mixture was diluted with EtOAc (10 mL) and washed with water (10 mL x 2). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column (DCM/MeOH = 20/1) to give a yellow solid (85 mg, 53% yield). LCMS m/z = 680.3 (M+1).

[00238] Step 2. (R)-3-(6-(2,5-diazaspiro[3.4]octan-2-yl)pyridazin-3-yl)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole. To a solution of tert-butyl 2-[6-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]pyridazin-3-yl]-2,5-diazaspiro[3.4]octane-5-carboxylate (80 mg, 0.12 mmol, 1.0 eq) in DCM (3 mL) was added TFA (1 mL) at 0 °C. The reaction mixture was stirred at 30 °C for 4 h. After completion, the reaction mixture was concentrated in vacuum. The crude product was treated with DCM/MeOH (V:V= 5:1, 30 mL), then solid $NaHCO_3$ was added to the solution to adjust pH to 7~8. The solids were filtered out and the filtrate was concentrated. The product was purified by Prep-HPLC (Prep-C18, 5 μ m Triart column, 20 $\times$ 150 mm, YMC-Actus; gradient elution of 40% MeCN in water to 60% MeCN in water over a 10 min period, where both solvents contain 0.05% $NH_3 \cdot H_2O$) to give a white solid (27 mg, 46% yield). LCMS m/z = 496.2

(M+H); ¹HNMR (400 MHz, DMSO-d₆) δ = 13.17 (brs, 1H), 8.56 (s, 2H), 7.96 (d, J = 9.2 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.09 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 6.88 (d, J = 9.6 Hz, 1H), 6.08 (q, J = 6.8 Hz, 1H), 4.08 (d, J = 8.0 Hz, 2H), 3.99 (d, J = 8.4 Hz, 2H), 2.88 (t, J = 6.8 Hz, 2H), 2.01 (t, J = 7.2 Hz, 2H), 1.81-1.71 (m, 5H).

[00239] Example 10. (R)-3-(6-(2,5-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole was synthesized using the procedure for example 7 and example 8 with 3-(6-chloropyridazin-3-yl)-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1-tetrahydropyran-2-yl-indazole and tert-butyl 2,5-diazaspiro[3.5]nonane-5-carboxylate. LCMS m/z = 510.2 (M+H); ¹HNMR (400 MHz, DMSO-d₆) δ = 13.18 (s, 1H), 8.56 (s, 2H), 7.97 (d, J = 9.2 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.09 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.90 (d, J = 9.2 Hz, 1H), 6.08 (q, J = 6.4 Hz, 1H), 3.97 (d, J = 8.4 Hz, 2H), 3.89 (d, J = 8.4 Hz, 2H), 2.76 (t, J = 4.8 Hz, 2H), 1.81-1.78 (m, 2H), 1.77 (d, J = 6.4 Hz, 3H), 1.61-1.54 (m, 2H), 1.49-1.41 (m, 2H).



Example 11

Example 11. 2-(2,6-diazaspiro[3.3]heptan-2-yl)-5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1H-indazol-3-yl]pyridine-3-carbonitrile

[00240] Step 1. tert-Butyl 6-(3-cyano-5-(5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyridin-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate. 5-[5-[(1R)-1-(3,5-Dichloro-4-pyridyl)ethoxy]-6-methoxy-1-tetrahydropyran-2-yl-indazol-3-yl]-2-fluoro-pyridine-3-carbonitrile (275 mg, 0.50 mmol) in acetonitrile (6 mL) was treated with triethylamine (0.50 mL, 3.6 mmol, 7 equiv) and tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate hemioxylate (147 mg, 0.60 mmol, 1.2 equiv) at room temperature. After 20 hours, the reaction was diluted with water (20 mL) and extracted with dichloromethane (3 x 5

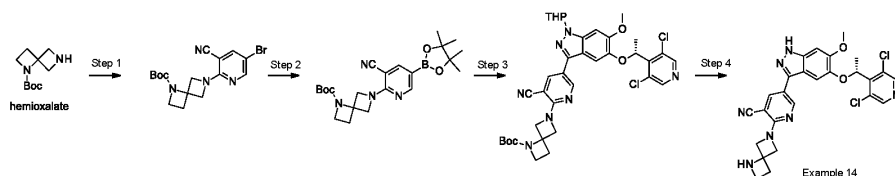
mL). The combined organic layers were washed with saturated sodium bicarbonate (10 mL), dried over sodium sulfate, and filtered. The filtrate was filtered through a plug of silica gel (4 g), which was washed with 70% ethyl acetate in hexanes (100 mL). The filtrate was concentrated under reduced pressure to give a white foam (400 mg, 100% yield). LCMS m/z = 720 (M+H).

[00241] Step 2. (R)-5-(5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazol-3-yl)-2-(2,6-diazaspiro[3.3]heptan-2-yl)nicotinonitrile. Dodecanethiol (0.30 mL, 1.25 mmol, 2.5 equiv) and 1.8M sulfuric acid (0.85 mL, 1.5 mmol, 3.0 equiv) were sequentially added to a solution of tert-butyl 6-(3-cyano-5-(5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyridin-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (400 mg, 0.5 mmol) in acetonitrile (8 mL). The reaction was heated at 60 °C for 4 hours, then cooled to room temperature and diluted with methyl tert-butyl ether (12 mL) and saturated sodium carbonate (5 mL). The biphasic mixture was concentrated under reduced pressure onto Celite (8 g). The residue was purified on a Biotage automated chromatography system (Redisep Gold 100g C18 column), eluting with a gradient of 0 to 100% acetonitrile in water. Product fractions were concentrated under reduced pressure and reconcentrated from ethanol (10 mL) to give an off-white solid (110 mg, 41% yield over two steps) after drying under vacuum at 40 °C for 8 hours. LCMS m/z = 536 (M+H); ¹HNMR (400 MHz, DMSO-*d*₆) δ = 12.97 (br s, 1H), 8.71 (d, *J* = 2.3 Hz, 1H), 8.58 (s, 2H), 8.06 (d, *J* = 2.3 Hz, 1H), 7.03 (s, 1H), 7.00 (s, 1H), 5.99 (q, *J* = 6.7 Hz, 1H), 4.38 (s, 4H), 3.86 (s, 3H), 3.65 (s, 4H), 1.76 (d, *J* = 6.7 Hz, 3H).

[00242] Example 12. 2-(2,5-diazaspiro[3.5]nonan-2-yl)-5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1H-indazol-3-yl]pyridine-3-carbonitrile was synthesized using the procedure for example 11 with 5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1-tetrahydropyran-2-yl-indazol-3-yl]-2-fluoro-pyridine-3-carbonitrile and tert-butyl 2,5-diazaspiro[3.5]nonane-5-carboxylate. LCMS m/z = 564 (M+H); ¹HNMR (400 MHz, DMSO-*d*₆) δ = 12.95 (br s, 1H), 8.71 (d, *J* = 2.2 Hz, 1H), 8.59 (s, 2H), 8.06 (d, *J* = 2.3 Hz, 1H), 7.03 (s, 1H), 7.00 (s, 1H), 5.99 (q, *J* = 6.7

Hz, 1H), 4.11 (d, J = 8.6 Hz, 2H), 4.02 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H), 2.72 - 2.66 (m, 2H), 1.76 (d, J = 6.7 Hz, 3H), 1.74 - 1.67 (m, 2H), 1.55 (br s, 2H), 1.41 (br s, 2H).

[00243] Example 13. (R)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-3-(5-fluoro-6-(1,6-diazaspiro[3.3]heptan-6-yl)pyridin-3-yl)-1H-indazole was synthesized using the procedure for example 1 with 5-[(1R)-1-(3,5-Dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole and tert-butyl 1,6-diazaspiro[3.3]heptane-1-carboxylate oxylate. LCMS m/z = 499.3 (M+H); ¹HNMR (400 MHz, DMSO-d₆) δ = 13.12 (s, 1H), 8.57 (s, 2H), 8.36 (s, 1H), 7.70 (dd, J = 13.2 Hz, 2.0 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 6.13 (q, J = 6.4 Hz, 1H), 4.27 (d, J = 8.8 Hz, 2H), 4.17 (d, J = 9.2 Hz, 2H), 3.36 (t, J = 6.8 Hz, 2H), 2.53-2.51 (m, 2H), 1.75 (d, J = 6.4 Hz, 3H).



Example 14. (R)-5-(5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazol-3-yl)-2-(1,6-diazaspiro[3.3]heptan-6-yl)nicotinonitrile

[00244] Step 1. tert-Butyl 6-(5-bromo-3-cyanopyridin-2-yl)-1,6-diazaspiro[3.3]heptane-1-carboxylate. N,N-Diisopropylethylamine (2.22 mL, 12.77 mmol, 5 equiv) was added to a mixture of 5-bromo-2-chloro-pyridine-3-carbonitrile (0.555 g, 2.554 mmol, 1 equiv) and tert-butyl 1,6-diazaspiro[3.3]heptane-1-carboxylate (0.81 g, 2.809 mmol, 1.1 equiv) in acetonitrile (40 mL) at room temperature. The mixture was stirred at room temperature for 3 days, then at 50 °C for 2 hours. The mixture was concentrated under reduced pressure, and the residue was dry loaded on silica gel (10 g) and purified on a Biotage automated chromatography system (Sorbtech silica gel column, 40 g), eluting with a gradient of 0 to 40% ethyl acetate in heptanes to give a white solid (0.75 g, 77% yield). LCMS m/z = 379, 381 (M+H).

[00245] Step 2. tert-Butyl 6-(3-cyano-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-1,6-diazaspiro[3.3]heptane-1-carboxylate. A mixture of tert-butyl 6-(5-bromo-3-cyanopyridin-2-yl)-1,6-diazaspiro[3.3]heptane-1-

carboxylate (743 mg, 1.959 mmol, 1 equiv), bis(pinacolato)diboron (746 mg, 2.939 mmol, 1.5 equiv), potassium acetate (384 mg, 3.918 mmol, 2 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (143 mg, 0.196 mmol, 0.1 equiv) in 1,4-dioxane (10 mL) was sparged with nitrogen for 10 minutes then heated at 85 °C for 22 hours. After cooling to room temperature, the reaction mixture was used directly in the next step. LCMS m/z = 345 (boronic acid) and 427 (M+H).

[00246] Step 3. tert-Butyl 6-(3-cyano-5-(5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyridin-2-yl)-1,6-diazaspiro-[3.3]heptane-1-carboxylate. Half of the mixture from step 2 (0.980 mmol, 1.5 equiv) in 1,4-dioxane (5 mL) was added 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-iodo-6-methoxy-1-tetrahydropyran-2-yl-indazole (358 mg, 0.653 mmol, 1 equiv), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (48 mg, 0.0653 mmol, 0.1 equiv) and potassium carbonate (181 mg, 1.306 mmol, 2 equiv) and water (1.0 mL). After sparging with nitrogen for 10 minutes, the reaction was heated at 80 °C for 20 hours. The mixture was cooled to room temperature and diluted with ethyl acetate (50 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with saturated brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified on a Biotage automated chromatography system (Sorbtech silica gel column, 25 g), eluting with a gradient of 0 to 100% ethyl acetate in heptanes to give compound 735-3 (428 mg, 91% yield for 2 steps) as a brown oil. LCMS m/z = 720 (M+H).

[00247] Step 4. (R)-5-(5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazol-3-yl)-2-(1,6-diazaspiro[3.3]heptan-6-yl)nicotinonitrile. Trifluoroacetic acid (6 mL) was added to a solution of tert-butyl 6-(3-cyano-5-(5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-3-yl)pyridin-2-yl)-1,6-diazaspiro-[3.3]heptane-1-carboxylate (428 mg, 0.594 mmol, 1.0 equiv) in dichloromethane (6 mL) at room temperature. After stirring at room temperature for 5 hours, the volatiles were removed under reduced pressure. The residue was diluted with dichloromethane (20 mL) and water 10 mL) and adjusted to

pH 9 with saturated sodium carbonate. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL), and the combined organic layers were washed with saturated brine (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified on a Biotage automated chromatography system (Redisep C18 HP reverse phase column, 50 g), eluting with a gradient of 0 to 100% acetonitrile in water to give a white solid (40 mg, 13% yield). LCMS m/z = 536.2 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ = 12.99 (br s, 1H), 8.74 (d, J = 2.3 Hz, 1H), 8.58 (s, 2H), 8.11 (d, J = 2.2 Hz, 1H), 7.04 (s, 1H), 7.01 (s, 1H), 5.99 (q, J = 6.7 Hz, 1H), 5.75 (s, 1H), 4.58 - 4.47 (m, 4H), 3.86 (s, 3H), 3.59 (br t, J = 7.7 Hz, 3H), 3.38 - 3.37 (m, 1H), 2.64 (t, J = 7.6 Hz, 2H), 2.55 - 2.53 (m, 1H), 1.76 (d, J = 6.7 Hz, 3H).

[00248] Example 15. (R)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-3-(5-fluoro-6-(2,5-diazaspiro[3.5]nonan-2-yl)pyridin-3-yl)-1H-indazole was synthesized using 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole and tert-butyl 2,5-diazaspiro[3.5]nonane-5-carboxylate. LCMS m/z = 527.3 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ 13.12 (s, 1H), 8.57 (s, 2H), 8.37 (t, J = 2.0 Hz, 1H), 7.69 (dd, J = 13.2 Hz, 1.6 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.14 (q, J = 6.4 Hz, 1H), 3.99-3.91 (m, 4H), 2.72 (t, J = 5.2 Hz, 2H), 1.76-1.74 (m, 5H), 1.61-1.54 (m, 2H), 1.47-1.39 (m, 2H).

[00249] Example 16. 3-[6-(2,5-diazaspiro[3.4]octan-2-yl)-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole was synthesized using the procedure for example 1 with 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole and tert-butyl 2,5-diazaspiro[3.4]octane-5-carboxylate. LCMS m/z = 495.4 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ = 13.08 (br s, 1H), 9.41 (br s, 2H), 8.59 (s, 2H), 8.55 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 2.3, 8.6 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.11 (dd, J = 2.2, 8.9 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 6.11 (q, J = 6.6 Hz, 1H), 4.34 (br d, J = 9.3 Hz, 4H), 4.18 (s, 2H), 4.15 (s, 1H), 4.05 (br s, 5H), 2.25 (t, J = 7.3 Hz, 2H), 1.98 (quin, J = 7.4 Hz, 2H), 1.76 (d, J = 6.6 Hz, 3H).

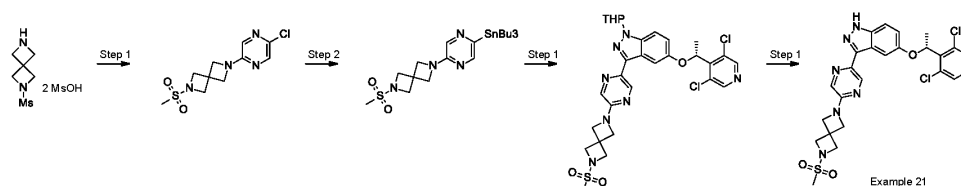
[00250] Example 17. 3-[6-(2,5-diazaspiro[3.5]nonan-2-yl)-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole was synthesized using 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(6-fluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole and tert-butyl 2,5-diazaspiro[3.5]nonane-5-carboxylate. LCMS m/z = 509.4 (M+H); ¹HNMR (400 MHz, DMSO-d₆) δ = 12.96 (br s, 1H), 8.59 (s, 2H), 8.50 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 2.3, 8.6 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.18 - 7.14 (m, 1H), 7.09 (dd, J = 2.3, 9.0 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 6.11 (q, J = 6.7 Hz, 1H), 3.83 (d, J = 7.9 Hz, 2H), 3.71 (d, J = 7.9 Hz, 2H), 2.71 - 2.66 (m, 2H), 2.63 (br s, 1H), 1.76 (d, J = 6.6 Hz, 3H), 1.72 - 1.67 (m, 2H), 1.59 - 1.52 (m, 2H), 1.46 - 1.37 (m, 2H).

[00251] Example 18. (R)-2-(5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)pyridin-2-yl)-8-oxa-2,5-diazaspiro[3.5]nonane was synthesized using 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(6-fluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole and tert-butyl 8-oxa-2,5-diazaspiro[3.5]nonane-5-carboxylate. LCMS m/z = 511.1 (M+H); ¹HNMR (400 MHz, DMSO-d₆) δ 12.98 (s, 1H), 8.60 (s, 2H), 8.51 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.16 (s, 1H), 7.09 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.56 (d, J = 8.8 Hz, 1H), 6.11 (q, J = 6.8 Hz, 1H), 3.90 (d, J = 8.0 Hz, 2H), 3.72 (d, J = 8.0 Hz, 2H), 3.67 (s, 2H), 3.56 (t, J = 4.4 Hz, 2H), 2.74 (t, J = 4.4 Hz, 2H), 1.76 (d, J = 6.4 Hz, 3H).

[00252] Example 19. 3-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-5-fluoro-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole was synthesized using 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(5,6-difluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole and tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate hemi-oxyate. LCMS m/z = 499.1 (M+H); ¹HNMR (400 MHz, DMSO-d₆) δ = 13.10 (br s, 1H), 8.57 (s, 2H), 8.38 - 8.35 (m, 1H), 7.69 (dd, J = 1.6, 13.2 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.10 (dd, J = 2.2, 9.0 Hz, 1H), 6.13 (q, J = 6.6 Hz, 1H), 4.22 (br s, 4H), 4.01 (br s, 1H), 3.78 - 3.57 (m, 4H), 1.76 (d, J = 6.6 Hz, 3H).

[00253] Example 20. 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[5-fluoro-6-(1-methylsulfonyl-1,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1H-

indazole. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(5-fluoro-6-(1,6-diazaspiro[3.3]heptan-6-yl)pyridin-3-yl)-1H-indazole (310 mg, 0.62 mmol, 1 equiv) in a mixture of dichloromethane (5 mL), acetonitrile (5 mL) and 1M sodium bicarbonate (5 mL, 8 equiv) was treated with a solution of methanesulfonyl chloride (108 mg, 0.94 mmol, 1.5 equiv) in dichloromethane (1 mL) at 0 °C for 30 minutes, then at room temperature for an additional 90 minutes. The layers were separated, and the aqueous layer was extracted with dichloromethane (10 mL). The combined organic layers were concentrated under reduced pressure onto a mixture of Celite (5 g) and silica gel (5 g), then purified on a Biotage automated chromatography system (Yamazen 55 g, 40 um silica gel column), eluting with a gradient of 10 to 100% ethyl acetate in hexanes to give a white solid (282 mg, 79% yield). LCMS m/z = 499.3 (M+H); ¹HNMR (400 MHz, DMSO-*d*₆) δ = 13.12 (s, 1H), 8.57 (s, 2H), 8.36 (s, 1H), 7.70 (dd, *J* = 13.2 Hz, 2.0 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 7.09 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 6.13 (q, *J* = 6.4 Hz, 1H), 4.27 (d, *J* = 8.8 Hz, 2H), 4.17 (d, *J* = 9.2 Hz, 2H), 3.36 (t, *J* = 6.8 Hz, 2H), 2.53-2.51 (m, 2H), 1.75 (d, *J* = 6.4 Hz, 3H).



Example 21. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(5-(6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrazin-2-yl)-1H-indazole.

[00254] Step 1. 2-(5-Chloropyrazin-2-yl)-6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptane. 2-Methylsulfonyl-2,6-diazaspiro[3.3]heptane dimesylate salt (1.11 g, 3.0 mmol) in acetonitrile (12 mL) was treated with *N,N*-diisopropylethylamine (4 mL, 23 mmol, 7.6 equiv) and 2,5-dichloropyrazine (0.91 g, 6.1 mmol, 2 equiv) at room temperature. The mixture was then heated at 60 °C for 24 hours. The mixture was cooled to room temperature then slowly diluted with water (60 mL). The resulting suspension was stirred for 1 hour, the resulting solids were

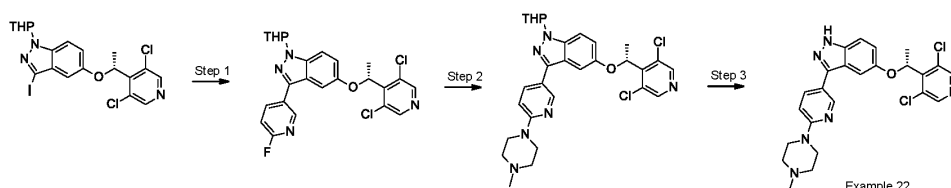
filtered, washed with water (12 mL) and dried under vacuum at 40 °C for 2 hours to give a light tan solid (695 mg, 80% yield). LCMS m/z = 289 (M+H).

[00255] Step 2. 2-(Methylsulfonyl)-6-(5-(tributylstannyl)pyrazin-2-yl)-2,6-diazaspiro [3.3]heptane. A mixture of 2-(5-chloropyrazin-2-yl)-6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptane (100 mg, 0.34 mmol, 1.08 equiv), bis(tributyltin) (245 mg, 0.42 mmol, 1.3 equiv) and tetrakis(triphenylphosphine)palladium(0) (39 mg, 0.034 mmol, 0.11 equiv) in N,N-dimethylacetamide (6 mL) was sparged with nitrogen for 10 minutes, then heated at 90 °C overnight. LSMS indicated complete conversion to product. The mixture was cooled to room temperature and the solution used directly in the next step. LCMS m/z = 543, 545 (M+H).

[00256] Step 3. 5-((R)-1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(5-(6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole. The reaction mixture from step 2 (~0.34 mmol, ~1.08 equiv) in N,N-dimethylacetamide (6 mL) was treated with 5-((R)-1-(3,5-dichloropyridin-4-yl)ethoxy)-3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (165 mg, 0.32 mmol, 1 equiv) and tetrakis(triphenylphosphine)palladium(0) (39 mg, 0.034 mmol, 0.11 equiv) then sparged with nitrogen for 10 minutes. The reaction was heated at 90 °C for four days then cooled to room temperature. The mixture was applied to a Celite filter column (20 g) and purified on a Biotage automated chromatography system (Redisep Gold C18, 100 g column), eluting with a gradient of 0 to 100% acetonitrile in water. Product fractions were concentrated under reduced pressure, azeotrope with acetonitrile (20 mL), then with toluene (20 mL) and reconcentrated from dichloromethane (10 mL) to give a yellow oil (135 mg, 65% yield) after drying under vacuum at 40 °C overnight. LCMS m/z = 644 (M+H).

[00257] Step 4. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(5-(6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrazin-2-yl)-1H-indazole. 5-((R)-1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(5-(6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (132 mg, 0.20 mmol) in dichloromethane (2 mL) was treated with trifluoroacetic acid (2 mL) at room temperature for 4 hours, then concentrated under reduced pressure.

The residue was dissolved in DMSO (4 mL), treated with 3M sodium hydroxide (1 mL, to pH 9), then purified on a Biotage automated chromatography system (Redisepp Gold C18, 100 g column), eluting with a gradient of 0 to 80% acetonitrile in water to give a light yellow solid (55 mg, 48% yield, 99.7% purity). LCMS m/z = 560 (M+H)⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.05 (br s, 1H), 8.72 (d, *J* = 1.5 Hz, 1H), 8.60 (s, 2H), 7.93 (d, *J* = 1.5 Hz, 1H), 7.67 (d, *J* = 2.3 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.08 (dd, *J* = 2.5, 9.0 Hz, 1H), 6.02 (q, *J* = 6.7 Hz, 1H), 4.33 - 4.25 (m, 4H), 4.13 (s, 4H), 3.03 (s, 3H), 1.76 (d, *J* = 6.6 Hz, 3H).



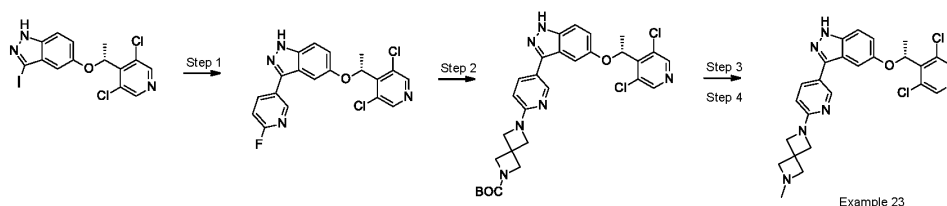
Example 22. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazole

[00258] Step 1. 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(6-fluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole. A solution of 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-iodo-1-tetrahydropyran-2-yl-indazole (3.0 g, 5.80 mmol, 1.0 equiv), 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (1.6 g, 6.96 mmol, 1.2 equiv), [1,1' bis(diphenylphosphino) ferrocene]dichloropalladium(II) (430 mg, 0.58 mmol, 0.1 equiv) and potassium carbonate (1.6 g, 11.66 mmol, 2.0 equiv) in 1,4-dioxane (30 mL) and water (3 mL) was sparged with nitrogen for 15 minutes and then heated at 100 °C for 16 hours. After cooling to room temperature, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified on a Büchi automated chromatography system (Sorbtech 40 g silica gel column), eluting with a gradient of 0 to 60% ethyl acetate in heptanes to give a white solid (2.5 g, 88% yield). LCMS m/z = 487.1 (M+H).

[00259] Step 2. 5-((R)-1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole. A mixture of 5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-(6-fluoro-3-pyridyl)-1-tetrahydropyran-2-yl-indazole (200 mg, 0.41 mmol, 1.0 equiv), 1-methylpiperazine

(411 mg, 4.1 mmol, 10 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.31 mL, 2.05 mmol, 5.0 equiv) in 1-methoxy-2-propanol (5 mL) was heated at 120 °C for 20 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate (20 mL) and washed with water (4 x 5 mL). The organic layer was concentrated under reduced pressure to give a yellow oil (200 mg, 86% yield) LCMS m/z = 567.2 (M+H). This material was used directly in the next step.

[00260] Step 3. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazole. 5-((R)-1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (200 mg, 0.35 mmol) in dichloromethane (2 mL) was treated with trifluoroacetic acid (2 mL) at room temperature for 3 hours. The reaction mixture was concentrated under reduced pressure, dissolved in dimethyl sulfoxide (4 mL) and basified with 3M sodium hydroxide (~1.5 mL) to pH ~10. The mixture was purified on a Biotage automated chromatography system (RediSep Rf GOLD 100 g HP C18 column), eluting with a gradient of 0 to 100% acetonitrile in water to give a white solid (78 mg, 46% yield). LCMS m/z = 483.1 (M+H)⁺; ¹H-NMR (400 MHz, DMSO-*d*₆) δ = 13.00 (br s, 1H), 8.60 (s, 2H), 8.54 (d, *J* = 2.1 Hz, 1H), 7.86 (dd, *J* = 2.4, 8.9 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 2.1 Hz, 1H), 7.09 (dd, *J* = 2.3, 9.0 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 6.10 (q, *J* = 6.6 Hz, 1H), 3.61 - 3.52 (m, 4H), 2.46 - 2.40 (m, 4H), 2.24 (s, 3H), 1.76 (d, *J* = 6.7 Hz, 3H).



Example 23. 3-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole.

[00261] Step 1. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(6-fluoropyridin-3-yl)-1H-indazole. A solution of product step 1 (1.0 g, 2.3 mmol, 1 equiv) and 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.67 g, 2.995 mmol, 1.3 equiv) in 20 to 1 mixture of 1,4-dioxane and water (21 mL) was

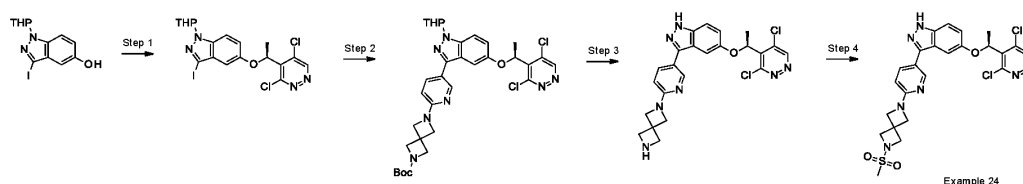
sparged with nitrogen for 15 minutes. Potassium carbonate (0.825 g, 5.98 mmol, 2.6 equiv) and (1,1'-bis(diphenylphosphino) ferrocene)palladium(II) dichloride (168 mg, 0.23 mmol, 0.01 equiv) were added and the reaction mixture was sparged with nitrogen for an additional 5 minutes. The reaction was heated at 90 °C for 2 hours. After cooling to room temperature, the reaction was concentrated under reduced pressure and diluted with saturated brine (30 mL) and dichloromethane (30 mL). The layers were separated and the organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was absorbed onto silica gel (2 g) and purified on an Interchim automated chromatography system (Sorbtech 40 g silica gel cartridge), eluting with a gradient of 20 to 80% ethyl acetate in heptanes to give a yellow solid (0.42 g, 45% yield). LCMS m/z = 403.1 (M+H); ^1H NMR (400 MHz, CDCl_3) δ 10.55 (br s, 1H), 8.68 (d, J = 2.1 Hz, 1H), 8.43 (s, 2H), 8.24 (dt, J = 2.4, 8.1 Hz, 1H), 7.39 (dd, J = 0.8, 8.7 Hz, 1H), 7.20 - 7.14 (m, 2H), 7.06 (dd, J = 2.8, 8.4 Hz, 1H), 6.06 (q, J = 6.7 Hz, 1H), 1.82 (d, J = 6.6 Hz, 3H).

[00262] Step 2. tert-Butyl (R)-6-(5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)pyridin-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate. A mixture of (R)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-3-(6-fluoropyridin-3-yl)-1H-indazole (0.295 g, 0.732 mmol, 1 equiv), tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (0.29 g, 1.464 mmol, 2 equiv), and potassium carbonate (0.4 g, 2.93 mmol, 4 equiv) in anhydrous N-methylpyrrolidone was heated at 120 °C for 16 hours. The reaction mixture was filtered through a syringe filter and the filtrate was pre-absorbed on Celite (5 g). The material was purified on an Interchim automated chromatography system (RediSep Rf Gold HP C18, 15.5 g cartridge), eluting with a gradient of 0 to 100% acetonitrile in water. The fractions containing product were collected and lyophilized to give a yellowish solid (0.3 g, 71% yield). LCMS m/z = 581 (M+H).

[00263] Step 3. 3-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole. A solution of tert-butyl (R)-6-(5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)pyridin-2-yl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (50 mg, 0.086 mmol, 1 equiv) in anhydrous dichloromethane (2 mL) was treated with trifluoroacetic acid (0.53 mL, 6.88 mmol, 80

equiv) at room temperature for 16 hours. Additional trifluoroacetic acid (0.23 mL, 3.01 mmol, 35 equiv) was added and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure to dryness. The residue was dissolved in methanol (10 mL), treated with MP-carbonate resin (3.2 mmol/g, 1 g), stirred for 30 minutes, filtered, and concentrated under reduced pressure. The residue was absorbed onto Celite (1 g) and purified on an Interchim automated chromatography system (RediSep Rf Gold HP C18, 15.5 g cartridge), eluting with a gradient of 0 to 100% acetonitrile in water. The fractions containing product were collected and lyophilized to give a white solid (30 mg, 73% yield). LCMS m/z = 481.1 (M+H); ^1H NMR (400 MHz, DMSO- d_6) δ 13.00 (br s, 1H), 8.59 (s, 2H), 8.50 (d, J = 1.8 Hz, 1H), 7.84 (dd, J = 2.3, 8.7 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 7.08 (dd, J = 2.3, 9.0 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.10 (q, J = 6.6 Hz, 1H), 4.20 - 3.82 (m, 5H), 3.66 (br s, 4H), 1.76 (d, J = 6.6 Hz, 3H).

[00264] Step 4. (R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(6-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)pyridin-3-yl)-1H-indazole. 3-[6-(2,6-Diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole (200 mg, 0.416 mmol, 1 equiv) in trifluoroacetic acid (2 mL) was treated with paraformaldehyde (37 mg, 1.24 mmol, 3 equiv) and sodium borohydride (79 mg, 2.08 mmol, 5 equiv) at room temperature for 16 hours. The reaction was concentrated under reduced pressure. The residue was diluted with dimethyl sulfoxide (1 mL) and 2M sodium hydroxide (1 mL) and purified directly on a Biotage automated chromatography system (RediSep Rf GOLD 100 g HP C18 column), eluting with a gradient of 0 to 100% acetonitrile in water to give ADE-1032 (17 mg, 6% yield, 95.4% purity) as a white solid. LCMS m/z = 995.3, 997.3 (M+H); ^1H -NMR (400 MHz, DMSO- d_6) δ = 8.58 (s, 3H), 8.48 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 2.3, 8.6 Hz, 1H), 7.57 (d, J = 9.5 Hz, 1H), 7.19 - 7.12 (m, 2H), 6.56 (d, J = 8.6 Hz, 1H), 6.12 (q, J = 6.6 Hz, 1H), 4.20 (d, J = 5.1 Hz, 8H), 3.99 (s, 3H), 1.76 (d, J = 6.6 Hz, 3H).



Example 24

Example 24. 5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-3-[6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1H-indazole.

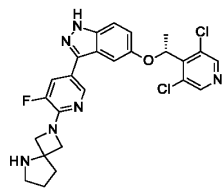
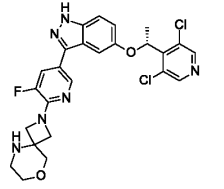
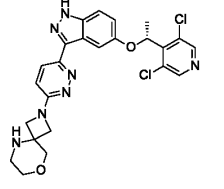
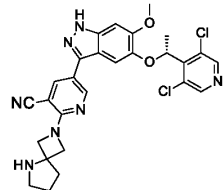
[00265] Step 1. 5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-3-iodo-1-tetrahydropyran-2-yl-indazole. A mixture of 3-iodo-1-tetrahydropyran-2-yl-indazol-5-ol (1.1 equiv), [(1R)-1-(3,5-dichloropyridazin-4-yl)ethyl] methanesulfonate (1 equiv) and cesium carbonate (2 equiv) in acetonitrile (20 mL) was heated at 80 °C overnight. The reaction was cooled to room temperature and was diluted with ethyl acetate (100 mL) and saturated brine solution (100 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was absorbed onto Celite (30 g) and was purified on an Interchim automated chromatography system (Sorbtech, 80 g silica gel column), eluting with a gradient of 0 to 100% ethyl acetate in heptanes to give a white solid. LCMS m/z = 519 (M+H).

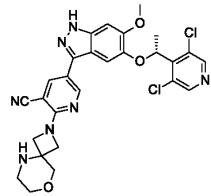
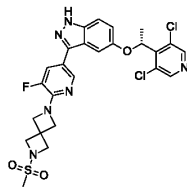
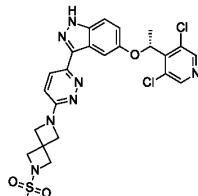
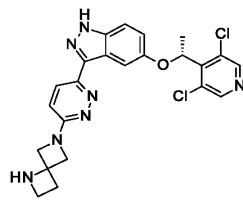
[00266] Step 2. tert-butyl 6-[5-[5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]-2-pyridyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate. To a solution of 5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-3-iodo-1-tetrahydropyran-2-yl-indazole (160 mg, 0.308 mmol, 1.0 eq) and [6-(2-tert-butoxycarbonyl-2,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]boronic acid (128 mg, 0.401 mmol, 1.3 eq) in dioxane (3 mL) and H₂O (0.3 mL) was added K₂CO₃ (128 mg, 0.925 mmol, 3.0 eq), Pd(dppf)Cl₂ (25.6 mg, 0.0308 mmol, 0.1 eq) at rt. The resulting mixture was stirred at 85 °C for 6 h under nitrogen. After the reaction was completed, the reaction mixture was concentrated in vacuum. The residue was purified by silica gel column (Petroleum ether/Ethyl acetate = 1/1) to give a white solid (120 mg, 58% yield). LCMS m/z = 666 (M+1).

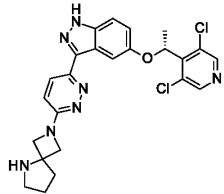
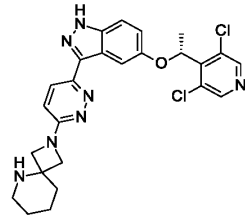
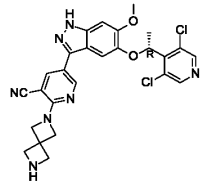
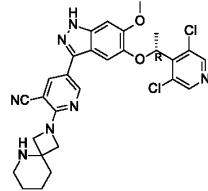
[00267] Step 3. 3-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-1H-indazole. To a solution of tert-butyl 6-[5-[5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-1-tetrahydropyran-2-yl-indazol-3-yl]-2-pyridyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate (120 mg, 0.18 mmol, 1.0 eq) in DCM (5 mL) was added TFA (2 mL) at rt. The resulting mixture was stirred at rt for 3 h. After the reaction was completed, the reaction mixture was concentrated in vacuum to give a yellow solid (110 mg). LCMS $m/z = (M+1)$.

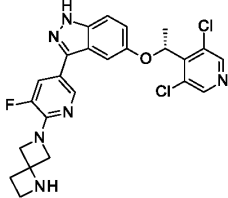
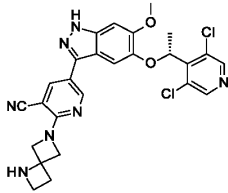
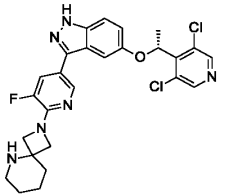
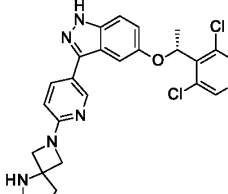
[00268] Step 4. 5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-3-[6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1H-indazole. To a solution of 3-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-1H-indazole (110 mg, 0.184 mmol, 1.0 eq), TEA (93.3 mg, 0.922 mmol, 5.0 eq) in DCM (5 mL) was added MsCl (33.8 mg, 0.295 mmol, 1.6 eq) at 0 °C. The resulting mixture was stirred at rt for 2 h. After the reaction was completed, the reaction mixture was quenched with H₂O (30 mL) and extracted with DCM (30 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by Prep-TLC (DCM/MeOH = 20/1) and further purified by Pre-HPLC (Prep-C18, 5 μ M Triart column, 20 $\times$ 150 mm, YMC-Actus; gradient elution of 45% MeCN in water to 60% MeCN in water over a 8 min period, where both solvents contain 0.05% NH₃.H₂O) to give an off-white solid (46 mg, 45% yield). LCMS: $m/z = 560.2 (M+H)$; ¹H NMR (400 MHz, DMSO-d₆) δ 13.03 (s, 1H), 9.36 (s, 1H), 8.55 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 7.11 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.55 (d, J = 9.2 Hz, 1H), 6.13 (q, J = 6.8 Hz, 1H), 4.18 (s, 4H), 4.12 (s, 4H), 3.03 (s, 3H), 1.78 (d, J = 6.4 Hz, 3H).

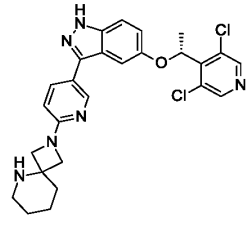
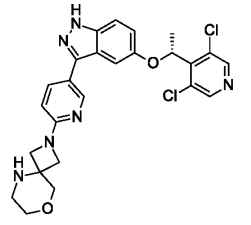
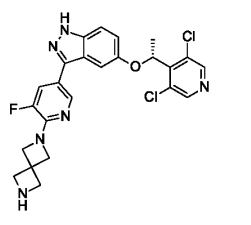
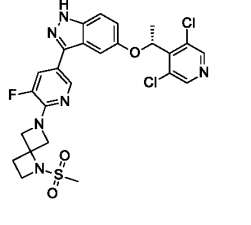
[00269] Other exemplified compounds may be made by analogous procedures. The table below provides characterization data for the exemplified compounds.

Ex.	Structure	Chemical Name	Characterization Data
1.		3-[6-(2,5-diazaspiro[3.4]octan-2-yl)-5-fluoro-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole	LCMS m/z = 513.1 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ 13.13 (br s, 1H), 8.57 (s, 2H), 8.36 (s, 1H), 7.69 (br d, J = 13.2 Hz, 1H), 7.50 - 7.45 (m, J = 8.8 Hz, 1H), 7.19 (s, 1H), 7.14 - 7.05 (m, J = 8.9 Hz, 1H), 6.14 (br d, J = 6.5 Hz, 1H), 4.10 - 3.98 (m, 4H), 2.96 (br s, 1H), 2.84 (br t, J = 6.4 Hz, 2H), 1.98 (br t, J = 7.1 Hz, 2H), 1.78 - 1.69 (m, 5H)
2.		(R)-2-(5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)-3-fluoropyridin-2-yl)-8-oxa-2,5-diazaspiro[3.5]nonane	LCMS m/z = 529.2 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ 13.12 (s, 1H), 8.57 (s, 2H), 8.38 (t, J = 1.2 Hz, 1H), 7.71 (dd, J = 13.2 Hz, 1.6 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 6.13 (q, J = 6.8 Hz, 1H), 4.00 (d, J = 7.2 Hz, 2H), 3.89 (d, J = 8.0 Hz, 2H), 3.69 (s, 2H), 3.55 (t, J = 4.0 Hz, 2H), 2.73 (t, J = 4.4 Hz, 2H), 1.76 (d, J = 6.8 Hz, 3H)
3.		(R)-2-(6-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)pyridazin-3-yl)-8-oxa-2,5-diazaspiro[3.5]nonane	LCMS m/z = 512.2 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ 13.19 (s, 1H), 8.56 (s, 2H), 7.98 (d, J = 9.2 Hz, 1H), 7.95 (d, J = 1.6 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.09 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 6.93 (d, J = 9.6 Hz, 1H), 6.08 (q, J = 6.4 Hz, 1H), 4.01 (d, J = 8.4 Hz, 2H), 3.84 (d, J = 8.4 Hz, 2H), 3.70 (s, 2H), 3.57 (t, J = 4.4 Hz, 2H), 2.76 (t, J = 4.0 Hz, 2H), 1.77 (d, J = 6.4 Hz, 3H)
4.		2-(2,5-diazaspiro[3.4]octan-2-yl)-5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1H-indazol-3-	LCMS m/z = 550.1 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ 12.96 (br s, 1H), 8.71 (d, J = 2.3 Hz, 1H), 8.58 (s, 2H), 8.06 (d, J = 2.3 Hz, 1H), 7.04 (s, 1H), 7.00 (s, 1H), 5.99 (q, J = 6.7 Hz, 1H), 4.26 (d, J = 8.8 Hz, 2H), 4.17 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 2.86

Ex.	Structure	Chemical Name	Characterization Data
		yl]pyridine-3-carbonitrile	(t, J = 6.9 Hz, 2H), 2.01 - 1.94 (m, 2H), 1.78 - 1.68 (m, 5H)
5.		(R)-5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazol-3-yl)-2-(8-oxa-2,5-diazaspiro[3.5]nonan-2-yl)nicotinonitrile	LCMS m/z = 566.2 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ 12.96 (brs, 1H), 8.73 (d, J = 2.0 Hz, 1H), 8.59 (s, 2H), 8.08 (d, J = 2.0 Hz, 1H), 7.03-7.01 (m, 2H), 6.02 (q, J = 6.4 Hz, 1H), 4.17 (d, J = 8.8 Hz, 2H), 4.03 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.67 (s, 2H), 3.56-3.54 (m, 2H), 3.10 (s, 1H), 2.7-2.73 (m, 2H), 1.77 (d, J = 6.4 Hz, 3H)
6.		5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[5-fluoro-6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1H-indazole	LCMS m/z = 577.1 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 13.12 (br s, 1H), 8.57 (s, 2H), 8.38 (s, 1H), 7.72 (dd, J = 1.7, 13.1 Hz, 1H), 7.47 (d, J = 8.9 Hz, 1H), 7.24 - 7.15 (m, 1H), 7.10 (dd, J = 2.2, 8.9 Hz, 1H), 6.14 (q, J = 6.6 Hz, 1H), 4.31 (d, J = 1.5 Hz, 4H), 4.12 (s, 4H), 3.02 (s, 3H), 1.76 (d, J = 6.6 Hz, 3H)
7.		5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)pyridazin-3-yl]-1H-indazole	LCMS m/z = 560 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ 1H NMR (400 MHz, METHANOL-d ₄) δ = 8.43 (s, 2H), 8.05 (d, J = 9.3 Hz, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 7.15 (dd, J = 2.3, 9.0 Hz, 1H), 6.93 (d, J = 9.3 Hz, 1H), 6.21 (q, J = 6.7 Hz, 1H), 4.36 (s, 4H), 4.19 (s, 4H), 2.98 (s, 3H), 1.82 (d, J = 6.7 Hz, 3H)
8.		(R)-3-(6-(1,6-diazaspiro[3.3]heptan-6-yl)pyridazin-3-yl)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole	LCMS m/z = 482.2 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 13.27 (s, 1H), 9.49 (brs, 1H), 8.56 (s, 2H), 8.06 (d, J = 9.2 Hz, 1H), 7.92 (d, J = 1.6 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.11 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.06 (d, J = 9.6 Hz, 1H), 6.08 (q, J = 6.8 Hz, 1H), 4.66 (d, J = 10.8 Hz, 2H), 4.42 (d, J = 10.4 Hz, 2H), 3.90-3.83 (m, 2H), 2.78 (t, J = 8.0 Hz, 2H), 1.78 (d, J = 6.4 Hz, 3H)

Ex.	Structure	Chemical Name	Characterization Data
9.		(R)-3-(6-(2,5-diazaspiro[3.4]octan-2-yl)pyridazin-3-yl)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole	LCMS m/z = 496.2 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 13.17 (brs, 1H), 8.56 (s, 2H), 7.96 (d, J = 9.2 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.09 (dd, J = 9.2 Hz, 2.8 Hz, 1H), 6.88 (d, J = 9.6 Hz, 1H), 6.08 (q, J = 6.8 Hz, 1H), 4.08 (d, J = 8.0 Hz, 2H), 3.99 (d, J = 8.4 Hz, 2H), 2.88 (t, J = 6.8 Hz, 2H), 2.01 (t, J = 7.2 Hz, 2H), 1.81-1.71 (m, 5H)
10.		(R)-3-(6-(2,5-diazaspiro[3.5]nonan-2-yl)pyridazin-3-yl)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazole	LCMS m/z = 510.2 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 13.18 (s, 1H), 8.56 (s, 2H), 7.97 (d, J = 9.2 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.09 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.90 (d, J = 9.2 Hz, 1H), 6.08 (q, J = 6.4 Hz, 1H), 3.97 (d, J = 8.4 Hz, 2H), 3.89 (d, J = 8.4 Hz, 2H), 2.76 (t, J = 4.8 Hz, 2H), 1.81-1.78 (m, 2H), 1.77 (d, J = 6.4 Hz, 3H), 1.61-1.54 (m, 2H), 1.49-1.41 (m, 2H)
11.		2-(2,6-diazaspiro[3.3]heptan-2-yl)-5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)-ethoxy]-6-methoxy-1H-indazol-3-yl]pyridine-3-carbonitrile	LCMS m/z = 536 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 12.97 (br s, 1H), 8.71 (d, J = 2.3 Hz, 1H), 8.58 (s, 2H), 8.06 (d, J = 2.3 Hz, 1H), 7.03 (s, 1H), 7.00 (s, 1H), 5.99 (q, J = 6.7 Hz, 1H), 4.38 (s, 4H), 3.86 (s, 3H), 3.65 (s, 4H), 1.76 (d, J = 6.7 Hz, 3H)
12.		2-(2,5-diazaspiro[3.5]nonan-2-yl)-5-[5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-6-methoxy-1H-indazol-3-yl]pyridine-3-carbonitrile	LCMS m/z = 564 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 12.95 (br s, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.59 (s, 2H), 8.06 (d, J = 2.3 Hz, 1H), 7.03 (s, 1H), 7.00 (s, 1H), 5.99 (q, J = 6.7 Hz, 1H), 4.11 (d, J = 8.6 Hz, 2H), 4.02 (d, J = 8.7 Hz, 2H), 3.86 (s, 3H), 2.72 - 2.66 (m, 2H), 1.76 (d, J = 6.7 Hz, 3H), 1.74 - 1.67 (m, 2H), 1.55 (br s, 2H), 1.41 (br s, 2H)

Ex.	Structure	Chemical Name	Characterization Data
13.		(R)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-3-(5-fluoro-6-(1,6-diazaspiro[3.3]heptan-6-yl)pyridin-3-yl)-1H-indazole	LCMS m/z = 499.3 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 13.12 (s, 1H), 8.57 (s, 2H), 8.36 (s, 1H), 7.70 (dd, J = 13.2 Hz, 2.0 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.09 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 6.13 (q, J = 6.4 Hz, 1H), 4.27 (d, J = 8.8 Hz, 2H), 4.17 (d, J = 9.2 Hz, 2H), 3.36 (t, J = 6.8 Hz, 2H), 2.53-2.51 (m, 2H), 1.75 (d, J = 6.4 Hz, 3H)
14.		(R)-5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-6-methoxy-1H-indazol-3-yl)-2-(1,6-diazaspiro[3.3]heptan-6-yl)nicotinonitrile	LCMS m/z = 536.2 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 12.99 (br s, 1H), 8.74 (d, J = 2.3 Hz, 1H), 8.58 (s, 2H), 8.11 (d, J = 2.2 Hz, 1H), 7.04 (s, 1H), 7.01 (s, 1H), 5.99 (q, J = 6.7 Hz, 1H), 5.75 (s, 1H), 4.58 - 4.47 (m, 4H), 3.86 (s, 3H), 3.59 (br t, J = 7.7 Hz, 3H), 3.38 - 3.37 (m, 1H), 2.64 (t, J = 7.6 Hz, 2H), 2.55 - 2.53 (m, 1H), 1.76 (d, J = 6.7 Hz, 3H)
15.		(R)-5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-3-(5-fluoro-6-(2,5-diazaspiro[3.5]nonan-2-yl)pyridin-3-yl)-1H-indazole	LCMS m/z = 527.3 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 13.12 (s, 1H), 8.57 (s, 2H), 8.37 (t, J = 2.0 Hz, 1H), 7.69 (dd, J = 13.2 Hz, 1.6 Hz, 1H), 7.47 (d, J = 9.2 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.14 (q, J = 6.4 Hz, 1H), 3.99-3.91 (m, 4H), 2.72 (t, J = 5.2 Hz, 2H), 1.76-1.74 (m, 5H), 1.61-1.54 (m, 2H), 1.47-1.39 (m, 2H)
16.		3-[6-(2,5-diazaspiro[3.4]octan-2-yl)-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole	LCMS m/z = 495.4 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 13.08 (br s, 1H), 9.41 (br s, 2H), 8.59 (s, 2H), 8.55 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 2.3, 8.6 Hz, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.11 (dd, J = 2.2, 8.9 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 6.11 (q, J = 6.6 Hz, 1H), 4.34 (br d, J = 9.3 Hz, 4H), 4.18 (s, 2H), 4.15 (s, 1H), 4.05 (br s, 5H), 2.25 (t, J = 7.3 Hz, 2H), 1.98 (quin, J = 7.4 Hz, 2H), 1.76 (d, J = 6.6 Hz, 3H)

Ex.	Structure	Chemical Name	Characterization Data
17.		3-[6-(2,5-diazaspiro[3.5]nonan-2-yl)-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole	LCMS m/z = 509.4 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 12.96 (br s, 1H), 8.59 (s, 2H), 8.50 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 2.3, 8.6 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.18 - 7.14 (m, 1H), 7.09 (dd, J = 2.3, 9.0 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 6.11 (q, J = 6.7 Hz, 1H), 3.83 (d, J = 7.9 Hz, 2H), 3.71 (d, J = 7.9 Hz, 2H), 2.71 - 2.66 (m, 2H), 2.63 (br s, 1H), 1.76 (d, J = 6.6 Hz, 3H), 1.72 - 1.67 (m, 2H), 1.59 - 1.52 (m, 2H), 1.46 - 1.37 (m, 2H)
18.		(R)-2-(5-(5-(1-(3,5-dichloropyridin-4-yl)ethoxy)-1H-indazol-3-yl)pyridin-2-yl)-8-oxa-2,5-diazaspiro[3.5]nonane	LCMS m/z = 511.1 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ 12.98 (s, 1H), 8.60 (s, 2H), 8.51 (d, J = 2.0 Hz, 1H), 7.84 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.16 (s, 1H), 7.09 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.56 (d, J = 8.8 Hz, 1H), 6.11 (q, J = 6.8 Hz, 1H), 3.90 (d, J = 8.0 Hz, 2H), 3.72 (d, J = 8.0 Hz, 2H), 3.67 (s, 2H), 3.56 (t, J = 4.4 Hz, 2H), 2.74 (t, J = 4.4 Hz, 2H), 1.76 (d, J = 6.4 Hz, 3H)
19.		3-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-5-fluoro-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole	LCMS m/z = 499.1 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ = 13.10 (br s, 1H), 8.57 (s, 2H), 8.38 - 8.35 (m, 1H), 7.69 (dd, J = 1.6, 13.2 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.10 (dd, J = 2.2, 9.0 Hz, 1H), 6.13 (q, J = 6.6 Hz, 1H), 4.22 (br s, 4H), 4.01 (br s, 1H), 3.78 - 3.57 (m, 4H), 1.76 (d, J = 6.6 Hz, 3H)
20.		5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-3-[5-fluoro-6-(1-methylsulfonyl-1,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1H-indazole	LCMS m/z = 577 (M+H); 1HNMR (400 MHz, DMSO-d ₆) δ 13.13 (s, 1H), 8.57 (s, 2H), 8.39 (s, 1H), 7.78 - 7.71 (m, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 2.2, 9.0 Hz, 1H), 6.15 (q, J = 6.5 Hz, 1H), 4.57 (d, J = 9.0 Hz, 2H), 4.32 (br d, J = 8.6 Hz, 2H), 3.86 (t, J = 7.4 Hz, 2H), 3.07 (s, 3H), 2.66 (t, J =

Ex.	Structure	Chemical Name	Characterization Data
			7.4 Hz, 2H), 1.76 (d, J = 6.6 Hz, 3H)
21.		(R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(5-(6-(methylsulfonyl)-2,6-diazaspiro[3.3]heptan-2-yl)pyrazin-2-yl)-1H-indazole	LCMS m/z = 560 (M+H) ⁺ ; ¹ H NMR (400 MHz, DMSO-d ₆) δ = 13.05 (br s, 1H), 8.72 (d, J = 1.5 Hz, 1H), 8.60 (s, 2H), 7.93 (d, J = 1.5 Hz, 1H), 7.67 (d, J = 2.3 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.08 (dd, J = 2.5, 9.0 Hz, 1H), 6.02 (q, J = 6.7 Hz, 1H), 4.33 - 4.25 (m, 4H), 4.13 (s, 4H), 3.03 (s, 3H), 1.76 (d, J = 6.6 Hz, 3H)
22.		(R)-5-(1-(3,5-Dichloropyridin-4-yl)ethoxy)-3-(6-(4-methylpiperazin-1-yl)pyridin-3-yl)-1H-indazole	LCMS m/z = 483.1 (M+H) ⁺ ; ¹ H-NMR (400 MHz, DMSO-d ₆) δ = 13.00 (br s, 1H), 8.60 (s, 2H), 8.54 (d, J = 2.1 Hz, 1H), 7.86 (dd, J = 2.4, 8.9 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 7.16 (d, J = 2.1 Hz, 1H), 7.09 (dd, J = 2.3, 9.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 6.10 (q, J = 6.6 Hz, 1H), 3.61 - 3.52 (m, 4H), 2.46 - 2.40 (m, 4H), 2.24 (s, 3H), 1.76 (d, J = 6.7 Hz, 3H)
23.		3-[6-(2,6-diazaspiro[3.3]heptan-2-yl)-3-pyridyl]-5-[(1R)-1-(3,5-dichloro-4-pyridyl)ethoxy]-1H-indazole	LCMS m/z = 995.3, 997.3 (M+H); ¹ H-NMR (400 MHz, DMSO-d ₆) δ = 8.58 (s, 3H), 8.48 (d, J = 2.1 Hz, 1H), 7.84 (dd, J = 2.3, 8.6 Hz, 1H), 7.57 (d, J = 9.5 Hz, 1H), 7.19 - 7.12 (m, 2H), 6.56 (d, J = 8.6 Hz, 1H), 6.12 (q, J = 6.6 Hz, 1H), 4.20 (d, J = 5.1 Hz, 8H), 3.99 (s, 3H), 1.76 (d, J = 6.6 Hz, 3H)
24.		5-[(1S)-1-(3,5-dichloropyridazin-4-yl)ethoxy]-3-[6-(2-methylsulfonyl-2,6-diazaspiro[3.3]heptan-6-yl)-3-pyridyl]-1H-indazole	LCMS: m/z = 560.2 (M+H); ¹ H NMR (400 MHz, DMSO-d ₆) δ 13.03 (s, 1H), 9.36 (s, 1H), 8.55 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 1.6 Hz, 1H), 7.11 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.55 (d, J = 9.2 Hz, 1H), 6.13 (q, J = 6.8 Hz, 1H), 4.18 (s, 4H), 4.12 (s, 4H), 3.03 (s, 3H), 1.78 (d, J = 6.4 Hz, 3H).

Kinase Assays

[00270] Kinase-tagged T7 phage strains were prepared in an E. coli host derived from the BL21 strain. E. coli were grown to log-phase and infected with T7 phage and incubated with shaking at 32°C until lysis. The lysates were centrifuged and filtered to remove cell debris. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock, 0.17x PBS, 0.05% Tween 20, 6 mM DTT).

[00271] Test compounds were prepared as 111X stocks in 100% DMSO. Kds were determined using an 11-point 3-fold compound dilution series with three DMSO control points. All compounds for Kd measurements are distributed by acoustic transfer (non-contact dispensing) in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.9%. All reactions performed in polypropylene 384-well plate. Each was a final volume of 0.02 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

[00272] Binding constants (Kds)

[00273] Binding constants were calculated with a standard dose-response curve using the Hill equation:

$$Response = Background + \frac{Signal - Background}{1 + \left(\frac{Kd^{Hill\ Slope}}{Dose^{Hill\ Slope}}\right)}$$

[00274] The Hill Slope was set to -1. Curves were fitted using a non-linear least square fit with the Levenberg-Marquardt algorithm.

Table 1. Kinase Assays

A= 1-50 nM
B= >50 to 300 nM
C= >300 to 1000 nM
D= >1000 nM

Example	FGFR1 (K _d nM)	FGFR2 (K _d nM)	FGFR3 (K _d nM)	FGFR4 (K _d nM)
1.	A	A	A	A
2.	A		A	
3.	A		A	
4.	A	A	A	A
5.	A	A	A	A
6.	A		A	
7.	A		A	
8.	A		A	
9.	A		A	
10.	A		A	
11.	A	A	A	A
12.	A	A	A	A
13.	A		A	
14.	A	A	A	A
15.	A		A	
16.	A		A	
17.	A		A	
18.	A		A	
19.	A		A	
20.	A	A	A	A
21.	A	A	A	A
22.	A	A	A	A
23.				
24.	C	B	A	C

Cell Viability Assays

1. Ba/F3 Cell Viability Assay

Cell line	Mutation or Fusion	Source
Ba/F3 BCR-FGFR1	FGFR1-fusion	Advanced Cellular Dynamics, (Seattle, WA)
Ba/F3 BCR-FGFR2	FGFR2-fusion	Advanced Cellular Dynamics, (Seattle, WA)
Ba/F3 FGFR3-BAIAP2L1	FGFR3-fusion	Advanced Cellular Dynamics, (Seattle, WA)
Ba/F3 ETV5-FGFR4	FGFR4-fusion	Kyinno (Waltham, MA)

[00275] Experimental Purpose: Recombinant kinase fusions are transduced into parental Ba/F3, which becomes dependent upon this constitutive kinase activity for IL3-independent survival. Inhibition of kinase activity leads to cell death, which is monitored using CellTiter-Glo® 2.0 (Promega) which measures intracellular ATP concentration that in turn serves as a marker for viability. BCR-FGFR1 Ba/F3, BCR-FGFR2 and FGFR3-BAIAP2L1 Ba/F3 were obtained from Advanced Cellular Dynamics (Seattle, WA). ETV6-FGFR4 was obtained from Kyinno (Waltham, MA).

[00276] Cell Viability Assay Procedure: Cell Titer-Glo® 2.0 Luminescent cell viability assay reagent was purchased from Promega (Madison, WI). Ba/F3 cell lines were cultured in RPMI1640 media supplemented with 10% fetal bovine serum. Cultures were maintained at 37°C in a humidified atmosphere of 5% CO₂ and 95% air.

[00277] Cells were plated in 96-well clear bottom/white plates (Corning #3903) at 10,000 cells/well in 100µl of media, incubated overnight. The next day, test compound DMSO stock solutions were made at 10 mM and 2 µM final concentration. Compounds were then added to cells in a 9-dose, 10-fold dilution series starting at 30 µM with an HP 300e Digital Dispenser (each dose was applied in triplicate). DMSO was backfilled to each well up to 301 nL total volume of test compound + DMSO, and a total of 301 nL DMSO was added to a control/no test compound well in triplicate. The cells in cell culture plates were incubated with the compounds at 37 °C and 5% CO₂ for 48 hours. Then 50 µl of Cell Titer Glo 2.0 reagent was added to each well of the cell culture plates. The contents were covered from light and mixed on an orbital

shaker at room temperature for 10 min. Luminescence was recorded by a Synergy H1 Microplate Reader (Biotek, Winooski, VT). Cells were assessed as a percentage of DMSO only treated control cells. Curves were plotted and IC₅₀ values were calculated using the GraphPad Prism 8 program based on a sigmoidal dose-response equation (4 parameter).

Table 2. Ba/F3 Cell data

A = 0.1 – 50 nM
 B = >50 – 200nM
 C = >200 – 1000 nM
 D = > 1000 nM

Example	FGFR1	FGFR2	FGFR3	FGFR4
1.	B	B	A	B
2.	B	B	A	A
3.	C	C	A	C
4.	B	B	A	A
5.	B	B	A	A
6.	B	B	A	B
7.	B	C	A	C
8.	C	C	A	C
9.	B	C	A	C
10.	B	C	A	C
11.				
12.				
13.	A	B	A	A
14.	C	B	B	A
15.	B	B	A	B
16.	B	B	A	B
17.	C	B	A	B
18.	B	B	A	A
19.				
20.	C	B	A	A
21.	B	B	A	A

2. Cancer Cell Line Cell Viability Assays

Cell line	Mutation or Fusion	Source
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KG-1	FGFR1-fusion	American Type Culture Collection (Manassas, VA)
KATO-III	FGFR2 amplification	American Type Culture Collection (Manassas, VA)
RT112/84	FGFR3-fusion	Millipore Sigma (St. Louis, MO)
HuH7	FGF19 amplification	Sekisui Xenotech (Kansas City, KS)
MDA-MB-453	FGFR4-Y367C	American Type Culture Collection (Manassas, VA)

[00278] Experimental Purpose: To detect the change of intracellular ATP by Cell Titer-Glo® and to evaluate the inhibitory effect of the compounds on cancer cell lines by determining the in vitro IC₅₀ value of the compounds.

[00279] Cell Titer-Glo® 2.0 Luminescent cell viability assay reagent was purchased from Promega (Madison, WI). KG-1, KATO-III, and MDA-MB-453 cell lines were purchased from American Type Culture Collection (Manassas, VA). RT112/84 cell line was purchased from Millipore-Sigma (St. Louis, MO). HuH7 cells were purchased from Seikisui Xenotech (Kansas City, KS). RT112/84 and MDA-MB-453 cells were cultured in RPMI1640 media supplemented with 10% fetal bovine serum. KG-1 and KATO-III cell lines were cultured in IMDM media supplemented with 20% FBS. HuH7 cells were cultured in IMDM media supplemented with 10% FBS. Cultures were maintained at 37°C in a humidified atmosphere of 5% CO₂ and 95% air.

[00280] Cell Viability Assay Procedure: Cells were plated in 96-well clear bottom/white plates (Corning #3903) at a range of densities depending on the optimal assay window (5,000-20,000 cells/well in 100µl of media), incubated overnight. The next day, test compound DMSO stock solutions were made at 10 mM and 2 µM final concentration. Compounds were then added to cells in a 9-dose, 4-fold dilution series starting at 3 µM with an HP 300e Digital Dispenser (each dose was applied in triplicate). DMSO was backfilled to each well up to 301 nL total volume of test compound + DMSO, and a total of 301 nL DMSO was added to a control/no test compound well in triplicate. The cells in cell culture plates were incubated with the

compounds at 37 °C and 5% CO₂ for 72 hours-120 hours depending on the cell line. Then 50 µl of Cell Titer Glo 2.0 reagent was added to each well of the cell culture plates. The contents were covered from light and mixed on an orbital shaker at room temperature for minimum of 10 min. Luminescence was recorded by a Clariostar Plus Microplate Reader (BMG Labtech, Cary, NC). Cells were assessed as a percentage of DMSO only treated control cells. Curves were plotted and IC₅₀ values were calculated using the GraphPad Prism 9 program based on a sigmoidal dose-response equation (log (inhibitor) vs. response – Variable slope, 4-parameter).

Cell Viability Assay Protocol Details							
Cell Line	Phenotype	Vendor	Format	Duration	Complete Media	Cell #/well	Passage #
KG1	suspension	ATCC	96-Well	72hr	IMDM (+20% FBS)	20,000	5 to 25
			384-Well			5,000	
Kato III	adherent	ATCC	96-Well	72hr	IMDM (+20% FBS)	5,000	5 to 30
RT112/84	adherent	Millipore-Sigma	96-Well	72hr	RPMI1640 (+10% FBS)	10,000	15 to 45
			384-Well			5,000	
MDA-MB-453	adherent	ATCC	96-Well	120hr	RPMI1640 (+10% FBS)	5,000	10 to 45
			384-Well			2,500	
HuH7	adherent	Sekisui Xenotech	96-Well	120hr	IMDM (+10% FBS)	2,500	5 to 30

Table 3. Cancer Cell Data

A = 0.1 – 50 nM
 B = >50 – 200nM
 C = >200 – 1000 nM
 D = > 1000 nM

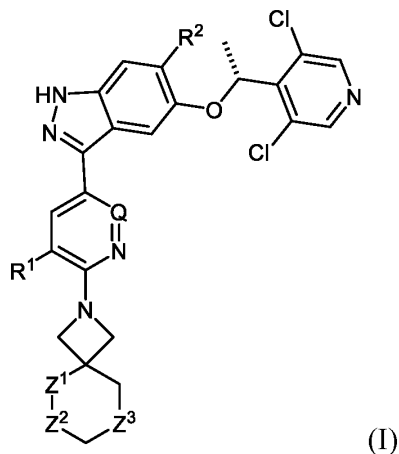
Example	KG-1 IC50 nM	KatoIII IC50 nM	RT112/84 IC50 nM	HuH7 IC50 nM	MDA-MB-453
1.	B	A	A		B

Example	KG-1 IC50 nM	KatoIII IC50 nM	RT112/84 IC50 nM	HuH7 IC50 nM	MDA- MB- 453
2.	B	A	A		A
3.	C	B	A		
4.	B	C	A	A	A
5.	B	C	A	A	A
6.	B	A	A		B
7.	C	B	A		C
8.	B	B	A		
9.	B	B	A		
10.	B	B	A		
11.				A	
12.				A	
13.	B	B	A		
14.	B	B	A	A	
15.	B	B	A		
16.	A	A	A		B
17.	A	A	A		B
18.	A	A	A		

CLAIMS

What is claimed:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein

Q is CH or N;

R¹ is H, F, or -CN;

R² is H or OCH₃;

Z¹ is absent, CH₂, NR³, or O;

Z² is absent, CH₂, NR³, or O;

Z³ is absent, CH₂, NR³, or O;

wherein at least one of Z¹, Z², and Z³ is NR³ or O;

wherein if R¹ is H or CN and Q is CH, then Z¹ is NR³, Z² is absent or CH₂, and Z³ is CH₂, NR³, or O;

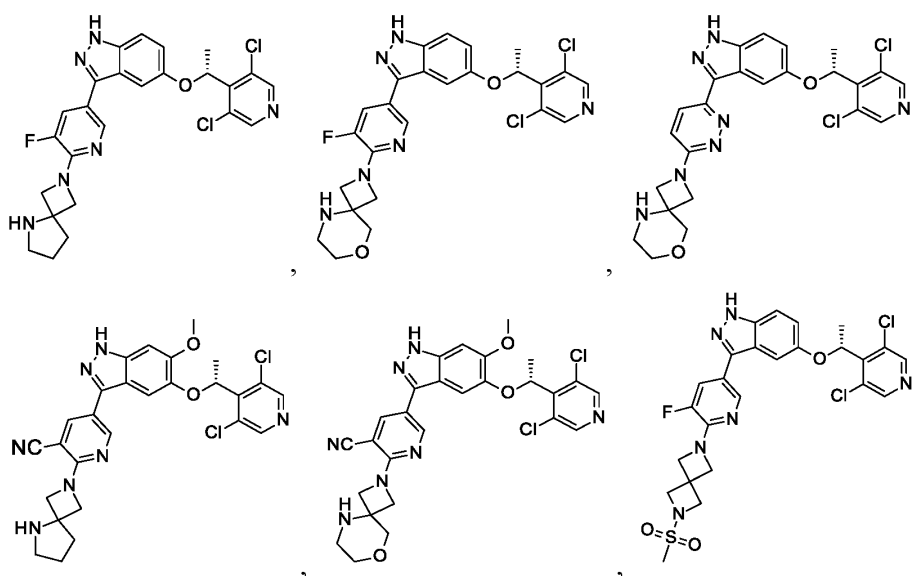
wherein if R¹ is F or CN and R² is OCH₃, then Z¹ is NR³, Z² is absent or CH₂, and Z³ is CH₂, NR³, or O;

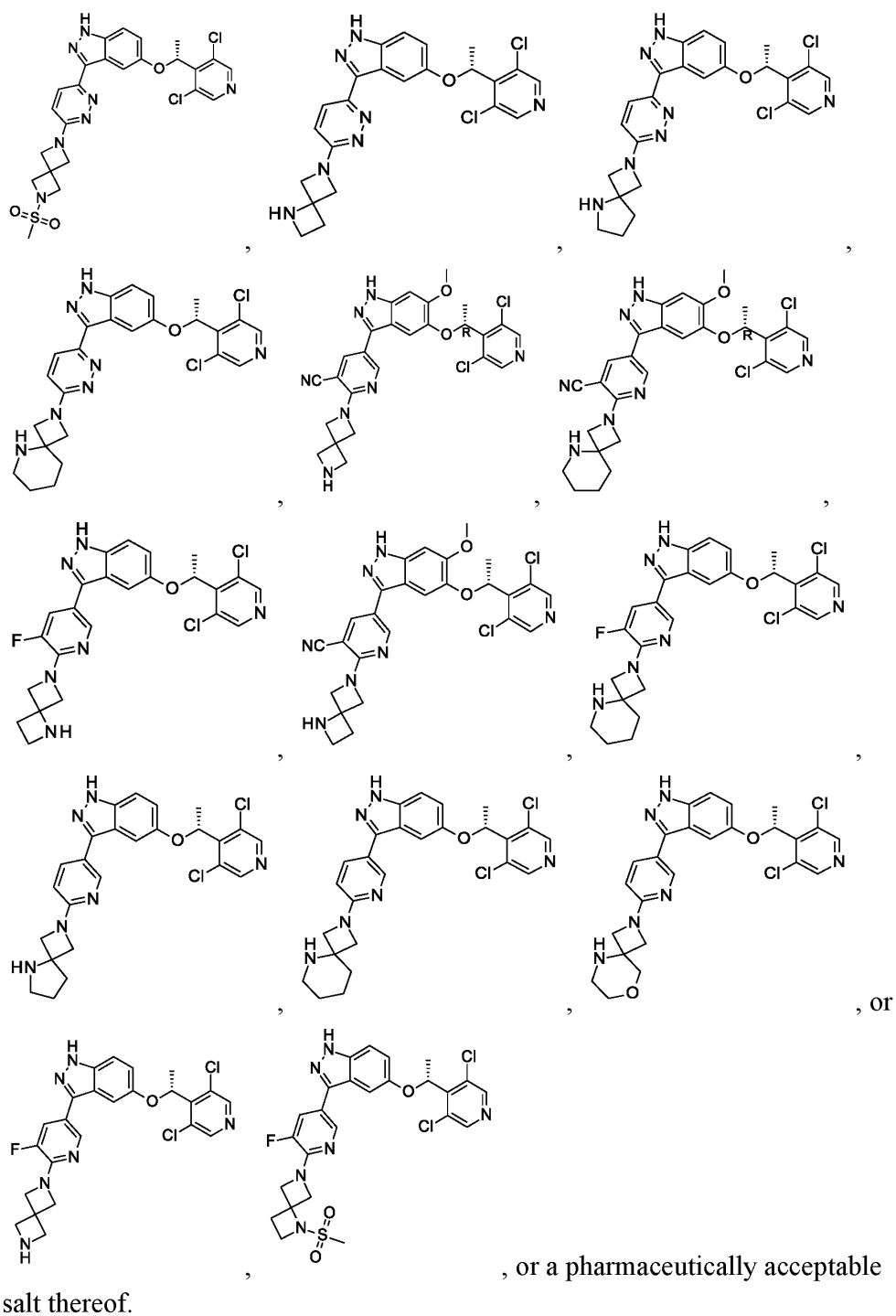
and

each R³ is independently H or SO₂CH₃.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z^1 is NR^3 ; Z^2 is CH_2 ; and Z^3 is CH_2 .
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z^1 is NR^3 ; Z^2 is absent; and Z^3 is CH_2 .
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z^1 is absent; Z^2 is absent; and Z^3 is NR^3 .
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z^1 is NR^3 ; Z^2 is absent; and Z^3 is absent.
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z^1 is NR^3 ; Z^2 is CH_2 ; and Z^3 is O.
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^3 is H.
8. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^3 is SO_2CH_3 .
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^1 is H.
10. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^1 is F.
11. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^1 is CN.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^2 is H.

13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt thereof, wherein R^2 is OCH_3 .
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein Q is N.
15. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein Q is CH.
16. The compound of claim 1, wherein the compound is:





17. A pharmaceutical composition comprising a compound of any one of claims 1-16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
18. A method of treating a disease or disorder in a subject in need thereof comprising administering to the subject a compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof.
19. The method of claim 18, wherein the disease or disorder is cancer.
20. The method of claim 19, wherein the cancer is urothelial carcinoma, hepatocellular carcinoma, breast carcinoma, endometrial adenocarcinoma, ovarian carcinoma, primary glioma, cholangiocarcinoma, gastric adenocarcinoma, non-small cell lung carcinoma, pancreatic exocrine carcinoma, oral cancer, prostate cancer, bladder cancer, colorectal carcinoma, renal cell carcinoma, neuroendocrine carcinoma, myeloproliferative neoplasms, head and neck (squamous), melanoma, leiomyosarcoma, and/or sarcomas.
21. The method of claim 19 or 20, wherein the cancer is an FGFR-mutant cancer.
22. The method of claim 21, wherein the disease or disorder is a developmental disorder.
23. The method of claim 22, wherein the developmental disorder is Achondroplasia (Ach) and related chondrodysplasia syndromes, including Hypochondroplasia (Hch), severe achondroplasia with developmental delay and Acanthosis Nigricans (SADDAN), and Thanatophoric dysplasia (TD).