

CHEMICAL COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

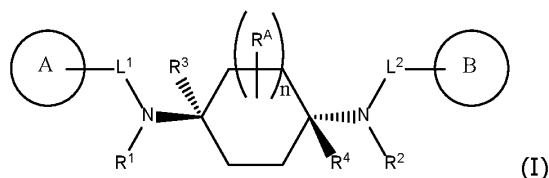
Disclosed herein are certain compounds that induce cell death in cells with microsatellite instability (MSI), and are therefore useful in treating cancers, which include cancers characterized by MSI and/or
5 defective DNA mismatch repair system (dMMR). Also disclosed are pharmaceutical compositions comprising such compounds and methods of making the same.

BACKGROUND TO THE INVENTION

Cancer is a leading cause of death throughout the world. A limitation of prevailing therapeutic approaches, e.g. chemotherapy is that their cytotoxic effects are not restricted to cancer cells and
10 adverse side effects can occur within normal tissues. Consequently, novel strategies are needed to better target cancer cells, specifically for patients having tumor cells with microsatellite instability (MSI). Microsatellites are repetitive DNA sequences with varying unit lengths (e.g. ranging from one (mononucleotides) to six bases (di-, tri-, tetra-, penta-, esa-nucleotides)) distributed along coding and/or noncoding regions of the genome. Mutations of such microsatellites, for example, repeat length
15 alterations, can represent microsatellite instability and this instability is a marker of DNA mismatch repair (dMMR). As known in the art and more fully described herein, MSI can be detected by molecular testing (e.g., with respect to certain microsatellites) or by immunohistochemical evaluation (e.g., with respect to expression of certain MMR proteins). Based on a consensus NCI-Reference Panel (Bethesda, 1998), MSI can be assessed by molecular testing of five microsatellites – including two
20 mononucleotides (BAT25 and BAT26) and three dinucleotides (D2S123, D5S346, D17S250). Tumors can be classified into different subtypes based on such a NCI-Reference Panel approach for molecular testing, including MSI-high (MSI-H) if two or more of the microsatellite markers show instability, MSI-low (MSI-L) if only one microsatellite marker shows instability, and MS-stable (MSS) if none of the five microsatellite markers show instability (i.e., each of the five microsatellite markers are determined as
25 stable). In some instances where molecular testing or immunohistochemical evaluation is not able to distinguish between MSI-L and general chromosomal instability, tumors can be classified as a MSS neoplasms. Disruptions in DNA repair pathways predispose cells to accumulating DNA damage. Therefore, in cells where a DNA Damage Repair pathway is already disrupted (in the case of cells exhibiting MSI the pathway is dMMR) disrupting a second pathway that cells require for survival can
30 induce tumor death, a mechanism known as “synthetic lethality” (for example PARPi in BRCAmut cells). Accordingly, there is a need for further compounds for treating cancer.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a compound of Formula (I):



wherein:

5 R^1 and R^2 are each independently selected from hydrogen, C_{1-3} alkyl, halo(C_{2-3})alkyl, $-CH_2-C_{5-9}$ aryl wherein the C_{5-9} aryl is optionally substituted with C_{1-3} alkoxy;

R^3 and R^4 are each independently selected from hydrogen or C_{1-3} alkyl;

n is an integer selected from 1 to 3;

10 R^A is independently selected from C_{1-2} alkyl, halo, $-NR^aR^b$, hydroxy, carboxy, halo(C_{1-3})alkyl, hydroxy(C_{1-3})alkyl, methoxy(C_{1-3})alkyl, C_{1-3} alkoxy, and halo(C_{1-3})alkoxy or R^A and R^1 are taken together to form a nitrogen containing 5- or 6- membered ring which optionally contains one or two heteroatoms independently selected from N, O, and S and is optionally substituted with C_{1-2} alkyl;

15 L^1 and L^2 are each independently selected from a C_{1-2} alkylene optionally substituted with one or two substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy(C_{1-3})alkyl, halo(C_{1-3})alkyl, and cyano;

Ring A and B are each independently selected from C_{5-14} aryl or C_{5-14} heteroaryl containing one, two, or three heteroatoms independently selected from N, O, and S, wherein rings A and B are independently mono-, bicyclic or fused and optionally substituted with one to five substituents independently selected from halo, cyano, nitro, hydroxy, carboxy, C_{1-3} alkyl, C_{1-3} alkoxy, halo(C_{1-3})alkyl, 20 halo(C_{1-3})alkoxy, hydroxy(C_{1-3})alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, $-C_{1-3}$ alkylene- NR^aR^b , $-CONR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SO_2NR^aR^b$, and L^A-W ;

L^A is independently selected from a bond, $-(CH_2)_p-$, $-CH_2O-$, $-C(O)-NH-$, $-C(O)-$, and $-CH_2C(O)NH-$, wherein p is 1 or 2;

25 W is independently selected from hydrogen, C_{1-3} alkyl, $-O(C_{1-4})$ alkyl, C_{3-7} cycloalkyl, 5- or 6-membered heteroaryl and 4- to 6-membered heterocycloalkyl ring containing one, two, or three heteroatoms independently selected from N, O, and S, wherein W is optionally substituted with up to

three substituents independently selected from halo, cyano, nitro, hydroxy, $-NR^aR^b$, carboxy, $-CONR^aR^b$, C_{1-3} alkyl, C_{1-3} alkoxy, halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, hydroxy(C_{1-3})alkyl, cyano(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, $-C(O)O(C_{1-4})$ alkyl, and C_{3-7} cycloalkyl; and

R^a and R^b are each independently hydrogen, C_{1-3} alkyl, or C_{3-7} cycloalkyl;

5 or a pharmaceutically acceptable salt thereof.

In a second aspect, the present invention provides a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of the invention disclosed herein and a pharmaceutically acceptable excipient.

10 In a third aspect, the present invention provides a compound of the invention disclosed herein for use in therapy.

In a fourth aspect, the present invention provides a compound of the invention disclosed herein for use in the treatment of cancer.

15 In a fifth aspect, the present invention provides a method of treatment of cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt thereof of the invention disclosed herein or pharmaceutical composition as disclosed herein.

In a sixth aspect, the present invention provides the use of a compound of the invention disclosed herein in the manufacture of a medicament for use in the treatment of cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

20 **FIG. 1** shows an efficacy study of the compound of Example 6 in a mouse model bearing SW48 human colorectal cancer cell line xenografts.

FIG. 2 shows an efficacy study of the compound of Example 34 in a mouse model bearing SW48 human colorectal cancer cell line xenografts.

25 **FIG. 3** shows an efficacy study of the compound of Example 40 in a mouse model bearing SW48 human colorectal cancer cell line xenografts.

DETAILED DESCRIPTION OF THE EMBODIMENTS

DEFINITIONS

As used herein, the terms "halogen" and "halo" represent chloro, fluoro, bromo, or iodo substituents.

As used herein, the term "cyano" refers to the group -CN.

As used herein, the term "nitro" refers to the group -NO₂.

As used herein, the term "hydroxy" or "hydroxyl" refers to the group -OH.

As used herein, the term "carboxy" refers to the group -COOH.

5 As used herein, the term "alkyl" refers to a saturated hydrocarbon radical, straight or branched, having the specified number of carbon atoms. For example, the term "C₁₋₅alkyl" refers to an alkyl group having 1 to 5 carbon atoms, the term "C₁₋₄ alkyl" refers to an alkyl group having 1 to 4 carbon atoms, the term "C₁₋₃ alkyl" refers to an alkyl group having 1 to 3 carbon atoms. Exemplary groups include, but are not limited to, methyl, ethyl, propyl (n-propyl and isopropyl), butyl (n-butyl, sec-butyl, isobutyl
10 and tert-butyl), pentyl. When the term "alkyl" is used in combination with other substituent groups, such as "halo(C₁₋₃)alkyl" and "hydroxy(C₁₋₃)alkyl" the term "alkyl" is intended to encompass a divalent straight or branched chain hydrocarbon radical, wherein the point of attachment is through the alkyl moiety.

As used herein, the term "halo(C_{m-n})alkyl" is intended to mean a radical having one or more halogen
15 atoms, which may be the same or different, at one or more carbon atoms of an alkyl moiety containing from m to n carbon atoms, which is a straight or branched chain carbon radical. For example, the term "halo(C₁₋₃)alkyl" is intended to mean a radical having one or more halogen atoms, which may be the same or different, at one or more carbon atoms of an alkyl moiety containing from 1 to 3 carbon atoms, which is a straight or branched chain carbon radical. Exemplary groups include, but are not
20 limited to, -CF₃ (trifluoromethyl), difluoromethyl, -CCl₃ (trichloromethyl), 1,1-difluoroethyl, 2,2,2-trifluoroethyl, and hexafluoroisopropyl.

As used herein, the term "hydroxy(C₁₋₃)alkyl" is intended to mean a radical having one or more hydroxy groups at one or more carbon atoms of an alkyl moiety containing from 1 to 3 carbon atoms, which is a straight or branched chain carbon radical. Exemplary groups include, but are not limited to,
25 hydroxymethyl (-CH₂OH), hydroxyethyl (-CH₂CH₂OH), and hydroxyisopropyl.

The term "alkenyl" refers to a straight or branched hydrocarbon radical containing the specified number of carbon atoms and at least 1 double bond. For example, "C₂₋₅ alkenyl" has 2 to 5 carbon atoms. Exemplary groups include, but are not limited to, ethenyl and propenyl.

The term "alkynyl" refers to a straight or branched hydrocarbon radical containing the specified
30 number of carbon atoms and at least 1 triple bond. For example, "C₂₋₅ alkynyl" has 2 to 5 carbon atoms. Exemplary groups include, but are not limited to, ethynyl and propynyl.

The term "alkylene" refers to a divalent radical derived from a straight or branched, saturated hydrocarbon group of, for example, 1 to 3 carbon atoms (C₁₋₃alkylene). Exemplary groups include, but are not limited to, -CH₂-, -CH₂CH₂-, and -CH₂CH₂CH₂-.

- As used herein, the term "cycloalkyl" refers to a non-aromatic, saturated, hydrocarbon ring containing the specified number of carbon atoms, which may be monocyclic or bicyclic. Bicyclic cycloalkyl groups may be bridged, fused, or spiro bicyclic groups. For example, "C₃₋₈cycloalkyl" refers to a cycloalkyl group containing 3 to 8 carbon atoms. Exemplary groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, bicyclo[1.1.1]pentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, cyclooctyl, octahydropentalenyl (such as (3a*s*,6*a**s*)-octahydropentalenyl), spirodecyl (such as spiro[4.5]decyl), bicyclo[2.1.1]hexyl, bicyclo[2.1.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, bicyclo[4.3.1]decyl, bicyclo[2.2.0]hexyl, bicyclo[3.1.0]hexyl, bicyclo[3.2.0]heptyl, bicyclo[4.1.0]heptyl, octahydropentalenyl, bicyclo[4.2.0]octyl, decahydronaphthalenyl, spiro[3.3]heptyl, spiro[2.4]heptyl, spiro[3.4]octyl, spiro[2.5]octyl, spiro[4.4]nonyl, spiro[3.5]nonyl, and spiro[4.5]decyl.
- 15 The term "alkoxy" refers to an -O-alkyl group, i.e. an alkyl group which is attached through an oxygen linking atom, wherein "alkyl" is defined above. For example, the term "C₁₋₆ alkoxy" refers to an alkoxy group having 1 to 6 carbon atoms, and the term "C₁₋₃ alkoxy" refers to an alkoxy group having 1 to 3 carbon atoms. Exemplary groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *s*-butoxy, isobutoxy, and *t*-butoxy.
- 20 The term "halo(C₁₋₃)alkoxy" refers to a straight or branched chain hydrocarbon radical, having at least 1 and up to 3 carbon atoms with one or more halogen atoms, which may be the same or different, attached to one or more carbon atoms, which radical is attached through an oxygen linking atom. Exemplary groups include, but are not limited to, -OCHF₂ (difluoromethoxy), -OCF₃ (trifluoromethoxy), and -OCH(CF₃)₂ (hexafluoroisopropoxy).
- 25 The term "heterocycloalkyl" refers to a saturated or unsaturated 3 to 10 membered monocyclic or bicyclic ring, which must contain at least one heteroatom, which is selected from nitrogen, oxygen, and sulfur. Heterocycloalkyl groups may contain one or more C(O), S(O) or SO₂ groups. Bicyclic heterocycloalkyl groups may be bridged, fused or spiro bicyclic groups. However, heterocycloalkyl groups are not aromatic. Heterocycloalkyl groups containing more than one heteroatom may contain different heteroatoms. "5- or 6- membered heterocycloalkyl" refers to a saturated or unsaturated 5- or 6-membered monocyclic ring, which must contain 1, 2 or 3 non-carbon atoms which are selected from nitrogen, oxygen, and sulfur. Exemplary groups include, but are not limited to, pyrrolidinyl,
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pyrazolidinyl, pyrazolinyl, imidazolidinyl, imidazoliny, oxazoliny, thiazoliny, piperidinyl, piperazinyl, tetrahydrofuranyl, dihydrofuranyl, 1,3-dioxolanyl, tetrahydro-2H-pyranyl, dihydropyranyl, morpholinyl, morpholinyl-3-one, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-oxathiolanyl, 1,3-oxathianyl, 1,3-dithianyl, 1,4-oxathiolanyl, 1,4-oxathianyl, 1,4-dithianyl, piperidyl-2-one, pyrimidinyl-2,4(1H,3H)-dione, 5 thiomorpholinyl, and thiomorpholinyl 1,1-dioxide.

The term "aryl" refers to a monocyclic or bicyclic, hydrocarbon, aromatic radical. Aryl includes, for example, phenyl and naphthyl. An aryl group may contain 5 to 14 carbon atoms.

The term "heteroaryl" refers to a group or moiety comprising an aromatic monovalent monocyclic or bicyclic radical, containing 5 to 14 ring atoms, including one to heteroatoms each independently selected from nitrogen, oxygen and sulfur. This term also encompasses bicyclic heterocyclic-aryl compounds containing an aryl ring moiety fused to a heterocycloalkyl ring moiety, containing 5 to 14 ring atoms, including at least one heteroatom independently selected from nitrogen, oxygen and sulfur. Exemplary groups include, but are not limited to furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl (for example, 4H-1,2,4-triazolyl), thiazolyl, oxazolyl (for example, 1,3,4-oxadiazolyl), 15 isoxazolyl, oxadiazolyl, thiadiazolyl (for example 1,3,4-thiadiazolyl), isothiazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, benzofuranyl, isobenzofuryl, 1,3-dihydroisobenzofuranyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxolyl, dihydrobenzodioxinyl, furopyridazinyl (such as furo[2,3-d]pyridazinyl), benzothienyl, indoliziny, indolyl, isoindolyl, dihydroindolyl, benzimidazolyl, dihydrobenzimidazolyl, benzoxazolyl, dihydrobenzoxazolyl, benzthiazolyl, benzoisothiazolyl, 20 dihydrobenzoisothiazolyl, indazolyl, imidazopyridinyl, thienopyridinyl (such as thieno[3,2-b]pyridinyl), thienopyrimidinyl (such as thieno[2,3-d]pyrimidinyl), pyrazolopyridyl, benzotriazolyl, triazolopyridyl, purinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinoxaliny, quinoxaliny, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, and pteridinyl. Examples of 5-membered 25 "heteroaryl" groups include furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, tetrahydropyridopyridazinyl (such as 5,6,7,8-tetrahydropyrido[3,4-d]pyridazinyl and isothiazolyl. Examples of 6-membered "heteroaryl" groups include oxo-pyridyl, pyridyl, pyridazinyl, pyrazinyl, and pyrimidinyl. Examples of 6,6-fused "heteroaryl" groups include quinolinyl, isoquinolinyl, quinoxaliny, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, and pteridinyl. Examples of 30 6,5-fused "heteroaryl" groups include benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, indoliziny, indolyl, isoindolyl, and indazolyl.

The term "5- or 6-membered heteroaryl" represents a group or moiety comprising an aromatic monovalent monocyclic radical, containing 5 or 6 ring atoms, including at least one carbon atom and one, two or three heteroatoms each independently selected from nitrogen, oxygen, and sulfur. Exemplary groups include, but are not limited to furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, and triazinyl. For the avoidance of doubt, all bicyclic ring systems may be attached at any suitable position on either ring.

The term "optionally substituted" indicates that a group may be unsubstituted or substituted with one or more substituents as defined herein. The term "substituted" in reference to a group indicates that a hydrogen atom attached to a member atom within a group is replaced by one of the defined substituents. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

The term "pharmaceutically acceptable" refers to those compounds (including salts), materials, compositions, and dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The term "independently selected" means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different. Thus, each substituent is separately selected from the entire group of recited possible substituents.

The term "treatment" refers to ameliorating or stabilising the specified condition, reducing or eliminating the symptoms of the condition, slowing or eliminating the progression of the condition, and preventing or delaying reoccurrence of the condition in a previously afflicted patient or subject.

The term "therapeutically effective amount" refers to the quantity of a compound of formula (I) disclosed herein, or a pharmaceutically acceptable salt thereof, which will elicit the desired biological response in a human body. It may vary depending on the compound, the disease and its severity and the age and weight of the subject to be treated.

The term "subject" or "patient" refers to a human body.

As used herein, a reference to a compound of Formula (I) encompasses a reference to any one of Formulae (II) to (Vf).

As used herein, the term "pharmaceutically acceptable salt" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. Such

pharmaceutically acceptable salt may be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid or free base form with a suitable base or acid, respectively. When compounds disclosed herein contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines, such as arginine, betaine, caffeine, choline, *N,N*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogen carbonic, phosphoric, monohydrogen phosphoric, dihydrogen phosphoric, sulfuric, monohydrogen sulfuric, hydriodic, or phosphorous acids, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic. Also included are salts of amino acids such as arginate, and salts of organic acids like glucuronic or galactunoric acids (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

Certain compounds of Formula (I) can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended

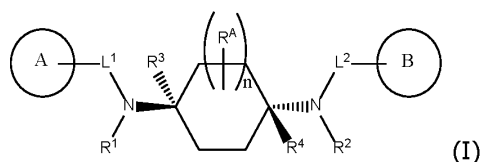
to be encompassed within the scope of the present invention. Certain compounds of Formula (I) may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

- 5 Compounds of Formula (I) possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers, regioisomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. When a stereochemical depiction is shown, it is meant to refer the compound in which one of the isomers is present and substantially free of the other isomer. "Substantially free of" another isomer indicates at least an 80/20 ratio of the two isomers, more preferably 90/10, or 95/5 or more. In some embodiments, one of the isomers will be present in an amount of at least 99%.

Certain compounds of the present invention can exist as tautomers and/or geometric isomers. All possible tautomers and *cis* and *trans* isomers, as individual forms and mixtures thereof are within the scope of this invention.

15 COMPOUNDS

In one aspect, the present invention provides a compound of Formula (I):



wherein:

- 20 R¹ and R² are each independently selected from hydrogen, C₁₋₃alkyl, halo(C₂₋₃)alkyl, -CH₂-C₅₋₉aryl wherein the C₅₋₉aryl is optionally substituted with C₁₋₃alkoxy;

R³ and R⁴ are each independently selected from hydrogen or C₁₋₃alkyl;

n is an integer selected from 1 to 3;

- 25 R^A is independently selected from C₁₋₂alkyl, halo, -NR^aR^b, hydroxy, carboxy, halo(C₁₋₃)alkyl, hydroxy(C₁₋₃)alkyl, methoxy(C₁₋₃)alkyl, C₁₋₃alkoxy, and halo(C₁₋₃)alkoxy, or R^A and R¹ are taken together to form a nitrogen containing 5- or 6- membered ring which optionally contains one or two heteroatoms independently selected from N, O, and S and is optionally substituted with C₁₋₂alkyl;

L¹ and L² are each independently selected from a C₁₋₂alkylene optionally substituted with one or two substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, hydroxy(C₁₋₃)alkyl, halo(C₁₋₃)alkyl, and cyano;

5 Ring A and B are each independently selected from C₅₋₁₄aryl or C₅₋₁₄heteroaryl containing one, two, or three heteroatoms independently selected from N, O, and S, wherein rings A and B are independently mono-, bicyclic or fused and optionally substituted with one to five substituents independently selected from halo, cyano, nitro, hydroxy, carboxy, C₁₋₃alkyl, C₁₋₃alkoxy, halo(C₁₋₃)alkyl, halo(C₁₋₃)alkoxy, hydroxy(C₁₋₃)alkyl, C₂₋₅alkenyl, C₂₋₅alkynyl, -C₁₋₃alkylene-NR^aR^b, -CONR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -SO₂NR^aR^b, and L^A-W;

10 L^A is independently selected from a bond, -(CH₂)_p-, -CH₂O-, -C(O)-NH-, -C(O)-, and -CH₂C(O)NH-, wherein p is 1 or 2;

W is independently selected from hydrogen, C₁₋₃alkyl, -O(C₁₋₄)alkyl, C₃₋₇cycloalkyl, 5- or 6-membered heteroaryl and 4- to 6-membered heterocycloalkyl ring containing one, two, or three heteroatoms independently selected from N, O, and S, wherein W is optionally substituted with up to
15 three substituents independently selected from halo, cyano, nitro, hydroxy, -NR^aR^b, carboxy, -CONR^aR^b, C₁₋₃alkyl, C₁₋₃alkoxy, halo(C₁₋₃)alkyl, halo(C₁₋₃)alkoxy, hydroxy(C₁₋₃)alkyl, cyano(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, -C(O)O(C₁₋₄)alkyl, and C₃₋₇cycloalkyl; and

R^a and R^b are each independently hydrogen, C₁₋₃alkyl, or C₃₋₇cycloalkyl;

or a pharmaceutically acceptable salt thereof.

20 In one embodiment, L¹ and L² are independently selected from -CH₂- and -CH(CH₃)-

In one embodiment, L¹ and L² are both -CH₂-. In one embodiment, L¹ is -CH₂- and L² is -CH(CH₃)-. In one embodiment, L² is -CH₂- and L¹ is -CH(CH₃)-

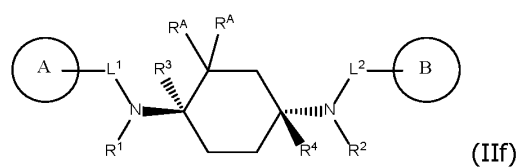
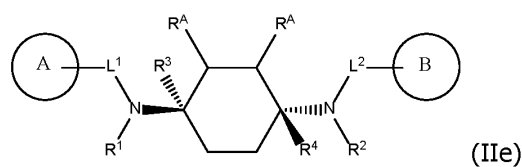
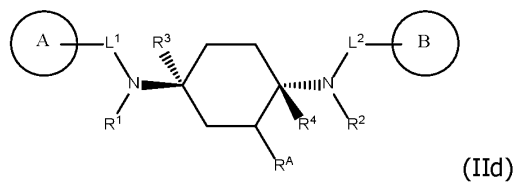
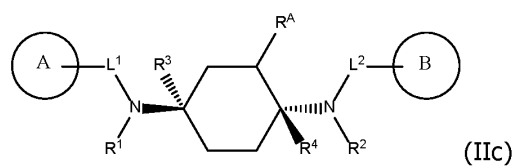
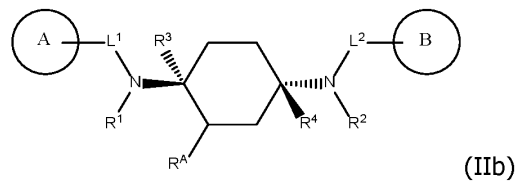
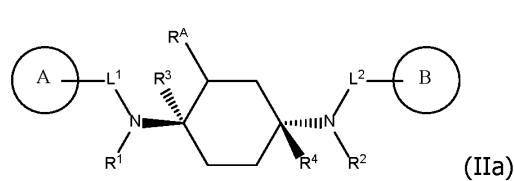
In one embodiment, R¹ and R² are independently selected from the group consisting of H and methyl.

In one embodiment, R¹ and R² are both H. In one embodiment, R¹ and R² are both methyl. In one
25 embodiment, R¹ is H and R² is methyl. In one embodiment, R² is H and R¹ is methyl.

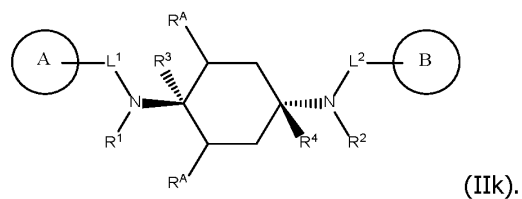
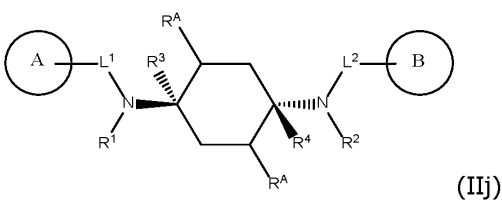
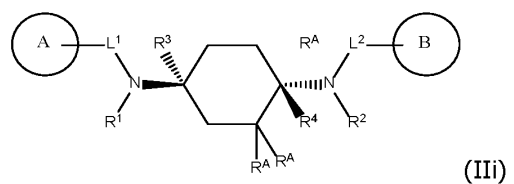
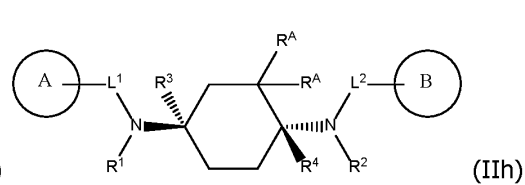
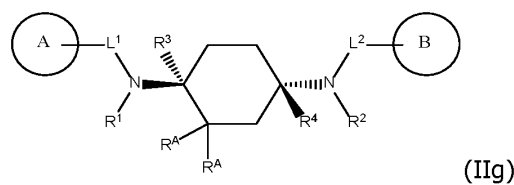
In one embodiment, the compounds of Formula (I) contain at least one R^A which is selected from the group consisting of hydroxy, methoxy and halo.

In one embodiment, wherein n is 1 and the compound of formula (I) is substituted by only one R^A group.

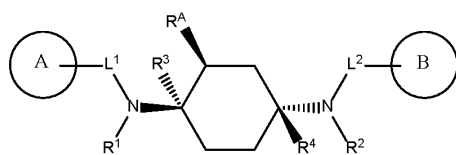
In one embodiment, the compound of the invention has a structure selected from Formulae IIa-IIk:



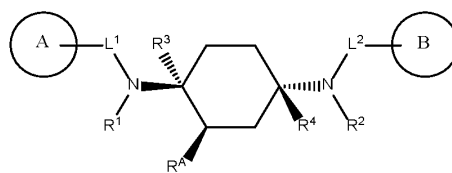
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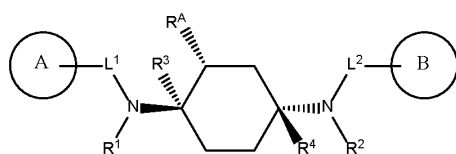
In one aspect of this embodiment, the compound of the invention has a structure selected from Formulae IIIa-IIIk:



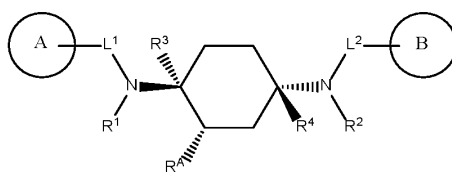
(IIIa)



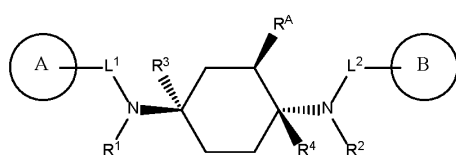
(IIIb)



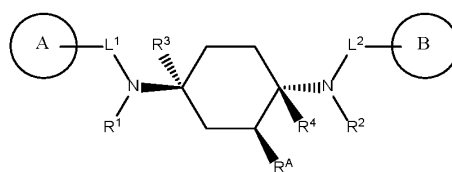
(IIIc)



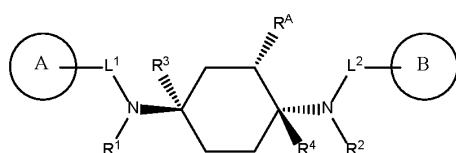
(IIId)



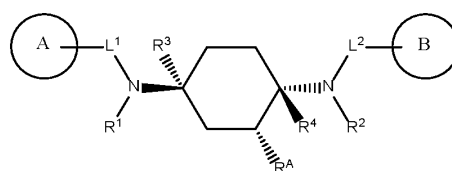
(IIIe)



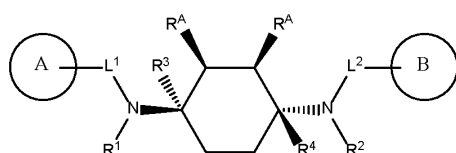
(IIIIf)



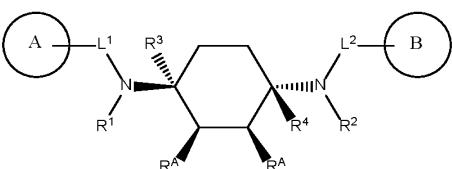
(IIIg)



(IIIh)



(IIIi)



(IIIj)

5

In one embodiment, n is 2 (i.e., the compound of Formula (I) is substituted by 2 R^A substituents).

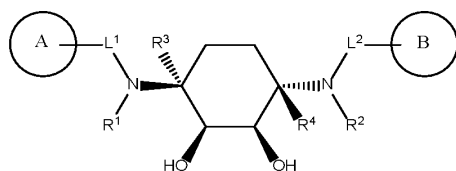
In one embodiment, R^A is selected from the group consisting of hydroxy, methoxy and halo.

In one embodiment, R^A is hydroxy.

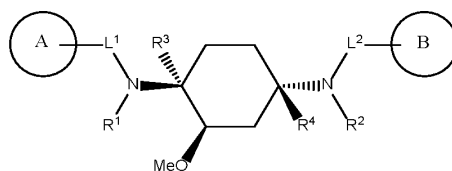
10 In one embodiment, R^A is methoxy.

In one embodiment, R^A is fluoro.

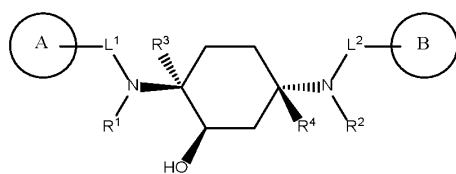
In one embodiment, the compound of the present invention has a structure selected from Formulae IVa-IVo:



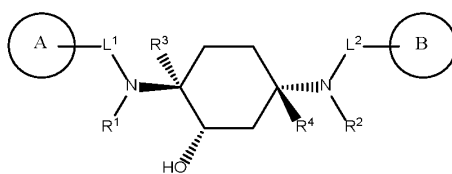
(IVa)



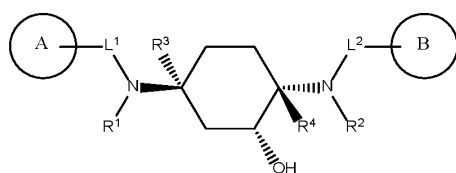
(IVb)



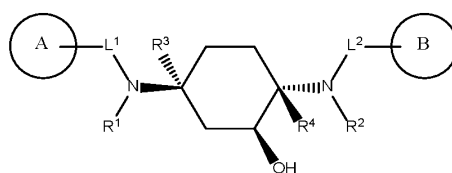
(IVc)



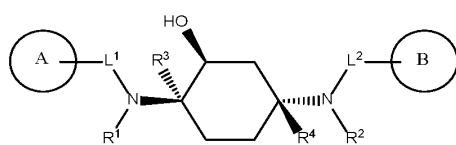
(IVd)



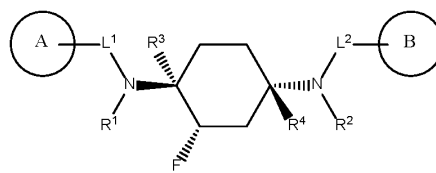
(IVe)



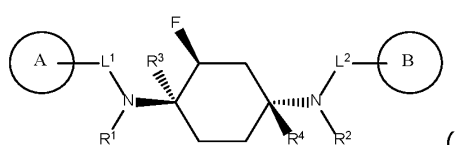
(IVf)



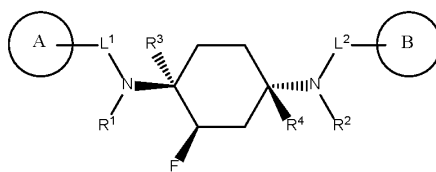
(IVg)



(IVh)

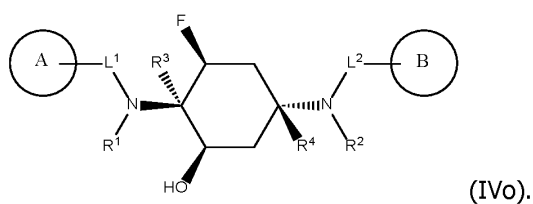
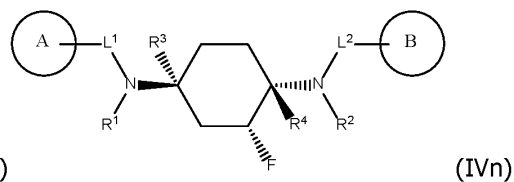
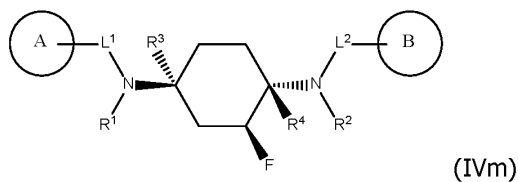
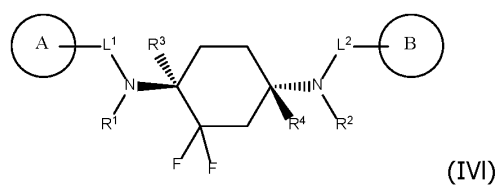
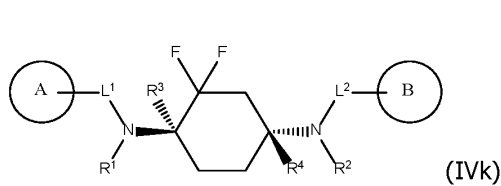


(IVi)

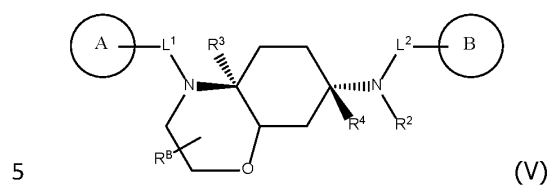


(IVj)

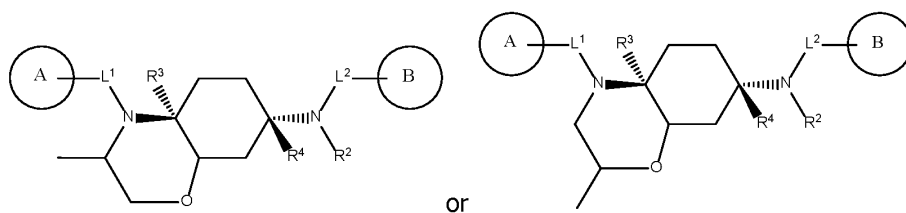
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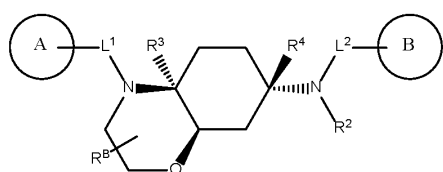
In one embodiment, the present invention provides a compound of Formula V:



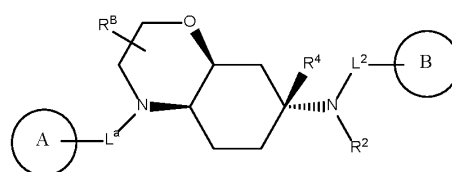
wherein R^B is absent or C_{1-3} alkyl. In one aspect of this embodiment, R^B is methyl such that the compound of Formula V is selected from one of the following structures:



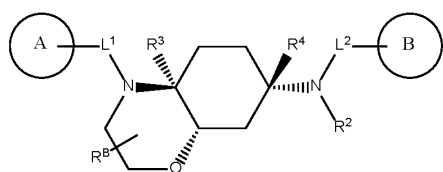
In one embodiment, the present invention provides a compound having a structure selected from Formulae Va to Vf:



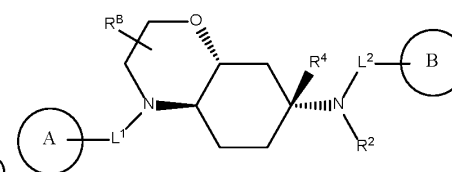
(Va)



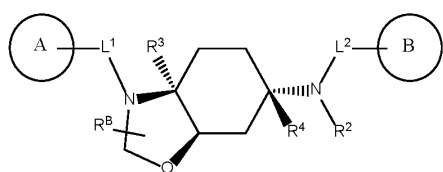
(Vb)



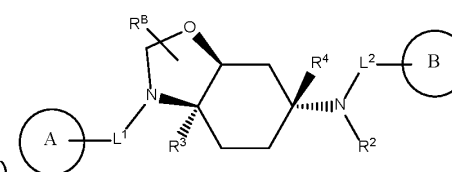
(Vc)



(Vd)



(Ve)



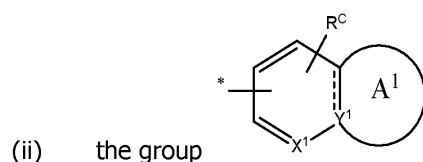
(Vf)

wherein R^B is absent or C_{1-3} alkyl. In one aspect of this embodiment, R^B is methyl.

5 In one embodiment, Ring A and Ring B are each independently selected from:

- (i) phenyl or a 5 or 6-membered heteroaryl, optionally substituted with R^{1B} , R^{2B} and R^{3B} , wherein R^{1B} is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heterocycloalkyl, 5-membered heteroaryl, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$, and wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, cycloalkenyl, heterocycloalkyl, 5 membered heteroaryl, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, and $-COOR^{4B}$ may be optionally substituted with one to three substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-8} cycloalkyl, cycloalkenyl, heterocycloalkyl, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$; wherein R^{2B} is C_{1-3} alkyl, C_{1-3} alkoxy, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$, and wherein the C_{1-3} alkyl and C_{1-3} alkoxy may be optionally substituted with one to three substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, and $-COOR^{4B}$; and wherein R^{3B} is C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, halogen or cyano, wherein the C_{1-3} alkyl is optionally substituted with one or more substituents independently selected from hydroxy and halogen; wherein R^{4B} is hydrogen or C_{1-3} alkyl, and R^{5B} is hydrogen, C_{1-3} alkyl or C_{3-8} cycloalkyl, or R^{4B} and R^{5B} together with the nitrogen to which they are attached form a 5 to 6-membered ring containing one, two or three heteroatoms independently selected from N, O and S, and further wherein the ring may be optionally substituted with one or more substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy,

cyano, hydroxy, oxo and halogen, wherein the C₁₋₃alkyl is optionally substituted with one or more substituents independently selected from hydroxy and halogen; or



wherein X¹ is N, CH, or C(halo), Y¹ is C or N and Ring A¹ is a 5 or 6-membered ring which optionally contains one or two heteroatoms independently selected from N, O and S, wherein R^C is hydrogen, C₁₋₃alkyl, C₁₋₃alkoxy, oxo, cyano, hydroxy, halogen or -NR^{4B}R^{5B}, and wherein the 5 or 6-membered ring may be optionally substituted with one, two or three substituents independently selected from C₁₋₃alkyl, C₁₋₃alkoxy, oxo, cyano, hydroxy, halogen and -NR^{4B}R^{5B}, wherein C₁₋₃alkyl is optionally substituted with one or more independently selected halogen substituents, wherein R^{4B} is hydrogen or C₁₋₃alkyl, and R^{5B} is hydrogen, C₁₋₃alkyl or C₃₋₈cycloalkyl, where the dashed bond indicates that the bond may be a single or double bond as appropriate.

In one embodiment, Ring A and B are each independently selected from the group consisting of

thiazole, phenyl, indenyl, pyridinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, 4H-1,2,4-triazolyl, thiazolyl, oxazolyl, indolyl, isoxazolyl, oxadiazolyl, thiadiazolyl (for example 1,3,4-thiadiazolyl), isothiazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, benzofuranyl, isobenzofuranyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydro-1H-benzo[d]imidazolyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxolyl, dihydrobenzodioxinyl, furopyridazinyl (such as furo[2,3-d]pyridazinyl), benzothienyl, indolizynyl, indolyl, isoindolyl, dihydroindolyl, benzimidazolyl, dihydrobenzimidazolyl, benzoxazolyl, dihydrobenzoxazolyl, benzthiazolyl, benzoisothiazolyl, dihydrobenzoisothiazolyl, indazolyl, imidazopyridinyl, thienopyridinyl (such as thieno[3,2-b]pyridinyl), thienopyrimidinyl, pyrazolopyridyl, benzotriazolyl, triazolopyridinyl, purinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinoxalyl, quinoxalyl, cinnolyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-naphthyridinyl, 1,8-naphthyridinyl, 3a,7a-dihydrobenzo[d][1,3]dioxolyl, 1,2-dihydroquinolinyl, indyl, indazyl, azaindolyl, pyrazole[1,5-a]pyrimidinyl, benzothiophenyl, 1,2-dihydropyrazolo[1,5-a]pyridinyl, and pteridinyl;

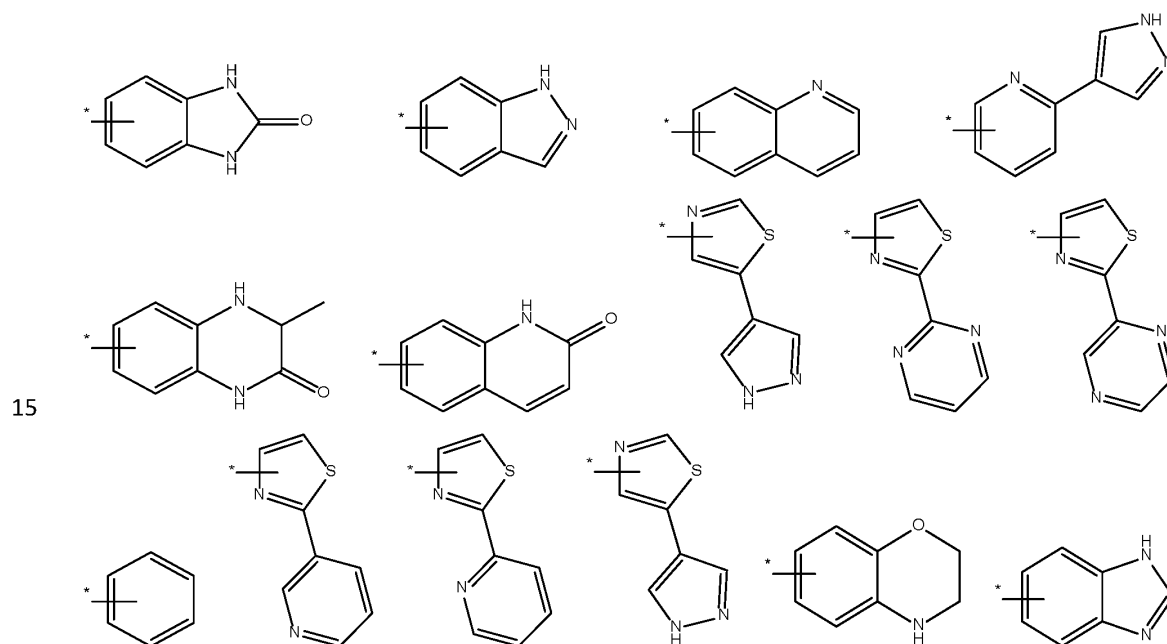
wherein Ring A and B are each independently optionally substituted with one to three substituents independently selected from halo, oxo, cyano, nitro, hydroxy, -NR^aR^b, carboxy, -CONR^aR^b,

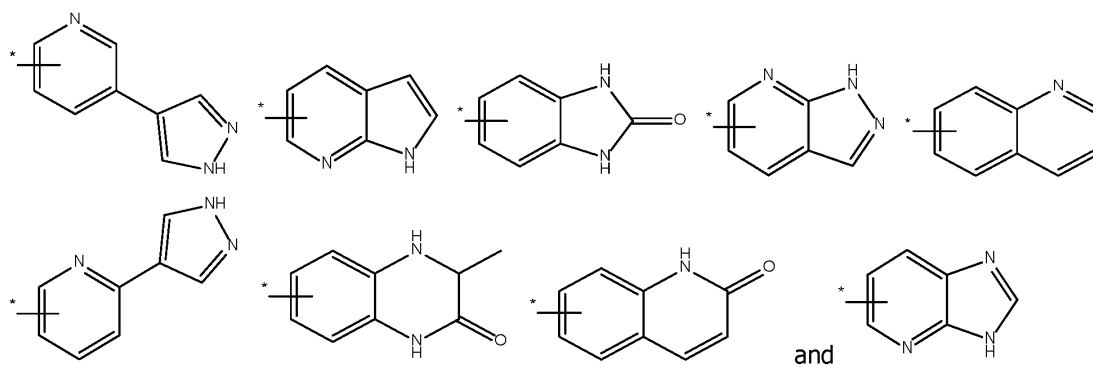
C₁₋₃alkyl, C₁₋₃alkoxy, halo(C₁₋₃)alkyl, halo(C₁₋₃)alkoxy, hydroxy(C₁₋₃)alkyl, cyano(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, -C(O)O(C₁₋₄)alkyl, C₃₋₇cycloalkyl, and 5 or 6-membered heteroaryl.

In one embodiment, Ring A and B are each independently selected from the group consisting of thiazole, phenyl, pyridyl, 2,3-dihydro-1H-benzo[d]imidazole, quinoline, quinazoline, indene, indoline, indole, indolizine, indazole, benzimidazole, azaindole, pyrazole[1,5-a]pyrimidine, benzofuran, isobenzofuran, benzothiophene, 1,2-dihydropyrazolo[1,5-a]pyridine, triazolo[1,5-a]pyridine, imidazopyridine, benzo[d]oxazole, benzo[d][1,3]dioxole, 1,2,3,4-tetrahydroquinoxaline, 1,2-dihydroquinoline, 3a,7a-dihydrobenzo[d][1,3]dioxole and benzthiazole;

wherein Ring A and B are each independently optionally substituted with one to three substituents independently selected from halo, oxo, cyano, nitro, hydroxy, -NR^aR^b, carboxy, -CONR^aR^b, C₁₋₃alkyl, C₁₋₃alkoxy, halo(C₁₋₃)alkyl, halo(C₁₋₃)alkoxy, hydroxy(C₁₋₃)alkyl, cyano(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, -C(O)O(C₁₋₄)alkyl, C₃₋₇cycloalkyl, and 5 or 6-membered heteroaryl.

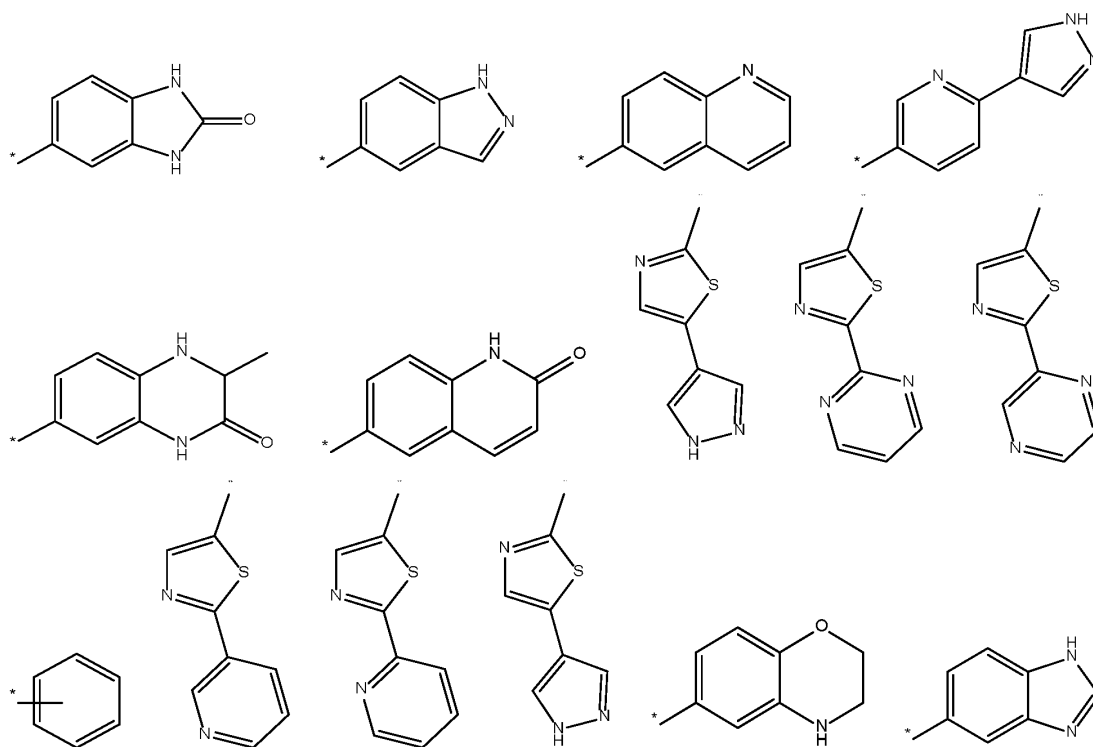
In one embodiment, Ring A is selected from the group consisting of:

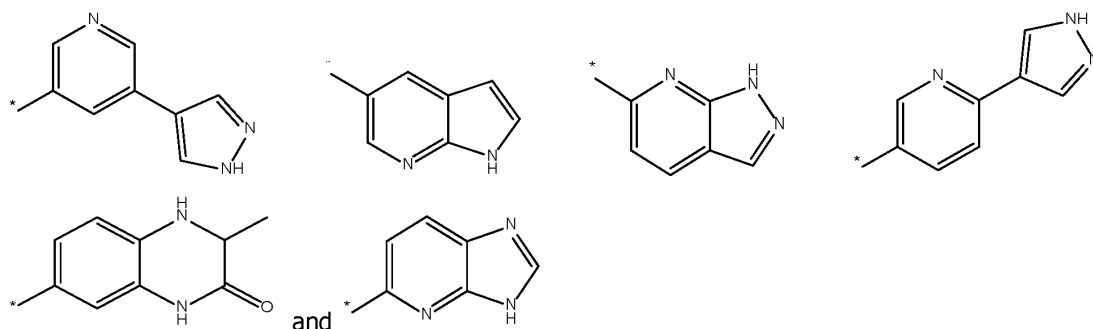




wherein Ring A is optionally substituted by halo, C₁₋₅alkyl, -OC₁₋₅alkyl, -OC₁₋₅haloalkyl, -NR^{4B}R^{5B},
 wherein wherein R^{4B} and R^{5B} are independently hydrogen or C₁₋₃alkyl, and where * indicates a binding
 5 site to L¹.

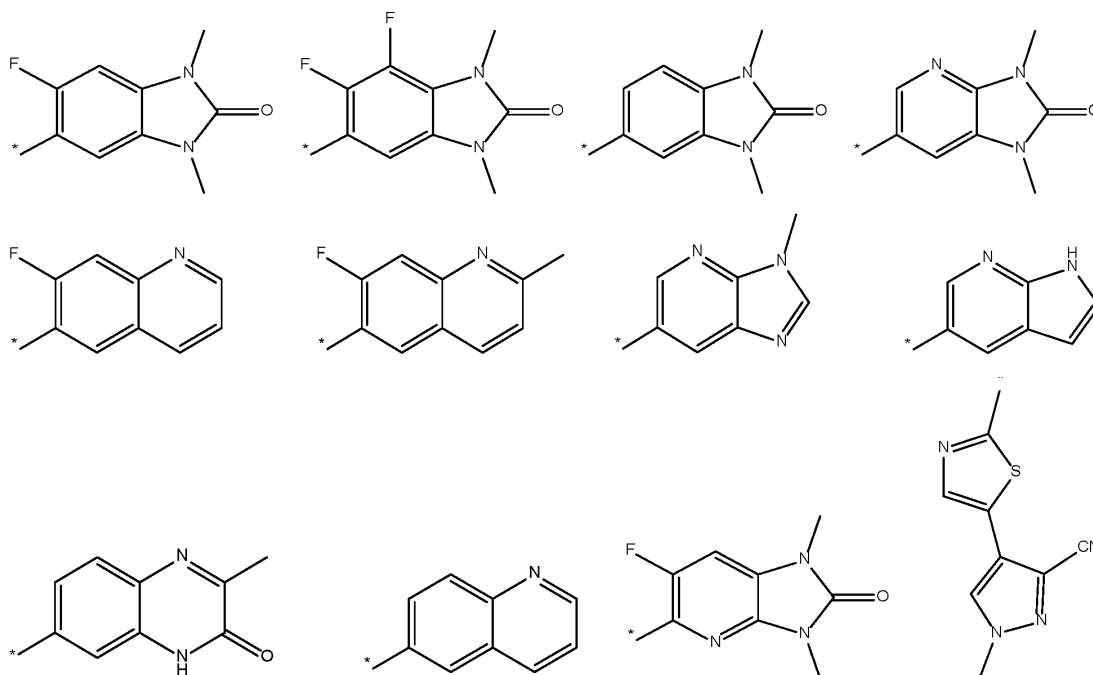
In one embodiment, Ring A is selected from the group consisting of:

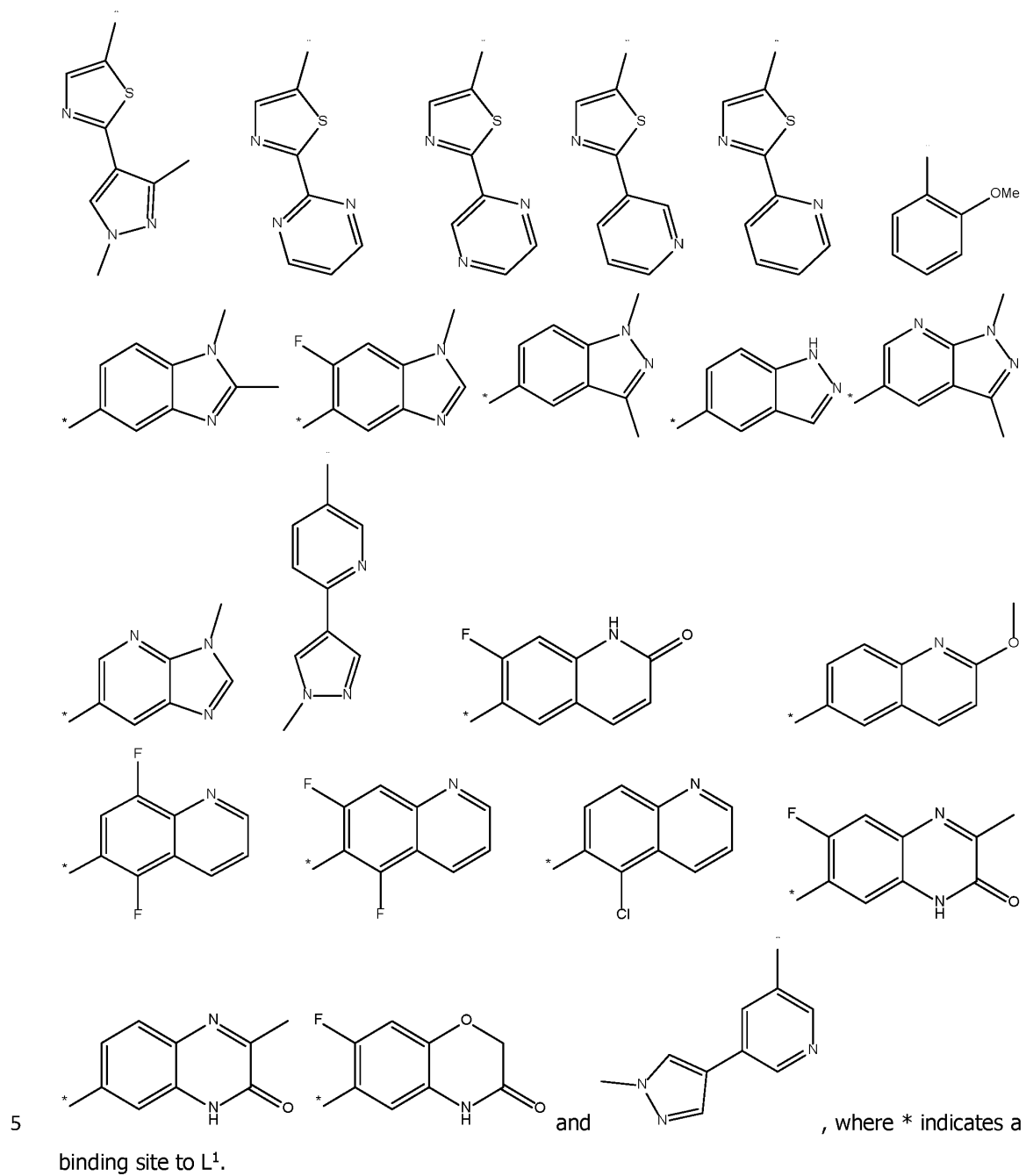




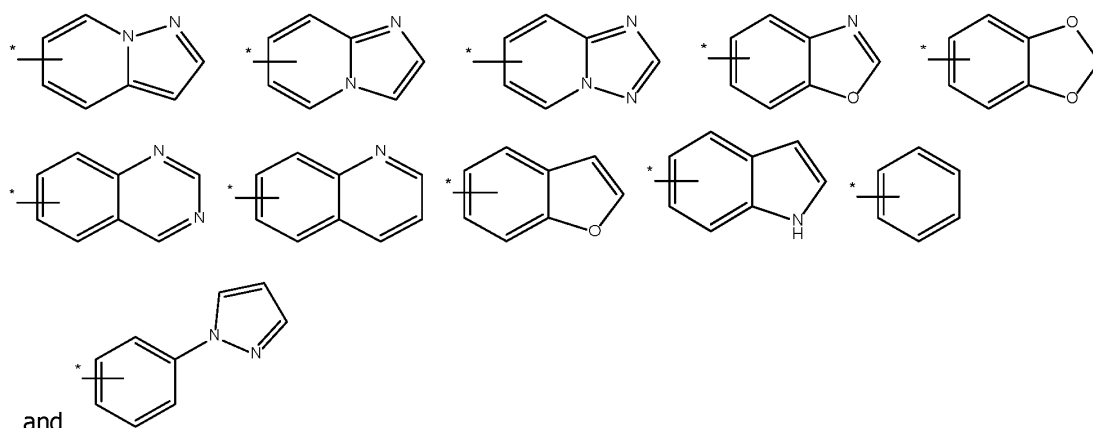
wherein Ring A is optionally substituted with one to five (e.g, one, two, three, four or five) substituents each independently selected from the group consisting of halo (e.g., fluoro), -C₁₋₃alkyl, -OC₁₋₃alkyl, -OC₁₋₃haloalkyl, and NR^{4b}R^{5b}, wherein R^{4b} and R^{5b} are each independently hydrogen or C₁₋₃alkyl, and where * indicates a binding site to L¹. In one embodiment, Ring A is substituted by one substituent. In one embodiment, Ring A is substituted by two substituents. In one embodiment, Ring A is substituted by three substituents. In one embodiment, Ring A is substituted by four substituents. In one embodiment, the substituent is selected from the group consisting of fluoro, methyl and oxo.

10 In one embodiment, Ring A is selected from the group consisting of:



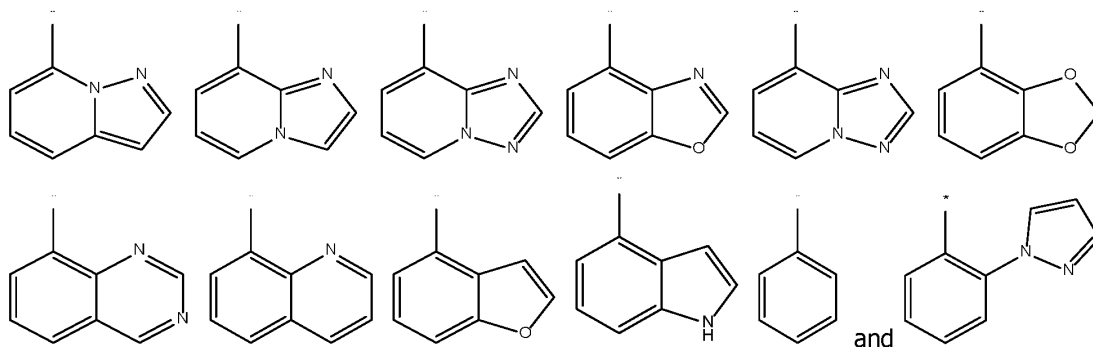


In one embodiment, Ring B is selected from the group consisting of:



wherein Ring B is optionally substituted with one to five substituents each independently selected from the group consisting of halo, C₁₋₅alkyl, -OC₁₋₅alkyl, -OC₁₋₅haloalkyl, and -NR^{4B}R^{5B}, wherein R^{4B} are independently hydrogen or C₁₋₃alkyl, where * indicates a binding site to L². In one embodiment, Ring B is substituted by one substituent. In one embodiment, Ring B is substituted by two substituents. In one embodiment, Ring B is substituted by three substituents. In one embodiment, Ring B is substituted by four substituents. In one embodiment, the substituent is selected from the group consisting of fluoro, methyl and oxo.

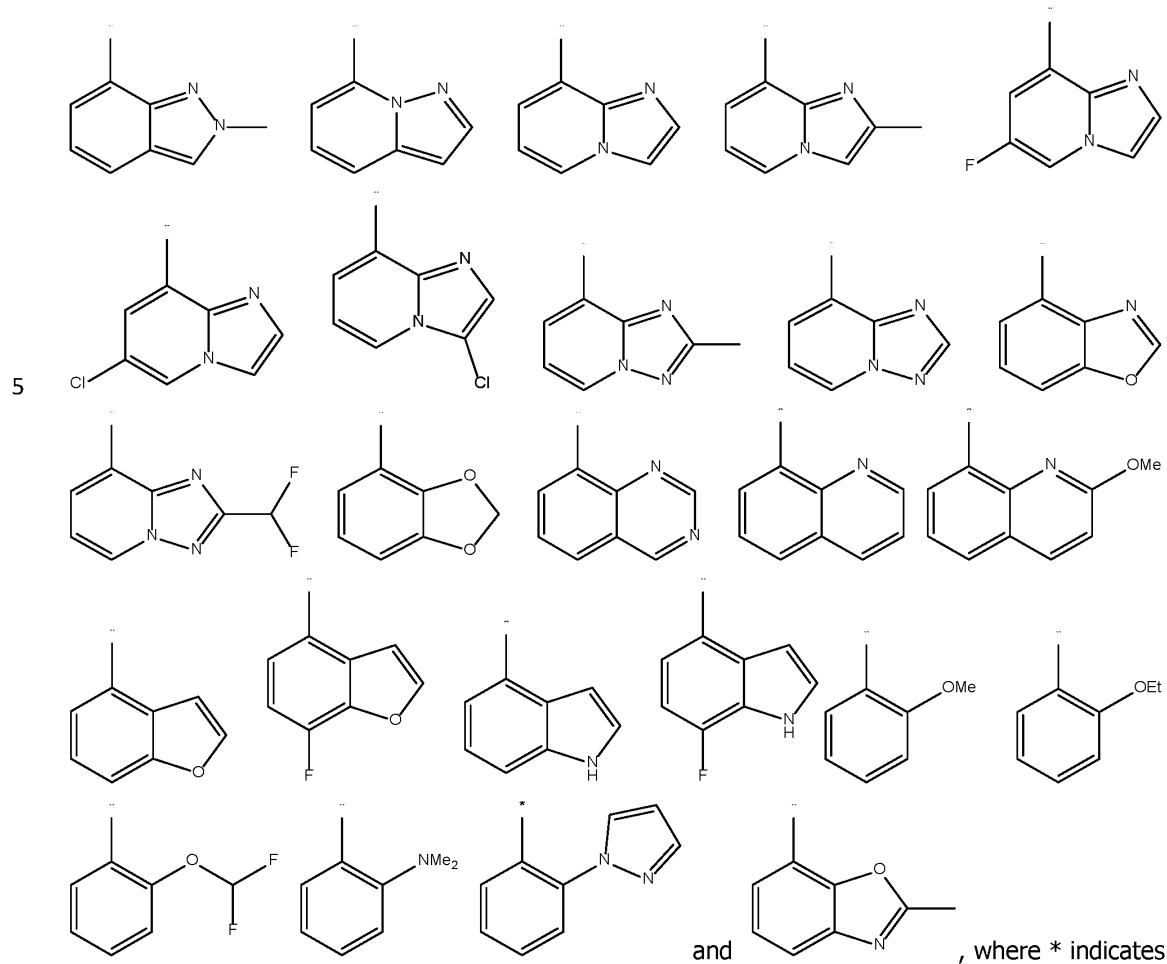
In one embodiment, Ring B is selected from the group consisting of:



wherein Ring B is optionally substituted by one to five substituents each independently selected from the group consisting of halo, -C₁₋₅alkyl, -OC₁₋₅alkyl, -OC₁₋₅haloalkyl, and -NR^{4B}R^{5B}, wherein R^{4B} are independently hydrogen or C₁₋₃alkyl, and where * indicates a binding site to L². In one embodiment, Ring A is substituted by one substituent. In one embodiment, Ring B is substituted by two substituents. In one embodiment, Ring B is substituted by three substituents. In one embodiment,

Ring B is substituted by four substituents. In one embodiment, the substituent is selected from the group consisting of fluoro, methyl and oxo.

In one embodiment, Ring B is selected from the group consisting of:



a binding site to L².

- 10 In one aspect, the present invention provides a compound selected from the group consisting of:

5-((((1S,2S,3R,4S)-2,3-Dihydroxy-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,2R,3S,4R)-2,3-Dihydroxy-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5 (1R,2S,3S,6S)-3-(((7-Fluoroquinolin-6-yl)methyl)amino)-6-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexane-1,2-diol;

(1S,2R,3R,6R)-3-(((7-Fluoroquinolin-6-yl)methyl)amino)-6-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexane-1,2-diol;

(1S,2R,3S,6S)-3-((2-Methoxybenzyl)amino)-6-((quinolin-6-ylmethyl)amino)cyclohexane-1,2-diol;

10 (1R,2S,3R,6R)-3-((2-Methoxybenzyl)amino)-6-((quinolin-6-ylmethyl)amino)cyclohexane-1,2-diol;

5-Fluoro-6-((((1S,2R,4S)-2-methoxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

15 (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)(methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol;

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((2-methyl-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)cyclohexan-1-ol;

20 (1R,2S,5S)-5-((benzo[d]oxazol-4-ylmethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-5-((1,2,4-Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

25 (1R,2S,5S)-2-(((6-Fluoroquinolin-7-yl)methyl)amino)-5-(((2-methoxyquinolin-8-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-5-((2-(1H-Pyrazol-1-yl)benzyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

- 5-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-((quinazolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-((2-methylbenzo[d]oxazol-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5 5-Fluoro-6-((((1S,2R,4S)-4-(((6-fluoroimidazo[1,2-a]pyridin-8-yl)methyl)amino)-2-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 6-((((1S,2R,4S)-4-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-hydroxycyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,5S)-2-(((8-Fluoro-2-methylquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- 10 5-Fluoro-6-((((1S,3R,4S)-3-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 7-((((1S,2R,4S)-4-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-hydroxycyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;
- 15 5-((((1R,2S,4R)-4-((2-(Difluoromethoxy)benzyl)amino)-2-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1S,2S,4S)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 20 5-((((1S,2S,4S)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- (1S,2S,5S)-5-(((7-fluoroquinolin-6-yl)methyl)amino)-2-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- 5-((((1S,2S,4S)-2-Hydroxy-4-((quinolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 25 6-fluoro-5-((((1R,2S,4S)-2-fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- 5-Fluoro-6-((((1R,3S,4R)-3-hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

- 4-(5-(((1S,2R,4S)-2-Hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-thiazol-2-yl)-1-methyl-1H-pyrazole-3-carbonitrile;
- 5-Fluoro-6-(((1R,2R,4R)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5 (1R,2S,5S)-5-((2-Methoxybenzyl)amino)-2-((quinolin-8-ylmethyl)amino)cyclohexan-1-ol;
- (1S,2R,5R)-2-(((1,2-Dimethyl-1H-benzo[d]imidazol-5-yl)methyl)amino)-5-((2-methoxybenzyl)amino)cyclohexan-1-ol;
- (1S,2R,5R)-2-(((1,3-Dimethyl-1H-indazol-5-yl)methyl)amino)-5-((2-methoxybenzyl)amino)cyclohexan-1-ol;
- 10 5-(((4aR,7R,8aS)-7-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((4aS,7R,8aR)-7-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 1,3-Dimethyl-5-(((4aR,7R,8aS)-7-((quinolin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 15 5-Fluoro-6-(((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((1R,2S,4R)-4-((Benzo[d][1,3]dioxol-4-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 20 5-(((1R,2S,4R)-4-((2-(Dimethylamino)benzyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((1R,2S,4R)-4-((6-Chloroimidazo[1,2-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 25 5-(((1R,2S,4R)-4-((3-Chloroimidazo[1,2-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((1R,2S,4R)-2-Fluoro-4-((2-methylimidazo[1,2-a]pyridin-8-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,2S,4R)-4-(((2-(Difluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,4R)-2,2-Difluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5 (1R,4R)-2,2-Difluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)cyclohexane-1,4-diamine;

(1R,4R)-2,2-Difluoro-N¹-((7-Fluoroquinolin-6-yl)methyl)-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;

10 7-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-quinolin-2(1H)-one;

(1R,2S,5S)-5-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)-2-(((2-methoxyquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((5,8-Difluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

15 (1R,2S,5S)-2-(((5,7-Difluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((5-Chloroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

20 6-fluoro-7-((((1S,2R,4S)-2-hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;

(1R,2S,5S)-2-(((2-(1,3-Dimethyl-1H-pyrazol-4-yl)thiazol-5-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((2-methyl-2H-indazol-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

25 5-((((1S,3S,4S)-4-(((3a,7a-Dihydrobenzo[d]oxazol-4-yl)methyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,2S,4R)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)-methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

- 5-((((1R,2S,4R)-2-Fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,4R)-2-Fluoro-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)-N¹-((2-(pyrimidin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 5 7-((((1R,2S,4R)-2-Fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)quinazoline-2,4(1H,3H)-dione;
- (1R,2S,4R)-2-Fluoro-N¹-((2-(pyrazin-2-yl)thiazol-5-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;
- (1R,2S,4R)-2-Fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((2-(pyridin-3-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 10 (1R,2S,4R)-N¹-((1,3-Dimethyl-1H-pyrazolo[3,4-b]pyridin-6-yl)methyl)-2-fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;
- 6-Fluoro-5-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 15 (1R,2S,4R)-2-Fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((2-(pyridin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 6-((((1R,2S,4R)-4-((1,2,4-Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,4R)-N⁴-([1,2,4-Triazolo[1,5-a]pyridin-8-ylmethyl)-2-fluoro-N¹-((2-(pyrazin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 20 6-((((1S,2R,4S)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- 7-((((1S,2R,4S)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;
- 25 5-((((1S,2R,4S)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 7-fluoro-6-((((1S,2R,4S)-2-fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one;

(1S,2R,4S)-2-fluoro-N¹-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;

(1S,2R,4S)-2-fluoro-N¹-((6-fluoro-1-methyl-1H-benzo[d]imidazol-5-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;

5 5-((((1R,4R)-4-((Benzo[d]oxazol-4-ylmethyl)amino)-2,2-difluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,4R)-2,2-difluoro-4-((7-fluorobenzofuran-4-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

10 5-((((1R,4R)-2,2-difluoro-4-((7-fluoro-1H-indol-4-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,4R)-2,2-Difluoro-4-((quinolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,2S,4R)-4-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

15 (1R,2S,4R)-2-Fluoro-N¹-((7-fluoroquinolin-6-yl)methyl)-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;

4,5-Difluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

20 5-((((1S,3R,4S)-4-((2-Ethoxybenzyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

(1S,2R,4S)-N¹-(2-Ethoxybenzyl)-2-fluoro-N⁴-((3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)methyl)cyclohexane-1,4-diamine;

(1S,2R,4S)-N⁴-((1H-Pyrrolo[2,3-b]pyridin-5-yl)methyl)-N¹-(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine;

25 (1S,2R,4S)-N⁴-((1H-Indazol-5-yl)methyl)-N¹-(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine;

5-((((1S,3S,4S)-3-Fluoro-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

(1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-(((R)-1-(pyrazolo[1,5-a]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(pyrazolo[1,5-a]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol;

5 (1R,2S,5S)-5-(((R)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-5-(((S)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

10 (1R,2S,5S)-5-(((R)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-5-(((S)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

15 (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

20 (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

25 5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one; and

(1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl-
d₂)amino)cyclohexan-1-ol;

5-((((1*R*,2*S*,4*R*,6*R*)-2-fluoro-6-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-
ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

5 (1*R*,2*R*,3*S*,5*R*)-3-fluoro-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-
ylmethyl)amino)cyclohexan-1-ol;

(1*R*,2*R*,3*S*,5*R*)-2-(((1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)methyl)amino)-3-fluoro-5-
((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

10 4,5-difluoro-6-((((1*R*,2*S*,4*R*,6*R*)-2-fluoro-6-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-
ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

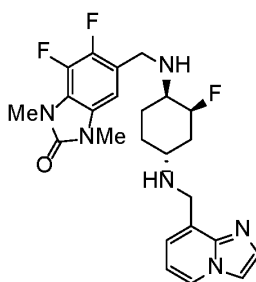
5-fluoro-6-((((1*R*,2*S*,4*R*,6*R*)-2-fluoro-6-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-
ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

6-((((1*R*,2*S*,4*R*,6*R*)-4-((1,2,4]triazolo[1,5-*a*]pyridin-8-ylmethyl)amino)-2-fluoro-6-
hydroxycyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

15 (1*R*,2*R*,3*S*,5*R*)-3-fluoro-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-2-(((5-(1-methyl-1*H*-
pyrazol-4-yl)pyridin-3-yl)methyl)amino)cyclohexan-1-ol;

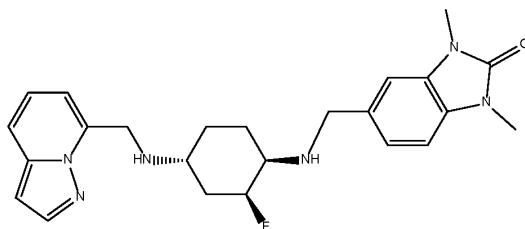
or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound which is 4,5-Difluoro-6-((((1*R*,2*S*,4*R*)-
2-fluoro-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-
20 dihydro-2*H*-benzo[*d*]imidazol-2-one as represented by the following structure



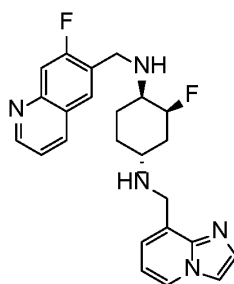
or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound which is 5-((((1R,2S,4R)-2-fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



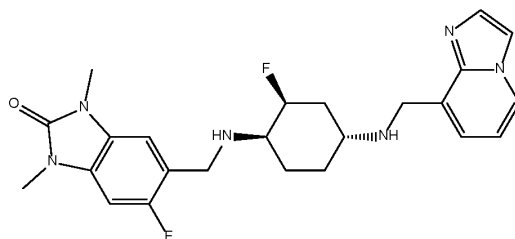
5 or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound which is (1R,2S,4R)-2-Fluoro-*N*⁴-((7-fluoroquinolin-6-yl)methyl)-*N*¹-(imidazo[1,2-*a*]pyridin-8-ylmethyl)cyclohexane-1,4-diamine as represented by the following structure



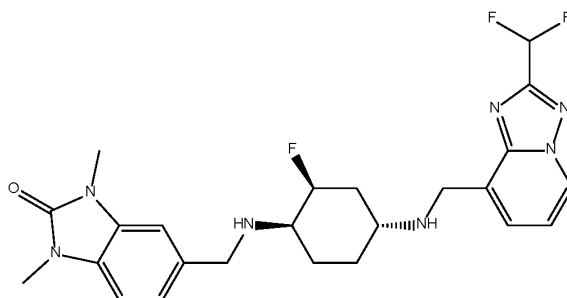
10 or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound which is 5-fluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



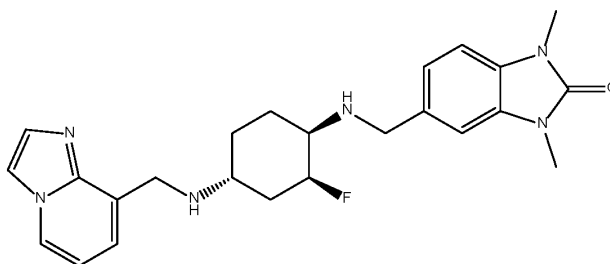
15 or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound which is 5-((((1R,2S,4R)-4-(((2-(difluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



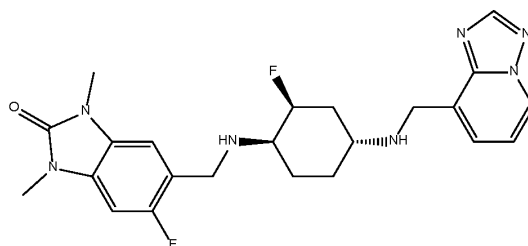
5 or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound which is 5-((((1R,2S,4R)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-yl)methyl)amino)cyclohexyl)amino)-methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



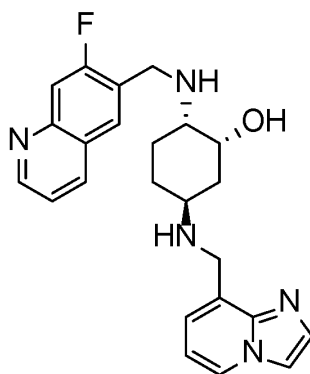
10 or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound which is 5-((((1R,2S,4R)-4-(((1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



15 or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound which is (1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol as represented by the following structure:



5 or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may also contain unnatural amounts of isotopes at one or more of the atoms that constitute such compounds. Unnatural amounts of an isotope may be defined as ranging from the amount found in nature to an amount 100% of the atom in question. That differ only in the presence of one or more isotopically enriched atoms. The present invention also includes

10 all suitable isotopic variations of a compound of formula (I) or a pharmaceutically acceptable salt thereof. An isotopic variation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Exemplary isotopes that can be incorporated into compounds of the present invention, such as a compound of

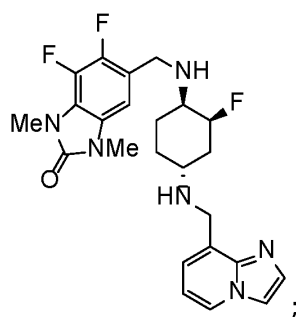
15 Formula (I) (and any embodiment thereof disclosed herein including specific compounds) include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}N , ^{15}O , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , ^{123}I , and ^{125}I . Certain isotopic variations of a compound of formula (I) or a salt or solvate thereof, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue

20 distribution studies. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Thus, in one embodiment, the present invention includes Examples 1-93 (e.g., 1-86)

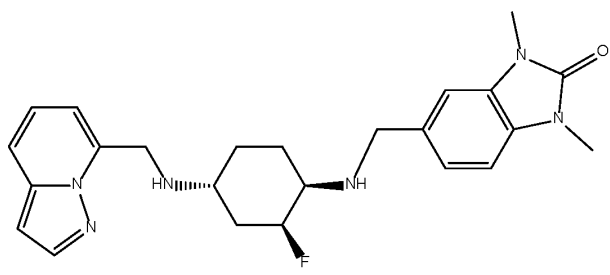
25 wherein one or more hydrogen atoms attached to carbon atoms are replaced by deuterium. Isotopic

variations of a compound of formula (I), or a pharmaceutically salt thereof, can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples hereafter using appropriate isotopic variations of suitable reagents. In one embodiment, the present invention includes:

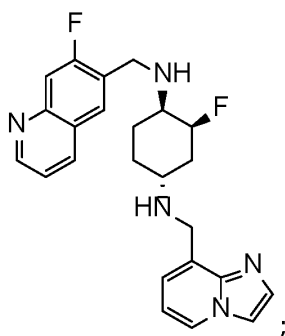
- 5 4,5-Difluoro-6-((((1*R*,2*S*,4*R*)-2-fluoro-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one as represented by the following structure:



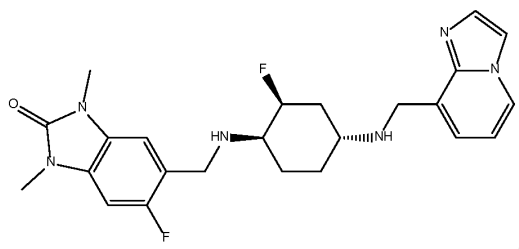
- 10 5-((((1*R*,2*S*,4*R*)-2-fluoro-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one as represented by the following structure:



(1*R*,2*S*,4*R*)-2-Fluoro-*N*⁴-((7-fluoroquinolin-6-yl)methyl)-*N*¹-(imidazo[1,2-*a*]pyridin-8-ylmethyl)cyclohexane-1,4-diamine as represented by the following structure:

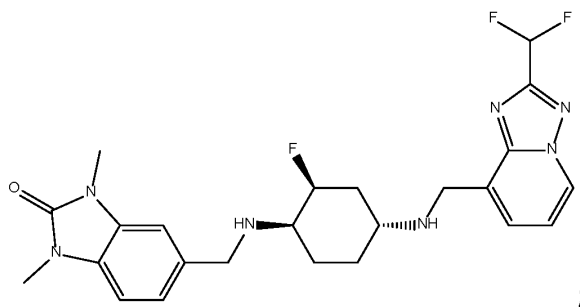


5-fluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:

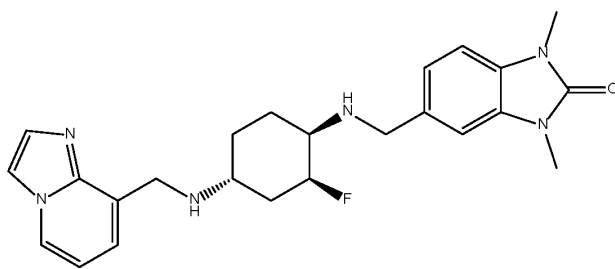


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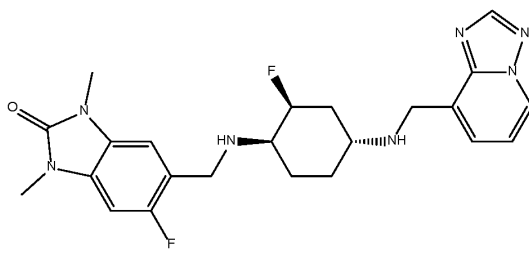
5-((((1R,2S,4R)-4-(((2-(difluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



10 5-((((1R,2S,4R)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)-methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:

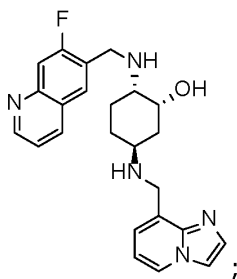


5-((((1R,2S,4R)-4-([1,2,4]triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



5

(1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol as represented by the following structure:



wherein one or more hydrogen atoms attached to carbon atoms are replaced by deuterium. Isotopic variations of a compound of formula (I), or a pharmaceutically salt thereof, can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Examples hereafter using appropriate isotopic variations of suitable reagents.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof of the invention as disclosed herein and a pharmaceutically acceptable excipient. For example, a pharmaceutical composition comprising a

compound or pharmaceutically acceptable salt thereof of any one of Examples 1 to 93 (e.g., 1 to 86) and a pharmaceutically acceptable excipient.

In another aspect, the present invention provides compounds of Formula (I) or a pharmaceutically acceptable salt thereof as disclosed herein, suitable for use in therapy. In one embodiment, the present invention provides a compound or pharmaceutically acceptable salt thereof of Examples 1 to 93 (e.g., 1 to 86) for use in therapy.

In another aspect, the present invention provides a compound or pharmaceutically acceptable salt thereof of the invention as disclosed herein, suitable for use in the treatment of cancer. In a further embodiment, the cancer is characterised by MSI-H and/or dMMR.

In another aspect, the present invention provides a method for treating a cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt thereof of the invention as disclosed herein.

In another aspect, the present invention provides a method of treating a cancer characterized by MSI-H and/or dMMR in a patient comprising administering to the patient, a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof as disclosed herein, or a pharmaceutically acceptable salt thereof. In an embodiment, the patient is in recognized need of such treatment. In an embodiment, the Compounds of Formula (I) or pharmaceutically acceptable salts thereof are administered in a pharmaceutical composition.

In an embodiment, the cancer is characterized by MSI-L or MSI-H according to any method known in the art. For example, a cancer characterized by MSI-L or MSI-H can comprise one or more MSI markers (MSI-L), or preferably two or more MSI markers (MSI-H), in each case selected from the group consisting of BAT25, BAT26, D2S123, D5S346, and D17S250. In an embodiment, the cancer is characterized by dMMR and comprises a mutation that impairs DNA mismatch repair, preferably the cancer comprises a mutation in a MutS homolog and/or a mutation in a MutL homolog. In a subembodiment, the MutS homolog is selected from the group consisting of MSH2, MSH3, and MSH6, and the MutL homolog is selected from the group consisting of MLH1, MLH3, PMS1, and PMS2, with some embodiments having a mutation in MLH1, MSH2, and/or PMS2.

In another aspect, the present invention provides Compounds of Formula (I) or pharmaceutically acceptable salts thereof disclosed herein, or a pharmaceutically acceptable salt thereof, is suitable for use in the treatment of cancer characterized by high MSI and/or dMMR in a patient. In an embodiment, the patient is in recognized need of such treatment. In an embodiment, the compound of the present

invention or a pharmaceutically acceptable salt thereof is administered in a pharmaceutical composition. In an embodiment, the cancer is characterized by MSI-L or MSI-H according to any method known in the art. For example, a cancer characterized by MSI-L or MSI-H can comprise one or more MSI markers (MSI-L), or preferably two or more MSI markers (MSI-H), in each case selected
5 from the group consisting of BAT25, BAT26, D2S123, D5S346, and D17S250. In an embodiment, the cancer is characterized by dMMR and comprises a mutation that impairs DNA mismatch repair, preferably the cancer comprises a mutation in a MutS homolog and/or a mutation in a MutL homolog. In an embodiment, the MutS homolog is selected from the group consisting of MSH2, MSH3, and MSH6, and the MutL homolog is selected from the group consisting of MLH1, MLH3, PMS1, and PMS2,
10 with some embodiments having a mutation in MLH1, MSH2, and/or PMS2.

In another aspect, the present invention provides a method of treating a cancer in a patient, comprising:

- (i) determining if the cancer comprises high MSI and/or dMMR; and
- (ii) if the cancer comprises high MSI and/or dMMR, then administering to the patient a
15 therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof as disclosed herein.

In an embodiment, provided herein is a Compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt thereof, suitable for use in a method of treating an individual with a proliferative disease, the method comprising determining the presence of a low
20 microsatellite instability (MSI-L) or preferably, a high microsatellite instability (MSI-H), or a marker associated with an MSI-L or an MSI-H, in a population of proliferative cells from the individual, determining a likelihood that the individual will respond to a therapy comprising administering to the individual said compound of Formula (I) or a pharmaceutically acceptable salt thereof as disclosed herein, or a pharmaceutically acceptable salt thereof, based on the determination of the presence of
25 MSI-L or MSI-H, respectively, or a marker associated with MSI-L or MSI-H, respectively, in the population of proliferative cells, and administering to the individual said compound of Formula (I) or a pharmaceutically acceptable salt thereof as disclosed herein, if the individual is predicted to respond to the therapy. In some embodiments, the determination of the presence of MSI-L or MSI-H in the population of proliferative cells comprises determining the presence of one or more MSI markers (MSI-
30 L), preferably two or more MSI markers (MSI-H), in each case selected from the group consisting of BAT25, BAT26, D2S123, D5S346, and D17S250. In some embodiments, the individual is predicted to respond to the therapy if the amount of cells in the population of proliferative cells determined to have

at least one of the MSI markers (MSI-L), or preferably at least two of the MSI markers (MSI-H), respectively above a pre-determined threshold for the proliferative disease. In some embodiments, the individual is predicted not to respond to the therapy if (a) the amount of cells in the population of proliferative cells determined to have at least one of the MSI markers (MSI-L), or preferably at least
5 two of the MSI markers (MSI-H) , respectively, below a pre-determined threshold for the proliferative disease; or (b) the population of proliferative cells is determined to have none of the MSI markers (e.g., is considered microsatellite stable (MSS)).

In an embodiment, according to any of the embodiments described above, the determination of the presence of a marker associated with MSI-H in the population of proliferative cells comprises
10 determining the presence of a mutation that impairs DNA mismatch repair. In some embodiments, the mutation comprises a mutation in a MutS homolog and/or a mutation in a MutL homolog. In some embodiments, the MutS homolog is selected from the group consisting of MSH2, MSH3, and MSH6, and the MutL homolog is selected from the group consisting of MLH1, MLH3, PMS1, and PMS2. In some embodiments, the mutation comprises a mutation in MLH1, MSH2, and/or PMS2.

15 In some embodiments, according to any of the embodiments described above, the determination of the presence of a marker associated with MSI-H in the population of proliferative cells comprises determining the presence of one or more markers of DNA damage. In some embodiments, the one or more markers of DNA damage are selected from the group consisting of high p21 expression and high γ H2AX expression.

20 In some embodiments, according to any of the embodiments described above, the individual is predicted to respond to the therapy if the amount of cells in the population of proliferative cells determined to have (i) at least one mutation that impairs DNA mismatch repair and/or (ii) at least one marker of DNA damage is above a pre-determined threshold for the proliferative disease. In some
25 embodiments, the at least one mutation that impairs DNA mismatch repair comprises a mutation in MLH1, MSH2, and/or PMS2, and the at least one marker of DNA damage comprises high p21 expression and/or high γ H2AX expression.

In one approach for this embodiment, the cancer can be characterized by MSI-H according to any method known in the art. For example, a cancer characterized by MSI-H can comprise two or more MSI markers selected from the group consisting of BAT25, BAT26, D2S123, D5S346, and D17S250.

30 In an embodiment, the cancer is characterized by dMMR and comprises a mutation that impairs DNA mismatch repair, preferably the cancer comprises a mutation in a MutS homolog and/or a mutation in a MutL homolog. In an embodiment, the MutS homolog is selected from the group consisting of

MSH2, MSH3, and MSH6, and the MutL homolog is selected from the group consisting of MLH1, MLH3, PMS1, and PMS2, preferably a mutation in MLH1, MSH2, and/or PMS2. In an embodiment, the cancer comprises two or more markers of DNA damage.

5 In an embodiment, the cancer is endometrial cancer, biliary cancer, gastric cancer, pancreatic cancer, small intestine cancer, breast cancer, prostate cancer, bladder cancer, esophageal cancer, sarcoma, retroperitoneal adenocarcinoma, small lung cancer or renal cell cancer. Preferably, the cancer is uterine corpus endometrial carcinoma, stomach adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, prostate adenocarcinoma, adrenal cortical carcinoma, oesophageal carcinoma, liver hepatocellular carcinoma, cervical squamous cell carcinoma, head and neck squamous cell carcinoma, 10 lung squamous cell carcinoma, kidney renal clear cell carcinoma, papillary kidney carcinoma, pancreatic cancer, urothelial bladder cancer, ovarian cancer, breast cancer, glioblastoma multiforme, or low grade glioma (see Isidro Cortes-Ciriano et. al. Nature Communication DOI: 10.1038/ncomms15180).

In one embodiment, the cancer is colorectal cancer. In one embodiment, the present invention 15 provides Compounds of Formula (I) or pharmaceutically acceptable salts thereof disclosed herein (e.g., the compounds of Examples 1 to 93 or a pharmaceutically acceptable salt thereof) for use in the treatment of colorectal cancer characterized by high MSI and/or dMMR in a patient. In one embodiment, the present invention provides a method of treatment comprising administering a Compound of Formula (I) or a pharmaceutically acceptable salt thereof disclosed herein (e.g., the 20 compounds of Examples 1 to 93 or a pharmaceutically acceptable salt thereof) in a patient that has colorectal cancer characterized by high MSI and/or dMMR.

Pharmaceutical Composition

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof, provided herein may be in the form of compositions suitable for administration to a subject. In general, such compositions 25 are pharmaceutical compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients. The pharmaceutical compositions may be used in the methods disclosed herein; thus, for example, the pharmaceutical compositions can be administered *ex vivo* or *in vivo* to a subject in order to practice the therapeutic methods and uses described herein.

30 The pharmaceutical compositions can be formulated to be compatible with the intended method or route of administration; exemplary routes of administration are set forth herein. Furthermore, the pharmaceutical compositions may be used in combination with other therapeutically active agents or

compounds as described herein in order to treat the diseases, disorders and conditions contemplated by the present invention.

The pharmaceutical compositions containing the active ingredient (e.g., a compound of Formula (I), a pharmaceutically acceptable salt thereof) may be in a form suitable for oral use, for example, as
5 tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups, solutions, microbeads or elixirs. Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents and preserving
10 agents in order to provide pharmaceutically elegant and palatable preparations. Tablets and/or capsules contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets and/or capsules. These excipients may be, for example, diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid;
15 binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc.

The pharmaceutical compositions typically comprise a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipient. Suitable pharmaceutically acceptable excipients include, but are not limited to,
20 antioxidants (e.g., ascorbic acid and sodium bisulfate), preservatives (e.g., benzyl alcohol, methyl parabens, ethyl or n-propyl, p-hydroxybenzoate), emulsifying agents, suspending agents, dispersing agents, solvents, fillers, bulking agents, detergents, buffers, vehicles, diluents, and/or adjuvants. For example, a suitable vehicle may be physiological saline solution or citrate buffered saline, possibly supplemented with other materials common in pharmaceutical compositions for parenteral
25 administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Those skilled in the art will readily recognize a variety of buffers that can be used in the pharmaceutical compositions and dosage forms contemplated herein. Typical buffers include, but are not limited to, pharmaceutically acceptable weak acids, weak bases, or mixtures thereof. As an example, the buffer components can be water soluble materials such as phosphoric acid, tartaric acids,
30 lactic acid, succinic acid, citric acid, acetic acid, ascorbic acid, aspartic acid, glutamic acid, and salts thereof. Acceptable buffering agents include, for example, a Tris buffer, N-(2-Hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid) (HEPES), 2-(N-Morpholino)ethanesulfonic acid

(MES), 2-(N-Morpholino)ethanesulfonic acid sodium salt (MES), 3-(N-Morpholino)propanesulfonic acid (MOPS), and N-tris[Hydroxymethyl]methyl-3-aminopropanesulfonic acid (TAPS).

All the compounds and pharmaceutical compositions provided herein can be used in all the methods provided herein. For example, the compounds and pharmaceutical compositions provided herein can be used in all the methods for treatment and/or prevention of all diseases or disorders provided herein. Thus, the compounds and pharmaceutical compositions provided herein are for use as a medicament.

Routes of Administration

Compounds of Formula (I), or a pharmaceutically acceptable salt thereof and compositions containing the same may be administered in any appropriate manner. Suitable routes of administration include oral, parenteral (e.g., intramuscular, intravenous, subcutaneous (e.g., injection or implant), intraperitoneal, intracisternal, intraarticular, intracerebral (intraparenchymal) and intracerebroventricular), sublingual, intraocular, and inhalation. Depot injections, which are generally administered subcutaneously or intramuscularly, may also be utilized to administer the compounds of Formula (I), or a pharmaceutically acceptable salt thereof over a defined period of time. Particular embodiments of the present invention contemplate oral administration.

Treatment of Patients Having Tumors Characterized by High Microsatellite Instability

In one aspect, provided herein is a method for decreasing proliferation in a proliferative cell having a microsatellite instability (MSI), comprising administering a compound of Formula (I) or pharmaceutically acceptable salt thereof as described herein. In some embodiments, the proliferative cell is characterized as having MSI low (MSI-L). In some embodiments, the proliferative cell is characterized as having high MSI (MSI-H), used interchangeably with MIS-high. Cells can be characterized as MSI, including MSI-L or MSI-H, or as microsatellite stable (MSS), according to any method known in the art (*see*, for example, Dudley, Jonathan C., *et al.*, *Clinical Cancer Research*, 22(4): 813-820, 2016.). MSI-H is used to classify tumors as having a high frequency of MSI. A tumor can be classified as MSI, including MSI-low or MSI-high, using polymerase chain reaction (PCR) and/or immunohistochemistry (IHC) assays. As stated in Dudley et al. (*supra*), a tumor is classified as MSI-H by PCR if (i) there is a shift (usually downward) in the size of at least two microsatellite loci from a reference panel of five microsatellite loci in tumor relative to normal, where the reference panel can be the "Bethesda Panel," also referred to herein as the "NCI-Reference Panel (Bethesda, 1998)", which includes two mononucleotide loci (BAT-25 and BAT-26) and three dinucleotide loci (D2S123, D5S346, and D17S250), or alternatively, the reference panel can be Promega Corporation's MSI Analysis System, which includes five mononucleotide loci (BAT-25, BAT-

26, NR-21, NR-24, and MONO-27); or (ii) there is a shift in the size of 30% or more microsatellite loci from a reference panel of more than five microsatellite loci in tumor relative to normal. The MSI-H phenotype is associated with germline defects in the mismatch repair genes MLH1, MSH2, MSH6, and PMS2, and is the primary phenotype observed in tumors from patients with HNPCC/Lynch syndrome.

- 5 A tumor is classified as MSI-H in IHC test if it shows a loss of protein expression for at least 1 of the above 4 mismatch repair genes. Cells can be similarly classified as MSI-H using the tests described herein for tumors.

10 In some embodiments, a tumor or cell is classified as MSI-H using PCR to amplify the five microsatellite loci of the "Bethesda Panel" (BAT-25, BAT-26, D2S123, D5S346, and D17S250) from both tumor tissue or cells and normal tissue or cells, wherein the tumor or cell is classified as MSI-H if there is a shift in the size of at least two of the microsatellite loci from the tumor tissue or cells relative to the normal tissue or cells. In some embodiments, the shift in size of the microsatellite loci is a downward shift.

15 In some embodiments, a tumor or cell is classified as MSI-H using PCR to amplify the five microsatellite loci of Promega Corporation's MSI Analysis System (BAT-25, BAT-26, NR-21, NR-24, and MONO-27) from both tumor tissue or cells and normal tissue or cells, wherein the tumor or cell is classified as MSI-H if there is a shift in the size of at least two of the microsatellite loci from the tumor tissue or cells relative to the normal tissue or cells. In some embodiments, the shift in size of the microsatellite loci is a downward shift.

20 In some embodiments, a tumor is classified as MSI-H using IHC to determine the expression level of the MMR proteins MLH1, MSH2, MSH6, and/or PMS2 in both tumor tissue and normal tissue, wherein the tumor is classified as MSI-H if there is a loss of protein expression for at least one of the MMR proteins in the tumor tissue relative to the normal tissue. In some embodiments, the loss of protein expression is a decrease of at least 20% (such as a decrease of 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or more).

25 In contrast, a tumor is classified as MSI-L by PCR if (i) there is a shift in the size of one microsatellite locus from a reference panel of five microsatellite loci in tumor relative to normal, where the reference panel can be the "Bethesda Panel" or Promega Corporation's MSI Analysis System; or (ii) there is a shift in the size of less than 30% microsatellite loci from a reference panel of more than five microsatellite loci in tumor relative to normal. MSI-L tumors are thought to represent a distinct mutator
30 phenotype with potentially different molecular etiology than MSI-H tumors (Thibodeau, 1998; Wu et al., 1999, Am J Hum Genetics 65:1291-1298). Cells can be similarly classified as MSI-L using the tests described herein for tumors.

Combination Therapy

The present invention contemplates the use of compounds of Formula (I), or a pharmaceutically acceptable salt thereof in combination with one or more active therapeutic agents (e.g., chemotherapeutic agents) or other prophylactic or therapeutic modalities (e.g., radiation). In such combination therapy, the various active agents frequently have different, complementary mechanisms of action. Such combination therapy may be especially advantageous by allowing a dose reduction of one or more of the agents, thereby reducing or eliminating the adverse effects associated with one or more of the agents. Furthermore, such combination therapy may have a synergistic therapeutic or prophylactic effect on the underlying disease, disorder, or condition.

As used herein, "combination" is meant to include therapies that can be administered separately, for example, formulated separately for separate administration (e.g., as may be provided in a kit), and therapies that can be administered together in a single formulation (i.e., a "co-formulation").

In certain embodiments, the compounds of Formula (I), or a pharmaceutically acceptable salt thereof are administered or applied sequentially, e.g., where one agent is administered prior to one or more other agents. In other embodiments, the compounds of Formula (I), or a pharmaceutically acceptable salt thereof are administered simultaneously, e.g., where two or more agents are administered at or about the same time; the two or more agents may be present in two or more separate formulations or combined into a single formulation (i.e., a co-formulation). Regardless of whether the two or more agents are administered sequentially or simultaneously, they are considered to be administered in combination for purposes of the present invention.

The present invention provides methods for treating cancer with a compound of Formula (I), or a pharmaceutically acceptable salt thereof and at least one additional therapeutic or diagnostic agent.

In some embodiments, the compound of Formula (I), or a pharmaceutically acceptable salt thereof is administered in combination with at least one additional therapeutic agent, selected from Temozolomide, Pemetrexed, Pegylated liposomal doxorubicin (Doxil), Eribulin (Halaven), Ixabepilone (Ixempra), Protein-bound paclitaxel (Abraxane), Oxaliplatin, Irinotecan, Venatoclax (bcl2 inhibitor), 5-azacytadine, Anti-CD20 therapeutics, such as Rituxan and obinutuzumab, Hormonal agents (anastrozole, exemestand, letrozole, zoladex, lupon eligard), CDK4/6 inhibitors, Palbociclib, Abemaciclib, CPI (Avelumab, Cemiplimab-rwlc, and Bevacizumab).

In certain embodiments, the present invention provides methods for treating cancer comprising administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof described

herein in combination with a signal transduction inhibitor (STI) to achieve additive or synergistic suppression of tumor growth. As used herein, the term "signal transduction inhibitor" refers to an agent that selectively inhibits one or more steps in a signaling pathway. Examples of signal transduction inhibitors (STIs) useful in methods described herein include, but are not limited to: (i) bcr/abl kinase inhibitors (e.g., GLEEVEC); (ii) epidermal growth factor (EGF) receptor inhibitors, including kinase inhibitors and antibodies; (iii) her-2/neu receptor inhibitors (e.g., HERCEPTIN); (iv) inhibitors of Akt family kinases or the Akt pathway (e.g., rapamycin); (v) cell cycle kinase inhibitors (e.g., flavopiridol); and (vi) phosphatidyl inositol kinase inhibitors. Agents involved in immunomodulation can also be used in combination with one or more compounds of Formula (I), or a pharmaceutically acceptable salt thereof described herein for the suppression of tumor growth in cancer patients.

In certain embodiments, the present invention provides methods for treating cancer comprising administration of a compound of Formula (I), or a pharmaceutically acceptable salt thereof described herein in combination with a chemotherapeutic agent. Examples of chemotherapeutic agents include, but are not limited to, alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolmelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabacin, caminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU; androgens such as calusterone, dromostanolone propionate, epitostanol, mepitostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone;

aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; sizofiran; 5 spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (Ara-C); cyclophosphamide; thiotepa; taxoids, e.g., paclitaxel and doxetaxel; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum and platinum coordination complexes such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; 10 vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT11; topoisomerase inhibitors; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. In a particular embodiment, Compounds of Formula (I) or pharmaceutically acceptable salts thereof are coadministered with a cytostatic compound selected from the group consisting of cisplatin, 15 doxorubicin, taxol, taxotere and mitomycin C. In a particular embodiment, the cytostatic compound is doxorubicin.

Chemotherapeutic agents also include anti-hormonal agents that act to regulate or inhibit hormonal action on tumors such as anti-estrogens, including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, onapristone, and toremifene; 20 and antiandrogens such as flutamide, nilutamide, bicalutamide, enzalutamide, apalutamide, abiraterone acetate, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. In certain embodiments, combination therapy comprises administration of a hormone or related hormonal agent.

The present invention also contemplates the use of the compounds of Formula (I), or a 25 pharmaceutically acceptable salt thereof described herein in combination with immune checkpoint inhibitors. The tremendous number of genetic and epigenetic alterations that are characteristic of all cancers provides a diverse set of antigens that the immune system can use to distinguish tumor cells from their normal counterparts. In the case of T cells, the ultimate amplitude (e.g., levels of cytokine production or proliferation) and quality (e.g., the type of immune response generated, such as the 30 pattern of cytokine production) of the response, which is initiated through antigen recognition by the T-cell receptor (TCR), is regulated by a balance between co-stimulatory and inhibitory signals (immune checkpoints). Under normal physiological conditions, immune checkpoints are crucial for the prevention of autoimmunity (i.e., the maintenance of self-tolerance) and also for the protection of

tissues from damage when the immune system is responding to pathogenic infection. The expression of immune checkpoint proteins can be dysregulated by tumors as an important immune resistance mechanism. Examples of immune checkpoint inhibitors include but are not limited to CTLA-4, PD-1, PD-L1, BTLA, TIM3, LAG3, OX40, 41BB, VISTA, CD96, TGF β , CD73, CD39, A2AR, A2BR, IDO1, TDO2, Arginase, B7-H3, B7-H4. Cell-based modulators of anti-cancer immunity are also contemplated. Examples of such modulators include but are not limited to chimeric antigen receptor T-cells, tumor infiltrating T-cells, and dendritic-cells.

The present invention contemplates the use of compounds of Formula (I), or a pharmaceutically acceptable salt thereof described herein in combination with inhibitors of the aforementioned immune-checkpoint receptors and ligands, for example ipilimumab, abatacept, nivolumab, pembrolizumab, atezolizumab, dostarlimab, and durvalumab.

Additional treatment modalities that may be used in combination with a compound of Formula (I), or a pharmaceutically acceptable salt thereof disclosed herein include radiotherapy, a monoclonal antibody against a tumor antigen, a complex of a monoclonal antibody and toxin, a T-cell adjuvant, bone marrow transplant, or antigen presenting cells (e.g., dendritic cell therapy).

The present invention contemplates the use of compounds of Formula (I), or a pharmaceutically acceptable salt thereof described herein for the treatment of glioblastoma either alone or in combination with radiation and/or temozolomide (TMZ), avastin, or lomustine.

Dosing

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof provided herein may be administered to a subject in an amount that is dependent upon, for example, the goal of administration (e.g., the degree of resolution desired); the age, weight, sex, and health and physical condition of the subject to which the formulation is being administered; the route of administration; and the nature of the disease, disorder, condition or symptom thereof. The dosing regimen may also take into consideration the existence, nature, and extent of any adverse effects associated with the agent(s) being administered.

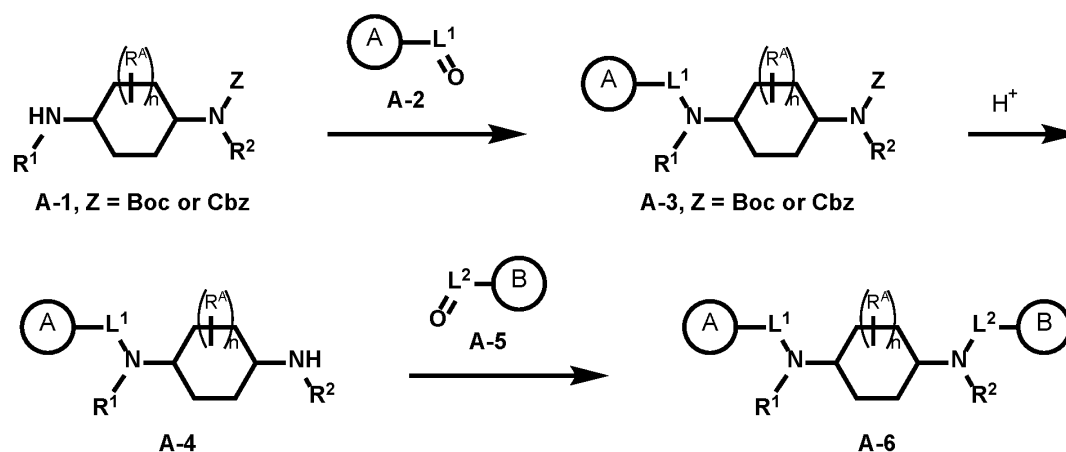
An effective dose (ED) is the dose or amount of an agent that produces a therapeutic response or desired effect in some fraction of the subjects taking it. The "median effective dose" or ED₅₀ of an agent is the dose or amount of an agent that produces a therapeutic response or desired effect in 50% of the population to which it is administered. Although the ED₅₀ is commonly used as a measure of reasonable expectance of an agent's effect, it is not necessarily the dose that a clinician might deem

appropriate taking into consideration all relevant factors. Thus, in some situations the effective amount is more than the calculated ED₅₀, in other situations the effective amount is less than the calculated ED₅₀, and in still other situations the effective amount is the same as the calculated ED₅₀.

GENERAL SYNTHETIC ROUTES

- 5 As illustrated in Scheme A, in general, compounds of Formula (I) or pharmaceutically acceptable salts thereof can be prepared by reductive amination reaction of an appropriately functionalized di-amine core A-1 with an aldehyde or ketone A-2 and reductant to give intermediates of A-3. These intermediates are then predisposed for deprotection by reaction with a variety of organic acids (Z=Boc or Cbz) or hydrogenation reaction (Z=Cbz) to afford intermediates of A-4. Intermediate A-4 can then
 10 undergo reductive amination reaction in the presence of an aldehyde or ketone source and reductant to deliver compounds of formula A-6. In some cases, the sequence of reductive amination reactions corresponding to Ring A and Ring B can be interchanged. In some instances, additional reductive amination reactions are required to install R¹ and R². In some embodiments, addition of Ti(OⁱPr)₄ can be utilized to promote imine condensation. Aldehydes of type A-2 or A-5 are commercially available
 15 or may be synthesized from the appropriate intermediates. The unique synthesis of di-amine cores of A-1 are disclosed within.

Scheme A



EXAMPLES

- 20 The following examples illustrate the invention. These examples are not intended to limit the scope of the present invention, but rather to provide guidance to the skilled artisan to prepare and use the compounds, compositions, and methods of the present invention. While embodiments of the present

invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the scope of the invention.

It will be understood by the skilled artisan that purification methods (using acidic or basic modifiers) or compound workup procedures (using acidic or basic conditions) may result in formation of a salt of a title compound (for example, hydrobromic acid, formic acid, hydrochloric acid, trifluoroacetic acid, or ammonia salts of a title compound). The present invention is intended to encompass such salts.

Final compounds were characterized with LCMS (conditions listed below) and NMR.

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Unless otherwise indicated, all temperatures are expressed in 0 °C (degrees Centigrade). Unless otherwise indicated, all reactions are conducted under an inert atmosphere at ambient temperature. All temperatures are given in degrees Celsius, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon (Ar) or nitrogen (N₂) atmosphere where necessary.

INSTRUMENTATION

¹H NMR or ¹⁹F NMR spectra were recorded using a BrukerAvance NEO NanoBay V4-3 400 MHz spectrometer, BrukerAvance III 400 MHz spectrometer, BrukerAvance III 500 MHz spectrometer, BrukerAvance 400 MHz spectrometer or Varian Mercury Plus-300 MHz spectrometer. CDCl₃ is deuteriochloroform, DMSO-d₆ is hexadeuteriodimethylsulfoxide, and CD₃OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (ppm) downfield from the internal standard tetramethylsilane (TMS) or the NMR solvent. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz.

Instrument 1: Mass spectra were run on open access LC-MS systems, Waters Acquity QDa mass detector. The compound is analyzed using a reverse phase column, e.g., Xbridge-C18, Sunfire-C18, Thermo Aquasil/Aquasil C18, Acquity HPLC C18, Thermo Hypersil Gold eluted using an acetonitrile and water gradient with a low percentage of an acid modifier such as 0.02% TFA.

Instrument 2: Mass spectra were run on open access LC-MS systems, Shimadzu, LC-20, AD column, MSD:LCMS-2010

HPLC METHODS

Method A: LCMS: Waters Acquity equipped with an Acquity CSH, C18 (2.1 mm × 30 mm, 1.7 µm column) using a gradient of 1-100% MeCN/H₂O/0.1% TFA over 1.85 min at 1.3 mL/min flow rate. Mass determinations were conducted using an Agilent 6110 Quadrupole MS with positive ESI;

5 **Method B:** LCMS: Waters Acquity equipped with an Acquity CSH, C18 (2.1 mm × 30 mm, 1.7 µm column) using a gradient of 1-100% MeCN/H₂O/0.1% 10 mM ammonium Bicarbonate in water adjusted to pH 10 with 25% ammonium hydroxide solution, over 1.85 min at 1.3 mL/min flow rate. Mass determinations were conducted using an Agilent 6110 Quadrupole MS with positive ESI;

10 **Method C:** HPLC: Agilent 1290 Infinity II equipped with a CSH, C18, 2.1 × 30 mm, 1.7 µm column, using a gradient of 3-97% MeCN/H₂O/0.1% HCO₂H over 2.0 min. at 1.0 mL/min flow rate. Mass determinations were conducted using an Agilent 6110 Quadrupole MS with positive ESI;

Method D: D1: Shimadzu LC-20AB, equipped with an Acquity CSH, C18 (2.1 mm × 30 mm, 1.7 µm column) using a gradient of 5-95% MeCN (0.02% TFA)/H₂O (0.04% TFA) over 6 min at 1.0 mL/min flow rate; **D2:** Shimadzu LC-20ADXR, equipped with an Acquity CSH, C18 (2.1 mm × 30 mm, 1.7 µm column) using a gradient of 10-80% MeCN (0.02% TFA)/H₂O (0.04% TFA) over 13 min at 0.5 mL/min
15 flow rate.

Method E: Shimadzu LC-20AD, equipped with a CSH, C18, 2.1 × 30 mm, 3.5 µm column, using a gradient of 10%-80% MeCN /H₂O (10 mM NH₄NHCO₃) over 13 min. at 0.5 mL/min flow rate.

Method F: F1: Shimadzu LC-20AB, equipped with a Gemini, C18, 50 × 2 mm, 5 µm column, using a gradient of 10%-80% MeCN /H₂O (10 mM NH₄NHCO₃) over 4.5 min. at 0.8 mL/min flow rate; **F2:**
20 Shimadzu LC-20AB, equipped with a Gemini, C18, 50 × 2 mm, 5 µm column, using a gradient of 5%-95% MeCN /H₂O (10 mM NH₄NHCO₃) over 3.5 min. at 1.0 mL/min flow rate.

Method G: G1: Shimadzu LC-20AD, equipped with an Acquity CSH, C18 (2.1 mm × 30 mm, 1.7 µm column) using a gradient of 5-95% MeCN (0.02% TFA)/H₂O (0.04% TFA) over 3.5 min at 1.0 mL/min flow rate; **G2:** Shimadzu LC-20AD, equipped with an Acquity CSH, C18 (2.1 mm × 30 mm, 1.7 µm
25 column) using a gradient of 10-80% MeCN (0.02% TFA)/H₂O (0.04% TFA) over 13 min at 0.5 mL/min flow rate.

Method H: H1: HPLC: Agilent 1260 HPLC equipped with a Luna, C18, 2.0 × 50 mm, 5 µm column, using a gradient of 5-95% MeCN (0.02% TFA)/H₂O (0.04% TFA) over 6.0 min at 0.8 mL/min flow rate. Mass determinations were conducted using an 6135B single Quadrupole MSD with positive ESI;
30 **H2:** HPLC: Agilent 1260 HPLC equipped with a Luna, C18, 2.0 × 50 mm, 5 µm column, using a gradient of 5-95% MeCN (0.02% TFA)/H₂O (0.04% TFA) over 6.0 min at 1.0 mL/min flow rate. Mass

determinations were conducted using an 6125B single Quadrupole MSD with positive ESI; **H3**: HPLC: Agilent 1260 HPLC equipped with a CSH, C18, 2.1 x 30 mm, 1.7 μ m column, using a gradient of 3-97% MeCN (0.1% HCO₂H)/H₂O (0.1% HCO₂H) over 2.0 min at 1.0 mL/min flow rate. Mass determinations were conducted using an 6125B single Quadrupole MSD with positive ESI;

- 5 **Method I**: HPLC: Agilent 1260 HPLC equipped with a XBRIDGE, C8, 4.6 x 50 mm, 3.5 μ m column, using a gradient of 10-95% MeCN /H₂O (10 nM aq. NH₄HCO₃) over 6.5 min at 1.2 mL/min flow rate. Mass determinations were conducted using an 6135B single Quadrupole MSD with positive ESI;

CHIRAL HPLC METHODS

- 10 **Analytical Chiral SFC Method J1**: Shimadzu SFC HPLC equipped with ChromegaChiral CC4 (4.6 mm x 150 mm, 5 μ m column) using a mobile phase of 60% CO₂:40% MeOH (1% IPam) at 2.0 mL/min and temp = 35 °C, peak 1 = 1st eluting peak, peak 2 = 2nd eluting peak.

Preparative Chiral SFC Method J2: Shimadzu SFC equipped with ChromegaChiral CC4 (20 mm x 250 mm, 5 μ m column) using a mobile phase of 60% CO₂:40% MeOH (1% IPam) at 50.0 mL/min and temp = 30 °C, peak 1 = 1st eluting peak, peak 2 = 2nd eluting peak.

- 15 **Analytical Chiral SFC Method K1**: Shimadzu SFC HPLC equipped with ChromegaChiral CC4 (4.6 mm x 150 mm, 5 μ m column) using a mobile phase of 55% CO₂:45% MeOH (1% IPam) at 2.0 mL/min and temp = 35 °C, peak 1 = 1st eluting peak, peak 2 = 2nd eluting peak.

- 20 **Preparative Chiral SFC Method K2**: Shimadzu SFC equipped with ChromegaChiral CC4 (20 mm x 250 mm, 5 μ m column) using a mobile phase of 55% CO₂:45% MeOH (1% IPam) at 50.0 mL/min and temp = 30 °C, peak 1 = 1st eluting peak, peak 2 = 2nd eluting peak.

Analytical Chiral HPLC Method M1: Agilent 1260 HPLC equipped with CC4, C18 (4.6 mm x 150 mm, 5 μ m column) using a mobile phase of 85% MeCN (0.1% IPam):15% MeOH (IPam) at 1.5 mL/min, peak 1 = 1st eluting peak, peak 2 = 2nd eluting peak.

- 25 **Preparative Chiral HPLC Method M2**: Agilent 1200 HPLC equipped with CC4, C18 (20 mm x 250 mm, 5 μ m column) using a mobile phase of 85% MeCN (0.1% IPam):15% MeOH (IPam) at 20 mL/min, peak 1 = 1st eluting peak, peak 2 = 2nd eluting peak.

Analytical Chiral SFC Method N1: Shimadzu SFC HPLC equipped with Chiralpak IG (4.6 mm x 150 mm, 5 μ m column) using a mobile phase of 65% CO₂:35% MeOH (1% IPam) at 2.0 mL/min and temp = 35 °C, peak 1 = 1st eluting peak, peak 2 = 2nd eluting peak.

Preparative Chiral SFC Method N2: Shimadzu SFC equipped with Chiralpak IG (20 mm × 250 mm, 5 µm column) using a mobile phase of 65% CO₂:35% MeOH (1% IPam) at 50.0 mL/min and temp = 30 °C, peak 1 = 1st eluting peak, peak 2 = 2nd eluting peak.

MDAP Purification: Waters Acquity equipped with a QDa mass detector, alternate-scan (positive and negative electrospray) ionisation, and XSELCECT CSH C18 column (30 mm × 150 mm, 5 µm column) using the indicated mobile phase.

Abbreviations

In the following experimental descriptions, the following abbreviations may be used:

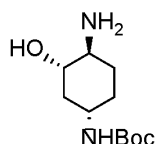
Abbreviation	Meaning	Abbreviation	Meaning
MeCN	acetonitrile	LHMDS	lithium bis(trimethylsilyl)amide
Ac ₂ O	acetic anhydride	LiCl	lithium chloride
AcOH	acetic acid	MgSO ₄	magnesium sulfate
aq.	aqueous	MDAP	mass directed auto purification
atm	standard atmosphere	ms	mass spectrum
Boc ₂ O	boc anhydride	Me	methyl
Brine	saturated aqueous sodium chloride	MeOH	methanol
nBuLi	butyllithium	MeI	methyl iodide
CDI	carbonyldiimidazole	mg, MG	milligram
Cat	catalytic	ml or mL or ML	milliliter
DCM	methylene chloride	Mmol or mmol	millimole
CPME	cyclopentyl methyl ether	min	minute (s)
Cs ₂ CO ₃	cesium carbonate	N ₂	nitrogen
Cbz	benzyloxycarbonyl	N	Normality
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	NaBH ₄	sodium borohydride

DIEA	<i>N,N</i> -diisopropylethylamine	Na(CN)BH ₃	sodium cyanoborohydride
DMF	<i>N,N</i> -dimethylformamide	NaCl	sodium chloride
DMSO	dimethylsulfoxide	Na ₂ CO ₃	sodium carbonate
EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride	NaHCO ₃	sodium bicarbonate
ESI	electron spray ionization	NaOH	sodium hydroxide
EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride	NaIO ₄	sodium periodate
Et	ethyl	Na ₂ SO ₃	sodium sulfite
TEA	triethylamine	Na ₂ SO ₄	sodium sulfate
EtOH	diethyl ether	NBS	<i>N</i> -bromosuccinimide
Et ₂ O	Ethanol	NH ₄ Cl	ammonium chloride
EtOAc	ethyl acetate	NH ₄ OH	ammonium hydroxide
g, G, gm, GM	gram	OsO ₄	osmium tetroxide
h or hr	hour (s)	pet	petroleum ether
H ₂	hydrogen	Pd/C or Pd-C	palladium on carbon
H ₂ O	water	Pd(dppf)Cl ₂ /PdCl ₂	1,1'-bis(di-tert-butylphosphino)ferrocene dichloropalladium
HCl	hydrochloric acid	Pd(Ph ₃) ₄ , tetrakis	tetrakis(triphenylphosphine) palladium(0)
HPLC	high performance liquid chromatography	Pd(OH) ₂	palladium hydroxide
HBr	hydrogen bromide	P(Ph) ₃	triphenylphosphine

K ₂ CO ₃	potassium carbonate	rt or RT Rt	room temperature or retention time
K ₃ PO ₄	tripotassium phosphate	sat'd	saturated
KHSO ₄	potassium hydrogen sulfate	STAB	sodium triacetoxyborohydride
KOAc	potassium acetate	sol'n	solution
KF	potassium fluoride	TEA	triethylamine
KOtBu	potassium <i>tert</i> -butoxide	Ti(O ⁱ Pr) ₄	titanium isopropoxide
KOH	potassium hydroxide	TFA	trifluoroacetic acid
L or l	liter	TREAT-HF	triethylamine trihydrofluoride
LAH or LiAlH ₄	lithium aluminum hydride	THF	Tetrahydrofuran
LCMS	liquid chromatography-mass spectroscopy	μL	microliter
μmol	micromole		

INTERMEDIATES

Intermediate 1: *tert*-Butyl ((1*S*,3*S*,4*S*)-4-amino-3-hydroxycyclohexyl)carbamate



- 5 **Step 1:** Benzyl (*S*)-cyclohex-3-en-1-ylcarbamate: Three reactions (3 x 1.5 kg) were carried out in parallel. To a 50 L flask, containing a solution of (*S*)-cyclohex-3-ene-1-carboxylic acid (1.50 kg, 11.9 mol) in toluene (15.0 L), was added TEA (1.82 L, 13.1 mol), dropwise, over 0.5 h at 25 °C. The reaction mixture was heated to 80 °C, to which was added DPPA (2.69 L, 12.5 mol), dropwise, over 0.5 h at 80 °C. The reaction mixture was heated to 110 °C, to which was added benzylalcohol (1.36
- 10 L, 13.1 mol) and the reaction mixture stirred at 110 °C for 8 h. The reaction mixture was cooled to 25 °C, H₂O (5 L) was added, the layers separated, and the aqueous phase extracted with MTBE (2 x

2.5 L). The combined organic extracts were washed with aq. citric acid (250 g in H₂O (5 L)), sat'd aq. NaHCO₃ (5 L), dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure. The three reactions were combined, triturated, and stirred with *n*-heptane (15 L) at RT for 12 h. The solid was filtered and dried under vacuo to afford the title compound (1.62 kg, 54% yield) as white solid.

5 HPLC (Method D1), Rt = 3.72 min. ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.37 (m, 5H), 5.68-5.59 (m, 2H), 5.10 (s, 2H), 4.79-4.80 (br s, 1H), 3.88 (br s, 1H), 2.38-2.43 (m, 1H), 2.12-2.14 (m, 2H), 1.87-1.92 (m, 2H), 1.59-1.59 (m, 1H).

Step 2: Benzyl ((1*S*,3*S*,6*R*)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate: Two reactions (2.00 kg & 2.20 kg) were carried out in parallel. To a 50-L flask was added a solution of benzyl (*S*)-cyclohex-3-en-1-ylcarbamate (2.20 kg, 9.51 mol) in DCM (13.2 L) followed by *m*-CPBA (3.86 kg, 85% Wt, 19.0 mol) at 10-20 °C. The reaction mixture was warmed to 10-20 °C over 1 h. The suspension was filtered, and the filter cake washed with DCM (2.0 L). The combined filtrates were washed with 22% aq. sol'n of Na₂SO₃ (10.0 L) and a aq. sol'n of 15% NaHCO₃ (10.0 L), and the organic layer washed with H₂O (10.0 L). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under

15 reduced pressure. The crude product was triturated with MeCN (3.0 L), the solid collected by filtration, washed with MeCN (500 mL), and the filtrate concentrated to afford crude product. Isopropyl ether: MTBE (2:1, 3 v, 10.0 L) was added to the crude product, the mixture stirred at 20-25 °C for 12 h, the solid collected by filtration, washed with isopropyl ether (500 mL) and dried to afford product (1.52 kg). This product was combined with an additional reaction (1.38 kg) to afford a white solid (2.90 kg).

20 The crude product (2.90 kg) was dissolved with EtOH (14.5 L) at 80 °C, H₂O (21.8 L) added dropwise at 80 °C over 1 h. The mixture was cooled to 25 °C and stirred at 25 °C for 12 h, filtered, the solid washed with EtOH: H₂O (5.80 L, 1:2, 2 v) to afford the title compound (1.70 kg, 29% yield) as a white solid, in 76% purity. HPLC/MS (Method E), Rt = 6.68 min. ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.37 (m, 5H), 5.08-5.14 (m, 3H), 3.18 (s, 2H), 2.10-2.22 (m, 2H), 1.83-1.96 (m, 2H), 1.50-1.52 (m, 2H).

25 **Step 3:** Benzyl ((1*S*,3*S*,4*S*)-3-hydroxy-4-(((*S*)-1-phenylethyl)amino)cyclohexyl)carbamate: (*S*)-1-Phenylethan-1-amine (326 g, 2.69 mol) was added drop-wised to a solution of benzyl ((1*S*,3*S*,6*R*)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (800 g, 75.5% Wt, 2.44 mol) and LiClO₄ (520 g, 210 mL, 4.88 mol) in MeCN (8.00 L) at 20 °C, then heated to 80 °C and stirred for 12 h. The reaction mixture was poured into ice-water (8.00 L), extracted with EtOAc (2 x 6.40 L). The combined organic layers were

30 washed with H₂O (6.40 L), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product (1.34 kg). The crude product was triturated with MTBE: EtOAc (4.69 L, 3:0.5) and stirred at 20-25 °C for 12 h. The reaction mixture was filtered, the filter cake was washed with MTBE (2.52 L) and dried under vacuum to afford the title compound (630 g, 70% yield) as a white solid. HPLC

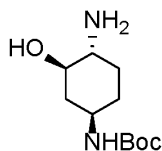
(Method F1), Rt = 2.75 min. ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.38 (m, 10H), 5.08 (s, 2H), 4.69 (s, 1H), 3.90 (dd, $J=12.8$ Hz, 6.4 Hz, 1H), 3.58 (s, 1H), 3.17-3.22 (m, 4H), 2.30-2.36 (m, 2H), 1.88-1.92 (m, 2H), 1.34 (d, $J=6.4$ Hz, 3H), 0.94-1.25 (m, 12H).

Step 4: *tert*-Butyl ((1*S*,3*S*,4*S*)-3-hydroxy-4-(((*S*)-1-phenylethyl)amino)cyclohexyl)carbamate:

- 5 Eighteen reactions (80.0 g each) were carried out in parallel. To a solution of benzyl ((1*S*,3*S*,4*S*)-3-hydroxy-4-(((*S*)-1-phenylethyl)amino)cyclohexyl)carbamate (80.0 g, 217 mmol) in MeOH (1.20 L) was added Boc_2O (47.4 g, 217 mmol) and 10% Pd/C (8.00 g, 7.52 mmol) at 25 °C and H_2 (g) was bubbled through the reaction mixture, the reaction mixture was stirred at 15 psi, 25 °C for 12 h. The 18 reactions were combined, the reaction mixtures were filtered, and concentrated under reduced pressure to afford a pale white solid (1.20 kg). The crude product was triturated with MTBE (3.60 L) and stirred at 20-25 °C for 12 h. The mixture was filtered, the filter cake washed with MTBE (240 mL) and dried under vacuum to afford the title compound (880 g, 68% yield) as a white solid. HPLC (Method E), Rt = 7.26 min. ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.36 (m, 5H), 4.43-4.57 (m, 1H), 3.92 (dd, $J=13.2$ Hz, 6.4 Hz, 1H), 3.17-3.22 (m, 1H), 2.31-2.36 (m, 3H), 1.88-1.92 (m, 3H), 1.44 (s, 9H), 1.35 (d, $J=6.8$ Hz, 3H), 0.91-1.22 (m, 4H).

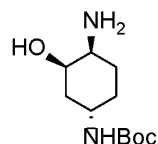
- Step 5:** *tert*-Butyl ((1*S*,3*S*,4*S*)-4-amino-3-hydroxycyclohexyl)carbamate: Ten reactions (84.0 g each) were carried out in parallel. To a solution of *tert*-butyl ((1*S*,3*S*,4*S*)-3-hydroxy-4-(((*S*)-1-phenylethyl)amino)cyclohexyl)carbamate (84.0 g, 1.0 eq, 251 mmol) in MeOH (1.26 L) was added 20% Pd(OH) $_2$ /C (8.40 g, 11.9 mmol) at 25 °C, H_2 (g) was bubbled through the reaction mixture and the reaction mixture was stirred at 50 psi, 30 °C for 12 h. The 10 reactions were combined, filtered, and concentrated under reduced pressure to afford the title compound (570 g, 99% yield) as a white solid. HPLC (Method F1), Rt = 1.45 min, m/z $[\text{M}+\text{H}]^+$: 231.1. ^1H NMR (400 MHz, CDCl_3) δ 4.45 (s, 1H), 3.54 (s, 1H), 3.18-3.24 (m, 1H), 2.40-2.41 (m, 1H), 2.27-2.30 (m, 1H), 1.86-2.01 (m, 2H), 1.45 (s, 9H), 1.14-1.23 (m, 3H).

- 25 Intermediate 2: *tert*-Butyl ((1*R*,3*R*,4*R*)-4-amino-3-hydroxycyclohexyl)carbamate



The title compound was prepared according to a similar synthetic procedure described in Intermediate 1, utilizing benzyl (*R*)-cyclohex-3-en-1-ylcarbamate as a starting material. LCMS (Method B (ELSD)), Rt = 0.54 min, m/z $[\text{M}+\text{H}]^+$: 231.3.

Intermediate 3: *tert*-Butyl ((1*S*,3*R*,4*S*)-4-amino-3-hydroxycyclohexyl)carbamate



Step 1: Benzyl *tert*-butyl ((1*S*,2*S*,4*S*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate: To a solution of *tert*-butyl ((1*S*,3*S*,4*S*)-4-amino-3-hydroxycyclohexyl)carbamate (420 g, 1.82 mol) in THF (6.30 L) was added Na₂CO₃ (290 g, 2.74 mol), the reaction mixture was cooled to 0 °C, to which was added Cbz-Cl (390 mL, 2.74 mol) dropwise, and the reaction mixture was stirred at 20 °C for 2 h. The residue was poured into ice H₂O (4.20 L), the aqueous phase extracted with 2-MeTHF 3 x (5.00 L), and the combined organic phase was washed with brine (5.00 L), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford crude product (840 g). The crude product was triturated with isopropyl ether (8.40 L), stirred at 20-25 °C for 3 h, filtered, and the filter cake was washed with isopropyl ether (1.00 L) and dried under vacuum to afford the title compound (605 g, 80% yield) as white solid, in 88% purity. HPLC (Method E), Rt = 6.96 min. ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.41 (m, 5H), 5.08-5.15 (m, 2H), 4.77 (s, 1H), 4.50 (s, 1H), 3.42-3.51 (m, 3H), 2.32 (d, *J*=10.8 Hz, 1H), 2.02 (d, *J*=8.8 Hz, 1H), 1.44 (s, 9H), 1.16-1.32 (m, 3H).

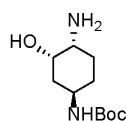
Step 2: (1*R*,2*S*,5*S*)-2-(((benzyloxy)carbonyl)amino)-5-((*tert*-butoxycarbonyl)amino)cyclohexyl 4-nitrobenzoate: Five reactions (2 x 240 g; 200g; 2 x 5.0 g) were carried out in parallel. A solution of benzyl *tert*-butyl ((1*S*,2*S*,4*S*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate (240 g, 658 mmol) in THF (2.40 L), *p*-nitrobenzoic acid (132 g, 790 mmol) and PPh₃ (259 g, 988 mmol) was added in portions to the reaction mixture at 20 °C, after which DIAD (200 g, 988 mmol) in THF (480 mL) was added dropwise to the reaction mixture at 20 °C, and the reaction mixture was allowed to stir at 25 °C for 1 h. The 5 reactions were combined, poured into the brine (7.50 L), and the aqueous phase exacted by EtOAc (2 x 3.00 L), the extracts combined, dried over Na₂SO₄, filtered, and concentrated under vacuum to afford crude product. The crude product (2.80 kg) was triturated with MeOH (6.00 L), stirred at 25 °C for 12 h, filtered, the filter cake washed with MeOH (3 x 280 mL) and dried under vacuum to afford the title compound (1.07 kg, 70% yield), as a white solid, in 87% purity. HPLC (Method E), Rt = 9.19 min. ¹H NMR (400 MHz, CDCl₃) δ 8.29 (d, *J*=8.8 Hz, 1H), 8.18 (d, *J*=8.8 Hz, 1H), 7.28-7.32 (m, 5H), 5.52 (s, 1H), 5.03-5.10 (m, 1H), 4.92 (d, *J*=8.0 Hz, 1H), 3.81-3.86 (m, 2H), 2.40 (d, *J*=14 Hz, 1H), 2.18 (d, *J*=8.0 Hz, 1H), 1.80-1.95 (m, 2H), 1.55-1.62 (m, 2H), 1.40 (s, 10H).

Step 3: Benzyl *tert*-butyl ((1*S*,2*R*,4*S*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate: To a solution of (1*R*,2*S*,5*S*)-2-(((benzyloxy)carbonyl)amino)-5-((*tert*-butoxycarbonyl)amino)cyclohexyl 4-

nitrobenzoate (950 g, 65% Wt, 1.20 mol) in MeOH (4.75 L) and THF (4.75 L) was added K₂CO₃ (498 g, 3.61 mol) in H₂O (3.80 L) at 25 °C. The reaction mixture was stirred at 25 °C for 12 h, at which time the reaction mixture was quenched by H₂O (5.70 L, 6 V) at 0 °C, then stirred at 20 °C for 2h. The mixture was filtered, the filter cake dissolved with isopropyl ether (5.70 L, 6 V), the mixture stirred at 20 °C for 2 h, and filtered. The filter cake was dissolved with 2Me-THF (7.60 L, 8 V), the organic layer washed with H₂O (5.70 L, 6 V), dried over Na₂SO₄, filtered, and concentrated in vacuo at 45 °C to afford the title compound (408 g, 89% yield) as a white solid. LCMS (Method G1), Rt = 1.85 min, *m/z* [M+H]⁺: 365.3. ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.35 (m, 5H), 5.32 (s, 1H), 5.08 (s, 2H), 4.41 (s, 1H), 4.08 (s, 1H), 3.81 (s, 1H), 3.59 (d, *J*=6.8 Hz, 1H), 2.13-2.17 (m, 1H), 1.96-2.00 (m, 1H), 1.74-1.77 (m, 1H), 1.43 (s, 9H), 1.40 (s, 10H), 1.17-1.27 (m, 1H).

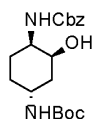
Step 4: *tert*-Butyl ((1*S*,3*R*,4*S*)-4-amino-3-hydroxycyclohexyl)carbamate: Six reactions (6 x 70.0 g) were carried out in parallel. To the solution of Pd/C (7.00 g, 0.36 eq, 65.8 mmol) in MeOH (700 mL) was added THF (700 mL) and benzyl *tert*-butyl ((1*S*,2*R*,4*S*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate (70.0 g, 182 mmol) at 25 °C and H₂ (g) was bubbled through the reaction mixture, and the reaction mixture was stirred at 25 °C, 15 psi for 12 h. The reaction mixture was filtered over celite (1 wt.), and the filter cake was washed with MeOH (5 V x 4). The filtrate from the 6 batches was combined and concentrated in vacuo at 45 °C. The crude product (252 g) was triturated with EtOAc (504 mL, 2 V) at 25 °C for 2 h, filtered, the filter cake washed with EtOAc (126 mL, 0.5 V) and dried under reduced pressure at 45 °C to afford the title compound (206 g, 79% yield) as a white solid. LCMS (Method H1, (ELSD)), Rt = 1.45 min, *m/z* [M+H]⁺: 461.3. ¹H NMR (400 MHz, CDCl₃) δ 4.33 (s, 1H), 3.81 (s, 2H), 2.82-2.84 (m, 1H), 2.16-2.20 (m, 1H), 1.99 (d, *J*=12 Hz, 1H), 1.62-1.65 (m, 1H), 1.52-1.55 (m, 1H), 1.44 (s, 9H), 1.27-1.33 (m, 1H), 1.12-1.21 (m, 1H).

Intermediate 4: *tert*-Butyl ((1*R*,3*S*,4*R*)-4-amino-3-hydroxycyclohexyl)carbamate



The title compound was prepared according to a similar synthetic procedure described in Intermediate 3, utilizing benzyl *tert*-butyl ((1*R*,2*R*,4*R*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate as a starting material. LCMS (Method B (ELSD)), Rt = 0.55 min, *m/z* [M+H]⁺: 231.2.

Intermediate 5: Benzyl *tert*-butyl ((1*R*,2*S*,4*R*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate

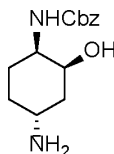


The title compound was prepared according to a similar synthetic procedure described in WO 2017/029602 (PCT/IB2016/054890), utilizing *tert*-butyl ((1*R*,3*S*,4*R*)-4-amino-3-hydroxycyclohexyl)carbamate as a starting material. LCMS (Method B), *R*_t = 0.58 min, *m/z* [M+H]⁺: 265.2.

Table 1. The following Intermediates (6-8) were prepared according to a similar synthetic procedure detailed by Intermediate 5.

Intermediate	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	<i>R</i> _t (min) LCMS Method
6		Benzyl <i>tert</i> -butyl ((1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i>)-2-hydroxycyclohexane-1,4-diyl)dicarbamate	(- ⁴ Bu) 309.2	0.92 min Method B
7		Benzyl <i>tert</i> -butyl ((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-hydroxycyclohexane-1,4-diyl)dicarbamate	(- ⁴ Bu) 309.2	0.97 min Method B
8		Benzyl <i>tert</i> -butyl ((1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i>)-2-hydroxycyclohexane-1,4-diyl)dicarbamate	(- ⁴ Bu) 309.1	0.92 min Method B

Intermediate 9: Benzyl ((1*R*,2*S*,4*R*)-4-amino-2-hydroxycyclohexyl)carbamate, hydrochloride



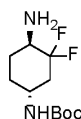
To a mixture of benzyl tert-butyl ((1*R*,2*S*,4*R*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate (1.00 g, 2.74 mmol) in DCM (27.4 mL) was added 4M HCl-dioxane (6.9 mL, 27.4 mmol) and the reaction mixture was allowed to stir at RT for 16 h. The solvent was evaporated under reduced pressure to afford the title compound (848 mg, 97% yield). ¹H NMR (400 MHz, CD₃OD) δ 7.27-7.40 (m, 5H), 5.08 (s, 2H), 4.06 (br s, 1H), 3.34-3.60 (m, 2H), 2.14 (dq, *J*=12.96, 3.51 Hz, 1H), 2.04 (dt, *J*=12.35, 3.36 Hz, 1H), 1.70-1.85 (m, 2H), 1.62 (td, *J*=12.59, 2.20 Hz, 1H), 1.48 (qd, *J*=12.47, 4.65 Hz, 1H). LCMS (Method B), *R*_t = 0.58 min, *m/z* [M+H]⁺: 265.2.

10

Table 2. The following Intermediates (10-12) were prepared according to a similar synthetic procedure detailed by Intermediate 9, utilizing HCl or TFA as deprotection reagents.

Intermediate	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	<i>R</i> _t (min) LCMS Method
10		Benzyl ((1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i>)-4-amino-2-hydroxycyclohexyl)carbamate	265.2	0.58 min Method B
11		Benzyl ((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-amino-2-hydroxycyclohexyl)carbamate	265.2	0.60 min Method B
12		Benzyl ((1 <i>R</i> ,2 <i>R</i> ,4 <i>R</i>)-4-amino-2-hydroxycyclohexyl)carbamate	265.2	0.59 min Method B

Intermediate 13: *tert*-Butyl ((1*R*, 4*R*)-4-amino-3,3-difluorocyclohexyl)carbamate

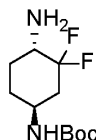


Step 1: Benzyl *tert*-butyl ((1*R*,4*R*)-2-oxocyclohexane-1,4-diyl)dicarbamate: To a mixture of benzyl ((1*R*,2*S*,4*R*)-4-amino-2-hydroxycyclohexyl)carbamate, hydrochloride (5.00 g, 113 mmol) in DCM (200 mL) at RT was added Dess-Martin periodinane (7.0 g, 16.5 mmol) and the reaction mixture was stirred at RT for 4 h. 5 N NaOH (50 mL) was added, and the reaction mixture was stirred until the organic layer was a clear solution. The reaction mixture was diluted with DCM, the layers separated, and the aqueous phase was extracted with DCM. The combined organic extracts were washed with brine, dried with MgSO₄, filtered, and evaporated under reduced pressure. The crude residue was triturated with PhMe and filtered to afford the title compound (4.65 g, 89% yield) as white solid. LCMS (Method B), Rt = 1.0 min, *m/z*: 307.0 (-^tBu).

Step 2: Benzyl *tert*-butyl ((1*R*,4*R*)-2,2-difluorocyclohexane-1,4-diyl)dicarbamate: To a mixture of benzyl *tert*-butyl ((1*R*,4*R*)-2-oxocyclohexane-1,4-diyl)dicarbamate (3.00 g, 8.28 mmol) in DCM (40 mL) under N₂, was added XtalFluor-E® (5.7 g, 24.8 mmol), TREAT-HF (5.3 g, 33.1 mmol), and TEA (2.3 mL, 16.6 mmol), and the reaction mixture was stirred at RT for 5 h. The reaction mixture was diluted with DCM and the solution basified using sat. aq. NaHCO₃. The organic phase was separated, the aqueous phase was extracted with DCM, and the combined extracts washed brine and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography (80 g) eluting with a 30-100% EtOAc/heptane gradient to afford the title compound (2.69 g, 72% yield), in 85% purity. LCMS (Method B), Rt = 1.09 min, *m/z* [M+H]⁺: 285.0 (-Boc).

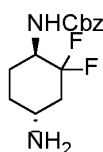
Step 3: *tert*-Butyl ((1*R*,4*R*)-4-amino-3,3-difluorocyclohexyl)carbamate: To a 250 mL flask, flushed with N₂, was added 10% Pd-C (0.72 g, 0.68 mmol) and MeOH (100 mL). Benzyl *tert*-butyl ((1*R*,4*R*)-2,2-difluorocyclohexane-1,4-diyl)dicarbamate (1.30 g, 3.40 mmol) was added under N₂ and the reaction mixture was stirred under 1 atm H₂ for 18 h. The reaction mixture was flushed with N₂ and filtered through celite, and the solvent evaporated under reduced pressure. To a 100 mL flask, flushed with N₂, was added 10% Pd-C (0.36 g, 0.34 mmol), MeOH (30 mL) and the crude material dissolved in MeOH (20 mL), under N₂, and the reaction mixture was stirred under 1 atm for 18 h. The reaction mixture was flushed with N₂ and filtered through celite, and the solvent evaporated under reduced pressure to afford the title compound (0.817 g, 97% yield). LCMS (Method B), Rt = 0.70 min, *m/z* [M+H]⁺: 251.1.

Intermediate 14: *tert*-Butyl ((1*S*,4*S*)-4-amino-3,3-difluorocyclohexyl)carbamate



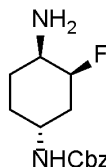
The title compound was prepared according to a similar synthetic procedure described by Intermediate 13, using benzyl ((1*S*,2*R*,4*S*)-4-amino-2-hydroxycyclohexyl)carbamate as a starting material. LCMS (Method B), *R*_t = 0.69 min, *m/z* [M+H]⁺: 251.1.

- 5 Intermediate 15: Benzyl ((1*R*,4*R*)-4-amino-2,2-difluorocyclohexyl)carbamate, TFA salt



- To a suspension of benzyl tert-butyl ((1*R*,4*R*)-2,2-difluorocyclohexane-1,4-diyl)dicarbamate (61 mg, 155 μmol) in DCM (3 mL) was added TFA (1.0 mL, 13.1 mmol). The mixture was stirred at RT for 2 h. The mixture was concentrated *in vacuo* to afford the title compound, (79 mg, 100% yield, 78.4% Purity). ¹H NMR (400 MHz, CD₃OD) δ 7.23-7.48 (m, 5H), 5.14 (d, *J*=4.50 Hz, 2H), 4.01 (s, 1H), 3.35 (s, 1H), 2.45-2.67 (m, 1H), 1.89-2.29 (m, 3H), 1.65 (br s, 2H). LCMS (Method B), *R*_t = 0.76 min, *m/z* [M+H]⁺: 265.3.
- 10

Intermediate 16: Benzyl ((1*R*,3*S*,4*R*)-4-amino-3-fluorocyclohexyl)carbamate



- 15 **Step 1:** Benzyl (*R*)-cyclohex-3-en-1-ylcarbamate: To a solution of (*R*)-cyclohex-3-ene-1-carboxylic acid (3.00 kg, 23.8 mol) in toluene (30.0 L) was added TEA (3.65 L, 26.2 mol), dropwise, at 25 °C. The reaction mixture was warmed to 80 °C, to which was added DPPA (5.33 L, 24.7 mol), dropwise, and the reaction mixture was stirred at 110 °C for 2 h. BnOH (2.71 L, 26.3 mol) was added to the reaction mixture at 110 °C and the reaction mixture was stirred at 110 °C for 12 h. Two reactions
- 20 were combined, cooled to 20-25 °C, to which was added H₂O (15.0 L). The aqueous phase was extracted with MTBE (2 x 7.50 L), the combined organic extracts washed with 10% aq. citric acid (2 x 15.0 L), sat'd aq. NaHCO₃ (15.0 L), H₂O (15.0 L), dried over Na₂SO₄, filtered, and concentrated

under reduced pressure. The crude product was triturated and stirred with *n*-heptane (6.00 L) for 4 h at 25-28 °C. The resulting solid was filtered, washed with *n*-heptane (1.00 L) and dried to afford the titled compound (3.1 kg) as an off-white solid. The mother liquid was concentrated *in vacuo* at 40 °C to afford crude product which was triturated and stirred with *n*-heptane (960 mL) for 4 h. The solid was filtered, washed with *n*-heptane (1.00 L) and dried to afford the titled compound (600 g) as an off-white solid. The isolated solids were combined to afford the titled compound (3.70 kg, 67% yield), in 84% purity. Two batches were carried out in parallel (50 L jacket, 1.5 kg x 2). ¹H NMR (400 MHz, DMSO-d₆) δ 7.32-7.37 (m, 5H), 7.24-7.32 (m, 1H), 5.56-5.64 (m, 2 H), 5.02 (s, 2H), 3.51-3.55 (m, 1H), 2.19-2.23 (m, 1H), 2.07-2.08 (m, 2H), 1.78-1.82 (m, 2H), 1.37-1.44 (m, 1H). HPLC (Method F1), Rt = 3.59 min.

Step 2: Benzyl ((1*R*,3*R*,6*S*)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate: A solution of benzyl (*R*)-cyclohex-3-en-1-ylcarbamate (3.40 kg, 14.7 mol) in DCM (34.0 L) was degassed with N₂ and the reaction mixture cooled to 10-20 °C. mCPBA (5.97 kg, 85% Wt, 29.4 mol) was added to the reaction mixture in ten portions at 10-20 °C and stirred at RT for 1 h. Two batches were combined, the suspension filtered, and the filter cake was washed with DCM (2.00 L). The combined filtrates were poured into 20% aq. Na₂SO₃ (34.0 L) and the organic layer washed with H₂O (17.0 L), and the combined organic layers dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was triturated with IPA (19.5 L), filtered, and the solid washed with IPA (1.00 L). The filtrate was concentrated, isopropyl ether (18.0 L) was added to the solution and the mixture stirred at 25-28 °C for 4 h. The resulting solid was collected by filtration, washed with isopropyl ether (500 mL) and dried to afford the titled product (2.23 kg, 45 %), as a white solid, in 73% purity. This material (2.20 kg, 8.90 mol) was suspended in EtOH (11.0 L) and warmed to 80 °C until a clear solution. Water (16.5 L) was added dropwise to the mixture at 80 °C and the mixture slowly cooled to 25 °C for 12 h. The resulting solid was filtered, washed with IPA/water (2 L, 1:2) and dried to afford the title product (1.04 kg) as well as crude product (580 g, 60% assay). The crude product was dissolved in DCM (1.00 L), to which was added silica gel (696 g), and the mixture was concentrated at 40 °C *in vacuo* and to give a dry flowing solid. The crude solid was loaded in 1.70 kg silica gel (100-200 mesh silica gel, self-prepared column chromatography) and eluted with a 10:1 *n*-heptane/EtOAc to 100% EtOAc gradient. The desired fractions were combined and evaporated *in vacuo* at 40 °C to afford the titled product (90.0 g) and crude product (290 g, 97.6%, 20% isomer on HPLC). The combined titled product totaled (1.12 kg, 31% yield) of a white solid. Two batches were carried out in parallel (50 L jacket, 1.70 kg x 2). ¹H NMR (400 MHz, DMSO-d₆) δ 7.31-7.39 (m, 5H), 7.12 (d,

$J=11.6$ Hz, 1H), 5.00 (s, 2 H), 3.23-3.31 (m, 1H), 2.15-2.20 (m, 1H), 2.01-2.05 (m, 1H), 1.75-1.82 (m, 1H), 1.38-1.61 (m, 3H), 1.24-1.27 (m, 1H). HPLC (Method G2), R_t = 6.29 min.

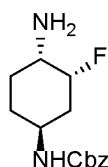
Step 3: Benzyl ((1*R*,3*S*,4*S*)-3-fluoro-4-hydroxycyclohexyl)carbamate: Benzyl ((1*R*,3*R*,6*S*)-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (200 g, 809 mmol) and triethylammonium fluoride (0.66 L, 4.04 mol) was added to a 2-L 3-neck flask and the reaction mixture stirred at 25-30 °C for 2 h. The reaction mixture was cooled to RT and slowly added to a sol'n of K_2CO_3 (1.10 kg) in H_2O (10 L), and the aqueous phase extracted with DCM (2 x 2 L). The combined organic extracts were washed with H_2O (2 L), dried over Na_2SO_4 , filtered and the solvent evaporated under reduced pressure. The crude residue was dissolved in DCM, silica gel added (240 g), and the suspension concentrated in vacuo to afford a dry flowing solid. The crude solid was purified by silica gel flash column chromatography (600 g) eluting with 10:1 *n*-heptane/EtOAc to 100% EtOAc gradient. Product fractions were combined and evaporated under reduced pressure to afford the title compound (110 g, 37% yield), in 73% purity and a mixture of regioisomers. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.30-7.38 (m, 5H), 5.00-5.05 (m, 2H), 4.50-4.65 (m, 2H), 3.62 (br 2, 1H), 1.76-1.80 (m, 2H), 1.49-1.60 (m, 3H). HPLC (Method F1), R_t = 2.59 min.

Step 4: Benzyl ((1*R*,3*S*,4*R*)-4-(1,3-dioxoisindolin-2-yl)-3-fluorocyclohexyl)carbamate: To a solution of benzyl ((1*R*,3*S*,4*S*)-3-fluoro-4-hydroxycyclohexyl)carbamate (1.12 kg, 4.19 mol) in THF (6.72 L), degassed with N_2 , was added phthalimide (616.5 g, 4.19 mol), PPh_3 (1.43 kg, 5.44 mol), followed by diisopropyl diazene-1,2-dicarboxylate (1.08 L, 5.45 mol) and the reaction mixture stirred at 40 °C for 12 h. The reaction mixtures were cooled to 10-15 °C, combined, poured into ice water (3.5 L) and extracted with DCM (1 x 5 L, 1 x 2L). The combined organic extracts were dried over Na_2SO_4 , filtered and the solvent evaporated under reduced pressure. The crude solid was triturated with EtOH (11 L), stirred for 12 h, filtered, washed with EtOH (800 mL) and dried to afford the title compound (730 g, 44 % yield) as a white solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.82-7.84 (m, 2H), 7.70-7.72 (m, 2H), 7.34-7.37 (m, 5H), 5.10 (s, 2H), 4.71-4.92 (m, 2H), 4.15-4.18 (m, 1H), 4.00-4.02 (br s, 1H), 3.22-3.25 (m, 1H), 2.45-2.47 (m, 1H), 2.25-2.29 (m, 1H), 1.80-1.83 (m, 1H), 1.65-1.69 (m, 1H). LCMS (Method D2), R_t = 7.85 min, m/z $[M+H]^+$: 397.1. This reaction was performed in 2 batches (30.0 g and 1.12 kg).

Step 5: Benzyl ((1*R*,3*S*,4*R*)-4-amino-3-fluorocyclohexyl)carbamate: A solution of benzyl ((1*R*,3*S*,4*R*)-4-(1,3-dioxoisindolin-2-yl)-3-fluorocyclohexyl)carbamate (500 g, 1.26 mol), in EtOH (4.7 L), was degassed with N_2 , to which was added hydrazine hydrate (786 mL, 80% Wt, 12.6 mol), dropwise at RT, and the reaction mixture stirred at 80 °C for 3 h. The reaction mixture was cooled to RT, filtered, and the filter cake washed with EtOH (500 mL). The combined filtrates were poured into ice water,

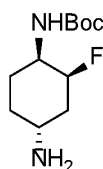
extracted with DCM (15 L), and the combined organic layers dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The solid was triturated with EtOAc, the mixture stirred for 12 h, filtered, washed with EtOAc, and dried to afford the title compound (250 g, 74% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.38-7.30 (m, 5H), 7.19 (m, 1H), 4.99 (s, 2H), 4.79-4.71 (m, 1H), 3.53-3.49 (m, 2H), 2.59-2.53 (m, 1H), 2.09-2.07 (m, 1H), 1.77-1.74 (m, 1H), 1.58-1.50 (m, 2H), 1.39-1.24 (m, 3H). HPLC (Method E), Rt = 5.29 min.

Intermediate 17 :Benzyl ((1*S*,3*R*,4*S*)-4-amino-3-fluorocyclohexyl)carbamate



The title compound was prepared according to a similar synthetic procedure described by Intermediate 16, using benzyl ((1*S*,3*R*,4*R*)-3-fluoro-4-hydroxycyclohexyl)carbamate as a starting material. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.1-7.5 (m, 5H), 4.99 (s, 2H), 4.5-4.8 (m, 1H), 3.4-3.6 (m, 1H), 3.00 (br s, 6H), 2.5-2.7 (m, 1H), 2.0-2.2 (m, 1H), 1.76 (td, *J*=3.3, 12.0 Hz, 1H), 1.6-1.7 (m, 1H), 1.5-1.6 (m, 1H), 1.3-1.5 (m, 1H), 1.3-1.5 (m, 1H), 1.2-1.3 (m, 1H). LCMS (Method A), Rt = 0.45 min, *m/z* [M+H]⁺: 267.2.

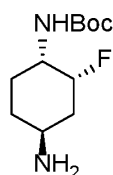
Intermediate 18: *tert*-Butyl ((1*R*,2*S*,4*R*)-4-amino-2-fluorocyclohexyl)carbamate



Step 1: Benzyl *tert*-butyl ((1*R*,2*S*,4*R*)-2-fluorocyclohexane-1,4-diyl)dicarbamate: A suspension of benzyl ((1*R*,3*S*,4*R*)-4-amino-3-fluorocyclohexyl)carbamate (2.41 g, 9.05 mmol), in DCM (50.0 mL), was added Boc₂O (2.96 g, 13.6 mmol) and the reaction mixture stirred at RT for 1 h. The reaction mixture was concentrated under reduced pressure, the solid triturated with Et₂O, filtered, washed with Et₂O, and dried under vacuo to afford the title compound (2.97 g, 87% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.3-7.4 (m, 5H), 6.9-7.3 (m, 2H), 5.00 (s, 2H), 4.6-4.9 (m, 1H), 3.3-3.6 (m, 2H), 2.0-2.2 (m, 1H), 1.7-1.9 (m, 1H), 1.4-1.7 (m, 3H), 1.38 (s, 9H), 1.2-1.4 (m, 1H). LCMS (Method B), Rt = 1.10 min, *m/z* [M+H]⁺: 267.3.

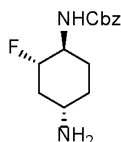
Step 2: *tert*-Butyl ((1*R*,2*S*,4*R*)-4-amino-2-fluorocyclohexyl)carbamate: To a solution of benzyl *tert*-butyl ((1*R*,2*S*,4*R*)-2-fluorocyclohexane-1,4-diyl)dicarbamate (3.23 g, 8.37 mmol), in MeOH (39.0 mL) and THF (39.0 mL) was added 20% Pd(OH)₂ (2.35 g, 3.35 mmol) under N₂ atmosphere. The suspension was purged with H₂ (5x), then stirred under H₂ overnight at RT for 20 h. The reaction mixture was purged with N₂, filtered through a pad of celite, washed with MeOH, and the solvent evaporated under reduced pressure to afford the title compound (1.94 g, 97% yield). ¹H NMR (400 MHz, CD₃OD) δ 4.7-4.8 (m, 1H), 3.4-3.6 (m, 1H), 2.9-3.0 (m, 1H), 2.2-2.3 (m, 1H), 1.9-2.0 (m, 1H), 1.6-1.8 (m, 2H), 1.44 (s, 9H), 1.2-1.4 (m, 2H). LCMS (Method B), Rt = 0.65 min (ELSD), *m/z* [M+H]⁺: 233.3.

Intermediate 19: *tert*-Butyl ((1*S*,2*R*,4*S*)-4-amino-2-fluorocyclohexyl)carbamate



The title compound was prepared according to a similar synthetic procedure described by Intermediate 16, using benzyl *tert*-butyl ((1*S*,2*R*,4*S*)-2-fluorocyclohexane-1,4-diyl)dicarbamate as a starting material. ¹H NMR (400 MHz, CD₃OD) δ 4.80 (m, 1H), 4.63-4.80 (m, 1H), 3.34-3.54 (m, 1H), 2.83-2.97 (m, 1H), 2.13-2.26 (m, 1H), 1.82-1.94 (m, 1H), 1.57-1.73 (m, 2H), 1.40 (s, 9H), 1.16-1.32 (m, 2H). LCMS (Method B), Rt = 0.66 min, *m/z* [M+H]⁺: 233.2.

Intermediate 20: Benzyl ((1*S*,2*S*,4*S*)-4-amino-2-fluorocyclohexyl)carbamate, hydrochloride

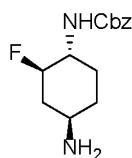


Step 1: Benzyl *tert*-butyl ((1*S*,2*S*,4*S*)-2-fluorocyclohexane-1,4-diyl)dicarbamate: A solution of benzyl *tert*-butyl ((1*S*,2*R*,4*S*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate (4.50 g, 12.4 mmol) in toluene (80.0 mL) was charged with DBU (3.70 mL, 24.7 mmol) and nonafluorobutanesulfonyl fluoride (2.42 mL, 13.6 mmol) and the reaction mixture stirred at 45 °C for 19 h. The reaction mixture was quenched with H₂O and extracted with EtOAc. The organic layer was washed with a solution of sat'd aq. NaHCO₃, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel flash column chromatography (330 g) eluting with a 0-50% EtOAc-heptanes gradient. Product fractions were combined, evaporated under reduced pressure, and resubjected to a

second silica gel flash column chromatography (330 g), eluting with a 0-50% EtOAc-heptanes gradient. Product fractions were combined and evaporated under reduced pressure to afford the title compound (1.06 g, 21% yield) as a white solid. LCMS (Method B), R_t = 1.06 min, m/z [M+H]⁺: 311.1.

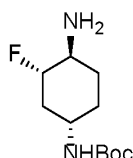
5 Step 2: Benzyl ((1*S*,2*S*,4*S*)-4-amino-2-fluorocyclohexyl)carbamate, hydrochloride: To a mixture of benzyl *tert*-butyl ((1*S*,2*S*,4*S*)-2-fluorocyclohexane-1,4-diyl)dicarbamate (300 mg, 819 μ mol) in DCM (16.0 mL) was added a solution of 4M HCl-dioxane (2.00 mL, 8.19 mmol) and the reaction mixture was allowed to stir at RT for 16 h. The solvent was evaporated under reduced pressure to afford the title compound (259 mg, 94% yield) as a white solid. LCMS (Method B), R_t = 0.70 min, m/z [M+H]⁺: 267.1.

10 Intermediate 21: Benzyl ((1*R*,2*R*,4*R*)-4-amino-2-fluorocyclohexyl)carbamate, hydrochloride



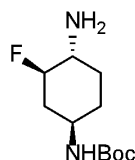
The title compound was prepared according to a similar synthetic procedure described by Intermediate 20, using benzyl *tert*-butyl ((1*R*,2*S*,4*R*)-2-hydroxycyclohexane-1,4-diyl)dicarbamate as a starting material. ¹H NMR (400 MHz, CD₃OD) δ 7.30-7.40 (m, 4H), 5.07-5.17 (m, 2H), 4.28-4.55 (m, 1H), 3.56-3.70 (m, 1H), 3.18-3.31 (m, 1H), 2.43-2.58 (m, 1H), 2.01-2.12 (m, 2H), 1.61-1.74 (m, 1H), 1.37-1.60 (m, 2H). LCMS (Method B), R_t = 0.67 min, m/z [M+H]⁺: 267.1.

Intermediate 22: *tert*-Butyl ((1*S*,3*S*,4*S*)-4-amino-3-fluorocyclohexyl)carbamate



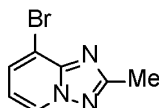
20 To a solution of benzyl *tert*-butyl ((1*S*,2*S*,4*S*)-2-fluorocyclohexane-1,4-diyl)dicarbamate (300 mg, 819 μ mol) in MeOH (16.4 mL), purged with N₂, was added 10% Pd/C (87.0 mg, 82 μ mol), the reaction mixture purged with N₂ then stirred under H₂ atmosphere for 3 h. The reaction mixture was purged with N₂, the solution filtered through celite, the celite washed with MeOH, and the solvent evaporated under reduced pressure to afford the title compound (185 mg, 92% yield). LCMS (Method B), R_t = 0.64 min, m/z [M+H]⁺: 233.1.

Intermediate 23: *tert*-Butyl ((1*R*,3*R*,4*R*)-4-amino-3-fluorocyclohexyl)carbamate



The title compound was prepared according to a similar synthetic procedure described by Intermediate 22, using benzyl *tert*-butyl ((1*R*,2*R*,4*R*)-2-fluorocyclohexane-1,4-diyl)dicarbamate as a starting material. ¹H NMR (400 MHz, CD₃OD) δ 4.05-4.30 (m, 1H), 3.42-3.52, 2.71 (qd, J=10.42, 4.25 Hz, 1H), 2.26-2.33 (m, 1H), 1.84-2.03 (m, 3H), 1.46 (s, 11H), 1.22-1.38 (m, 3H). LCMS (Method B), Rt = 0.64 min, *m/z* [M+H]⁺: 233.1.

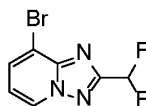
Intermediate 24: 8-Bromo-2-methyl-[1,2,4]triazolo[1,5-*a*]pyridine



Step 1: Pyridinium, 1,2-diamino-3-bromo-, 2,4,6-trimethylbenzenesulfonate: The title compound was prepared according to a similar synthetic procedure disclosed in WO 2023/064669 (PCT/US2022/076803).

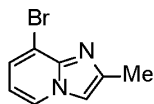
Step 2: 8-Bromo-2-methyl-[1,2,4]triazolo[1,5-*a*]pyridine: To solution of pyridinium, 1,2-diamino-3-bromo-, 2,4,6-trimethylbenzenesulfonate (20.0 g, 51.5 mmol) in Ac₂O (20.0 mL, 51.5 mmol), was added HCl (1.88 g, 51.5 mmol) and the reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was quenched with sat'd aq. NaHCO₃ (100 mL) and extracted with EtOAc (2 x 300 mL). The combined organic extracts were washed with brine (100 mL) and concentrated *in vacuo* to afford the title compound (14.0 g, > 100% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.10-9.08 (m, 1H), 8.15-8.13 (m, 1H), 7.34-7.21 (m, 2H), 3.32 (s, 3H). LCMS (Method H3), Rt = 0.68 min, *m/z* [M+H]⁺: did not ionize.

Intermediate 25: 8-Bromo-2-(difluoromethyl)-[1,2,4]triazolo[1,5-*a*]pyridine



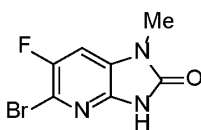
The title compound was prepared according to a similar synthetic procedure disclosed in Intermediate 24. LCMS (Method H3), $R_t = 0.68$, m/z $[M+H]^+$: 248.1.

Intermediate 26: 8-Bromo-2-methylimidazo[1,2-*a*]pyridine



- 5 To solution of 3-bromopyridin-2-amine (15.0 g, 86.7 mmol) in EtOH (150 mL), was added chloroacetone (8.40 mL, 104 mmol) and the reaction mixture stirred at 80 °C for 16 h. The reaction mixture was quenched with aq. sat'd NaHCO₃ (100 mL) and extracted with EtOAc (2 x 300 mL). The combined organic extracts were washed with brine (100 mL) and evaporated under reduced pressure. The crude residue was dissolved in DCM (20 mL), adsorbed onto silica gel (35 g) and purified by silica
- 10 gel flash column chromatography (350 g) eluting with a 0-100% EtOAc-hexanes gradient to afford the title compound (10.0 g, 52% yield). LCMS (Method H3), $R_t = 0.16$ min, m/z $[M+H]^+$: 213.1.

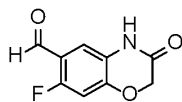
Intermediate 27: 5-Bromo-6-fluoro-1-methyl-1,3-dihydro-2H-imidazo[4,5-*b*]pyridin-2-one



- Step 1:** 6-Fluoro-1-methyl-1,3-dihydro-2H-imidazo[4,5-*b*]pyridin-2-one: The title compound was prepared according to a similar synthetic procedure outlined in US 2013/0225552 (application number
- 15 13/780,557).

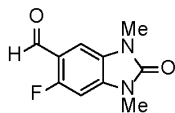
- Step 2:** 5-Bromo-6-fluoro-1-methyl-1,3-dihydro-2H-imidazo[4,5-*b*]pyridin-2-one: To a solution of 6-fluoro-1-methyl-1,3-dihydro-2H-imidazo[4,5-*b*]pyridin-2-one (10.0 g, 59.8 mmol) in DMF (100 mL) was added NBS (21.3 g, 119 mmol) and the reaction mixture stirred at 25 °C for 16 h. The reaction
- 20 mixture was quenched with ice cold water (50 mL), the solid filtered, and dried *in vacuo* to afford the title compound (12.0 g, 82% yield) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 11.86 (m, 2H), 7.75-7.73 (s, 1H), 2.89 (s, 3H). LCMS (Method B), $R_t = 0.642$ min, m/z $[M+H]^+$: 246.1.

Intermediate 28: 7-Fluoro-3-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-6-carbaldehyde



The title compound was prepared according to a similar synthetic procedure as outlined in WO 2017/029602 (PCT/IB2016/054890).

Intermediate 29: 6-Fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde



5 **Step 1:** 5-Bromo-6-fluoro-1,3-dihydro-2H-benzo[d]imidazol-2-one: To a solution of 4-bromo-5-fluorobenzene-1,2-diamine (245 g, 1.19 mol) in THF (1.96 L), cooled to 0-10 °C, was added CDI (174 g, 1.08 mol) in five portions, and the reaction mixture stirred at 0-10 °C for 10 min, then allowed to warmup to 25 °C and stirred for 16 h. The reaction mixture was triturated with DCM (735 mL), stirred for 3 h, filtered and the solid dried *in vacuo* at 45 °C to afford the title compound (158 g, 57% yield)
10 as a solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.92 (s, 1H), 10.78 (s, 1H), 8.11-7.10 (d, 1H), 6.96-6.94 (d, 1H).

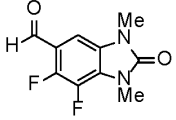
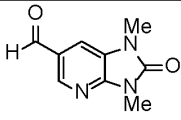
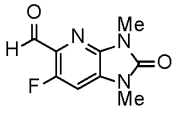
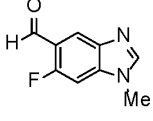
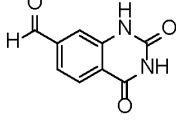
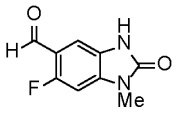
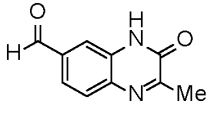
Step 2: 5-Bromo-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one: To a solution of 5-bromo-6-fluoro-1,3-dihydro-2H-benzo[d]imidazol-2-one (155 g, 671 mmol) in MeCN (1.55 L), cooled to 0-10 °C, was added KOH (94 g, 1.68 mol), in five portions at 0-10 °C, the reaction mixture stirred
15 at 0-10 °C for 10 min. MeI (238 g, 1.68 mol) was added dropwise over 10 min, the reaction mixture allowed to warm to RT and stirred for 16 h. The reaction mixtures were combined, slowly poured into a solution of aq. sat'd NH₄Cl (500 mL), cooled to 0-5 °C, and extracted with EtOAc (2 x 600 mL). The combined organic extracts were washed with brine (600 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* at 45 °C. The crude material was triturated and stirred with *n*-heptane (3V) at
20 25 °C for 3 h, filtered, and the filter cake concentrated in vacuo at 45 °C to afford the title compound (95 g, 55% yield) as a solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.51-7.50 (d, 1H), 7.36-7.34 (d, 1H), 3.35 (s, 6H). LCMS (Method F2), Rt = 1.58 min, *m/z* [M+H]⁺: 258.9 / 260.9. This reaction was carried in two batches (7.7 g & 154 g).

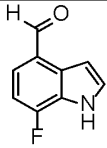
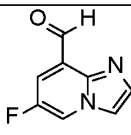
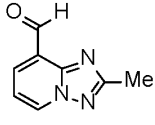
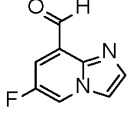
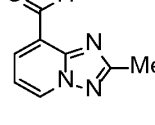
Step 3: 5-Fluoro-1,3-dimethyl-6-vinyl-1,3-dihydro-2H-benzo[d]imidazol-2-one: To a solution of 5-bromo-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (155 g, 598 mmol) in 1,4-dioxane (2.33 L) and H₂O (155 mL) was added Cs₂CO₃ (585 g, 1.79 mol) and potassium trifluoro(vinyl)borate (160 g, 1.20 mol), under N₂ atmosphere, and the reaction mixture was stirred
25 to 100 °C, to which was added Pd(dppf)Cl₂ (43.8 g, 59.8 mmol), portionwise, at 90-95 °C, and the reaction mixture stirred at 100 °C for 12 h. The reaction mixture was cooled RT, stirred for 0.5 h, and
30 filtered. The mother liquor was cooled to 0 °C, quenched with aq. sat'd NH₄Cl, diluted with EtOAc

(800 mL) and extracted with EtOAc (3 x 1.5 L). The combined organic extracts were washed with aq. LiCl (2 x 500 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* at 40 °C. The crude product (125 g) was dissolved in THF (800 mL), 200 g of silica gel (100-200 mesh silica gel) was added, and the mixture concentrated at 45 °C until a dry flowing solid was observed. The solid was purified by silica gel flash column chromatography (375 g) eluting with a 100:1 *n*-heptane/THF gradient to afford the title compound (110 g, 86% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.42-7.40 (d, 1H), 7.14-7.11 (d, 1H), 6.89-6.82 (m, 1H), 5.90-5.85 (q, 1H), 5.31-5.28 (t, 1H), 3.33 (s, 6H). LCMS (Method F2), Rt = 1.60 min, *m/z* [M+H]⁺: 207.0.

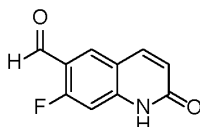
Step 4: 6-Fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde: To a solution of 5-fluoro-1,3-dimethyl-6-vinyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (110 g, 533 mmol) in THF (3.33 L) and H₂O (3.33 L) was added OsO₄ (13.6 g, 53.3 mmol) and NaIO₄ (342 g, 1.60 mol), in portions while under N₂ atm, and the reaction mixture stirred at 25 °C for 1 h. The reaction mixture was quenched with 100% aq. Na₂SO₃ (2.50 L) at RT, diluted with H₂O (2.00 L), and extracted with EtOAc (3 x 3.00 L). The combined organic extracts were washed with brine (2 x 2.00 L), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was triturated and stirred in *n*-heptanes (300 mL) for 12 h, filtered, and concentrated *in vacuo* to afford the title compound (96 g, 83% yield) as a solid. ¹H NMR (400 MHz, CDCl₃) δ 10.33 (s, 1H), 7.43 (d, 1H), 6.77-6.75 (d, 1H), 5.90-5.85 (q, 1H), 3.44 (s, 6H). LCMS (Method H2), Rt = 1.86 min, *m/z* [M+H]⁺: 209.0.

Table 3. The following Intermediates (30-41) were prepared according to a similar synthetic procedure described for Intermediate 29:

Intermediate	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
30		6,7-Difluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde	226.1	1.98 min Method I
31		1,3-dimethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-6-carbaldehyde	192.2	0.51 min Method C
32		6-Fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridine-5-carbaldehyde	210.1	1.30 min Method I
33		6-Fluoro-1-methyl-1H-benzo[d]imidazole-5-carbaldehyde	179.0	0.28 min Method B
34		2,4-Dioxo-1,2,3,4-tetrahydroquinazoline-7-carbaldehyde	N/A	0.33 min Method C
35		6-Fluoro-1-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde	195.1	0.57 min Method H3
36		2-Methyl-3-oxo-3,4-dihydroquinoxaline-6-carbaldehyde	189.0	0.40 min Method B

37		7-Fluoro-1 <i>H</i> -indole-4-carbaldehyde	163.9	0.62 min Method A
38		6-Fluoroimidazo[1,2- <i>a</i>]pyridine-8-carbaldehyde	165.0	0.42 min Method B
39		2-Methyl-[1,2,4]triazolo[1,5- <i>a</i>]pyridine-8-carbaldehyde	162.1	0.95 min Method I
40		6-Fluoroimidazo[1,2- <i>a</i>]pyridine-8-carbaldehyde	165.0	0.42 min Method B
41		2-Methyl-[1,2,4]triazolo[1,5- <i>a</i>]pyridine-8-carbaldehyde	162.1	0.95 min Method I

Intermediate 42: 7-Fluoro-2-oxo-1,2-dihydroquinoline-6-carbaldehyde

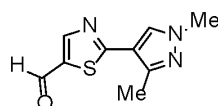


To a solution of 6-bromo-7-fluoroquinolin-2(1*H*)-one (319 mg, 1.32 mmol) in THF (12 mL) cooled to
 5 -78 °C, under N₂, was added a sol'n of 1.6M *n*-BuLi-hexanes (1.73 mL, 2.77 mmol), dropwise over 5
 min. The reaction mixture was stirred at -78 °C for 30 min, to which was added DMF (124 μL, 1.58
 mmol), and the reaction mixture stirred for 1 h. The reaction mixture was quenched with sat'd aq.
 NH₄Cl, extracted with EtOAc, the organic phase dried over Na₂SO₄, filtered, and evaporated under
 reduced pressure. The crude residue was purified by silica gel flash column chromatography (24 g)
 10 eluting with a 30-90% EtOAc/hexanes gradient to afford the title compound (211 mg, 74% yield). ¹H
 NMR (400 MHz, CDCl₃) δ 12.03-11.86 (m, 1H), 7.77 (s, 1H), 7.73-7.67 (m, 1H), 7.04-6.97 (m, 1H),
 6.69-6.65 (m, 1H). LCMS (Method B), Rt = 0.50 min, *m/z* [M+H]⁺: 192.1.

Table 4. The following Intermediates (43-45) were prepared according to a similar synthetic procedure described for Intermediate 42.

Intermediate	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
43		2-Methoxyquinoline-6-carbaldehyde	188.1	0.86 min Method B
44		5,8-Difluoroquinoline-6-carbaldehyde	194.1	0.65 min Method B
45		8-Fluoro-2-methylquinoline-6-carbaldehyde	190.1	0.62 min Method C

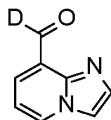
5 Intermediate 46: 2-(1,3-Dimethyl-1H-pyrazol-4-yl)thiazole-5-carbaldehyde



To a mixture of 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.73 g, 7.81 mmol), 2-bromothiazole-5-carbaldehyde (1.00 g, 5.21 mmol), K₃PO₄ (2.21 g, 10.4 mmol), Pd(PPh₃)₄ (361 mg, 312 μmol) was added 1,4-dioxane (10 mL) and H₂O (500 μL). The reaction mixture was stirred at 100 °C for 16 h, the reaction allowed to cool to RT and the solvent evaporated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (40 g) eluting with a 0-10% MeOH/DCM gradient. The product fractions were combined, the solvent evaporated under reduced pressure, and the solid dissolved in EtOAc, stirred with activated charcoal, filtered, the solvent evaporated under reduced pressure, and crystallized from EtOAc-hexanes to afford the title compound (300 mg, 28% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.61 (s,

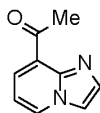
1H), 8.12-8.10 (m, 2H), 4.46-4.40 (m, 2H), 4.03 (s, 3H), 1.44-1.38 (s, 3H). LCMS (Method B), R_t = 0.64 min, m/z $[M+H]^+$: 222.3.

Intermediate 47: Imidazo[1,2-*a*]pyridine-8-carbaldehyde-d



- 5 To a solution of 8-bromoimidazo[1,2-*a*]pyridine (0.980 g, 5.00 mmol) in THF (50 mL), cooled to -78 °C, was added a solution of 2.5M *n*-BuLi-hexane (2.20 mL, 5.50 mmol), dropwise. The reaction mixture was stirred at -78 °C for 30 min, allowed to warm to 0 °C for 5 min, then recooled to -78 °C. DMF-d₇ (466 µL, 6.00 mmol) was added and the reaction mixture stirred for 2 h, warmed to RT, at which time the reaction mixture was quenched with sat'd aq. NH₄Cl (10 mL) and stirred at RT for 30 min.
- 10 The reaction mixture was extracted with DCM several times, the combined organic layers dried over Na₂SO₄, filtered, and the solvent evaporated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (24 g) eluting with a 0-10% MeOH/DCM gradient to afford the title compound (580 mg, 61% yield) as solid. LCMS (Method B), R_t = 0.43 min, m/z $[M+H]^+$: 148.0.

- 15 Intermediate 48: 1-(Imidazo[1,2-*a*]pyridin-8-yl)ethan-1-one

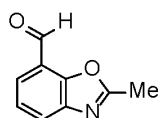


- Step 1:** *N*-Methoxy-*N*-methylimidazo[1,2-*a*]pyridine-8-carboxamide: To a 100 mL RBF was added imidazo[1,2-*a*]pyridine-8-carboxylic acid (2.00 g, 12.3 mmol), DCM (12 mL), cat. DMF, the reaction mixture was cooled to 0 °C, to which was added (COCl)₂ (6.47 mL, 12.9 mmol), dropwise, and the
- 20 reaction mixture was allowed warm to RT and stir for 16 h. The solvent was removed under reduced pressure, the reaction re-dissolved in in DCM (20 mL), charged with *O,N*-dimethyl-hydroxylamine-HCl (1.22 g, 12.5 mmol) to which was added TEA (5.16 mL, 37.0 mmol), dropwise, and the reaction mixture stirred at RT for 24 h. The reaction mixture was quenched with H₂O, the layers separated, and the organic layer washed with 1 M NaOH, dried over Na₂SO₄, filtered, and reduced under reduced
- 25 pressure to afford the title compound (150 mg, 6% yield) as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.61 (d, *J*=6.85 Hz, 1H), 8.02 (d, *J*=0.98 Hz, 1H), 7.59 (s, 1H), 7.26 (d, *J*=6.85 Hz, 1H),

6.94 (t, $J=6.85$ Hz, 1H), 3.56 (br s, 3 H), 3.29-3.15 (m, 3H). LCMS (Method B), $R_t = 0.52$ min, m/z $[M+H]^+$: 206.1.

Step 2: 1-(Imidazo[1,2-*a*]pyridin-8-yl)ethan-1-one: To a solution of *N*-methoxy-*N*-methylimidazo[1,2-*a*]pyridine-8-carboxamide (295 mg, 1.44 mmol) in THF (28.8 mL), cooled to -78 °C, was added a solution of 1.6M MeLi-Et₂O (3.60 mL, 5.75 mmol), dropwise, and the reaction mixture was allowed to stir at -78 °C for 3 h. The reaction mixture was quenched by the addition of a sat'd aq. NH₄Cl solution, dropwise, and the reaction mixture diluted with EtOAc and additional sat'd aq. NH₄Cl solution. The layers were separated, the aqueous phase with EtOAc (3x), the combined organic extracts washed with brine, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (24 g) eluting with a 0-100% heptanes/EtOAc gradient to afford the title compound (261 mg, > 100% yield). ¹H NMR (400 MHz, CD₃OD) δ 2.86 (s, 3 H) 7.03 (t, $J=7.09$ Hz, 1H) 7.68 (d, $J=1.47$ Hz, 1H) 7.91 (d, $J=6.96$ Hz, 1H) 7.97 (d, $J=1.47$ Hz, 1H) 8.67 (d, $J=6.66$ Hz, 1H). LCMS (Method B), $R_t = 0.42$ min, m/z $[M+H]^+$: 161.0.

Intermediate 49: 2-Methylbenzo[*d*]oxazole-7-carbaldehyde

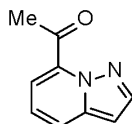


Step 1: *N*-Methoxy-*N*,2-dimethylbenzo[*d*]oxazole-7-carboxamide: A 20-mL scintillation vial was charged 2-methylbenzo[*d*]oxazole-7-carboxylic acid (750 mg, 4.23 mmol), EDCI (819 mg, 4.27 mmol), *O,N*-dimethyl-hydroxylamine HCl (417 mg, 4.27 mmol), TEA (708 μ L, 5.08 mmol) and DCM (10 mL). The reaction mixture was sealed and stirred at RT for 22 h. The reaction mixture was washed with 1 M HCl, 1M NaHCO₃, brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the title compound (610 mg, 60% yield), which was used without further purification. LCMS (Method A), $R_t = 0.50$ min, m/z $[M+H]^+$: 221.0.

Step 2: 2-Methylbenzo[*d*]oxazole-7-carbaldehyde: To a solution of *N*-methoxy-*N*,2-dimethylbenzo[*d*]oxazole-7-carboxamide (610 mg, 2.77 mmol) in THF (10 mL), cooled to -70 °C, was added solid LiAlH₄ (120 mg, 5.54 mmol), and the reaction mixture was stirred at -70 °C for 1 h under N₂. The reaction mixture was slowly quenched with H₂O (0.25 mL), followed by the addition of 15% aq. NaOH (0.25 mL) and H₂O (0.75 mL). The reaction mixture was filtered, the filtrate dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude was adsorbed onto silica gel and purified by silica gel flash column chromatography (40 g) eluting with a 0-60% heptanes/EtOAc gradient to afford the title compound (164 mg, 34% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.29 (s, 1H), 8.07 (d,

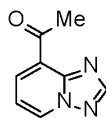
$J=7.50$ Hz, 1H), 7.95 (d, $J=7.50$ Hz, 1H), 7.61 (t, $J=7.75$ Hz, 1H), 2.74 (s, 3H). LCMS (Method B), $R_t = 0.51$ min, m/z $[M+H]^+$: 161.9.

Intermediate 50: 1-(Pyrazolo[1,5-*a*]pyridin-7-yl)ethan-1-one



- 5 To a solution of pyrazolo[1,5-*a*]pyridine (2.50 g, 21.2 mmol) in THF (50 mL), cooled to -78 °C, was added a sol'n of 2.5M *n*-BuLi-THF (12.7 mL, 31.7 mmol) and the reaction mixture was stirred at -78 °C for 1 h. *N*-Methoxy-*N*-methylacetamide (2.62 g, 25.4 mmol) was added at -78 °C and the reaction mixture stirred at RT for 2 h. Two reaction mixtures were combined, quenched with H_2O (20 mL), stirred for 5 min, and extracted with EtOAc (2 x 40 mL). The combined extracts were washed with
- 10 brine (10 mL), dried over Na_2SO_4 , filtered and the solvent evaporated under reduced pressure. The crude residue was adsorbed onto silica gel (15 g) and purified by silica gel flash column chromatography (75 g) eluting with a 12% EtOAc-pet ether gradient to afford the title compound (5.20 g, 76% yield). 1H NMR (400 MHz, $DMSO-d_6$) δ 8.06-8.06 (d, 1H), 7.76-7.65 (d, 1H), 7.74-7.73 (d, 1H), 7.28-7.16 (m, 1H), 6.69 (s, 1H), 2.98 (s, 3H). LCMS (Method H3), $R_t = 0.64$ min, m/z
- 15 $[M+H]^+$: 161.2.

Intermediate 51: 1-([1,2,4]Triazolo[1,5-*a*]pyridin-8-yl)ethan-1-one

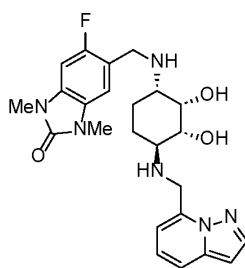


- Step 1:** 8-(1-Ethoxyvinyl)-[1,2,4]triazolo[1,5-*a*]pyridine: To a solution of 8-bromo-[1,2,4]triazolo[1,5-*a*]pyridine (15.0 g, 75.8 mmol) and tributyl(1-ethoxyvinyl)stannane (30.1 g, 83.3 mmol) in DMF (150
- 20 mL), stirred under N_2 at RT, was added $Pd(PPh_3)_4$ (8.75 g, 7.58 mmol) and the reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was cooled to RT, quenched with H_2O (200 mL), and extracted with EtOAc (3 x 500 mL). The combined organic extracts were treated with sat'd aq. KF (200 mL), stirred at RT for 0.5 h, filtered through a bed of celite, and the resultant filtrate washed with H_2O , brine, dried over Na_2SO_4 , filtered, and evaporated under reduced pressure. The crude
- 25 residue was adsorbed on silica gel (40 g) and purified by silica gel flash column chromatography (350 g) eluting with a 3% EtOAc-pet ether gradient to afford the title compound (7.0 g, 44% yield). 1H NMR (400 MHz, $DMSO-d_6$) δ 8.94-8.92 (d, 1H), 8.56 (s, 1H), 7.93-7.91 (d, 1H), 7.26-7.23 (m, 1H),

6.31 (s, 1H), 4.82 (s, 1H), 4.00-3.95 (q, 2H), 1.41-1.38 (t, 3H). LCMS (Method H3), R_t = 0.84 min, m/z [M+H]⁺: 190.0.

Step 2: 1-([1,2,4]Triazolo[1,5-*a*]pyridin-8-yl)ethan-1-one: To a solution of 8-(1-ethoxyvinyl)-[1,2,4]triazolo[1,5-*a*]pyridine (7.00 g, 36.9 mmol) in THF (70 mL) was added 50% w/w HCl (14.8 g, 203 mmol) at RT and the reaction mixture stirred at RT for 5 h. The reaction mixture was concentrated, diluted with H₂O (100 mL) and extracted with EtOAc (2 x 300 mL). The aqueous phase was basified with NaHCO₃ (pH:9) and extracted with EtOAc (2 x 300 mL). The combined organic extracts were washed with brine (100 mL) and evaporated under reduced pressure to afford the title compound (4.70 g, 77% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.26-9.24 (m, 1H), 8.68 (s, 1H), 8.19-8.17 (m, 1H), 7.37-7.34 (m, 1H), 2.93 (s, 3H). LCMS (Method H3), R_t = 0.42 min, m/z [M+H]⁺: 162.0.

EXAMPLE 1: 5-((((1*S*,2*S*,3*R*,4*S* and 1*R*,2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one



15

Step 1: *tert*-Butyl ((3*aR*,4*S*,7*R*,7*aS* and 3*aS*,4*R*,7*S*,7*aR*)-7-hydroxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate: The title compound was prepared using a similar procedure as outlined in Heterocycles (2002), 58, 471-504.

Step 2: (3*aR*,4*R*,7*S*,7*aR* and 3*aS*,4*S*,7*R*,7*aS*)-7-((*tert*-Butoxycarbonyl)amino)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl methanesulfonate: To a solution of *tert*-butyl ((3*aR*,4*S*,7*R*,7*aS* and 3*aS*,4*R*,7*S*,7*aR*)-7-hydroxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate (18.5 g, 64.4 mmol) in DCM (250 mL) and TEA (13.5 mL, 96.6 mmol), was added MeSO₂Cl (5.98 mL, 77.3 mmol), dropwise, at RT over 15 min, and the reaction mixture stirred for 4 h. The reaction mixture was quenched with H₂O, washed with sat'd aq. NaHCO₃, brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The residue was crystallized from EtOAc, filtered, washed with 20% EtOAc-hexanes to afford the title compound (19.9 g, 85% yield). ¹H NMR

(400 MHz, CDCl₃) δ 4.76-4.91 (m, 1H), 4.62 (br d, *J*=5.5 Hz, 1H), 4.14-4.30 (m, 2H), 4.03 (br s, 1H), 3.12-3.24 (m, 3H), 1.94-2.20 (m, 2H), 1.70-1.88 (m, 2H), 1.63 (s, 3H), 1.53 (s, 9H), 1.45 (s, 3H).

Step 3: *tert*-Butyl ((3*aR*,4*S*,7*S*,7*aS* and 3*aS*,4*R*,7*R*,7*aS*)-7-azido-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate: To a solution of (3*aR*,4*R*,7*S*,7*aR* and 3*aS*,4*S*,7*R*,7*aS*)-7-((*tert*-butoxycarbonyl)amino)-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl methanesulfonate (10.0 g, 27.4 mmol) in DMSO (150 mL), was added NaN₃ (3.56 g, 54.7 mmol) and the reaction mixture stirred at 110 °C for 60 hr. The reaction mixture was quenched with H₂O and extracted with EtOAc. The organic extract was washed with H₂O, brine, dried over MgSO₄, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (330 g) eluting with a 20% EtOAc-hexanes (20 min), then ramped to 40% EtOAc-hexanes gradient to afford the title compound (3.17 g, 37% yield). ¹H NMR (400 MHz, CDCl₃) δ 4.41-4.59 (m, 1H), 4.37 (t, *J*=4.3 Hz, 1H), 3.86 (br dd, *J*=8.5, 5.0 Hz, 1H), 3.47-3.62 (m, 2H), 2.03-2.11 (m, 1H), 1.85-1.95 (m, 2H), 1.59 (s, 5H), 1.44 (s, 9H), 1.40 (s, 3H), 1.26-1.33 (m, 1H).

Step 4: *tert*-Butyl ((3*aR*,4*S*,7*R*,7*aS* and 3*aS*,4*R*,7*S*,7*aR*)-7-amino-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate: To *tert*-butyl ((3*aR*,4*S*,7*S*,7*aS* and 3*aS*,4*R*,7*R*,7*aS*)-7-azido-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate (7.30 g, 23.4 mmol), P(Ph)₃ (12.3 g, 46.7 mmol), H₂O (12.7 mL, 701 mmol) was added THF (150 mL) and the reaction mixture was heated at 50 °C for 20 h. The reaction mixture was concentrated and purified by silica gel flash column chromatography (220 g) eluting with a 0-10% MeOH(10% NH₄OH)/DCM (15 min) gradient to afford the title compound (6.70 g, 100% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.55 (br d, *J*=8.3 Hz, 1H), 4.22 (t, *J*=4.2 Hz, 1H), 3.75 (dd, *J*=8.8, 4.9 Hz, 1H), 3.48 (dtd, *J*=12.8, 8.3, 4.4 Hz, 1H), 2.88-3.01 (m, 1H), 1.87-1.96 (m, 1H), 1.65-1.73 (m, 1H), 1.55-1.61 (m, 3H), 1.54 (s, 3H), 1.43 (s, 9H), 1.36 (s, 3H), 1.15 (qd, *J*=12.9, 2.9 Hz, 1H).

Step 5: *tert*-Butyl ((1*S*,2*R*,3*S*,4*S* and 1*R*,2*S*,3*R*,4*R*)-4-(((6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)amino)-2,3-dihydroxycyclohexyl)carbamate: To a solution of *tert*-butyl ((3*aR*,4*S*,7*R*,7*aS* and 3*aS*,4*R*,7*S*,7*aR*)-7-hydroxy-2,2-dimethylhexahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate (500 mg, 1.75 mmol) and 6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde (363 mg, 1.75 mmol) in DCE (15 mL) was added AcOH (629 mg, 10.5 mmol), the reaction mixture stirred at RT for 10 min, to which was added STAB (1.11 g, 5.24 mmol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was quenched with H₂O and the reaction mixture basified with solid Na₂CO₃. The reaction mixture was filtered, washed with DCE, the filtrate was concentrated *in vacuo*. The crude residue purified by silica gel flash column

chromatography (80 g) eluting with a 50-70% 3:1 EtOAc/EtOH-heptanes gradient to afford the title compound (195 mg, 23% yield). LCMS (Method B), Rt = 0.95 min, m/z [M+H]⁺: 479.4.

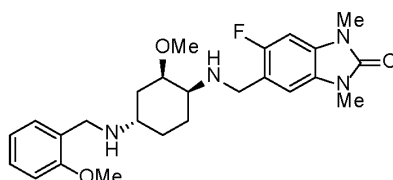
Step 6: 5-((((1*S*,2*S*,3*R*,4*S* and 1*R*,2*R*,3*S*,4*R*)-4-Amino-2,3-dihydroxycyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one: To a solution of *tert*-butyl (((1*S*,2*R*,3*S*,4*S* and 1*R*,2*S*,3*R*,4*R*)-4-(((6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)amino)-2,3-dihydroxycyclohexyl)carbamate (190 mg, 397 μ mol) in DCM (4 mL) was added TFA (3.00 mL, 39.7 mmol) and the reaction mixture was stirred at RT for 20 h. The reaction mixture was concentrated under reduced pressure to afford the title compound (380 mg, 93 % yield) as a TFA salt, in 55% purity. LCMS (Method B), Rt = 0.48 min, m/z [M+H]⁺: 339.3.

Step 7: 5-((((1*S*,2*S*,3*R*,4*S* and 1*R*,2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one: To a solution of 5-((((1*S*,2*S*,3*R*,4*S* and 1*R*,2*R*,3*S*,4*R*)-4-amino-2,3-dihydroxycyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, TFA salt (19 mg, 335 μ mol), in EtOH (4 mL) was added pyrazolo[1,5-*a*]pyridine-7-carbaldehyde (49 mg, 335 μ mol) and TEA (187 μ L, 1.34 mmol) and the reaction mixture was stirred at 50 °C for 16 h. Additional aldehyde (25 mg) and STAB (213 mg, 1.00 mmol) were added, and reaction mixture was stirred at RT for 6 h. The reaction mixture was quenched with H₂O and basified with solid Na₂CO₃. The solid was filtered, washed with DCE, the filtrate concentrated, and the crude residue purified using a semi-prep HPLC (MDAP) system eluting with a 15%-55% MeCN-H₂O (10 nM ammonium carbonate pH10 buffer) gradient. Product fractions were combined, extracted with EtOAc, the organic extract washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo* to afford the title compound (52 mg, 33% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.98 (d, *J*=2.0 Hz, 1H), 7.52 (d, *J*=9.0 Hz, 1H), 7.11 (dd, *J*=8.5, 7.0 Hz, 1H), 6.94 (d, *J*=6.0 Hz, 1H), 6.78 (d, *J*=6.5 Hz, 1H), 6.70 (d, *J*=9.5 Hz, 1H), 6.57 (d, *J*=2.5 Hz, 1H), 4.24-4.41 (m, 2H), 4.23 (br s, 1H), 3.81-3.98 (m, 2H), 3.40 (s, 3H), 3.38 (s, 3H), 3.33-3.38 (m, 1H), 2.91 (td, *J*=10.4, 3.8 Hz, 1H), 2.65 (br d, *J*=10.0 Hz, 1H), 1.87-1.96 (m, 1H), 1.63-1.72 (m, 1H), 1.50-1.63 (m, 1H), 1.11 (qd, *J*=12.3, 3.5 Hz, 1H). LCMS (Method B), Rt = 0.72 min, m/z [M+H]⁺ = 469.4.

Table 5. The following Examples (2-3) were prepared according to a similar synthetic procedure described for Example 1, using HCl or TFA for the Boc deprotection step.

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
2		(1 <i>R</i> ,2 <i>S</i> ,3 <i>S</i> ,6 <i>S</i> and 1 <i>S</i> ,2 <i>R</i> ,3 <i>R</i> ,6 <i>R</i>)-3-(((7-Fluoroquinolin-6-yl)methyl)amino)-6-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexane-1,2-diol	436.3	0.63 Method B
3		(1 <i>S</i> ,2 <i>R</i> ,3 <i>S</i> ,6 <i>S</i> and 1 <i>R</i> ,2 <i>S</i> ,3 <i>R</i> ,6 <i>R</i>)-3-(((2-Methoxybenzyl)amino)-6-((quinolin-6-ylmethyl)amino)cyclohexane-1,2-diol	408.3	0.75 Method B

EXAMPLE 4: 5-Fluoro-6-((((1*S*,2*R*,4*S*)-2-methoxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one

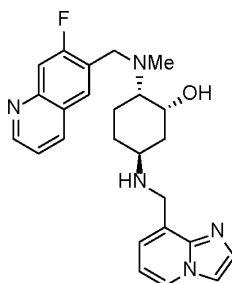


Step 1: 5-Fluoro-6-((((1*S*,2*R*,4*S*)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one: The title compound was prepared according to a similar synthetic procedure described for 5-fluoro-6-((((1*R*,2*R*,4*R*)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, utilizing the appropriate enantiomer of starting material.

Step 2: *tert*-Butyl ((1*S*,3*R*,4*S*)-4-((*tert*-butoxycarbonyl)((6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)amino)-3-hydroxycyclohexyl)(2-methoxybenzyl)carbamate: To a

- suspension of 5-fluoro-6-((((1*S*,2*R*,4*S*)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (835 mg, 1.85 mmol) in DCM (30 mL) was added Boc₂O (1.00 g, 4.60 mmol) followed by TEA (773 µL, 5.50 mmol), and the reaction mixture was stirred at RT for 20 h. Additional Boc₂O (404 mg) and TEA (309 µL) were added, and the reaction mixture was stirred at RT for another 16 h. The mixture was diluted with DCM, washed with brine, the organic phase dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash column chromatography (40 g) eluting with a 10-60% EtOAc/hexanes gradient to afford the title compound (885 mg, 73% yield). LCMS (Method B), Rt = 0.72 min, *m/z* [M+H]⁺: 643.5.
- 10 **Step 3:** *tert*-Butyl (((1*S*,3*R*,4*S*)-4-((*tert*-butoxycarbonyl)((6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)amino)-3-methoxycyclohexyl)(2-methoxybenzyl)carbamate: To a solution of *tert*-butyl (((1*S*,3*R*,4*S*)-4-((*tert*-butoxycarbonyl)((6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)amino)-3-hydroxycyclohexyl)(2-methoxybenzyl)carbamate (100 mg, 153 µmol) in THF (3 mL) at 0 °C, under N₂, was added a sol'n of 1M LHMDS-THF (169 µL, 169 µmol) and the reaction mixture was stirred at the 0 °C for 15 min, at which time MeI (11.9 µL, 184 µmol) was added. The reaction mixture was stirred at RT for 6.5 h, quenched with sat'd aq. NH₄Cl and extracted with EtOAc. The combined organic solution was washed with H₂O, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (12 g) eluting with a 0-10% MeOH/DCM gradient to afford the title compound
- 15 (14 mg, 14% yield). LCMS (Method C), Rt = 1.51 min, *m/z* [M+H]⁺: 657.5.
- 20 **Step 4:** 5-Fluoro-6-((((1*S*,2*R*,4*S*)-2-methoxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one: To a solution of *tert*-butyl (((1*S*,3*R*,4*S*)-4-((*tert*-butoxycarbonyl)((6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)amino)-3-methoxycyclohexyl)(2-methoxybenzyl)-carbamate (13.0 mg, 19.4 µmol) in DCM (1.0 mL) was added
- 25 TFA (221 mg, 1.9 mmol) and the reaction mixture was stirred at RT for 2 h. The mixture was diluted with DCM, basified with 1 N NaOH, the layers separated, and the aqueous phase extracted with DCM. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to afford the title compound (8.3 mg, 93% yield). ¹H NMR (400 MHz, CD₃OD) δ 7.11-7.19 (m, 2H), 7.06 (d, *J*=6.36 Hz, 1H), 6.88 (br d, *J*=9.78 Hz, 2H), 6.77-6.84 (m, 1H), 3.76 (s, 5H), 3.67 (d, *J*=1.96 Hz, 2H), 3.53-3.57 (m, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 3.20 (s, 3H), 2.53-2.64 (m, 1H), 2.43-2.51 (m, 1H), 2.22-2.32 (m, 1H), 1.81-1.91 (m, 1H), 1.65-1.74 (m, 1H), 1.32-1.46 (m, 1H), 0.94-1.14 (m, 2H). LCMS (Method B), Rt = 0.93 min, *m/z* [M+H]⁺: 457.4.
- 30

EXAMPLE 5: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)(methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexan-1-ol

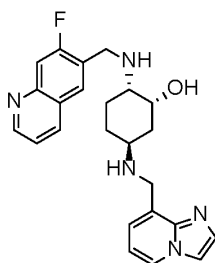


- Step 1:** *tert*-Butyl ((1*S*,3*R*,4*S*)-4-(((7-fluoroquinolin-6-yl)methyl)(methyl)amino)-3-hydroxycyclohexyl)carbamate: To a mixture of *tert*-butyl ((1*S*,3*R*,4*S*)-4-(((7-fluoroquinolin-6-yl)methyl)amino)-3-hydroxycyclohexyl)-carbamate (0.11 g, 224 μ mol) and 38% wt CH₂O (49 μ L, 672 μ mol) in DCM (10 mL) was added TEA (47 μ L, 336 μ mol) and the reaction mixture was stirred at RT for 4 h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in DCM (10 mL), to which was added STAB (142 mg, 672 μ mol) and the reaction mixture stirred at RT for 1.5 h. The reaction mixture was diluted with DCM, washed with sat'd aq. NaHCO₃, the layers separated, the aqueous phase extracted with DCM, and the combined organic extracts washed with H₂O, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash column chromatography (12 g) eluting with a 0-10% MeOH(2% NH₄OH)/DCM gradient to afford the title compound. LCMS (Method B): Rt = 1.03 min, *m/z* [M+H]⁺: 404.3.
- Step 2:** (1*R*,2*S*,5*S*)-5-Amino-2-(((7-fluoroquinolin-6-yl)methyl)(methyl)amino)cyclohexan-1-ol: The title compound was prepared according to a TFA deprotection procedure of similar synthetic procedure described in 5-Fluoro-6-(((1*S*,2*R*,4*S*)-2-methoxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, starting from *tert*-butyl ((1*S*,3*R*,4*S*)-4-(((7-fluoroquinolin-6-yl)methyl)(methyl)amino)-3-hydroxycyclohexyl)carbamate. LCMS (Method B): Rt = 0.66 min, *m/z* [M+H]⁺: 304.2.

- Step 3:** (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)(methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclo-hexan-1-ol: To a mixture of (1*R*,2*S*,5*S*)-5-amino-2-(((7-fluoroquinolin-6-yl)methyl)(methyl)amino)cyclohexan-1-ol (191 mg, 221 μ mol) and imidazo[1,2-*a*]pyridine-8-carboxaldehyde (32.3 mg, 221 μ mol) in DCM (5 mL) was added TEA (185 μ L, 1.33 mmol) and the mixture was stirred at RT for 3 h. The mixture was concentrated *in vacuo* and the residue redissolved in DCM (5 mL) to which was added STAB (141 mg, 664 μ mol) and the reaction mixture was stirred at RT for 1 h. The reaction mixture was diluted with DCM, washed with sat'd aq. NaHCO₃, the layers

separated, and the aqueous phase was extracted with DCM. The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash column chromatography (12 g) eluting with a 0-20% MeOH (2% NH₄OH)/DCM gradient to afford the title compound (80.1 mg, 84% yield) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.79-8.86 (m, 1H), 8.33-8.42 (m, 2H), 8.02-8.09 (m, 1H), 7.86 (d, *J*=1.47 Hz, 1H), 7.61-7.69 (m, 1H), 7.58 (d, *J*=1.47 Hz, 1H), 7.47-7.54 (m, 1H), 7.26-7.33 (m, 1H), 6.91 (t, *J*=6.85 Hz, 1H), 4.32-4.39 (m, 1H), 4.10-4.21 (m, 2 H), 3.88-4.04 (m, 2H), 2.93-3.07 (m, 1H), 2.44-2.54 (m, 1H), 2.34 (s, 3H), 2.10-2.27 (m, 2H), 1.75-1.93 (m, 2H), 1.33-1.45 (m, 1H), 1.19-1.32 (m, 1H). LCMS (Method B), Rt = 0.80 min, *m/z* [M+H]⁺: 434.3.

EXAMPLE 6: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-yl)methyl)amino)-cyclohexan-1-ol



Step 1: *tert*-Butyl ((1*S*,3*R*,4*S*)-4-(((7-fluoroquinolin-6-yl)methyl)amino)-3-hydroxycyclohexyl)-carbamate: To a 500 mL RBF was charged a mixture of *tert*-butyl ((1*S*,3*R*,4*S*)-4-amino-3-hydroxycyclohexyl)carbamate (14.9 g, 64.5 mmol) and 7-fluoroquinoline-6-carbaldehyde (11.3 g, 64.5 mmol) in THF (323 mL). The reaction mixture was stirred at RT for 72 h, at which time STAB (41.0 g, 193 mmol) was added in 4 batches over the course of 10 min. The reaction mixture was stirred for 1 h and transferred into 1 M NaOH (2 L). The resulting suspension was stirred for 2 h, then filtered, dried on the frit, transferred to a vacuum oven, and dried overnight to afford the title compound (22.1 g, 86% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (dd, *J*=4.16, 1.71 Hz, 1H) 8.40 (d, *J*=8.41 Hz, 1H) 8.10 (d, *J*=8.31 Hz, 1H) 7.71 (d, *J*=11.74 Hz, 1H) 7.51 (dd, *J*=8.07, 4.16 Hz, 1H) 6.61 (br d, *J*=8.31 Hz, 1H) 4.42 (d, *J*=3.42 Hz, 1H) 3.87-4.02 (m, 3H) 3.62 (br d, *J*=6.85 Hz, 1H) 2.37-2.45 (m, 1H) 1.97 (br s, 1H) 1.84 (br d, *J*=11.74 Hz, 1H) 1.69-1.79 (m, 1H) 1.60-1.68 (m, 1H) 1.44-1.55 (m, 1H) 1.37 (s, 9H) 1.24-1.34 (m, 1H) 1.04-1.21 (m, 1H). LCMS (Method B), Rt = 0.88 min, *m/z* [M+H]⁺: 390.5.

Step 2: (1*R*,2*S*,5*S*)-5-Amino-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol, 2 Hydrochloride: A 1-L three-neck flask, equipped with an overhead stirrer, was added a solution of *tert*-

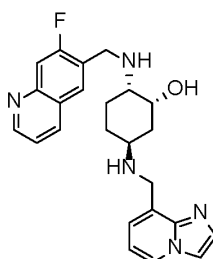
butyl ((1*S*,3*R*,4*S*)-4-(((7-fluoroquinolin-6-yl)methyl)amino)-3-hydroxycyclohexyl)-carbamate (22.1 g, 56.7 mmol) in DCM (567 mL) followed by 4 M HCl-dioxane (142 mL, 567 mmol). The reaction mixture was stirred at RT for 16 h, diluted with Et₂O (300 mL), filtered under a cone of N₂, and dried under vacuum for 1 h, then under high vacuum oven overnight to afford the title compound (23.8 g, >100% yield) as a solid. ¹H NMR (400 MHz, CD₃OD) δ 9.30 (dd, *J*=5.38, 1.47 Hz, 1H) 9.22 (d, *J*=8.31 Hz, 1H) 8.70 (d, *J*=7.34 Hz, 1H) 8.06-8.13 (m, 2H) 4.54-4.69 (m, 3H) 3.48-3.59 (m, 2H) 2.27-2.35 (m, 1H) 2.14-2.22 (m, 2H) 1.96-2.09 (m, 1H) 1.72-1.81 (m, 1H) 1.55-1.66 (m, 1H). LCMS (Method B): Rt = 0.54 min, *m/z* [M+H]⁺: 290.4.

Step 3: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol, acetic acid salt: To a 500 mL RBF was added a mixture of (1*R*,2*S*,5*S*)-5-amino-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol, 2Hydrochloride (10.0 g, 24.8 mmol) and imidazo[1,2-*a*]pyridine-8-carboxaldehyde (5.0 g, 34.2 mmol) in MeOH (250 mL) followed by DIEA (17.0 mL, 99.4 mmol) and the reaction mixture was stirred for 20 min, at which time STAB (15.8 g, 74.5 mmol) was added and the reaction mixture was stirred at RT for 30 min. Silica gel was added to the reaction mixture, the solvent concentrated *in vacuo* and the solid material loaded onto an isco redisepp column and purified by silica gel flash column chromatography (330 g) eluting with a 60-100% 3:1 EtOAc/EtOH(2% NH₄OH)/DCM gradient. The desired product fractions were combined, concentrated *in vacuo*, dissolved in MeOH (20 mL) and precipitated with Et₂O (200 mL). The suspension was sonicated for 5 min, filtered, washed with Et₂O, and dried to afford the title compound (7.25 g, 69% yield) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.88 (dd, *J*=4.40, 1.47 Hz, 1H) 8.46 (dd, *J*=6.85, 0.98 Hz, 1H) 8.39-8.44 (m, 1H) 8.11 (d, *J*=7.83 Hz, 1H) 7.92 (d, *J*=1.47 Hz, 1H) 7.72 (d, *J*=11.25 Hz, 1H) 7.63 (d, *J*=1.47 Hz, 1H) 7.56 (dd, *J*=8.31, 4.40 Hz, 1H) 7.37 (d, *J*=6.36 Hz, 1H) 6.96 (t, *J*=7.09 Hz, 1H) 4.32 (s, 2H) 4.26-4.30 (m, 1H) 4.12-4.23 (m, 2H) 3.18-3.28 (m, 1H) 2.80-2.86 (m, 1H) 2.32 (dq, *J*=13.63, 3.44 Hz, 1H) 2.20 (dt, *J*=12.35, 3.36 Hz, 1H) 1.87-1.99 (m, 4H) 1.66-1.78 (m, 1H) 1.49-1.57 (m, 1H) 1.38 (qd, *J*=12.47, 3.67 Hz, 1H). LCMS (Method B), Rt = 0.70 min, *m/z* [M+H]⁺: 420.3.

Step 4: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexan-1-ol, dihydrochloride: To a solution of (1*R*,2*S*,5*S*)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol, acetic acid salt (20.8 g, 43.4 mmol) in MeOH (434 mL) was added 3M HCl-CPME (35.3 mL, 106 mmol). The reaction was stirred at RT for 10 min, Et₂O (900 mL) was added, and the reaction mixture was stirred for 20 min, filtered, and the solid washed with Et₂O (300 mL). The solid was dissolved in H₂O, froze, and lyophilized for 72 h to afford the dihydrochloride salt of the title compound (18.2 g, 69%) as a white

powder. ^1H NMR (400 MHz, CD_3OD) δ 8.97 (dd, $J=1.5, 4.5$ Hz, 1H), 8.6-8.6 (m, 1H), 8.5-8.5 (m, 1H), 8.31 (d, $J=8.0$ Hz, 1H), 8.01 (d, $J=1.5$ Hz, 1H), 7.84 (d, $J=11.0$ Hz, 1H), 7.71 (d, $J=1.5$ Hz, 1H), 7.63 (dd, $J=4.3, 8.3$ Hz, 1H), 7.54 (d, $J=6.5$ Hz, 1H), 7.04 (t, $J=7.0$ Hz, 1H), 4.5-4.7 (m, 5H), 3.7-3.8 (m, 1H), 3.5-3.5 (m, 1H), 2.4-2.6 (m, 2H), 2.2-2.3 (m, 1H), 2.04 (dd, $J=3.5, 12.5$ Hz, 1H), 1.8-1.9 (m, 1H), 1.72 (dd, $J=3.8, 12.8$ Hz, 1H). LCMS (Method B), $R_t = 0.67$ min, m/z $[\text{M}+\text{H}]^+$: 420.5.

EXAMPLE 6B: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol



(1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol, dihydrochloride was suspended in 15 volumes (60 mL) of 10% MeOH:DCM, resulting in a stirrable slurry. 1M aqueous NaOH solution (14.4 mL) was added over 5 minutes via syringe. Addition of the first 2 ml of NaOH solution resulted in a thickening of the mixture. As the NaOH addition proceeded, stirring became easier and two distinct phases were observed: a cloudy upper aqueous layer and a clear light orange organic layer. After addition was complete, stirring was halted and the pH of the aqueous layer was found to be pH 9. Additional 1N NaOH was added (0.7 ml) and the biphasic mixture was stirred for 5 minutes. pH of the aqueous layer was pH 12. The mixture was transferred to a separatory funnel and 4.33 volumes of saturated NaCl solution was added (17 ml). The layers were separated and the aqueous layer was extracted with 10% MeOH:DCM. The combined organics were dried over sodium sulfate, filtered, concentrated *in vacuo*, and pumped under high vacuum to give the title compound (2.82g, 97.9% yield) as an off-white free-flowing solid, 100% purity. LCMS (Method B), $R_t = 0.67$ min, m/z $[\text{M}+\text{H}]^+$: 420.3.

NMR in $\text{DMSO}-d_6$ indicated free-base product.

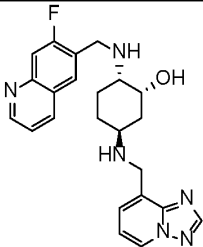
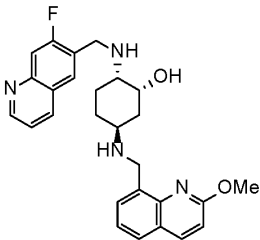
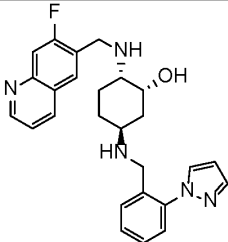
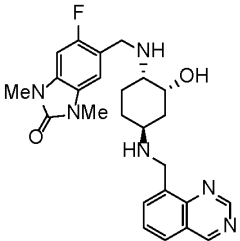
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm 8.84 - 8.94 (m, 1 H) 8.35 - 8.48 (m, 2 H) 8.09 (d, $J=8.25$ Hz, 1 H) 7.93 (d, $J=1.25$ Hz, 1 H) 7.71 (d, $J=11.76$ Hz, 1 H) 7.46 - 7.56 (m, 2 H) 7.19 (dd, $J=6.75, 1.25$ Hz, 1 H) 6.85 (t, $J=6.75$ Hz, 1 H) 4.31 (d, $J=3.50$ Hz, 1 H), 3.84 - 4.10 (m, 5 H) 2.70 - 2.84 (m, 1 H) 2.51 (dt, $J=3.75, 1.88$ Hz, 1 H) 2.16 (br s, 1 H) 1.85 - 2.06 (m, 3 H) 1.62 - 1.75 (m, 1 H) 1.36 - 1.52 (m, 1 H) 1.14 - 1.29 (m, 1 H) 0.95 - 1.12 (m, 1 H).

D₂O was added to the above sample and exchanged protons were observed:

¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.85 (dd, *J*=4.13, 1.63 Hz, 1 H) 8.32 - 8.46 (m, 2 H) 8.05 (d, *J*=8.26 Hz, 1 H) 7.91 (d, *J*=1.25 Hz, 1 H) 7.69 (d, *J*=11.51 Hz, 1 H) 7.44 - 7.56 (m, 2 H) 7.19 (dd, *J*=6.75, 1.00 Hz, 1 H) 6.85 (t, *J*=6.88 Hz, 1 H) 3.95 - 4.04 (m, 3 H) 3.85 - 3.95 (m, 2 H) 2.65 - 2.80 (m, 1 H) 2.44 - 2.57 (m, 1 H) 1.94 - 2.03 (m, 1 H) 1.80 - 1.92 (m, 1 H) 1.57 - 1.70 (m, 1 H) 1.39 (br dd, *J*=11.88, 1.88 Hz, 1 H) 1.17 - 1.27 (m, 1 H) 0.97 - 1.13 (m, 1H).

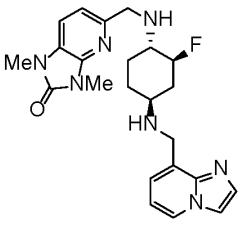
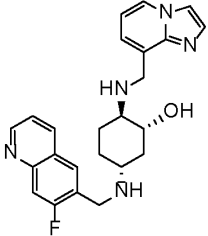
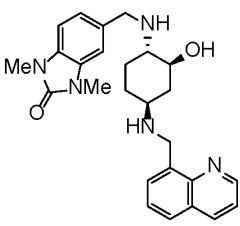
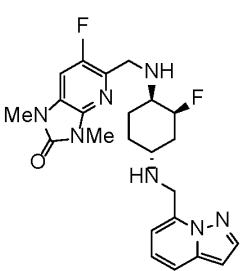
Table 6. The following Examples (7-25) were prepared by a similar synthetic procedure described for Example 6, using the reducing reagents (STAB, Polymer-NaCNBH₃, or NaBH₄) and deprotection reagents (HCl or TFA).

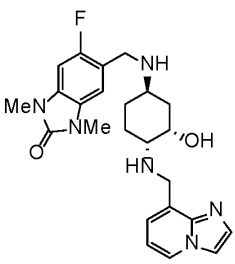
Example	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	Rt (min) LCMS Method
7		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((2-methyl-[1,2,4]triazolo[1,5- <i>a</i>]pyridin-8-yl)methyl)amino)cyclohexan-1-ol	435.4	0.68 min Method B
8		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-5-(((Benzo[<i>d</i>]oxazol-4-yl)methyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol	421.0	0.32 min Method A

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
9		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-5-(((1,2,4]Triazolo[1,5- <i>a</i>]pyridin-8-ylmethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol	421.0	0.33 min Method A
10		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(((6-Fluoroquinolin-7-yl)methyl)amino)-5-(((2-methoxyquinolin-8-yl)methyl)amino)cyclohexan-1-ol	461.4	0.99 Method B
11		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-5-((2-(1 <i>H</i> Pyrazol-1-yl)benzyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol	446.3	0.80 min Method B
12		5-Fluoro-6-(((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-hydroxy-4-((quinazolin-8-ylmethyl)amino)cyclohexylamino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	465.4	0.72 min Method B

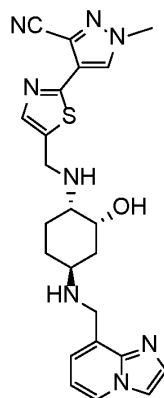
Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
13		5-Fluoro-6-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-hydroxy-4-(((2-methylbenzo[<i>d</i>]oxazol-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	468.3	0.76 min Method B
14		5-Fluoro-6-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-(((6-fluoroimidazo[1,2- <i>a</i>]pyridin-8-yl)methyl)amino)-2-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	471.5	0.71 min Method B
15		6-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-(((1,2,4-Triazolo[1,5- <i>a</i>]pyridin-8-yl)methyl)amino)-2-hydroxycyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	472.4	0.69 min Method B
16		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-((((8-Fluoro-2-methylquinolin-6-yl)methyl)amino)-5-((imidazo[1,2- <i>a</i>]pyridin-8-yl)methyl)amino)cyclohexan-1-ol	434.4	0.71 min Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
17		5-Fluoro-6-((((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	443.5	0.85 min Method B
18		7-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-((([1,2,4]Triazolo[1,5- <i>a</i>]pyridin-8-ylmethyl)amino)-2-hydroxycyclohexyl)amino)methyl)-3-methylquinoxalin-2(1 <i>H</i>)-one	434.3	0.54 min Method B
19		5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-4-((2-(difluoromethoxy)benzyl)amino)-2-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	461.4	0.85 min Method B
20		5-((((1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i>)-2-Fluoro-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	437.2	0.68 min Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
21		5-((((1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i>)-2-Fluoro-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -imidazo[4,5- <i>b</i>]pyridin-2-one	438.5	0.64 min Method B
22		(1 <i>S</i> ,2 <i>S</i> ,5 <i>S</i>)-5-(((7-Fluoroquinolin-6-yl)methyl)amino)-2-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexan-1-ol	420.4	0.68 min Method B
23		5-((((1 <i>S</i> ,2 <i>S</i> ,4 <i>S</i>)-2-Hydroxy-4-((quinolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	446.3	0.76 min Method B
24		6-Fluoro-5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-fluoro-4-((pyrazolo[1,5- <i>a</i>]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -imidazo[4,5- <i>b</i>]pyridin-2-one	456.1	0.37 min Method A

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
25		5-Fluoro-6-((((1 <i>R</i> ,3 <i>S</i> ,4 <i>R</i>)-3-hydroxy-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	453.3	0.69 min Method B

EXAMPLE 26: 4-(5-((((1*S*,2*R*,4*S*)-2-Hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-thiazol-2-yl)-1-methyl-1*H*-pyrazole-3-carbonitrile



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Step 1: Benzyl ((1*S*,2*R*,4*S*)-2-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)carbamate: To a mixture of benzyl ((1*S*,2*R*,4*S*)-4-amino-2-hydroxycyclohexyl)carbamate (848 mg, 2.26 mmol) and imidazo[1,2-*a*]pyridine-8-carboxaldehyde (364 mg, 2.48 mmol) in MeOH (23 mL) was added DIEA (1.60 mL, 9.05 mmol) and the reaction mixture stirred at RT for 1 h. STAB (1.44 g, 6.79 mmol) was added, the reaction mixture stirred at RT for 16 h, diluted with EtOAc, quenched with 1 M NaOH, extracted with EtOAc (2x), and the combined organic extracts washed with brine, dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (40 g) eluting

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with a 0-30% MeOH (2%NH₄OH)/DCM gradient. Product fractions were combined and evaporated under reduced pressure to afford the title compound (837 mg, 91% yield) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ 8.37 (d, *J*=6.85 Hz, 1H), 7.86 (d, *J*=1.47 Hz, 1H), 7.57 (d, *J*=0.98 Hz, 1H), 7.27-7.38 (m, 6H), 6.90 (t, *J*=6.85 Hz, 1H), 5.06 (s, 2H), 4.14 (s, 2H), 4.02 (br s, 1H), 3.47-3.55 (m, 1H), 2.89-3.00 (m, 1H), 2.16 (br dd, *J*=13.45, 2.69 Hz, 1H), 2.07 (br d, *J*=12.7 Hz, 1H), 1.62-1.73 (m, 2H), 1.44 (br t, *J*=11.4 Hz, 1H), 1.21-1.35 (m, 1H). LCMS (Method B), *R*_t = 0.74 min, *m/z* [M+H]⁺: 395.3.

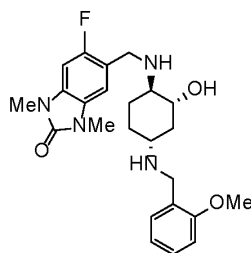
Step 2: Benzyl ((1*S*,2*R*,4*S*)-2-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)carbamate: To a solution of benzyl ((1*S*,2*R*,4*S*)-2-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)carbamate (524 mg, 1.33 mmol) in DCM (23 mL) was added a sol'n of 33% HBr-AcOH (2.19 mL, 13.3 mmol) and the reaction mixture was stirred at RT for 16 h. The reaction mixture was diluted with Et₂O (30 mL), filtered, the solid washed with Et₂O, and dried under a cone of N₂ to afford the title compound (612 mg, 100% yield) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 8.93 (dd, *J*=6.85, 0.98 Hz, 1H), 8.36 (d, *J*=1.96 Hz, 1H), 8.26 (d, *J*=6.85 Hz, 1H), 8.20 (d, *J*=1.96 Hz, 1H), 7.60 (t, *J*=7.09 Hz, 1H), 4.77 (s, 2H), 4.25-4.31 (m, 1H), 3.88 (tt, *J*=12.23, 3.91 Hz, 1H), 3.33-3.41 (m, 1H), 2.41-2.58 (m, 2H), 1.92-2.05 (m, 3H), 1.75-1.88 (m, 1H). LCMS (Method B), *R*_t = 0.39 min, *m/z* [M+H]⁺: 261.3.

Step 3: (1*R*,2*S*,5*S*)-2-(((2-Bromothiazol-5-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol: A solution of 2-bromothiazole-5-carboxaldehyde (90.9 mg, 474 μmol) and (1*R*,2*S*,5*S*)-2-amino-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexan-1-ol (200 mg, 474 μmol) in EtOH (4.7 mL) was stirred at RT for 16 h. NaBH₄ (26.8 mg, 711 μmol) was added to the reaction mixture in one-portion and stirred at RT. The reaction mixture was quenched with 1 M NaOH, extracted with EtOAc (2x), the combined extracts dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel flash column chromatography (12 g) eluting with a 0-45% MeOH (2% NH₄OH)/DCM gradient to afford the title compound (143 mg, 67% yield). ¹H NMR (400 MHz, CD₃OD) δ 8.39 (d, *J*=7.00 Hz, 1H), 7.87-7.88 (m, 1H), 7.58-7.59 (m, 1H), 7.49 (s, 1H), 7.29 (d, *J*=6.50 Hz, 1H), 6.92 (t, *J*=7.00 Hz, 1H), 4.08-4.18 (m, 3H), 4.02 (s, 2H), 2.93 (tt, *J*=11.26, 4.00 Hz, 1H), 2.55 (dt, *J*=12.01, 3.50 Hz, 1H), 2.19 (dq, *J*=13.51, 3.50 Hz, 1H), 2.06 (dt, *J*=12.76, 3.63 Hz, 1H), 1.71-1.77 (m, 1H), 1.46-1.58 (m, 1H), 1.31-1.40 (m, 1H), 1.18-1.26 (m, 1H). LCMS (Method B), *R*_t = 0.66 min, *m/z* [M+H]⁺: 438.2.

Step 4: 4-(5-(((1*S*,2*R*,4*S*)-2-Hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)thiazol-2-yl)-1-methyl-1*H*-pyrazole-3-carbonitrile: A mixture of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-3-carbonitrile (91.7 mg, 393 μmol), (1*R*,2*S*,5*S*)-2-(((2-bromothiazol-5-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-

ylmethyl)amino)-cyclohexan-1-ol (143 mg, 328 μ mol), K_3PO_4 (139 mg, 655 μ mol), and $Pd(Ph_3)_4$ (22.7 mg, 19.7 μ mol) in 1,4-dioxane (3.12 mL) and H_2O (156 μ L) was purged with N_2 , sealed, and heated at 100 $^{\circ}C$ for 16 h. The reaction mixture was filtered through celite, washed with EtOAc, the filtrate washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude material was purified using a MDAP system, eluting with a 15-55% MeCN- H_2O (10 nM ammonium carbonate pH10 buffer) over 22 min to afford the title compound (40 mg, 25% yield). 1H NMR (400 MHz, CD_3OD) δ 8.37 (dd, $J=6.85, 0.98$ Hz, 1H), 8.28 (s, 1H), 7.86 (d, $J=1.47$ Hz, 1H), 7.70 (s, 1H), 7.57 (d, $J=1.47$ Hz, 1H), 7.27 (d, $J=6.66$ Hz, 1H), 6.90 (t, $J=6.85$ Hz, 1H), 4.12 (s, 3H), 4.05-4.09 (m, 2H), 4.02 (s, 3H), 2.93 (tt, $J=11.43, 3.97$ Hz, 1H), 2.54-2.61 (m, 1H), 2.15-2.23 (m, 1H), 2.01-2.09 (m, 1H), 1.72-1.79 (m, 1H), 1.47-1.58 (m, 1H), 1.35 (ddd, $J=13.57, 11.37, 2.45$ Hz, 1H), 1.15-1.26 (m, 1H). LCMS (Method B), R_t = 0.68 min, m/z $[M+H]^+$: 463.3.

Example 27: 5-Fluoro-6-((((1*R*,2*R*,4*R*)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one



15

Step 1: Benzyl ((1*R*,2*R*,4*R*)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)carbamate: The title compound was prepared according to a similar synthetic procedure described for that of 5-((((1*S*,3*R*,4*S*)-4-((2-ethoxybenzyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, utilizing STAB as a reducing reagent. 1H NMR (400 MHz, CD_3OD) δ 7.18-7.48 (m, 7H), 6.85-7.06 (m, 2H), 5.07 (s, 2H), 3.74-3.98 (m, 5H), 2.51-2.74 (m, 1H), 1.85-2.08 (m, 2H), 1.11-1.43 (m, 3H). LCMS (Method B), R_t = 0.93, m/z $[M+H]^+$: 385.3.

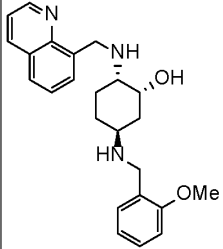
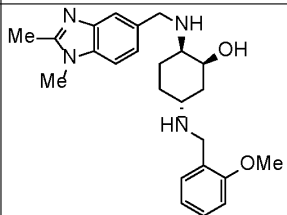
Step 2: (1*R*,2*R*,5*R*)-2-Amino-5-((2-methoxybenzyl)amino)cyclohexan-1-ol: To a solution of benzyl ((1*R*,2*R*,4*R*)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)carbamate (147 mg, 382 μ mol) in MeOH (10 mL) under N_2 was added 10% $Pd(OH)_2/C$ (40.7 mg, 38.2 μ mol) and the reaction mixture was stirred under 1 atm for 30 min. The reaction mixture was filtered and the concentrated *in vacuo* to afford the title compound (96 mg, 95% yield). 1H NMR (400 MHz, CD_3OD) δ 7.13-7.34 (m,

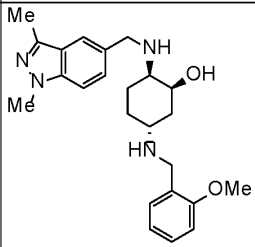
25

2H), 6.77-7.01 (m, 2H), 3.82 (s, 3H), 3.77 (s, 2H), 3.05-3.21 (m, 1H), 2.40-2.63 (m, 2H), 2.07-2.25 (m, 1H), 1.77-2.00 (m, 2H), 1.16 (s, 3H). LCMS (Method B), Rt = 0.56 min, m/z [M+H]⁺ = 251.21.

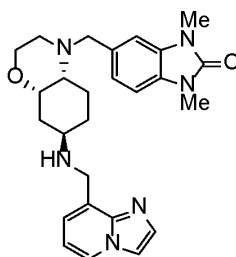
Step 3: 5-Fluoro-6-((((1*R*,2*R*,4*R*)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one: The title compound was prepared according to a similar synthetic procedure described for that of 5-((((1*S*,3*R*,4*S*)-4-((2-ethoxybenzyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, utilizing STAB as a reducing reagent. ¹H NMR (400 MHz, CD₃OD) δ 7.10-7.19 (m, 2H), 7.04-7.09 (m, 1H), 6.85-6.93 (m, 2H), 6.77-6.83 (m, 1H), 3.76 (s, 5H), 3.69 (s, 2H), 3.31 (s, 3H), 3.29 (s, 3H), 3.13-3.19 (m, 1H), 2.39-2.51 (m, 1H), 2.17-2.27 (m, 1H), 2.01-2.13 (m, 2H), 1.83-1.93 (m, 1H), 0.92-1.21 (m, 3H). LCMS (Method B), Rt = 0.81 min, m/z [M+H]⁺: 433.3.

Table 7. The following Examples (28-30) were prepared according to a similar procedure described for Example 27.

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) Method
28		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-5-((2-Methoxybenzyl)amino)-2-((quinolin-8-ylmethyl)amino)cyclohexan-1-ol	392.3	0.91 min Method B
29		(1 <i>S</i> ,2 <i>R</i> ,5 <i>R</i>)-2-(((1,2-Dimethyl-1 <i>H</i> -benzo[<i>d</i>]imidazol-5-yl)methyl)amino)-5-((2-methoxybenzyl)amino)-cyclohexan-1-ol	409.3	0.77 min Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) Method
30		(1 <i>S</i> ,2 <i>R</i> ,5 <i>R</i>)-2-(((1,3-Dimethyl-1 <i>H</i> -indazol-5-yl)methyl)amino)-5-((2-methoxybenzyl)amino)cyclohexan-1-ol	409.3	0.86 min Method B

EXAMPLE 31: 5-(((4*aR*,7*R*,8*aS*)-7-((Imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)octahydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one



5

Step 1: *tert*-Butyl ((1*R*,3*S*,4*R*)-4-(((1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)amino)-3-hydroxycyclohexyl)carbamate: The title compound was prepared according to a similar synthetic procedure described for that of 5-(((1*S*,3*R*,4*S*)-4-((2-ethoxybenzyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, utilizing STAB followed by NaBH₄ as reducing reagents. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.13 (s, 1H), 7.04 (d, *J*=2.4 Hz, 2H), 6.4-6.7 (m, 1H), 4.3-4.4 (m, 1H), 3.9-4.0 (m, 1H), 3.7-3.8 (m, 2H), 3.5-3.6 (m, 1H), 3.31 (d, *J*=2.0 Hz, 6H), 2.2-2.4 (m, 1H), 1.82 (br d, *J*=9.8 Hz, 2H), 1.70 (br d, *J*=11.7 Hz, 1H), 1.5-1.6 (m, 1H), 1.37 (s, 11H), 1.23 (br s, 1H), 1.06 (br dd, *J*=3.2, 12.0 Hz, 1H). LCMS (Method B), Rt = 0.80 min, m/z [M+H]⁺: 405.3.

Step 2: *tert*-Butyl ((4*aR*,7*R*,8*aS*)-4-((1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)-3-oxooctahydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)carbamate: To a solution of *tert*-butyl ((1*R*,3*S*,4*R*)-4-(((1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)amino)-3-hydroxycyclohexyl)carbamate (916 mg, 2.26 mmol) in DCM (25.0 mL) was added TEA (947 μL, 6.79

mmol) followed by 2-chloroacetyl chloride (271 μ L, 3.39 mmol) and the reaction mixture stirred for 10 min, to which was added 1N KO^tBu-THF (9.06 mL, 9.06 mmol) and the reaction mixture stirred at RT for 18 h. Additional 1N KO^tBu-THF (1.4 mL) was added, and the reaction mixture stirred at RT for 1 h. The reaction mixture was quenched with sat'd aq. NaHCO₃ and brine, the layers separated, and the organic phase further extracted with DCM. The combined organic extracts were combined, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash column chromatography (120 g) eluting with a 0-40% MeOH/DCM gradient to afford the title compound (1.06 g, 100% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.0-7.0 (m, 1H), 6.9-6.9 (m, 2H), 5.3-5.4 (m, 1H), 4.2-4.5 (m, 3H), 3.7-4.0 (m, 3H), 3.42 (d, *J*=3.5 Hz, 6H), 2.9-3.1 (m, 1H), 2.1-2.3 (m, 1H), 1.9-2.1 (m, 2H), 1.7-1.9 (m, 2H), 1.43 (s, 11H), 1.0-1.2 (m, 1H). LCMS (Method A), Rt = 0.81 min, *m/z* [M+H]⁺: 445.4.

Step 3: *tert*-Butyl ((4*aR*,7*R*,8*aS*)-4-((1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)carbamate: To a solution of *tert*-butyl ((4*aR*,7*R*,8*aS*)-4-((1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)-3-oxooctahydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)carbamate (1.06 g, 2.38 mmol) in THF (24.0 mL), cooled to 0 °C, was added a solution of 1M BH₃-THF (11.9 mL, 11.9 mmol), dropwise, and the reaction mixture was allowed to slowly warm to RT and stirred for 4 h. The reaction mixture was slowly quenched by drop-wise addition of MeOH (5 mL) at 5 °C and allowed to warm up to RT and stirred overnight. The reaction mixture was concentrated *in vacuo*, the residue dissolved in MeOH and concentrated *in vacuo*, then dissolved in DCM and concentrated *in vacuo* to afford the title compound (851 mg, 80% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.9-7.2 (m, 2H), 6.5-6.7 (m, 1H), 4.3-4.4 (m, 1H), 3.6-3.8 (m, 2H), 3.4-3.6 (m, 2H), 3.3-3.3 (m, 7H), 2.58 (dt, *J*=3.4, 11.7 Hz, 1H), 2.4-2.5 (m, 1H), 2.2-2.3 (m, 1H), 1.7-1.9 (m, 3H), 1.5-1.6 (m, 1H), 1.3-1.5 (m, 9H), 0.9-1.1 (m, 1H). LCMS (Method A), Rt = 0.59 min, *m/z* [M+H]⁺: 431.4.

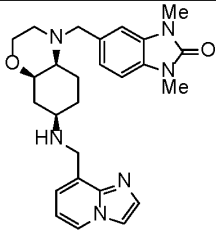
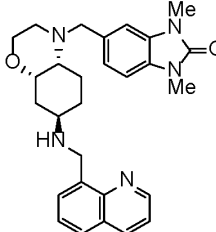
Step 4: 5-(((4*aR*,7*R*,8*aS*)-7-Aminooctahydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, dihydrochloride: To a solution of *tert*-butyl ((4*aR*,7*R*,8*aS*)-4-((1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-yl)carbamate (845 mg, 1.96 mmol), in DCM (10.0 mL) was added a solution of 4M HCl-dioxane (14.7 mL, 58.9 mmol) and the reaction mixture stirred at RT for 1 h. The reaction mixture was diluted with Et₂O, filtered, the solid washed with Et₂O and dried under *vacuo* to afford the title compound (964 mg, >100% yield) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 7.41 (d, *J*=1.5 Hz, 1H), 7.22 (d, *J*=1.5 Hz, 1H), 7.08 (d, *J*=7.8 Hz, 1H), 4.2-4.4 (m, 2H), 4.1-4.2 (m, 1H), 3.9-

4.0 (m, 1H), 3.7-3.8 (m, 1H), 3.5-3.6 (m, 6H), 3.4-3.5 (m, 3H), 3.30 (d, $J=11.2$ Hz, 9H), 3.0-3.0 (m, 1H), 2.10 (br d, $J=2.0$ Hz, 4H). LCMS (Method A), $R_t = 0.28$ min, m/z [M+H]⁺: 331.2.

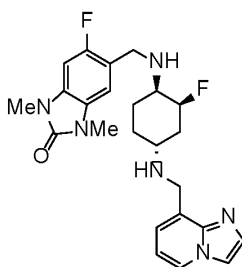
Step 5: 5-(((4*aR*,7*R*,8*aS*)-7-((Imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)octahydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one,

- 5 dihydrochloride: To a mixture of 5-(((4*aR*,7*R*,8*aS*)-7-aminooctahydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, dihydrochloride (126 mg, 312 μ mol) and imidazo[1,2-*a*]pyridine-8-carbaldehyde (54.8 mg, 375 μ mol) in EtOH (3.00 mL) was added TEA (218 μ L, 1.56 mmol) and the reaction mixture was stirred at RT overnight. NaBH₄ (59.1 mg, 1.56 mmol) was added, and the reaction mixture stirred at RT for 4 h. The solvent was evaporated under
- 10 reduced pressure, the material partitioned between 1N NaOH and EtOAc, the layers separated, the organic phase washed with brine, dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure. The crude residue was dissolved in DCM, adsorbed onto a silica gel packed pre-column and purified by silica gel flash column chromatography (24 g) eluting with a 0-50% MeOH(2% NH₄OH)/DCM gradient. Product fractions were combined and evaporated under reduced pressure,
- 15 dissolved in DCM (min. amt), to which was added 2M HCl-Et₂O (200 μ L), the suspension triturated, filtered, washed with Et₂O, and dried under vacuo to afford the title compound (37.1 mg, 22% yield). ¹H NMR (400 MHz, CD₃OD) δ 8.92 (dd, $J=1.0, 6.8$ Hz, 1H), 8.36 (d, $J=2.4$ Hz, 1H), 8.2-8.3 (m, 1H), 8.19 (d, $J=2.0$ Hz, 1H), 7.60 (s, 1H), 7.52 (d, $J=1.0$ Hz, 1H), 7.38 (d, $J=1.5$ Hz, 1H), 7.26 (d, $J=8.3$ Hz, 1H), 4.76 (s, 2H), 4.3-4.4 (m, 1H), 4.1-4.2 (m, 1H), 3.9-4.0 (m, 1H), 3.7-3.8 (m, 1H), 3.6-3.7 (m,
- 20 1H), 3.46 (d, $J=11.7$ Hz, 8H), 3.1-3.2 (m, 1H), 2.5-2.7 (m, 2H), 2.34 (br d, $J=3.4$ Hz, 2H), 1.9-2.1 (m, 1H), 1.7-1.9 (m, 1H). LCMS (Method B), $R_t = 0.76$ min, m/z [M+H]⁺: 461.4.

Table 8. The following Examples (32-33) were prepared according to a similar synthetic procedure described for Example 31.

Example	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	Rt (min) Method
32		5-(((4 <i>aS</i> ,7 <i>R</i> ,8 <i>aR</i>)-7-((Imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)octahydro-4 <i>H</i> -benzo[<i>b</i>][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	461	0.30 Method A
33		1,3-Dimethyl-5-(((4 <i>aR</i> ,7 <i>R</i> ,8 <i>aS</i>)-7-((quinolin-8-ylmethyl)amino)-octahydro-4 <i>H</i> -benzo[<i>b</i>][1,4]oxazin-4-yl)methyl)-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	472.4	0.94 Method B

EXAMPLE 34: 5-Fluoro-6-(((1*R*,2*S*,4*R*)-2-fluoro-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one



Step 1: Benzyl ((1*R*,3*S*,4*R*)-3-fluoro-4-(((6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)-amino)cyclohexyl)carbamate: A suspension of 6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde (2.36 g, 11.3 mmol) and benzyl ((1*R*,3*S*,4*R*)-

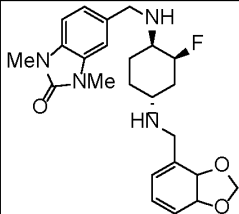
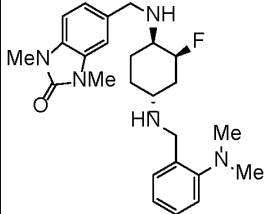
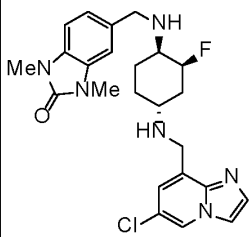
4-amino-3-fluorocyclohexyl)carbamate (3.00 g, 11.3 mmol) was suspended in DCE (113 mL) and STAB (7.16 g, 33.8 mmol) added to the reaction mixture and stirred at RT for 2 h. The reaction mixture was quenched with 1N NaOH, the layers separated, and the aqueous phase extracted with DCM (2x). The organic extracts were combined, dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was dissolved in DCM with minimal MeOH, adsorbed onto a silica gel prepacked column, and purified by silica gel flash column chromatography eluting with a 40-100% 3:1 EtOAc:EtOH/heptanes gradient. Product fractions were combined, evaporated under reduced pressure, and the crude material re-purified eluting with a 40-85% 3:1 EtOAc:EtOH/heptanes gradient to afford the title compound (3.09 g, 59% yield). ¹H NMR (400 MHz, CD₃OD) δ 7.34 (d, *J*=4.40 Hz, 5H) 7.14-7.22 (m, 1H) 6.96-7.03 (m, 1H) 5.02-5.08 (m, 2H) 4.80-5.00 (m, 1H) 3.88-3.93 (m, 2H) 3.65-3.82 (m, 1H) 3.40 (d, *J*=8.31 Hz, 6H) 2.51-2.68 (m, 1H) 2.22-2.36 (m, 1H) 1.86-2.02 (m, 2H) 1.25-1.68 (m, 4H). LCMS (Method B), Rt = 0.95 min, *m/z* [M+H]⁺: 459.2.

Step 2: 5-((((1*R*,2*S*,4*R*)-4-Amino-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo-[*d*]imidazol-2-one, dihydrobromide: To a solution of benzyl ((1*R*,3*S*,4*R*)-3-fluoro-4-(((6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-5-yl)methyl)-amino)cyclohexyl)carbamate (3.09 g, 6.70 mmol) in DCM (50 mL) was added a solution of 33% HBr-AcOH (30.0 mL, 168 mmol) and the reaction mixture was stirred at RT for 24 h. The reaction mixture was diluted with Et₂O, filtered, the solid washed with Et₂O, then dried under a cone of N₂ followed by high vacuum to afford the title compound (3.94 g, >100% yield). ¹H NMR (400 MHz, CD₃OD) δ 7.33-7.42 (m, 1H) 7.11-7.20 (m, 1H) 5.32-5.54 (m, 1H) 4.39-4.53 (m, 2H) 3.58-3.81 (m, 1H) 3.43 (d, *J*=12.23 Hz, 7H) 2.51-2.63 (m, 1H) 2.18-2.38 (m, 2H) 1.8-2.0 (m, 2H) 1.61-1.77 (m, 1H). LCMS (Method B), Rt = 0.56 min, *m/z* [M+H]⁺: 325.1.

Step 3: 5-Fluoro-6-((((1*R*,2*S*,4*R*)-2-fluoro-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one: To a solution of imidazo[1,2-*a*]pyridine-8-carbaldehyde (504 mg, 3.45 mmol) in EtOH (20 mL) and THF (20 mL) was added 5-((((1*R*,2*S*,4*R*)-4-amino-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo-[*d*]imidazol-2-one, dihydrobromide (1.56 g, 3.21 mmol), and TEA (2.24 mL, 16.0 mmol) and the reaction was stirred at RT for 70 h. NaBH₄ (607 mg, 16.0 mmol) was added portion-wise at 0 °C and the reaction mixture stirred for an additional 4.5 h and allowed to warm to RT. The reaction mixture was concentrated under reduced pressure, the solid partitioned between EtOAc and 1N NaOH, and the organic layer washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude material was dissolved in DCM with minimal MeOH, adsorbed onto a silica gel prepacked column, and purified by silica gel flash column chromatography (24 g)

eluting with a 5-50% MeOH (2% NH₄OH)/DCM gradient to afford the title compound (838 mg, 57% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.35-8.49 (m, 1H) 7.92 (s, 1H) 7.48-7.60 (m, 1H) 7.13-7.25 (m, 2H) 7.01-7.10 (m, 1H) 6.75-6.90 (m, 1H) 4.79-5.06 (m, 1H) 3.96-4.08 (m, 2H) 3.69-3.88 (m, 2H) 3.29 (d, *J* = 3.91 Hz, 8H) 2.62-2.74 (m, 1H) 2.45-2.60 (m, 1H) 2.16-2.25 (m, 1H) 1.87-2.00 (m, 1H) 1.69-1.82 (m, 1H) 1.23-1.48 (m, 2H) 1.01-1.17 (m, 1H). LCMS (Method B), Rt = 0.74 min, *m/z* [M+H]⁺: 455.4.

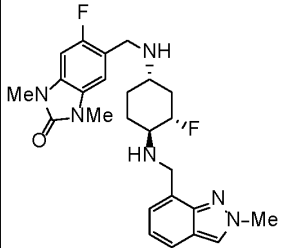
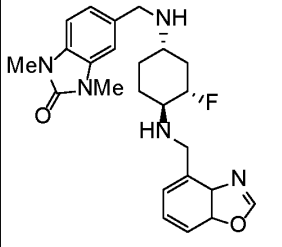
Table 9. The following Examples (35-52) were prepared according to a similar synthetic procedure described for Example 34, utilizing STAB or NaBH₄ as reducing reagents.

Example	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	Rt (min) Method
35		5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-4-((Benzo[d][1,3]dioxol-4-ylmethyl)amino)-2-fluorocyclohexyl)-amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[d]imidazol-2-one	441.5	0.86 Method B
36		5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-4-((2-(Dimethylamino)benzyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[d]imidazol-2-one	440.4	0.96 Method B
37		5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-4-(((6-Chloroimidazo[1,2- <i>a</i>]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[d]imidazol-2-one	471.3	0.80 Method B

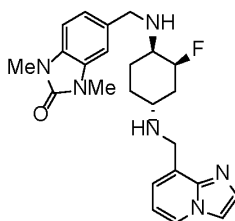
Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) Method
38		5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-4-(((3-Chloroimidazo[1,2- <i>a</i>]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	471.3	0.82 Method B
39		5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-Fluoro-4-(((2-methylimidazo[1,2- <i>a</i>]pyridin-8-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	451.4	0.75 Method B
40		5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-4-(((2-(Difluoromethyl)-[1,2,4]triazolo[1,5- <i>a</i>]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	488.4	0.78 Method B
41		5-((((1 <i>R</i> ,4 <i>R</i>)-2,2-Difluoro-4-((imidazo[1,2- <i>a</i>]pyridin-8-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	455.2	0.73 min Method B
42		(1 <i>R</i> ,4 <i>R</i>)-2,2-Difluoro- <i>N</i> ⁴ -(imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)- <i>N</i> ¹ -((6-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)methyl)cyclohexane-1,4-diamine	452.2	0.68 min Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) Method
43		(1 <i>R</i> ,4 <i>R</i>)-2,2-Difluoro- <i>N</i> ⁴ -((7-Fluoroquinolin-6-yl)methyl)- <i>N</i> ⁴ -(imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)cyclohexane-1,4-diamine	440.2	0.82 min Method B
44		7-Fluoro-6-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-hydroxy-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)-methyl)quinolin-2(1 <i>H</i>)-one	436.4	0.60 Method B
45		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-5-((Imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)-2-(((2-methoxyquinolin-6-yl)methyl)amino)-cyclohexan-1-ol	432.4	0.82 Method B
46		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(((5,8-Difluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol	438.4	0.71 min Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) Method
47		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(((5,7-Difluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol	438.3	0.71 min Method B
48		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(((5-Chloroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol	436.3	0.76 min Method B
49		6-Fluoro-7-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-hydroxy-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-3-methylquinoxalin-2(1 <i>H</i>)-one	451.4	0.63 min Method B
50		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(((2-(1,3-Dimethyl-1 <i>H</i> -pyrazol-4-yl)thiazol-5-yl)methyl)amino)-5-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexan-1-ol	452.3	0.63 min Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) Method
51		5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-((2-methyl-2H-indazol-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one	469.4	0.85 min Method B
52		5-((((1S,3S,4S)-4-(((3a,7a-Dihydrobenzo[d]oxazol-4-yl)methyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one	438.3	0.81 min Method B

Example 53: 5-((((1R,2S,4R)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)-methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one

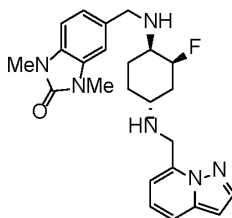


5

The title compound was prepared according to a similar synthetic procedure described for 5-fluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one, utilizing NaBH₄ or STAB as reducing reagents. ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (d, *J*=6.5 Hz, 1H), 7.69 (d, *J*=11.0 Hz, 2H), 7.1-7.2 (m, 3H), 6.99 (d, *J*=7.5 Hz, 1H), 6.8-6.9 (m, 1H), 4.9-5.2 (m, 1H), 4.26 (s, 2H), 3.98 (d, *J*=4.5 Hz, 2H), 3.51 (d, *J*=3.0 Hz, 6H), 2.9-3.1 (m, 1H), 2.6-2.8 (m, 1H), 2.53 (br s, 1H), 2.1-2.3 (m, 1H), 2.0-2.1 (m, 1H), 1.90 (br s, 2H), 1.2-1.7 (m, 3H). LCMS (Method B), Rt = 0.70 min, m/z [M+H]⁺: 437.5.

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Example 54: 5-((((1R,2S,4R)-2-Fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one



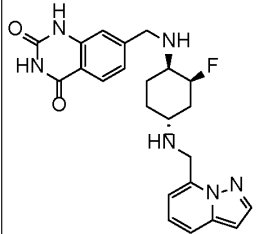
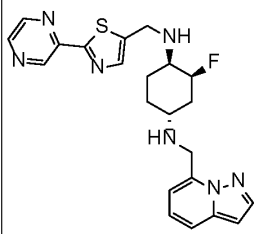
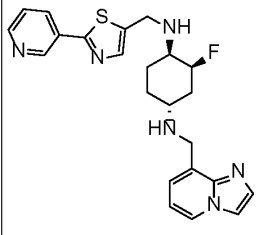
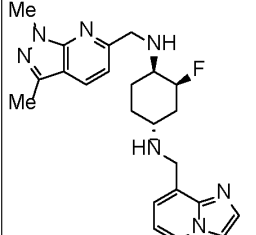
Step 1: *tert*-Butyl ((1*R*,2*S*,4*R*)-2-fluoro-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)carbamate: To pyrazolo[1,5-*a*]pyridine-7-carbaldehyde (1.34 g, 9.19 mmol) and *tert*-butyl ((1*R*,2*S*,4*R*)-4-amino-2-fluorocyclohexyl)-carbamate (1.94 g, 8.35 mmol), was added EtOH (100 mL) and the reaction mixture was stirred at RT for 23 h. The reaction mixture was cooled to 0 °C, to which was added NaBH₄ (1.58 g, 41.8 mmol) and the reaction mixture stirred at RT for 4 h. The reaction mixture was concentrated *in vacuo*, diluted with EtOAc, washed with 1M NaOH, brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was dissolved in DCM and purified by silica gel flash column chromatography eluting with a 2-20% MeOH/DCM gradient to afford the title compound (2.55 g; 82% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J*=2.4 Hz, 1H), 7.50 (dd, *J*=1.2, 9.0 Hz, 1H), 7.10 (dd, *J*=6.8, 8.8 Hz, 1H), 6.7-6.8 (m, 1H), 6.55 (d, *J*=2.4 Hz, 1H), 4.7-4.9 (m, 2H), 4.27 (s, 2H), 3.5-3.8 (m, 1H), 2.82 (s, 1H), 2.3-2.5 (m, 1H), 1.7-2.1 (m, 2H), 1.2-1.6 (m, 13H). LCMS (Method B), Rt = 1.00 min, *m/z* [M+H]⁺: 363.4.

Step 2: (1*R*,3*S*,4*R*)-3-Fluoro-*N*-(pyrazolo[1,5-*a*]pyridin-7-ylmethyl)cyclohexane-1,4-diamine, dihydrochloride: To *tert*-butyl ((1*R*,2*S*,4*R*)-2-fluoro-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)carbamate (2.55 g, 7.04 mmol), in DCM (50 mL), was added as solution of 3M HCl-CPME (23.5 mL, 70.4 mmol) and the reaction mixture stirred at RT for 3 h. The reaction mixture was diluted with Et₂O, filtered, the solid washed with Et₂O, and dried *in vacuo* to afford the title compound (2.44 g, 100% yield). ¹H NMR (400 MHz, CD₃OD) δ 8.10 (d, *J*=2.4 Hz, 1H), 7.82 (dd, *J*=1.5, 8.8 Hz, 1H), 7.29 (dd, *J*=6.8, 9.3 Hz, 1H), 7.19 (d, *J*=6.4 Hz, 1H), 6.77 (d, *J*=2.4 Hz, 1H), 5.1-5.3 (m, 1H), 4.83 (d, *J*=1.0 Hz, 2H), 3.5-3.7 (m, 2H), 2.75 (br s, 1H), 2.4-2.5 (m, 1H), 2.0-2.2 (m, 2H), 1.8-2.0 (m, 2H). LCMS (Method B), Rt = 0.62 min, *m/z* [M+H]⁺: 263.3.

Step 3: 5-((((1*R*,2*S*,4*R*)-2-Fluoro-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[d]imidazol-2-one: To a solution of (1*R*,3*S*,4*R*)-3-fluoro-*N*-(pyrazolo[1,5-*a*]pyridin-7-ylmethyl)-cyclohexane-1,4-diamine,

- dihydrochloride (1.59 g, 3.75 mmol) and 6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde (784 mg, 4.12 mmol), in MeOH (40 mL) was added TEA (2.61 mL, 18.7 mmol) and the reaction mixture was stirred at RT for 5 h, to which was added STAB (2.38 g, 11.2 mmol) and the reaction mixture stirred for 17 h. Additional 6-fluoro-1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde (784.3 mg, 4.12 mmol) was added to the reaction mixture and stirred at RT for 3 h, to which was added additional STAB (2.38 g, 11.2 mmol) and the reaction mixture stirred for 2 h. NaBH₄ (709 mg, 18.7 mmol) was added carefully to the reaction mixture and stirred for 1 h. Another portion of NaBH₄ (709 mg, 18.7 mmol) was added to the reaction mixture and it was stirred at RT for 18 h. The reaction mixture was concentrated under reduced pressure, the solid partitioned between EtOAc and 1N NaOH, the layers separated, the organic layer washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was dissolved in DCM, adsorbed onto a silica gel prepacked column, and purified by silica gel flash column chromatography (120 g) eluting with a 0-50% MeOH(2% NH₄OH)/DCM gradient to afford the title compound (1.51 g, 90% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (d, *J*=2.0 Hz, 1H), 7.62 (dd, *J*=1.0, 8.8 Hz, 1H), 7.22 (dd, *J*=6.8, 8.8 Hz, 1H), 7.12 (s, 1H), 7.03 (s, 2H), 6.9-7.0 (m, 1H), 6.65 (d, *J*=2.4 Hz, 1H), 4.8-5.0 (m, 1H), 4.16 (s, 2H), 3.78 (s, 2H), 3.30 (d, *J*=1.5 Hz, 6H), 2.6-2.8 (m, 1H), 2.5-2.6 (m, 1H), 2.4-2.5 (m, 1H), 2.1-2.3 (m, 2H), 1.9-2.0 (m, 1H), 1.76 (br s, 1H), 1.2-1.4 (m, 2H), 1.08 (br d, *J*=13.2 Hz, 1H). LCMS (Method B), Rt = 0.82 min, *m/z* [M+H]⁺: 437.5.
- Table 10. The following Examples (55-73) were prepared according to a similar procedure described for Example 54, utilizing STAB or NaBH₄ as reducing reagents.

Example	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	Rt (min) LCMS Method
55		(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-Fluoro- <i>N</i> ⁴ -((pyrazolo[1,5- <i>a</i>]pyridin-7-ylmethyl)- <i>N</i> ⁴ -((2-(pyrimidin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine	438.4	0.80 Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
56		7-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-Fluoro-4-((pyrazolo[1,5- <i>a</i>]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)quinazoline-2,4(1 <i>H</i> ,3 <i>H</i>)-dione	437.3	0.71 Method B
57		(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-Fluoro- <i>N</i> ⁴ -((2-(pyrazin-2-yl)thiazol-5-yl)methyl)- <i>N</i> ⁴ -(pyrazolo[1,5- <i>a</i>]pyridin-7-ylmethyl)cyclohexane-1,4-diamine	438.4	0.88 Method B
58		(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-Fluoro- <i>N</i> ⁴ -(imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)- <i>N</i> ¹ -((2-(pyridin-3-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine	437.4	0.72 Method B
59		(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)- <i>N</i> ¹ -((1,3-Dimethyl-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-6-yl)methyl)-2-fluoro- <i>N</i> ⁴ -(imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)cyclohexane-1,4-diamine	422.4	0.70 Method B

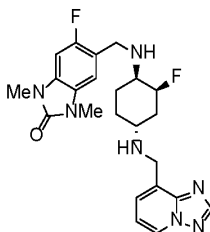
Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
60		6-Fluoro-5-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-fluoro-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1-methyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	441.4	0.69 Method B
61		(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-Fluoro- <i>N</i> ⁴ -(imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)- <i>N</i> ¹ -((2-(pyridin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine	437.4	0.77 Method B
62		6-((((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-4-((1,2,4)Triazolo[1,5- <i>a</i>]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	474.3	0.75 Method B
63		(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)- <i>N</i> ⁴ -([1,2,4]Triazolo[1,5- <i>a</i>]pyridin-8-ylmethyl)-2-fluoro- <i>N</i> ¹ -((2-(pyrazin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine	439.4	0.68 Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
64		6-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-Fluoro-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -imidazo[4,5- <i>b</i>]pyridin-2-one	438.4	0.63 Method B
65		7-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-Fluoro-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-3-methylquinoxalin-2(1 <i>H</i>)-one	435.4	0.64 Method B
66		5-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-Fluoro-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	437.4	0.70 Method B
67		7-Fluoro-6-((((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-fluoro-4-((pyrazolo[1,5- <i>a</i>]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-2 <i>H</i> -benzo[<i>b</i>][1,4]oxazin-3(4 <i>H</i>)-one	442.4	0.87 Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
68		(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-Fluoro- <i>M</i> ⁴ -((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)- <i>M</i> ⁴ -(pyrazolo[1,5- <i>a</i>]pyridin-7-ylmethyl)cyclohexane-1,4-diamine	434.5	0.77 Method B
69		(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-Fluoro- <i>M</i> ⁴ -((6-fluoro-1-methyl-1H-benzimidazol-5-yl)methyl)- <i>M</i> ⁴ -(pyrazolo[1,5- <i>a</i>]pyridin-7-ylmethyl)cyclohexane-1,4-diamine	425.5	0.83 Method B
70		5-((((1 <i>R</i> ,4 <i>R</i>)-4-((Benzo[d]oxazol-4-ylmethyl)amino)-2,2-difluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[d]imidazol-2-one	456.2	0.85 Method B
71		5-((((1 <i>R</i> ,4 <i>R</i>)-2,2-Difluoro-4-(((7-fluorobenzofuran-4-yl)methyl)amino)cyclohexyl)-amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[d]imidazol-2-one	473.0	1.03 Method B

Example	Structure	IUPAC Name	Obs. m/z [M+H] ⁺	Rt (min) LCMS Method
72		5-((((1 <i>R</i> ,4 <i>R</i>)-2,2-Difluoro-4-((7-fluoro-1 <i>H</i> -indol-4-yl)methyl)amino)-cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	472.2	0.92 Method B
73		5-((((1 <i>R</i> ,4 <i>R</i>)-2,2-Difluoro-4-((quinolin-8-yl)methyl)amino)cyclohexyl)-amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	466.1	0.92 Method B

Example 74: 5-((((1*R*,2*S*,4*R*)-4-((1,2,4-Triazolo[1,5-*a*]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, hydrochloride



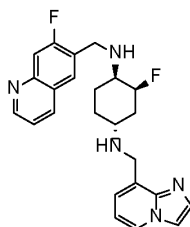
5

Step 1: 5-((((1*R*,2*S*,4*R*)-4-((1,2,4-Triazolo[1,5-*a*]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one: The title compound was prepared according to a similar synthetic procedure described for 5-((((1*R*,2*S*,4*R*)-2-fluoro-4-((pyrazolo[1,5-*a*]pyridin-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one.

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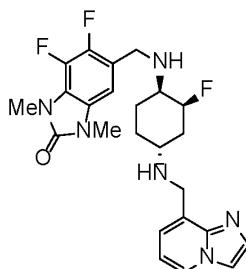
Step 2: 5-((((1*R*,2*S*,4*R*)-4-([1,2,4]Triazolo[1,5-*a*]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one, hydrochloride: To a solution of 5-((((1*R*,2*S*,4*R*)-4-([1,2,4]triazolo[1,5-*a*]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one in DCM (2 mL) and MeOH (2 mL) was added a solution of 3M HCl-CPME (1 mL), and the reaction mixture was concentrated under a stream of N₂ to afford the title compound. ¹H NMR (400 MHz, CD₃OD) δ 8.94 (dd, *J*=6.85, 0.98 Hz, 1H) 8.59 (s, 1H) 7.95-7.99 (m, 1H) 7.32-7.39 (m, 2H) 7.13-7.19 (m, 1H) 5.41-5.59 (m, 1H) 4.72 (s, 2H) 4.46 (br d, *J*=7.34 Hz, 2H) 3.69 (br s, 2H) 3.45 (s, 3H) 3.43 (s, 3H) 2.80-2.90 (m, 1H) 2.49-2.59 (m, 1H) 2.34-2.42 (m, 1H) 1.93-2.18 (m, 2H) 1.76-1.91 (m, 1H). LCMS (Method B), Rt = 0.70 min, *m/z* [M+H]⁺: 456.4.

Example 75: (1*R*,2*S*,4*R*)-2-Fluoro-*N*¹-((7-fluoroquinolin-6-yl)methyl)-*N*⁴-(imidazo[1,2-*a*]pyridin-8-ylmethyl)cyclohexane-1,4-diamine



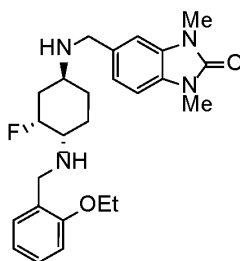
The title compound was prepared according to a similar synthetic procedure described for 5-((((1*R*,2*S*,4*R*)-2-fluoro-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one. ¹H NMR (400 MHz, CDCl₃) δ 8.80-8.93 (m, 1H) 8.10-8.18 (m, 1H) 8.01-8.09 (m, 1H) 7.85-7.93 (m, 1H) 7.66-7.75 (m, 1H) 7.54-7.64 (m, 2H) 7.32-7.41 (m, 1H) 7.05-7.17 (m, 1H) 6.67-6.81 (m, 1H) 4.93-5.14 (m, 1H) 4.13-4.23 (m, 2H) 3.99-4.13 (m, 2H) 2.87-3.00 (m, 1H) 2.56-2.74 (m, 1H) 2.41-2.52 (m, 1H) 2.08-2.18 (m, 1H) 1.91-2.02 (m, 1H) 1.74-1.83 (br s, 2H) 1.17-1.64 (m, 3H). LCMS (Method B), Rt = 0.76 min, *m/z* [M+H]⁺: 422.4.

Example 76: 4,5-Difluoro-6-((((1*R*,2*S*,4*R*)-2-fluoro-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one



5 The title compound was prepared according to a similar synthetic procedure described for 5-((((1*R*,2*S*,4*R*)-2-fluoro-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one. ¹H NMR (CDCl₃, 400 MHz) δ 7.98-8.09 (m, 1H) 7.58 (s, 2H) 7.04-7.15 (m, 1H) 6.66-6.84 (m, 2H) 4.88-5.10 (m, 1H) 4.10-4.24 (m, 2H) 3.86-3.97 (m, 2H) 3.58 (d, *J*=1.47 Hz, 3H) 3.38 (s, 3H) 2.82-3.00 (m, 1H) 2.50-2.65 (m, 1H) 2.33-2.49 (m, 1H) 2.01-2.18 (m, 1H) 1.88-1.95 (m, 1H) 1.71-1.85 (br s, 2H) 1.31-1.58 (m, 2H) 1.17-1.30 (m, 1H). LCMS (Method B), Rt = 0.78 min, *m/z* [M+H]⁺: 473.4.

Example 77: 5-((((1*S*,3*R*,4*S*)-4-((2-Ethoxybenzyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one



15 **Step 1:** Benzyl ((1*S*,3*R*,4*S*)-4-((2-ethoxybenzyl)amino)-3-fluorocyclohexyl)carbamate: To a solution of benzyl ((1*S*,3*R*,4*S*)-4-amino-3-fluorocyclohexyl)carbamate (780 mg, 2.90 mmol) and 2-ethoxybenzaldehyde (400 mg, 2.70 mmol) in MeOH (25 mL), was added borane-2-methylpyridine complex (329 μL, 4.00 mmol) and the reaction mixture stirred at 50 °C for 22 h. The reaction mixture was cooled to RT, the solvent evaporated under reduced pressure, 1N HCl added to the residue, the
20 reaction mixture stirred at RT for 30 min, to which was added solid Na₂CO₃. The reaction mixture was extracted with EtOAc (2x), the organic extracts combined, washed with brine, dried over Na₂SO₄,

filtered and the solvent evaporated under reduced pressure. The crude residue was dissolved in DCM and purified by silica gel flash column chromatography (120 g) eluting with a 0:40% MeOH(1% NH₄OH):DCM gradient to afford the title compound (873 mg, 79% yield). LCMS (Method B), Rt = 1.15 min, m/z [M+H]⁺: 401.2.

- 5 **Step 2:** (1*S*,2*R*,4*S*)-*M*-(2-Ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine: To a solution of benzyl ((1*S*,3*R*,4*S*)-4-((2-ethoxybenzyl)amino)-3-fluorocyclohexyl)carbamate (873 mg, 2.20 mmol), in DCM (9 mL) was added a solution of 33% HBr-AcOH (9.00 mL, 54.5 mmol) and the reaction mixture was stirred at RT for 3 h. The reaction mixture was diluted with Et₂O, filtered, the solid washed with Et₂O, filtered, and dried under a cone of N₂ while under *vacuo*. This material was partitioned between EtOAc and 1N NaOH, the layers separated, the organic phase dried over Na₂SO₄, filtered and the solvent evaporated under reduced pressure to afford the title compound (430 mg). LCMS (Method B), Rt = 0.7 min, m/z [M+H]⁺: 267.2.

- Step 3:** 5-((((1*S*,3*R*,4*S*)-4-((2-Ethoxybenzyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one: To 1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-5-carbaldehyde (34.0 mg, 179 μmol), was added a solution of (1*S*,2*R*,4*S*)-*M*-(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine (52.4 mg, 197 μmol in 0.5 mL of solution in DCE), and the reaction mixture was stirred for 15 min, to which was added STAB (113 mg, 536 μmol) and DCE (0.6 mL) and the reaction mixture stirred at RT for 20 h. The reaction mixture was quenched with 1N NaOH, extracted with EtOAc (2x), the combined organic phase washed with brine, dried over Na₂SO₄, filtered and the solvent evaporated *in vacuo*. The crude material was dissolved in DCM, preabsorbed onto a silica gel prepacked column and purified by silica gel flash column chromatography (12 g) eluting with a 0-80% MeOH(1% NH₄OH)/DCM gradient. Pure product fractions were combined and evaporated under reduced pressure. This material was dissolved in DMSO (1 mL) and purified by semi-prep HPLC (MDAP Method C) eluting with a 35-85% MeCN-H₂O (10 nM ammonium carbonate pH10 buffer) gradient to afford the title compound (46.4 mg, 57% yield). ¹H NMR (400 MHz, CD₃OD) δ 7.1-7.2 (m, 2H), 7.0-7.1 (m, 3H), 6.8-6.9 (m, 2H), 4.8-5.0 (m, 1H), 3.98 (d, *J*=7.0 Hz, 2H), 3.71 (dd, *J*=2.8, 5.8 Hz, 4H), 3.31 (d, *J*=4.5 Hz, 6H), 2.73 (s, 1H), 2.4-2.6 (m, 1H), 2.27 (br d, *J*=1.5 Hz, 1H), 1.9-2.0 (m, 1H), 1.7-1.8 (m, 1H), 1.3-1.5 (m, 4H), 1.0-1.3 (m, 1H), 1.0-1.5 (m, 1H). LCMS (Method B), Rt = 0.94 min, m/z [M+H]⁺: 441.2.

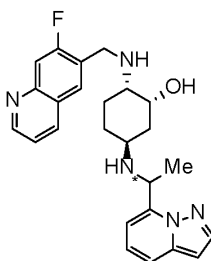
30

Table 11. The following Examples (78-81) were prepared according to a similar synthetic procedure described for Example 77, utilizing STAB or NaBH₄ as reducing reagents.

Example	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	Rt (min) LCMS Method
78		(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-N ¹ -(2-Ethoxybenzyl)-2-fluoro-N ⁴ -((3-methyl-3 <i>H</i> -imidazo[4,5- <i>b</i>]pyridin-6-yl)methyl)cyclohexane-1,4-diamine	412.3	0.82 Method B
79		(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-N ⁴ -((1 <i>H</i> -Pyrrolo[2,3- <i>b</i>]pyridin-5-yl)methyl)-N ⁴ -(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine	397.2	0.94 Method B
80		(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-N ⁴ -((1 <i>H</i> -Indazol-5-yl)methyl)-N ⁴ -(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine	397.2	0.94 Method B
81		5-((((1 <i>S</i> ,3 <i>S</i> ,4 <i>S</i>)-3-Fluoro-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	427.3	0.89 Method B

5 **EXAMPLES 82A and 82B: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((*R*)-1-(pyrazolo[1,5-*a*]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol and (1*R*,2*S*,5*S*)-2-(((7-**

fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(pyrazolo[1,5-*a*]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol

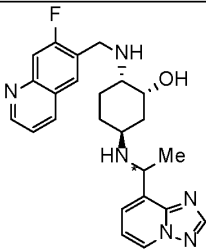


Step 1: (1*R*,2*S*,5*S*)-5-Amino-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol: To a mixture of *tert*-butyl ((1*S*,3*R*,4*S*)-4-(((7-fluoroquinolin-6-yl)methyl)amino)-3-hydroxycyclohexyl)carbamate (596.0 mg, 1.53 mmol) in DCM (15.3 mL) was added a sol'n of 4M HCl-dioxane (3.83 mL, 15.3 mmol) and the reaction mixture was stirred at RT for 72 h. The solvent was evaporated *in vacuo*, the resultant solid dissolved in 1 M NaOH, extracted with DCM (3x), the combined organic layers dried over Na₂SO₄, filtered, and reduced *in vacuo*. The resulting thick oil was titrated in Et₂O and dried under vacuo to afford the title compound (406 mg, 87% yield) as a white solid. LCMS (Method B), Rt = 0.53 min, *m/z* [M+H]⁺: 290.1. ¹H NMR (400 MHz, CD₃OD) δ 1.13-1.36 (m, 2H) 1.56-1.71 (m, 1H) 1.75-1.95 (m, 2H) 2.08 (dq, *J*=13.51, 3.50 Hz, 1H) 2.56-2.67 (m, 1H) 3.04 (tt, *J*=11.51, 4.00 Hz, 1H) 3.57-3.78 (m, 1H) 4.01-4.17 (m, 3H) 7.54 (dd, *J*=8.01, 4.50 Hz, 1H) 7.68 (d, *J*=11.51 Hz, 1H) 8.06 (d, *J*=8.01 Hz, 1H) 8.40 (dd, *J*=8.51, 1.00 Hz, 1H) 8.86 (dd, *J*=4.50, 1.50 Hz, 1H)

Step 2: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((*R* or *S*)-1-(pyrazolo[1,5-*a*]pyridin-7-yl)ethyl)amino)-cyclohexan-1-ol: To a microwave vial equipped with a stir bar a was charged with 1-(pyrazolo[1,5-*a*]pyridin-7-yl)ethan-1-one (58.0 mg, 362 μmol), (1*R*,2*S*,5*S*)-5-amino-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol (120 mg, 415 μmol), and THF (3.62 mL). The vial was charged with Ti(O^{*i*}Pr)₄ (215 μL, 724 μmol) by syringe and the reaction mixture was heated at 65 °C for 16 h. The reaction mixture was diluted with MeOH (3.62 mL), to which was added NaBH₄ (27.4 mg, 724 μmol) and the reaction mixture was stirred at RT for 1 h. The reaction was quenched with 1M NaOH, the aqueous layer extracted with EtOAc (3x), and the combined organic extracts washed with brine, dried over Na₂SO₄, filtered, and the solvent evaporated under reduced pressure. The crude residue was purified by silica gel flash column chromatography (12 g) eluting with a 0-40% MeOH (2% NH₄OH)/DCM gradient to afford the title compound as a mixture of diastereomers. LCMS (Method B), Rt = 0.88 min, *m/z* [M+H]⁺: 434.4.

Step 3: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((*R* or *S*)-1-(pyrazolo[1,5-*a*]pyridin-7-yl)ethyl)amino)-cyclohexan-1-ol: The mixture of (1*R*,2*S*,5*S*)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-(((*R* or *S*)-1-(pyrazolo[1,5-*a*]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol were purified by chiral-SFC (Method J2) to afford the title compounds: first eluted peak 82A LCMS (Method B), *R*_t = 0.87 min, *m/z* [M+H]⁺: 434.3. ¹H NMR (400 MHz, CD₃OD) δ 8.83 (dd, *J*=4.40, 1.96 Hz, 1H), 8.36 (d, *J*=8.41 Hz, 1H), 8.01 (d, *J*=7.83 Hz, 1H), 7.96 (d, *J*=1.96 Hz, 1H), 7.64 (d, *J*=11.25 Hz, 1H), 7.57 (dd, *J*=8.80, 1.47 Hz, 1H), 7.51 (dd, *J*=8.31, 4.40 Hz, 1H), 7.19 (dd, *J*=8.80, 6.85 Hz, 1H), 6.89 (d, *J*=6.71 Hz, 1H), 6.61 (d, *J*=2.45 Hz, 1H), 4.65 (d, *J*=6.85 Hz, 2H), 3.95-4.08 (m, 4H), 2.69 (s, 1H), 2.59 (br d, *J*=10.76 Hz, 1H), 1.91-2.08 (m, 2H), 1.71 (br s, 1H), 1.57 (d, *J*=6.85 Hz, 3H), 1.33 - 1.44 (m, 2H), 1.15 (s, 1H); second eluted peak 82B LCMS (Method B), *R*_t = 0.88 min, *m/z* [M+H]⁺: 434.4. ¹H NMR (400 MHz, CD₃OD) δ 8.83 (dd, *J*=4.40, 1.47 Hz, 1H), 8.37 (d, *J*=8.31 Hz, 1H), 8.01 (d, *J*=7.83 Hz, 1H), 7.96 (d, *J*=1.96 Hz, 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.57 (d, *J*=7.83 Hz, 1H), 7.51 (dd, *J*=8.31, 4.40 Hz, 1H), 7.19 (dd, *J*=8.80, 6.85 Hz, 1H), 6.90 (d, *J*=6.36 Hz, 1H), 6.61 (d, *J*=2.45 Hz, 1H), 4.63 (d, *J*=6.85 Hz, 1H), 4.11 (br s, 1H), 4.01 (d, *J*=7.83 Hz, 3H), 2.74 (s, 1H), 2.51-2.64 (m, 1H), 2.13-2.27 (m, 1H), 1.75 (br s, 2H), 1.56 (d, *J*=6.85 Hz, 3H), 1.35-1.52 (m, 1H), 1.27 (br d, *J*=11.74 Hz, 2H).

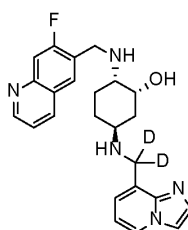
Table 12. The following Examples (83A-85B) were prepared according to a similar synthetic procedure described for Examples 82A and 82B.

Example	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	<i>R</i> _t (min) LCMS Method	Conditions
83A		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-5-(((<i>R</i> or <i>S</i>)-1-((1,2,4)Triazolo[1,5- <i>a</i>]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol	435.3	0.67 Method B	Method K1/K2 Peak 1

83B		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-5-(((<i>R</i> or <i>S</i>)-1-([1,2,4]Triazolo[1,5- <i>a</i>]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol	435.3	0.67 Method B	Method K1/K2 Peak 2
84A		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((<i>R</i> or <i>S</i>)-1-(imidazo[1,2- <i>a</i>]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol	434.4	0.73 Method B	Method M1/M2 Peak 1
84B		(1 <i>R</i> ,2 <i>S</i> ,5 <i>S</i>)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((<i>R</i> or <i>S</i>)-1-(imidazo[1,2- <i>a</i>]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol	434.4	0.74 Method B	Method M1/M2 Peak 2
85A		5-Fluoro-6-((((1 <i>S</i> ,3 <i>S</i> ,4 <i>S</i>)-3-fluoro-4-(((<i>R</i> or <i>S</i>)-1-(imidazo[1,2- <i>a</i>]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	469.4	0.78 Method B	Method N1/N2 Peak 1
85B		5-Fluoro-6-((((1 <i>S</i> ,3 <i>S</i> ,4 <i>S</i>)-3-fluoro-4-(((<i>R</i> or <i>S</i>)-1-(imidazo[1,2- <i>a</i>]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	469.3	0.78 Method B	Method N1/N2 Peak 2

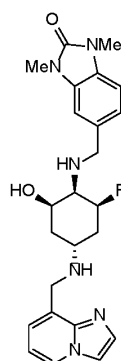
		dihydro-2H-benzo[d]imidazol-2-one			
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Example 86: (1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl-*d*₂)amino)cyclohexan-1-ol



- 5 The title compound was prepared according to a similar synthetic procedure described for (1*R*,2*S*,5*S*)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol, utilizing imidazo[1,2-*a*]pyridine-8-carbaldehyde-*d* as the aldehyde in the reductive amination step being reduced with NaBD₄ (22.5 mg, 538 μmol). ¹H NMR (400 MHz, CD₃OD) δ 8.84 (dd, *J*=4.4, 1.5 Hz, 1H), 8.43-8.36 (m, 2H), 8.05 (d, *J*=8.3 Hz, 1H), 7.68-7.65 (d, 1H), 7.57-7.50 (m, 3H), 7.36-7.30 (m, 1H), 7.00-6.95 (m, 1H), 4.19-3.99 (m, 4H), 3.02-2.89 (m, 1H), 2.69-2.60 (m, 1H), 2.27-2.14 (m, 1H), 2.14-2.00 (m, 1H), 1.85-1.78 (m, 1H), 1.61 (br dd, *J*=12.2, 2.9 Hz, 1H), 1.35 (ddd, *J*=13.5, 11.5, 2.4 Hz, 1H), 1.25-1.14 (m, 1H). LCMS (Method B), Rt = 0.70 min, *m/z* [M+H]⁺: 422.3.
- 10

- EXAMPLE 87: 5-((((1*R*,2*S*,4*R*,6*R*)-2-fluoro-6-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one**
- 15



Step 1: *tert*-butyl ((1*R*,3*R*,5*S*,6*S*)-5-hydroxy-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate: To a solution of *tert*-butyl ((1*S*,5*S*)-5-hydroxycyclohex-3-en-1-yl)carbamate (2.0 g, 9.4 mmol) in DCM (40 mL) was added mCPBA (2.3 g, 70% wt, 9.4 mmol) portion wise at 0 °C. After addition, the reaction was stirred for 18 h at RT. The mixture was treated with saturated Na₂SO₃ (aq) (15 mL) and stirred for 10 min.

5 It was diluted with brine (30 mL) and extracted with DCM. The organic extract was washed with saturated NaHCO₃ (aq) (3 x 30 mL), water (30 mL), and dried over MgSO₄. It was filtered and concentrated *in vacuo* to afford the title compound (1.68 g, 74.2% yield) as white solid used as the intermediate without further purification. The LCMS had no chromophore, the NMR was consistent with the desired structure. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 6.78 (br d, *J* = 8.0 Hz, 1H), 4.99 (d, *J* = 5.5 Hz, 1H), 3.91 (dtd, *J* = 1.5, 5.4, 10.8 Hz, 1H), 3.28 - 3.18 (m, 1H), 3.14 - 3.10 (m, 1H), 3.07 (d, *J* = 4.0 Hz, 1H), 2.11 - 1.99 (m, 1H), 1.57 - 1.50 (m, 1H), 1.49 - 1.41 (m, 1H), 1.37 (s, 9H), 1.30 - 1.19 (m, 1H).

Step 2: (1*R*,2*R*,4*S*,6*R*)-4-((*tert*-butoxycarbonyl)amino)-7-oxabicyclo[4.1.0]heptan-2-yl 4-nitrobenzoate: To a solution of *tert*-butyl ((1*R*,3*R*,5*S*,6*S*)-5-hydroxy-7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (1.58 g, 6.9 mmol), *p*-nitrobenzoic acid (1.3 g, 7.6 mmol), and triphenylphosphine (2.2 g, 8.3 mmol) in THF (40 mL) was added diisopropyl diazene-1,2-dicarboxylate (1.7 g, 8.3 mmol) dropwise at RT. The reaction mixture was stirred for 1 h at RT. The mixture was treated with saturated NaHCO₃ (aq) (20 mL) and diluted with brine (20 mL), extracted with EtOAc (30 mL). The organic extract was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography eluting with a gradient of 0 to 30% EtOAc in heptane to afford the title compound (2.46 g, 84% yield) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.40 (d, *J* = 8.8 Hz, 2H), 8.26 - 8.22 (m, 2H), 6.77 (br d, *J* = 7.8 Hz, 1H), 5.62 - 5.53 (m, 1H), 3.65 (br s, 1H), 3.30 (br d, *J* = 4.4 Hz, 1H), 3.26 (d, *J* = 2.0 Hz, 1H), 2.34 - 2.24 (m, 1H), 1.81 - 1.58 (m, 3H), 1.35 (s, 9H). LCMS (Method B), *R*_t = 1.11 min, *m/z* [M+H]⁺: 379.1.

25 Step 3: (1*R*,2*S*,3*S*,5*R*)-5-((*tert*-butoxycarbonyl)amino)-3-fluoro-2-hydroxycyclohexyl 4-nitrobenzoate: A mixture of (1*R*,2*R*,4*S*,6*R*)-4-((*tert*-butoxycarbonyl)amino)-7-oxabicyclo[4.1.0]heptan-2-yl 4-nitrobenzoate (2.6 g, 6.7 mmol) and triethylammoniumfluoride (7.9 g, 49 mmol) stirred for 3 h at 100 °C. After cooling to the RT, the mixture was slowly added into ice cold saturated NaHCO₃ (aq) (30 mL) and EtOAc (60 mL) with stirring. The layers were separated, and the organic layer was washed with water (2 x 50 mL) and dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography eluting with a gradient of 0 to 50% EtOAc in heptane to afford the title compound (1.51 g, 50.6% yield) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.41 - 8.35 (m, 2H), 8.22 - 8.15 (m, 2H), 7.22 - 7.02 (m, 1H), 5.71 (d, *J* = 4.9 Hz, 1H), 5.19

- 5.09 (m, 1H), 4.87 - 4.67 (m, 1H), 3.96 - 3.85 (m, 1H), 3.76 (br dd, $J = 4.4, 10.3$ Hz, 1H), 2.00 - 1.86 (m, 3H), 1.82 - 1.72 (m, 1H), 1.38 (s, 9H). LCMS (Method A), $R_t = 0.88$ min, m/z $[M+H-^tBu]^+$: 299.1.

Step 4: (1*R*,2*R*,3*S*,5*R*)-5-((*tert*-butoxycarbonyl)amino)-2-(1,3-dioxoisindolin-2-yl)-3-fluorocyclohexyl 4-nitrobenzoate: To a solution of (1*R*,2*S*,3*S*,5*R*)-5-((*tert*-butoxycarbonyl)amino)-3-fluoro-2-hydroxycyclohexyl 4-nitrobenzoate (1.5 g, 90% wt, 3.4 mmol), phthalimide (548 mg, 3.7 mmol), and triphenylphosphine (1.2 g, 4.4 mmol) in THF (30 mL) was added diisopropyl diazene-1,2-dicarboxylate (891 mg, 4.4 mmol) dropwise at RT. After addition, the reaction mixture was heated to 40 °C and stirred for 18 h. After cooling to the RT, the mixture was diluted with water (30 mL) and brine (20 mL), extracted with EtOAc (30 mL). The organic extract was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel flash column chromatography eluting with a gradient of 0 to 35% EtOAc in heptane to afford the title compound (1.0 g, 53.7% yield) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) $\delta = 8.44 - 8.36$ (m, 2H), 8.23 (d, $J = 9.3$ Hz, 2H), 7.88 - 7.77 (m, 4H), 6.97 (br d, $J = 8.3$ Hz, 1H), 5.69 (br s, 1H), 5.33 - 5.14 (m, 1H), 4.64 - 4.49 (m, 1H), 4.10 (br dd, $J = 3.9, 7.8$ Hz, 1H), 2.37 - 2.25 (m, 1H), 2.22 - 2.12 (m, 1H), 1.98 - 1.79 (m, 2H), 1.37 (s, 9H). LCMS (Method B), $R_t = 1.29$ min, m/z $[M+H-^tBu]^+$: 428.1.

Step 5: *tert*-butyl ((1*R*,3*S*,4*R*,5*R*)-4-amino-3-fluoro-5-hydroxycyclohexyl)carbamate: To a solution of (1*R*,2*R*,3*S*,5*R*)-5-((*tert*-butoxycarbonyl)amino)-2-(1,3-dioxoisindolin-2-yl)-3-fluorocyclohexyl 4-nitrobenzoate (300 mg, 569 μ mol) in EtOH (6.0 mL) was added hydrazinehydrate (285 mg, 5.7 mmol). The reaction mixture was stirred for 90 min at 60 °C. After cooling to RT, the mixture was filtered, the precipitate was washed with EtOH. The filtrate was passed through a SCX cartridge (5g), flashing with MeOH, followed by 1.0 M NH₃ in MeOH solution. The NH₃ in MeOH solution was collected and concentrated *in vacuo*. The resulting solid was triturated with Et₂O and filtered. The solid was washed with Et₂O and dried to afford the title compound (162 mg, 60% pure, 68.8% yield) which was used as the intermediate without further purification. LCMS (Method B), $R_t = 0.54$ min, m/z $[M+H]^+$: 249.1.

Step 6: *tert*-butyl ((1*R*,3*S*,4*R*,5*R*)-4-(((1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)amino)-3-fluoro-5-hydroxycyclohexyl)carbamate: A mixture of *tert*-butyl ((1*R*,3*S*,4*R*,5*R*)-4-amino-3-fluoro-5-hydroxycyclohexyl)carbamate (160 mg, 60% wt, 386.63 μ mol) and 1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-5-carbaldehyde (120 mg, 631 μ mol) in THF (6.0 mL) was stirred 18 h at RT. To the mixture was added STAB (160 mg, 755 μ mol) and the mixture was stirred for 1 h at RT. To the mixture was added additional THF (6.0 mL) and STAB (160 mg, 755 μ mol). It was stirred for 20 h at RT. The mixture was diluted with 10 mL MeOH/DCM (1:1) and the resulting mixture was passed through a SCX cartridge (5 g), flashing with MeOH, followed by 1.0 M NH₃ in

MeOH solution. The NH₃ solution was collected and concentrated *in vacuo*. The crude product was purified by a semi-prep HPLC (MDAP) system eluting with a 15%-55% MeCN-H₂O (10 nM ammonium carbonate pH10 buffer) gradient to afford the title compound (39 mg, 22.7% yield) as white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.13 (s, 1H), 7.08 - 7.02 (m, 2H), 6.72 (br d, *J* = 8.3 Hz, 1H), 4.93 - 4.76 (m, 1H), 4.53 (d, *J* = 3.9 Hz, 1H), 4.01 (br s, 1H), 3.95 - 3.75 (m, 3H), 3.32 (s, 3H), 3.31 (s, 3H), 2.48 - 2.39 (m, 1H), 2.19 - 2.01 (m, 2H), 1.84 (br d, *J* = 11.7 Hz, 1H), 1.55 - 1.43 (m, 1H), 1.37 (s, 9H), 1.36 - 1.29 (m, 1H). LCMS (Method B), Rt = 0.75 min, *m/z* [M+H]⁺: 423.2.

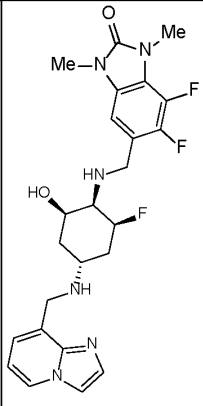
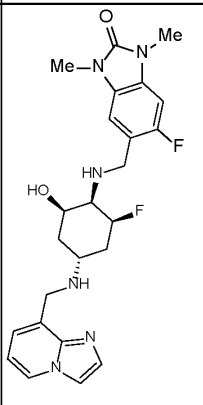
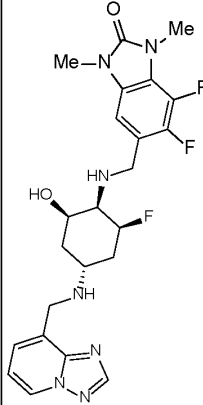
Step 7: 5-((((1*R*,2*S*,4*R*,6*R*)-4-amino-2-fluoro-6-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one, 2hydrochloride: To a solution of *tert*-butyl (((1*R*,3*S*,4*R*,5*R*)-4-(((1,3-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)methyl)amino)-3-fluoro-5-hydroxycyclohexyl)carbamate (37 mg, 95% wt, 83 μmol) in MeOH (1.2mL) and DCM (1.2 mL) was added 4.0 M HCl in dioxane (438 μL, 4.0 molar, 1.75 mmol). The reaction mixture was stirred for 4 h at RT. The mixture was concentrated *in vacuo* to afford the title compound (2HCl salt) (33 mg, 99.3% yield) as white solid used as the intermediate without further purification. ¹H NMR (400 MHz, DMSO-d₆) δ = 9.50 - 9.36 (m, 1H), 9.20 - 9.05 (m, 1H), 8.26 - 8.10 (m, 3H), 7.45 (s, 1H), 7.26 (dd, *J* = 1.2, 8.1 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 5.81 (br d, *J* = 4.4 Hz, 1H), 5.29 - 5.13 (m, 1H), 4.35 - 4.15 (m, 3H), 3.55 - 3.46 (m, 1H), 3.34 (d, *J* = 2.4 Hz, 6H), 3.21 (br dd, *J* = 5.1, 9.0 Hz, 1H), 2.44 - 2.32 (m, 1H), 2.15 (br dd, *J* = 3.2, 13.5 Hz, 1H), 1.86 - 1.59 (m, 2H). LCMS (Method B), Rt = 0.46 min, *m/z* [M+H]⁺: 323.1.

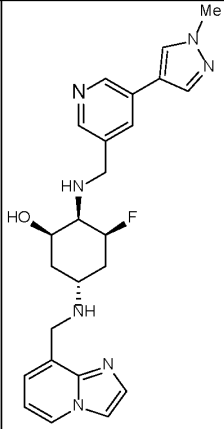
Step 8: 5-((((1*R*,2*S*,4*R*,6*R*)-2-fluoro-6-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one: To a suspension of 5-((((1*R*,2*S*,4*R*,6*R*)-4-amino-2-fluoro-6-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one, 2hydrochloride in EtOH (2.0 mL) was added DIPEA (54 mg, 417 μmol). The mixture was turned to clear solution. To the solution was added imidazo[1,2-*a*]pyridine-8-carboxaldehyde (14 mg, 96 μmol). The reaction mixture was stirred for 2 h at RT. It was turned to cloudy. To the mixture was added DCM (2.0 mL) and it was turned clear solution. The mixture was stirred for additional 2 h, and STAB (53 mg, 250 μmol) was added. The reaction mixture was stirred for 18 h at RT. To the mixture was added additional STAB (53 mg, 250 μmol) and stirred for 30 min. The reaction was still not completed. Repeating two more additions of STAB (53 mg, 250 μmol) and the reaction was completed. The mixture was diluted with water (2 mL) and the mixture was passed through a SCX cartridge (5g), flashing with MeOH, followed by 1.0 M NH₃ in MeOH solution. The NH₃ solution was collected and concentrated *in vacuo*. The crude product was purified by a semi-prep HPLC (MDAP) system eluting with a 15%-55% MeCN-H₂O (10 nM ammonium

carbonate pH10 buffer) gradient to afford the title compound (19.5 mg, 51.6% yield) as white solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.45 - 8.40 (m, 1H), 7.93 (d, *J* = 1.0 Hz, 1H), 7.53 (d, *J* = 1.0 Hz, 1H), 7.19 (dd, *J* = 1.0, 6.8 Hz, 1H), 7.13 (s, 1H), 7.08 - 7.02 (m, 2H), 6.85 (t, *J* = 6.8 Hz, 1H), 4.89 (td, *J* = 3.0, 48.8 Hz, 1H), 4.49 (d, *J* = 4.4 Hz, 1H), 4.06 - 3.98 (m, 3H), 3.82 (s, 3H), 3.31 (s, 3H), 3.30 (s, 3H), 3.05 - 2.95 (m, 1H), 2.75 - 2.63 (m, 1H), 2.34 - 2.05 (m, 3H), 1.96 - 1.87 (m, 1H), 1.55 - 1.39 (m, 1H), 1.37 - 1.28 (m, 1H). LCMS (Method B), *R*_t = 0.60 min, *m/z* [M+H]⁺: 453.2.

Table 13. The following Example (88-93) were prepared according to a similar synthetic procedure described for Example 87.

Example	Structure	IUPAC Name	Obs. <i>m/z</i> [M+H] ⁺	<i>R</i> _t (min) Method
88		(1 <i>R</i> ,2 <i>R</i> ,3 <i>S</i> ,5 <i>R</i>)-3-fluoro-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2- <i>a</i>]pyridin-8-yl)methyl)amino)cyclohexan-1-ol	438.2	0.66 Method B
89		(1 <i>R</i> ,2 <i>R</i> ,3 <i>S</i> ,5 <i>R</i>)-2-(((1,3-dimethyl-1 <i>H</i> -pyrazolo[3,4- <i>b</i>]pyridin-5-yl)methyl)amino)-3-fluoro-5-((imidazo[1,2- <i>a</i>]pyridin-8-yl)methyl)amino)cyclohexan-1-ol	438.2	0.61 Method B

90		4,5-difluoro-6-(((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,6 <i>R</i>)-2-fluoro-6-hydroxy-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	489.1	0.70 Method B
91		5-fluoro-6-(((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,6 <i>R</i>)-2-fluoro-6-hydroxy-4-((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	471.3	0.65 Method B
92		6-(((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i> ,6 <i>R</i>)-4-((1,2,4-triazolo[1,5- <i>a</i>]pyridin-8-ylmethyl)amino)-2-fluoro-6-hydroxycyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2 <i>H</i> -benzo[<i>d</i>]imidazol-2-one	490.3	0.67 Method B

93		(1 <i>R</i> ,2 <i>R</i> ,3 <i>S</i> ,5 <i>R</i>)-3-fluoro-5-(((imidazo[1,2- <i>a</i>]pyridin-8-ylmethyl)amino)-2-(((5-(1-methyl-1 <i>H</i> -pyrazol-4-yl)pyridin-3-yl)methyl)amino)cyclohexan-1-ol	450.3	0.58 Method B
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BIOLOGICAL ASSAYS**Example A - SW48 Cell Viability Assay Procedure**

SW48 (RRID:CVCL_1724) human colorectal cancer cells were obtained from the American Type Culture Collection and maintained in growth medium composed of RPMI-1640 (Gibco Cat# 22400-071) supplemented with 10% fetal bovine serum (SAFC Cat# 12176C-1000mL). Cells were maintained in a humidified 5% CO₂ incubator at 37 °C. Cell dissociation was conducted using TrypLE Select (Gibco Cat# 12563029) to detach cells from culture flasks. Following dissociation, cells were centrifuged briefly and resuspended in assay medium RPMI-1640 (Gibco Cat# 22400-071) +10% fetal bovine serum (SAFC Cat# 12176C-1000mL). Black 384-well assay plates (Greiner Bio-One Cat# 781079) were prepared from source plates of DMSO and compounds dissolved in DMSO prior to cell dispensation. These source plates were prepared in eleven point, 3-fold serial dilutions from 10 mM stocks stored at 4 °C. Compounds and DMSO controls were dispensed into assay plates at 150 nanoliters per well from source plates using Labcyte Echo 555 or Echo 655T (Beckman Coulter, Inc) dispensers with Column 6 and Column 18 containing DMSO only. Cells were then seeded into prepared assay plates in 50 microliters assay medium at 250 cells per well into Columns 1 thru 17 and Columns 19-24. Assay medium without cells was added to column 18 to serve as a surrogate for 100% cell cytotoxicity. Following incubation for 120 hours in a humidified 5% CO₂ incubator at 37 °C, cellular ATP concentration of each well was measured and used as a surrogate of cell viability. This was performed by adding 50 microliters of CellTiter-Glo reagent (Promega Cat# G8462) to each well followed by a 10-minute incubation at RT. Luminescence was measured on a Synergy Neo or Synergy Neo2 multimode plate reader (BioTek). Compound cytotoxic response (%C) was normalized to the robust means of column 6 (Control 1, 0% Cytotoxicity) and column 18 (Control 2, 100% Cytotoxicity) and normalized % cytotoxicity (%C) calculated. $\%C = 100 - 100 * ((\text{Compound} - \text{Control 2}) / (\text{Control 1} - \text{Control 2}))$. These normalized data were then used to determine a 50% cytotoxic response (CC₅₀) using 4-parameter logistic curve model 201 in Activity Base XE:

Four (4) Parameter Logistic Model fit = $A + (B-A)/(1+(10^{C/x})^D)$

where A = minimum asymptote (% cytotoxicity), B = maximum asymptote (% cytotoxicity), C = Log CC₅₀ (pCC₅₀), D = Hill slope, and x = [inhibitor], (M).

Table A. pCC₅₀ values for Examples in the SW48 Cell Viability Assay

Example	SW48, pCC ₅₀	Example	SW48, pCC ₅₀	Example	SW48, pCC ₅₀
1	6.3	31	7.5	61	6.7
2	6.4	32	6.1	62	7.0
3	6.3	33	7.4	63	6.2
4	7.2	34	7.6	64	6.2
5	7.1	35	7.0	65	6.8
6	7.7	36	7.2	66	7.0
6B	7.7	37	6.4	67	6.4
7	7.0	38	6.5	68	6.3
8	7.4	39	7.2	69	6.2
9	6.8	40	7.1	70	6.3
10	6.6	41	6.4	71	6.5
11	6.5	42	6.3	72	6.9
12	7.2	43	6.6	73	7.0
13	7.0	44	6.2	74	7.0
14	6.9	45	7.9	75	7.4
15	7.4	46	7.7	76	7.5
16	7.8	47	7.3	77	7.5
17	7.0	48	6.9	78	6.4
18	6.2	49	6.4	79	6.8
19	7.1	50	7.4	80	7.0

20	6.7	51	7.0	81	7.4
21	6.1	52	6.6	82A	5.5
22	6.8	53	7.7	82B	7.1
23	6.5	54	7.0	83A	5.1
24	6.2	55	6.0	83B	7.4
25	6.9	56	6.9	84A	5.9
26	7.6	57	6.5	84B	7.3
27	7.2	58	7.0	85A	6.6
28	6.3	59	7.2	85B	5.7
29	6.6	60	7.9	86	7.8
30	6.8	90	7.0	92	6.7
87	7.4	91	7.1	93	7.2
88	6.9				
89	7.0				

Example B – SW620 Cell Viability Assay Procedure

SW620 (RRID:CVCL_0547) human colorectal cancer cells were obtained from the American Type Culture Collection and maintained in growth medium composed of RPMI-1640 (Gibco Cat# 22400-071) supplemented with 10% fetal bovine serum (SAFC Cat# 12176C-1000mL). Cells were maintained in a humidified 5% CO₂ incubator at 37 °C. Cell dissociation was conducted using TrypLE Select (Gibco Cat# 12563029) to detach cells from culture flasks. Following dissociation, cells were centrifuged briefly and resuspended in assay medium RPMI-1640 (Gibco Cat# 22400-071) +10% fetal bovine serum (SAFC Cat# 12176C-1000mL). Black 384-well assay plates (Greiner Bio-One Cat# 781079) were prepared from source plates of DMSO and compounds dissolved in DMSO prior to cell dispensation. These source plates were prepared in eleven point, 3-fold serial dilutions from 10 mM stocks stored at 4 °C. Compounds and DMSO controls were dispensed into assay plates at 150 nanoliters per well from source plates using Labcyte Echo 555 or Echo 655T (Beckman Coulter, Inc) dispensers with Column 6 and Column 18 containing DMSO only. Cells were then seeded into prepared

assay plates in 50 microliters assay medium at 250 cells per well into Columns 1 thru 17 and Columns 19-24. Assay medium without cells was added to column 18 to serve as a surrogate for 100% cell cytotoxicity. Following incubation for 120 hours in a humidified 5% CO₂ incubator at 37 °C, cellular ATP concentration of each well was measured and used as a surrogate of cell viability. This was performed by adding 50 microliters of CellTiter-Glo reagent (Promega Cat# G8462) to each well followed by a 10-minute incubation at RT. Luminescence was measured on a Synergy Neo or Synergy Neo2 multimode plate reader (BioTek). Compound cytotoxic response (%C) was normalized to the robust means of column 6 (Control 1, 0% Cytotoxicity) and column 18 (Control 2, 100% Cytotoxicity) and normalized % cytotoxicity (%C) calculated. $\%C = 100 - 100 * ((\text{Compound} - \text{Control 2}) / (\text{Control 1} - \text{Control 2}))$. These normalized data were then used to determine a 50% cytotoxic response (CC₅₀) using 4-parameter logistic curve model 201 in Activity Base XE:

Four (4) Parameter Logistic Model fit = $A + (B - A) / (1 + (10^{C/x})^D)$

where A = minimum asymptote (% cytotoxicity), B = maximum asymptote (% cytotoxicity), C = Log CC₅₀ (pCC₅₀), D = Hill slope, and x = [inhibitor], (M).

Table B. pCC₅₀ values for Examples in the SW620 Cell Viability Assay

<u>Example</u>	<u>SW620,</u> <u>pCC₅₀</u>	<u>Example</u>	<u>SW620,</u> <u>pCC₅₀</u>	<u>Example</u>	<u>SW620,</u> <u>pCC₅₀</u>
1	<4.5	34	-	67	<4.5
2	<4.5	35	<4.5	68	<4.5
3	<4.5	36	4.9	69	<4.5
4	<4.5	37	<4.5	70	<4.5
5	<4.5	38	<4.5	71	5.1
6	<4.5	39	<4.5	72	5
6B	<4.5	40	<4.5	73	<4.5
7	<4.5	41	<4.5	74	<4.5
8	<4.5	42	<4.5	75	4.6
9	<4.5	43	<4.5	76	4.9

10	5.2	44	<4.5	77	4.6
11	<4.5	45	4.6	78	<4.5
12	<4.5	46	<4.5	79	<4.5
13	<4.5	47	<4.5	80	-
14	<4.5	48	<4.5	81	<4.5
15	<4.5	49	<4.5	82A	<4.5
16	<4.5	50	<4.5	82B	<4.5
17	<4.5	51	<4.5	83A	<4.5
18	<4.5	52	4.7	83B	<4.5
19	4.8	53	<4.5	84A	<4.5
20	<4.5	54	<4.5	84B	<4.5
21	<4.5	55	<4.5	85A	<4.5
22	<4.5	56	<4.5	85B	<4.5
23	<4.5	57	<4.5	86	<4.5
24	<4.5	58	<4.5	87	<4.5
25	<4.5	59	<4.5	88	<4.5
26	<4.5	60	<4.5	89	<4.5
27	<4.5	61	<4.5	90	<4.5
28	4.6	62	<4.5	91	<4.5
29	<4.5	63	<4.5	92	<4.5
30	4.6	64	<4.5	93	<4.5
31	<4.5	65	<4.5		
32	<4.5	66	<4.5		
33	<4.5				

Example C – In vivo efficacy study in mouse model bearing SW48 human colorectal cancer cell line xenografts

Experiments were performed with female Crl:Nu-Foxn1^{nu} (strain #088) nude mice (Charles River). Animals were housed under optimized hygienic condition with food and water at libitum and a 12h:12h light:dark cycle. Animals were allowed to acclimatize for at least 4 days before being enrolled in the experimental design.

SW48 human colorectal cancer cells (RRID:CVCL1724) were obtained from ATCC. The cells were cultured in RPMI 1640 (Thermos Fischer 11875093) with 10% Fetal Bovine Serum (Thermos Fischer 16140071) at 37°C in atmosphere of 5% CO₂ in air. To establish SW48 xenografts, cells were harvested and re-suspended in serum free RPMI1640 and Matrigel (Corning, 354234) before inoculation and 5 x 10⁶ SW48 tumor cells were injected subcutaneously in 100µL volume using 27G1/2 needle. Cells were inoculated in the right hind flank of the animals.

Post cell inoculation, tumor growth was monitored daily, and animals were randomized into treatment groups (n=10/group) once the tumor volume reached an appropriate size (80-150 mm³). Throughout the treatment period, both tumor volume and body weight were measured approximately twice a week. The tumor size, in mm³, was computed using the formula: 0.5 x L x W², where W = width and L = length of the tumor.

To prepare compound for oral administration, between 9 mg of the test compound was dissolved in 3 mL vehicle solution consisting of 0.5% Methylcellulose (cp 400) and 0.5% Tween 80. The compound was freshly prepared one hour prior to daily administration. The resulting solution formulation was utilized for in vivo studies.

Animals received either a vehicle or test compounds at dosage of 30mg/kg daily through oral gavage (10mL/kg). Body weight was measured twice a week using the Ohaus electronic scale (STX421) and the data was automatically added to the study log. Moreover, daily clinical observations were performed to closely monitor the animals.

Tumor growth inhibition was computed using the following formula:

$$\text{Mean \% } \Delta \text{ Inhibition} = [(\text{Mean}(C) - \text{Mean}(C_0)) - (\text{Mean}(T) - \text{Mean}(T_0))] / (\text{Mean}(C) - \text{Mean}(C_0)) * 100\%$$

where T = current group value; T₀ = Current group initial value; C = Control group Value; C₀ = control group initial value.

Data of tumor volume were exported and analyzed in GraphPad Prism (9.5). The analysis included a two-way ANOVA test, comparing the vehicle control vs. treatments at different time points, followed by a Tukey HSD post hoc test.

The calculation of tumor regression was conducted as per the following formula:

5 Tumor Regression = $(\Delta \text{ tumor volume} / \text{ tumor volume at Day 0}) * 100$

Here, Day 0 = treatment start day; Δ tumor volume = mean tumor volume on the evaluation day - mean tumor volume Day 0

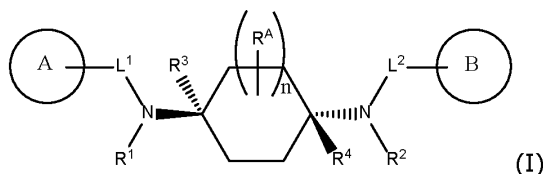
Treatment with Example 6 was initiated at a dosage of 30 mg/kg, administered orally once daily when the average tumor volume reached 100.4 mm³ (n=10/group). The 21-day treatment course resulted
10 in a significant mean tumor regression of -52.7% compared to the Vehicle group (p<0.0001), as shown in Figure 1.

Similarly, Example 34 was administered daily at 30 mg/kg once the average tumor volume reached 96.8 mm³ (n=10/group). By day 21, the SW48 tumor exhibited a significant regression of -46.98% relative to the Vehicle (p<0.0001), as illustrated in Figure 2.

15 Example 40, treatment commenced with daily oral administration of 30 mg/kg once the average tumor volume reached 93.54 mm³ (n=10/group). This regimen led to a 97.12% tumor growth inhibition in the SW48 tumor by day 21 (p<0.0001 vs. Vehicle), as depicted in Figure 3.

Embodiments of the invention

1. A compound of Formula (I):



wherein:

5 R^1 and R^2 are each independently selected from hydrogen, C_{1-3} alkyl, halo(C_{2-3})alkyl, $-CH_2-C_{5-9}$ aryl wherein the C_{5-9} aryl is optionally substituted with C_{1-3} alkoxy;

R^3 and R^4 are each independently selected from hydrogen or C_{1-3} alkyl;

n is an integer selected from 1 to 3;

10 R^A is independently selected from C_{1-2} alkyl, halo, $-NR^aR^b$, hydroxy, carboxy, halo(C_{1-3})alkyl, hydroxy(C_{1-3})alkyl, methoxy(C_{1-3})alkyl, C_{1-3} alkoxy, and halo(C_{1-3})alkoxy, or R^A and R^1 are taken together to form a nitrogen containing 5- or 6- membered ring which optionally contains one or two heteroatoms independently selected from N, O, and S and is optionally substituted with C_{1-2} alkyl;

15 L^1 and L^2 are each independently selected from a C_{1-2} alkylene optionally substituted with one or two substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy(C_{1-3})alkyl, halo(C_{1-3})alkyl, and cyano;

20 Ring A and B are each independently selected from C_{5-14} aryl or C_{5-14} heteroaryl containing one, two, or three heteroatoms independently selected from N, O, and S, wherein rings A and B are independently mono-, bicyclic or fused and optionally substituted with one to five substituents independently selected from halo, cyano, nitro, hydroxy, carboxy, C_{1-3} alkyl, C_{1-3} alkoxy, halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, hydroxy(C_{1-3})alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, $-C_{1-3}$ alkylene- NR^aR^b , $-CONR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SO_2NR^aR^b$, and L^A-W ;

L^A is independently selected from a bond, $-(CH_2)_p-$, $-CH_2O-$, $-C(O)-NH-$, $-C(O)-$, and $-CH_2C(O)NH-$, wherein p is 1 or 2;

25 W is independently selected from hydrogen, C_{1-3} alkyl, $-O(C_{1-4})$ alkyl, C_{3-7} cycloalkyl, 5- or 6-membered heteroaryl and 5- to 6-membered heterocycloalkyl ring containing one, two, or three heteroatoms independently selected from N, O, and S, wherein W is optionally substituted with up

to three substituents independently selected from halo, cyano, nitro, hydroxy, -NR^aR^b, carboxy, -CONR^aR^b, C₁₋₃alkyl, C₁₋₃alkoxy, halo(C₁₋₃)alkyl, halo(C₁₋₃)alkoxy, hydroxy(C₁₋₃)alkyl, cyano(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, -C(O)O(C₁₋₄)alkyl, and C₃₋₇cycloalkyl; and

R^a and R^b are each independently hydrogen, C₁₋₃ alkyl, or C₃₋₇ cycloalkyl;

5 or a pharmaceutically acceptable salt thereof.

2. A compound or a pharmaceutically acceptable salt thereof according to embodiment 1, wherein L¹ and L² are independently selected from -CH₂- and -CH(CH₃)-.

3. A compound or a pharmaceutically acceptable salt thereof according to embodiment 1 or 2, wherein L¹ and L² are both -CH₂-.

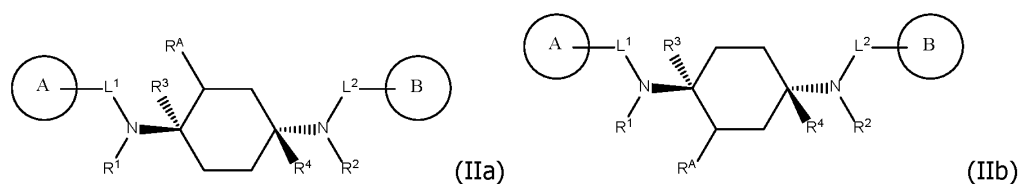
10 4. A compound or a pharmaceutically acceptable salt thereof according to any one of
embodiments 1 to 3, wherein R¹ and R² are independently selected from the group consisting of H
and methyl.

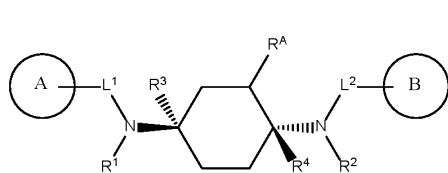
5. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 4, wherein R¹ and R² are both H.

15 6. A compound or a pharmaceutically acceptable salt thereof according to any one of
embodiments 1 to 5, wherein at least one R^A is selected from the group consisting of hydroxy,
methoxy, and halo.

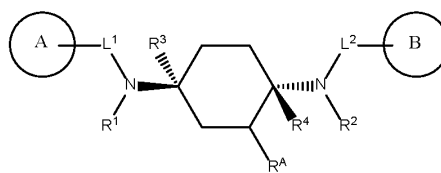
7. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 6, wherein n is 1.

20 8. A compound or a pharmaceutically acceptable salt thereof according to any one of
embodiments 1 to 6, wherein the compound has a structure selected from Formulae IIa-IIk

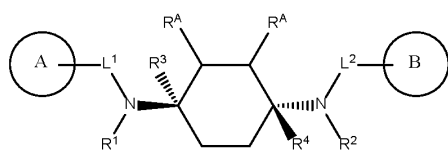




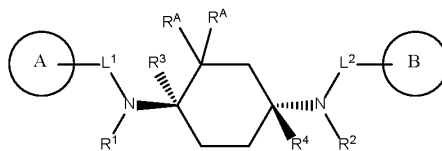
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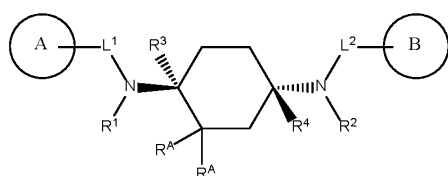
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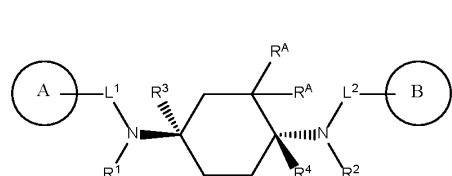
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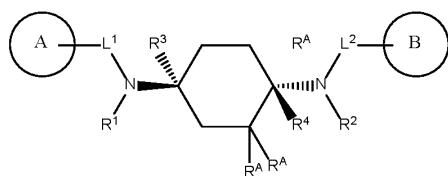
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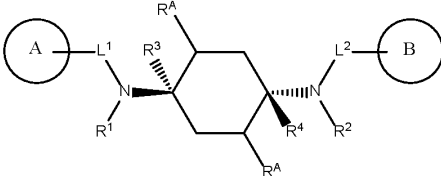
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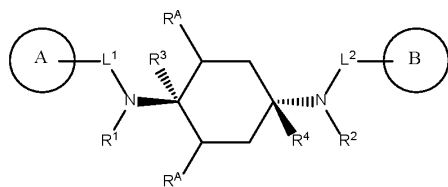
(IIh)



(IIi)



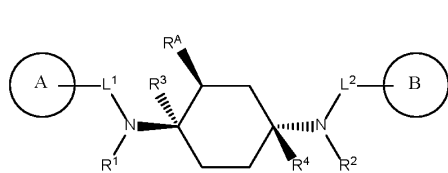
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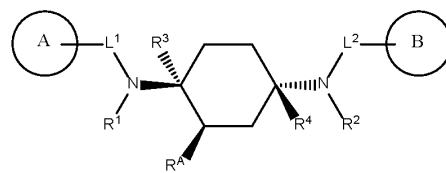
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5

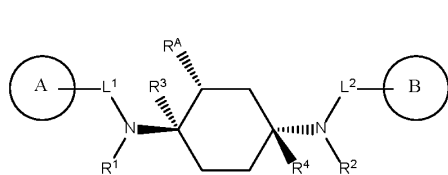
9. A compound or a pharmaceutically acceptable salt thereof according to embodiment 8, wherein the compound has a structure selected from Formulae IIIa-IIIj



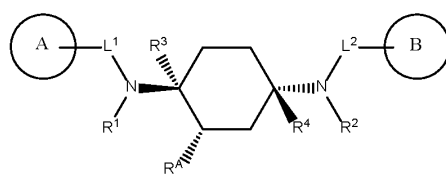
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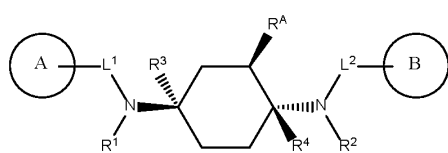
(IIIb)



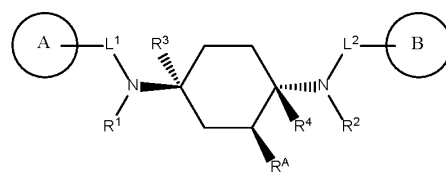
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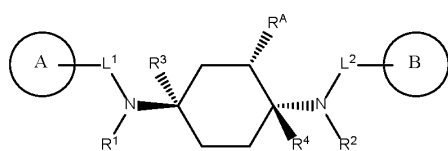
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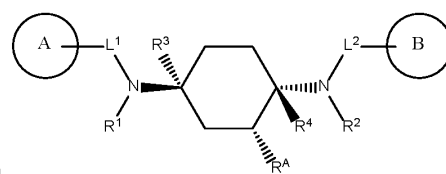
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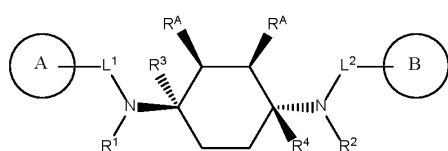
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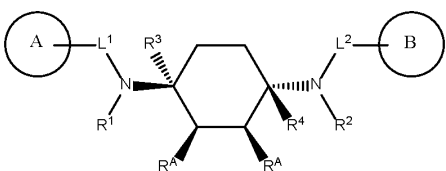
(IIIg)



(IIIh)



(IIIi)



(IIIj).

5 10. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 6, wherein n is 2.

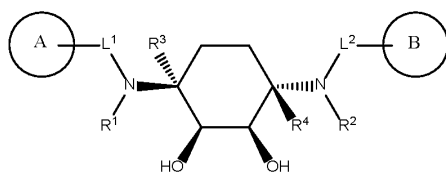
11. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 10, wherein R^A is selected from the group consisting of hydroxy, methoxy, and halo.

10 12. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 11, wherein R^A is hydroxy.

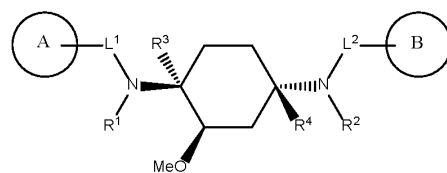
13. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 11, wherein R^A is methoxy.

15 14. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 11, wherein R^A is fluoro.

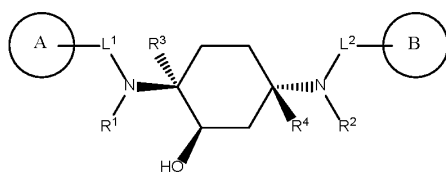
15. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 5, wherein the compound has a structure selected from Formulae IVa-IVn:



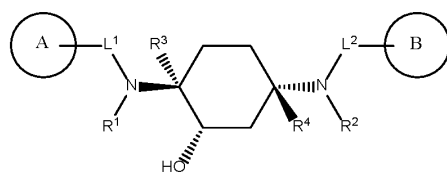
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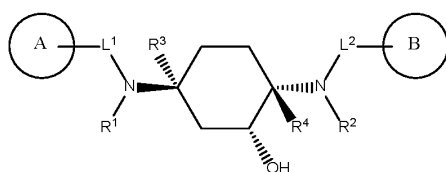
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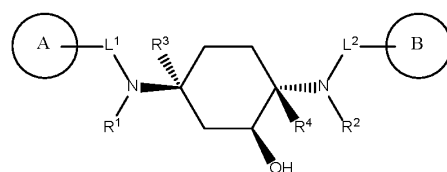
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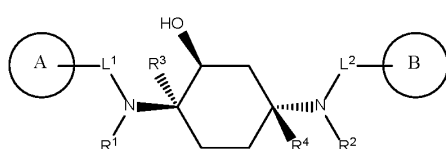
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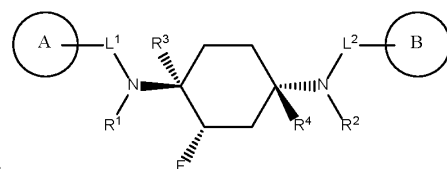
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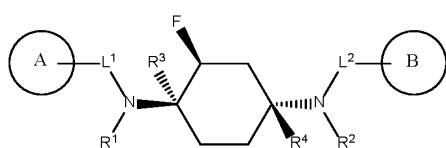
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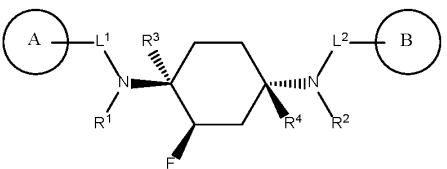
(IVg)



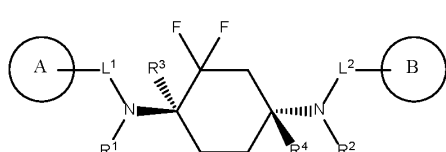
(IVh)



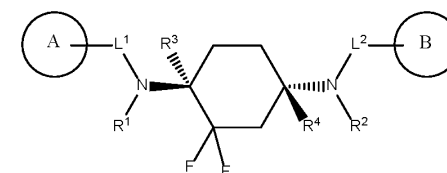
(IVi)



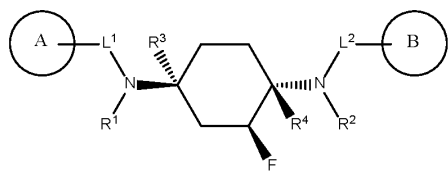
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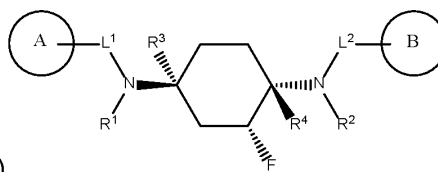
(IVk)



(IVl)

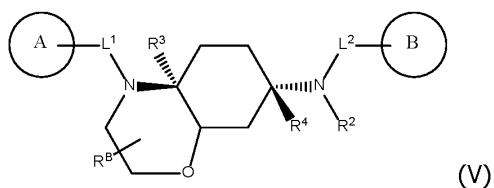


(IVm)



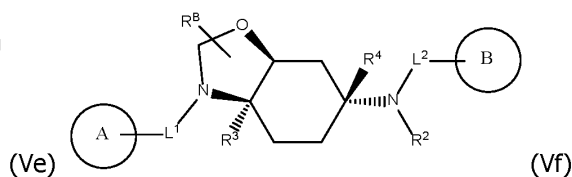
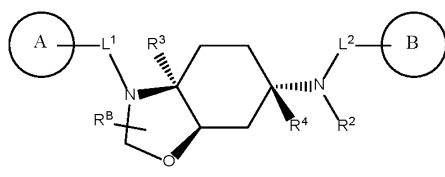
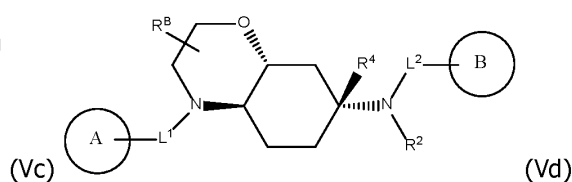
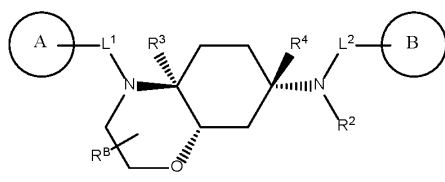
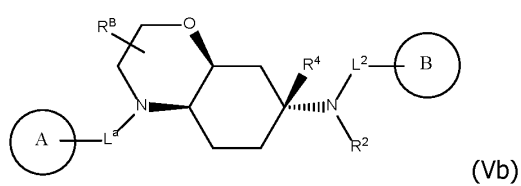
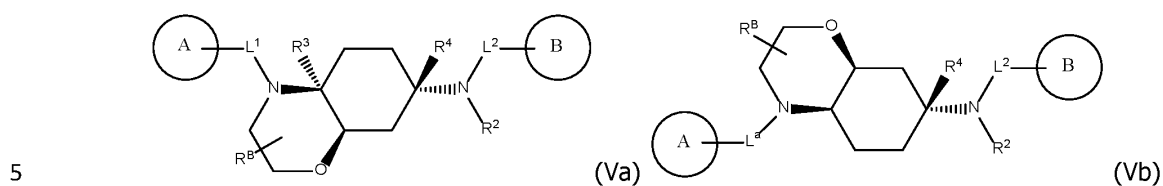
(IVn).

16. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 5, wherein the compound has a structure of Formula V:



wherein R^B is absent or C_{1-3} alkyl.

17. A compound or a pharmaceutically acceptable salt thereof according to embodiment 16, wherein the compound has a structure selected from Formulae Va to Vf:

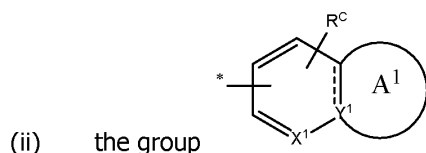


wherein R^B is absent or C_{1-3} alkyl.

18. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 17, wherein Ring A and Ring B are each independently selected from:

(i) phenyl or a 5 or 6-membered heteroaryl, optionally substituted with R^{1B} , R^{2B} and R^{3B} , wherein R^{1B} is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heterocycloalkyl, 5-membered heteroaryl, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$, and wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, cycloalkenyl, heterocycloalkyl, 5 membered heteroaryl, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, and $-COOR^{4B}$ may be optionally substituted with one to three substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-8} cycloalkyl, cycloalkenyl, heterocycloalkyl, cyano,

- hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$; wherein R^{2B} is C_{1-3} alkyl, C_{1-3} alkoxy, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$, and wherein the C_{1-3} alkyl and C_{1-3} alkoxy may be optionally substituted with one to three substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, and $-COOR^{4B}$; and
- 5 wherein R^{3B} is C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, halogen or cyano, wherein the C_{1-3} alkyl is optionally substituted with one or more substituents independently selected from hydroxy and halogen; wherein R^{4B} is hydrogen or C_{1-3} alkyl, and R^{5B} is hydrogen, C_{1-3} alkyl or C_{3-8} cycloalkyl, or R^{4B} and R^{5B} together with the nitrogen to which they are attached form a 5 to 6-membered ring containing one, two or three heteroatoms independently selected from N, O and S, and further wherein the ring may be
- 10 optionally substituted with one or more substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, cyano, hydroxy, oxo and halogen, wherein the C_{1-3} alkyl is optionally substituted with one or more substituents independently selected from hydroxy and halogen; or



- wherein X^1 is N, CH, or C(halo), Y^1 is C or N and Ring A^1 is a 5 or 6-membered ring which
- 15 optionally contains one or two heteroatoms independently selected from N, O and S, wherein R^C is hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, oxo, cyano, hydroxy, halogen or $-NR^{4B}R^{5B}$, and wherein the 5 or 6-membered ring may be optionally substituted with one, two or three substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, oxo, cyano, hydroxy, halogen and $-NR^{4B}R^{5B}$, wherein C_{1-3} alkyl is optionally substituted with one or more independently selected halogen substituents, wherein R^{4B} is
- 20 hydrogen or C_{1-3} alkyl, and R^{5B} is hydrogen, C_{1-3} alkyl or C_{3-8} cycloalkyl.

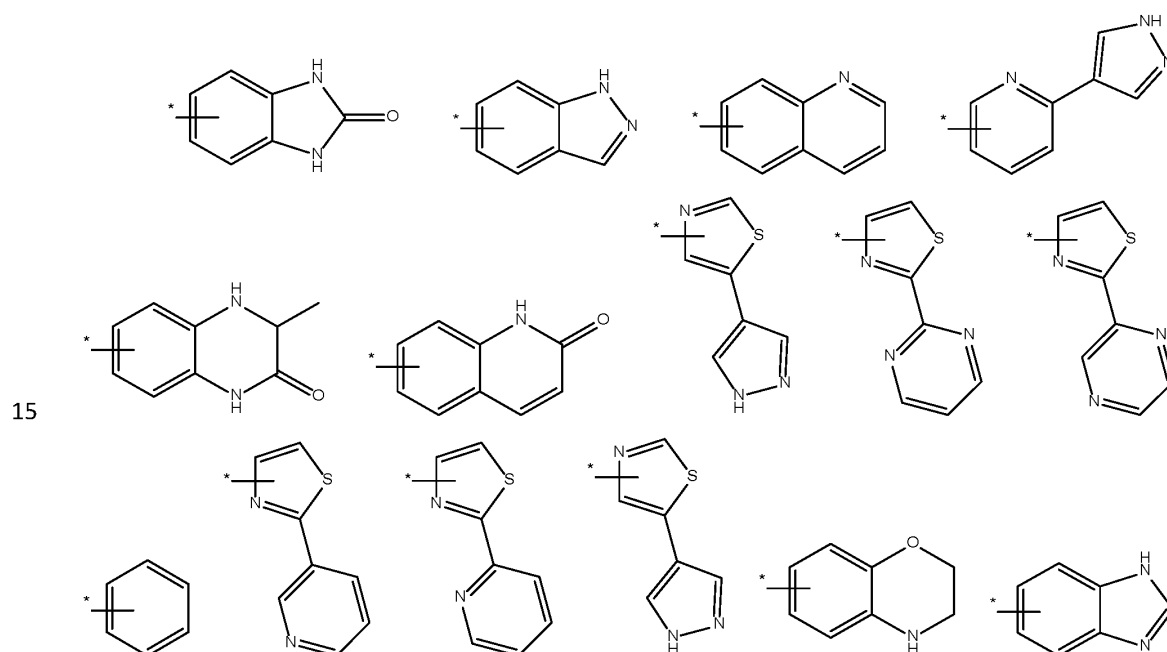
19. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiment 1 to 18, wherein Ring A and B are each independently selected from the group consisting of

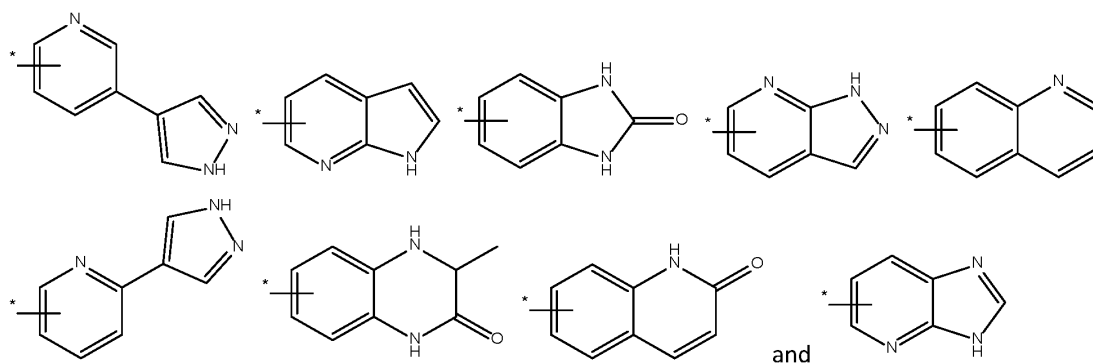
- thiazole, phenyl, indenyl, pyridinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, 4H-
- 25 1,2,4-triazolyl, thiazolyl, oxazolyl, indolyl, isoxazolyl, oxadiazolyl, thiadiazolyl (for example 1,3,4-thiadiazolyl), isothiazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, benzofuranyl, isobenzofuranyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydro-1H-benzo[d]imidazolyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxolyl, dihydrobenzodioxinyl, furopyridazinyl (such as furo[2,3-d]pyridazinyl), benzothienyl, indoliziny, indolyl, isoindolyl, dihydroindolyl, benzimidazolyl,
- 30 dihydrobenzimidazolyl, benzoxazolyl, dihydrobenzoxazolyl, benzthiazolyl, benzoisothiazolyl,

dihydrobenzothiazolyl, indazolyl, imidazopyridinyl, thienopyridinyl (such as thieno[3,2-b]pyridinyl),
 thienopyrimidinyl, pyrazolopyridyl, benzotriazolyl, triazolopyridinyl, purinyl, quinolinyl,
 tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinoxalyl,
 quinoxalyl, cinnolinyl, phthalazinyl, quinazolinyl, 1,5-naphthyridinyl, 1,6-naphthyridinyl, 1,7-
 5 naphthyridinyl, 1,8-naphthyridinyl, 3a,7a-dihydrobenzo[d][1,3]dioxolyl, 1,2-dihydroquinolinyl, indyl,
 indazyl, azaindolyl, pyrazole[1,5-a]pyrimidinyl, benzothiophenyl, 1,2-dihydropyrazolo[1,5-a]pyridinyl,
 and pteridinyl,

wherein Ring A and B are each independently optionally substituted with one to three
 substituents independently selected from halo, oxo, cyano, nitro, hydroxy, -NR^aR^b, carboxy, -CONR^aR^b,
 10 C₁₋₃alkyl, C₁₋₃alkoxy, halo(C₁₋₃)alkyl, halo(C₁₋₃)alkoxy, hydroxy(C₁₋₃)alkyl, cyano(C₁₋₃)alkyl, sulfonyl(C₁₋₃-
 3)alkyl, -C(O)O(C₁₋₄)alkyl, C₃₋₇cycloalkyl, and 5 or 6-membered heteroaryl.

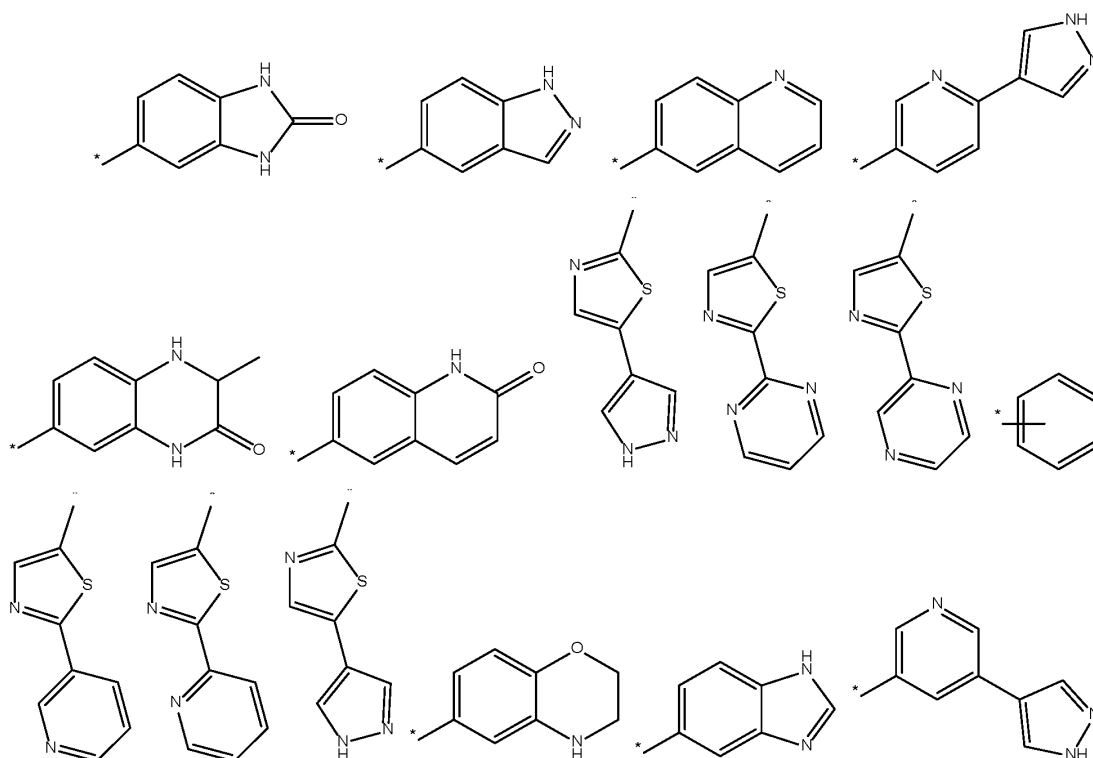
20. A compound or a pharmaceutically acceptable salt thereof according to any one of
 embodiments 1 to 19, wherein Ring A is selected from the group consisting of:

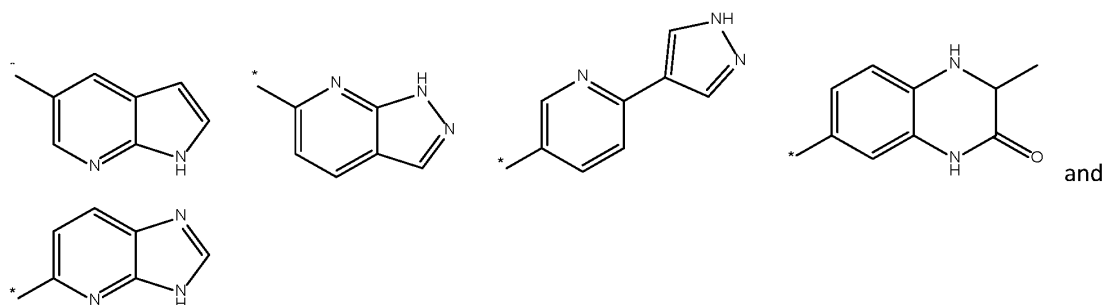




wherein Ring A is optionally substituted by halo, C_{1-5} alkyl, $-OC_{1-5}$ alkyl, $-OC_{1-5}$ haloalkyl, $-NR^{4B}R^{5B}$, wherein R^{4B} and R^{5B} are independently hydrogen or C_{1-3} alkyl.

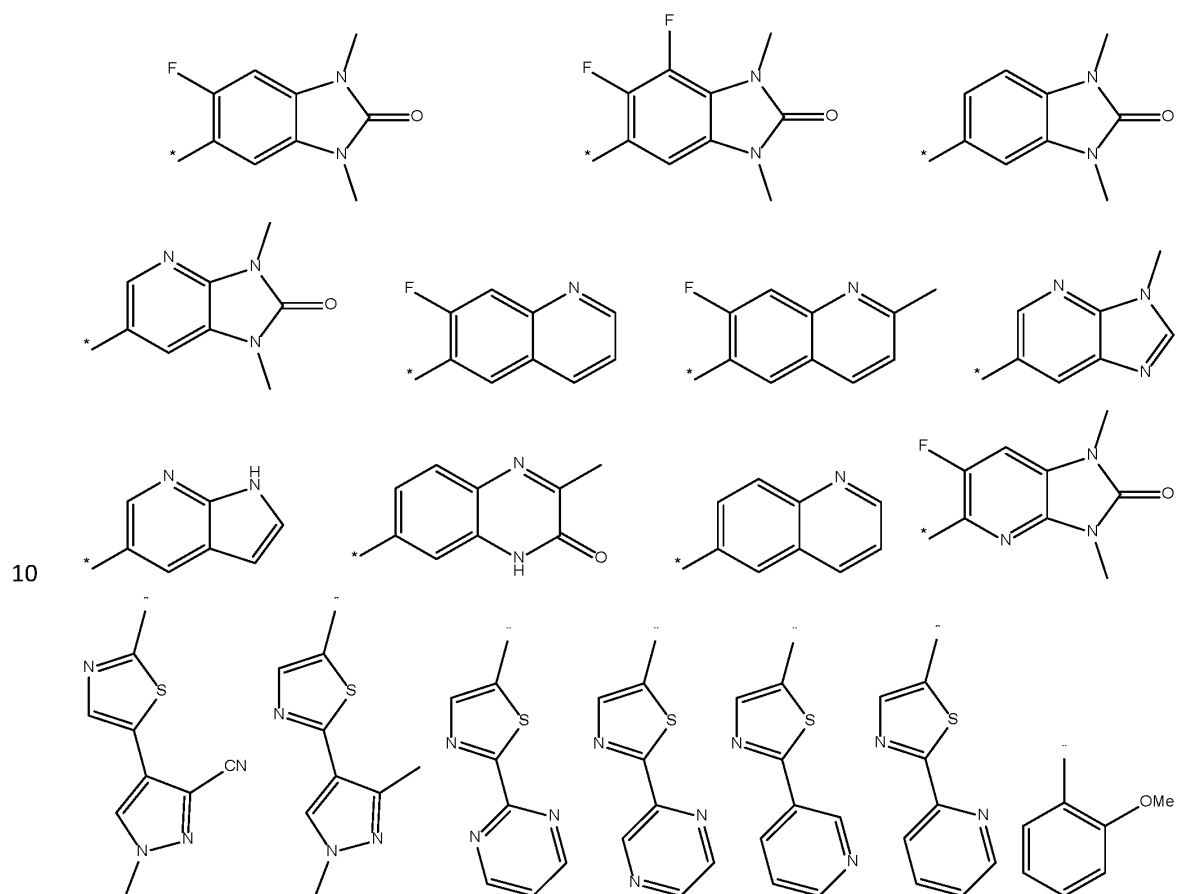
- 5 21. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 20, wherein Ring A is selected from the group consisting of:

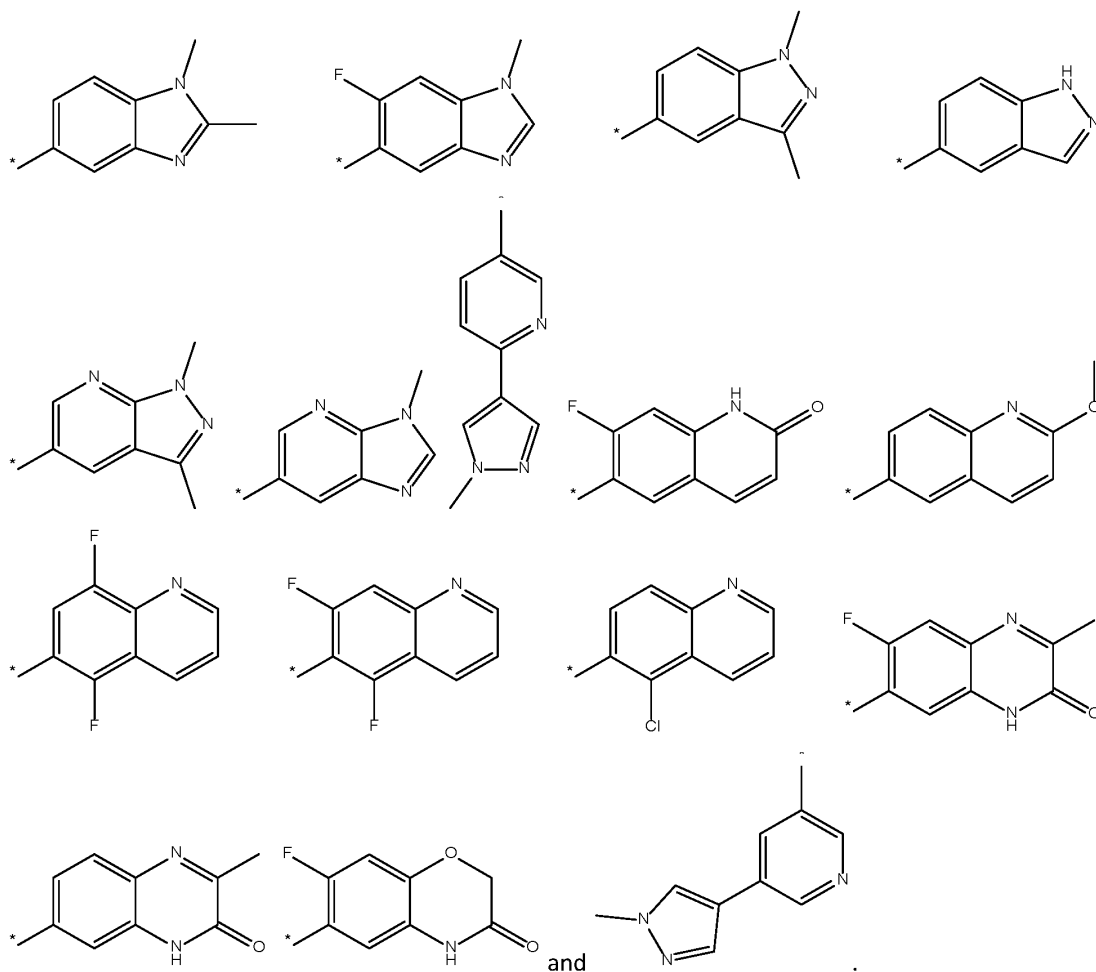




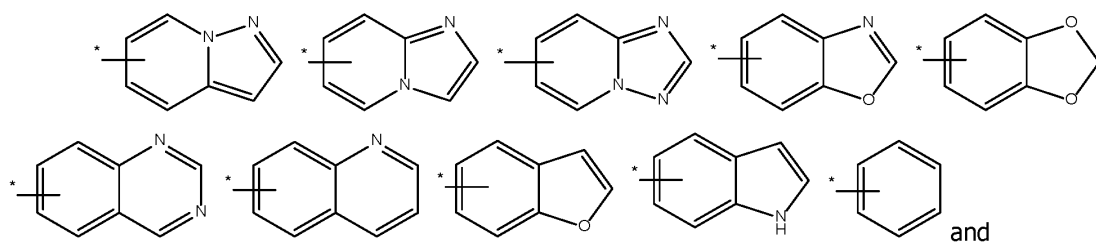
wherein Ring A is optionally substituted with one to five substituents each independently selected from the group consisting of halo, -C₁₋₅alkyl, -OC₁₋₅haloalkyl, and NR^{4B}R^{5B},
 5 wherein R^{4B} and R^{5B} are each independently hydrogen or C₁₋₃alkyl.

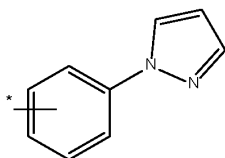
22. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 21, wherein Ring A is selected from the group consisting of:





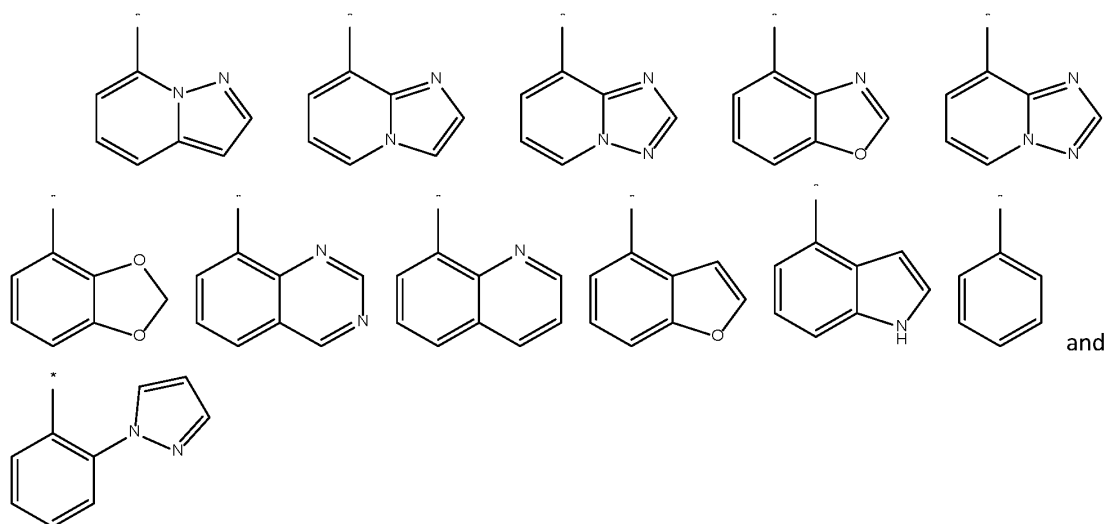
- 5 23. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 22, wherein Ring B is selected from the group consisting of:





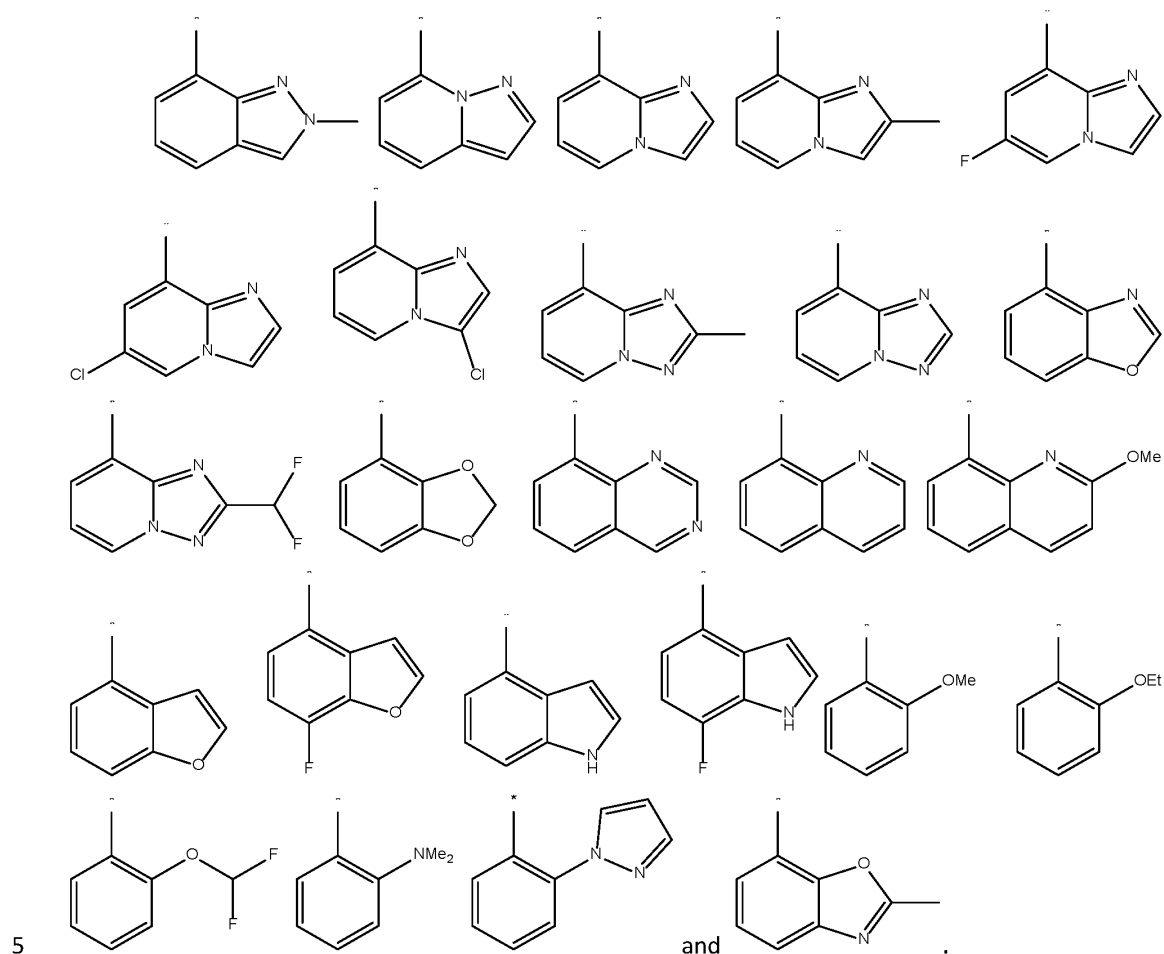
wherein Ring B is optionally substituted with one to five substituents each independently selected from the group consisting of halo, C_{1-5} alkyl, $-OC_{1-5}$ alkyl, $-OC_{1-5}$ haloalkyl, and $-NR^{4B}R^{5B}$, wherein R^{4B} are independently hydrogen or C_{1-3} alkyl.

- 5 24. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 23, wherein Ring B is selected from the group consisting of:



- 10 wherein Ring B is optionally substituted by one to five substituents each independently selected from the group consisting of halo, $-C_{1-5}$ alkyl, $-OC_{1-5}$ alkyl, $-OC_{1-5}$ haloalkyl, $-NR^{4B}R^{5B}$, wherein R^{4B} are independently hydrogen or C_{1-3} alkyl.

25. A compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 24, wherein Ring B is selected from the group consisting of:



26. A compound selected from the group consisting of:

5-((((1S,2S,3R,4S)-2,3-Dihydroxy-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

10 5-((((1R,2R,3S,4R)-2,3-Dihydroxy-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

(1R,2S,3S,6S)-3-(((7-Fluoroquinolin-6-yl)methyl)amino)-6-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexane-1,2-diol;

- (1S,2R,3R,6R)-3-(((7-Fluoroquinolin-6-yl)methyl)amino)-6-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexane-1,2-diol
- (1S,2R,3S,6S)-3-((2-Methoxybenzyl)amino)-6-((quinolin-6-ylmethyl)amino)cyclohexane-1,2-diol;
- 5 (1R,2S,3R,6R)-3-((2-Methoxybenzyl)amino)-6-((quinolin-6-ylmethyl)amino)cyclohexane-1,2-diol;
- 5-Fluoro-6-((((1S,2R,4S)-2-methoxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 10 (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)(methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol;
- (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((2-methyl-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)cyclohexan-1-ol;
- 15 (1R,2S,5S)-5-((benzo[d]oxazol-4-ylmethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-5-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-2-(((6-Fluoroquinolin-7-yl)methyl)amino)-5-(((2-methoxyquinolin-8-yl)methyl)amino)cyclohexan-1-ol;
- 20 (1R,2S,5S)-5-((2-(1H-Pyrazol-1-yl)benzyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- 5-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-((quinazolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 25 5-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-(((2-methylbenzo[d]oxazol-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-Fluoro-6-((((1S,2R,4S)-4-(((6-fluoroimidazo[1,2-a]pyridin-8-yl)methyl)amino)-2-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

- 6-((((1S,2R,4S)-4-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-hydroxycyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,5S)-2-(((8-Fluoro-2-methylquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- 5 5-Fluoro-6-((((1S,3R,4S)-3-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 7-((((1S,2R,4S)-4-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-hydroxycyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;
- 10 5-((((1R,2S,4R)-4-((2-(Difluoromethoxy)benzyl)amino)-2-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1S,2S,4S)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1S,2S,4S)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- 15 (1S,2S,5S)-5-(((7-fluoroquinolin-6-yl)methyl)amino)-2-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- 5-((((1S,2S,4S)-2-Hydroxy-4-((quinolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 20 6-fluoro-5-((((1R,2S,4S)-2-fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- 5-Fluoro-6-((((1R,3S,4R)-3-hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 4-(5-((((1S,2R,4S)-2-Hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-thiazol-2-yl)-1-methyl-1H-pyrazole-3-carbonitrile;
- 25 5-Fluoro-6-((((1R,2R,4R)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,5S)-5-((2-Methoxybenzyl)amino)-2-((quinolin-8-ylmethyl)amino)cyclohexan-1-ol;

- (1S,2R,5R)-2-(((1,2-Dimethyl-1H-benzo[d]imidazol-5-yl)methyl)amino)-5-((2-methoxybenzyl)amino)cyclohexan-1-ol;
- (1S,2R,5R)-2-(((1,3-Dimethyl-1H-indazol-5-yl)methyl)amino)-5-((2-methoxybenzyl)amino)cyclohexan-1-ol;
- 5 5-(((4aR,7R,8aS)-7-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((4aS,7R,8aR)-7-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 10 1,3-Dimethyl-5-(((4aR,7R,8aS)-7-((quinolin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-Fluoro-6-(((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((1R,2S,4R)-4-((Benzo[d][1,3]dioxol-4-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 15 5-(((1R,2S,4R)-4-((2-(Dimethylamino)benzyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((1R,2S,4R)-4-((6-Chloroimidazo[1,2-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((1R,2S,4R)-4-((3-Chloroimidazo[1,2-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 20 5-(((1R,2S,4R)-2-Fluoro-4-((2-methylimidazo[1,2-a]pyridin-8-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-(((1R,2S,4R)-4-((2-(Difluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 25 5-(((1R,4R)-2,2-Difluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,4R)-2,2-Difluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)cyclohexane-1,4-diamine;

(1R,4R)-2,2-Difluoro-N¹-((7-Fluoroquinolin-6-yl)methyl)-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;

7-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-quinolin-2(1H)-one;

5 (1R,2S,5S)-5-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)-2-(((2-methoxyquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((5,8-Difluoroquinolin-6-yl)methyl)amino)-5-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

10 (1R,2S,5S)-2-(((5,7-Difluoroquinolin-6-yl)methyl)amino)-5-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((5-Chloroquinolin-6-yl)methyl)amino)-5-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

6-fluoro-7-((((1S,2R,4S)-2-hydroxy-4-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;

15 (1R,2S,5S)-2-(((2-(1,3-Dimethyl-1H-pyrazol-4-yl)thiazol-5-yl)methyl)amino)-5-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-((2-methyl-2H-indazol-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

20 5-((((1S,3S,4S)-4-(((3a,7a-Dihydrobenzo[d]oxazol-4-yl)methyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,2S,4R)-2-Fluoro-4-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)-methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-((((1R,2S,4R)-2-Fluoro-4-(pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

25 (1R,2S,4R)-2-Fluoro-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)-N¹-((2-(pyrimidin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;

7-((((1R,2S,4R)-2-Fluoro-4-(pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)quinazoline-2,4(1H,3H)-dione;

- (1R,2S,4R)-2-Fluoro-N¹-((2-(pyrazin-2-yl)thiazol-5-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;
- (1R,2S,4R)-2-Fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((2-(pyridin-3-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 5 (1R,2S,4R)-N¹-((1,3-Dimethyl-1H-pyrazolo[3,4-b]pyridin-6-yl)methyl)-2-fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;
- 6-Fluoro-5-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,4R)-2-Fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((2-(pyridin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 10 (1R,2S,4R)-4-(((1,2,4-Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,4R)-N⁴-([1,2,4-Triazolo[1,5-a]pyridin-8-ylmethyl)-2-fluoro-N¹-((2-(pyrazin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 15 6-((((1S,2R,4S)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- 7-((((1S,2R,4S)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;
- 5-((((1S,2R,4S)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 20 7-fluoro-6-((((1S,2R,4S)-2-fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one;
- (1S,2R,4S)-2-fluoro-N¹-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;
- 25 (1S,2R,4S)-2-fluoro-N¹-((6-fluoro-1-methyl-1H-benzo[d]imidazol-5-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;
- 5-((((1R,4R)-4-((Benzo[d]oxazol-4-ylmethyl)amino)-2,2-difluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

- 5-((((1R,4R)-2,2-difluoro-4-(((7-fluorobenzofuran-4-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,4R)-2,2-difluoro-4-(((7-fluoro-1H-indol-4-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,4R)-2,2-Difluoro-4-((quinolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-4-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,4R)-2-Fluoro-N¹-((7-fluoroquinolin-6-yl)methyl)-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;
- 4,5-Difluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1S,3R,4S)-4-((2-Ethoxybenzyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1S,2R,4S)-N¹-(2-Ethoxybenzyl)-2-fluoro-N⁴-((3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)methyl)cyclohexane-1,4-diamine;
- (1S,2R,4S)-N⁴-((1H-Pyrrolo[2,3-b]pyridin-5-yl)methyl)-N¹-(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine;
- (1S,2R,4S)-N⁴-((1H-Indazol-5-yl)methyl)-N¹-(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine;
- 5-((((1S,3S,4S)-3-Fluoro-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-(((R)-1-(pyrazolo[1,5-a]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(pyrazolo[1,5-a]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-5-(((R)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-5-(((S)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-5-(((R)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

5 (1R,2S,5S)-5-(((S)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

10 (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

15 5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

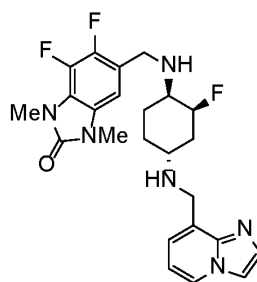
20 5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one; and

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl-d₂)amino)cyclohexan-1-ol;

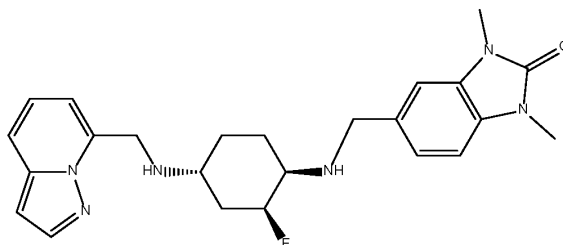
25 or a pharmaceutically acceptable salt thereof.

27. A compound which is 4,5-Difluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure



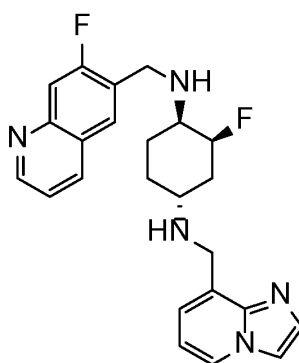
or a pharmaceutically acceptable salt thereof.

28. A compound which is 5-((((1R,2S,4R)-2-fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzimidazol-2-one as
5 represented by the following structure:



or a pharmaceutically acceptable salt thereof.

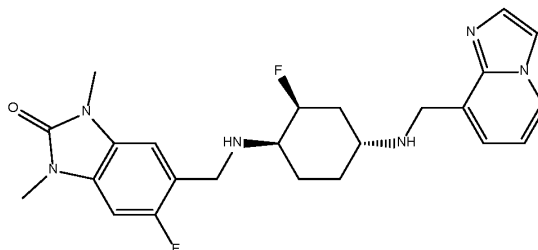
29. A compound which is (1R,2S,4R)-2-Fluoro-N-((7-fluoroquinolin-6-yl)methyl)-N-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine as represented by the following structure



10

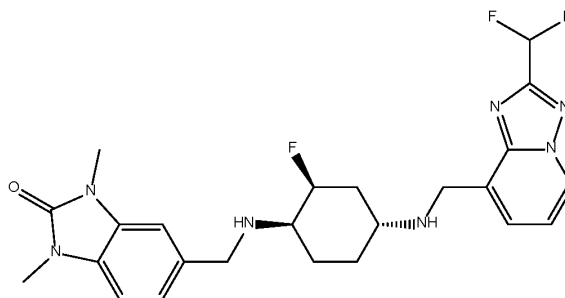
or a pharmaceutically acceptable salt thereof.

30. A compound which is 5-fluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



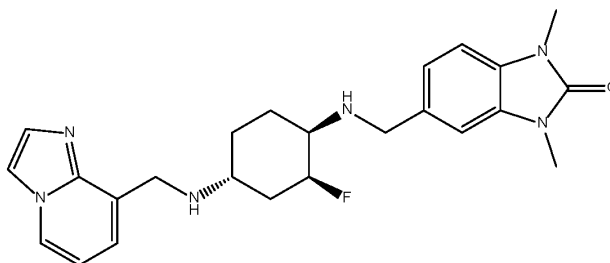
5 or a pharmaceutically acceptable salt thereof.

31. A compound which is 5-((((1R,2S,4R)-4-(((2-(difluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



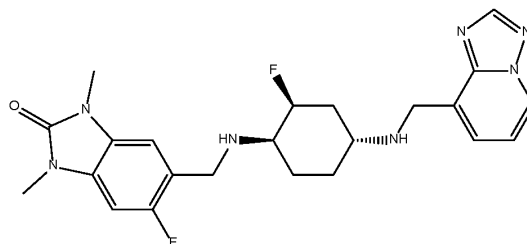
10 or a pharmaceutically acceptable salt thereof.

32. A compound which is 5-((((1R,2S,4R)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)-methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



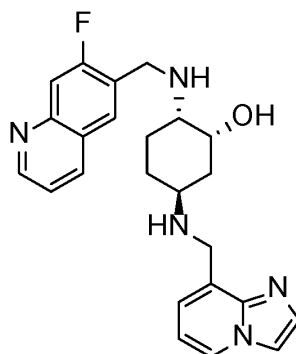
5 or a pharmaceutically acceptable salt thereof.

33. A compound which is 5-((((1R,2S,4R)-4-(((1,2,4]triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



10 or a pharmaceutically acceptable salt thereof.

34. A compound which is (1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol as represented by the following structure:



or a pharmaceutically acceptable salt thereof.

35. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 34 and a pharmaceutically acceptable excipient.

36. A compound or a pharmaceutically acceptable salt thereof of any one of embodiments 1 to 34 or the pharmaceutical composition of embodiment 35 for use in therapy.

5 37. A compound or pharmaceutically acceptable salt thereof of any one of embodiments 1 to 34 or a pharmaceutical composition of embodiment 35 for use in the treatment of cancer.

38. A compound or pharmaceutically acceptable salt thereof of any one of embodiments 1 to 34 or a pharmaceutical composition of embodiment 35 for use in the treatment of cancer, wherein the cancer is characterized by MSI-H and/or dMMR.

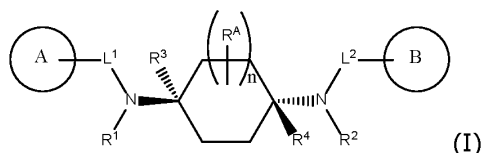
10 39. A method of treatment of cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt thereof according to any one of embodiments 1 to 34 or a pharmaceutical composition according to embodiment 35.

15 40. A method of treatment of cancer according to embodiment 39, wherein the cancer is characterized by MSI-H and/or dMMR.

41. Use of a compound or pharmaceutically acceptable salt thereof of any one of embodiments 1 to 34 or a pharmaceutical composition of embodiment 35, in the manufacture of a medicament for use in the treatment of cancer.

CLAIMS

1. A compound of Formula (I):



wherein:

5 R^1 and R^2 are each independently selected from hydrogen, C_{1-3} alkyl, halo(C_{2-3})alkyl, $-CH_2-C_5$ -aryl wherein the C_5 -aryl is optionally substituted with C_{1-3} alkoxy;

R^3 and R^4 are each independently selected from hydrogen or C_{1-3} alkyl;

n is an integer selected from 1 to 3;

R^A is independently selected from C_{1-2} alkyl, halo, $-NR^aR^b$, hydroxy, carboxy, halo(C_{1-3})alkyl, hydroxy(C_{1-3})alkyl, methoxy(C_{1-3})alkyl, C_{1-3} alkoxy, and halo(C_{1-3})alkoxy, or R^A and R^1 are taken together to form a nitrogen containing 5- or 6- membered ring which optionally contains one or two heteroatoms independently selected from N, O, and S and is optionally substituted with C_{1-2} alkyl;

10

L^1 and L^2 are each independently selected from a C_{1-2} alkylene optionally substituted with one or two substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy(C_{1-3})alkyl, halo(C_{1-3})alkyl, and cyano;

15

Ring A and B are each independently selected from C_{5-14} aryl or C_{5-14} heteroaryl containing one, two, or three heteroatoms independently selected from N, O, and S, wherein rings A and B are independently mono-, bicyclic or fused and optionally substituted with one to five substituents independently selected from halo, cyano, nitro, hydroxy, carboxy, C_{1-3} alkyl, C_{1-3} alkoxy, halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, hydroxy(C_{1-3})alkyl, C_2 -alkenyl, C_2 -alkynyl, $-C_{1-3}$ alkylene- NR^aR^b , $-CONR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-SO_2NR^aR^b$, and L^A-W ;

20

L^A is independently selected from a bond, $-(CH_2)_p-$, $-CH_2O-$, $-C(O)-NH-$, $-C(O)-$, and $-CH_2C(O)NH-$, wherein p is 1 or 2;

W is independently selected from hydrogen, C_{1-3} alkyl, $-O(C_{1-4})$ alkyl, C_{3-7} cycloalkyl, 5- or 6-membered heteroaryl and 5- to 6-membered heterocycloalkyl ring containing one, two, or three heteroatoms independently selected from N, O, and S, wherein W is optionally substituted with up to three substituents independently selected from halo, cyano, nitro, hydroxy, $-NR^aR^b$, carboxy, -

25

CONR^aR^b, C₁₋₃alkyl, C₁₋₃alkoxy, halo(C₁₋₃)alkyl, halo(C₁₋₃)alkoxy, hydroxy(C₁₋₃)alkyl, cyano(C₁₋₃)alkyl, sulfonyl(C₁₋₃)alkyl, -C(O)O(C₁₋₄)alkyl, and C₃₋₇cycloalkyl; and

R^a and R^b are each independently hydrogen, C₁₋₃ alkyl, or C₃₋₇ cycloalkyl;

or a pharmaceutically acceptable salt thereof.

5

2. A compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein L¹ and L² are independently selected from -CH₂- and -CH(CH₃)-.

3. A compound or a pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein
10 L¹ and L² are both -CH₂-.

4. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein R¹ and R² are independently selected from the group consisting of H and methyl.

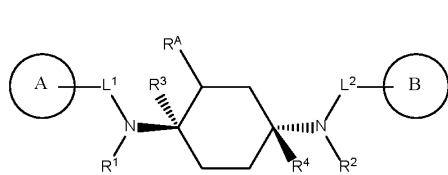
15 5. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein R¹ and R² are both H.

6. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein at least one R^A is selected from the group consisting of hydroxy, methoxy, and halo.

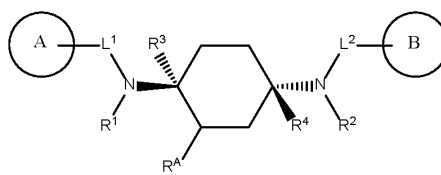
20

7. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein n is 1.

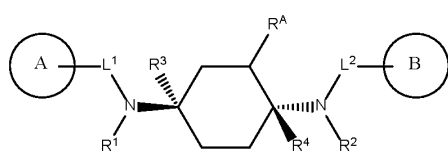
8. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1
25 to 6, wherein the compound has a structure selected from Formulae IIa-IIk



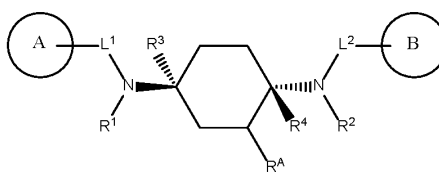
(IIa)



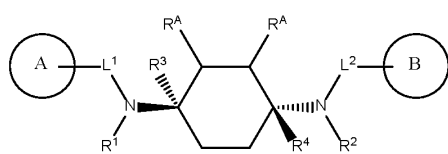
(IIb)



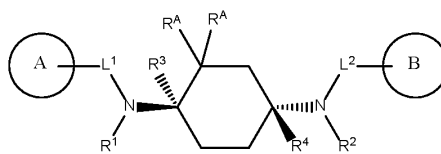
(IIc)



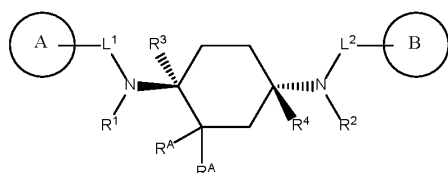
(IIId)



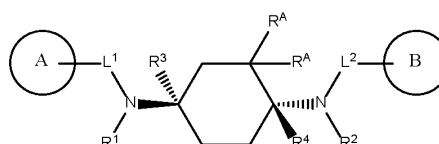
(IIe)



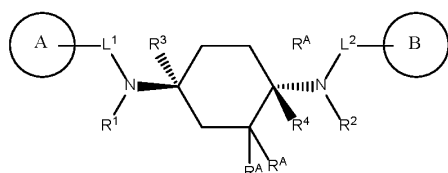
(IIIf)



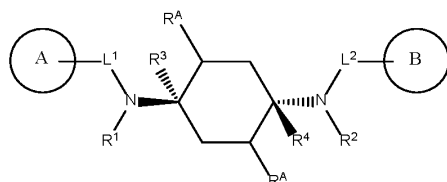
(IIg)



(IIh)

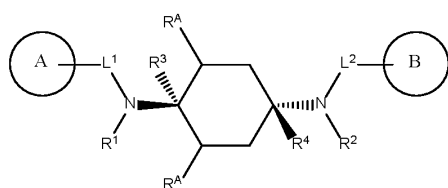


(IIi)



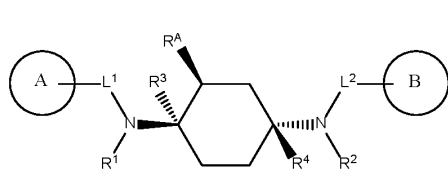
(IIj)

5

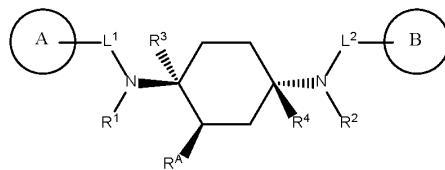


(IIk).

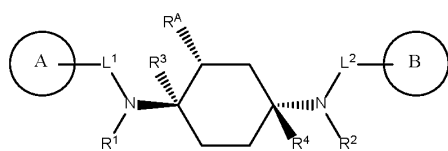
9. A compound or a pharmaceutically acceptable salt thereof according to claim 8, wherein the compound has a structure selected from Formulae IIIa-IIIj



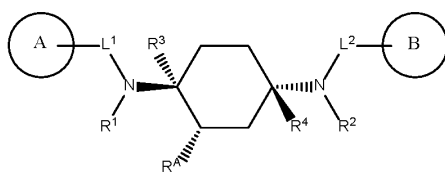
(IIIa)



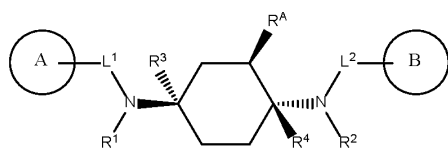
(IIIb)



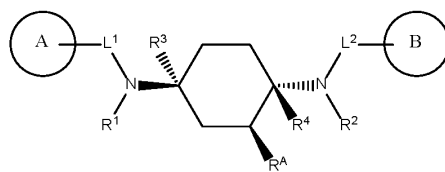
(IIIc)



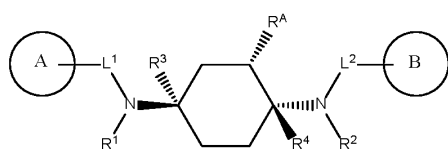
(IIIId)



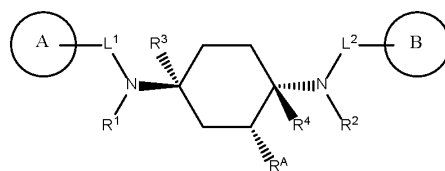
(IIIe)



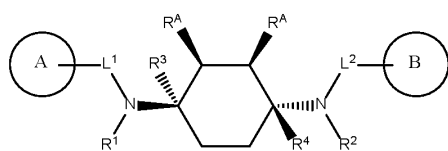
(IIIIf)



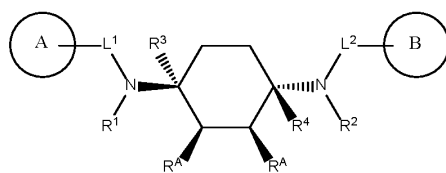
(IIIg)



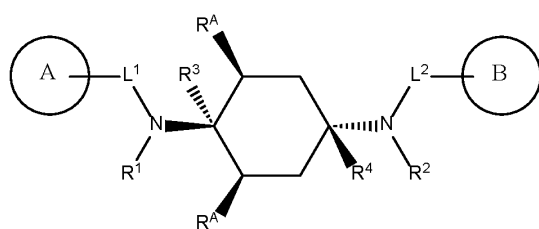
(IIIh)



(IIIi)



(IIIj)



(IIIk).

10. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein n is 2.

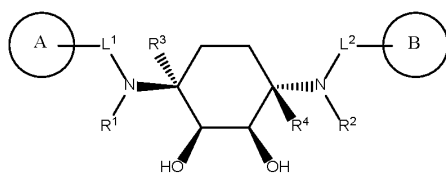
11. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 10, wherein R^A is selected from the group consisting of hydroxy, methoxy, and halo.

12. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 11, wherein R^A is hydroxy.

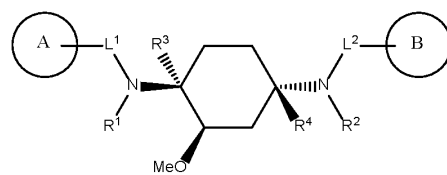
13. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 11, wherein R^A is methoxy.

14. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 11, wherein R^A is fluoro.

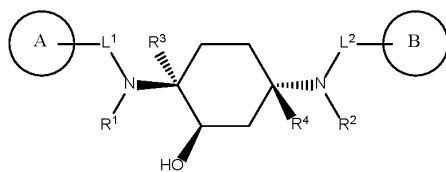
15. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein the compound has a structure selected from Formulae IVa-IVo:



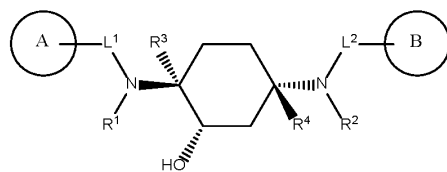
(IVa)



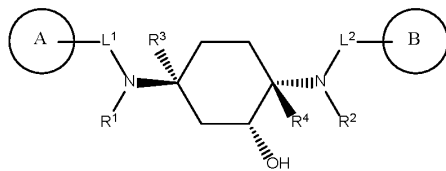
(IVb)



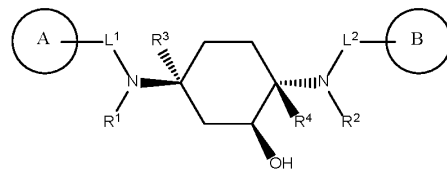
(IVc)



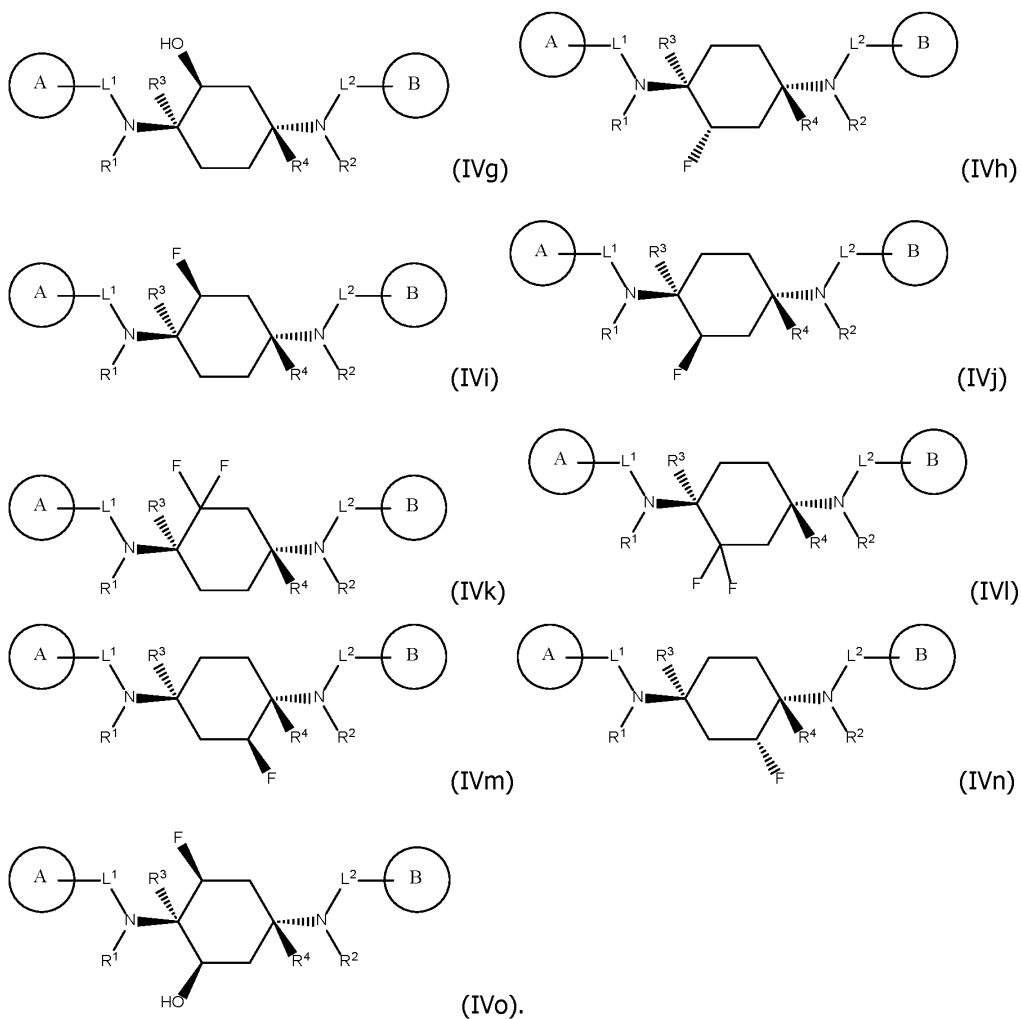
(IVd)



(IVe)

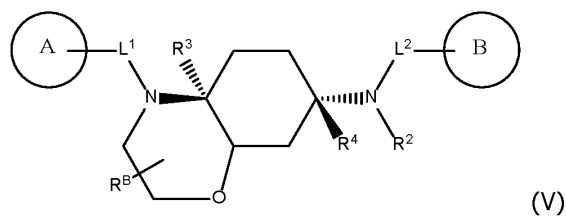


(IVf)



5

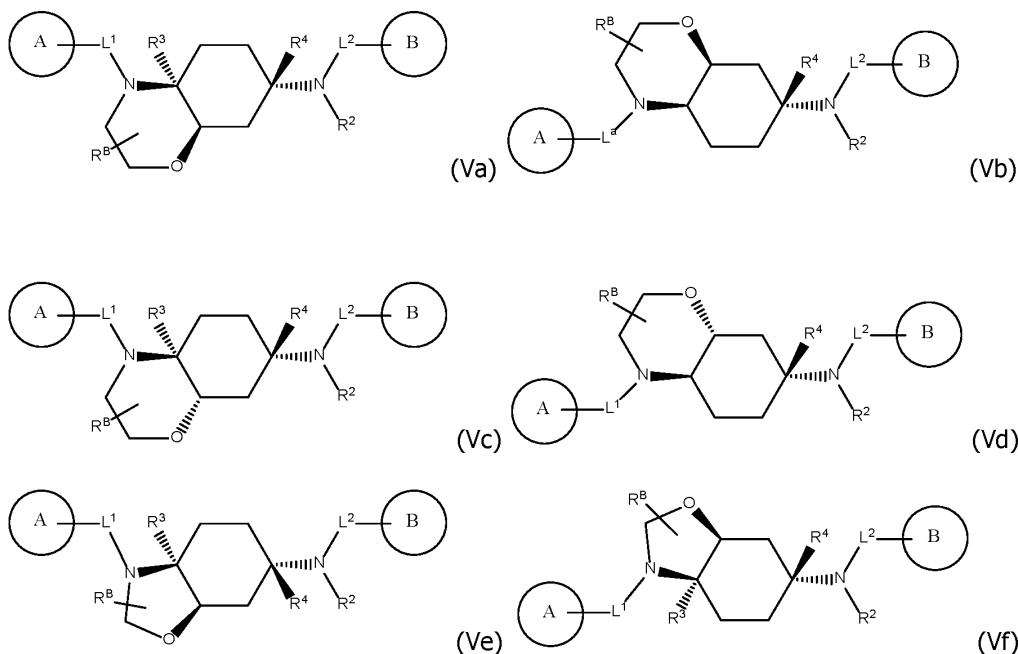
16. A compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein the compound has a structure of Formula V:



10

wherein R^B is absent or C_{1-3} alkyl.

17. A compound or a pharmaceutically acceptable salt thereof according to claim 16, wherein the compound has a structure selected from Formulae Va to Vf:

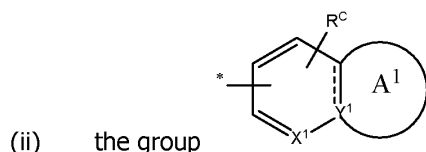


wherein R^B is absent or C_{1-3} alkyl.

18. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 17, wherein Ring A and Ring B are each independently selected from:

- (i) phenyl or a 5 or 6-membered heteroaryl, optionally substituted with R^{1B} , R^{2B} and R^{3B} , wherein R^{1B} is C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, heterocycloalkyl, 5-membered heteroaryl, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$, and wherein the C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, cycloalkenyl, heterocycloalkyl, 5 membered heteroaryl, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, and $-COOR^{4B}$ may be optionally substituted with one to three substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, C_{3-8} cycloalkyl, cycloalkenyl, heterocycloalkyl, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$; wherein R^{2B} is C_{1-3} alkyl, C_{1-3} alkoxy, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, $-COOR^{4B}$, and wherein the C_{1-3} alkyl and C_{1-3} alkoxy may be optionally substituted with one to three substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, cyano, hydroxy, halogen, $-NR^{4B}R^{5B}$, $-CONR^{4B}R^{5B}$, $-NR^{4B}COR^{5B}$, and $-COOR^{4B}$; and

- wherein R^{3B} is C_{1-3} alkyl, C_{1-3} alkoxy, hydroxy, halogen or cyano, wherein the C_{1-3} alkyl is optionally substituted with one or more substituents independently selected from hydroxy and halogen; wherein R^{4B} is hydrogen or C_{1-3} alkyl, and R^{5B} is hydrogen, C_{1-3} alkyl or C_{3-8} cycloalkyl, or R^{4B} and R^{5B} together with the nitrogen to which they are attached form a 5 to 6-membered ring containing one, two or three heteroatoms independently selected from N, O and S, and further wherein the ring may be optionally substituted with one or more substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, cyano, hydroxy, oxo and halogen, wherein the C_{1-3} alkyl is optionally substituted with one or more substituents independently selected from hydroxy and halogen; or



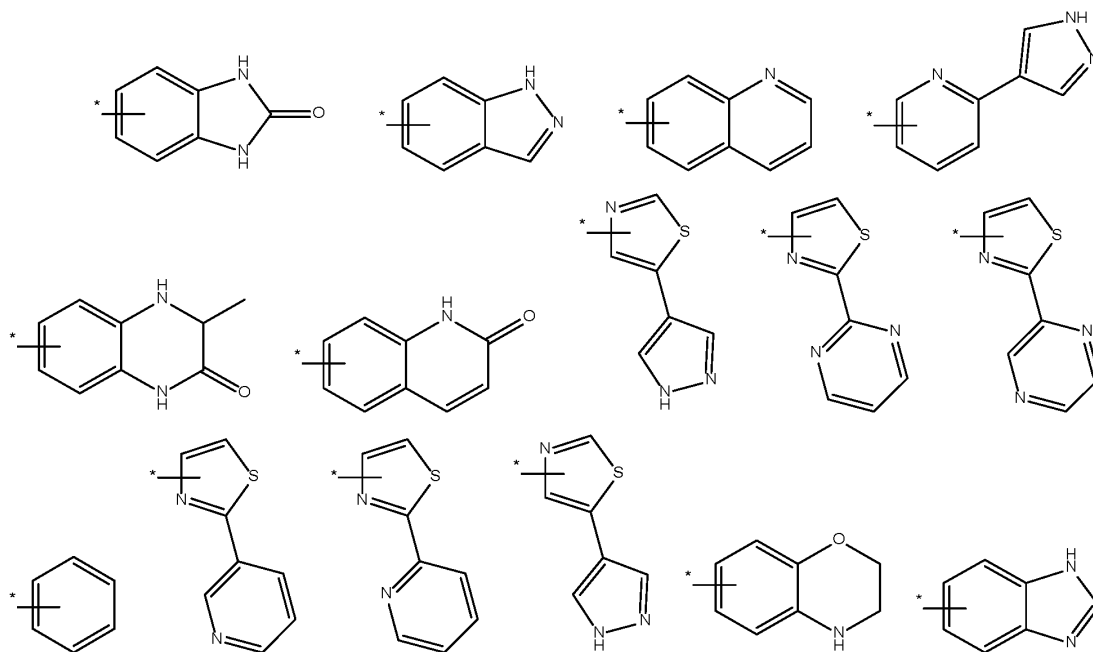
- wherein X^1 is N, CH, or C(halo), Y^1 is C or N and Ring A^1 is a 5 or 6-membered ring which optionally contains one or two heteroatoms independently selected from N, O and S, wherein R^C is hydrogen, C_{1-3} alkyl, C_{1-3} alkoxy, oxo, cyano, hydroxy, halogen or $-NR^{4B}R^{5B}$, and wherein the 5 or 6-membered ring may be optionally substituted with one, two or three substituents independently selected from C_{1-3} alkyl, C_{1-3} alkoxy, oxo, cyano, hydroxy, halogen and $-NR^{4B}R^{5B}$, wherein C_{1-3} alkyl is optionally substituted with one or more independently selected halogen substituents, wherein R^{4B} is hydrogen or C_{1-3} alkyl, and R^{5B} is hydrogen, C_{1-3} alkyl or C_{3-8} cycloalkyl.

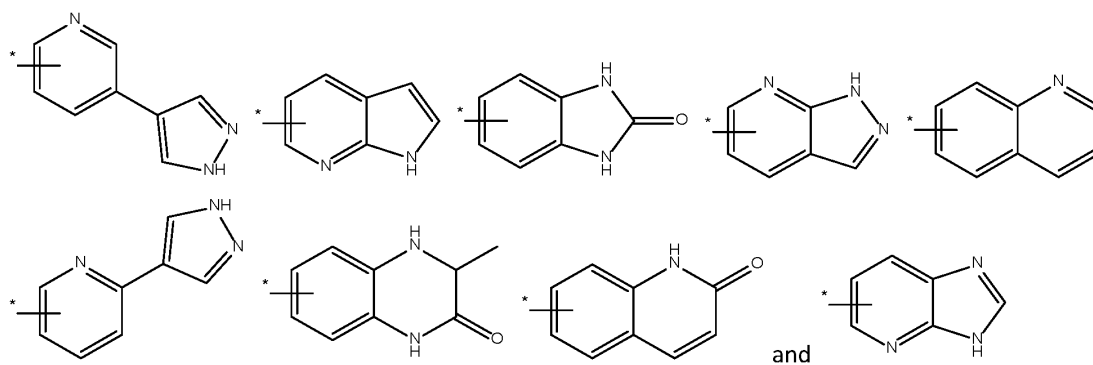
19. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 18, wherein Ring A and B are each independently selected from the group consisting of
- thiazole, phenyl, indenyl, pyridinyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, 4H-1,2,4-triazolyl, thiazolyl, oxazolyl, indolinyl, isoxazolyl, oxadiazolyl, thiadiazolyl (for example 1,3,4-thiadiazolyl), isothiazolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, triazinyl, benzofuranyl, isobenzofuranyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydro-1H-benzo[d]imidazolyl, 2,3-dihydrobenzofuryl, 1,3-benzodioxolyl, dihydrobenzodioxinyl, furopyridazinyl (such as furo[2,3-d]pyridazinyl), benzothienyl, indolizinyl, indolyl, isoindolyl, dihydroindolyl, benzimidazolyl, dihydrobenzimidazolyl, benzoxazolyl, dihydrobenzoxazolyl, benzthiazolyl, benzoisothiazolyl, dihydrobenzoisothiazolyl, indazolyl, imidazopyridinyl, thienopyridinyl (such as thieno[3,2-b]pyridinyl), thienopyrimidinyl, pyrazolopyridyl, benzotriazolyl, triazolopyridinyl, purinyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinoxalyl,

quinoxaliny, cinnoliny, phthalaziny, quinazoliny, 1,5-naphthyridiny, 1,6-naphthyridiny, 1,7-naphthyridiny, 1,8-naphthyridiny, 3a,7a-dihydrobenzo[d][1,3]dioxoly, 1,2-dihydroquinoliny, indyl, indazyl, azaindolyl, pyrazole[1,5-a]pyrimidinyl, benzothiophenyl, 1,2-dihydropyrazolo[1,5-a]pyridiny, and pteridinyl,

- 5 wherein Ring A and B are each independently optionally substituted with one to three substituents independently selected from halo, oxo, cyano, nitro, hydroxy, $-NR^aR^b$, carboxy, $-CONR^aR^b$, C_{1-3} alkyl, C_{1-3} alkoxy, halo(C_{1-3})alkyl, halo(C_{1-3})alkoxy, hydroxy(C_{1-3})alkyl, cyano(C_{1-3})alkyl, sulfonyl(C_{1-3})alkyl, $-C(O)O(C_{1-4})$ alkyl, C_{3-7} cycloalkyl, and 5 or 6-membered heteroaryl.

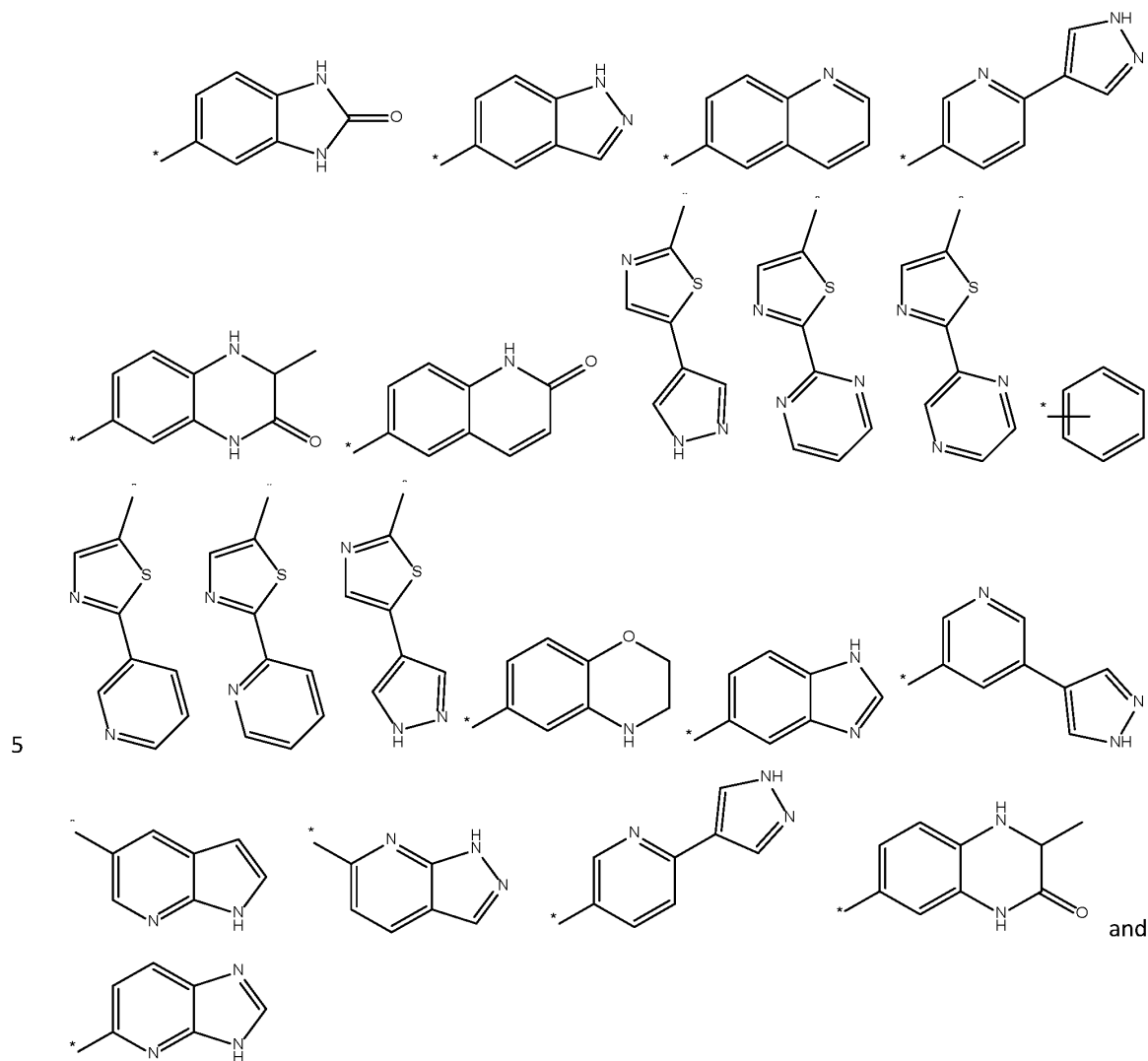
- 10 20. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 19, wherein Ring A is selected from the group consisting of:





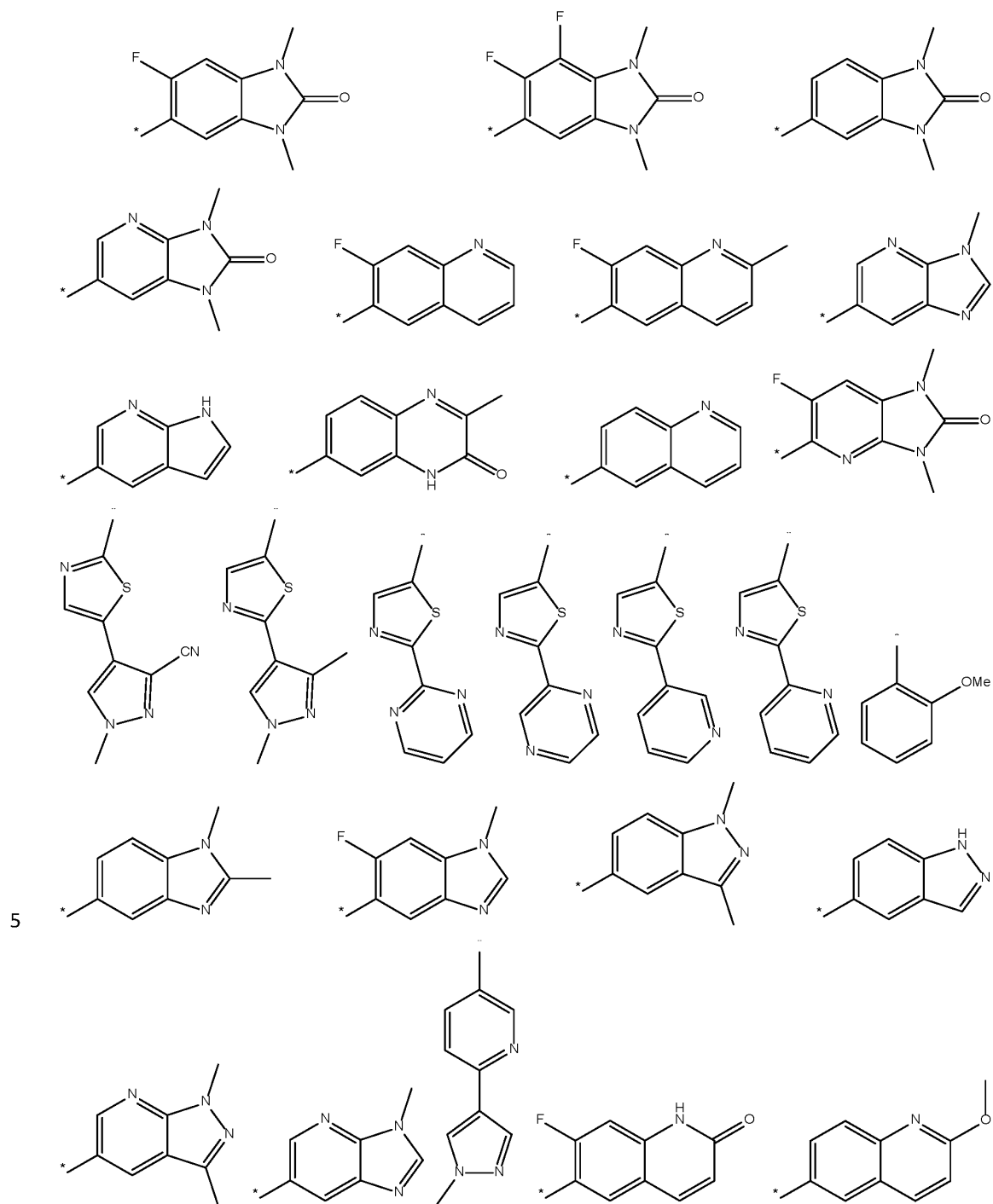
wherein Ring A is optionally substituted by halo, C₁₋₅alkyl, -OC₁₋₅alkyl, -OC₁₋₅haloalkyl, -NR^{4B}R^{5B}, wherein wherein R^{4B} and R^{5B} are independently hydrogen or C₁₋₃alkyl.

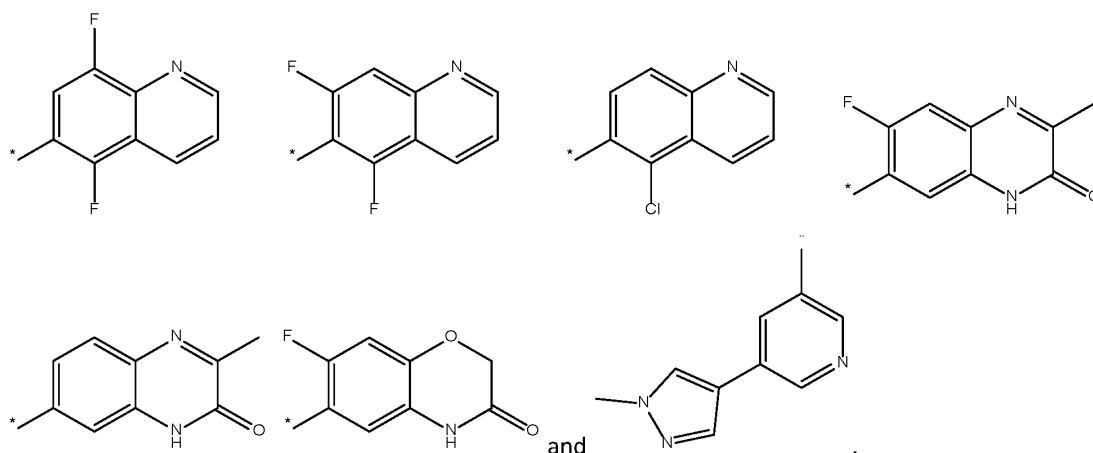
21. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 20, wherein Ring A is selected from the group consisting of:



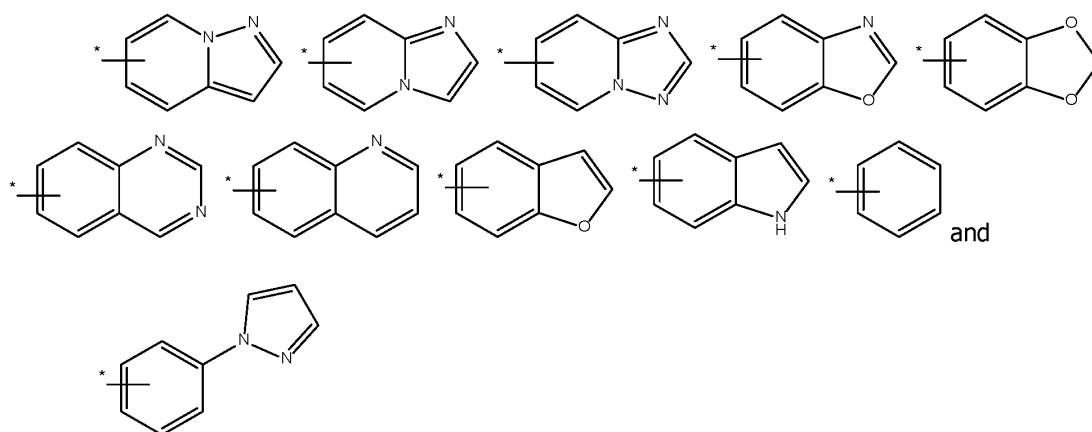
wherein Ring A is optionally substituted with one to five substituents each independently selected from the group consisting of halo, -C₁₋₃alkyl, -OC₁₋₃alkyl, -OC₁₋₃shaloalkyl, and NR^{4B}R^{5B},
10 wherein R^{4B} and R^{5B} are each independently hydrogen or C₁₋₃alkyl.

22. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 21, wherein Ring A is selected from the group consisting of:



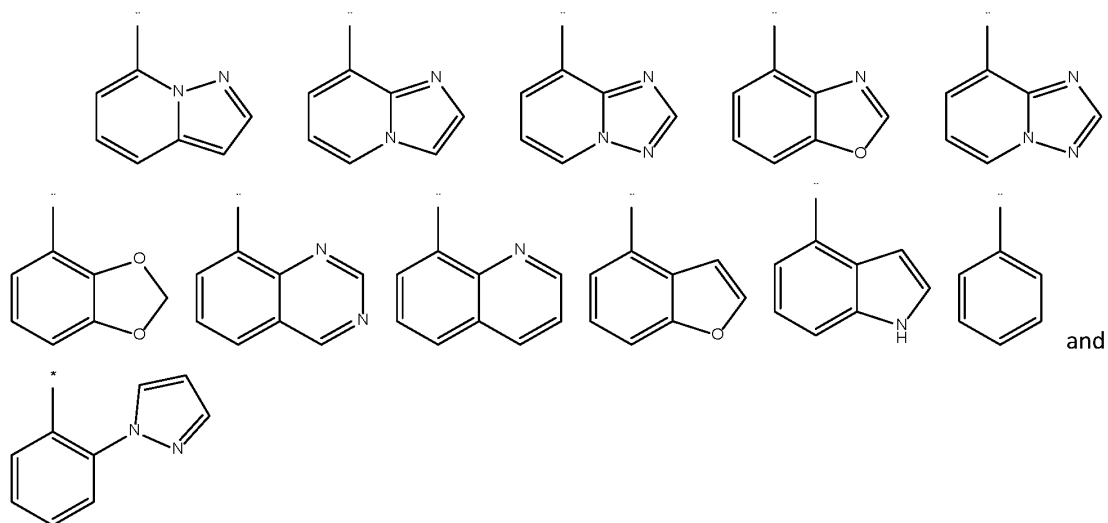


23. A compound or a pharmaceutically acceptable salt thereof according to any one of claims
 5 1 to 22, wherein Ring B is selected from the group consisting of:



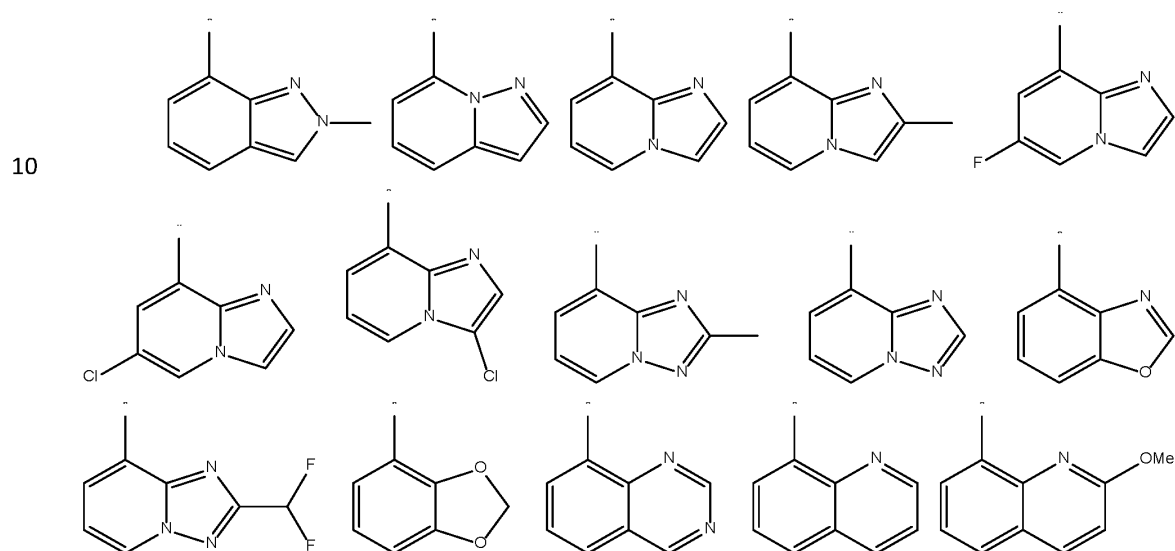
wherein Ring B is optionally substituted with one to five substituents each independently
 10 selected from the group consisting of halo, C₁₋₅alkyl, -OC₁₋₅alkyl, -OC₁₋₅haloalkyl, and -NR^{4B}R^{5B}, wherein
 R^{4B} are independently hydrogen or C₁₋₃alkyl.

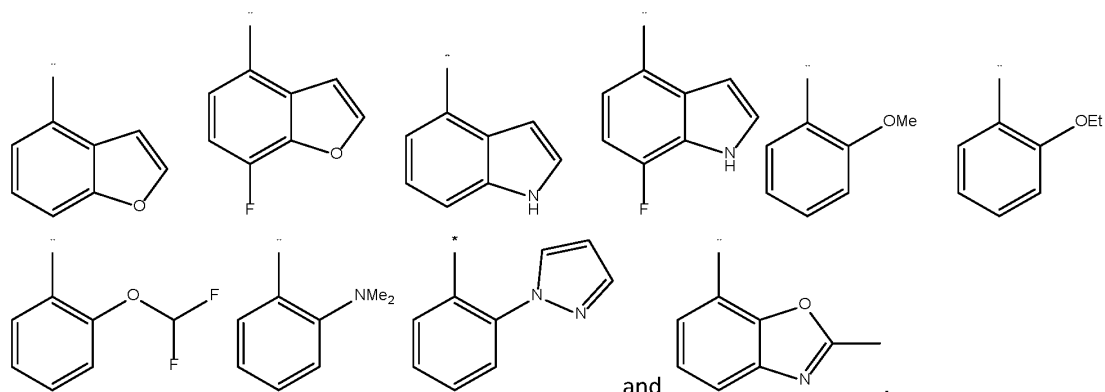
24. A compound or a pharmaceutically acceptable salt thereof according to any one of claims
 1 to 23, wherein Ring B is selected from the group consisting of:



- wherein Ring B is optionally substituted by one to five substituents each independently
 5 selected from the group consisting of halo, -C₁₋₅alkyl, -OC₁₋₅alkyl, -OC₁₋₅haloalkyl, -NR^{4B}R^{5B}, wherein
 wherein R^{4B} are independently hydrogen or C₁₋₃alkyl.

25. A compound or a pharmaceutically acceptable salt thereof according to any one of claims
 1 to 24, wherein Ring B is selected from the group consisting of:





26. A compound selected from the group consisting of:

5 5-((((1S,2S,3R,4S)-2,3-Dihydroxy-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

10 5-((((1R,2R,3S,4R)-2,3-Dihydroxy-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

(1R,2S,3S,6S)-3-(((7-Fluoroquinolin-6-yl)methyl)amino)-6-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexane-1,2-diol;

(1S,2R,3R,6R)-3-(((7-Fluoroquinolin-6-yl)methyl)amino)-6-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexane-1,2-diol

15 (1S,2R,3S,6S)-3-((2-Methoxybenzyl)amino)-6-((quinolin-6-ylmethyl)amino)cyclohexane-1,2-diol;

(1R,2S,3R,6R)-3-((2-Methoxybenzyl)amino)-6-((quinolin-6-ylmethyl)amino)cyclohexane-1,2-diol;

20 5-Fluoro-6-((((1S,2R,4S)-2-methoxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

(1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)(methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

- (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol;
- (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((2-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-8-yl)methyl)amino)cyclohexan-1-ol;
- 5 (1R,2S,5S)-5-((benzo[d]oxazol-4-ylmethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-5-([1,2,4]Triazolo[1,5-*a*]pyridin-8-ylmethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-2-(((6-Fluoroquinolin-7-yl)methyl)amino)-5-(((2-methoxyquinolin-8-yl)methyl)amino)cyclohexan-1-ol;
- 10 (1R,2S,5S)-5-((2-(1H-Pyrazol-1-yl)benzyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- 5-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-((quinazolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 15 5-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-(((2-methylbenzo[d]oxazol-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-Fluoro-6-((((1S,2R,4S)-4-(((6-fluoroimidazo[1,2-*a*]pyridin-8-yl)methyl)amino)-2-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 6-((((1S,2R,4S)-4-([1,2,4]Triazolo[1,5-*a*]pyridin-8-ylmethyl)amino)-2-hydroxycyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 20 (1R,2S,5S)-2-(((8-Fluoro-2-methylquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- 5-Fluoro-6-((((1S,3R,4S)-3-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 25 7-((((1S,2R,4S)-4-([1,2,4]Triazolo[1,5-*a*]pyridin-8-ylmethyl)amino)-2-hydroxycyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;
- 5-((((1R,2S,4R)-4-((2-(Difluoromethoxy)benzyl)amino)-2-hydroxycyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

- 5-((((1S,2S,4S)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1S,2S,4S)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- 5 (1S,2S,5S)-5-(((7-fluoroquinolin-6-yl)methyl)amino)-2-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- 5-((((1S,2S,4S)-2-Hydroxy-4-((quinolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 6-fluoro-5-((((1R,2S,4S)-2-fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- 10 5-Fluoro-6-((((1R,3S,4R)-3-hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 4-(5-((((1S,2R,4S)-2-Hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-thiazol-2-yl)-1-methyl-1H-pyrazole-3-carbonitrile;
- 15 5-Fluoro-6-((((1R,2R,4R)-2-hydroxy-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,5S)-5-((2-Methoxybenzyl)amino)-2-((quinolin-8-ylmethyl)amino)cyclohexan-1-ol;
- (1S,2R,5R)-2-(((1,2-Dimethyl-1H-benzo[d]imidazol-5-yl)methyl)amino)-5-((2-methoxybenzyl)amino)cyclohexan-1-ol;
- 20 (1S,2R,5R)-2-(((1,3-Dimethyl-1H-indazol-5-yl)methyl)amino)-5-((2-methoxybenzyl)amino)cyclohexan-1-ol;
- 5-((((4aR,7R,8aS)-7-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((4aS,7R,8aR)-7-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 25 1,3-Dimethyl-5-((((4aR,7R,8aS)-7-((quinolin-8-ylmethyl)amino)octahydro-4H-benzo[b][1,4]oxazin-4-yl)methyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

- 5-Fluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-4-(Benzo[d][1,3]dioxol-4-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-4-((2-(Dimethylamino)benzyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-4-((6-Chloroimidazo[1,2-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-4-((3-Chloroimidazo[1,2-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-2-Fluoro-4-((2-methylimidazo[1,2-a]pyridin-8-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-4-((2-(Difluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,4R)-2,2-Difluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,4R)-2,2-Difluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)cyclohexane-1,4-diamine;
- (1R,4R)-2,2-Difluoro-N¹-((7-Fluoroquinolin-6-yl)methyl)-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;
- 7-Fluoro-6-((((1S,2R,4S)-2-hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-quinolin-2(1H)-one;
- (1R,2S,5S)-5-((Imidazo[1,2-a]pyridin-8-ylmethyl)amino)-2-(((2-methoxyquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-2-(((5,8-Difluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-2-(((5,7-Difluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

- (1R,2S,5S)-2-(((5-Chloroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- 6-fluoro-7-((((1S,2R,4S)-2-hydroxy-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;
- 5 (1R,2S,5S)-2-(((2-(1,3-Dimethyl-1H-pyrazol-4-yl)thiazol-5-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;
- 5-Fluoro-6-((((1S,3S,4S)-3-fluoro-4-((2-methyl-2H-indazol-7-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 10 5-((((1S,3S,4S)-4-(((3a,7a-Dihydrobenzo[d]oxazol-4-yl)methyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)-methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,2S,4R)-2-Fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 15 (1R,2S,4R)-2-Fluoro-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)-N¹-((2-(pyrimidin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 7-((((1R,2S,4R)-2-Fluoro-4-((pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)quinazoline-2,4(1H,3H)-dione;
- (1R,2S,4R)-2-Fluoro-N¹-((2-(pyrazin-2-yl)thiazol-5-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;
- 20 (1R,2S,4R)-2-Fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((2-(pyridin-3-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- (1R,2S,4R)-N¹-((1,3-Dimethyl-1H-pyrazolo[3,4-b]pyridin-6-yl)methyl)-2-fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;
- 25 6-Fluoro-5-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,4R)-2-Fluoro-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)-N¹-((2-(pyridin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;

- 6-((((1R,2S,4R)-4-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,4R)-N⁴-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)-2-fluoro-N¹-((2-(pyrazin-2-yl)thiazol-5-yl)methyl)cyclohexane-1,4-diamine;
- 5 6-((((1S,2R,4S)-2-fluoro-4-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one;
- 7-((((1S,2R,4S)-2-fluoro-4-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-3-methylquinoxalin-2(1H)-one;
- 10 5-((((1S,2R,4S)-2-Fluoro-4-(imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 7-fluoro-6-((((1S,2R,4S)-2-fluoro-4-(pyrazolo[1,5-a]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-2H-benzo[b][1,4]oxazin-3(4H)-one;
- (1S,2R,4S)-2-fluoro-N¹-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;
- 15 (1S,2R,4S)-2-fluoro-N¹-((6-fluoro-1-methyl-1H-benzo[d]imidazol-5-yl)methyl)-N⁴-(pyrazolo[1,5-a]pyridin-7-ylmethyl)cyclohexane-1,4-diamine;
- 5-((((1R,4R)-4-(Benzo[d]oxazol-4-ylmethyl)amino)-2,2-difluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 20 5-((((1R,4R)-2,2-difluoro-4-((7-fluorobenzofuran-4-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,4R)-2,2-difluoro-4-((7-fluoro-1H-indol-4-yl)methyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1R,4R)-2,2-Difluoro-4-(quinolin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 25 5-((((1R,2S,4R)-4-([1,2,4]Triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,4R)-2-Fluoro-N¹-((7-fluoroquinolin-6-yl)methyl)-N⁴-(imidazo[1,2-a]pyridin-8-ylmethyl)cyclohexane-1,4-diamine;

- 4,5-Difluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5-((((1S,3R,4S)-4-((2-Ethoxybenzyl)amino)-3-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- 5 (1S,2R,4S)-N¹-(2-Ethoxybenzyl)-2-fluoro-N⁴-((3-methyl-3H-imidazo[4,5-b]pyridin-6-yl)methyl)cyclohexane-1,4-diamine;
- (1S,2R,4S)-N⁴-((1H-Pyrrolo[2,3-b]pyridin-5-yl)methyl)-N¹-(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-diamine;
- (1S,2R,4S)-N⁴-((1H-Indazol-5-yl)methyl)-N¹-(2-ethoxybenzyl)-2-fluorocyclohexane-1,4-
- 10 diamine;
- 5-((((1S,3S,4S)-3-Fluoro-4-((2-methoxybenzyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;
- (1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-(((R)-1-(pyrazolo[1,5-a]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol;
- 15 (1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(pyrazolo[1,5-a]pyridin-7-yl)ethyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-5-(((R)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-5-(((S)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-
- 20 yl)methyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-5-(((R)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-5-(((S)-1-([1,2,4]Triazolo[1,5-a]pyridin-8-yl)ethyl)amino)-2-(((7-fluoroquinolin-6-yl)methyl)amino)cyclohexan-1-ol;
- 25 (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((R)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;
- (1R,2S,5S)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((S)-1-(imidazo[1,2-a]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

(1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((*R*)-1-(imidazo[1,2-*a*]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

(1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-(((*S*)-1-(imidazo[1,2-*a*]pyridin-8-yl)ethyl)amino)cyclohexan-1-ol;

5 5-Fluoro-6-((((1*S*,3*S*,4*S*)-3-fluoro-4-(((*R*)-1-(imidazo[1,2-*a*]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

5-Fluoro-6-((((1*S*,3*S*,4*S*)-3-fluoro-4-(((*R*)-1-(imidazo[1,2-*a*]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

10 5-Fluoro-6-((((1*S*,3*S*,4*S*)-3-fluoro-4-(((*S*)-1-(imidazo[1,2-*a*]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

5-Fluoro-6-((((1*S*,3*S*,4*S*)-3-fluoro-4-(((*S*)-1-(imidazo[1,2-*a*]pyridin-8-yl)ethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one; and

(1*R*,2*S*,5*S*)-2-(((7-Fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl-*d*₂)amino)cyclohexan-1-ol;

15 5-((((1*R*,2*S*,4*R*,6*R*)-2-fluoro-6-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

(1*R*,2*R*,3*S*,5*R*)-3-fluoro-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

20 (1*R*,2*R*,3*S*,5*R*)-2-(((1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)methyl)amino)-3-fluoro-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexan-1-ol;

4,5-difluoro-6-((((1*R*,2*S*,4*R*,6*R*)-2-fluoro-6-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

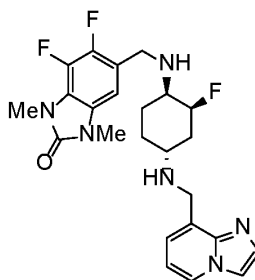
5-fluoro-6-((((1*R*,2*S*,4*R*,6*R*)-2-fluoro-6-hydroxy-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

25 6-((((1*R*,2*S*,4*R*,6*R*)-4-([1,2,4]triazolo[1,5-*a*]pyridin-8-ylmethyl)amino)-2-fluoro-6-hydroxycyclohexyl)amino)methyl)-4,5-difluoro-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one;

(1*R*,2*R*,3*S*,5*R*)-3-fluoro-5-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)-2-(((5-(1-methyl-1*H*-pyrazol-4-yl)pyridin-3-yl)methyl)amino)cyclohexan-1-ol;

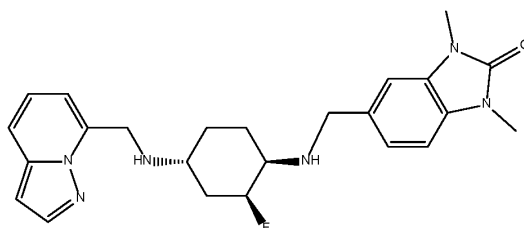
or a pharmaceutically acceptable salt thereof.

27. A compound which is 4,5-Difluoro-6-((((1*R*,2*S*,4*R*)-2-fluoro-4-((imidazo[1,2-*a*]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one as
5 represented by the following structure



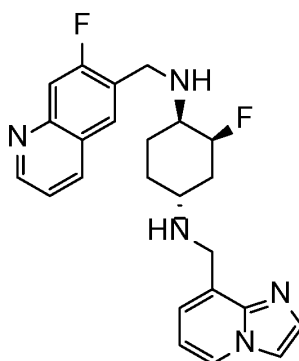
or a pharmaceutically acceptable salt thereof.

28. A compound which is 5-((((1*R*,2*S*,4*R*)-2-fluoro-4-((pyrazolo[1,5-*a*]pyridin-7-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one as
10 represented by the following structure:



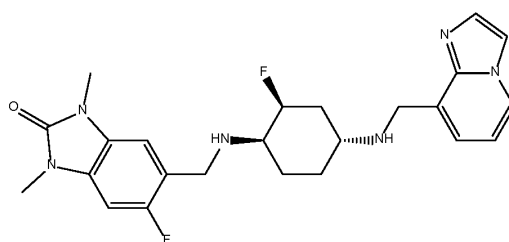
or a pharmaceutically acceptable salt thereof.

29. A compound which is (1*R*,2*S*,4*R*)-2-Fluoro-*N*¹-((7-fluoroquinolin-6-yl)methyl)-*N*⁴-(imidazo[1,2-*a*]pyridin-8-ylmethyl)cyclohexane-1,4-diamine as represented by the following structure
15



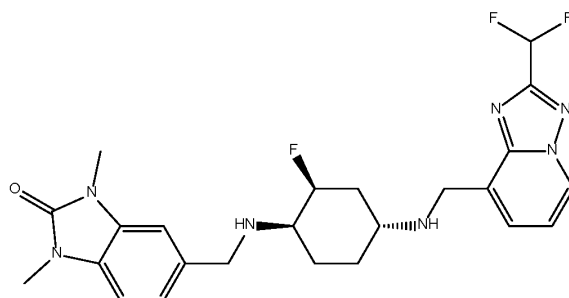
or a pharmaceutically acceptable salt thereof.

30. A compound which is 5-fluoro-6-((((1R,2S,4R)-2-fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



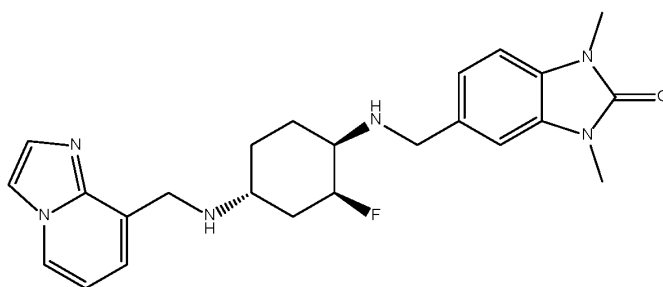
or a pharmaceutically acceptable salt thereof.

31. A compound which is 5-((((1R,2S,4R)-4-(((2-(difluoromethyl)-[1,2,4]triazolo[1,5-a]pyridin-8-yl)methyl)amino)-2-fluorocyclohexyl)amino)methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



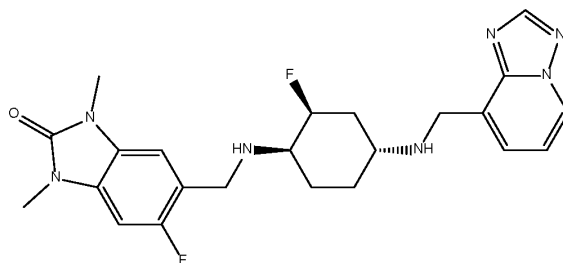
or a pharmaceutically acceptable salt thereof.

32. A compound which is 5-((((1R,2S,4R)-2-Fluoro-4-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)cyclohexyl)amino)-methyl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



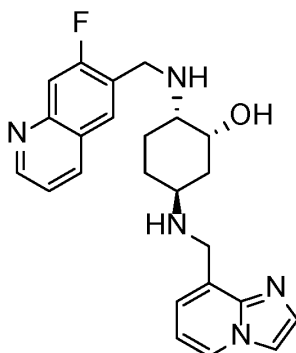
or a pharmaceutically acceptable salt thereof.

33. A compound which is 5-((((1R,2S,4R)-4-(([1,2,4]triazolo[1,5-a]pyridin-8-ylmethyl)amino)-2-fluorocyclohexyl)amino)methyl)-6-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one as represented by the following structure:



or a pharmaceutically acceptable salt thereof.

34. A compound which is (1R,2S,5S)-2-(((7-fluoroquinolin-6-yl)methyl)amino)-5-((imidazo[1,2-a]pyridin-8-ylmethyl)amino)-cyclohexan-1-ol as represented by the following structure:



or a pharmaceutically acceptable salt thereof.

35. A compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 34, which is in free acid or free base form or is in the form a besylate or di-besylate salt.

36. A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 35 and a pharmaceutically acceptable excipient.

37. A compound or a pharmaceutically acceptable salt thereof of any one of claims 1 to 35 or the pharmaceutical composition of claim 36 for use in therapy.

38. A compound or pharmaceutically acceptable salt thereof of any one of claims 1 to 35 or a pharmaceutical composition of claim 36 for use in the treatment of cancer.

39. A compound or pharmaceutically acceptable salt thereof of any one of claims 1 to 35 or a pharmaceutical composition of claim 36 for use in the treatment of cancer, wherein the cancer is characterized by MSI-H and/or dMMR.

5 40. A method of treatment of cancer in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 35 or a pharmaceutical composition according to claim 36.

10 41. A method of treatment of cancer according to claim 40, wherein the cancer is characterized by MSI-H and/or dMMR.

15 42. Use of a compound or pharmaceutically acceptable salt thereof of any one of claims 1 to 35 or a pharmaceutical composition of claim 36, in the manufacture of a medicament for use in the treatment of cancer.