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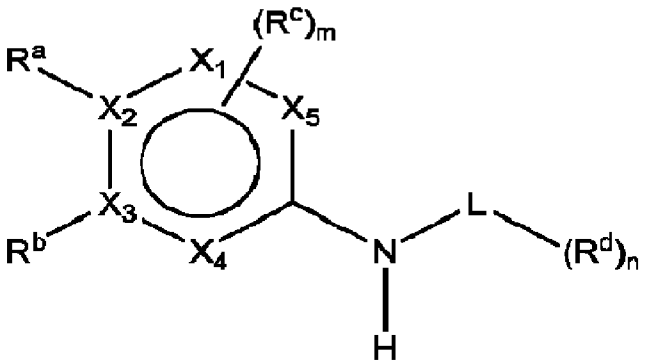
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(54) **Titre : MODULATEURS DE LA FERROPTOSE, PREPARATIONS ET UTILISATIONS DE CEUX-CI**
(54) **Title: FERROPTOSIS MODULATORS, PREPARATIONS, AND USES THEREOF**



(57) **Abrégé/Abstract:**
This disclosure provides compounds of Formula I, compositions comprising the same, and methods of using the same, including use in treating various diseases and conditions, e.g., those involving ferroptosis.

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Abstract:

This disclosure provides compounds of Formula I, compositions comprising the same, and methods of using the same, including use in treating various diseases and conditions, e.g., those involving ferroptosis.

FERROPTOSIS MODULATORS, PREPARATIONS, AND USES THEREOF

Field of the Disclosure

The present disclosure relates to compounds that modulate ferroptosis, compositions comprising the compounds, methods of preparing the compounds, and methods of using the compounds to treat various diseases or conditions, e.g., those involving ferroptosis.

Background of the Disclosure

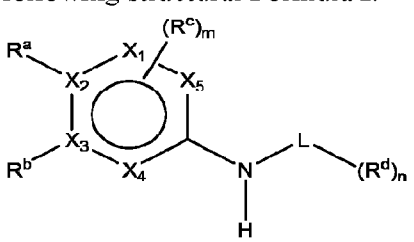
Ferroptosis is a type of programmed cell death dependent on iron and characterized by the accumulation of lipid peroxides, and is genetically and biochemically distinct from other forms of regulated cell death such as apoptosis, autophagy, and necrosis. (Dixon et al., Cell 149, 1060–1072 (2012).) Certain mechanisms of ferroptosis and key contributors to ferroptotic cell death is reviewed and illustrated by Conrad et al., Nature Chemical Biology, vol. 15, Dec. 2019, 1137–1147.

Ferroptosis has been implicated in a number of diseases or conditions, including neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. For example, inactivation of the the ferroptosis regulator Gpx4 triggers acute renal failure in mice. (Angeli, et al., Nature Cell Biology, published online Nov. 17, 2014; DOI: 10.1038/ncb3064.) Ferroptosis has been considered to be implicated in several pathophysiological contexts such as tumor suppression, antiviral immunity, neurodegeneration, and ischemia/reperfusion injury (IRI). (Angeli et al., Trends in Pharmacological Sciences, May 2017, Vol. 38, No. 5, 489-498 (2017).)

Certain compounds that modulate ferroptosis are disclosed by Skouta et al., J. Am. Chem. Soc., dx.doi.org/10.1021/ja411006a; and in WO2013152039A1, WO2015084749A1, WO2019154795A1, WO2016075137A1, WO2020185738A1, and PCT/CN2021/078601.

Summary of the Disclosure

One aspect of this disclosure provides a compound selected from compounds of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, which can be employed in the treatment of various diseases or conditions, such as diseases or conditions involving ferroptosis. For example, disclosed herein is a compound of the following structural Formula I:



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Formula (I)

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

L is cycloalkyl, heterocyclyl, or C;

X_1, X_2, X_3, X_4, and X_5 are each independently C or N;

R^a is absent or selected from H, halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is absent or selected from H, halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl;

R^a and R^b may join together to form an optionally substituted 3- to 10-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring;

R^c, for each occurrence, is independently selected from halogen, optionally substituted heteroatom, and optionally substituted alkyl;

R^b and one of R^c may join together to form an optionally substituted 3- to 10-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring;

R^d, for each occurrence, is independently selected from halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and

m and n are each an integer independently selected from 0, 1, 2, and 3.

In one aspect of the disclosure, the compounds of the Formulae disclosed herein are selected from Compounds 1 to 573 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

In some embodiments, the disclosure provides pharmaceutical compositions comprising a compound of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical compositions may comprise a compound selected from Compounds 1 to 573 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and a pharmaceutically acceptable carrier. These compositions may further comprise an additional active pharmaceutical agent.

In one aspect of the disclosure, the compounds of the Formulae disclosed herein are selected from Compounds 574 to 661 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

In some embodiments, the disclosure provides pharmaceutical compositions comprising a compound of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical

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compositions may comprise a compound selected from Compounds 574 to 661 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and a pharmaceutically acceptable carrier. These compositions may further comprise an additional active pharmaceutical agent.

Another aspect of the disclosure provides methods of treating a disease or condition, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing, wherein the disease or condition is selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure.

A further aspect of the disclosure provides methods of treating a disease or condition involving ferroptosis, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing.

In some embodiments, the methods of treatment comprise administering to a subject in need thereof, a compound selected from Compounds 1 to 573 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing.

In some embodiments, the methods of treatment comprise administration of an additional active pharmaceutical agent to the subject in need thereof, either in the same pharmaceutical composition as a compound of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or in a separate composition. In some embodiments, the methods of treatment comprise administering a compound selected from Compounds 1 to 573 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing with an additional active pharmaceutical agent either in the same pharmaceutical composition or in a separate composition. When administered as a separate composition, the additional therapeutic agent may be administered prior to, at the same time as, or following administration of the compound, tautomer, solvate, stereoisomer, or a pharmaceutically acceptable salt disclosed herein.

Also disclosed herein are methods of modulating, e.g., inhibiting, ferroptosis in a subject in need thereof, comprising contacting the subject with a compound of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical

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composition comprising any of the foregoing. In some embodiments, the methods of modulating, e.g., inhibiting, ferroptosis in a subject in need thereof comprise contacting the subject with a compound selected from Compounds 1 to 573 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing.

In some embodiments, the methods of treatment comprise administering to a subject in need thereof, a compound selected from Compounds 574 to 661 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing.

In some embodiments, the methods of treatment comprise administration of an additional active pharmaceutical agent to the subject in need thereof, either in the same pharmaceutical composition as a compound of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or in a separate composition. In some embodiments, the methods of treatment comprise administering a compound selected from Compounds 574 to 661 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing with an additional active pharmaceutical agent either in the same pharmaceutical composition or in a separate composition. When administered as a separate composition, the additional therapeutic agent may be administered prior to, at the same time as, or following administration of the compound, tautomer, solvate, stereoisomer, or a pharmaceutically acceptable salt disclosed herein.

Also disclosed herein are methods of modulating, e.g., inhibiting, ferroptosis in a subject in need thereof, comprising contacting the subject with a compound of the Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing. In some embodiments, the methods of modulating, e.g., inhibiting, ferroptosis in a subject in need thereof comprise contacting the subject with a compound selected from Compounds 574 to 661 shown below, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing.

Detailed Description of the Disclosure

I. Definitions

The term “a” or “an” when referring to a noun as used herein encompasses the expression “at least one” and therefore encompasses both singular and plural units of the noun. For example, “an additional pharmaceutical agent” means a single or two or more additional pharmaceutical agents.

The term "alkyl" refers to a hydrocarbon group selected from linear and branched saturated hydrocarbon groups, containing 1-20, e.g., 1-18, 1-12, 1-10, 1-8, 1-6, 1-4, or 1-3, carbon atoms. Examples of the alkyl group include methyl, ethyl, 1-propyl or n-propyl ("n-Pr"), 2-propyl or

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isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), and 1,1-dimethylethyl or t-butyl ("t-Bu"). Other examples of an alkyl group include 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, and 3,3-dimethyl-2-butyl groups. Lower alkyl contains 1-8, preferably 1-6, more preferably 1-4 carbon atoms, and more preferably 1-3 carbon atoms.

The term "alkenyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon groups, comprising at least one C=C double bond and 2-20, e.g., 2-18, 2-12, 2-10, 2-8, 2-6, or 2-4, carbon atoms. Examples of the alkenyl group may be selected from ethenyl or vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1,3-dienyl groups. Lower alkenyl contains 2-8, preferably 2-6, and more preferably 2-4 carbon atoms.

The term "alkynyl" refers to a hydrocarbon group selected from linear and branched hydrocarbon groups, comprising at least one C≡C triple bond and 2-20, e.g., 2-18, 2-12, 2-10, 2-8, 2-6, or 2-4, carbon atoms. Examples of the alkynyl group include ethynyl, 1-propynyl, 2-propynyl (propargyl), 1-butynyl, 2-butynyl, and 3-butynyl groups. Lower alkynyl contains 2-8, preferably 2-6, and more preferably 2-4 carbon atoms.

The term "heteroalkyl" refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by a heteroatom, e.g., nitrogen, oxygen, or sulfur, *e.g.*, CH_3CH_2OH, $CH_3CH_2OC_2H_5$, CH_3CH_2SH, $CH_3CH_2SC_2H_5$, $CH_3CH_2NH_2$, $CH_3CH_2NHC_2H_5$, etc. In some embodiments, in addition to the replacement of one or more of the constituent carbon atoms by nitrogen, oxygen, or sulfur, a heteroalkyl group is further optionally substituted as defined herein.

The term "cycloalkyl" refers to a hydrocarbon group selected from saturated and partially unsaturated cyclic hydrocarbon groups, e.g., monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups. For example, the cycloalkyl group may be of 3-12, 3 to 10, or 3-8, or 3-6, or 3-4, or 5-6 carbon atoms. Even further for example, the cycloalkyl group may be a monocyclic group of 3-12, or 3-8, or 3-6, or 3-4, or 5-6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups. Examples of the bicyclic cycloalkyl groups include those having 7-12 ring atoms arranged as a bicycle ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems, or as a bridged bicyclic ring selected from bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane. The ring may be saturated or have at least one double bond (i.e., partially unsaturated), but is not fully conjugated, and is not aromatic, as aromatic is defined herein.

The term "heterocyclic" or "heterocycle" or "heterocyclyl" refers to a ring selected from 4- to 12-membered, e.g., 3- to 6-membered, 3- to 5-membered, 4- to 5-membered, or 5- to 6-membered, monocyclic, bicyclic, and tricyclic, saturated and partially unsaturated rings comprising at least one carbon atom in addition to 1, 2, 3, or 4 heteroatoms, selected from, e.g.,

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oxygen, sulfur, nitrogen, and silicon. "Heterocycle" also refers to a 5- to 7-membered heterocyclic ring comprising at least one heteroatom selected from N, O, and S fused with 5-, 6-, and/or 7-membered cycloalkyl, carbocyclic aromatic, or heteroaromatic ring, provided that the point of attachment is at the heterocyclic ring when the heterocyclic ring is fused with a carbocyclic aromatic or a heteroaromatic ring, and that the point of attachment can be at the cycloalkyl or heterocyclic ring when the heterocyclic ring is fused with cycloalkyl.

"Heterocycle" also refers to an aliphatic spirocyclic ring comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the heterocyclic ring. The rings may be saturated or have at least one double bond (i.e., partially unsaturated). A heterocycle may be substituted with oxo. The point of the attachment may be carbon or heteroatom in the heterocyclic ring. A heterocycle is not a heteroaryl as defined herein.

Examples of heterocycles include, but are not limited to, (as numbered from the linkage position assigned priority 1) 1-pyrrolidinyl, 2-pyrrolidinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2,5-piperazinyl, pyranyl, 2-morpholinyl, 3-morpholinyl, oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, 1,4-oxathianyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl, 1,4-diazepanyl, 1,4-dithianyl, 1,4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1,4-dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinylimidazolinyl, pyrimidinonyl, 1,1-dioxo-thiomorpholinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. Substituted heterocycle also includes ring systems substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1-thiomorpholinyl, and 1, 1-dioxo-1-thiomorpholinyl.

The term "fused ring" herein refers to a polycyclic ring system, e.g., a bicyclic or tricyclic ring system, in which two rings share only two ring atoms and one bond in common. Examples of fused rings may comprise a fused bicyclic cycloalkyl ring such as those having from 7 to 12 ring atoms arranged as a bicyclic ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems as mentioned above; a fused bicyclic aryl ring such as 7 to 12 membered bicyclic aryl ring systems as mentioned above, a fused tricyclic aryl ring such as 10 to 15 membered tricyclic aryl ring systems mentioned above; a fused bicyclic heteroaryl ring such as 8- to 12-membered bicyclic heteroaryl rings as mentioned above, a fused tricyclic heteroaryl ring such as 11- to 14-membered tricyclic heteroaryl rings as mentioned above; and a fused bicyclic or tricyclic heterocyclyl ring as mentioned above.

The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, and silicon, including, any oxidized form of nitrogen or sulfur; the quaternized form of any basic nitrogen or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (wherein R is, e.g., an optionally substituted alkyl group) (as in N-substituted pyrrolidinyl).

The term "unsaturated", as used herein, means that a moiety has one or more units or

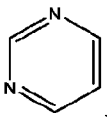
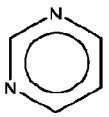
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degrees of unsaturation. Unsaturation is the state in which not all of the available valence bonds in a compound are satisfied by substituents and thus the compound contains one or more double or triple bonds.

The term "alkoxy" as used herein, refers to an alkyl group, as defined above, wherein one carbon of the alkyl group is replaced by an oxygen atom, provided that the oxygen atom is linked between two carbon atoms.

The term "halogen" includes F, Cl, Br, and I, i.e., fluoro, chloro, bromo, and iodo, respectively.

As used herein, a "CN," "cyano" or "nitrile" group refers to -C≡N.

As used herein, an "aromatic ring" refers to a carbocyclic or heterocyclic ring that contains conjugated, planar ring systems with delocalized pi electron orbitals comprised of [4n−2] p orbital electrons, wherein n is an integer of 0 to 6. A "non-aromatic" ring refers to a carbocyclic or heterocyclic that does not meet the requirements set forth above for an aromatic ring, and can be either completely or partially saturated. Non-limiting examples of aromatic rings include aryl and heteroaryl rings that are further defined as follows. An "aromatic ring" may be depicted as a cycle with conjugated double bonds, such as  , or as a cycle with an inside circle such as  .

The term "aryl" herein refers to a group selected from: monocyclic carbocyclic aromatic rings, for example, phenyl; bicyclic ring systems such as 7-12 membered bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, selected, for example, from naphthalene, indane, and 1,2,3,4-tetrahydroquinoline; and tricyclic ring systems such as 10-15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene.

For example, the aryl group may be a 6-membered carbocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl or heterocyclic ring optionally comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the carbocyclic aromatic ring when the carbocyclic aromatic ring is fused with a heterocyclic ring, and the point of attachment can be at the carbocyclic aromatic ring or at the cycloalkyl group when the carbocyclic aromatic ring is fused with a cycloalkyl group. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene.

The term "heteroaryl" refers to a group selected from: 5- to 7-membered, e.g., 5- to 6-memebered, aromatic, monocyclic rings comprising 1, 2, 3, or 4 heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon; 8- to 12-membered bicyclic rings comprising 1, 2, 3, or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in

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the aromatic ring; and 11- to 14-membered tricyclic rings comprising 1, 2, 3, or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring.

For example, the heteroaryl group may be a 5- to 7-membered heterocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings comprises at least one heteroatom, the point of attachment may be at the heteroaromatic ring or at the cycloalkyl ring.

When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of the heteroaryl group include, but are not limited to, (as numbered from the linkage position assigned priority 1) pyridyl (such as 2-pyridyl, 3-pyridyl, or 4-pyridyl), cinnolinyl, pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,4-imidazolyl, imidazopyridinyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, thienyl, triazinyl, benzothienyl, furyl, benzofuryl, benzoimidazolyl, indolyl, isoindolyl, indolinyl, phthalazinyl, pyrazinyl, pyridazinyl, pyrrolyl, triazolyl, quinolinyl, isoquinolinyl, pyrazolyl, pyrrolopyridinyl (such as 1H-pyrrolo[2,3-b]pyridin-5-yl), pyrazolopyridinyl (such as1H-pyrazolo[3,4-b]pyridin-5-yl), benzoxazolyl (such as benzo[d]oxazol-6-yl), pteridinyl, purinyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, benzothiazolyl (such as benzo[d]thiazol-6-yl), indazolyl (such as 1H-indazol-5-yl) and 5,6,7,8-tetrahydroisoquinolinyl.

The term "acyl" refers to a substituent group where a point of attachment in the substituent group is a carbonyl. Exemplary acyl groups include, but are not limited to, -C(=O)R', -C(=O)NR'R'', or -C(=O)OR', wherein R' and R'' are independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl, any of which may be further substituted by one or more substituents.

Some of the compounds may exist with different points of attachment of hydrogen, referred to as "tautomers." For example, compounds including carbonyl -$CH_2C(O)$- groups (keto forms) may undergo tautomerism to form hydroxyl -CH=C(OH)- groups (enol forms). Both keto and enol forms, individually as well as mixtures thereof, are also intended to be included where applicable.

The compounds, tautomers, solvates, or pharmaceutically acceptable salts of the disclosure may contain an asymmetric center and may thus exist as enantiomers. For example, where the compounds possess two or more asymmetric centers, they may additionally exist as diastereoisomers. Enantiomers and diastereoisomers fall within the broader class of stereoisomers. All such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereoisomers are intended to be included in this disclosure. All stereoisomers of the compounds, tautomers, solvates, and pharmaceutically acceptable salts thereof are intended to be included. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever

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the isomeric composition is unspecified, all possible isomers are included.

Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

A single stereoisomer, e.g., a substantially pure enantiomer, may be obtained by resolution of the racemic mixture using a method such as formation of diastereoisomers using optically active resolving agents. Racemic mixtures of chiral compounds of the disclosure can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereoisomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

The term "substantially pure" in the context of stereoisomers means that the target stereoisomer contains no more than 35%, such as no more than 30%, further such as no more than 25%, even further such as no more than 20%, by weight of any other stereoisomer(s). In some embodiments, the term "substantially pure" means that the target stereoisomer contains no more than 10%, for example, no more than 5%, such as no more than 1%, by weight of any other stereoisomer(s).

Unless otherwise indicated, structures depicted herein are meant to include all isomeric forms of the structure, e.g., racemic mixtures, cis/trans isomers, geometric (or conformational) isomers, such as (*Z*) and (*E*) double bond isomers, and (*Z*) and (*E*) conformational isomers. Therefore, geometric and conformational mixtures of the compounds disclosed herein are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure.

The disclosure provides pharmaceutically acceptable salts of the disclosed compounds, tautomers, solvates, and stereoisomers. A salt of a compound is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group.

The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure.

"Pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids, selected, for example, from hydrochlorates, phosphates, diphosphates, hydrobromates, sulfates, sulfinates, and nitrates; as well as salts with organic acids, selected, for example, from malates,

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maleates, fumarates, tartrates, succinates, citrates, lactates, methanesulfonates, p-toluenesulfonates, 2-hydroxyethylsulfonates, benzoates, salicylates, stearates, alkanoates such as acetate, and salts with HOOC-(CH_2)n-COOH, wherein n is selected from 0 to 4. Similarly, examples of pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, magnesium, aluminum, lithium, and ammonium. Suitable pharmaceutically acceptable salts are, for example, those disclosed in S. M. Berge, *et al. J. Pharmaceutical Sciences*, 1977, *66*, pp. 1 to 19.

Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, benzenesulfonic acid, fumaric acid, gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, and acetic acid. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate (i.e., caprate), caprylate, acrylate, formate, isobutyrate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In some embodiments, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid.

Pharmaceutically acceptable salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium, and $N^+(C_{1-4}alkyl)_4$ salts. This disclosure also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Suitable non-limiting examples of alkali and alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium salts. Further non-limiting examples of pharmaceutically acceptable salts include salts of ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate. Other suitable, non-limiting examples of pharmaceutically acceptable salts include besylate and glucosamine salts.

If a compound is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used without undue

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experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

The compounds, tautomers, solvates, stereoisomers, and pharmaceutically acceptable salts of the disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, $-CD_3$, $-CD_2H$ or $-CDH_2$ contains one or more deuteriums in place of hydrogen. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the disclosure, whether radioactive or not, are intended to be encompassed within the scope of the disclosure.

As used herein, "optionally substituted" is interchangeable with the phrase "substituted or unsubstituted." In general, the term "substituted," refers to the replacement of a hydrogen radical in a given structure with the radical of a specified substituent. Unless otherwise indicated, an "optionally substituted" group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent chosen from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this disclosure are those that result in the formation of stable or chemically feasible compounds.

In some embodiments, substituents are independently selected from optionally substituted heteroatom and optionally substituted, optionally hetero-, optionally cyclic C_1-C_{18} hydrocarbyl, particularly wherein the optionally substituted, optionally hetero-, optionally cyclic C_1-C_{18} hydrocarbyl is optionally-substituted, optionally hetero-, optionally cyclic alkyl, alkenyl or alkynyl, or optionally-substituted, optionally hetero-, aryl; and/or the optionally substituted heteroatom is halogen, optionally substituted hydroxyl (such as alkoxy, aryloxy), optionally substituted acyl (such as formyl, alkanoyl, carbamoyl, carboxyl, amido), optionally substituted amino (such as amino, alkylamino, dialkylamino, amido, sulfamidyl), optionally substituted thiol (such as mercapto, alkylthiol, aryl thiol), optionally substituted sulfinyl or sulfonyl (such as alkylsulfinyl, arylsulfinyl, alkyl sulfonyl, arylsulfonyl), nitro, or cyano.

In some embodiments, substituents are independently selected from: halogen, -R', -OR', =O, =NR', =N-OR', -NR'R", -SR', -SiR'R"R'", -OC(=O)R', -C(=O)R', $-CO_2R'$, -C(=O)NR'R", -OC(=O)NR'R", -NR"C(=O)R', -NR'-C(=O)NR"R'", -NR'-SO_2N R"R'", $-NR"CO_2R'$, -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', $-SO_2R'$, $-SO_2NR'R"$, -NR"SO_2R, -CN, $-NO_2$, $-N_3$, $-CH(Ph)_2$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to three, with those groups having zero, one, or two substituents being particularly preferred. R', R" and R'" each independently refer to hydrogen, unsubstituted C_1-C_8 alkyl and heteroalkyl, C_1-C_8 alkyl and heteroalkyl substituted with one to three halogens, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy, or thioalkoxy groups, or aryl-(C_1-C_4) alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. Hence, -NR'R" includes 1-pyrrolidinyl and 4-morpholinyl. When the aryl group is 1,2,3,4-tetrahydronaphthalenyl, it may be substituted with a substituted or unsubstituted C_3-C_7 spirocycloalkyl group. The C_3-C_7 spirocycloalkyl group may be substituted in the same manner as defined herein for "cycloalkyl."

In some embodiments, substituents are selected from: halogen, -R', -OR', =O, -NR'R", -SR',

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-SiR'R"R'", -OC(=O)R', -C(=O)R', -CO_2R', -C(=O)NR'R", -OC(=O)NR'R", -NR"C(=O)R', -NR"CO_2R', -NR'-SO_2NR"R'", -S(=O)R', -SO_2R', -SO_2NR'R", -NR"SO_2R, -CN, -NO_2, perfluoro C_1-C_4 alkoxy and perfluoro C_1-C_4 alkyl, where R' and R" are as defined above.

In some embodiments, substituents are independently selected from substituted or unsubstituted heteroatom, substituted or unsubstituted, 0-3 heteroatom-containing C_1-C_6 alkyl (e.g., C_1-C_3 alkyl or C_1-C_2 alkyl), substituted or unsubstituted, 0-3 heteroatom-containing C_2-C_6 alkenyl (e.g., C_2-C_4 alkenyl), substituted or unsubstituted, 0-3 heteroatom-containing C_2-C_6 alkynyl (e.g., C_2-C_4 alkynyl), or substituted or unsubstituted, 0-3 heteroatom-containing C_6-C_{14} aryl (e.g., C_5-C_6 aryl), wherein each heteroatom is independently oxygen, phosphorus, sulfur, or nitrogen.

In some embodiments, substituents are independently selected from aldehyde, aldimine, alkanoyloxy, alkoxy, alkoxycarbonyl, alkyloxy, alkyl, alkenyl, alkynyl, amine, azo, halogen, carbamoyl, carbonyl, carboxamido, carboxyl, cyanyl, ester, haloformyl, hydroperoxyl, hydroxyl, imine, isocyanide, iscyante, N-tert-butoxycarbonyl, nitrate, nitrile, nitrite, nitro, nitroso, phosphate, phosphono, sulfide, sulfonyl, sulfo, sulfhydryl, thiol, thiocyanyl, trifluoromethyl, and trifluromethyl ether (OCF_3) groups.

Preferred substituents are disclosed herein and exemplified in the tables, structures, examples, and claims, and may be applied across different compounds of this disclosure. For example, substituents of a given compound may be combinatorically used with other compounds.

It may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps are separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example, reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art may apply such techniques to achieve a desired separation.

Non-limiting examples of suitable solvents that may be used in this disclosure include water, methanol (MeOH), ethanol (EtOH), dichloromethane or methylene chloride (CH_2Cl_2), toluene, acetonitrile (MeCN), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), methyl acetate (MeOAc), ethyl acetate (EtOAc), heptanes, isopropyl acetate (IPAc), *tert*-butyl acetate (*t*-BuOAc), isopropyl alcohol (IPA), tetrahydrofuran (THF), 2-methyl tetrahydrofuran (2-Me THF), methyl ethyl ketone (MEK), *tert*-butanol, diethyl ether (Et_2O), methyl-*tert*-butyl ether (MTBE), 1,4-dioxane, and *N*-methyl pyrrolidone (NMP).

Non-limiting examples of suitable bases that may be used in this disclosure include 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), potassium tert-butoxide (KOtBu), potassium carbonate (K_2CO_3), *N*-methylmorpholine (NMM), triethylamine (Et_3N; TEA), diisopropyl-ethyl amine (*i*-Pr_2EtN; DIPEA), pyridine, potassium hydroxide (KOH), sodium hydroxide (NaOH), lithium hydroxide (LiOH), and sodium methoxide (NaOMe; $NaOCH_3$).

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The term "subject" refers to an animal including a human.

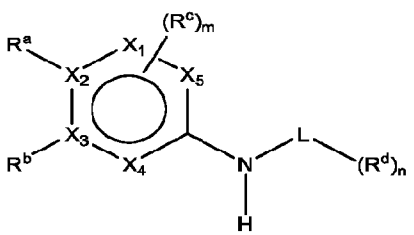
The term "therapeutically effective amount" refers to the amount of a compound that produces a desired effect for which it is administered (*e.g.*, improvement in a disease or condition, lessening the severity of a disease or condition, and/or reducing progression of a disease or condition, e.g., a disease or condition selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. The disease or condition may be involved with dysregulated, e.g., abnormal, ferroptosis. The exact amount of a therapeutically effective amount will depend on the purpose of the treatment and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lloyd (1999), The Art, Science and Technology of Pharmaceutical Compounding).

As used herein, the term "treatment" and its cognates refer to slowing or stopping disease progression. "Treatment" and its cognates as used herein include, but are not limited to the following: complete or partial remission, curing a disease or condition or a symptom thereof, lower risk of a disease or condition, e.g., neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. The disease or condition may be involved with dysregulated, e.g., abnormal, ferroptosis. Improvements in or lessening the severity of any of these symptoms can be assessed according to methods and techniques known in the art.

The terms "about" and "approximately," when used in connection with a number such as a percentage include the number as specified, and a range of the number (*e.g.*, a range of percentages, for example, a range of ±10% with respect to a specific point value) that is recognized by one of ordinary skill in the art.

II. Compounds and Compositions

In a first embodiment, a compound of this disclosure is a compound of the following structural Formula I:



Formula (I)

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

L is cycloalkyl, heterocyclyl, or C;

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X_1, X_2, X_3, X_4, and X_5 are each independently C or N;

R^a is absent or selected from H, halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is absent or selected from H, halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl;

R^a and R^b may join together to form an optionally substituted 3- to 10-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring;

R^c, for each occurrence, is independently selected from halogen, optionally substituted heteroatom, and optionally substituted alkyl;

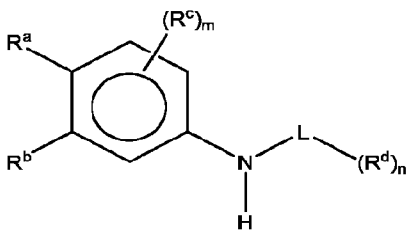
R^b and one of R^c may join together to form an optionally substituted 3- to 10-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring;

R^d, for each occurrence, is independently selected from halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and

m and n are each an integer independently selected from 0, 1, 2, and 3.

Combinations of substituents as disclosed herein are those that result in the formation of stable or chemically feasible compounds. For abbreviation or according to common practice, certain hydrogen atoms attached to a certain atom (e.g., a carbon atom C or a nitrogen atom N) are not specifically spelled out in a chemical structure, formula, or notation; hydrogen atoms are deemed to be present to the extent the valences of the certain atom (e.g., C or N) are completed.

In a second embodiment, a compound of the disclosure is a compound of the following structural Formula IIa:

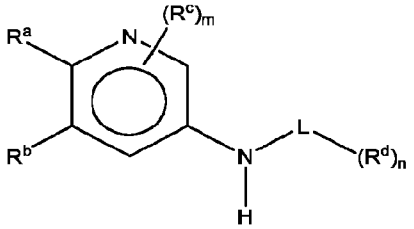


Formula IIa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a third embodiment, a compound of the disclosure is a compound of the following structural Formula IIb:

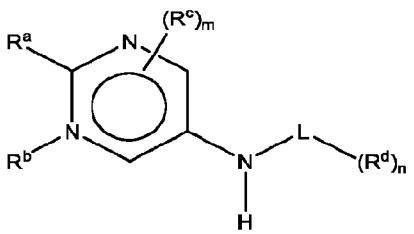
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Formula IIb

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

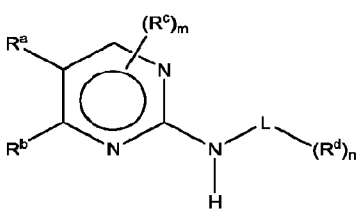
In a fourth embodiment, a compound of the disclosure is a compound of the following structural Formula IIc:



Formula IIc

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

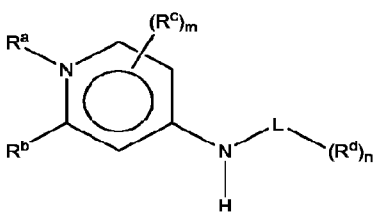
In a fifth embodiment, a compound of the disclosure is a compound of the following structural Formula IId:



Formula IId

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

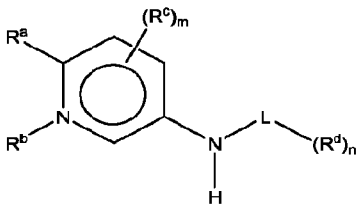
In a sixth embodiment, a compound of the disclosure is a compound of the following structural Formula IIe:



Formula IIe

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

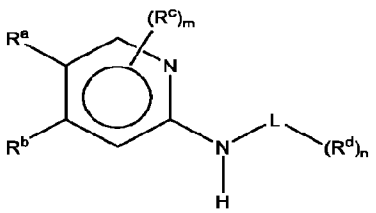
In a seventh embodiment, a compound of the disclosure is a compound of the following structural Formula IIf:



Formula IIf

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

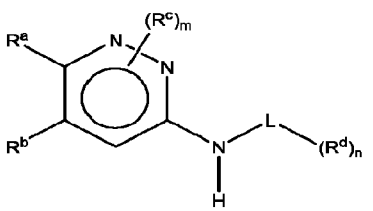
In an eighth embodiment, a compound of the disclosure is a compound of the following structural Formula IIg:



Formula IIg

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a ninth embodiment, a compound of the disclosure is a compound of the following structural Formula IIh:

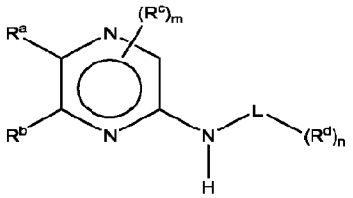


Formula IIh

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a tenth embodiment, a compound of the disclosure is a compound of the following structural Formula IIi:

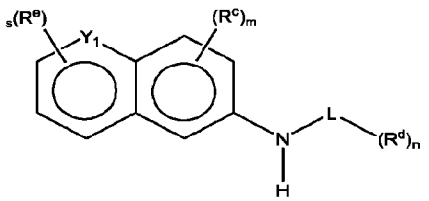
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Formula IIi

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

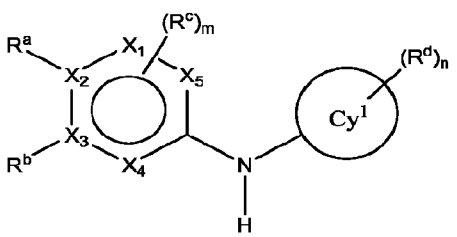
In an eleventh embodiment, a compound of the disclosure is a compound of the following structural Formula IIj:



Formula IIj

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

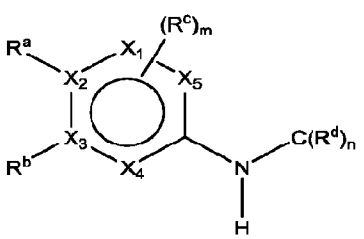
In a twelfth embodiment, a compound of the disclosure is a compound of the following structural Formula IIIa:



Formula IIIa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; wherein Cy^1 is 3- to 10-membered cycloalkyl or 3- to 10-membered heterocyclyl; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

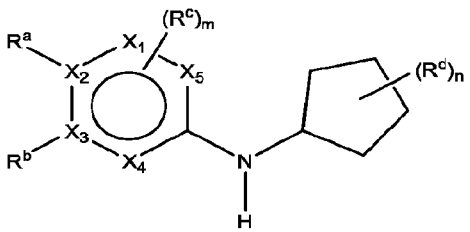
In a thirteenth embodiment, a compound of the disclosure is a compound of the following structural Formula IIIb:



Formula IIIb

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

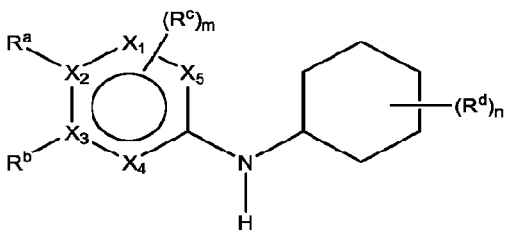
In a fourteenth embodiment, a compound of the disclosure is a compound of the following structural Formula IVa:



Formula IVa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

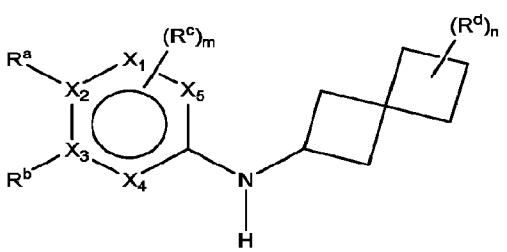
In a fifteenth embodiment, a compound of the disclosure is a compound of the following structural Formula IVb:



Formula IVb

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a sixteenth embodiment, a compound of the disclosure is a compound of the following structural Formula IVc:

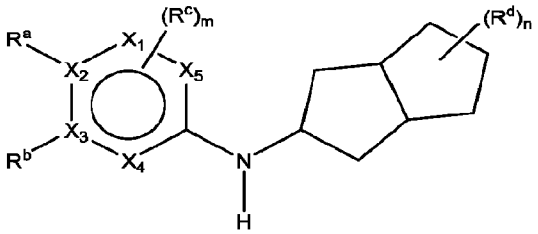


Formula IVc

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a seventeenth embodiment, a compound of the disclosure is a compound of the following structural Formula IVd:

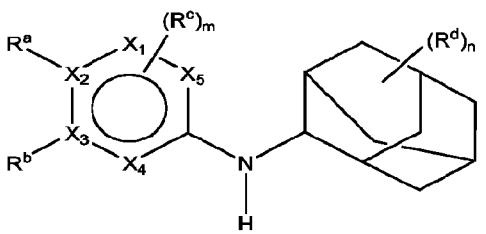
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Formula IVd

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

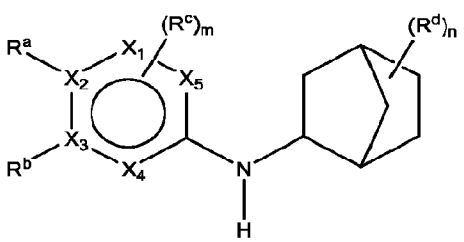
In an eighteenth embodiment, a compound of the disclosure is a compound of the following structural Formula IVe:



Formula IVe

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

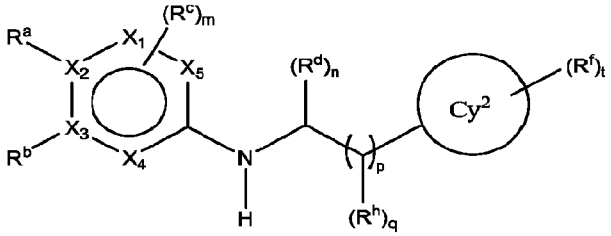
In a nineteenth embodiment, a compound of the disclosure is a compound of the following structural Formula IVf:



Formula IVf

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a twentieth embodiment, a compound of the disclosure is a compound of the following structural Formula Va:

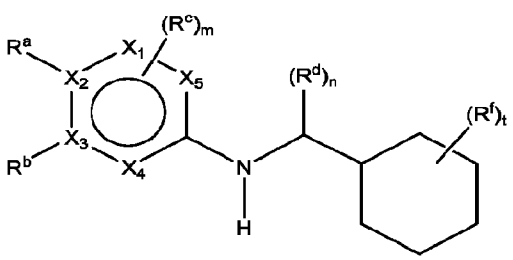


Formula Va

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Cy^2 is 3- to 10-membered cycloalkyl or 3- to 10-membered heterocyclyl; R^f, for each occurrence, is independently selected from halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; R^h, for each occurrence, is independently selected from halogen, CN, and optionally substituted C_1 to C_6 alkyl; n is an integer selected from 0, 1, and 2; p is an integer selected from 0, 1, 2, 3, 4, and 5; q is an integer selected from 0, 1, and 2; t is an integer independently selected from 0, 1, 2, and 3; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a twenty-first embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, n is 0, q is 0, and p is 0, 1, 2, and 3 each occurrence; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a twenty-second embodiment, a compound of the disclosure is a compound of the following structural Formula VIa:

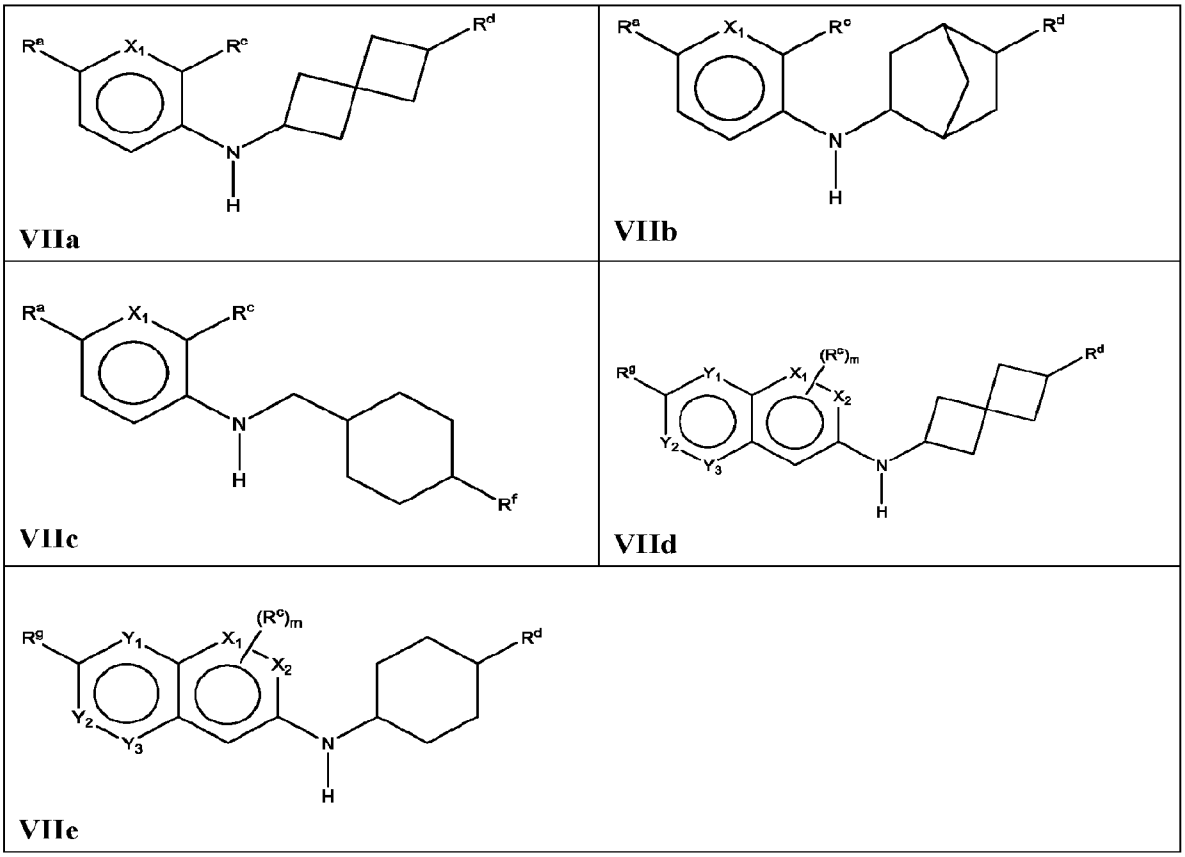


Formula VIa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing; and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a twenty-third embodiment, a compound of the disclosure is a compound of the following structural Formulae VIIa-VIIe:

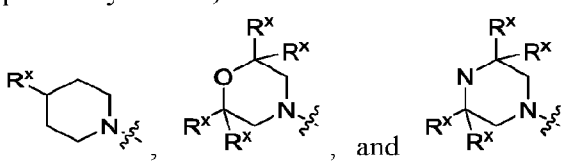
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a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

X_1 and X_2 are independently C or N;

Y_1, Y_2, and Y_3 are independently C or N;

R^a is selected from  , wherein R^x, for each occurrence, is independently selected from H, CF_3, $-CH_3$, and $-CH_2CH_3$;

R^c is selected from halogen, C_1 to C_2 alkyl, and C_1 to C_2 alkoxy;

R^d is selected from NH_2 and $-C(=O)NH_2$;

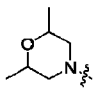
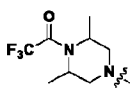
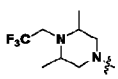
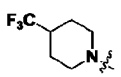
R^f is selected from NH_2 and $-C(=O)NH_2$; and

m is 0 or 1;

and all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a twenty-fourth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^e, for each occurrence, is independently selected from 5- to 6-membered cycloalkyl and 5- to 6-membered heterocyclyl; all other variables not specifically defined herein are as defined in any one of the

preceding embodiments.

In a twenty-fifth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^e is selected from  ,  ,  , and  ; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a twenty-sixth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^f, for each occurrence, is independently selected from halogen, cyano, C_1-C_{10} alkyl, phenyl, 5- to 7-membered heteroaryl, phenyl, 3- to 10-membered heterocyclyl, C_3-C_{10} cycloalkyl, $-C(=O)R^s$, C_2-C_{10} alkenyl, $=O$, $=NR^p$; $-C(=O)OR^s$, $-C(=O)NR^pR^q$, $-NR^pR^q$, and $-NR^pC(=O)R^s$, wherein

the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^f are each optionally substituted with 1 to 3 groups selected from 5- to 7-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, $-OR^s$, $-C(=O)NR^pR^q$, $-NR^pC(=O)NR^qR^r$, and $-NR^pR^q$;

the 3- to 10-membered heterocyclyl and C_3-C_{10} cycloalkyl of R^f and the 3- to 10-membered heterocyclyl and C_3-C_6 cycloalkyl of the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^f, are each optionally substituted with 1 to 3 groups selected from $=O$ and C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halogen and $-OR^s$;

the phenyl and 5- to 7-membered heteroaryl of R^f and the 5- to 7-membered heteroaryl of the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^f are each optionally substituted with 1 to 3 groups selected from C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halogen and $-OR^s$;

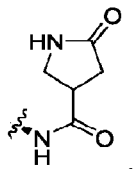
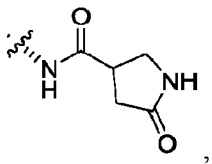
R^p, R^q, and R^r, for each occurrence, are independently selected from hydrogen, C_3-C_{10} cycloalkyl, and C_1-C_{10} alkyl, wherein the C_3-C_{10} cycloalkyl and C_1-C_{10} alkyl of R^p, R^q, and R^r are each optionally substituted with 1 to 3 groups selected from halogen, $-OR^s$ and $-C(=O)OR^s$;

R^s, for each occurrence, is independently selected from H, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, and C_1-C_{10} alkyl optionally substituted with 1 to 3 groups selected from halogen, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, and C_1-C_6 alkoxy, wherein

the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of R^s and the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of the C_1-C_{10} alkyl of R^s are each optionally substituted with 1 to 3 groups of C_1-C_6 alkyl optionally substituted by halogen, and the C_1-C_6 alkoxy of the C_1-C_{10} alkyl of R^s is optionally substituted with 1 to 3 groups of halogen; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a twenty-seventh embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^f, for

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each occurrence, is selected from H, methyl, NH_2,-$NH(CH_2)_2OH$, -CH_2NH_2,  ,  , -$NHC(=O)NH_2$, -$NHCH_3$, -$C(=O)NH_2$, and -NHBoc.

In a twenty-eighth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^a is absent or selected from hydrogen, halogen, cyano, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, 3- to 10- membered heterocyclyl, phenyl, 5- to 7- membered heteroaryl, -$C(=O)R^s$, -$C(=O)OR^s$, -NR^pR^q, -OR^s, wherein

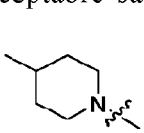
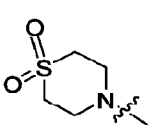
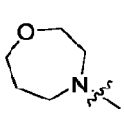
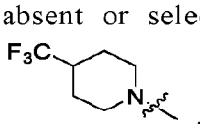
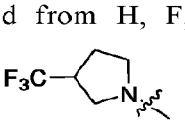
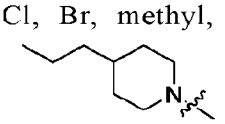
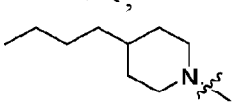
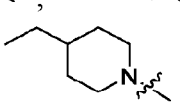
the C_3-C_{10} cycloalkyl, 3- to 10- membered heterocyclyl, phenyl, and 5- to 7- membered heteroaryl of R^a are each optionally substituted with 1-3 groups selected from halogen, OR^s, and C_1-C_{10} alkyl optionally substituted with 1 to 3 groups of halogen;

the C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl of R^a are each optionally substituted with 1 to 3 groups selected from halogen, 3- to 10- membered heterocyclyl, and -OR^s;

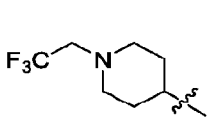
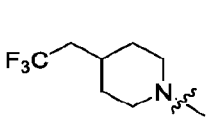
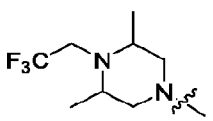
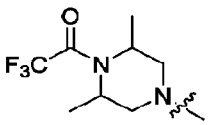
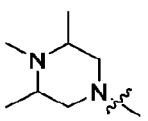
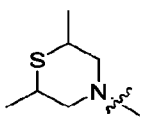
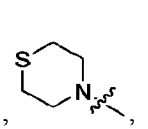
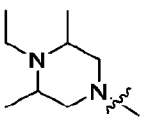
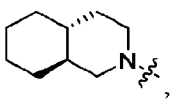
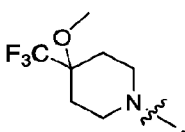
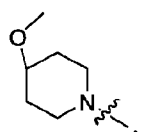
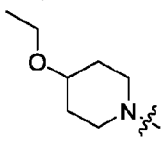
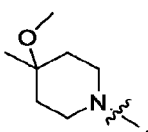
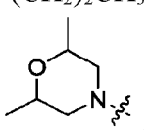
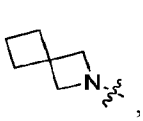
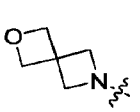
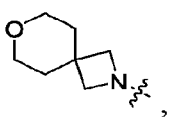
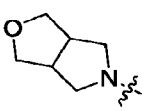
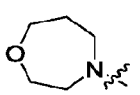
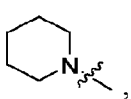
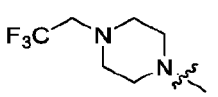
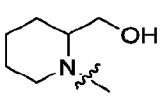
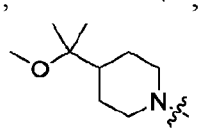
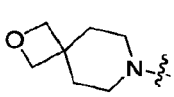
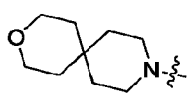
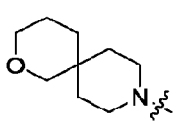
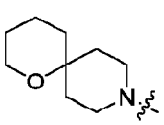
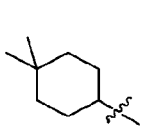
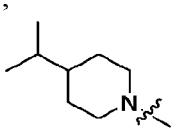
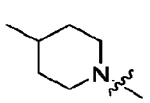
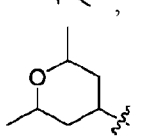
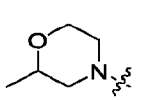
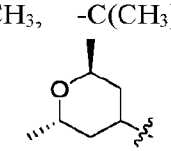
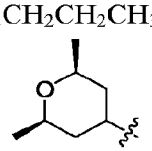
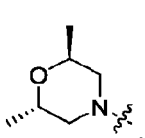
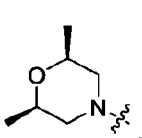
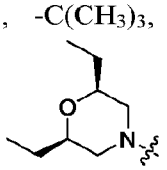
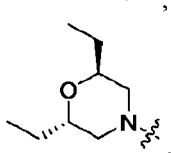
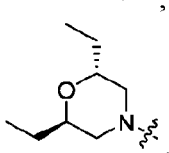
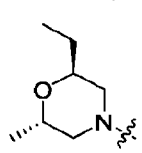
R^p and R^q, for each occurrence, are independently selected from hydrogen, C_3-C_{10} cycloalkyl, and C_1-C_{10} alkyl, wherein the C_3-C_{10} cycloalkyl and C_1-C_{10} alkyl of R^p and R^q are each optionally substituted with 1 to 3 groups selected from halogen, -OR^s and -$C(=O)OR^s$;

R^s, for each occurrence, is selected from H, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, 5- to 6-membered aryl, and C_1-C_{10} alkyl optionally substituted with 1 to 3 groups selected from halogen, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, and C_1-C_6 alkoxy, wherein the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of R^s and the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of the C_1-C_{10} alkyl of R^s are each optionally substituted with 1 to 3 groups of C_1-C_6 alkyl optionally substituted with halogen, and the C_1-C_6 alkoxy of the C_1-C_{10} alkyl of R^s is optionally substituted with 1 to 3 groups of halogen; and

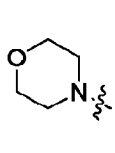
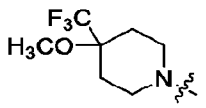
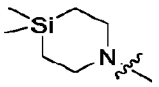
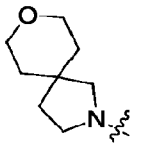
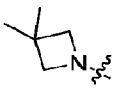
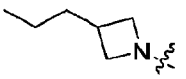
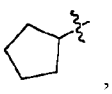
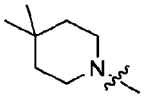
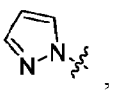
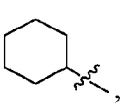
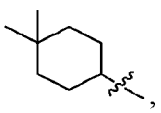
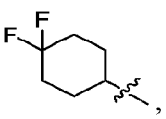
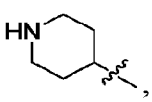
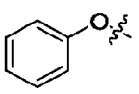
all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

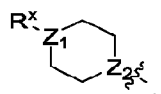
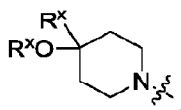
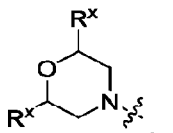
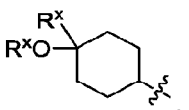
In a twenty-ninth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^a is absent or selected from H, F, Cl, Br, methyl,  ,  ,  ,  ,  ,  ,  ,  ,

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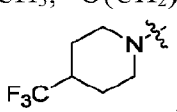









-CH(CH$_2$CH$_3$)$_2$, -CH(CH$_3$)$_2$, -OCH(CH$_3$)$_2$, -CH$_2$CH$_3$, -CH$_2$CH$_2$CH$_3$, -NHCH$_2$CF$_3$, -N(CH$_3$)CH$_2$CF$_3$, -O(CH$_2$)$_3$CH$_3$, -O(CH$_2$)$_2$CH$_3$, -(CH$_2$)$_2$CH$_3$, -(CH$_2$)$_4$CH$_3$, -(CH$_2$)$_3$CH$_3$,


















-N(CH$_2$CH$_3$)(CH$_2$)$_4$CH$_3$, -N(CH$_2$CH$_3$)(CH$_2$)$_3$OCH$_3$,



-C(CH$_3$)$_2$CH$_2$CH$_3$, -C(CH$_3$)$_2$CH$_2$CH$_2$CH$_3$, -C(CH$_3$)$_2$CH$_2$OCH$_2$CH$_3$, -C(CH$_3$)$_3$,











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 ,  ,  ,  ,  ,  ,  ,  , -$N(CH_3)_2$, -$O(CH_2)_2OCH_2CH_3$, -OCH_2CH_3, -$(CH_2)_2OCH_3$, -$(CH_2)_3OCH_2CH_3$,  ,  , -CF_3, - CH_2CF_3, -$N(CH_2CH_3)_2$,  ,  ,  ,  ,  , and  ; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirtieth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^a is selected from  ,  ,  ,  ,  , -OR^x, and -CH_2R^x, wherein Z_1 and Z_2 are independently selected from C and N, R^x, for each occurrence, is independently selected from C_1 to C_4 alkyl optionally substituted with 1 to 3 groups of halogen; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirty-first embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^b is absent or selected from H, halogen, C_1 to C_6 alkyl, -NR^pR^q, CN, C_1-C_6 alkoxy, and 5- to 6- membered heterocyclyl optionally substituted with C_1-C_3 alkyl optionally substituted with 1 to 3 groups selected from halogen, wherein R^p and R^q are each selected from C_1 to C_6 alkyl, and wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy of R^b and the C_1-C_6 alkyl of R^p and R^q are each optionally substituted with 1 to 3 groups selected from halogen; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

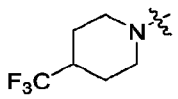
In a thirty-second embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^b is absent or H, methyl, ethyl, -$O(CH_2)_4OCH_3$, -$O(CH_2)_3OCH_3$, -$O(CH_2)_2OCH_3$, -$O(CH_2)_2NH_2$, -$(CH_2)_5CH_3$, -$O(CH_2)_5CH_3$, -$(CH_2)_2OCH_3$, -$O(CH_2)_2OH$, F, -OCH_3, -CF_3, Cl, CN, -$C(CH_3)_3$, and  ; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirty-third embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^b is

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absent or selected from halogen, C_1-C_2 alkyl, and C_1-C_2 alkoxy; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirty-fourth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^c, for each occurrence, is independently selected from halogen, C_1-C_6 alkyl, $-NR^pR^q$, CN, and C_1-C_6 alkoxy, wherein R^p and R^q are each selected from C_1 to C_6 alkyl, and wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy of R^b and the C_1-C_6 alkyl of R^p and R^q are each optionally substituted with 1 to 3 groups selected from halogen; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirty-fifth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^c is selected from methyl, ethyl, $-O(CH_2)_4OCH_3$, $-O(CH_2)_3OCH_3$, $-O(CH_2)_2OCH_3$, $-O(CH_2)_2NH_2$, $-(CH_2)_5CH_3$, $-O(CH_2)_5CH_3$, $-(CH_2)_2OCH_3$, $-O(CH_2)_2OH$, F, $-OCH_3$, $-CF_3$, Cl, CN,  , and $-C(CH_3)_3$; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirty-sixth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^c is selected from halogen, C_1-C_2 alkyl, and C_1-C_2 alkoxy; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirty-seventh embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^d, for each occurrence, is absent or independently selected from halogen, cyano, C_1-C_{10} alkyl, phenyl, 5- to 7-membered heteroaryl, phenyl, 3- to 10-membered heterocyclyl, C_3-C_{10} cycloalkyl, $-C(=O)R^s$, C_2-C_{10} alkenyl, =O, $=NR^p$; $-C(=O)OR^s$, $-C(=O)NR^pR^q$, $-NR^pR^q$, and $-NR^pC(=O)R^s$, wherein

the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^d are each optionally substituted with 1 to 3 groups selected from 5- to 7-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, $-OR^s$, $-C(=O)NR^pR^q$, $-NR^pC(=O)NR^qR^r$, and $-NR^pR^q$;

the 3- to 10-membered heterocyclyl and C_3-C_{10} cycloalkyl of R^d and the 3- to 10-membered heterocyclyl and C_3-C_6 cycloalkyl of the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^d, are each optionally substituted with 1 to 3 groups selected from =O and C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halogen and $-OR^s$;

the phenyl and 5- to 7-membered heteroaryl of R^d and the 5- to 7-membered heteroaryl of the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^d are each optionally substituted with 1 to 3 groups selected from C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halogen and $-OR^s$;

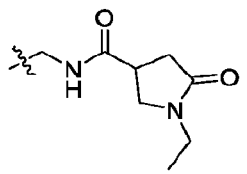
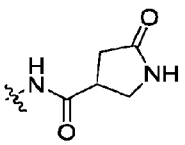
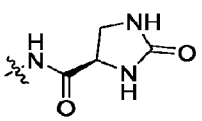
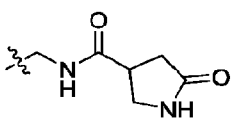
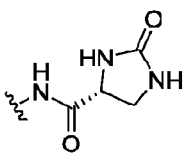
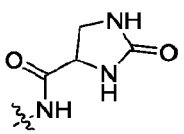
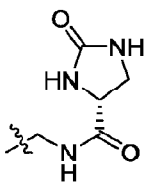
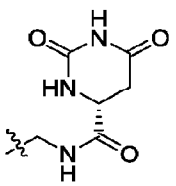
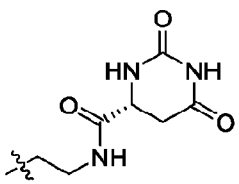
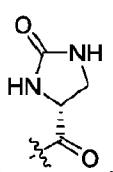
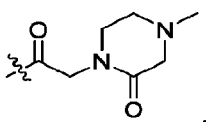
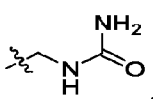
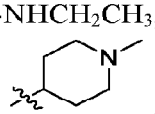
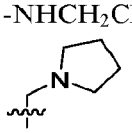
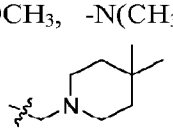
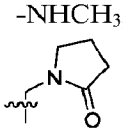
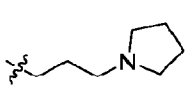
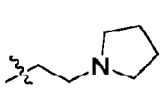
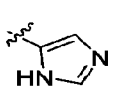
R^p, R^q, and R^r, for each occurrence, are independently selected from hydrogen, C_3-C_{10} cycloalkyl, and C_1-C_{10} alkyl, wherein the C_3-C_{10} cycloalkyl and C_1-C_{10} alkyl of R^p, R^q, and R^r are each optionally substituted with 1 to 3 groups selected from halogen, $-OR^s$ and $-C(=O)OR^s$;

R^s, for each occurrence, is independently selected from H, C_3-C_{10} cycloalkyl, 3- to 10-

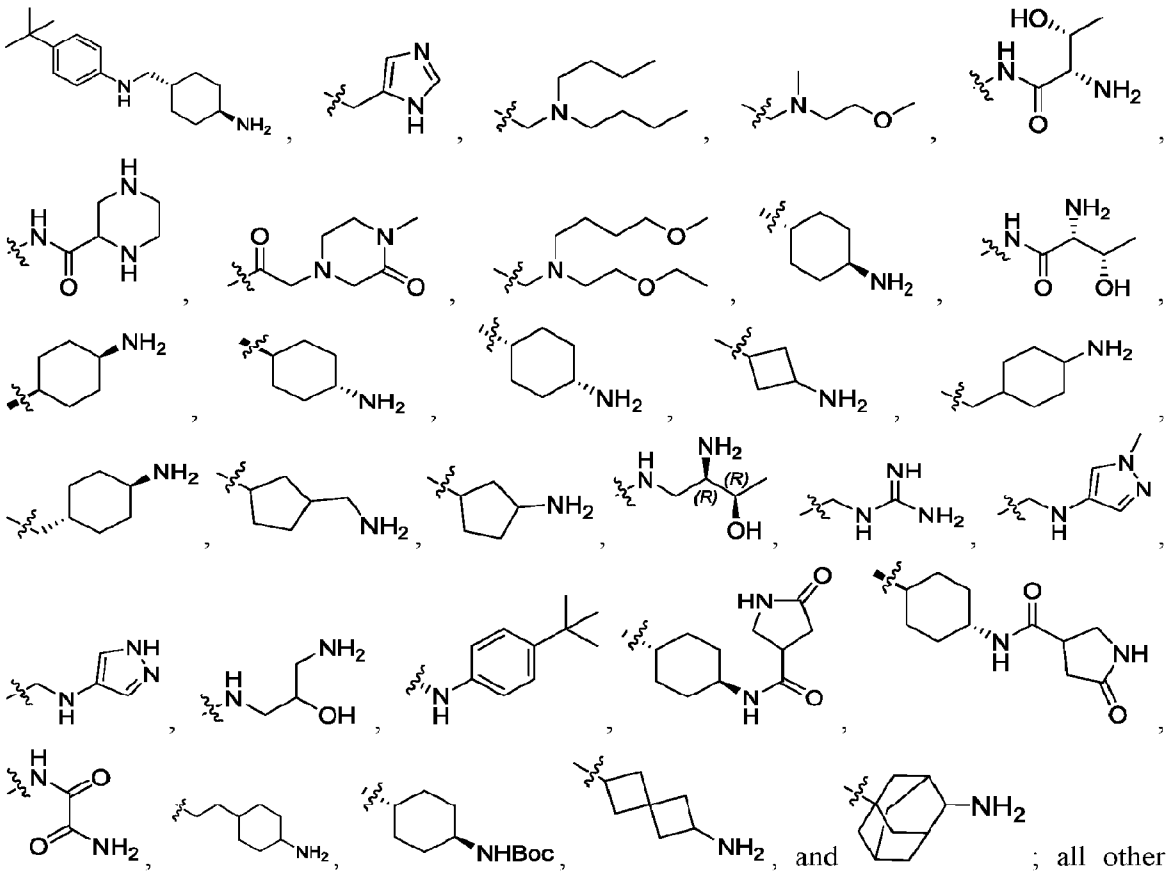
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membered heterocyclyl, and C_1-C_{10} alkyl optionally substituted with 1 to 3 groups selected from halogen, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, and C_1-C_6 alkoxy, wherein

the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of R^s and the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of the C_1-C_{10} alkyl of R^s are each optionally substituted with 1 to 3 groups of C_1-C_6 alkyl optionally substituted by halogen, and the C_1-C_6 alkoxy of the C_1-C_{10} alkyl of R^s is optionally substituted with 1 to 3 groups of halogen; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirty-eighth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^d is absent or selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , F, methyl, ethyl, propyl, butyl, $-(CH_2)_3NCH_3$, $-CH_2N(CH_3)_2$, $-CH_2N^+(CH_3)_3$, $-(CH_2)_3N(CH_3)_2$, $-(CH_2)_3NH_2$, $-(CH_2)_5NH_2$, $-(CH_2)_4NH_2$, $-CH_2CH_2NH_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CHCH_3NH_2$, $-C(CH_3)_2NH_2$, $-CH_2NH(CH_2)_2OH$, $-(CH_2)_2NHC(=O)NH_2$, $-CH_2OCH_2CH_2NH_2$, $-CH_2CH_2OH$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2OCH_2CH_2OH$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_3$, $-C(=O)NHNH_2$, $-C(=O)NHOH$, $-CH_2OH$, OH, $-O(CH_2)_2N(CH_3)_2$, =O, $-C(=O)OCH_3$, $-C(=O)OH$, $-C(=O)NH_2$, $-NH_2$, $-NHC(=O)CH_3$, $-NHC(=O)NH_2$, $-NH(CH_2)_2OH$, $-NH(CH_2)_3OH$, $-NH(CH_2)_4OH$, $-NH(CH_2)_3NH_2$, $-NH(CH_2)_2NH_2$, $-NHCH_2CH_2N(CH_3)_2$, $-NHCH_2CF_3$, $-NHCH_2CH_2F$, $-NHCH_2CHF_2$, $-NHCH_2CH_3$, $-NHCH_2CH_2OCH_3$, $-N(CH_3)_2$, $-NHCH_3$, $-NHOH$, $-NHSO_2NH_2$, $-SO_2NH_2$,  ,  ,  ,  ,  ,  ,  ,

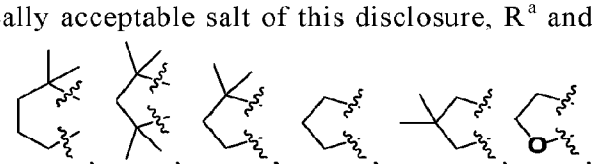
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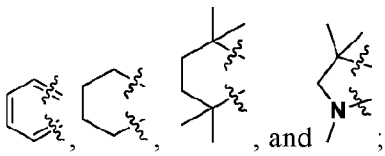
; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a thirty-ninth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^d is selected from $-C(=O)NR^pR^q$, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with 1 to 3 groups selected from C_1-C_3 alkoxy, $-C(=O)NR^pR^q$, and $-NR^pR^q$, wherein R^p and R^q are each selected from H and C_1-C_3 alkyl; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a fortieth embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^a and R^b join to form a 5- to 6-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring optionally substituted with 1 to 4 groups selected from optionally substituted C_1-C_6 alkyl; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

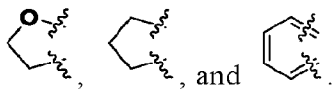
In a forty-first embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^a and R^b join to form a structure selected from: 

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; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a forty-second embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^b and R^c join to form a 5- to 6-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring optionally substituted with 1 to 4 groups selected from optionally substituted C_1-C_6 alkyl; all other variables not specifically defined herein are as defined in any one of the preceding embodiments.

In a forty-third embodiment, in a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt of this disclosure, R^b and R^c join to form a structure selected from: 

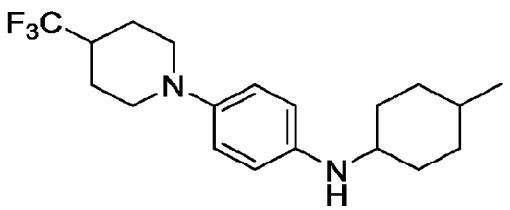
.

In certain embodiments, the at least one compound of the disclosure is selected from Compounds 1 to 573 depicted in Table 1, a tautomer thereof, a solvate or stereoisomer of the compound depicted in Table 1 or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

In certain embodiments, the at least one compound of the disclosure is selected from Compounds 574 to 661 depicted in Table 1, a tautomer thereof, a solvate or stereoisomer of the compound depicted in Table 1 or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

Certain compounds in this disclosure were prepared and obtained as a mixture of stereoisomers. For example, Compound 124 was prepared and obtained as a mixture of two stereoisomers of the compound in a 1 to 0.3 ratio (described as a "1:0.3 mixture" in the following paragraph), wherein the ratio of the stereoisomers was determined by NMR.

In this disclosure, when a compound is denoted with a compound number with an affix, e.g., "A/B" or "A/B/C/D", it means that stereoisomers, e.g., two or four stereoisomers, denoted as A and B, respectively, or denoted as A, B, C, and D, respectively, of the compound were prepared, isolated, and tested. For example,

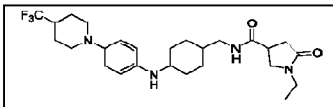
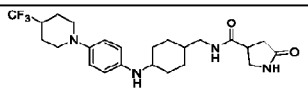
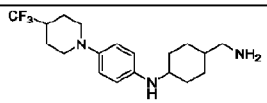
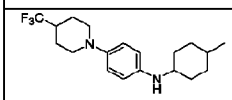
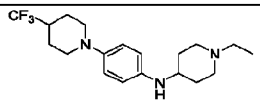
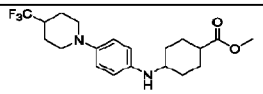
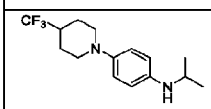
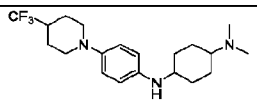
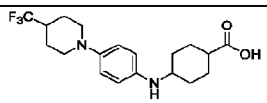
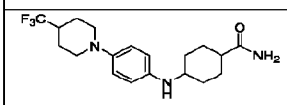
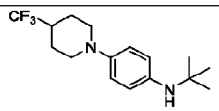
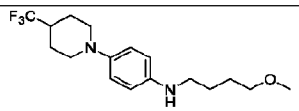
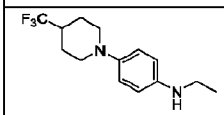
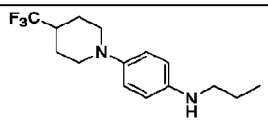
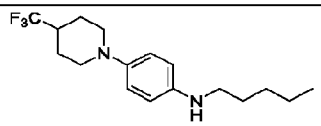
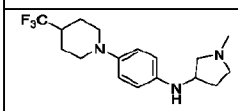
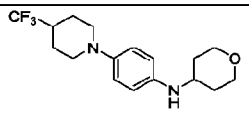
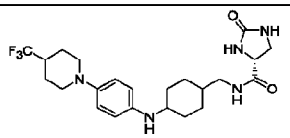
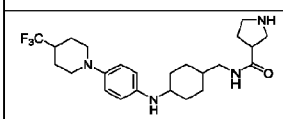
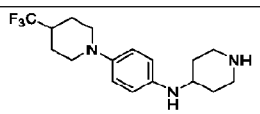
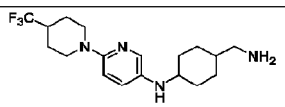
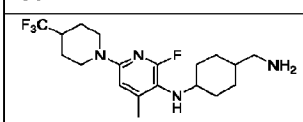
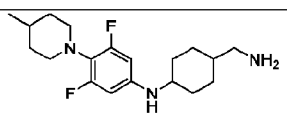
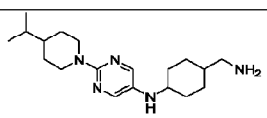
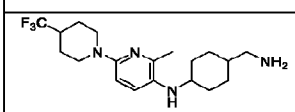
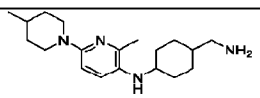
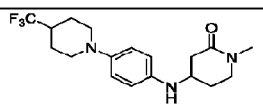
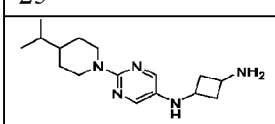
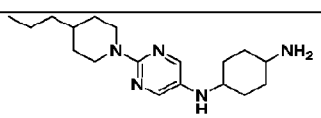
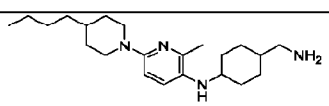


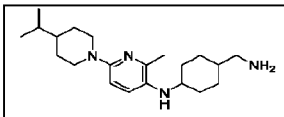
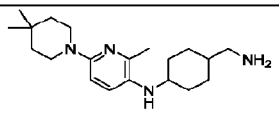
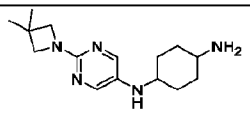
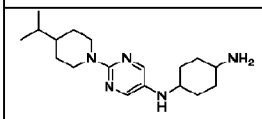
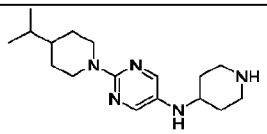
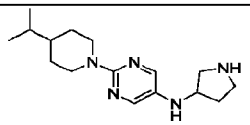
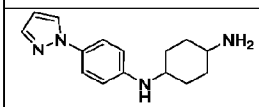
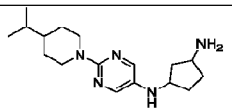
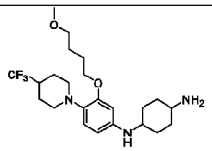
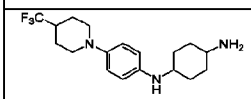
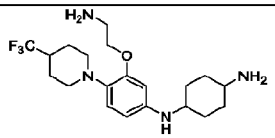
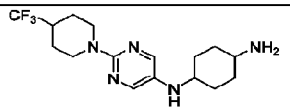
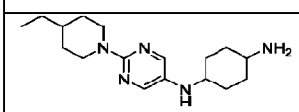
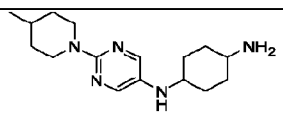
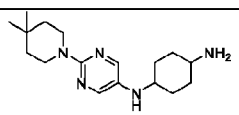
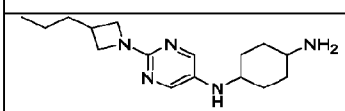
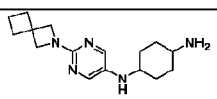
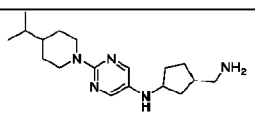
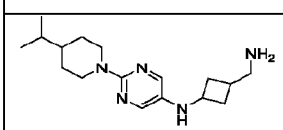
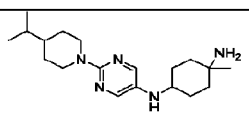
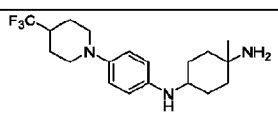
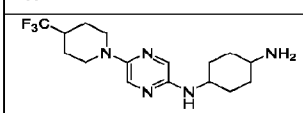
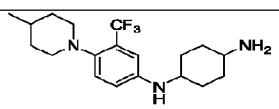
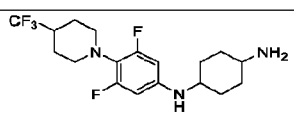
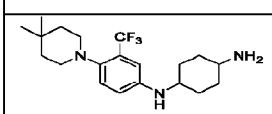
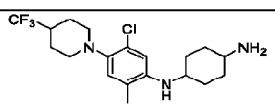
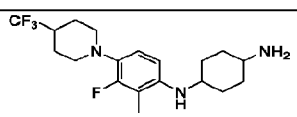
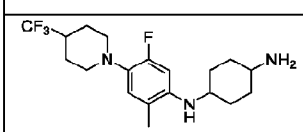
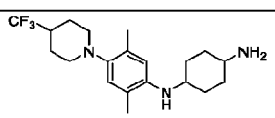
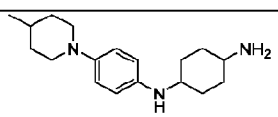
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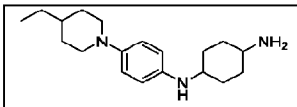
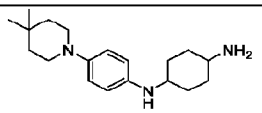
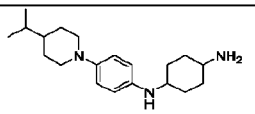
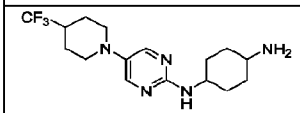
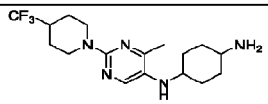
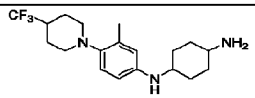
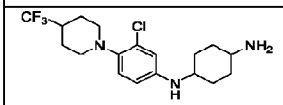
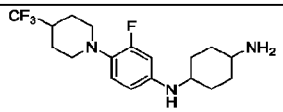
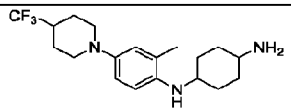
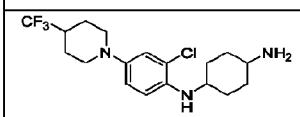
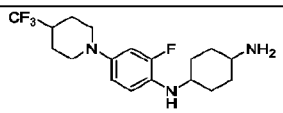
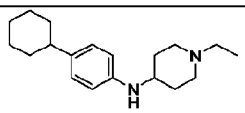
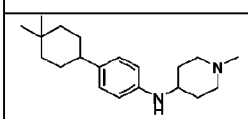
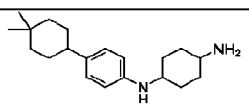
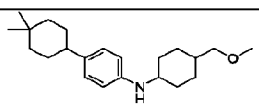
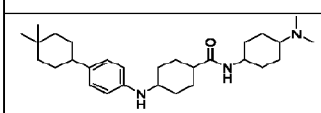
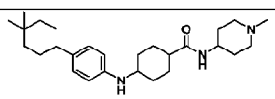
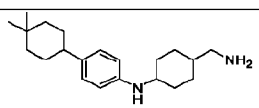
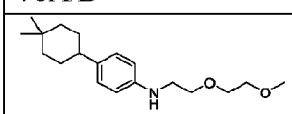
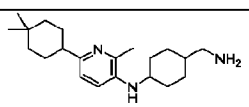
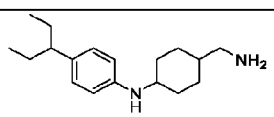
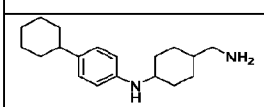
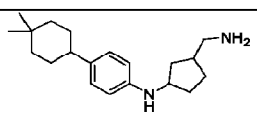
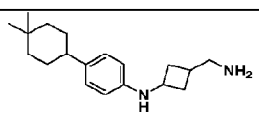
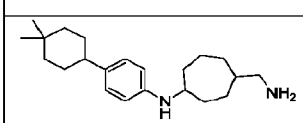
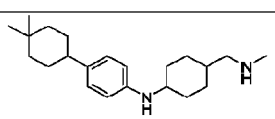
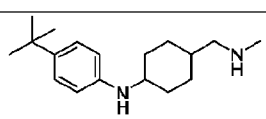
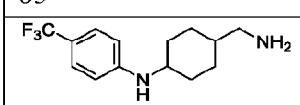
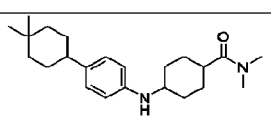
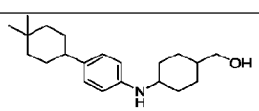
means that two stereoisomers of compound 4 (4A and 4B) were prepared and isolated (see the paragraph in Example 1) and tested (see the paragraphs in Example 2).

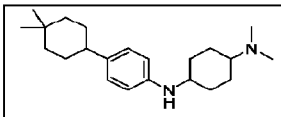
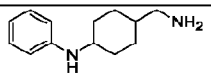
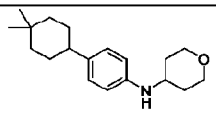
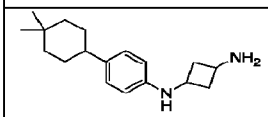
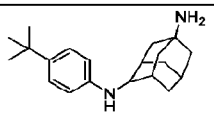
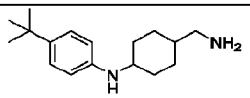
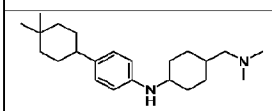
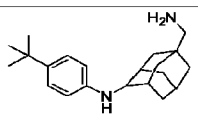
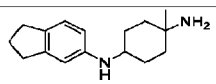
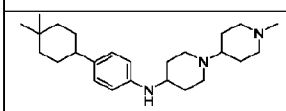
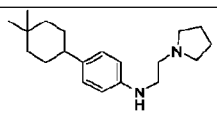
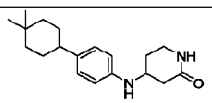
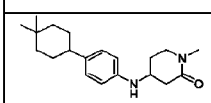
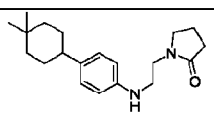
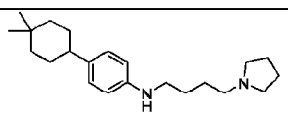
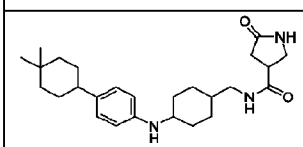
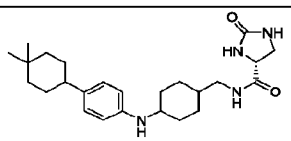
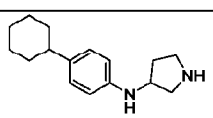
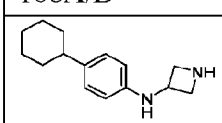
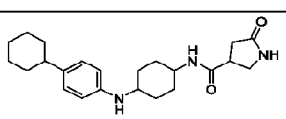
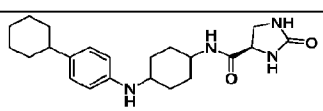
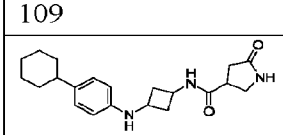
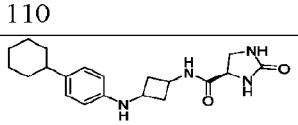
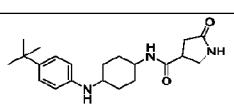
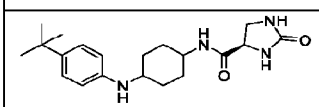
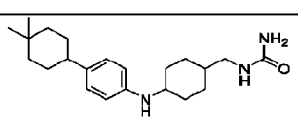
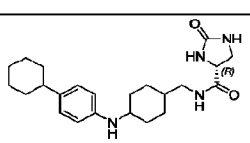
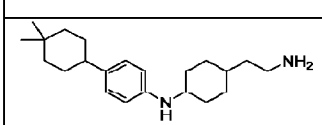
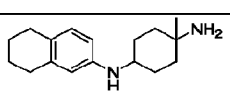
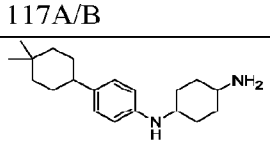
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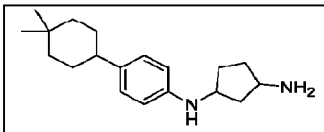
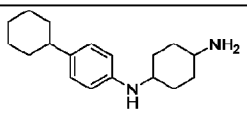
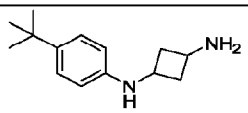
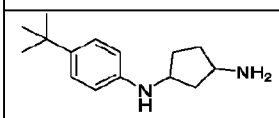
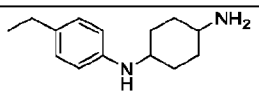
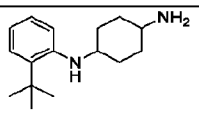
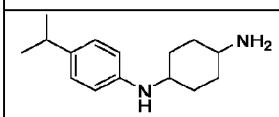
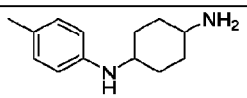
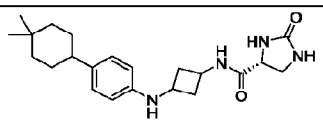
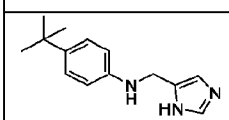
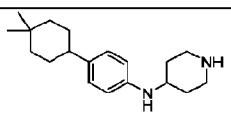
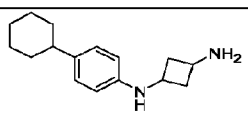
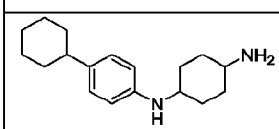
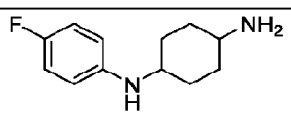
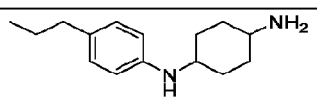
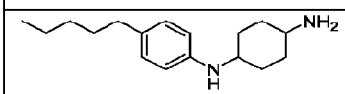
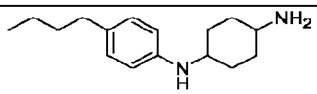
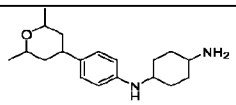
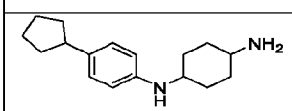
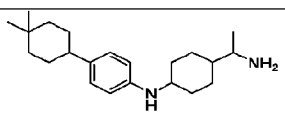
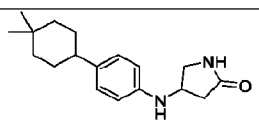
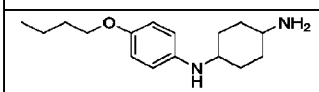
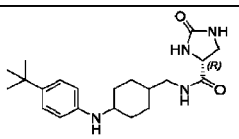
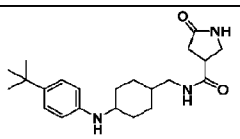
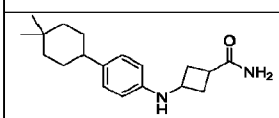
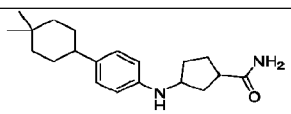
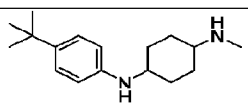
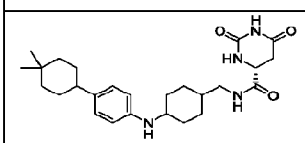
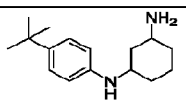
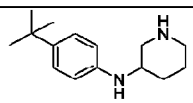
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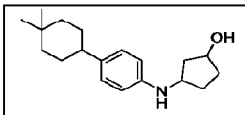
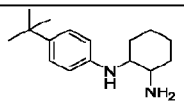
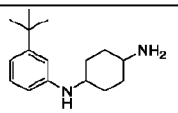
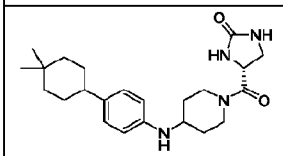
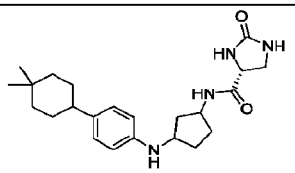
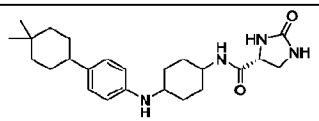
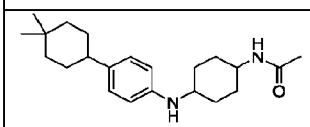
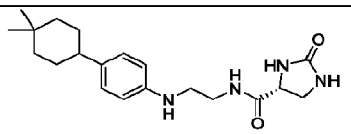
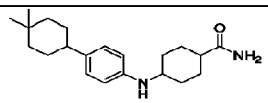
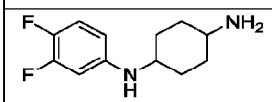
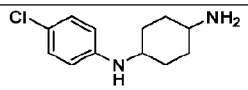
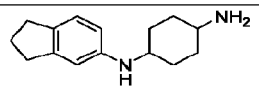
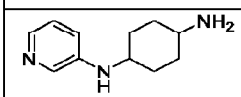
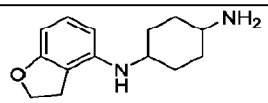
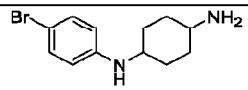
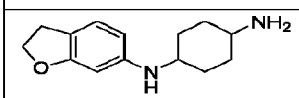
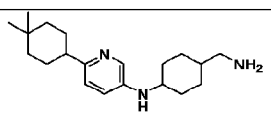
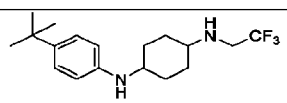
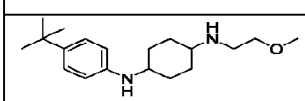
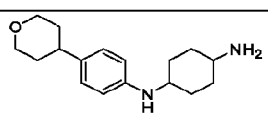
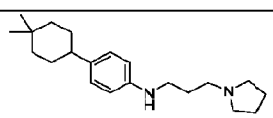
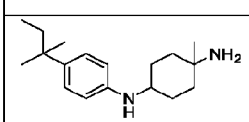
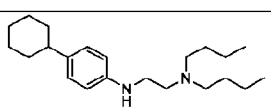
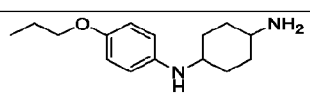
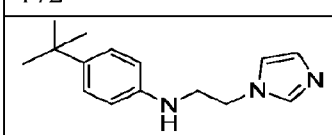
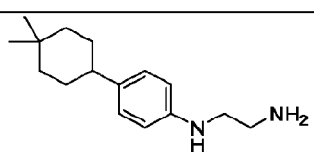
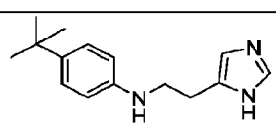
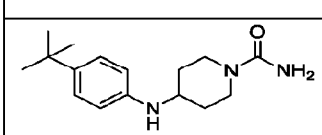
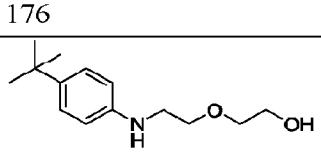
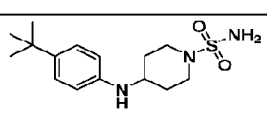
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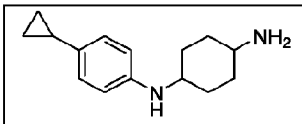
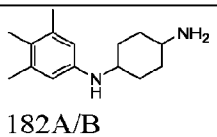
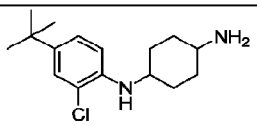
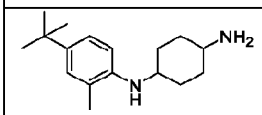
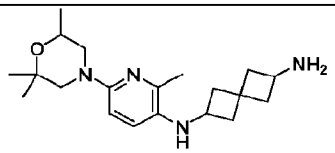
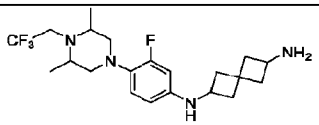
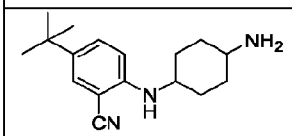
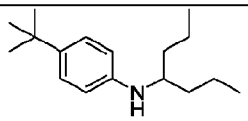
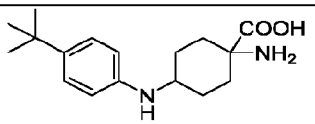
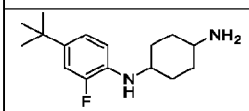
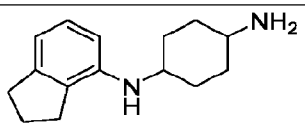
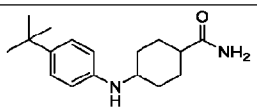
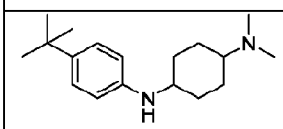
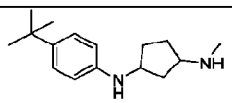
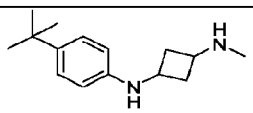
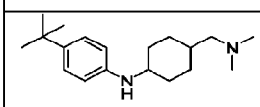
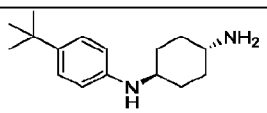
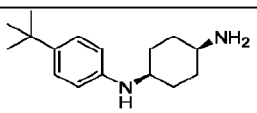
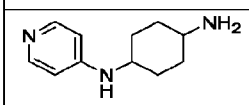
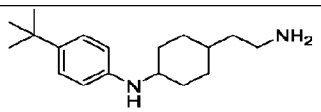
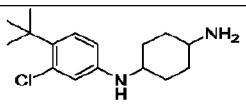
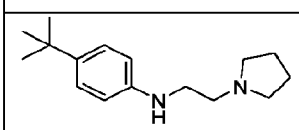
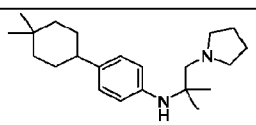
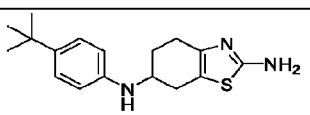
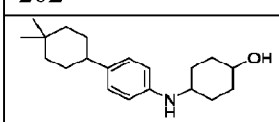
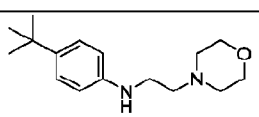
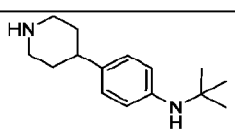
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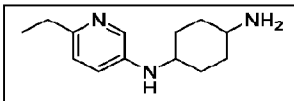
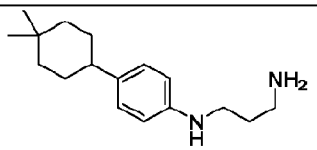
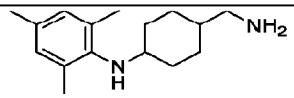
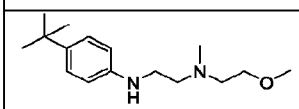
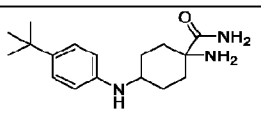
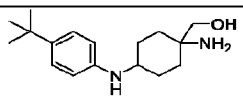
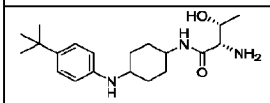
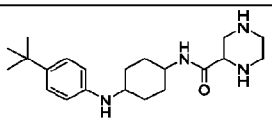
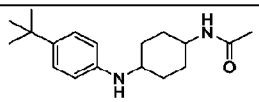
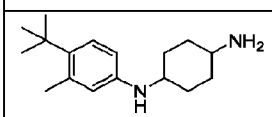
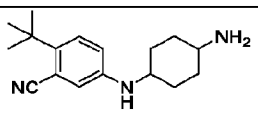
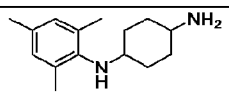
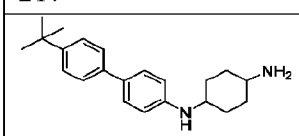
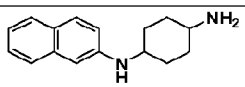
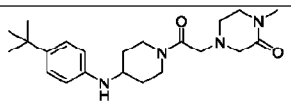
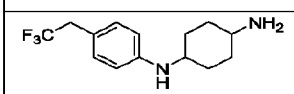
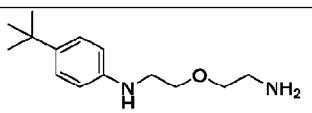
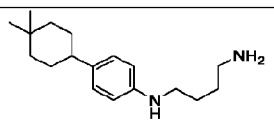
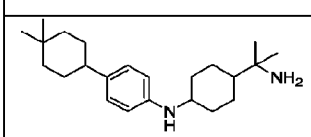
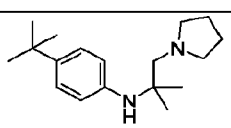
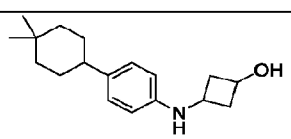
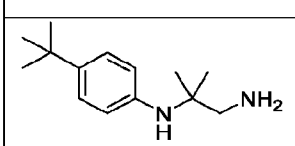
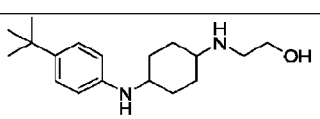
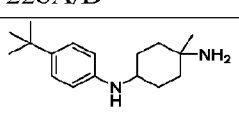
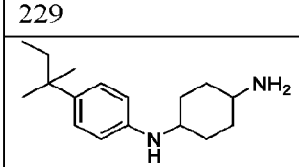
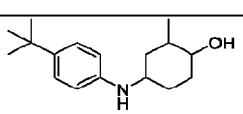
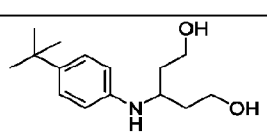
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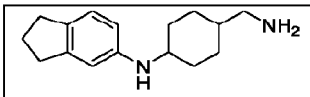
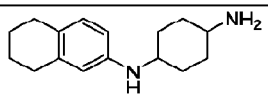
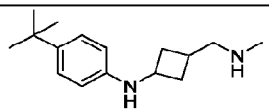
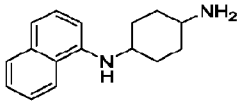
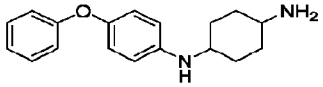
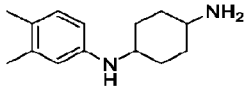
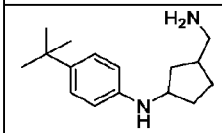
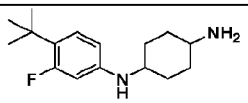
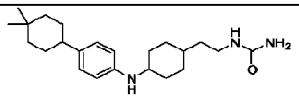
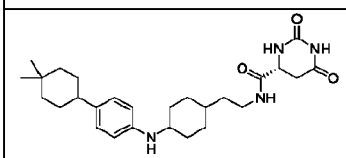
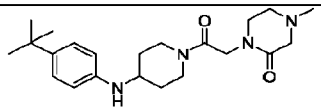
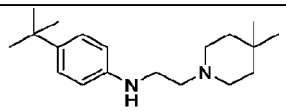
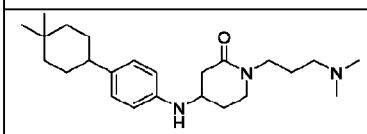
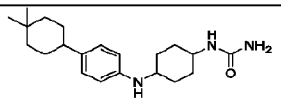
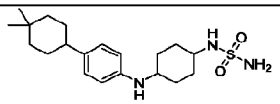
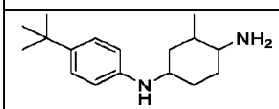
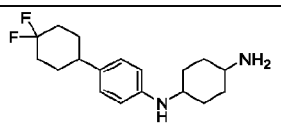
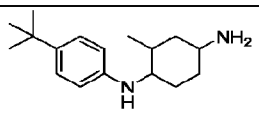
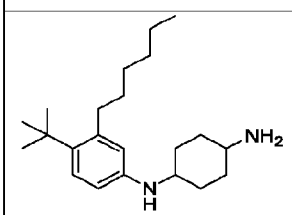
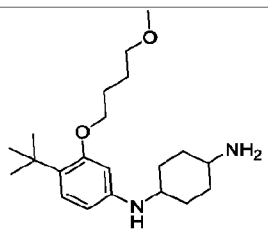
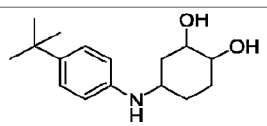
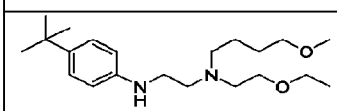
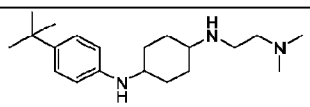
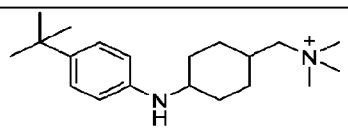
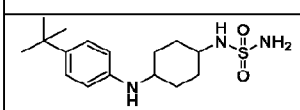
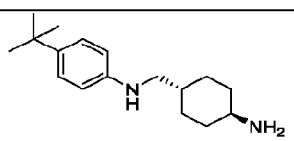
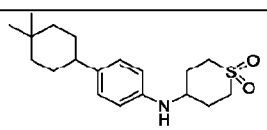
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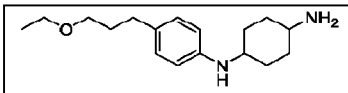
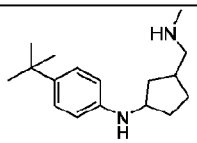
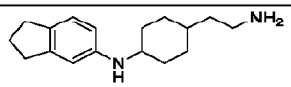
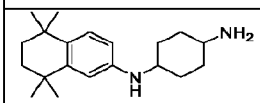
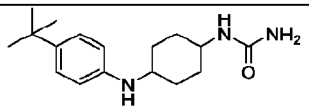
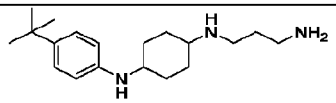
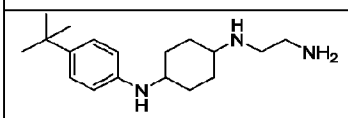
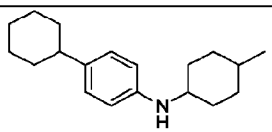
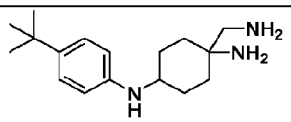
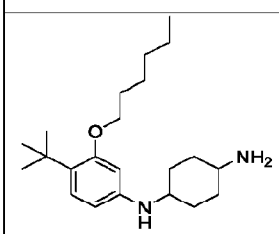
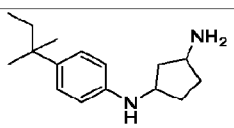
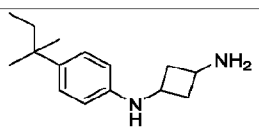
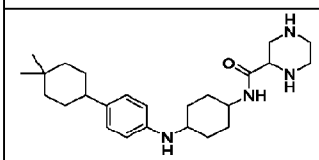
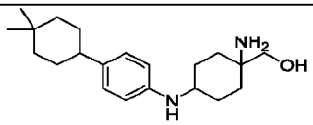
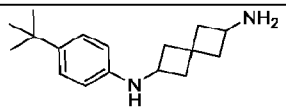
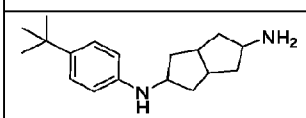
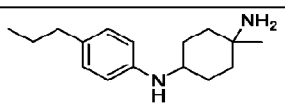
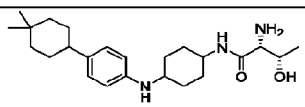
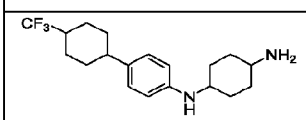
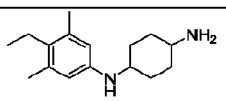
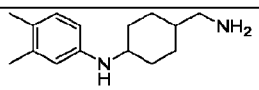
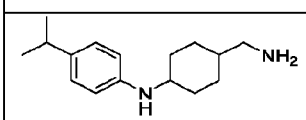
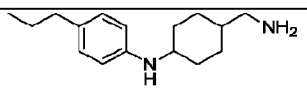
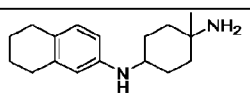
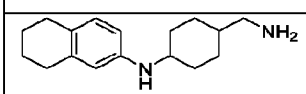
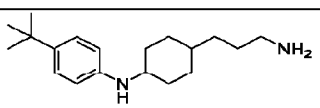
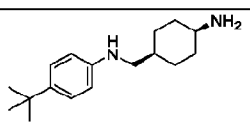
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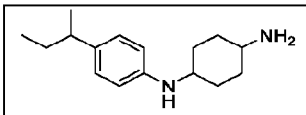
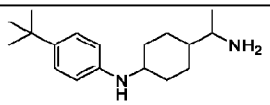
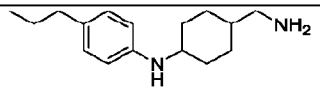
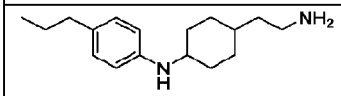
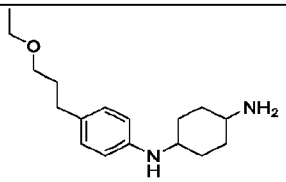
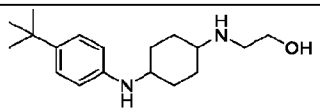
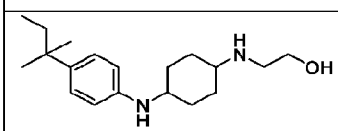
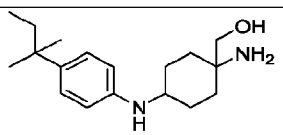
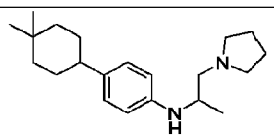
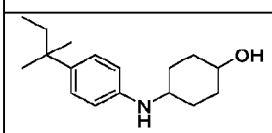
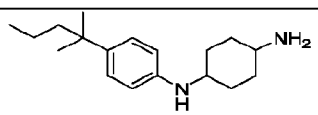
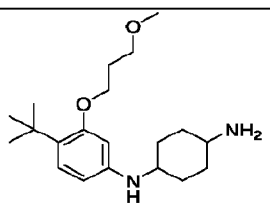
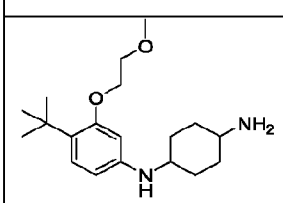
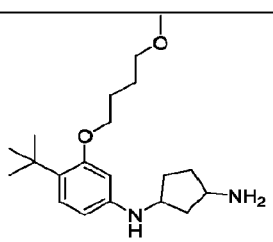
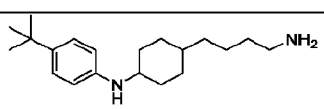
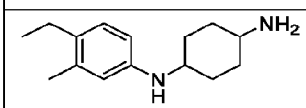
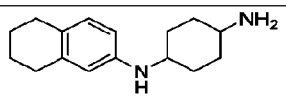
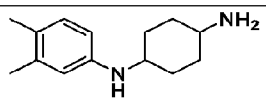
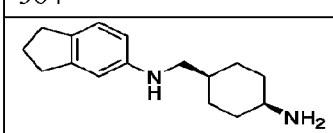
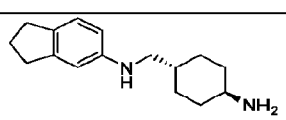
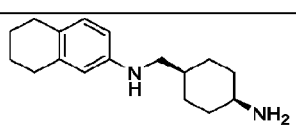
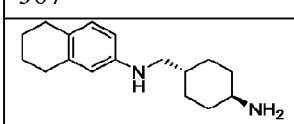
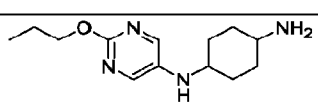
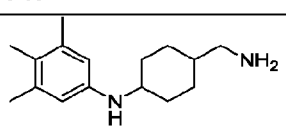
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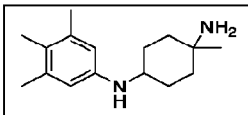
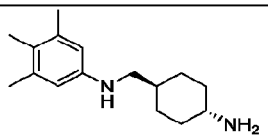
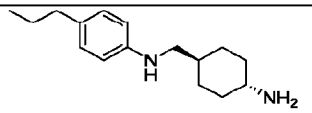
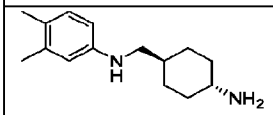
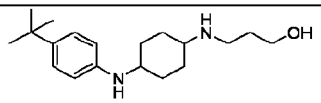
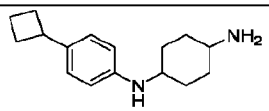
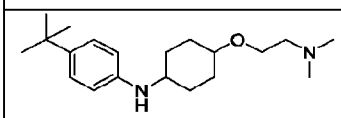
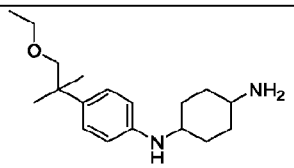
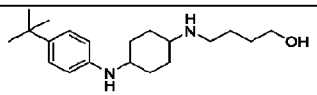
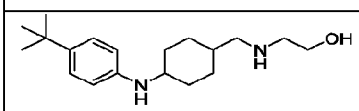
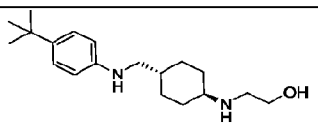
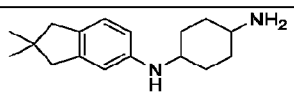
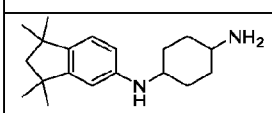
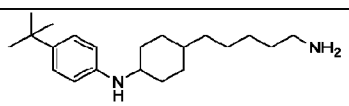
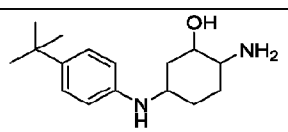
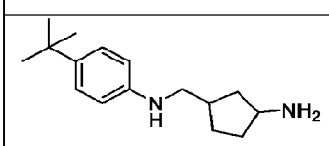
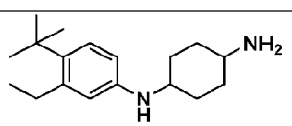
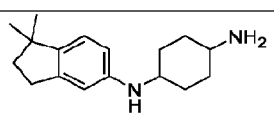
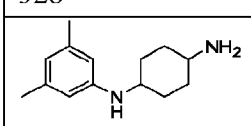
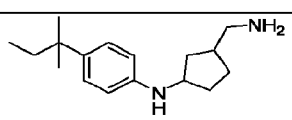
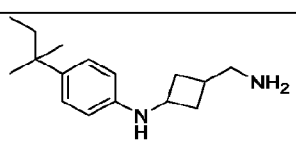
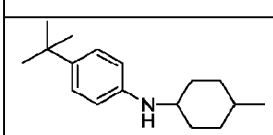
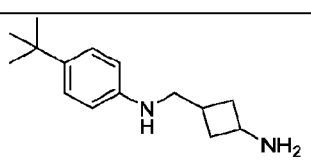
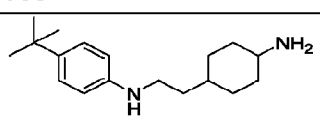
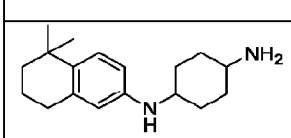
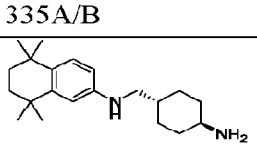
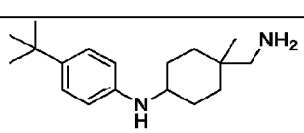
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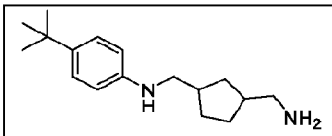
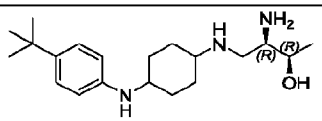
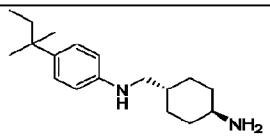
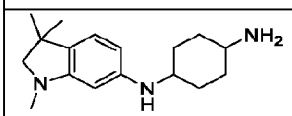
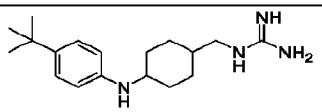
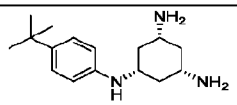
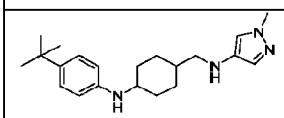
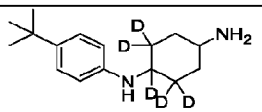
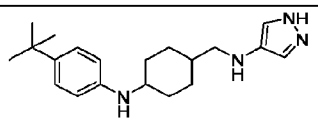
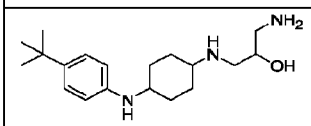
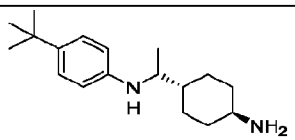
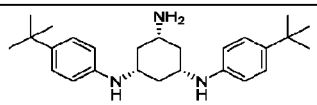
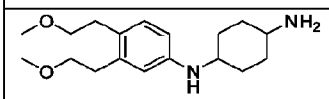
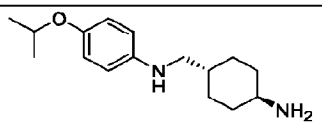
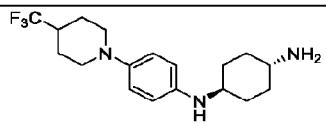
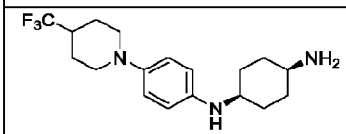
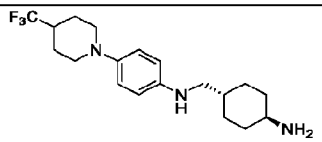
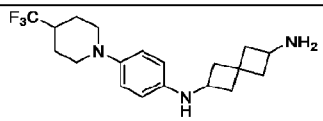
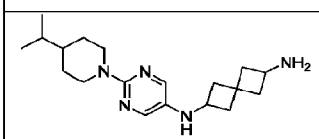
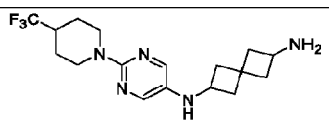
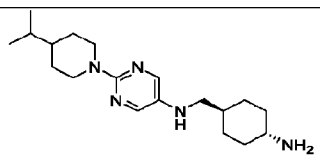
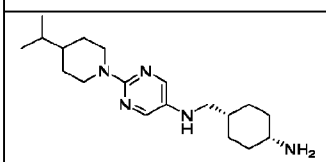
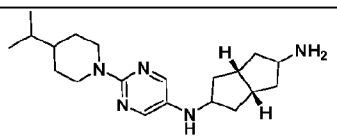
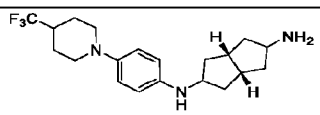
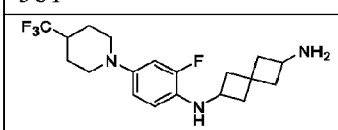
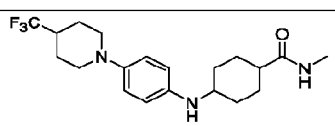
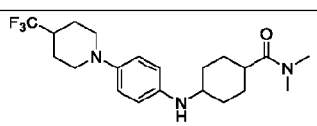
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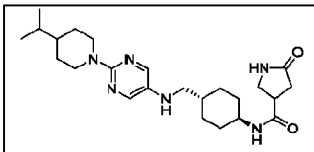
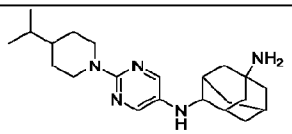
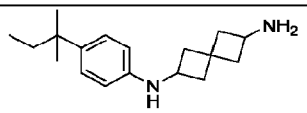
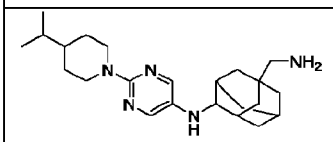
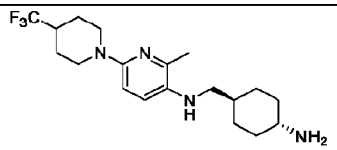
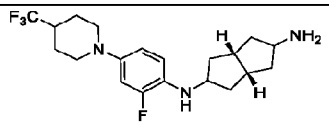
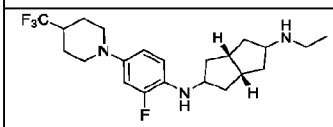
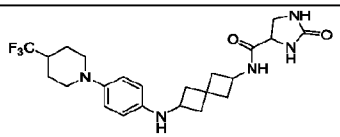
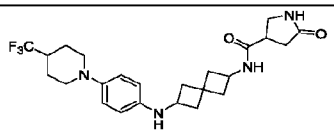
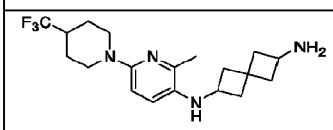
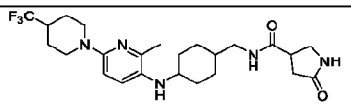
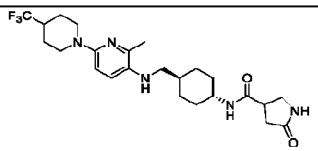
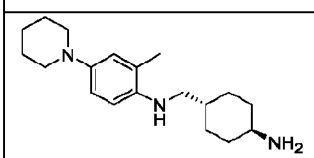
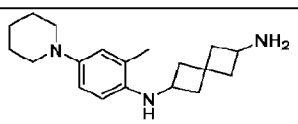
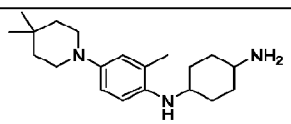
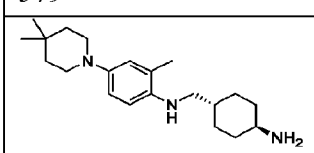
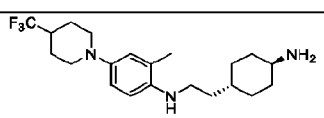
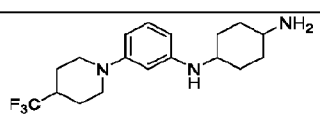
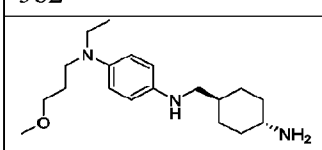
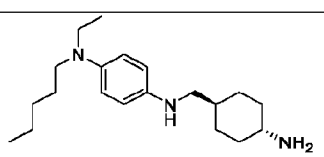
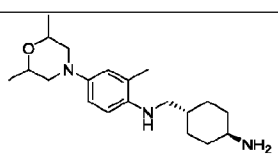
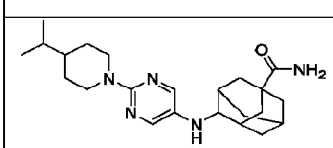
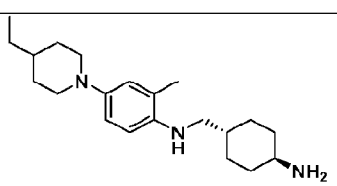
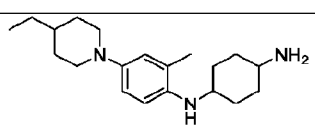
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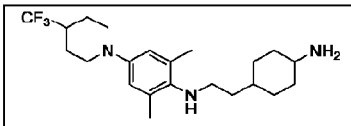
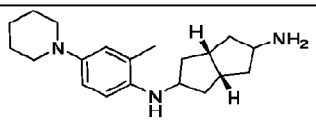
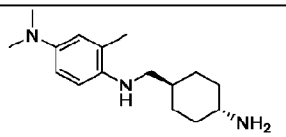
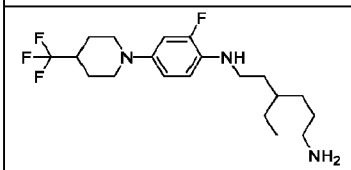
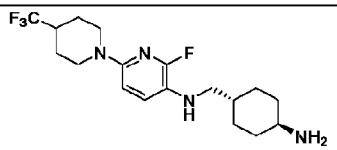
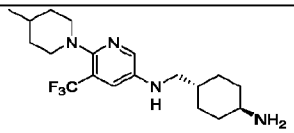
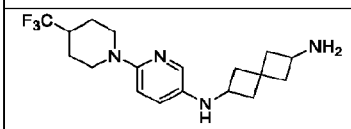
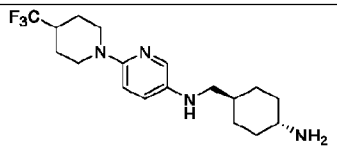
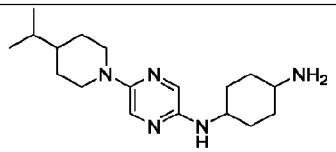
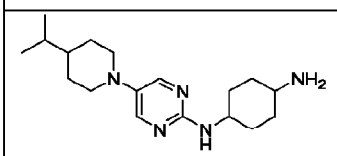
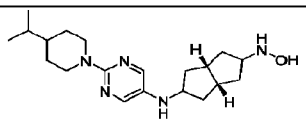
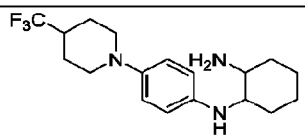
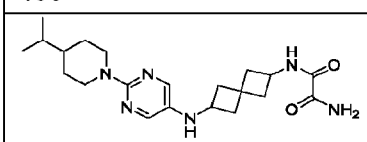
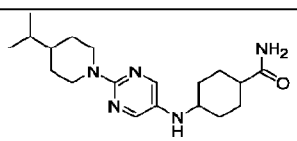
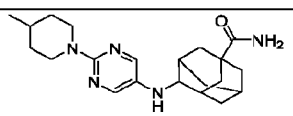
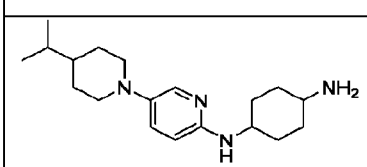
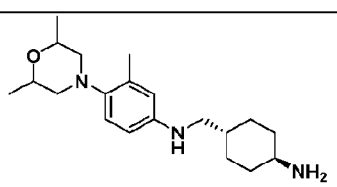
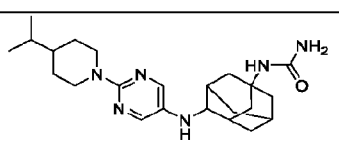
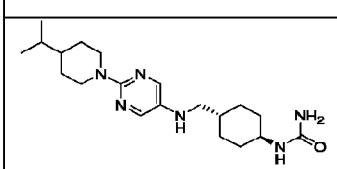
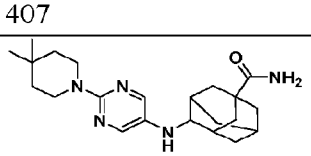
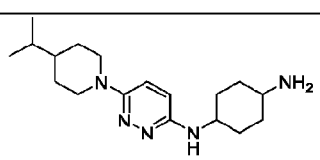
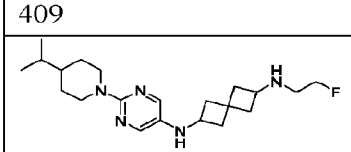
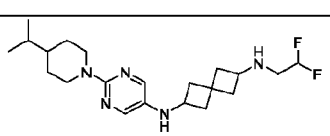
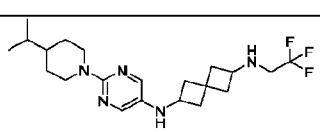
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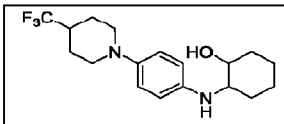
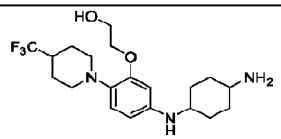
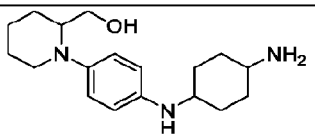
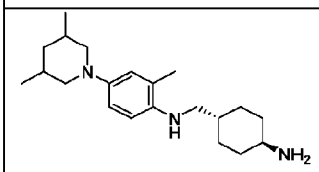
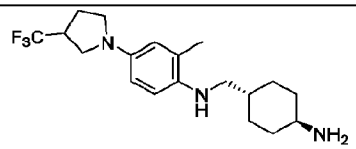
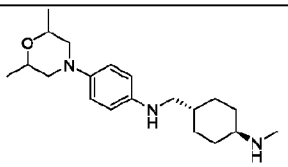
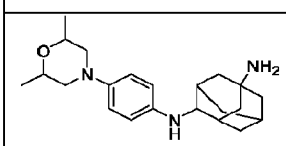
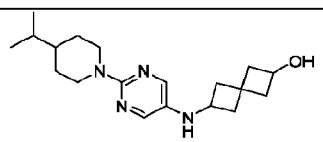
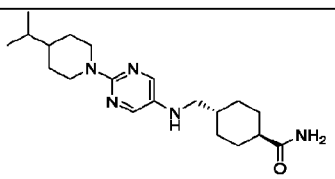
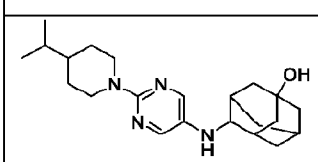
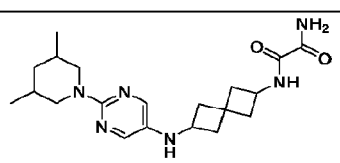
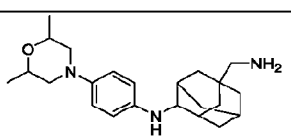
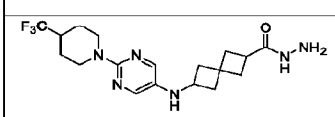
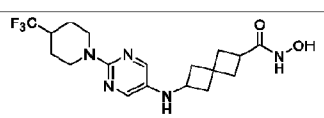
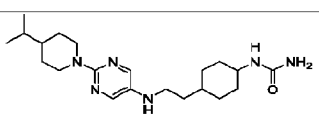
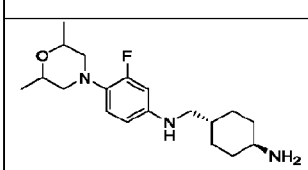
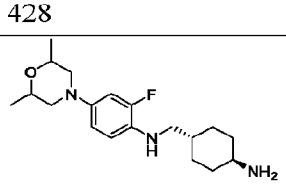
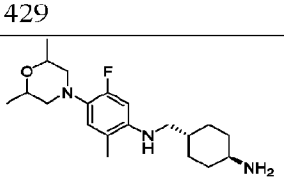
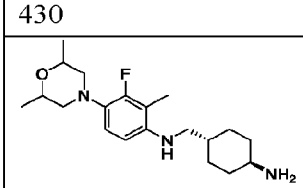
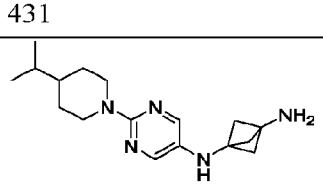
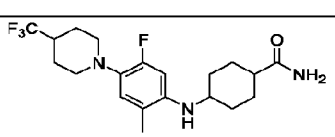
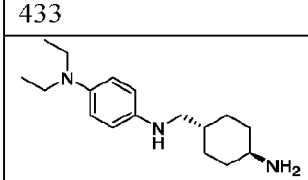
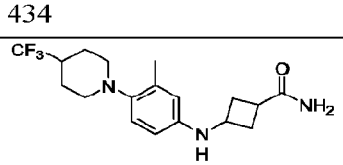
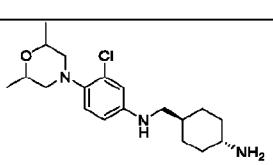
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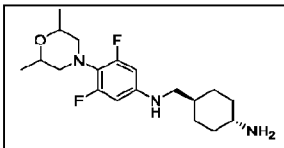
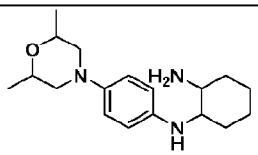
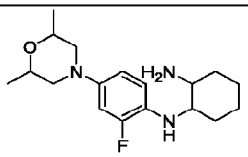
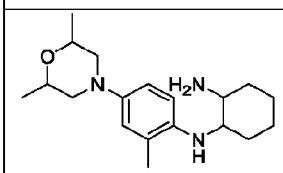
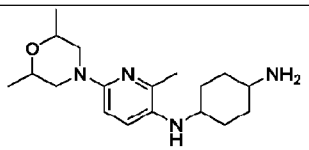
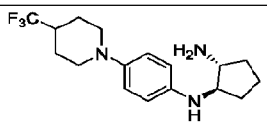
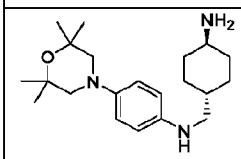
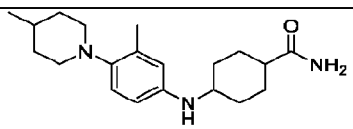
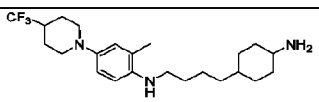
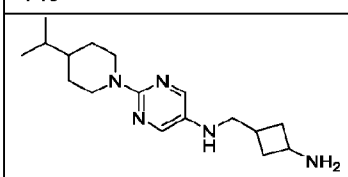
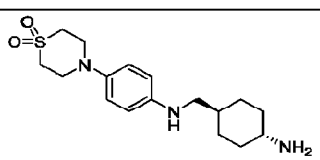
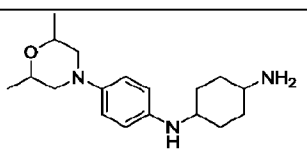
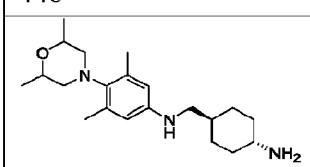
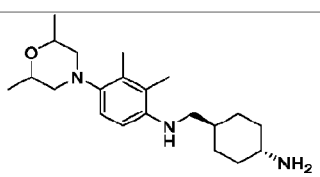
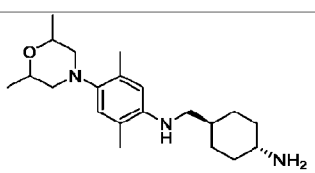
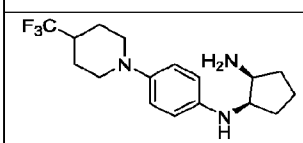
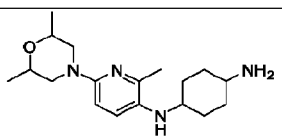
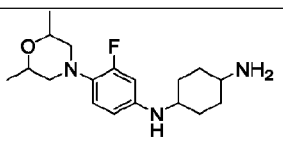
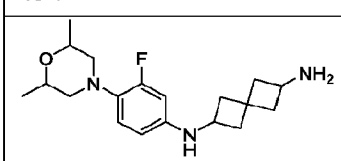
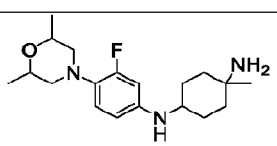
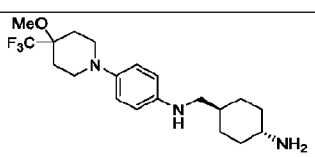
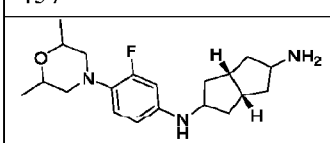
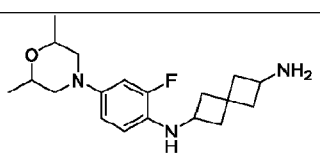
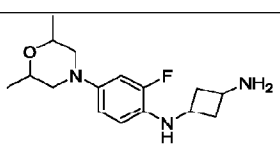
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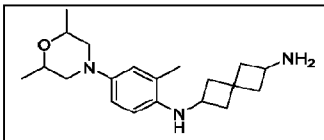
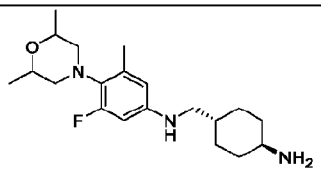
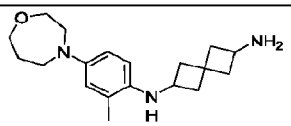
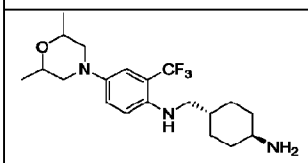
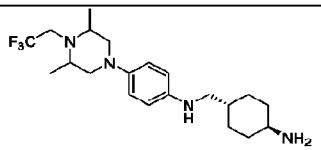
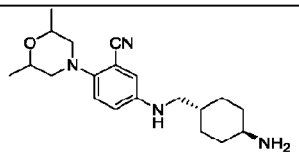
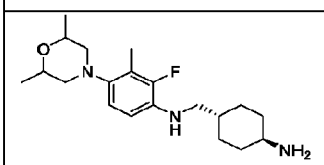
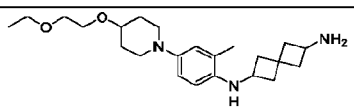
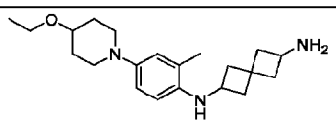
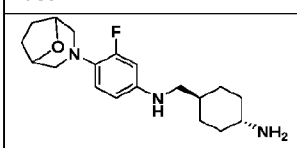
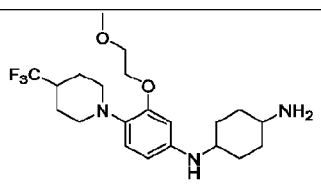
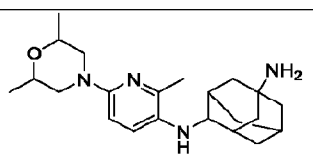
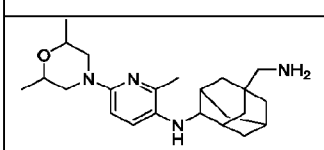
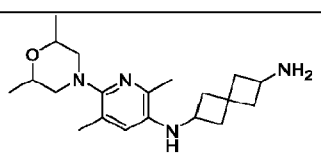
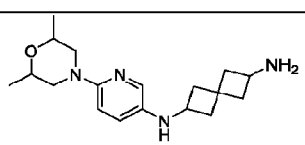
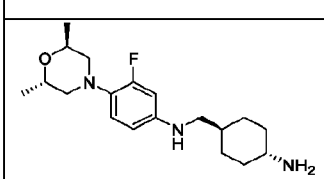
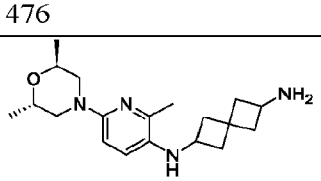
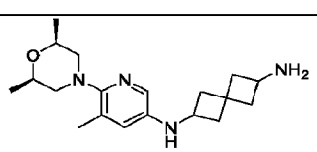
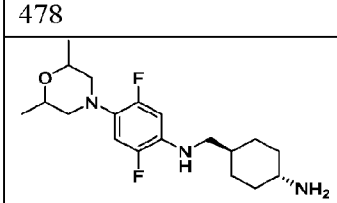
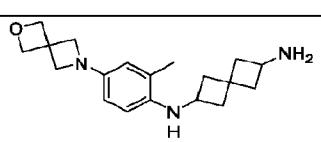
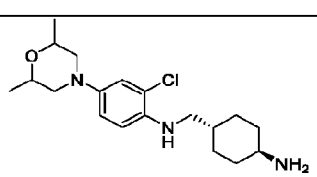
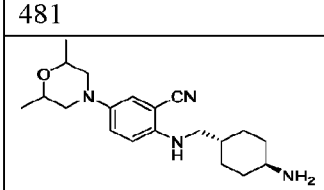
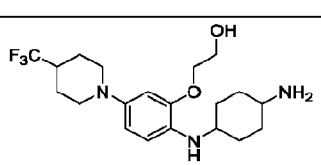
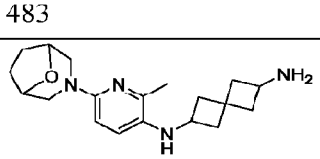
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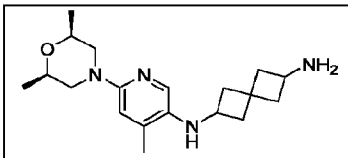
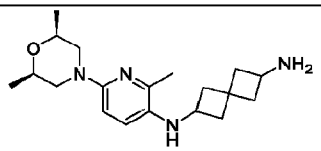
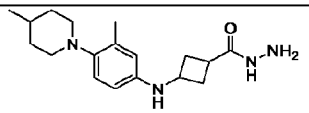
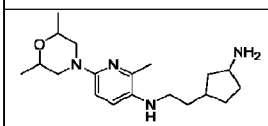
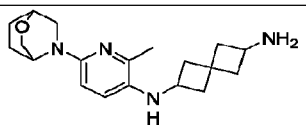
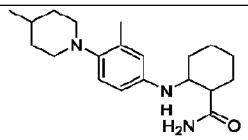
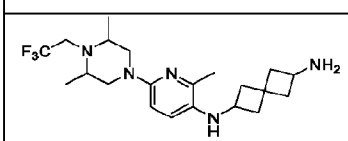
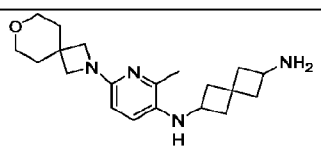
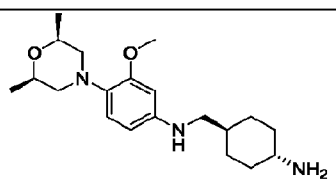
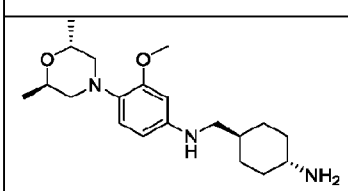
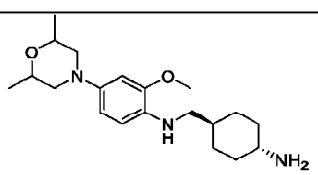
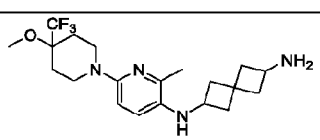
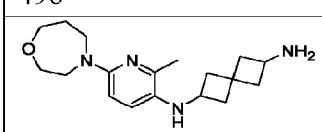
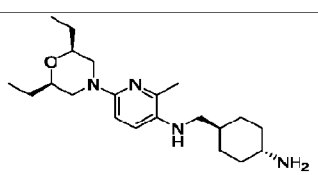
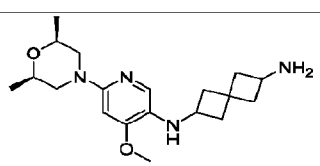
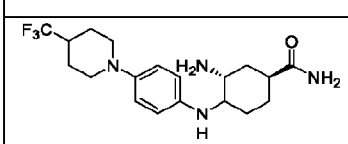
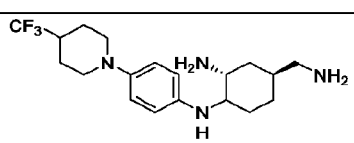
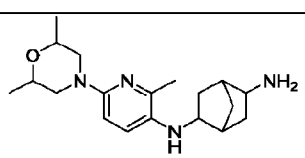
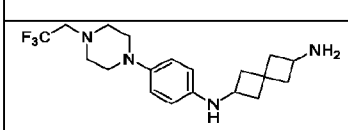
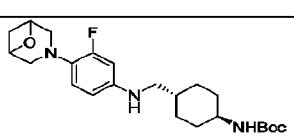
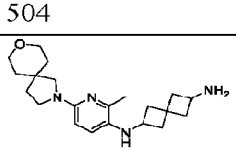
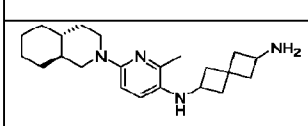
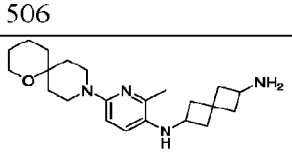
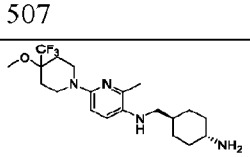
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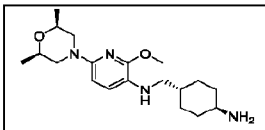
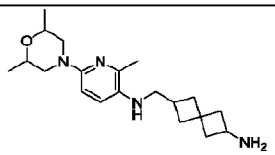
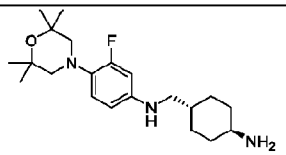
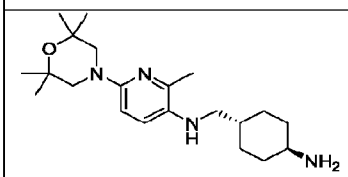
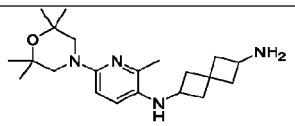
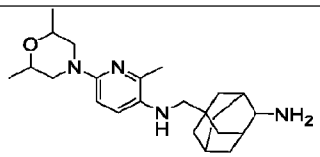
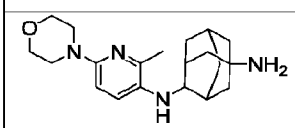
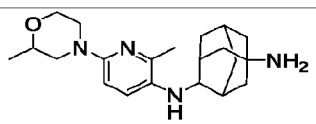
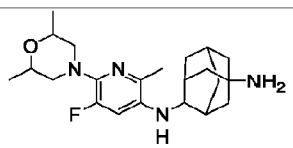
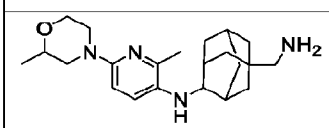
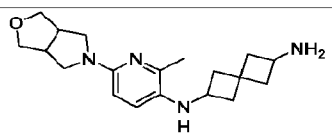
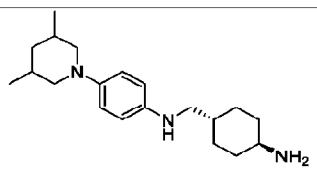
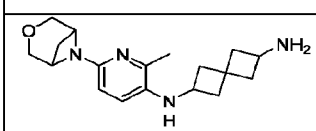
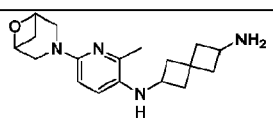
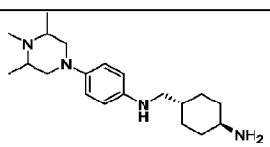
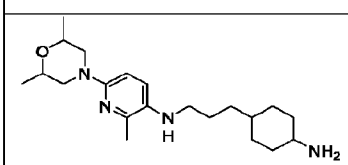
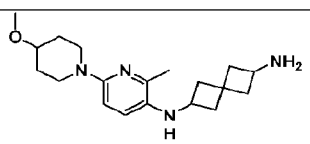
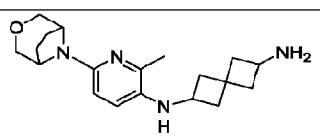
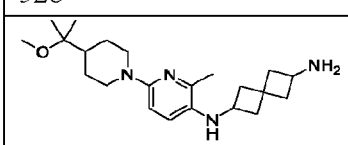
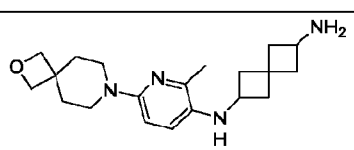
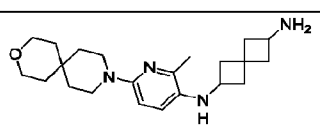
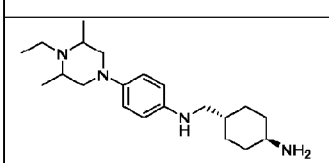
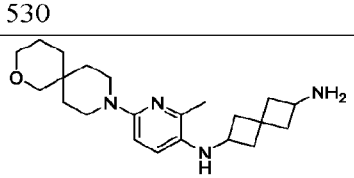
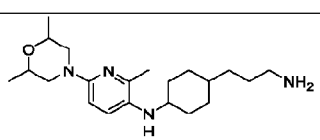
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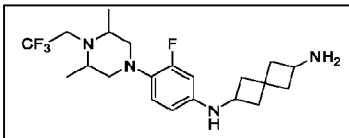
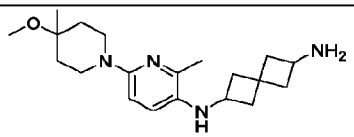
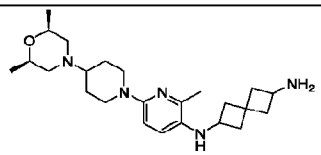
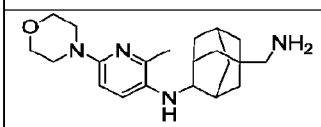
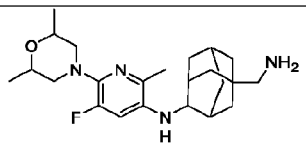
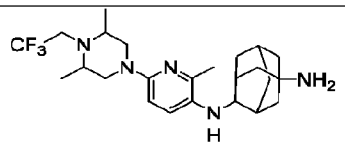
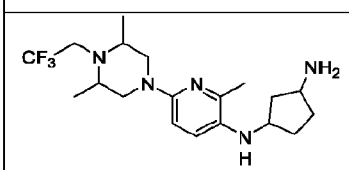
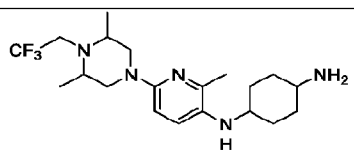
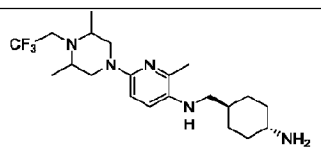
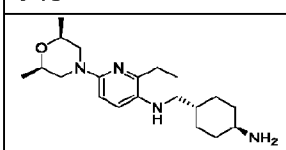
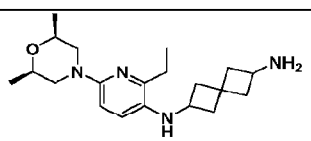
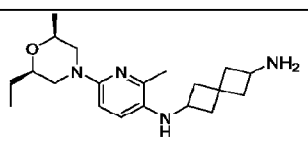
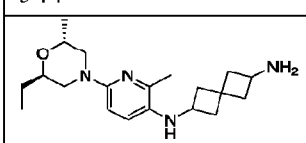
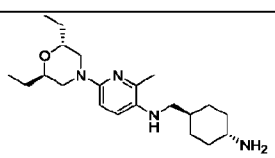
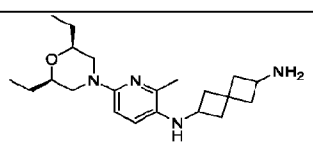
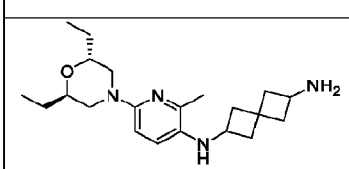
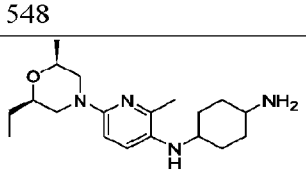
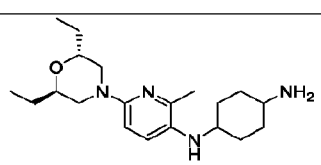
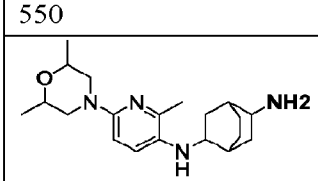
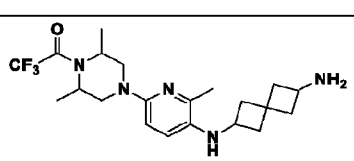
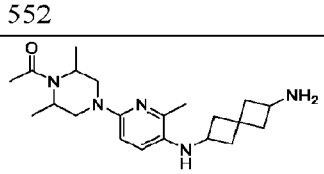
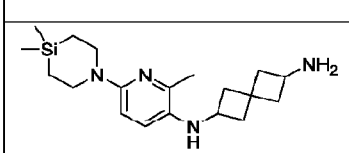
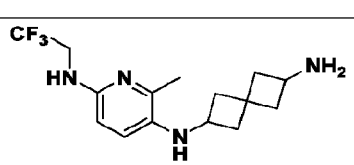
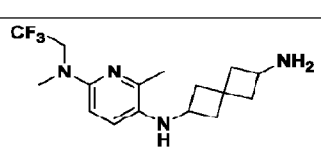
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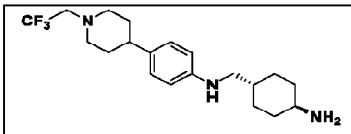
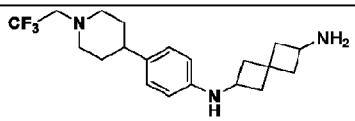
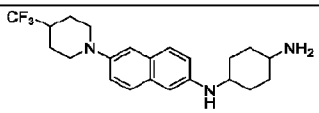
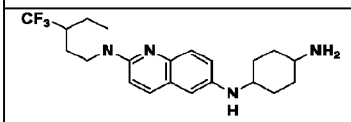
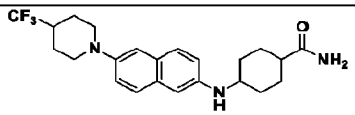
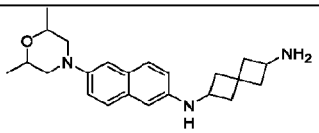
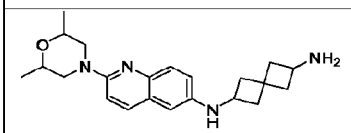
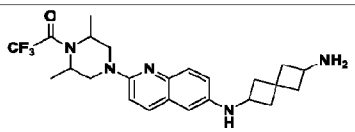
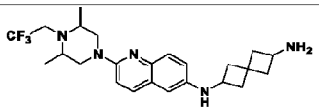
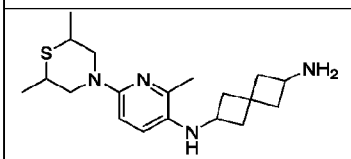
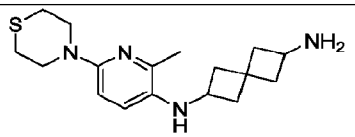
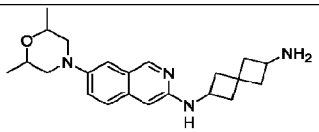
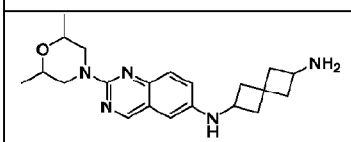
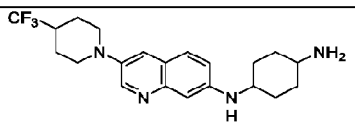
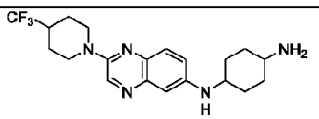
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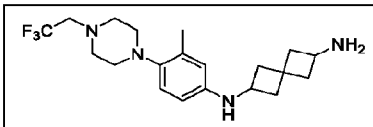
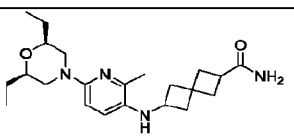
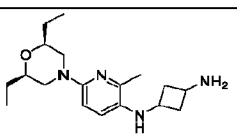
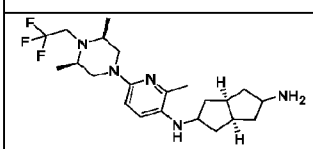
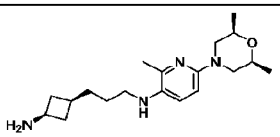
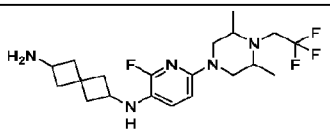
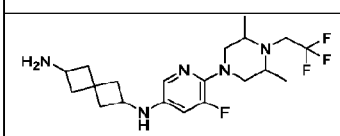
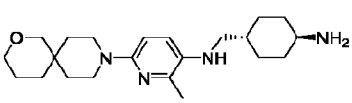
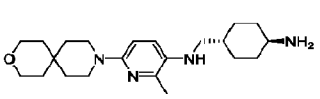
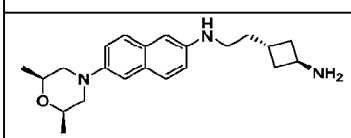
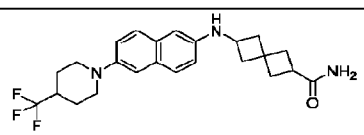
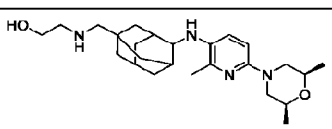
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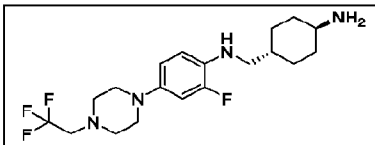
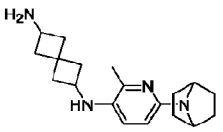
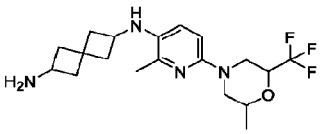
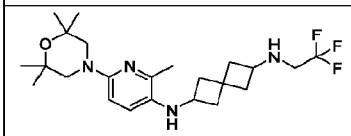
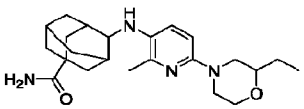
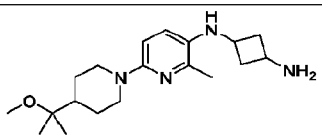
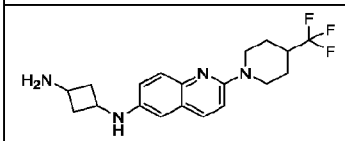
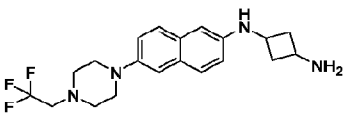
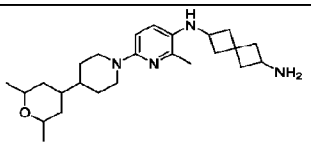
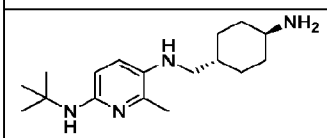
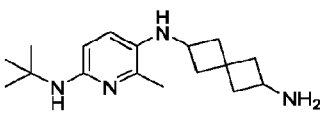
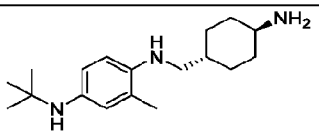
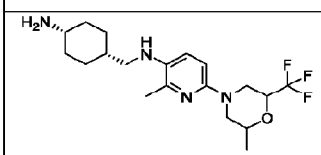
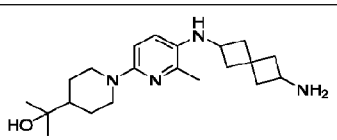
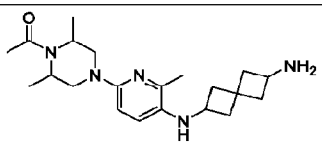
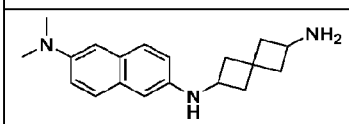
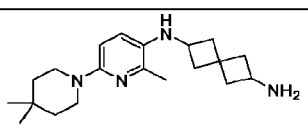
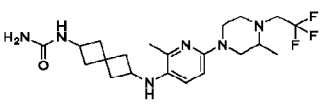
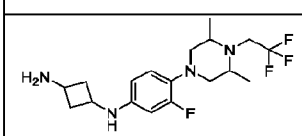
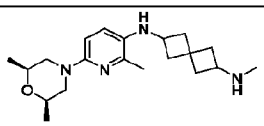
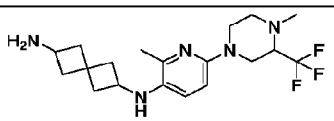
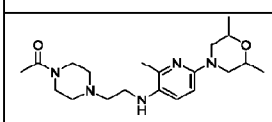
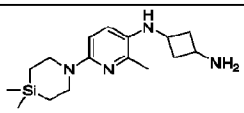
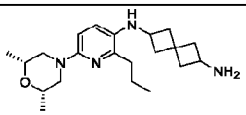
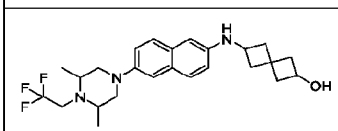
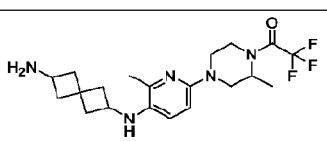
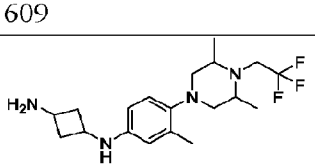
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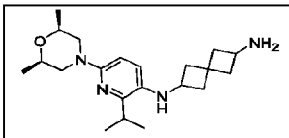
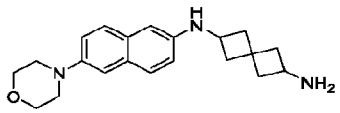
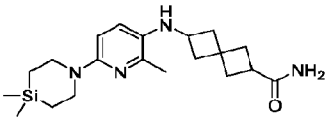
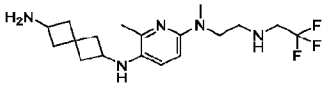
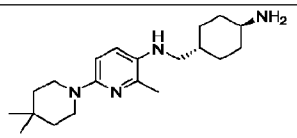
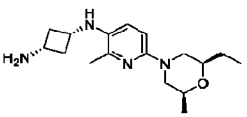
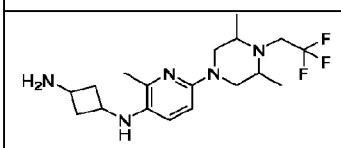
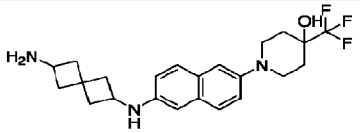
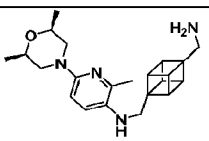
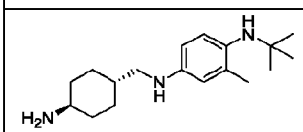
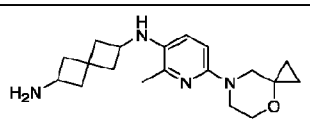
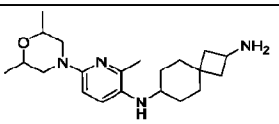
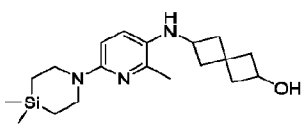
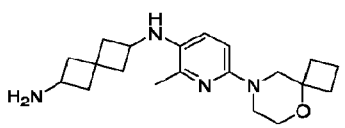
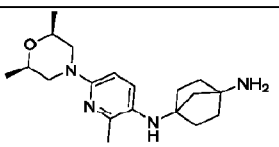
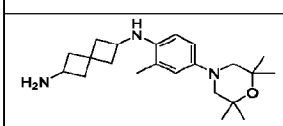
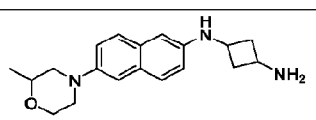
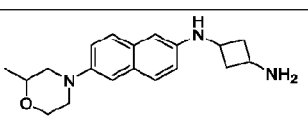
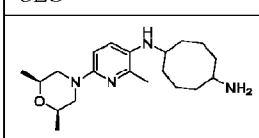
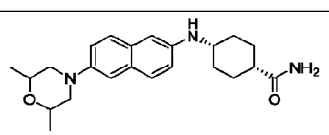
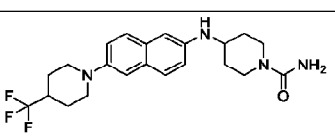
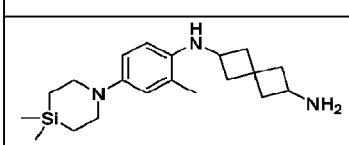
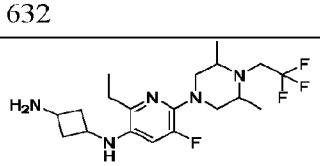
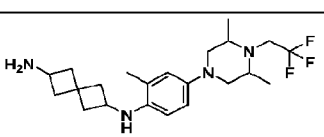
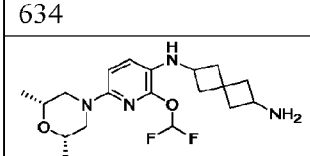
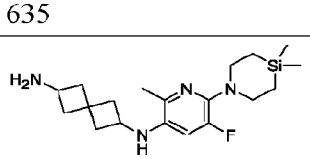
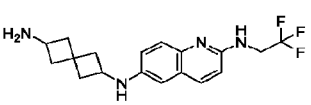
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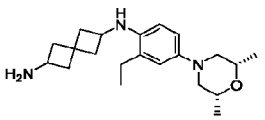
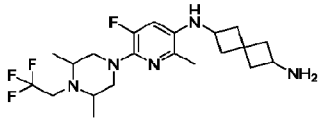
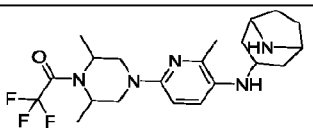
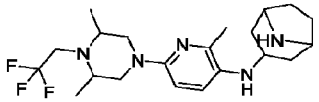
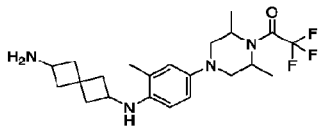
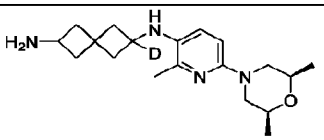
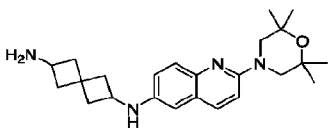
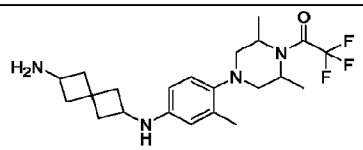
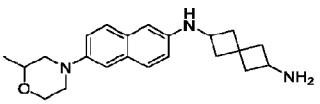
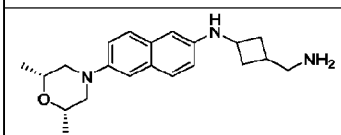
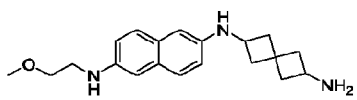
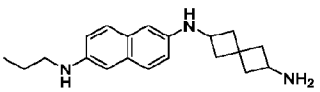
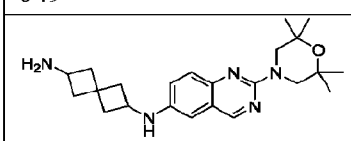
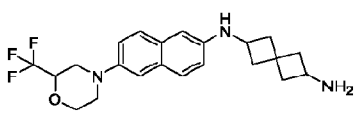
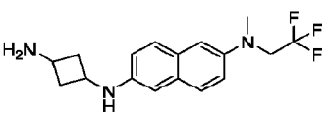
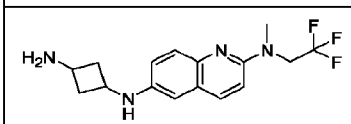
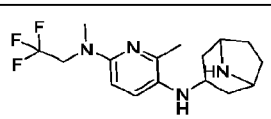
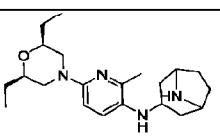
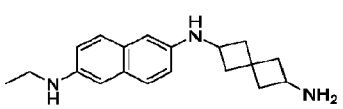
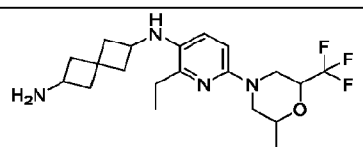
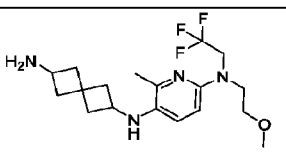
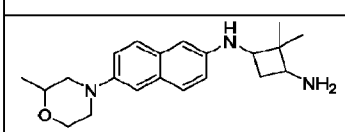
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Another aspect of the disclosure provides a pharmaceutical composition comprising at least one compound selected from a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and at least one pharmaceutically acceptable carrier.

Another aspect of the disclosure provides a pharmaceutical composition comprising at least one compound selected from a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, and at least one pharmaceutically acceptable carrier.

In some embodiments, the pharmaceutically acceptable carrier is selected from pharmaceutically acceptable vehicles and pharmaceutically acceptable adjuvants. In some embodiments, the pharmaceutically acceptable carrier is chosen from pharmaceutically acceptable fillers, disintegrants, surfactants, binders, and lubricants.

It will also be appreciated that a pharmaceutical composition of this disclosure can be employed in combination therapies; that is, the pharmaceutical compositions described herein can further include an additional active pharmaceutical agent. Alternatively, a pharmaceutical composition comprising a compound selected from a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing can be administered as a separate composition concurrently with, prior to, or subsequent to, a composition comprising an additional active pharmaceutical agent.

It will also be appreciated that a pharmaceutical composition of this disclosure can be employed in combination therapies; that is, the pharmaceutical compositions described herein can further include an additional active pharmaceutical agent. Alternatively, a pharmaceutical composition comprising a compound selected from a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing can be administered as a separate composition concurrently with, prior to, or subsequent to, a composition comprising an additional active pharmaceutical agent.

In some embodiments, the pharmaceutically acceptable carrier may be chosen from adjuvants and vehicles. The pharmaceutically acceptable carrier, as used herein, can be chosen, for example, from any and all solvents, diluents, other liquid vehicles, dispersion aids, suspension aids, surface active agents, isotonic agents, thickening agents, emulsifying agents, preservatives, solid binders, and lubricants, which are suited to the particular dosage form desired. Remington: *The Science and Practice of Pharmacy*, 21st edition, 2005, ed. D.B. Troy, Lippincott Williams & Wilkins, Philadelphia, and *Encyclopedia of Pharmaceutical Technology*, eds. J. Swarbrick and J. C. Boylan, 1988 to 1999, Marcel Dekker, New York discloses various carriers used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier is incompatible with the compounds of this disclosure, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this disclosure. Non-limiting examples of suitable pharmaceutically acceptable carriers include ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (such as human serum albumin), buffer substances (such as phosphates, glycine, sorbic acid, and potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts, and electrolytes (such as protamine sulfate,

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disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, and zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars (such as lactose, glucose and sucrose), starches (such as corn starch and potato starch), cellulose and its derivatives (such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate), powdered tragacanth, malt, gelatin, talc, excipients (such as cocoa butter and suppository waxes), oils (such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil), glycols (such as propylene glycol and polyethylene glycol), esters (such as ethyl oleate and ethyl laurate), agar, buffering agents (such as magnesium hydroxide and aluminum hydroxide), alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, phosphate buffer solutions, non-toxic compatible lubricants (such as sodium lauryl sulfate and magnesium stearate), coloring agents, releasing agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservatives, and antioxidants.

A compound selected from a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition disclosed herein can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, e.g., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

A compound selected from a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition disclosed herein can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, e.g., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules containing a compound, a tautomer thereof, a solvate or stereoisomer of the

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compound or the tautomer, and/or a pharmaceutically acceptable salt of the foregoing disclosed herein and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like, can also be used. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can further comprise at least one agent selected from coloring and flavoring agents to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols can be examples of suitable carriers for parenteral solutions. Solutions for parenteral administration may comprise a water soluble salt of the at least one compound describe herein, at least one suitable stabilizing agent, and if necessary, at least one buffer substance. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, can be examples of suitable stabilizing agents. Citric acid and its salts and sodium EDTA can also be used as examples of suitable stabilizing agents. In addition, parenteral solutions can further comprise at least one preservative, selected, for example, from benzalkonium chloride, methyl- and propylparaben, and chlorobutanol.

A pharmaceutically acceptable carrier is, for example, selected from carriers that are compatible with active ingredients of the composition (and in some embodiments, capable of stabilizing the active ingredients) and not deleterious to the subject to be treated. For example, solubilizing agents, such as cyclodextrins (which can form specific, more soluble complexes with the at least one compound and/or at least one pharmaceutically acceptable salt disclosed herein), can be utilized as pharmaceutical excipients for delivery of the active ingredients. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, cellulose, sodium lauryl sulfate, and pigments such as D&C Yellow # 10. Suitable pharmaceutically acceptable carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol.

For administration by inhalation, the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein may also be delivered as powders, which may be formulated, and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. One exemplary delivery system for inhalation can be metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein in at least one suitable propellant, selected, for example, from fluorocarbons and hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percentage of a solution or suspension of the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein in an appropriate ophthalmic vehicle, such that the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein is maintained in contact with the ocular

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surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions. In some embodiments, the pharmaceutical compositions disclosed herein may be in the form of controlled release or sustained release compositions as known in the art.

The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules, lozenges or the like in the case of solid compositions. In such compositions, the active material is usually a component ranging from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form. Unit dosage formulations are preferably about of 5, 10, 25, 50, 100, 250, 500, or 1,000 mg per unit. In a particular embodiment, unit dosage forms are packaged in a multipack adapted for sequential use, such as blisterpack comprising sheets of at least 6, 9 or 12 unit dosage forms.

In some embodiments, unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with, for example, 100 milligrams of the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein in powder, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

In some embodiments, a mixture of the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein and a digestible oil such as soybean oil, cottonseed oil or olive oil can be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

In some embodiments, tablets can be prepared by conventional procedures so that the dosage unit comprises, for example, 100 milligrams of the compound, stereoisomers thereof, or pharmaceutically acceptable salts thereof, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

In some embodiments, a parenteral composition suitable for administration by injection can be prepared by stirring 1.5% by weight of the compound and/or at least an enantiomer, a diastereoisomer, or pharmaceutically acceptable salt thereof disclosed herein in 10% by volume propylene glycol. The solution is made to the expected volume with water for injection and sterilized.

In some embodiment, an aqueous suspension can be prepared for oral administration. For example, each 5 milliliters of an aqueous suspension comprising 100 milligrams of finely divided compound, stereoisomers thereof, or pharmaceutically acceptable salts thereof, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of

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sorbitol solution, U.S.P., and 0.025 milliliters of vanillin can be used.

The same dosage forms can generally be used when the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein is administered stepwise or in conjunction with at least one other therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus, the term coadministration is understood to include the administration of at least two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the at least two active components.

The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt disclosed herein can be administered as the sole active ingredient or in combination with at least one second active ingredient.

The compound, tautomer, solvate, or stereoisomer described herein may be used per se, or in the form of their pharmaceutically acceptable salts, such as hydrochlorides, hydrobromides, acetates, sulfates, citrates, carbonates, trifluoroacetates and the like. When the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein contain relatively acidic functionalities, salts can be obtained by addition of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salts, or the like. When the compound, tautomer, solvate, or stereoisomer described herein contain relatively basic functionalities, salts can be obtained by addition 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, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic,benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge et al., "Pharmaceutical Salts," Journal of Pharmaceutical Science, 1977, 66, 1-19).

Neutral forms of the pharmaceutically acceptable salt described herein may be regenerated by contacting the salt with a base or acid, and isolating the parent compound in the conventional manner.

This disclosure provides prodrugs. Prodrugs of the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein that readily undergo chemical changes under physiological conditions to provide the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of the present disclosure. Additionally, prodrugs can be converted to the compound, tautomer, solvate, stereoisomer, or a pharmaceutically acceptable salt of the present disclosure by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to the compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of the present disclosure when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent

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drug. They may, for instance, be more bioavailable by oral administration than the parent drug. The prodrug may also have improved solubility in pharmacological compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the present disclosure which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, i.e., the active entity.

Certain compound, tautomer, stereoisomer, or pharmaceutically acceptable salt of the disclosure can exist in unsolvated forms as well as solvated forms, including hydrate forms. Certain compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of the disclosure may exist in multiple crystalline or amorphous forms.

Certain compound, tautomer, solvate, or pharmaceutically acceptable salt in this disclosure possesses asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereoisomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present disclosure.

III. Methods of Treatment and Uses

Another aspect of the disclosure provides a method of treating a disease or condition, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing, wherein the disease or condition is selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. In some embodiments, the disease or condition is involved with dysregulated ferroptosis, e.g., abnormal ferroptosis.

In another aspect, disclosed herein is a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, for use as a medicament.

In another aspect, disclosed herein is a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, for use as a medicament.

In another aspect, disclosed herein is use of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, for the manufacture of a

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medicament for treating a disease or condition selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. In some embodiments, the disease or condition is involved with dysregulated ferroptosis, e.g., abnormal ferroptosis.

In another aspect, disclosed herein is use of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, for the manufacture of a medicament for treating a disease or condition selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. In some embodiments, the disease or condition is involved with dysregulated ferroptosis, e.g., abnormal ferroptosis.

In a further aspect of this disclosure, a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, is for use in treating a disease or condition selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. In some embodiments, the disease or condition is involved with dysregulated ferroptosis, e.g., abnormal ferroptosis.

In a further aspect of this disclosure, a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, is for use in treating a disease or condition selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. In some embodiments, the disease or condition is involved with dysregulated ferroptosis, e.g., abnormal ferroptosis.

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Another aspect of the disclosure provides a method of modulating, e.g., inhibiting, ferroptosis in a subject in need thereof, comprising administering to the subject, a therapeutically effective amount of a compound of Formulae disclosed herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition comprising any of the foregoing.

In another aspect, disclosed herein is use of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, for modulating, e.g., inhibiting, ferroptosis in a subject in need thereof.

In another aspect, disclosed herein is use of a compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, for modulating, e.g., inhibiting, ferroptosis in a subject in need thereof.

In another aspect of this disclosure, a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, is for use in modulating, e.g., inhibiting, ferroptosis in a subject in need thereof by contacting the subject with the compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, pharmaceutically acceptable salt, or pharmaceutical composition.

In another aspect of this disclosure, a compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, or pharmaceutically acceptable salt as described herein, including a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof, is for use in modulating, e.g., inhibiting, ferroptosis in a subject in need thereof by contacting the subject with the compound, tautomer, a solvate or stereoisomer of the compound or the tautomer, pharmaceutically acceptable salt, or pharmaceutical composition.

A compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof may be administered once daily, twice daily, or three times daily, for example, for the treatment of a disease or condition, selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia

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reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. In some embodiments, the disease or condition is involved with dysregulated ferroptosis, e.g., abnormal ferroptosis.

A compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof may be administered once daily, twice daily, or three times daily, for example, for the treatment of a disease or condition, selected from neuropathy, stroke, neurodegenerative disease (e.g., Alzheimer's disease), Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction such as acute kidney failure. In some embodiments, the disease or condition is involved with dysregulated ferroptosis, e.g., abnormal ferroptosis.

A compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof may be administered, for example, various manners, such as orally, topically, rectally, parenterally, by inhalation spray, or via an implanted reservoir, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques. The compositions disclosed herein may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art. Parenteral administration can be by continuous infusion over a selected period of time. Other forms of administration contemplated in this disclosure are as described in International Patent Application Nos. WO 2013/075083, WO 2013/075084, WO 2013/078320, WO 2013/120104, WO 2014/124418, WO 2014/151142, and WO 2015/023915.

A compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof may be administered, for example, various manners, such as orally, topically, rectally, parenterally, by inhalation spray, or via an implanted reservoir, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques. The compositions disclosed herein may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art. Parenteral administration can be by continuous infusion over a selected period of time. Other forms of administration contemplated in this disclosure are as described in International Patent Application Nos. WO 2013/075083, WO 2013/075084, WO 2013/078320, WO 2013/120104, WO

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2014/124418, WO 2014/151142, and WO 2015/023915.

The contacting is generally effected by administering to the subject an effective amount of one or more compounds, tautomers, solvates, stereoisomers, and pharmaceutically acceptable salt disclosed herein. Generally, administration is adjusted to achieve a therapeutic dosage of about 0.1 to 50, preferably 0.5 to 10, more preferably 1 to 10 mg/kg, though optimal dosages are compound specific, and generally empirically determined for each compound.

The dosage administered will be dependent on factors, such as the age, health and weight of the recipient, the extent of disease, type of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired. In general, a daily dosage of the active ingredient can vary, for example, from 0.1 to 2000 milligrams per day. For example, 10-500 milligrams once or multiple times per day may be effective to obtain the desired results.

In some embodiments, 2 mg to 1500 mg or 5 mg to 1000 mg of a compound of the Formulae disclosed herein, Compounds 1 to 573, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof are administered once daily, twice daily, or three times daily. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein is administered for morning/daytime dosing, with off period at night.

In some embodiments, 2 mg to 1500 mg or 5 mg to 1000 mg of a compound of the Formulae disclosed herein, Compounds 574 to 661, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, or a pharmaceutical composition thereof are administered once daily, twice daily, or three times daily. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt described herein is administered for morning/daytime dosing, with off period at night.

Examples

In order that the disclosure described herein may be more fully understood, the following examples are disclosed herein. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this disclosure in any way.

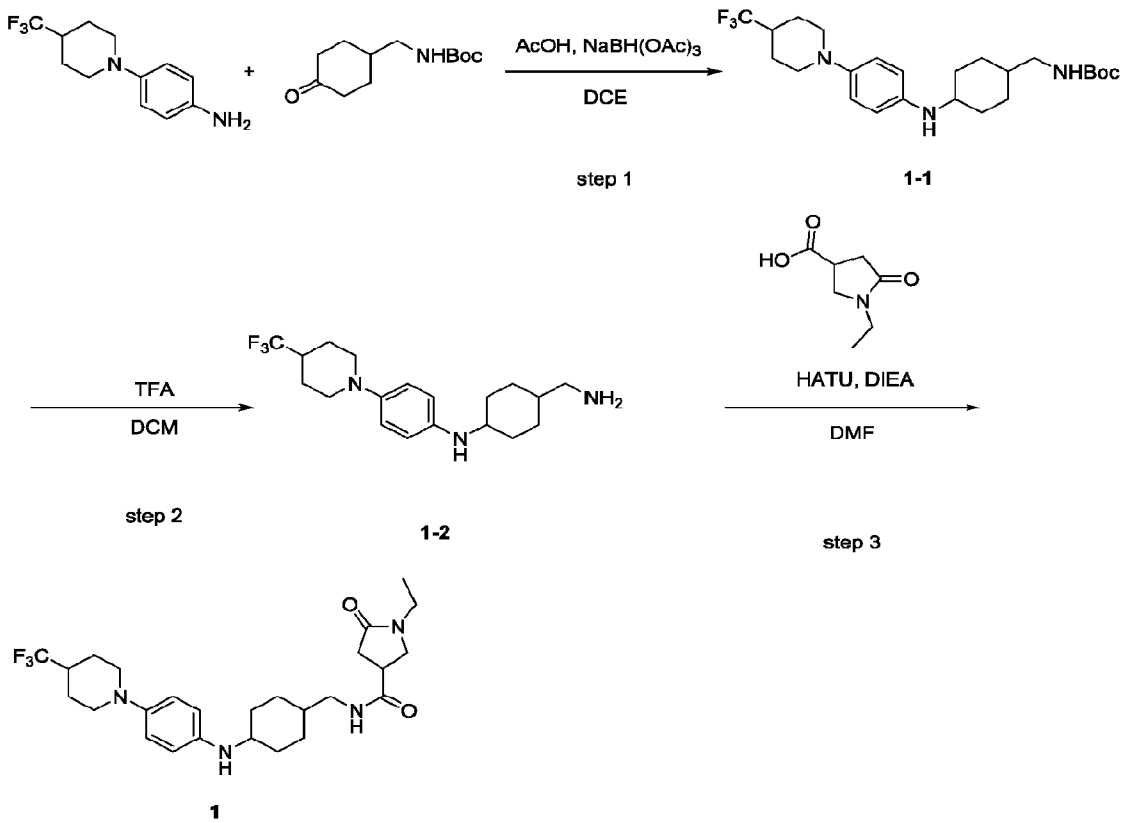
Example 1. Synthesis of Exemplary Compounds

The compounds of the disclosure, selected from a compound of the Formulae depicted herein, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, can be made according to standard chemical practices or as illustrated herein, including the following synthetic schemes for Compounds 1 to 661 as representative examples of Formula I.

Compound 1

1-ethyl-5-oxo-N-((4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)methyl)pyrrolidine-3-carboxamide

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Step 1. Preparation of tert-butyl ((4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)methyl)carbamate (**1-1**)

A solution of 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (100 mg, 0.41 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (140 mg, 0.62 mmol) and AcOH (0.1 mL) in DCE (10 mL) was stirred at room temperature for 30 min. $NaBH(OAc)_3$ (174 mg, 0.82 mmol) was added, and the mixture was stirred at room temperature for 2 h. The mixture was extracted by DCM (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4 and concentrated to give the crude product, which was purified by TLC (MeOH/DCM = 1/20) to give the desired product (130 mg, 69.9%) as a purple solid. Mass (m/z): 456.3 $[M+H]^+$.

Step 2. Preparation of N-(4-(aminomethyl)cyclohexyl)-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (**1-2**)

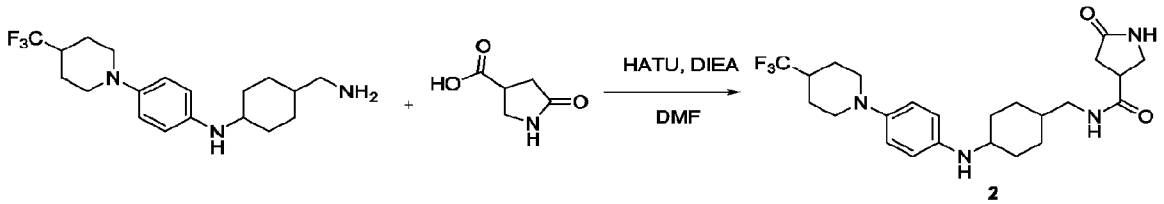
To a solution of **1-1** (130 mg, 0.29 mmol) in DCM (10 mL) was added TFA (1 mL). The solution was stirred at room temperature for 1 h. The mixture was basified by 1M NaOH to pH = 9, concentrated, and then extracted by DCM (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4 and concentrated, which was purified by TLC (MeOH/DCM = 1/5) to give the desired product (79.2 mg,78.2%) as a purple solid. Mass (m/z): 356.3 $[M+H]^+$.

Step 3. Preparation of 1-ethyl-5-oxo-N-((4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)methyl)pyrrolidine-3-carboxamide (**1**)

To a solution of **1-2** (50 mg, 0.141 mmol), 1-ethyl-5-oxopyrrolidine-3-carboxylic acid (28 mg, 0.183 mmol), HATU (33 mg,0.183 mmol) and DIEA (23 mg, 0183 mmol) in DMF (5 mL) was stirred at room temperature for 2 h. The mixture was extracted by EA (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4 and concentrated to give the crude product, which was purified by TLC (MeOH/DCM = 1/10) to give the desired product (23.7 mg, 34.0%) as a purple solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (t, J = 5.6 Hz, 1H), 6.74 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 4.87 (s, 1H), 3.50 (t, J = 9.2 Hz, 1H), 3.41 (d, J = 14.4 Hz, 2H), 3.33 – 3.30 (m, 1H), 3.22 – 3.15 (m, 2H), 3.13 – 3.06 (m, 1H), 3.04 (d, J = 12.0 Hz, 1H), 2.94 (t, J = 6.4 Hz, 2H), 2.55 (s, 1H), 2.38 (dd, J = 8.8, 3.0 Hz, 3H), 1.96 (d, J = 10.4 Hz, 2H), 1.85 (d, J = 12.4 Hz, 2H), 1.71 (d, J = 10.8 Hz, 2H), 1.57 (tt, J = 12.8, 6.4 Hz, 2H), 1.37 (s, 1H), 1.06 – 0.93 (m, 7H). Mass (m/z): 495.3 $[M+H]^+$.

Compound 2

5-oxo-N-((4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)methyl)pyrrolidine-3-carboxamide

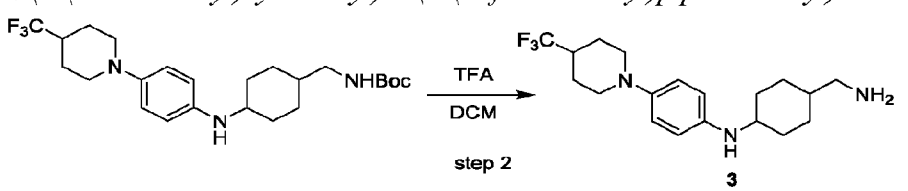


2

The title compound **2** (23.7 mg) was prepared in a total yield of 34.0% as a purple solid from trifluoromethyl)piperidin-1-yl)aniline (50 mg, 0.141 mmol), 5-oxopyrrolidine-3-carboxylic acid (24 mg, 0.183 mmol), HATU (33 mg, 0.183 mmol) and DIEA (23 mg, 0183 mmol) in DMF (5 mL) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.50 (s, 1H), 6.86 - 6.38 (m, 4H), 3.34 (s, 2H), 3.16 – 2.94 (m, 4H), 2.85 (t, J = 6.4 Hz, 2H), 2.33 (s, 1H), 2.20 (dd, J = 8.4, 1.6 Hz, 2H), 1.88 (d, J = 11.4 Hz, 2H), 1.79 (d, J = 12.4 Hz, 2H), 1.64 (d, J = 12.0 Hz, 2H), 1.49 (s, 2H), 1.30 (d, J = 7.6 Hz, 1H), 1.24 – 1.13 (m, 2H), 1.02 (s, 1H), 0.91 (t, J = 12.0 Hz, 2H). Mass (m/z): 466.55 $[M+H]^+$.

Compound 3

N-(4-(aminomethyl)cyclohexyl)-4-(4-(trifluoromethyl)piperidin-1-yl)aniline



3

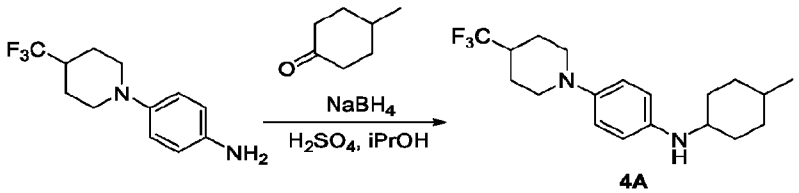
To a solution of tert-butyl ((4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)methyl)carbamate (**1-1**; 130 mg, 0.29 mmol) in DCM (10 mL) was added TFA (1 mL). The solution was stirred at room temperature for 1 h. The mixture was basified by 1M NaOH to pH = 9 and concentrated, then extracted by DCM (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4 and concentrated, which was purified by TLC (MeOH/DCM = 1/5) to give the desired product as a purple solid (79.2 mg, 78.2 %) with 1:2 mixture by ^{1}H NMR. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 2H), 6.75 (dd, J = 9.2, 2.4 Hz, 2H), 6.57 –

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6.51 (m, 1.4H), 6.50 – 6.45 (m, 0.7H), 4.95 (d, *J* = 29.2 Hz, 1H), 3.44 (t, *J* = 3.2 Hz, 4H), 2.68 (d, *J* = 6.8 Hz, 1.4H), 2.63 (d, *J* = 6.8 Hz, 0.7H), 2.55 (d, *J* = 2.4 Hz, 2H), 2.42 – 2.30 (m, 1H), 1.98 (d, *J* = 8.8 Hz, 1H), 1.89 – 1.81 (m, 2H), 1.71 – 1.36 (m, 9H). Mass (m/z): 356.3 $[M+H]^+$.

Compound 4

N-(4-methylcyclohexyl)-4-(4-(trifluoromethyl)piperidin-1-yl)aniline

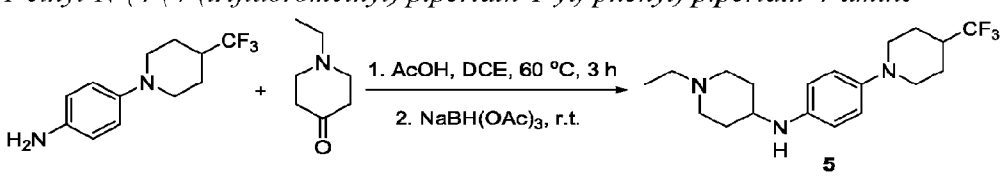


4A
4B

To a solution of 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (100 mg, 0.4 mmol) and 4-methylcyclohexan-1-one (55 mg, 0.49 mmol) in isopropanol (5 mL) was added 3 drops of sulfuric acid dropwise at 0 °C. The mixture was stirred for 30 min at room temperature before $NaBH_4$ (31 mg, 0.8 mmol) was added slowly at 0 °C. The resulting mixture was stirred overnight. The reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with dichloromethane (5 mL) 3 times. The organic layers were combined and washed with water, sat. $NaHCO_3$, and brine respectively, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 4/1) and then purified by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10 min-11 min-15.0 min) to give 33.4 mg of **4A** (Rt = 6.05 min) as a white powder in a yield of 23.9% and 20.4 mg of **4B** (Rt = 6.16 min) as a white powder in a yield of 14.6%. **4A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.73 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 8.9 Hz, 2H), 4.94 (s, 1H), 3.41 (d, *J* = 12.0 Hz, 2H), 2.54 (d, *J* = 2.6 Hz, 2H), 2.35 (m, 1H), 1.89 – 1.79 (m, 2H), 1.54 (m, 7H), 1.42 (m, 2H), 1.38 – 1.26 (m, 2H), 1.23 (s, 1H), 0.89 (d, *J* = 6.6 Hz, 3H). Mass (m/z): 341.3 $[M+H]^+$. **4B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.73 (d, *J* = 8.4 Hz, 2H), 6.47 (d, *J* = 8.4 Hz, 2H), 4.85 (s, 1H), 3.41 (d, *J* = 11.9 Hz, 2H), 3.00 (s, 1H), 2.43 – 2.22 (m, 1H), 1.89 (dd, *J* = 31.5, 12.0 Hz, 4H), 1.67 (d, *J* = 12.0 Hz, 2H), 1.56 (qd, *J* = 12.4, 3.9 Hz, 2H), 1.40 – 1.25 (m, 1H), 1.14 – 0.93 (m, 4H), 0.87 (d, *J* = 6.5 Hz, 3H). Mass (m/z): 341.3 $[M+H]^+$.

Compound 5

1-ethyl-N-(4-(4-(trifluoromethyl) piperidin-1-yl) phenyl) piperidin-4-amine



5

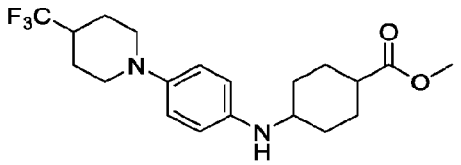
To a solution of 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (150 mg, 0.61 mmol) in DCE (5 ml) was added 1-ethylpiperidin-4-one (94 mg, 0.73 mmol) and acetic acid (3.7 mg, 0.061 mmol). The resulting mixture was stirred at 60 °C for 3 h, and then cooled to room temperature. Sodium triacetoxyborohydride (388 mg, 1.83 mmol) was added and the reaction was stirred for 3 h at R.T. The reaction was quenched with water (10 mL), and extracted by EA (10 mL) for 3 times. The combined organic phase was dried over sodium sulfate, and removed under vacuum.

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The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford the desired product (35 mg, 16.2%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 3.52 (d, J = 12.1 Hz, 2H), 3.35 (s, 2H), 2.93 (d, J = 9.0 Hz, 2H), 2.70 (d, J = 10.8 Hz, 2H), 2.59 (t, J = 11.8 Hz, 2H), 2.26 (s, 2H), 2.06 – 1.89 (m, 5H), 1.86 – 1.68 (m, 3H), 1.40 (t, J = 9.0 Hz, 3H). Mass (m/z): 356.2 $[M+H]^+$.

Compound 6

methyl 4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylate

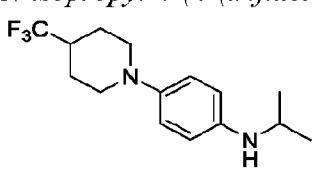


6A
6B

The title compound **6A** (Rt = 5.37 min; 89.3 mg, 28.4%) as a rosy brown solid and **6B** (Rt = 5.31 min; 93.6 mg, 29.7%) as a rosy brown solid were prepared from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (200 mg, 0.82 mmol), methyl 4-oxocyclohexane-1-carboxylate (192 mg, 1.23 mmol) and $NaBH(OAc)_3$ (347 mg, 1.64 mmol) according to the procedure for **4**, which were purified by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10 min-11 min-15.0 min). **6A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, J = 8.9 Hz, 2H), 6.51 (d, J = 8.9 Hz, 2H), 5.01 (d, J = 7.8 Hz, 1H), 3.60 (s, 3H), 3.41 (d, J = 12.1 Hz, 2H), 3.29 (d, J = 8.1 Hz, 1H), 2.56 – 2.51 (m, 2H), 2.42 – 2.28 (m, 1H), 1.93 – 1.81 (m, 4H), 1.53-1.72 (m, 6H), 1.52 – 1.39 (m, 3H). Mass (m/z): 385.4 $[M+H]^+$. **6B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, J = 8.5 Hz, 2H), 6.49 (d, J = 8.8 Hz, 2H), 4.90 (s, 1H), 3.59 (s, 3H), 3.42 (dd, J = 14.7, 5.8 Hz, 2H), 3.07 (s, 1H), 2.55 (s, 2H), 2.46 – 2.35 (m, 3H), 2.31 – 2.19 (m, 4H), 2.19 – 2.06 (m, 3H), 1.56 (qd, J = 12.3, 3.9 Hz, 2H), 1.45 (qd, J = 13.1, 3.1 Hz, 2H). Mass (m/z): 385.4 $[M+H]^+$.

Compound 7

N-isopropyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline



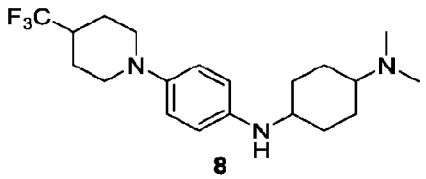
7

The title compound 7 (12.0 mg) was prepared in a total yield of 12.6% as a yellow solid from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (81 mg, 0.3 mmol), acetone (0.2 mL), a drop of con. H_2SO_4, $NaBH(AcO)_3$ (76 mg, 0.36 mmol) and THF (10 mL) according to the procedure for **5**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.78 (d, J = 8.2 Hz, 2H), 6.54 (d, J = 7.6 Hz, 2H), 3.52 – 3.41 (m, 3H), 2.62 – 2.52 (m, 2H), 2.43 – 2.35 (m, 1H), 1.86 (d, J = 12.5 Hz, 2H), 1.61 – 1.50 (m, 2H), 1.09 (d, J = 6.2 Hz, 6H). Mass (m/z): 287.2 $[M+H]^+$.

Compound 8

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N1,N1-dimethyl-N4-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

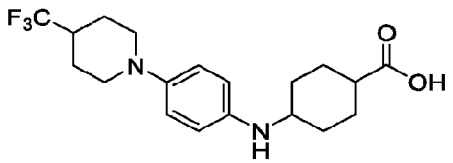


8

The title compound **8** (53 mg) was prepared in a total yield of 19.4% as brown oil from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (180 mg, 0.74 mmol), 4-(dimethylamino)cyclohexan-1-one (125 mg, 0.89 mmol), acetic acid (3.7 mg, 0.061 mmol), sodium triacetoxyborohydride (469 mg, 2.22 mmol) and DCE (5 mL) according to the procedure for **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.84 (d, *J* = 8.7 Hz, 2H), 6.64 – 6.50 (m, 2H), 3.51 (d, *J* = 10.8 Hz, 2H), 3.13 (t, *J* = 11.0 Hz, 1H), 2.58 (t, *J* = 12.0 Hz, 2H), 2.30 (d, *J* = 4.2 Hz, 6H), 2.24 – 2.14 (m, 2H), 1.95 (m, 4H), 1.89 – 1.73 (m, 4H), 1.62 (m, 3H), 1.45 – 1.28 (m, 1H). Mass (m/z): 185.7 $[M+2H]^{2+}/2$.

Compound 9

4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylic acid

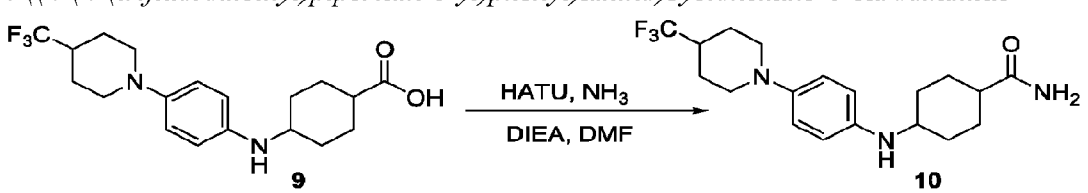


9

The title compound **9** (127 mg) was prepared in a yield of 41.8% as a rosy brown solid with 1:1 mixture by ^{1}H NMR from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (200 mg, 0.82 mmol), 4-oxocyclohexane-1-carboxylic acid (140 mg, 0.98 mmol) and $NaBH(OAc)_3$ (347 mg, 1.64 mmol) according to the procedure for **4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, *J* = 8.1 Hz, 2H), 6.50 (s, 2H), 3.41 (d, *J* = 11.7 Hz, 2H), 3.25 (s, 1H), 3.05 (s, 1H), 2.42 – 2.27 (m, 2H), 2.15 (tt, *J* = 11.9, 3.5 Hz, 1H), 1.91 (dt, *J* = 35.0, 14.3 Hz, 5H), 1.69 – 1.49 (m, 4H), 1.41 (qd, *J* = 13.2, 3.2 Hz, 2H), 1.09 (q, *J* = 12.0 Hz, 1H). Mass (m/z): 371.5 $[M+H]^+$.

Compound 10

4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxamide



9 **10**

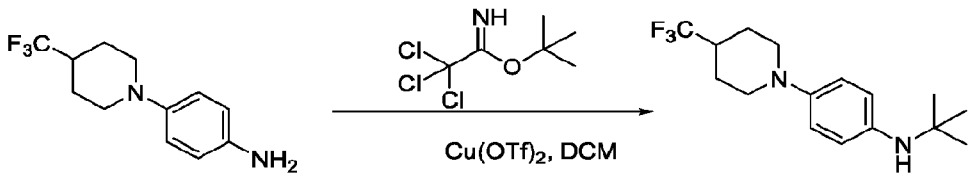
To a solution of 4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylic acid (70 mg, 0.19 mmol) and HATU (86 mg, 0.23 mmol) in super dry *N,N*-dimethylformamide (5 mL) was added *N*-ethyl-*N*-isopropylpropan-2-amine (94 mL, 0.57 mmol). The mixture was stirred for 30 mins and ammonium hydroxide (0.5 mL) was added dropwise at 0 °C slowly. The resulting solution was stirred overnight at room temperature. The reaction mixture was added into water (15 mL) drop by drop with stirring. The precipitate was filtered, and the filter cake was wash

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with water 3 times and dry *in vacuo*. The residue was purified by prep-TLC to give desired product **10** (28.3 mg) as pale peach powder with 1:1 mixture by ^{1}H NMR in a yield of 40.5%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (s, 1H), 6.74 (d, J = 8.3 Hz, 2H), 6.67 (s, 1H), 6.49 (d, J = 8.2 Hz, 2H), 4.89 (s, 1H), 3.42 (d, J = 11.8 Hz, 2H), 3.04 (s, 1H), 2.54 (d, J = 11.2 Hz, 2H), 2.41 – 2.28 (m, 1H), 2.10 – 1.92 (m, 3H), 1.85 (d, J = 12.7 Hz, 2H), 1.76 (d, J = 13.1 Hz, 2H), 1.56 (td, J = 13.9, 10.1 Hz, 2H), 1.50 – 1.36 (m, 2H), 1.06 (q, J = 12.3 Hz, 2H). Mass (m/z): 370.3 $[M+H]^+$.

Compound 11

N-(tert-butyl)-4-(4-(trifluoromethyl)piperidin-1-yl)aniline

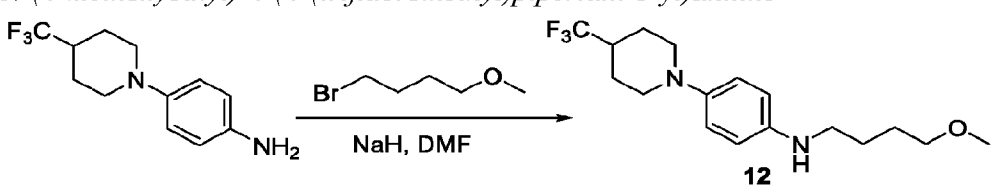


11

To a solution of 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (122 mg, 0.5 mmol) in dry DCM (20 mL) was added $Cu(OTf)_2$ (9.0 mg, 25 umol) and tert-butyl 2,2,2-trichloroacetimidate (272.5 mg, 1.25 mmol). Then the reaction was stirred at RT for 2 hr under argon. The reaction was washed with water (20 mL x 3), dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (EA/PE=1/2) to afford the desired product **11** (8.6 mg, 5.7%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 2H), 7.25 – 7.17 (m, 2H), 7.11 – 7.03 (m, 2H), 3.88 (d, J = 12.6 Hz, 2H), 2.79 (t, J = 11.6 Hz, 2H), 2.59 – 2.53 (m, 1H), 1.89 (d, J = 12.0 Hz, 2H), 1.57 – 1.44 (m, 2H), 1.27 (s, 9H). Mass (m/z): 301.2 $[M+H]^+$.

Compound 12

N-(4-methoxybutyl)-4-(4-(trifluoromethyl)piperidin-1-yl)aniline



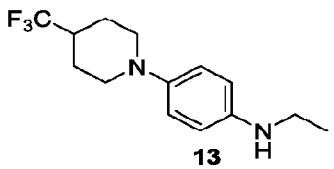
12

To a solution of 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (100 mg, 0.4 mmol) in super dry *N,N*-dimethylformamide (5 mL), was added NaH (19.7 mg, 0.5 mmol) at 0 °C. The mixture was stirred for 30 mins and 1-bromo-4-methoxybutane (68 mg, 0.4 mmol) was added. The resulting solution was stirred for overnight at 100 °C. The reaction was diluted with water (20 mL) at 0 °C and extracted with ethyl acetate (5 mL) 3 times. The organic layers were combined and washed with water, sat. NH_4Cl (aq), brine respectively, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC to give 28 mg of desired product **12** as pale rosy brown oil in a yield of 20.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (d, J = 8.8 Hz, 2H), 6.47 (d, J = 8.8 Hz, 2H), 5.09 (s, 1H), 3.41 (d, J = 12.0 Hz, 2H), 3.31 (d, J = 6.0 Hz, 2H), 3.21 (s, 3H), 2.92 (s, 2H), 2.53 (dd, J = 11.0, 2.0 Hz, 2H), 2.43 2.28 (m, 1H), 1.91 – 1.77 (m, 2H), 1.46-1.65 (m, 6H). Mass (m/z): 331.3 $[M+H]^+$.

Compound 13

N-ethyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline

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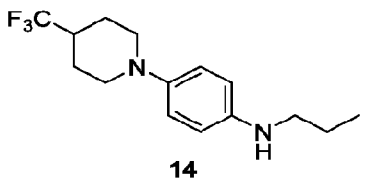


13

The title compound **13** (32 mg) was prepared in a yield of 28.7% as a soil powder from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (100 mg, 0.4 mmol), iodoethane (32 mg, 0.4 mmol) and potassium carbonate (57 mg, 0.4 mmol) according to the procedure for **12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.3 Hz, 2H), 5.05 (s, 1H), 3.41 (d, J = 11.9 Hz, 2H), 2.94 (q, J = 7.1 Hz, 2H), 2.54 (s, 2H), 2.40 – 2.26 (m, 1H), 1.84 (d, J = 12.4 Hz, 2H), 1.55 (qd, J = 12.3, 4.1 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H). Mass (m/z): 273.5 $[M+H]^+$.

Compound 14

N-propyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline

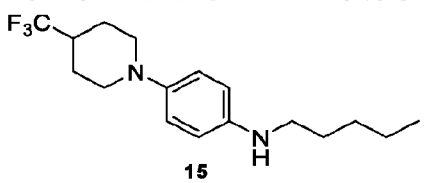


14

The title compound **14** (34.4 mg) was prepared in a yield of 58.7% as an off-white powder from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (50 mg, 0.2 mmol), 1-iodopropane (35 mg, 0.2 mmol) and potassium carbonate (42 mg, 0.3 mmol) according to the procedure for **12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (d, J = 8.8 Hz, 2H), 6.48 (d, J = 8.8 Hz, 2H), 5.12 (s, 1H), 3.42 (d, J = 12.1 Hz, 2H), 2.89 (t, J = 7.1 Hz, 2H), 2.55 (s, 2H), 2.29 – 2.42 (m, 1H), 1.85 (d, J = 12.1 Hz, 2H), 1.64 – 1.45 (m, 4H), 0.92 (t, J = 7.4 Hz, 3H). Mass (m/z): 287.3 $[M+H]^+$.

Compound 15

N-pentyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline



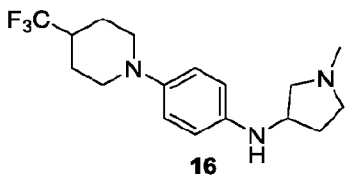
15

The title compound **15** (34.4 mg) was prepared in a yield of 51.4% as an off white powder from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (50 mg, 0.2 mmol), 1-iodopentane (40 mg, 0.2 mmol) and potassium carbonate (42 mg, 0.3 mmol) according to the procedure for **12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (d, J = 8.8 Hz, 2H), 6.47 (d, J = 8.8 Hz, 2H), 5.08 (s, 1H), 3.49 – 3.38 (m, 2H), 2.91 (t, J = 7.1 Hz, 2H), 2.56 – 2.52 (m, 2H), 2.36 (dt, J = 8.8, 4.4 Hz, 1H), 1.85 (d, J = 12.2 Hz, 2H), 1.64 – 1.43 (m, 4H), 1.32 (tq, J = 6.0, 2.8 Hz, 4H), 0.94 – 0.82 (m, 3H). Mass (m/z): 315.3 $[M+H]^+$.

Compound 16

1-methyl-N-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)pyrrolidin-3-amine

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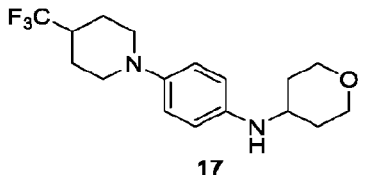


16

The title compound **16** (31.1 mg) was prepared in a yield of 23.2% as an off-white powder with 1:1 mixture by ^{1}H NMR from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (100 mg, 0.4 mmol), 1-methylpyrrolidin-3-one (48 mg, 0.49 mmol) and $NaBH(OAc)_3$ (173 mg, 0.82 mmol) according to the procedure for **4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.80 (d, J = 8.9 Hz, 2H), 6.51 (d, J = 8.9 Hz, 2H), 5.50 (s, 1H), 4.04 (s, 1H), 3.46 (d, J = 12.2 Hz, 3H), 3.07 (d, J = 46.4 Hz, 2H), 2.74 (s, 3H), 2.53 (d, J = 2.4 Hz, 2H), 2.45 – 2.25 (m, 2H), 1.84 (d, J = 3.7 Hz, 3H), 1.46-1.61 (m, 2H), 1.23 (d, J = 3.3 Hz, 2H). Mass (m/z): 328.2 $[M+H]^+$.

Compound 17

N-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)tetrahydro-2H-pyran-4-amine

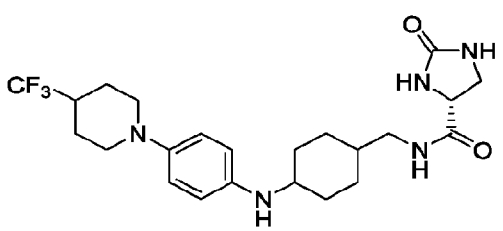


17

The title compound **17** (23.9 mg) was prepared in a total yield of 35.8% as a purple solid with 1:2 mixture by ^{1}H NMR from 4-(4-(trifluoromethyl)cyclohexyl)aniline (50 mg, 0.205 mmol), tetrahydro-4H-pyran-4-one (25 mg, 0.246 mmol), AcOH (0.1 mL), $NaBH(OAc)_3$ (87 mg, 0.41 mmol) and DCE (10 mL) according to the procedure for **1-1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 – 6.83 (m, 4H), 3.94 – 3.83 (m, 2H), 3.79 – 3.66 (m, 2H), 3.53 (s, 1H), 3.30 (s, 2H), 3.06 (s, 1H), 2.62 (s, 1H), 1.96 (s, 2H), 1.80 (d, J = 12.4 Hz, 2H), 1.74 – 1.38 (d, *m*, 4H). Mass (m/z): 329.3 $[M+H]^+$.

Compound 18

(R)-2-oxo-N-((4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)methyl)imidazolidine-4-carboxamide



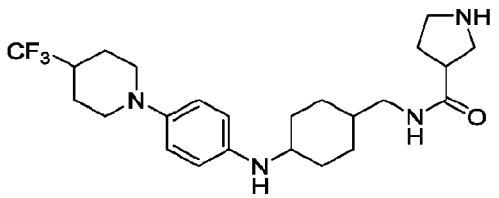
18

The title compound **18** (6.1 mg) was prepared in a total yield of 27% as a rosy brown solid from N-(4-(aminomethyl)cyclohexyl)-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (17 mg, 0.05 mmol)according to the procedure for compound **1.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.90 (s, 1H), 6.79 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 6.30 (s, 1H), 5.32 (s, 1H), 3.68 – 3.46 (m, 3H), 3.25 – 2.99 (m, 3H), 2.95 – 2.87 (m, 2H), 2.64 – 2.55 (m, 2H), 2.21 (m, 1H), 2.05 – 1.87 (m, 4H), 1.75 – 1.50 (m, 4H), 1.45 – 1.31 (m, 3H), 1.15 – 0.95 (m, 2H). Mass (m/z): 468.3 $[M+H]^+$.

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Compound 19

N-((4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)methyl)pyrrolidine-3-carboxamide

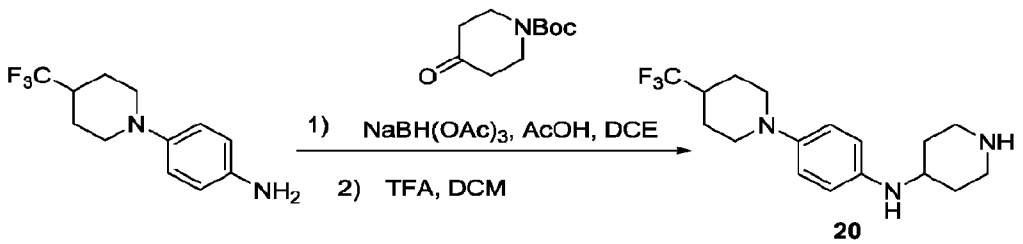


19

The title compound **19** (9.2 mg) was prepared in a total yield of 42% as a rosy brown solid from N-(4-(aminomethyl)cyclohexyl)-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (17 mg, 0.05 mmol)according to the procedure for compound **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.33 (s, 1H), 6.73 (d, J = 8.4 Hz, 2H), 6.46 (d, J = 8.4 Hz, 2H), 5.29 (s, 1H), 3.34 – 3.23 (m, 3H), 3.17 – 3.01 (m, 5H), 2.95 – 2.85 (m, 2H), 2.28 – 2.13 (m, 2H), 2.11 (m, 1H), 2.00 – 1.81 (m, 6H), 1.75 – 1.65 (m, 2H), 1.62 – 1.37 (m, 3H), 1.36 – 1.17 (m, 2H), 1.08-0.94 (m, 2H). Mass (m/z): 453.2 $[M+H]^+$.

Compound 20

N-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)piperidin-4-amine



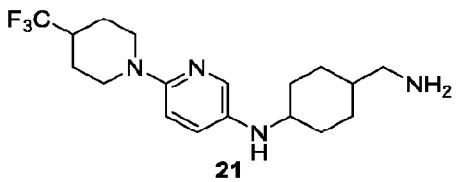
20

To a solution of 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (100 mg, 0.4 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (122.4 mg, 0.61 mmol) in 1,2-dichloroethane (5 mL) was added acetic acid (49 mg, 0.82 mmol). The mixture was stirred for 30 mins at room temperature before $NaBH(OAc)_3$ (173 mg, 0.8 mmol) was added at 0 °C slowly. The resulting mixture was stirred for overnight. Dichloromethane (5 mL) was added and 2,2,2-trifluoroacetic acid (1 mL) was added. The resulting mixture was stirred for further 2 h. The reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with dichloromethane (5 mL) for 3 times. The organic layers were combined and washed with water, sat. $NaHCO_3$, brine respectively, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/AcOEt, 1/1) to give 37.2 mg of desired product **20** as a pale rosy brown powder in a yield of 28.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (d, J = 52.9 Hz, 2H), 7.59 (s, 1H), 6.75 (d, J = 59.6 Hz, 3H), 3.46 (d, J = 23.1 Hz, 3H), 3.27 (d, J = 13.1 Hz, 2H), 2.95 (d, J = 11.0 Hz, 2H), 2.01 (d, J = 13.6 Hz, 3H), 1.88 (s, 2H), 1.60 (s, 4H), 1.24 (s, 2H). Mass (m/z): 328.6 $[M+H]^+$.

Compound 21

N-(4-(aminomethyl)cyclohexyl)-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine

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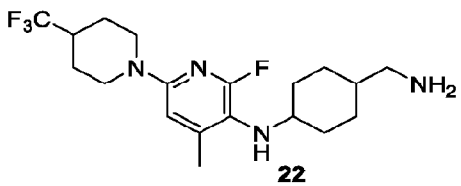


21

The title compound **21** (46.3 mg) was prepared in a yield of 32.87% as a pale yellow powder with 1:1 mixture by ^{1}H NMR from 6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (100 mg, 0.4 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (111 mg, 0.49 mmol) and $NaBH(OAc)_3$ (173 mg, 0.8 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 3H), 7.67 (s, 1H), 7.09 (s, 1H), 6.77 (d, J = 9.0 Hz, 1H), 4.12 (d, J = 12.7 Hz, 2H), 3.06 (s, 1H), 2.78 – 2.58 (m, 4H), 2.05 – 1.91 (m, 1H), 1.83 (d, J = 12.5 Hz, 3H), 1.74 (s, 1H), 1.62 (s, 1H), 1.57 – 1.37 (m, 5H), 1.05 (td, J = 25.1, 23.5, 10.3 Hz, 2H). Mass (m/z): 357.5 $[M+H]^+$.

Compound 22

N-(4-(aminomethyl)cyclohexyl)-2-fluoro-4-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine



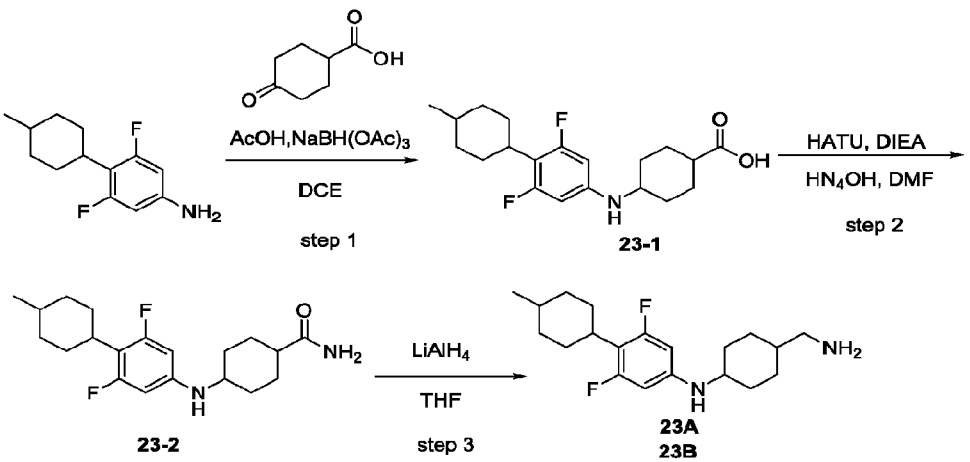
22

The title compound **22** (30.2 mg) was prepared in a yield of 42.56% as a pale rosy brown powder with 1:1 mixture by ^{1}H NMR from 2-fluoro-4-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (50 mg, 0.18 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (61 mg, 0.27 mmol) and $NaBH(OAc)_3$ (76 mg, 0.36 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 3H), 6.61 (s, 1H), 4.31 – 4.03 (m, 2H), 3.09 (s, 1H), 2.76 (d, J = 12.9 Hz, 2H), 2.61 (s, 1H), 2.29 (s, 3H), 2.07 – 1.94 (m, 1H), 1.82 (t, J = 16.8 Hz, 4H), 1.52 (s, 4H), 1.39 (qd, J = 12.5, 4.0 Hz, 2H), 0.95 (q, J = 10.3, 8.0 Hz, 1H). Mass (m/z): 389.4 $[M+H]^+$.

Compound 23

N-(4-(aminomethyl)cyclohexyl)-3,5-difluoro-4-(4-methylcyclohexyl)aniline

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Step 1. Preparation of 4-((3,5-difluoro-4-(4-methylcyclohexyl)phenyl)amino)cyclohexane-1-carboxylic acid (**23-1**)

The title compound **23-1** (605 mg) was prepared in a total yield of 77.7% as a brown solid from 3,5-difluoro-4-(4-methylcyclohexyl)aniline (500 mg, 2.212 mmol), 4-oxocyclohexane-1-carboxylic acid (377 mg, 2.655 mmol), AcOH (0.1 mL), $NaBH(OAc)_3$ (938 mg, 4.424 mmol) and DCE (15 mL) according to the procedure for **1-1**. Mass (m/z): 353.3 $[M+H]^+$.

Step 2. Preparation of 4-((3,5-difluoro-4-(4-methylcyclohexyl)phenyl)amino)cyclohexane-1-carboxamide **(23-2)**

The title compound **23-2** (453 mg) was prepared in a total yield of 75.1% as a yellow solid from 4-((3,5-difluoro-4-(4-methylcyclohexyl)phenyl)amino)cyclohexane-1-carboxylic acid (605 mg, 1.72 mmol), NH_4OH (3 mL), HATU (770 mg,2.23 mmol), DIEA (660 mg, 5.16 mmol) and DCE (15 mL) according to the procedure for **1**. Mass (m/z): 352.3 $[M+H]^+$.

Step 3. Preparation of N-(4-(aminomethyl)cyclohexyl)-3,5-difluoro-4-(4-methylcyclohexyl)aniline **(23)**

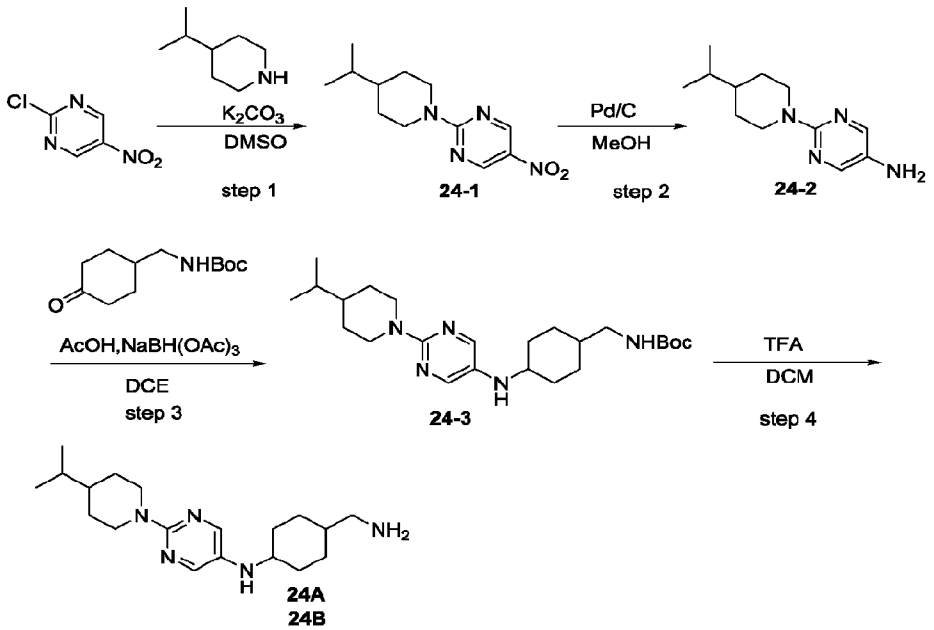
To a solution of 4-((3,5-difluoro-4-(4-methylcyclohexyl)phenyl)amino)cyclohexane-1-carboxamide (50 mg, 0.142 mmol) in THF (5 mL), $LiAlH_4$ (21 mg,0.57 mmol) was added at 0 °C . The mixture was stirred at room temperature for 16 h. The mixture was extracted by EA (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4 and concentrated to give the crude product, which was purified by prep HPLC (XSelect-CSH-Prep 5 μm OBD, 19*150 mm column; ACN/water (0.5% TFA) = 15%-25%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13 min) to give the desired product **23A** (Rt = 8.9 min) as a brown solid (2.4 mg, 5.0%) and **23B** (Rt = 9.8 min) as a brown solid (2.5 mg, 5.0%). **23A**: ^1H NMR (400 MHz, DMSO-d_6) δ 6.15 (d, J = 12.4 Hz, 2H), 3.08 (s, 1H), 2.93 – 2.87 (m, 3H), 2.72 – 2.63 (m, 2H), 1.97 (q, J = 6.0, 4.0 Hz, 2H), 1.78 (d, J = 7.2 Hz, 2H), 1.64 – 1.56 (m, 2H), 1.50 (s, 1H), 1.45 – 1.35 (m, 1H), 1.23 (q, J = 7.2, 6.4 Hz, 3H), 1.12 – 0.99 (m, 4H), 0.93 (d, J = 6.4 Hz, 3H). Mass (m/z): 338.3 $[M+H]^+$. **23B**: ^1H NMR (400 MHz, DMSO-d_6) δ 6.16 (d, J = 12.4 Hz, 2H), 3.36 (d, J = 4.8 Hz, 1H), 2.93 – 2.80 (m, 4H), 2.68 (q, J = 6.0 Hz, 2H), 1.65 – 1.46 (m, 9H), 1.41 – 1.28 (m, 3H), 1.19 (q, J = 7.2, 5.6 Hz, 4H), 0.89 (d, J = 6.4 Hz, 3H). Mass

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(m/z): 338.3 $[M+H]^+$.

Compound 24

N-(4-(aminomethyl)cyclohexyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine



Step 1. Preparation of 2-(4-isopropylpiperidin-1-yl)-5-nitropyrimidine **(24-1)**

To a solution of 4-isopropylpiperidine (500 mg, 3.94 mmol), 2-chloro-5-nitropyrimidine (688 mg, 4.33 mmol), K_2CO_3 (815 mg, 5.91 mmol) in DMSO (20 mL) was stirred at 100 °C for 16 h. The mixture was extracted by EA (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4 and concentrated to give the crude product, which was purified by TLC (EA:PE = 1:5) to give the desired product as a yellow solid (752 mg, 76.3%). Mass (m/z): 251.3 $[M+H]^+$.

Step 2. Preparation of 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine **(24-2)**

A solution of 2-(4-isopropylpiperidin-1-yl)-5-nitropyrimidine (752 mg, 3.42 mmol) and Pd/C (70 mg) in MeOH (20 mL) was stirred at rt for 2 h under H_2. The reaction was filtered and the filtrate was concentrated to give the desired product as a black solid (587 mg, 88%). Mass (m/z): 221.3 $[M+H]^+$.

Step 3. Preparation of tert-butyl ((4-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl)methyl)carbamate **(24-3)**

The title compound **24-3** (32 mg) was prepared in a total yield of 31% as a yellow oil from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (50 mg, 0.241 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (66 mg, 0.289 mmol), AcOH (0.1 mL), $NaBH(OAc)_3$ (102 mg, 0.428 mmol) and DCE (10 mL) according to the procedure for **1-1**. Mass (m/z): 432.3 $[M+H]^+$.

Step 4. Preparation of N-(4-(aminomethyl)cyclohexyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine **(24)**

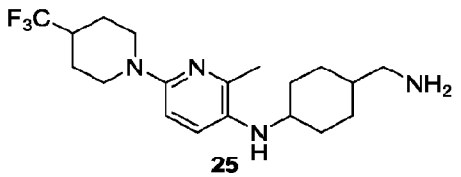
To a solution of **24-3** (32 mg, 0.074 mmol) in DCM (10 mL) was added TFA (1 mL). The solution was stirred at room temperature for 1 h. The mixture was basified by 1M NaOH to pH

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= 9 and concentrated, and then extracted by DCM (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4 and concentrated, which was purified by Prep-HPLC (XSelect-CSH-Prep 5 μm OBD, 19*150 mm column; solvent system (ACN/water (0.5% TFA) = 15%-24%-95%-95%-15%, 0-12 min-12.5 min-13.5 min-15 min) to give the desired product **24A** (Rt = 9.6 min) as a yellow solid (3.1 mg, 12.6%) and **24B** (Rt = 11.4 min) as yellow oil (5.1 mg, 6.3%). **24A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (s, 2H), 4.48 (d, J = 13.2 Hz, 1H), 2.63 (td, J = 10.4, 8.4, 6.0 Hz, 3H), 1.96 (dd, J = 14.4, 7.2 Hz, 3H), 1.69 (dd, J = 50.8, 12.4 Hz, 3H), 1.51 – 1.32 (m, 2H), 1.20 (d, J = 3.2 Hz, 9H), 1.10 – 0.95 (m, 4H), 0.84 – 0.80 (m, 6H). Mass (m/z): 332.3 $[M+H]^+$. **24B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (s, 2H), 4.48 (d, J = 12.8 Hz, 1H), 3.36 (s, 4H), 2.75 – 2.58 (m, 4H), 1.69 – 1.33 (m, 11H), 1.20 (d, J = 3.6 Hz, 4H), 1.10 – 0.98 (m, 2H), 0.83 (dd, J = 6.8, 2.8 Hz, 6H). Mass (m/z): 332.3 $[M+H]^+$.

Compound 25

N-(4-(aminomethyl)cyclohexyl)-2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine

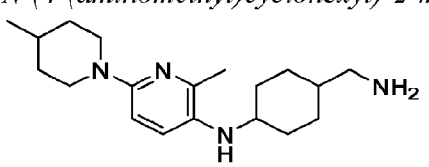


25

The title compound **25** (7.9 mg) was prepared in a yield of 11.8% as a yellow solid with 1:1 mixture by ^{1}H NMR from 2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (50 mg, 0.19 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (63 mg, 0.27 mmol) and $NaBH(OAc)_3$ (79 mg, 0.36 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 3H), 6.91 (d, J = 7.8 Hz, 1H), 6.56 (d, J = 8.9 Hz, 1H), 4.12 (d, J = 12.8 Hz, 2H), 3.04 (s, 1H), 2.75 (s, 1H), 2.70 – 2.55 (m, 3H), 2.25 (s, 1H), 2.21 (s, 2H), 2.05 – 1.91 (m, 2H), 1.83 (d, J = 12.5 Hz, 3H), 1.55 (d, J = 17.8 Hz, 3H), 1.44 (td, J = 12.8, 12.4, 8.1 Hz, 3H), 1.05 (t, J = 12.6 Hz, 2H), 0.88 – 0.81 (m, 1H). Mass (m/z): 371.5 $[M+H]^+$.

Compound 26

N-(4-(aminomethyl)cyclohexyl)-2-methyl-6-(4-methylpiperidin-1-yl)pyridin-3-amine



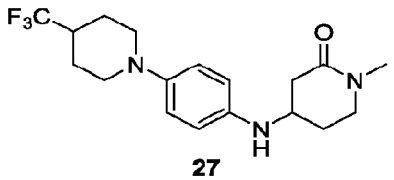
26

The title compound **26** (19.1 mg) was prepared in a yield of 24.8% as a pale yellow powder with 1:1 mixture by ^{1}H NMR from 2-methyl-6-(4-methylpiperidin-1-yl)pyridin-3-amine (50 mg, 0.24 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (83 mg, 0.37 mmol) and $NaBH(OAc)_3$ (103 mg, 0.48 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H), 8.16 (s, 3H), 6.68 (s, 1H), 4.21 (t, J = 6.5 Hz, 1H), 2.68 (d, J = 60.5 Hz, 4H), 2.37 (s, 3H), 2.04 – 1.91 (m, 1H), 1.82 (s, 2H), 1.73 – 1.42 (m, 9H), 1.06 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.4 Hz, 4H). Mass (m/z): 317.4 $[M+H]^+$.

Compound 27

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1-methyl-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)piperidin-2-one

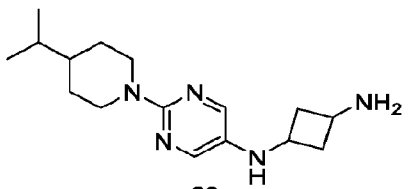


27

The title compound **27** (89 mg) was prepared in a yield of 64.2% as a white solid from 1-methylpiperidine-2,4-dione (50 mg, 0.39 mmol), MeOH (5 mL) was added 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (115 mg, 0.47 mmol), acetic acid (2.34 mg, 0.039 mmol) and sodium cyanoborohydride (73 mg, 1.17 mmol) according to the procedure for **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 8.7 Hz, 2H), 6.59 (d, J = 8.7 Hz, 2H), 3.75 – 3.72 (m, 1H), 3.53 (d, J = 11.7 Hz, 2H), 3.39 – 3.32 (m, 2H), 2.97 (s, 3H), 2.85 (dd, J = 18.0, 5.1, 1H), 2.59 (t, J = 8.7 Hz, 2H), 2.32 – 2.23 (m, 1H), 2.21 – 2.14 (m, 1H), 2.12 – 2.08 (m, 1H), 1.96 (d, J = 12.6 Hz, 2H), 1.86 – 1.71 (m, 3H). Mass (m/z): 356.2 $[M+H]^+$.

Compound 28

N1-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)cyclobutane-1,3-diamine

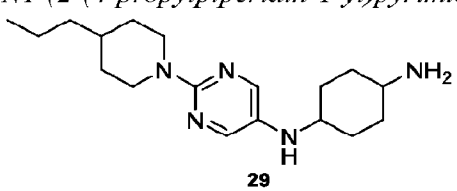


28

The title compound **28** (22.3 mg) was prepared in a yield of 57.1% as a white solid with 1:4 mixture by ^{1}H NMR from tert-butyl (3-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)cyclobutyl)carbamate (53 mg, 0.14 mmol), DCM (1 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 0.4 H), 7.72 (s, 1.6 H), 5.33 (d, J = 6.4 Hz, 0.8 H), 5.19 (d, J = 7.2 Hz, 0.2 H), 4.45 (dt, J = 12.6, 2.6 Hz, 2H), 3.80 – 3.70 (m, 1H), 3.56 – 3.49 (m, 1H), 3.32 – 3.20 (m, 2H), 2.62 – 2.55 (m, 2H), 2.50 – 2.48 (m, 0.8H), 2.08 – 1.95 (m, 3.2H), 1.66 – 1.56 (m, 2H), 1.52 – 1.42 (m, 0.2H), 1.39 – 1.30 (m, 0.8H), 1.21 – 1.12 (m, 1H), 1.08 – 0.96 (m, 2H), 0.82 (d, J = 6.8 Hz, 6H). Mass (m/z): 290.3 $[M+H]^+$.

Compound 29

N1-(2-(4-propylpiperidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine



29

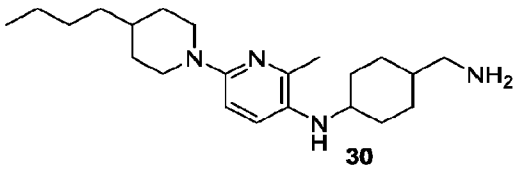
The title compound **29** (32.2 mg) was prepared in a total yield of 32.3% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl ((4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)methyl)carbamate (130 mg, 0.312 mmol), TFA (1 mL) and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 2H), 7.89 (d, J = 14.4 Hz, 2H), 4.86 (dd, J = 20.4, 7.2 Hz, 1H),

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4.38 (dd, J = 13.6, 3.2 Hz, 2H), 3.08 – 2.95 (m, 1H), 2.64 (tt, J = 12.8, 2.4 Hz, 2H), 1.95 (tt, J = 8.6, 3.2 Hz, 2H), 1.78 – 1.51 (m, 5H), 1.40 (ddd, J = 15.2, 12.0, 6.8 Hz, 2H), 1.31 – 1.23 (m, 2H), 1.19 – 1.07 (m, 3H), 0.97 (qd, J = 12.4, 4.0 Hz, 2H), 0.83 (t, J = 7.2 Hz, 3H). Mass (m/z): 318.3 $[M+H]^+$.

Compound 30

N-(4-(aminomethyl)cyclohexyl)-6-(4-butylpiperidin-1-yl)-2-methylpyridin-3-amine

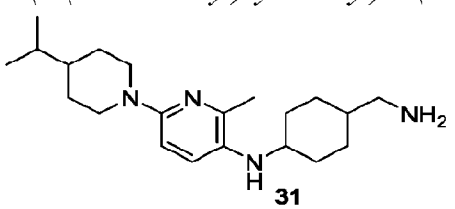


30

The title compound **30** (7.2 mg) was prepared in a yield of 10.1% as a pale yellow powder with 1:1 mixture by ^{1}H NMR from 6-(4-butylpiperidin-1-yl)-2-methylpyridin-3-amine (50 mg, 0.20 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (73 mg, 0.32 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (s, 3H), 7.43 (s, 1H), 2.79 (t, J = 6.5 Hz, 2H), 2.67 (d, J = 12.5 Hz, 1H), 2.39 (d, J = 9.0 Hz, 3H), 1.98 (td, J = 18.0, 16.5, 9.6 Hz, 2H), 1.85 – 1.73 (m, 4H), 1.66 – 1.40 (m, 8H), 1.28 (dd, J = 7.8, 3.3 Hz, 6H), 0.86 (dt, J = 10.8, 6.8 Hz, 4H). Mass (m/z): 331.3 $[M+H]^+$.

Compound 31

N-(4-(aminomethyl)cyclohexyl)-6-(4-isopropylpiperidin-1-yl)-2-methylpyridin-3-amine

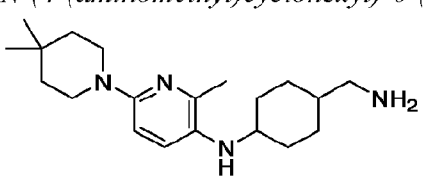


31

The title compound **31** (16.0 mg) was prepared in a yield of 20.6% as a pale yellow powder with 1:1 mixture by ^{1}H NMR from 6-(4-isopropylpiperidin-1-yl)-2-methylpyridin-3-amine (50 mg, 0.21 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (73 mg, 0.32 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 3H), 6.96 (s, 1H), 6.59 (s, 1H), 4.07 (s, 2H), 2.75 (s, 1H), 2.61 (s, 2H), 2.28 (s, 3H), 1.96 (s, 1H), 1.83 (s, 2H), 1.77 – 1.35 (m, 9H), 1.20 (d, J = 26.6 Hz, 4H), 1.02 (d, J = 11.7 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H). Mass (m/z): 345.6 $[M+H]^+$.

Compound 32

N-(4-(aminomethyl)cyclohexyl)-6-(4,4-dimethylpiperidin-1-yl)-2-methylpyridin-3-amine



32A

32B

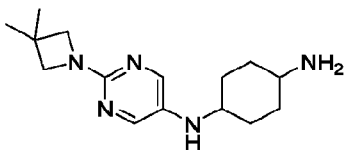
The title compound **32** was prepared from 6-(4,4-dimethylpiperidin-1-yl)-2-methylpyridin-3-amine (50 mg, 0.23 mmol), tert-butyl

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((4-oxocyclohexyl)methyl)carbamate (77 mg, 0.34 mmol) and according to the procedure for **20**. The mixture was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10.0 min-11.0 min-15.0 min) afford compound **32A** (Rt = 3.69 min) as a yellow solid and compound **32B** (Rt = 3.79 min) as a yellow solid. **32A** (18.2 mg, 23.9%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 3H),6.99(s, 1H), 6.68(s, 1H), 3.37-3.41(m, 3H), 2.75 (s, 1H), 2.61 (s, 1H), 2.32 (s, 3H), 1.82 (s, 2H), 1.55 (d, J = 25.7 Hz, 6H), 1.35 (s, 4H), 1.22 (s, 1H), 1.00 (d, J = 11.0 Hz, 1H), 0.94 (s, 6H). Mass (m/z): 331.5 $[M+H]^+$. **32B** (8.8 mg, 11.6%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 3H), 7.22(s, 1H), 6.66 (s, 1H), 3.52 (d, J = 17.5 Hz, 2H), 2.75 (s, 1H), 2.63 (s, 1H), 2.27 (s, 2H), 1.99 (q, J = 7.0 Hz, 3H), 1.80 (s, 2H), 1.48 (d, J = 31.8 Hz, 7H), 1.35 (s, 4H), 0.94 (s, 6H), 0.88 – 0.81 (m, 1H). Mass(m/z): 331.5 $[M+H]^+$.

Compound 33

N1-(2-(3,3-dimethylazetidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine

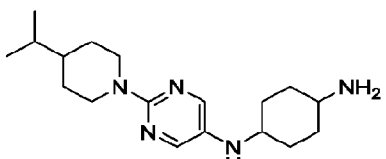


33A
33B

The title product **33A** (Rt = 6.8 min; 13.5 mg, 16.8%) as a yellow solid and **33B** (Rt = 8.0 min; 8.3 mg, 10.3%) as a yellow solid were prepared from tert-butyl (4-((2-(3,3-dimethylazetidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl) carbamate (110 mg, 0.293 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**, which was purified by Prep-HPLC (XSelect-CSH-Prep 5 μm OBD, 19*150 mm column; solvent system (ACN/water (0.5% TFA) = 15%-25%-95%-95%-15%, 0-13 min-13.5 min-14.5 min-16 min). **33A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 – 7.89 (m, 2H), 3.67 – 3.63 (m, 2H), 3.59 (d, J = 7.6 Hz, 3H), 2.94 (dd, J = 8.4, 2.4 Hz, 2H), 1.97 – 1.89 (m, 4H), 1.32 (td, J = 8.4, 3.2 Hz, 3H), 1.25 – 1.21 (m, 6H), 1.19 (dd, J = 9.2, 2.4 Hz, 3H). Mass (m/z): 276.3 $[M+H]^+$. **33B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 2H), 3.64 (d, J = 5.2 Hz, 3H), 3.22 (d, J = 7.6 Hz, 2H), 1.73 (t, J = 3.6 Hz, 8H), 1.26 (d, J = 6.0 Hz, 6H), 1.22 (d, J = 10.4 Hz, 3H). Mass (m/z): 276.3 $[M+H]^+$.

Compound 34

N1-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine



34A
34B

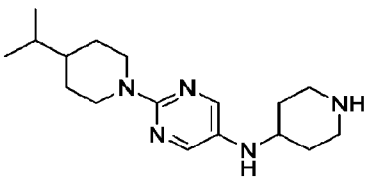
The title product **34A** (Rt = 5.8 min) as a white solid (18.8 mg, 19.2%) and **34B** (Rt = 6.6 min) as a yellow solid (16.8 mg, 17.2%) were prepared from tert-butyl (4-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl)carbamatee (130 mg, 0.312 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24** which was purified

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by Prep-HPLC (solvent system (ACN/water (0.5% TFA) = 10%-45%-95%-95%-10%, 0-7 min-7.5 min-8.5 min-10 min). **34A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.87 (s, 1H), 7.80 (d, J = 4.8 Hz, 2H), 4.50 (d, J = 12.8 Hz, 2H), 3.07 (d, J = 11.2 Hz, 1H), 2.95 (s, 1H), 2.71 – 2.61 (m, 2H), 1.99 – 1.86 (m, 4H), 1.64 (d, J = 12.4 Hz, 2H), 1.35 (dp, J = 22.0, 7.6, 7.2 Hz, 3H), 1.20 (q, J = 12.8, 10.0 Hz, 3H), 1.04 (qd, J = 12.4, 4.0Hz, 2H), 0.82 (d, J = 6.8 Hz, 6H). Mass (m/z): 318.3 $[M+H]^+$. **34B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.89 (s, 1H), 7.78 (s, 2H), 4.49 – 4.44 (m, 2H), 3.15 (d, J = 39.6 Hz, 1H), 2.64 (td, J = 12.8, 2.8 Hz, 2H), 1.74 – 1.54 (m, 10H), 1.37 (dq, J = 13.2, 6.8 Hz, 1H), 1.23 – 1.17 (m, 2H), 1.04 (qd, J = 12.4, 4.0 Hz, 2H), 0.85 – 0.80 (m, 6H). Mass(m/z): 318.3 $[M+H]^-$.

Compound 35

2-(4-isopropylpiperidin-1-yl)-N-(piperidin-4-yl)pyrimidin-5-amine

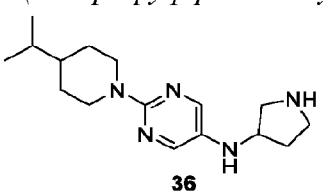


35

The title compound **35** (39.8 mg) was prepared in a total yield of 38.1% as yellow oil with 1:2 mixture by ^{1}H NMR from tert-butyl 4-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)piperidine-1-carboxylate (140 mg, 0.347 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 2H), 4.47 (dq, J – 12.4, 2.8 Hz, 2H), 3.44 – 3.36 (m, 1H), 3.28 (t, J = 15.2 Hz, 3H), 2.90 (p, J = 15.2, 13.2 Hz, 3H), 2.64 (td, J = 12.8, 2.8 Hz, 2H), 2.01 – 1.94 (m, 2H), 1.67 – 1.59 (m, 3H), 1.47 (dt, J = 11.2, 3.2 Hz, 1H), 1.35 (dd, J = 13.2, 6.4 Hz, 1H), 1.20 (d, J = 4.0 Hz, 1H), 1.05 (tt, J = 12.4, 6.4 Hz, 2H), 0.82 (d, J = 6.8 Hz, 6H). Mass (m/z): 304.3 $[M+H]^+$.

Compound 36

2-(4-isopropylpiperidin-1-yl)-N-(pyrrolidin-3-yl)pyrimidin-5-amine



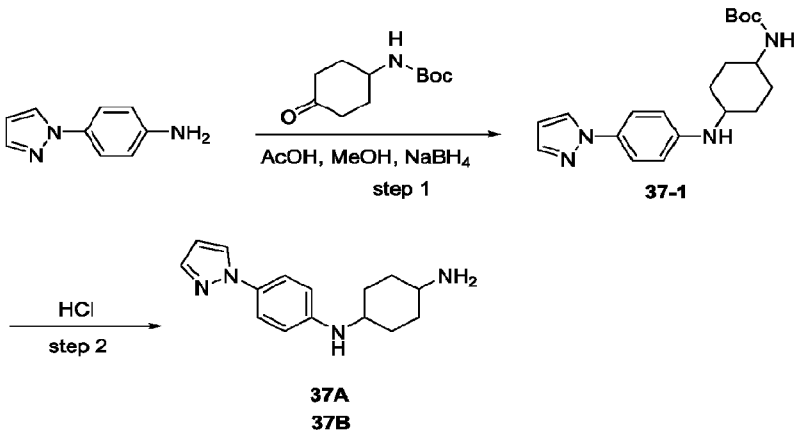
36

The title compound **36** (35.0 mg) was prepared in a total yield of 36.5% as a yellow oil from tert-butyl 4-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)piperidine-1-carboxylate (130 mg, 0.334 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 2H), 4.47 (dt, J = 14.0, 3.2 Hz, 2H), 3.97 (td, J = 6.4, 3.2 Hz, 1H), 3.87 (s, 1H), 3.35 (dd, J = 12.0, 6.0 Hz, 1H), 3.25 – 3.15 (m, 2H), 3.00 (dq, J = 9.6, 4.8 Hz, 1H), 2.64 (td, J = 12.8, 2.8 Hz, 2H), 2.23 – 2.14 (m, 1H), 1.66 – 1.58 (m, 3H), 1.37 (dq, J = 13.2, 6.4 Hz, 2H), 1.04 (qd, J = 12.4, 4.0 Hz, 3H), 0.83 (s, 3H), 0.81 (s, 3H). Mass (m/z): 290.3 $[M+H]^+$.

Compound 37

N1-(4-(1H-pyrazol-1-yl)phenyl)cyclohexane-1,4-diamine

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Step 1. Preparation of tert-butyl (4-((4-(1H-pyrazol-1-yl)phenyl)amino)cyclohexyl)carbamate **(37-1)**

To a solution of 4-(1H-pyrazol-1-yl)aniline (150 mg, 0.94 mmol) in MeOH (10 mL) were added a drop of AcOH and tert-butyl (4-oxocyclohexyl)carbamate (201.9 mg, 0.94 mmol), and the mixture was stirred at 50 °C for 1 h. Then $NaBH_4$ (71.24 mg, 1.88 mmol) was added after cooling to 25 °C. Then the mixture was stirred at 25 °C for 16 hrs. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to afford to give **37-1** (0.2 g, 59.3% yield) as a yellow solid. MS (m/z) 356.8 $[M+H]^+$.

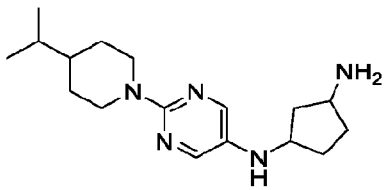
Step 2. Preparation of N-(4-(tert-butyl)phenyl)-N-(2,2,2-trifluoroethyl)cyclohexane-1,4-diamine **(37)**

compound **37-1** (200 mg, 0.56 mmol) and HCl in 1,4-dioxane (10 mL, 4N) were placed in a flask stirred at 25 °C for 16 hrs. Excess 1,4-dioxane was distilled under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 2%-20%) to afford **37A** (31.2 mg) as a white solid and **37B** (21.9 mg) as a white solid. **37A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 8.20 (d, J = 2.3 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 7.47 (d, J = 8.9 Hz, 2H), 6.64 (d, J = 8.9 Hz, 2H), 6.45 – 6.42 (m, 1H), 5.61 (d, J = 7.8 Hz, 1H), 3.17 (s, 1H), 2.89 (s, 1H), 1.97 (dd, J = 34.9, 11.9 Hz, 4H), 1.39 (d, J = 13.0 Hz, 2H), 1.23 – 1.14 (m, 2H). MS (m/z) 257.2 $[M+H]^+$. HPLC: Rt: 2.643 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **37B**: ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 7.96 (d, J = 2.2 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 7.40 (d, J = 8.9 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 6.45 (t, J = 2.1 Hz, 1H), 3.60 (s, 1H), 3.23 (s, 1H), 1.97 – 1.74 (m, 8H). MS (m/z) 257.2 $[M+H]^+$. HPLC: Rt: 3.112 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA) ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 38

N1-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)cyclopentane-1,3-diamine

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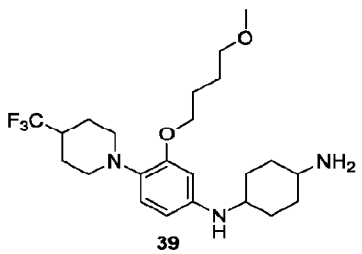


38

The title compound **38** (5.9 mg) was prepared in a total yield of 6.7% as a yellow solid from tert-butyl (3-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)cyclopentyl)carbamate (120 mg, 0.298 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 6.0 Hz, 2H), 4.46 (d, J = 12.8 Hz, 1H), 3.81 (d, J = 20.4 Hz, 2H), 3.61 (t, J = 6.8 Hz, 2H), 2.62 – 2.60 (m, 1H), 2.11 – 2.02 (m, 1H), 1.99 – 1.88 (m, 3H), 1.62 (d, J = 15.2 Hz, 3H), 1.57 – 1.48 (m, 1H), 1.36 (dt, J = 11.6, 5.8 Hz, 2H), 1.04 (qd, J = 12.4, 4.4 Hz, 2H), 0.83 (s, 3H), 0.81 (d, J = 2.0 Hz, 3H). Mass (m/z): 304.3 $[M+H]^+$.

Compound 39

N1-(3-(4-methoxybutoxy)-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

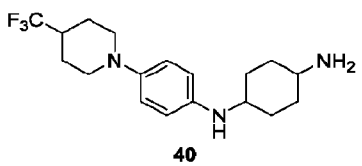


39

The title compound **39** (69.1 mg) was prepared in a total yield of 70.4% as a purple solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((3-(4-methoxybutoxy)-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (120 mg, 0.221 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 2H), 8.17 (s, 1H), 6.62 (d, J = 8.4 Hz, 1H), 6.23 (d, J = 24.8 Hz, 1H), 6.04 (s, 1H), 3.83 (d, J = 7.6 Hz, 2H), 3.37 – 3.34 (m, 2H), 3.19 (s, 5H), 2.96 (d, J = 51.2 Hz, 2H), 2.31 (s, 1H), 1.95 (d, J = 11.6 Hz, 3H), 1.84 – 1.60 (m, 10H), 1.57 – 1.40 (m, 4H), 1.11 (d, J = 12.0 Hz, 1H). Mass (m/z): 444.3 $[M+H]^+$.

Compound 40

N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



40

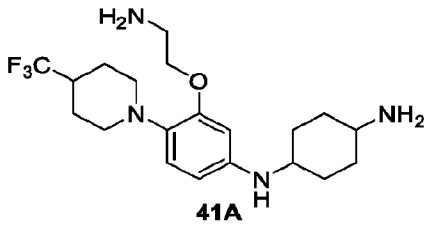
The title compound **40** (56.2 mg) was prepared in a total yield of 48.9% as a purple solid with 1:2 mixture by ^{1}H NMR from N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine (150 mg, 0.34 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 3H), 6.75 – 6.68 (m, 2H), 6.52 – 6.43 (m, 2H), 4.92 (d, J = 7.2 Hz, 1H), 3.41 – 3.29 (m, 4H), 3.01 (s, 1H), 2.94 – 2.82 (m, 1H), 2.32 (d, J = 9.2 Hz, 1H), 1.94 (d, J =

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12.0Hz, 2H), 1.81 (d, J = 12.0 Hz, 2H), 1.75 – 1.65 (m, 2H), 1.52 (qd, J = 12.4, 4.1 Hz, 3H), 1.45 – 1.36 (m, 1H), 1.15 – 1.06 (m, 1H). Mass (m/z): 342.3 $[M+H]^+$.

Compound 41

N1-(3-(2-aminoethoxy)-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

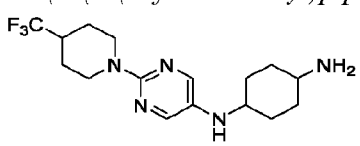


41A
41B

The title compound **41A**, **41B** was prepared from tert-butyl (2-(5-amino-2-(4-(trifluoromethyl)piperidin-1-yl)phenoxy)ethyl)carbamate (100 mg, 0.25 mmol), tert-butyl (4-oxocyclohexyl)carbamate (79 mg, 0.37 mmol) according to the procedure for compound **20**. The residue was purified by preparative HPLC ((Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 0%-30%-95%-95%-10%, 0 min-7 min-7.5 min-8.5 min-10.0 min) to afford compound **41A** (Rt = 4.39 min) in 5.6% yield as a white solid and **41B** (Rt = 4.82 min) in 6.24% yield as a white solid. **41A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 3H), 7.86 (s, 3H), 6.56 (s, 1H), 6.17 (d, J = 8.8 Hz, 1H), 3.13 (s, 2H), 2.01 – 1.85 (m, 8H), 1.87 – 1.46 (m, 9H), 1.45 (s, 2H), 0.85 (t, J = 6.5 Hz, 2H). Mass (m/z): 401.4 $[M+H]^+$. **41B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 3H), 7.80 (s, 3H), 6.37 (s, 1H), 6.28 (d, J = 8.8 Hz, 1H), 4.17 (s, 1H), 3.13 (s, 2H), 2.07 – 1.88 (m, 6H), 1.79 – 1.56 (m, 11H), 1.45 (s, 1H), 0.85 (t, J = 6.5 Hz, 2H). Mass (m/z): 401.4 $[M+H]^+$.

Compound 42

N1-(2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine



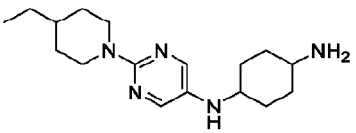
42

The title compound **42** (102.7 mg) was prepared in a total yield of 87.9% as a yellow solid with 2:3 mixture by ^{1}H NMR from tert-butyl (4-((2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl)carbamate (150 mg, 0.39 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 2H), 7.92 (d, J = 13.6 Hz, 2H), 5.04 (d, J = 6.0 Hz, 0.4H), 4.98 (d, J = 8.4 Hz, 0.6H), 4.49 (d, J = 13.2 Hz, 2H), 3.02 (dt, J = 9.6, 4.8 Hz, 1H), 2.89 (tt, J = 12.0, 3.6 Hz, 1H), 2.72 (td, J = 12.8, 2.4 Hz, 2H), 1.95 (dt, J = 12.4, 4.9 Hz, 2H), 1.80 – 1.74 (m, 2H), 1.70 (q, J = 6.4, 5.2 Hz, 2H), 1.59 – 1.49 (m, 1H), 1.41 (dd, J = 12.8, 3.2 Hz, 1H), 1.29 (tt, J = 12.4, 6.4 Hz, 2H), 1.09 (qd, J = 12.8, 11.6, 4.8 Hz, 1H). Mass (m/z): 344.3 $[M+H]^+$.

Compound 43

N1-(2-(4-ethylpiperidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine

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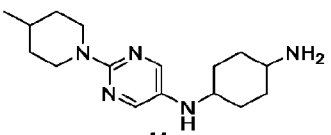


43

The title compound **43** (67.5 mg) was prepared in a total yield of 71.8% as a yellow solid with 1:1 mixture by ^{1}H NMR from tert-butyl (4-((2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl)carbamate (150 mg, 0.39 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 2H), 7.89 (d, J = 14.4 Hz, 2H), 4.91 (d, J = 6.0 Hz, 0.5H), 4.86 (d, J = 8.4 Hz, 0.5H), 4.45 – 4.31 (m, 2H), 3.32 (d, J = 21.6 Hz, 2H), 3.07 – 2.95 (m, 1H), 2.88 (dq, J = 11.6, 6.0, 4.0 Hz, 1H), 2.63 (tt, J = 12.4, 2.4 Hz, 2H), 1.94 (tt, J = 9.6, 3.6 Hz, 2H), 1.73 – 1.59 (m, 4H), 1.57 – 1.48 (m, 1H), 1.46 – 1.36 (m, 1H), 1.28 (dp, J = 11.2, 4.0 Hz, 1H), 1.18 (dd, J = 8.4, 5.6 Hz, 2H), 0.96 (qd, J = 12.4, 4.0 Hz, 2H), 0.82 (t, J = 7.6 Hz, 3H). Mass (m/z): 304.3 $[M+H]^+$.

Compound 44

N1-(2-(4-methylpiperidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine

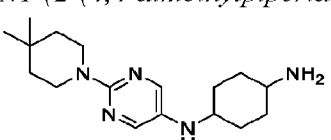


44

The title compound **44** (17.0 mg) was prepared in a total yield of 26.2% as a yellow solid with 2:3 mixture by ^{1}H NMR from tert-butyl (4-((2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl)carbamate (87 mg, 0.224 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 14.0 Hz, 2H), 5.04 (d, J = 6.0 Hz, 0.4H), 4.98 (d, J = 8.4 Hz, 0.6H), 4.41 – 4.28 (m, 2H), 3.01 (dd, J = 10.4, 5.6 Hz, 1H), 2.86 (t, J = 12.0 Hz, 1H), 2.65 (td, J = 12.4, 2.4 Hz, 2H), 1.93 (d, J = 11.2 Hz, 2H), 1.69 (d, J = 11.2 Hz, 2H), 1.55 (td, J = 13.2, 3.6 Hz, 3H), 1.41 – 1.34 (m, 1H), 1.10 (t, J = 11.6 Hz, 1H), 1.03 – 0.93 (m, 2H), 0.86 (d, J = 6.4 Hz, 3H). Mass (m/z): 290.3 $[M+H]^+$.

Compound 45

N1-(2-(4,4-dimethylpiperidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine



45

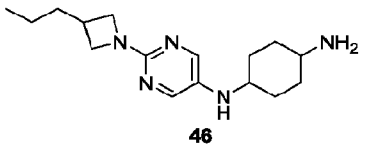
The title compound **45** (54.7 mg) was prepared in a total yield of 66.7% as a yellow solid with 1:1 mixture by ^{1}H NMR from tert-butyl (4-((2-(4,4-dimethylpiperidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl)carbamate (109 mg, 0.270 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 15.2 Hz, 2H), 4.92 (dd, J = 19.2, 6.8 Hz, 1H), 3.55 (td, J = 5.6, 2.0 Hz, 4H), 3.06 (d, J = 8.8 Hz, 2H), 2.92 (td, J = 11.6, 6.0 Hz, 1H), 2.03 – 1.96 (m, 2H), 1.83 – 1.65 (m, 3H), 1.58 (d, J = 13.6 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.32 – 1.26 (m, 4H), 1.19 – 1.08 (m,

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1H), 0.94 (s, 6H). Mass (m/z): 304.3 $[M+H]^+$.

Compound 46

N1-(2-(3-propylazetidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine

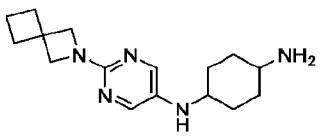


46

The title compound **46** (4.3 mg) was prepared in a total yield of 11.1% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((2-(3-propylazetidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl)carbamate (52 mg, 0.134 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 12.4 Hz, 2H), 4.97 (d, J = 22.4 Hz, 1H), 3.96 (t, J = 8.0 Hz, 2H), 3.49 (dd, J = 8.0, 5.6 Hz, 2H), 3.04 (s, 1H), 2.93 (s, 1H), 1.99 (s, 2H), 1.73 (d, J = 9.6 Hz, 2H), 1.57 – 1.52 (m, 2H), 1.47 – 1.40 (m, 2H), 1.32 – 1.19 (m, 5H), 1.16 – 1.10 (m, 1H), 0.88 (t, J = 7.2 Hz, 3H). Mass (m/z): 290.3 $[M+H]^+$.

Compound 47

N1-(2-(2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine

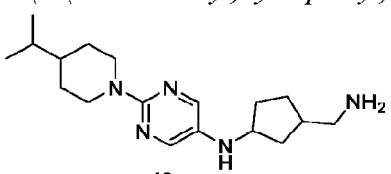


47

The title compound **47** (26.1 mg) was prepared in a total yield of 35.6% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((2-(2-azaspiro[3.3]heptan-2-yl)pyrimidin-5-yl)amino)cyclohexyl)carbamate (98 mg, 0.253 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J – 13.2 Hz, 2H), 5.04 (d, J – 6.0 Hz, 0.3H), 4.98 (d, J – 8.4 Hz, 0.7H), 3.84 (s, 3H), 2.96 (dd, J = 33.6, 21.6 Hz, 2H), 2.13 (t, J = 7.6 Hz, 4H), 2.03 – 1.93 (m, 3H), 1.84 – 1.71 (m, 4H), 1.57 – 1.38 (m, 2H), 1.16 – 1.10 (m, 1H). Mass (m/z): 288.3 $[M+H]^+$.

Compound 48

N-(3-(aminomethyl)cyclopentyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine



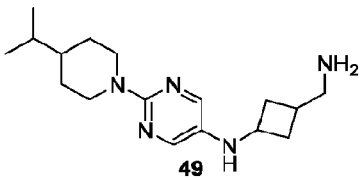
48

The title compound **48** (6.1 mg) was prepared in a yield of 8.4% as a white powder with 1:1 mixture by ^{1}H NMR from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (50 mg, 0.23 mmol), tert-butyl ((3-oxocyclopentyl)methyl)carbamate (73 mg, 0.34 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 3H), 7.86 (d, J = 2.8 Hz, 2H), 4.51 (q, J = 16.0, 14.9 Hz, 2H), 2.66 (d, J = 23.1 Hz, 2H), 1.64 (d, J = 12.9 Hz, 4H), 1.40 (q, J = 6.6 Hz, 3H), 1.34 – 1.15 (m, 5H), 1.09 (td, J = 12.5, 4.0 Hz, 3H), 0.86 (d, J = 2.8 Hz, 4H), 0.84 (s, 3H). Mass (m/z): 317.3 $[M+H]^+$.

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Compound 49

N-(3-(aminomethyl)cyclobutyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine

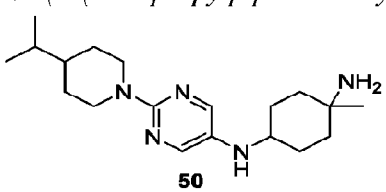


49

The title compound **49** (26.6 mg) was prepared in a three-step overall yield of 9.6% as a white powder with 1:1 mixture by ^{1}H NMR from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (200 mg, 0.91 mmol), 3-oxocyclobutane-1-carboxylic acid (155 mg, 1.36 mmol) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.07 (s, 1H), 8.16 (s, 3H), 6.68 (s, 1H), 4.21 (t, J = 6.5 Hz, 2H), 2.68 (d, J = 60.5 Hz, 3H), 2.37 (s, 3H), 2.03 – 1.89 (m, 1H), 1.82 (s, 2H), 1.73 – 1.39 (m, 7H), 1.22 (d, J = 3.1 Hz, 3H), 1.06 (d, J = 6.6 Hz, 2H), 0.91 (d, J = 6.4 Hz, 3H). Mass(m/z): 304.6 $[M+H]^+$.

Compound 50

N1-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)-4-methylcyclohexane-1,4-diamine

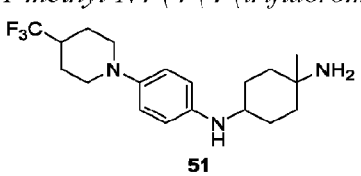


50

The title compound **50** (56.3 mg) was prepared in a yield of 53.4% as a pale yellow powder with 1:1 mixture by ^{1}H NMR from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (70 mg, 0.34 mmol), tert-butyl (1-methyl-4-oxocyclohexyl)carbamate (110 mg, 0.52 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 18.4 Hz, 3H), 7.92 (d, J = 11.0 Hz, 2H), 4.82 (dd, J = 36.7, 7.5 Hz, 1H), 4.56 – 4.42 (m, 2H), 3.13 (d, J = 43.4 Hz, 1H), 2.62 (td, J = 12.8, 2.5 Hz, 2H), 1.97 – 1.81 (m, 2H), 1.74 (d, J = 13.4 Hz, 2H), 1.69 – 1.57 (m, 4H), 1.53 (h, J = 7.5, 6.3 Hz, 1H), 1.40 (h, J = 6.7 Hz, 1H), 1.27 (d, J = 7.0 Hz, 4H), 1.07 (qd, J = 12.3, 4.2 Hz, 2H), 0.85 (d, J = 6.7 Hz, 6H). Mass (m/z): 332.4 $[M+H]^+$.

Compound 50

1-methyl-N4-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



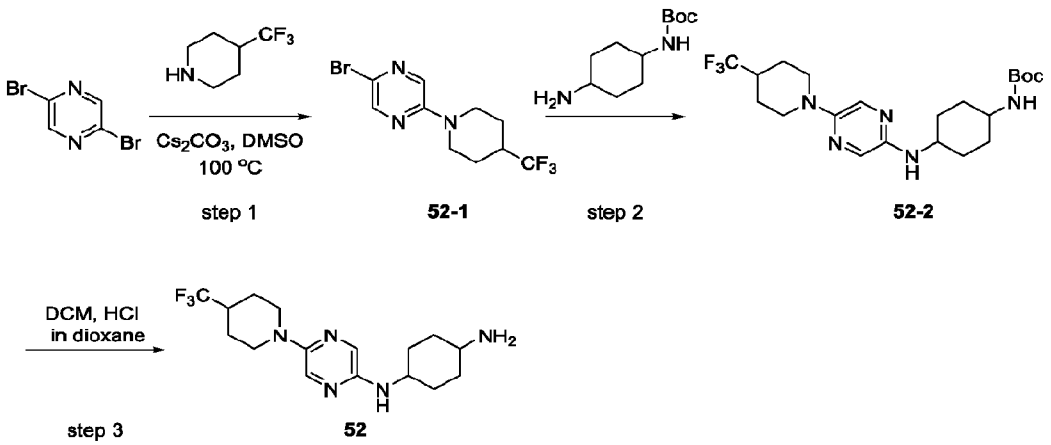
51

The title compound **51** (47.2 mg) was prepared in a total yield of 75.8% as a purple solid from tert-butyl (1-methyl-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (79 mg, 0.174 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 36.4 Hz, 3H), 6.78 (s, 2H), 6.68 – 6.39 (m, 2H), 3.16 (d, J = 55.2 Hz, 1H), 2.38 (s, 1H), 2.05 – 1.43 (m, 11H), 1.30 (d, J = 7.5 Hz, 3H). Mass (m/z): 356.3 $[M+H]^+$.

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Compound 52

N1-(5-(4-(trifluoromethyl)piperidin-1-yl)pyrazin-2-yl)cyclohexane-1,4-diamine



Step 1. Preparation of 2-bromo-5-(4-(trifluoromethyl)piperidin-1-yl)pyrazine **(52-1)**

To a solution of 2,5-dibromopyrazine (3 g, 12.6 mmol) in DMSO (30 mL) was added 4-(trifluoromethyl)piperidine (1.93 g, 12.6 mmol) and Cs_2CO_3 (6.16 g, 18.9 mmol). Then the mixture was stirred at 100 °C for 2 hrs. LCMS showed the reaction was completed. The mixture was added into H_2O and filtered to give compound **52-1** (3.5 g, 89.7% yield) as a yellow solid. MS (m/z): 310.0 $[M+H]^+$.

Step 2. Preparation of tert-butyl (4-((5-(4-(trifluoromethyl)piperidin-1-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate **(52-2)**

To a solution of 2-bromo-5-(4-(trifluoromethyl)piperidin-1-yl)pyrazine (0.2 g, 0.64 mmol), tert-butyl (4-aminocyclohexyl)carbamate (139 mg, 0.64 mmol), Cs_2CO_3 (420 mg, 1.29 mmol) and Ruphos (60 mg, 0.13 mmol) in dioxane (10 mL) was added $Pd_2(dba)_3$ (59 mg, 0.064 mmol) at 25 °C under N_2. Then the mixture was stirred at 90 °C overnight. LCMS showed the reaction was completed. The reaction was filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:2) to afford **52-2** (0.1 g, 34.8% yield) as a yellow solid. MS (m/z) 443.7 $[M+H]^+$.

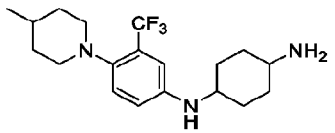
Step 3. Preparation of N1-(5-(4-(trifluoromethyl)piperidin-1-yl)pyrazin-2-yl)cyclohexane-1,4-diamine **(52)**

To a solution of compound 3 (100 mg, 0.22 mmol) in THF (2 mL) was added HCl in dioxane (2 mL). Then the mixture was stirred at 25 °C for 1 h. LCMS showed the reaction was completed. The reaction was concentrated. The residue was purified by prep-HPLC to give **52** (6 mg, 7.7% yield) as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 7.64 (d, J = 1.3 Hz, 1H), 7.62 (s, 1H), 3.96 (d, J = 12.6 Hz, 2H), 3.80 (s, 1H), 3.22 - 3.15 (m, 1H), 2.67 (t, J = 12.6 Hz, 2H), 2.36 - 2.21 (m, 1H), 1.94 - 1.54 (m, 12H). MS (m/z) 344.2 $[M+H]^+$.

Compound 53

N1-(4-(4-methylpiperidin-1-yl)-3-(trifluoromethyl)phenyl)cyclohexane-1,4-diamine

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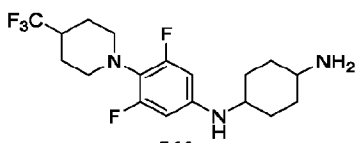
53A

53B

The desired product **53A** (Rt = 10.9 min) as a yellow solid (15.1 mg, 16.1%) and **53B** (Rt = 14.4 min) as yellow oil (14.3 mg, 15.5%) were prepared from tert-butyl (4-((4-(4-methylpiperidin-1-yl)-3-(trifluoromethyl)phenyl)amino)cyclohexyl)carbamate (121 mg, 0.266 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**, which were purified by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; solvent system (ACN/water (0.5% TFA) = 10%-90%-95%-95%-10%, 0-12 min-12.5 min-13.5 min-15 min). **53A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 10.0 Hz, 2H), 5.63 (d, J = 8.0 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.71 (dt, J = 11.6, 3.3 Hz, 2H), 2.58 (td, J = 11.6, 2.4 Hz, 2H), 1.91 – 1.81 (m, 2H), 1.77 – 1.66 (m, 2H), 1.58 (dd, J = 12.8, 3.5 Hz, 2H), 1.43 – 1.34 (m, 1H), 1.23 – 1.13 (m, 3H), 1.08 (t, J = 9.2 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H). Mass (m/z): 356.3 $[M+H]^+$. **53B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 10.0 Hz, 2H), 5.63 (d, J = 8.0 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.71 (dt, J = 11.6, 3.3 Hz, 2H), 2.58 (td, J = 11.6, 2.4 Hz, 2H), 1.91 – 1.81 (m, 2H), 1.77 – 1.66 (m, 2H), 1.58 (dd, J = 12.8, 3.5 Hz, 2H), 1.43 – 1.34 (m, 1H), 1.23 – 1.13 (m, 3H), 1.08 (t, J = 9.2 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H). Mass (m/z): 356.3 $[M+H]^+$.

Compound 54

N1-(3,5-difluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



54A

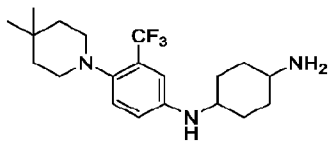
54B

The desired product **54A** (Rt = 12.2 min) as a white solid (44.4 mg, 37.0%) and **54B** (Rt = 12.9 min) as a yellow solid (42.0 mg,34.8%) were prepared from tert-butyl (4-((3,5-difluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (150 mg, 0.314 mmol), DCM (10 mL), and TFA (1 mL) according to the procedure for **24**, which were purified by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; solvent system (ACN/water (0.5% TFA) = 10%-85%-95%-95%-10%, 0-14 min-14.5 min-15.5 min-17 min). **54A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 5.2 Hz, 3H), 6.17 (d, J = 12.0 Hz, 2H), 3.05 (dq, J = 11.2, 6.0, 3.6 Hz, 1H), 3.00 – 2.89 (m, 5H), 2.33 (dq, J = 8.8, 5.2, 4.4 Hz, 1H), 1.99 – 1.84 (m, 4H), 1.82 – 1.73 (m, 2H), 1.54 – 1.33 (m, 4H), 1.11 (dt, J = 13.2, 10.4 Hz, 2H). Mass (m/z): 378.3 $[M+H]^+$. **54B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 5.2 Hz, 3H), 6.17 (d, J = 12.0 Hz, 2H), 3.05 (dq, J = 11.2, 6.0, 3.6 Hz, 1H), 3.00 – 2.89 (m, 5H), 2.33 (dq, J = 8.8, 5.2, 4.4 Hz, 1H), 1.99 – 1.84 (m, 4H), 1.82 – 1.73 (m, 2H), 1.54 – 1.33 (m, 4H), 1.11 (dt, J = 13.2, 10.4 Hz, 2H). Mass (m/z): 378.3 $[M+H]^+$.

Compound 55

N1-(4-(4,4-dimethylpiperidin-1-yl)-3-(trifluoromethyl)phenyl)cyclohexane-1,4-diamine

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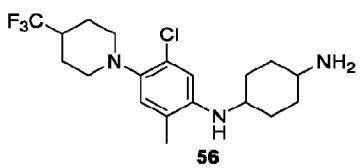


55

The title compound **55** (38.9 mg) was prepared in a total yield of 53.4% as a brown solid with 1:2 mixture by ^{1}II NMR from tert-butyl (4-((4-(4,4-dimethylpiperidin-1-yl)-3-(trifluoromethyl)phenyl)amino)cyclohexyl)carbamate (93 mg, 0.198 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (dd, J = 9.2, 6.8 Hz, 1H), 6.85 – 6.69 (m, 2H), 5.79 (dd, J = 12.8, 6.8 Hz, 1H), 3.40 – 3.32 (m, 2H), 3.06 (ddd, J = 19.6, 9.6, 4.4 Hz, 1H), 2.91 (tt, J = 11.6, 3.6 Hz, 1H), 2.68 – 2.57 (m, 4H), 1.99 – 1.91 (m, 2H), 1.71 (dd, J = 8.0, 4.0 Hz, 2H), 1.60 – 1.51 (m, 1H), 1.49 – 1.41 (m, 1H), 1.34 (t, J = 5.6 Hz, 4H), 1.16 – 1.10 (m, 1H), 0.92 (s, 6H). Mass (m/z): 370.3 $[M+H]^+$.

Compound 56

N1-(5-chloro-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

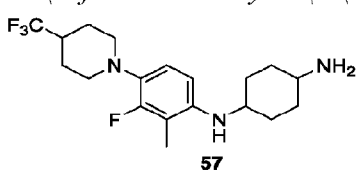


56

The title compound **56** (13.9 mg) was prepared in a total yield of 20% as a brown solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((4-(4,4-dimethylpiperidin-1-yl)-3-(trifluoromethyl)phenyl)amino)cyclohexyl)carbamate (88 mg, 0.18 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 (d, J = 14.8 Hz, 1H), 6.53 (d, J = 4.0 Hz, 1H), 4.34 (d, J = 8.0 Hz, 1H), 3.08 (d, J = 12.0 Hz, 3H), 2.61 – 2.52 (m, 3H), 2.09 (s, 1H), 2.00 (s, 2H), 1.98 – 1.91 (m, 3H), 1.87 – 1.76 (m, 3H), 1.69 (d, J = 6.0 Hz, 1H), 1.56 (td, J = 12.4, 4.0 Hz, 3H), 1.47 – 1.33 (m, 2H), 1.24 (d, J = 13.2 Hz, 1H). Mass (m/z): 390.3 $[M+H]^+$.

Compound 57

N1-(3-fluoro-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



57

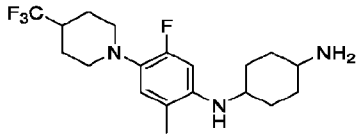
The title compound **57** (48.7 mg) was prepared in a total yield of 52.8% as a purple solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((3-fluoro-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (117 mg, 0.247 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.70 (td, J = 9.2, 5.6 Hz, 1H), 6.29 (dd, J = 8.8, 3.6 Hz, 1H), 4.21 (dd, J = 108.4, 7.2 Hz, 1H), 3.21 – 2.79 (m, 4H), 2.59 – 2.51 (m, 2H), 2.34 (d, J = 11.2 Hz, 1H), 2.01 (d, J = 2.0 Hz, 1H), 1.97 – 1.95 (m, 1H), 1.92 (d, J = 2.0 Hz, 2H), 1.82 (d, J = 14.4 Hz, 3H), 1.71 (dq, J = 12.8, 8.8, 8.0 Hz, 2H), 1.55 (ddt, J = 15.2, 12.4, 6.4 Hz, 3H), 1.49 – 1.41

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(m, 1H), 1.30 – 1.16 (m, 2H). Mass (m/z):3 74.3 $[M+H]^+$.

Compound 58

N1-(5-fluoro-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

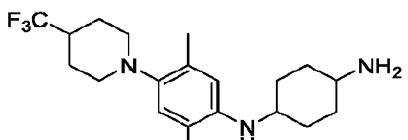


58

The title compound **58** (44.1 mg) was prepared in a total yield of 60.7% as a brown solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((5-fluoro-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (92 mg, 0.194 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.70 (dd, J = 14.8, 9.6 Hz, 1H), 6.34 (dd, J = 15.2, 6.4 Hz, 1H), 4.15 (dd, J = 104.4, 7.4 Hz, 1H), 3.48 – 3.30 (m, 2H), 3.20 – 3.03 (m, 3H), 2.87 (tt, J = 11.6, 3.6 Hz, 1H), 2.57 (tt, J = 12.0, 3.2 Hz, 2H), 2.37 – 2.26 (m, 1H), 2.06 (s, 1H), 1.96 (d, J = 8.0 Hz, 4H), 1.85 – 1.68 (m, 4H), 1.61 – 1.42 (m, 4H), 1.32 – 1.15 (m, 2H). Mass (m/z): 374.3 $[M+H]^+$.

Compound 59

N1-(2,5-dimethyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

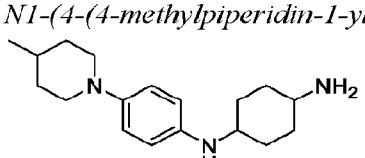


59

The title compound **59** (57.4 mg) was prepared in a total yield of 53.2% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((2,5-dimethyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (137 mg, 0.292 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.67 (d, J = 11.6 Hz, 1H), 6.36 (s, 1H), 3.87 (d, J = 75.6 Hz, 1H), 3.07 (d, J = 17.6 Hz, 1H), 2.89 (d, J = 10.4 Hz, 3H), 2.58 – 2.50 (m, 2H), 2.34 – 2.26 (m, 1H), 2.10 (d, J = 3.2 Hz, 4H), 2.06 (s, 2H), 1.96 (d, J = 7.2 Hz, 4H), 1.84 – 1.77 (m, 3H), 1.71 (dd, J = 7.6, 4.0 Hz, 2H), 1.52 (qd, J = 12.5, 10.4, 3.6 Hz, 4H), 1.23 (d, J = 12.0 Hz, 1H). Mass (m/z): 370.3 $[M+H]^+$.

Compound 60

N1-(4-(4-methylpiperidin-1-yl)phenyl)cyclohexane-1,4-diamine



60

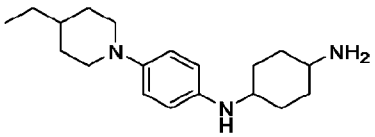
The title compound **60** (51.9 mg) was prepared in a yield of 53.7% as a brown solid with 1:1 mixture by ^{1}H NMR from 4-(4-methylpiperidin-1-yl)aniline (63.9 mg, 0.31 mmol), tert-butyl (4-oxocyclohexyl)carbamate (100 mg, 0.47 mmol) and according to the procedure for **20**. ^{1}H

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NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 33.4 Hz, 3H), 7.82 – 7.23 (m, 1H), 6.64 (s, 2H), 3.38 (s, 3H), 3.16 (d, J = 4.7 Hz, 1H), 3.08 (s, 1H), 2.94 (s, 1H), 2.00 (s, 2H), 1.75 (s, 7H), 1.47 (d, J = 12.3 Hz, 2H), 1.23 (s, 1H), 0.95 (d, J = 4.6 Hz, 3H). Mass (m/z): 288.5 $[M+H]^+$.

Compound 61

N1-(4-(4-ethylpiperidin-1-yl)phenyl)cyclohexane-1,4-diamine

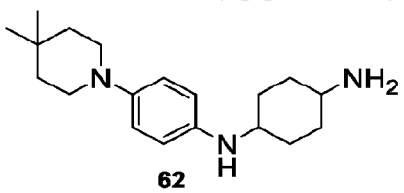


61

The title compound **61** (38.5 mg) was prepared in a yield of 40.8% as a brown solid with 1:1 mixture by ^{1}H NMR from 4-(4-ethylpiperidin-1-yl)aniline (63.9 mg, 0.31 mmol), tert-butyl (4-oxocyclohexyl)carbamate (100 mg, 0.47 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 31.7 Hz, 3H), 7.35 (d, J = 94.4 Hz, 1H), 6.56 (s, 3H), 3.33 (s, 4H), 3.12 (d, J = 5.0 Hz, 1H), 3.04 (s, 1H), 2.90 (s, 1H), 1.95 (s, 2H), 1.71 (s, 5H), 1.55 (s, 1H), 1.49 – 1.35 (m, 2H), 1.31 – 1.02 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H). MS (m/z): 302.5 $[M+H]^+$.

Compound 62

N1-(4-(4,4-dimethylpiperidin-1-yl)phenyl)cyclohexane-1,4-diamine

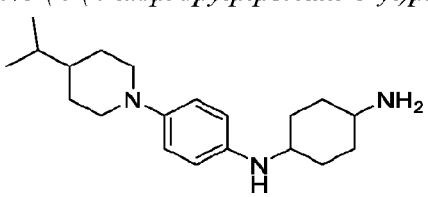


62

The title compound **62** (31.5 mg) was prepared in a yield of 35.8% as a brown solid with 1:1 mixture by ^{1}H NMR from 4-(4,4-dimethylpiperidin-1-yl)aniline (59 mg, 0.31 mmol), tert-butyl (4-oxocyclohexyl)carbamate (100 mg, 0.47 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 30.2 Hz, 3H), 6.78 (s, 1H), 6.56 (s, 2H), 3.17 (d, J = 5.1 Hz, 1H), 2.95 (s, 4H), 1.99 (s, 2H), 1.74 (s, 3H), 1.65 – 1.33 (m, 6H), 1.24 (s, 2H), 0.96 (s, 6H). Mass (m/z): 302.6 $[M+H]^+$.

Compound 63

N1-(4-(4-isopropylpiperidin-1-yl)phenyl)cyclohexane-1,4-diamine



63

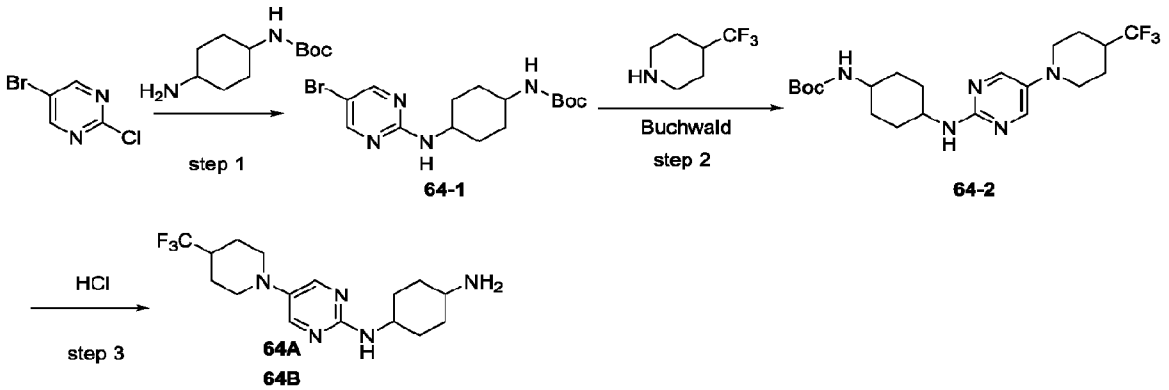
The title compound **63** (40.5 mg) was prepared in a yield of 40.4% as a brown solid with 1:1 mixture by ^{1}H NMR from 4-(4-isopropylpiperidin-1-yl)aniline (68 mg, 0.31 mmol), tert-butyl (4-oxocyclohexyl)carbamate (100 mg, 0.47 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 – 7.95 (m, 3H), 7.28 (s, 2H), 6.68 (s, 2H), 3.14 (s, 1H), 2.99 (s, 1H), 2.23 – 2.13 (m, 1H), 1.98 (s, 2H), 1.78 (dd, J = 27.0, 10.1 Hz, 7H), 1.62 (s, 1H),

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1.46 (s, 3H), 1.23 (s, 2H), 0.89 (d, J = 6.5 Hz, 6H). Mass(m/z): 316.6 $[M+H]^+$.

Compound 64

tert-butyl (4-((2R,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)phenyl)carbamate



Step 1. Preparation of tert-butyl (4-((5-bromopyrimidin-2-yl)amino)cyclohexyl)carbamate (**64-1**)

To a solution of 5-bromo-2-chloropyrimidine (0.5 g, 2.62 mmol) in DMF (10 mL) was added tert-butyl (4-aminocyclohexyl)carbamate (0.67 g, 3.14 mmol) and Cs_2CO_3 (2.56 g, 7.86 mmol) the mixture was stirred at 90 °C overnight. Diluting with water (30 mL), the reaction was extracted by EA (20 mL) for 3 times. The organic phase was washed 3 times by NaCl aq (20 mL), dried over sodium sulfate, concentrated under vacuum and the residue was purified by flash chromatography to afford the desired product (0.4 g, 41.2%) as yellow oil. Mass (m/z): 371.2 $[M+H]^+$.

Step 2. Preparation of tert-butyl (4-((5-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-2-yl)amino) cyclohexyl) carbamate (**64-2**)

To a solution of tert-butyl (4-((5-bromopyrimidin-2-yl)amino)cyclohexyl)carbamate (0.2 g, 0.5 mmol) in dioxane (5 mL) was added 4-(trifluoromethyl)piperidine (320 mg, 2 mmol), Cs_2CO_3 (0.5 g, 1.53 mmol), Ruphos (70 mg, 0.1 mmol) and $Pd_2(dba)_3$ (265 mg, 0.23 mmol). Then the mixture was stirred at 100 °C for 12 h. Quenched with water (10 mL), the reaction was extracted by EA (10 mL) for 3 times, dried over sodium sulfate, concentrated under vacuum and the residue was purified by flash chromatography to afford the desired product (0.16 g, 50.2%) as colorless oil. Mass (m/z): 248.2 $[M+H]^+$.

Step 3. Preparation of tert-butyl (4-((2R,6S)-2,6-dimethyltetrahydro-2H-pyran-4-yl)phenyl)carbamate (**64**)

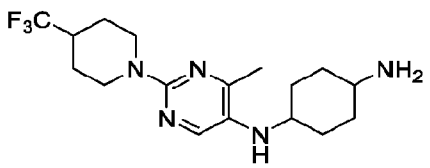
To a solution of tert-butyl (4-((2R,6S)-2,6-dimethyl-3,6-dihydro-2H-pyran-4-yl)phenyl)carbamate (0.16 g, 0.36 mmol) in THF (5 ml) was added HCl in dioxane (5 mL) and the mixture was stirred for 2 h. Quenched with $NaHCO_3$ (10 mL), the reaction was extracted by EA (10 mL) for 3 times, dried over sodium sulfate, concentrated under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford the desired product **64A** (14.5 mg) as a white solid and **64B** (20.2 mg) as a white solid. **64A**: ^1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 8.10 (s, 2H), 3.70 – 3.66 (m, 1H), 3.44 (d, J = 12.0 Hz, 2H), 3.18 – 3.03 (m, 1H), 2.68 (m, 2H), 2.34 – 2.18 (m, 1H), 2.19 – 2.02 (m, 4H),

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1.97 (d, *J* = 12.8 Hz, 2H), 1.71 (m, 2H), 1.52 (m, 2H), 1.44 – 1.29 (m, 2H). Mass (m/z): 344.2 $[M+H]^+$. HPLC: Rt: 4.333 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA) ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8min, ACN from 60% to 100%; 0.8 mL/min). **64B**: ^1H NMR (400 MHz, CD_3OD) δ = 8.53 (s, 1H), 8.13 (s, 2H), 3.95 (s, 1H), 3.46 (d, *J* = 12.0 Hz, 2H), 3.27 – 3.19 (m, 1H), 2.74 – 2.63 (m, 2H), 2.34 – 2.21 (m, 1H), 1.99 – 1.86 (m, 6H), 1.81 – 1.66 (m, 6H). Mass (m/z): 344.2 $[M+H]^+$. HPLC: Rt: 4.488 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA) ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 65

N1-(4-methyl-2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)cyclohexane-1,4-diamine

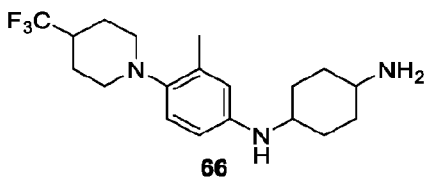


65A
65B

The title compounds **65A** (6.2 mg, 13%) as a white solid and **65B** (11.5 mg, 28%) as a white solid were prepared from To a solution of tert-butyl (4-((4-methyl-2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)amino)cyclohexyl)carbamate (53 mg, 0.12 mmol), HCl in dioxane (4N; 3 mL) and CH_2Cl_2 (3 mL) according to the procedure for **64**. **65A**: ^1H NMR (400 MHz, CD_3OD) δ 7.77 (s, 1H), 4.67 (d, J = 13.3 Hz, 2H), 2.94-2.88 (m, 1H), 2.80 (td, J = 13.1, 2.4 Hz, 2H), 2.51 – 2.34 (m, 1H), 2.34 (s, 3H), 1.87 (d, *J* = 1.4 Hz, 2H), 1.79 – 1.68 (m, 6H), 1.65 – 1.56 (m, 2H), 1.53 – 1.46 (m, 3H). Mass (m/z): 358.2 $[M+H]^+$. HPLC: Rt: 3.792 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **65B**: ^1H NMR (400 MHz, CD_3OD) δ 7.78 (s, 1H), 4.73 – 4.61 (m, 2H), 3.12 – 3.00 (m, 1H), 2.86 – 2.77 (m, 2H), 2.76 – 2.67 (m, 1H), 2.48 – 2.34 (m, 1H), 2.29 (s, 3H), 2.12 – 1.99 (m, 2H), 1.99 – 1.83 (m, 4H), 1.53 – 1.46 (m, 2H), 1.36 – 1.25 (m, 4H). Mass (m/z): 358.2 $[M+H]^+$. HPLC: Rt: 3.855 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 66

N1-(3-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



66

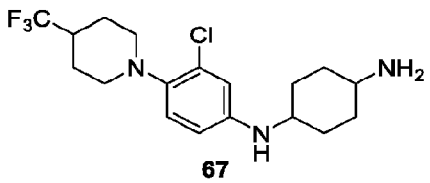
The title compound **66** (53.1 mg) was prepared in a total yield of 53.2% as a purple solid with 1:2 mixture by ^1H NMR from tert-butyl (4-((3-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (128

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mg, 0.281 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77 (t, J = 7.6 Hz, 1H), 6.54 – 6.28 (m, 2H), 3.08 – 2.97 (m, 1H), 2.93 – 2.86 (m, 2H), 2.56 – 2.48 (m, 2H), 2.34 – 2.25 (m, 1H), 2.08 (dd, J = 8.4, 2.3 Hz, 3H), 1.96 (dt, J = 13.2, 7.2 Hz, 3H), 1.85 – 1.65 (m, 6H), 1.61 – 1.35 (m, 5H). Mass (m/z): 356.3 $[M+H]^+$.

Compound 67

N1-(3-chloro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

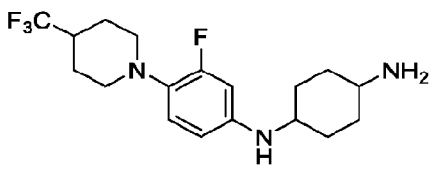


67

The title compound **67** (33.1 mg) was prepared in a total yield of 52.4% as a purple solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((3-chloro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (80 mg, 0.168 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (dd, J = 8.8, 6.4 Hz, 1H), 6.62 (dd, J = 21.2, 2.4 Hz, 1H), 6.48 (ddd, J = 14.8, 8.7, 2.7 Hz, 1H), 5.50 (d, J = 6.4 Hz, 1H), 3.32 (t, J = 4.4 Hz, 1H), 3.12 – 2.98 (m, 3H), 2.96 – 2.81 (m, 1H), 2.53 (tt, J = 11.6, 2.4 Hz, 2H), 2.38 – 2.27 (m, 1H), 1.92 (dt, J = 17.2, 13.6 Hz, 3H), 1.84 – 1.65 (m, 5H), 1.59 – 1.40 (m, 4H). Mass (m/z): 376.3 $[M+H]^+$.

Compound 68

N1-(3-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

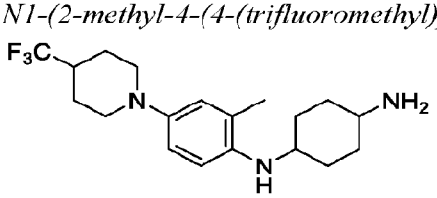


68

The title compound **68** (84.4 mg) was prepared in a total yield of 78.8% as a purple solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((3-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (137 mg, 0.299 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.85 – 6.72 (m, 1H), 6.44 – 6.23 (m, 2H), 5.46 (s, 1H), 3.35 – 3.27 (m, 1H), 3.12 (d, J = 11.4 Hz, 2H), 3.02 (s, 1H), 2.90 (s, 1H), 2.61 – 2.51 (m, 2H), 2.39 – 2.26 (m, 1H), 2.02 – 1.89 (m, 3H), 1.85 – 1.65 (m, 5H), 1.63 – 1.50 (m, 3H), 1.50 – 1.33 (m, 2H). Mass (m/z): 360.3 $[M+H]^+$.

Compound 69

N1-(2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



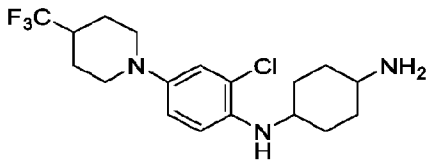
69

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The title compound **69** (84.4 mg) was prepared in a total yield of 81.9% as a purple solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (132 mg, 0.290 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 – 6.56 (m, 2H), 6.46 (s, 1H), 3.99 – 3.67 (m, 1H), 3.45 (d, J = 29.6 Hz, 3H), 3.05 (s, 1H), 2.89 (s, 1H), 2.34 (s, 1H), 2.15 – 1.89 (m, 6H), 1.88 – 1.65 (m, 6H), 1.63 – 1.35 (m, 5H). Mass (m/z): 356.3 $[M+H]^+$.

Compound 70

N1-(2-chloro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine

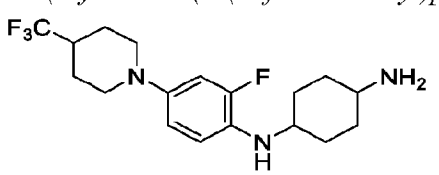


70

The title compound **70** (101.0 mg) was prepared in a total yield of 83.5% as a purple solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((3-chloro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (153 mg, 0.322 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (dd, J = 13.2, 2.7 Hz, 1H), 6.79 (ddd, J = 9.6, 6.8, 2.8 Hz, 1H), 6.68 (dd, J = 9.2, 4.8 Hz, 1H), 4.17 (dd, J = 40.4, 8.0 Hz, 1H), 3.49 3.43 (m, 2H), 3.18 3.05 (m, 1H), 2.88 (s, 1H), 2.53 (ddd, J – 12.8, 3.6, 2.0 Hz, 2H), 2.39 – 2.30 (m, 1H), 2.04 – 1.88 (m, 3H), 1.85 – 1.60 (m, 6H), 1.59 – 1.38 (m, 4H). Mass (m/z): 376.3 $[M+H]^+$.

Compound 71

N1-(2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



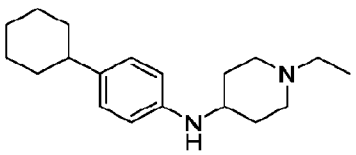
71

The title compound **71** (64.2 mg) was prepared in a total yield of 76.2% as a purple solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((3-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (107 mg, 0.233 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.67 (td, J = 28.8, 16.4 Hz, 3H), 4.57 – 4.11 (m, 1H), 3.48 (t, J = 9.6 Hz, 2H), 3.07 (s, 1H), 2.87 (s, 1H), 2.59 – 2.48 (m, 2H), 2.37 (dt, J = 22.4, 7.6 Hz, 1H), 2.02 – 1.86 (m, 3H), 1.85 – 1.65 (m, 4H), 1.60 – 1.36 (m, 4H), 1.20 (q, J = 12.4 Hz, 2H). Mass (m/z): 360.3 $[M+H]^+$.

Compound 72

N-(4-cyclohexylphenyl)-1-ethylpiperidin-4-amine

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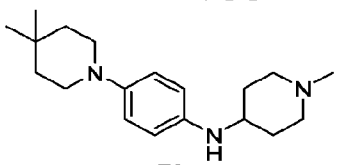


72

The title compound 72 (115 mg, 70.5%) was obtained as brown oil from 4-cyclohexylaniline (100 mg, 0.57 mmol), DCE (5 mL), 1-ethylpiperidin-4-one (87 mg, 0.69 mmol), acetic acid (3.42 mg, 0.057 mmol), and sodium triacetoxyborohydride (363 mg, 1.71 mmol) according to the procedure for **5**. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 6.87 (d, J = 8.4 Hz, 2H), 6.46 (d, J = 8.4 Hz, 2H), 5.15 (s, 1H), 2.80 (d, J = 11.4 Hz, 2H), 2.52 – 2.47 (m, 2H), 2.33 – 2.23 (m, 2H), 1.97 (t, J = 11.4 Hz, 2H), 1.83 (s, 1H), 1.70 (d, J = 11.4 Hz, 5H), 1.27 (m, 7H), 0.97 (t, J = 7.2 Hz, 3H). Mass (m/z): 287.3 $[M+H]^+$.

Compound 73

N-(4-(4,4-dimethylpiperidin-1-yl)phenyl)-1-methylpiperidin-4-amine

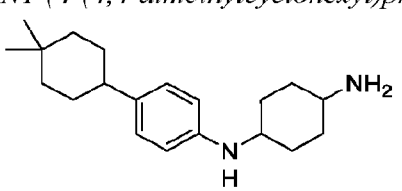


73

The title compound **73** (6.1 mg) was prepared in a total yield of 8.1% as a pink solid with 1:2 mixture by ^{1}H NMR from 4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.246 mmol), 1-methylpiperidin-4-one (33 mg, 0.295 mmol), AcOH (0.1 mL), $NaBH(OAc)_3$ (104 mg, 0.493 mmol) and DCE (10 mL) according to the procedure for **5**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.96 – 6.90 (m, 2H), 6.54 – 6.47 (m, 2H), 5.44 – 5.27 (m, 1H), 3.12 (d, J = 11.6 Hz, 3H), 2.68 (s, 2H), 2.22 (tt, J = 10.0, 5.2 Hz, 1H), 1.98 (dt, J = 14.4, 4.0 Hz, 2H), 1.64 – 1.37 (m, 9H), 1.31 – 1.21 (m, 3H), 0.93 (d, J = 8.4 Hz, 6H). Mass (m/z): 301.3 $[M+H]^+$.

Compound 74

N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclohexane-1,4-diamine



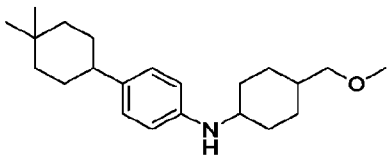
74

The title compound **74** (130 mg ,62.8%) as a white solid was prepared from tert-butyl (4-((4-(4,4-dimethylcyclohexyl) phenyl) amino) cyclohexyl)carbamate (180 mg ,0.45 mmol) and HCl in 1,4-dioxane (10 mL, 4 N) according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (brs, 2H), 7.36 (brs, 3H), 3.80 – 3.57 (m, 3H), 3.49 –3.25 (m, 1H), 2.96 (br, 1H), 2.44 2.37 (m, 1H), 2.04 1.63 (m, 4H), 1.61 1.46 (m, 4H), 1.31 (m, 6H), 0.91 (d, J =12.0 Hz, 6H). MS (m/z) 301.3.

Compound 75

N-(4-cyclohexylphenyl)-1-ethylpiperidin-4-amine

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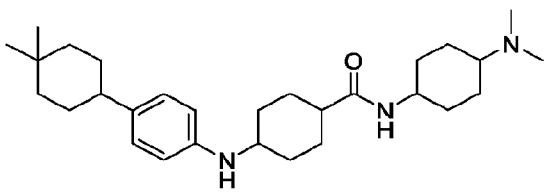


75

The title compound **75** (23 mg, 14.2%) was prepared as yellow oil from 4-(methoxymethyl)cyclohexan-1-one (84 mg, 0.59 mmol), DCE (5 mL), 4-(4,4-dimethylcyclohexyl)aniline (100 mg, 0.49 mmol) and acetic acid (2.9 mg, 0.059 mmol)according to the procedure for **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 – 6.98 (m, 2H), 6.59 – 6.50 (m, 2H), 3.35 (d, *J* = 2.0 Hz, 3H), 3.24 (dd, *J* = 12.3 Hz, 9.9 Hz, 2H), 2.33 – 2.25 (m, 1H), 1.87 – 1.84 (d, *J* = 6.9 Hz, 1H), 1.74 – 1.54 (m, 8H), 1.47 (d, *J* = 14.4 Hz, 2H), 1.38 – 1.24 (m, 4H), 1.09 (d, *J* = 9.9 Hz, 2H), 0.96 – 0.94 (m, 6H). Mass (m/z): 330.3 $[M+H]^+$.

Compound 76

(4-(dimethylamino)cyclohexyl)-4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexane-1-carboxamide

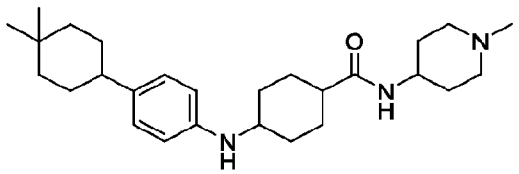


76A
76B

The desired products **76A** (Rt = 4.89 min; 4.2 mg, 20%) as a white solid and **76B** (Rt = 4.78 min; 4.0 mg, 19%) as a white solid were prepared from 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexane-1-carboxylic acid (15 mg, 0.046 mmol), N1,N1-dimethylcyclohexane-1,4-diamine (7.1 mg, 0.05 mmol), DIEA (16.5 mg, 0.05 mmol) in DMF (1 mL) and DMT-MM (14.8 mg, 0.05 mmol) according to the procedure for **1**, which were purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (5‰ TFA) = 10%-30%-95%-95%-10%, 0-7 min-7.5 min-8.5 min-10.0 min). **76A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 6.93 (m, 2H), 6.49 (m, 2H), 3.93 – 3.76 (m, 1 H), 3.63 – 3.54 (m, 1H), 3.18 – 3.04 (m, 2H), 2.68 (d, *J* = 4.8 Hz, 6H), 2.23 (m, 1H), 2.03 – 1.63 (m, 10H), 1.58 – 1.36 (m, 8H), 1.35 – 1.18 (m, 4H), 1.08 (m, 2H), 0.93 (d, *J* = 8.4 Hz, 6H). Mass (m/z): 454.3 $[M+H]^+$. **76B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 6.93 (m, 2H), 6.48 (m, 2H), 3.82 (m, 1H), 3.71 (s, 1H), 3.55 – 3.42 (m, 1H), 3.13 (m, 1H), 2.67 (d, *J* = 4.8 Hz, 6H), 2.22 (m, 1H), 2.05 – 1.65 (m, 10H), 1.91 – 1.63 (m, 8H), 1.59 – 1.01 (m, 6H), 0.93 (d, *J* = 8.4 Hz, 6H). Mass (m/z): 454.3 $[M+H]^+$.

Compound 77

4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-N-(1-methylpiperidin-4-yl)cyclohexane-1-carboxamide

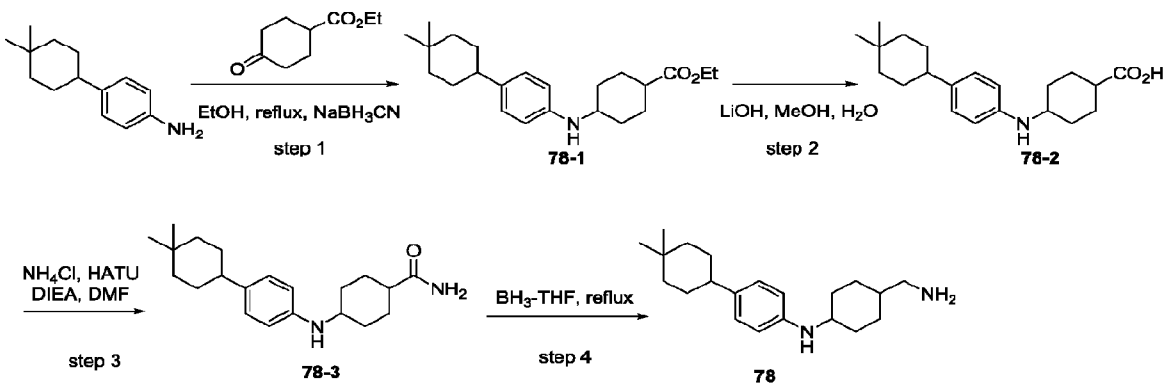


77

The title compound 77 (7.2 mg) was prepared in a total yield of 37% as a yellow solid with 1:2 mixture by ^{1}H NMR from 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexane-1-carboxylic acid (15 mg, 0.046 mmol), 1-methylpiperidin-4-amine (5.7 mg, 0.05 mmol), DIEA (16.5 mg, 0.05 mmol) and DMT-MM (14.8 mg, 0.05 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 6.93 (m, 2H), 6.51 (m, 2H), 3.93 (m, 1H), 3.82 (m, 1H), 3.72 (m, 1H), 3.65 – 3.55 (m, 1H), 3.31 – 2.91 (m, 3H), 2.69 (s, 1H), 2.69 (s, 2H), 2.28 – 2.13 (m, 1H), 2.13 – 1.63 (m, 8H), 1.62 – 1.37 (m, 6H), 1.36 – 1.17 (m, 4H), 1.14 – 1.05 (m, 2H), 0.94 (s, 3H), 0.92 (s, 3H). Mass(m/z): 426.2 $[M+H]^+$.

Compound 78

N-(4-(aminomethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline



Step 1. Preparation of ethyl 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexane-1-carboxylate (**78-1**)

A mixture of 4-(4,4-dimethylcyclohexyl)aniline (0.4 g, 1.97 mmol) and ethyl 4-oxocyclohexane-1-carboxylate (0.335 g, 1.97 mmol) in EtOH was stirred at 90 °C for 1 h. Then the mixture was added $NaBH_3CN$ (0.37 g, 5.91 mmol). The mixture was stirred at 25 °C for 4 h The mixture was quenched with H_2O and extracted with EA. The organic phase was concentrated and purified by a silica gel column chromatography, eluted with PE/ EA = 2:1 to give **78-1** as yellow oil (0.36 g, 51%). Mass(m/z): 358.3$[M+H]^+$.

Step 2. Preparation of 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexane-1-carboxylic acid (**78-2**)

To a solution of **78-1** (0.36 g, 1 mmol) in MeOH (10 mL) was added $LiOH{\cdot}H_2O$ (0.13 g, 3 mmol) at 25 °C. The reaction was stirred at 25 °C for 6 hrs. The pH of the mixture was adjusted to 3 with 1 N HCl, extracted with EA. The organic phase was concentrated to give **78-2** as yellow oil (0.28 g, 85.1%). Mass (m/z): 329.9$[M+H]^+$.

Step 3. Preparation of

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4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexane-1-carboxamide (**78-3**)

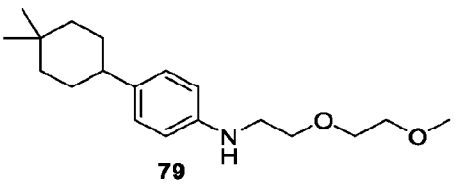
To a solution of **78-2** (0.18 g, 0.55 mmol) and HATU (0.21 g, 0.55 mmol) in DMF (5 mL) was added NH_4Cl (87 mg, 1.65 mmol) and DIEA (0.21 g, 1.65 mmol) at 25 °C. The reaction was stirred at 25 °C for 16 hrs. The mixture was diluted with EA and washed with water. The organic phase was concentrated and purified by a silica gel column chromatography , eluted with PE/ EA – 1:1 to give **78-3** as a yellow solid (0.11 g, 61%). Mass (m/z): 328.9$[M+H]^+$.

Step 4. Preparation of N-(4-(aminomethyl)cyclohexyl)-4-(4,4-dimethylcyclohex yl)aniline (**78**)

To a solution of **78-3** (0.15 g, 0.46 mmol) in THF (1 mL) was added BH_3-THF (10 mL). The reaction was stirred at 70 °C for 16 h. The mixture was quenched by MeOH and water, concentrated and extracted with EA. The organic phase was concentrated and purified by prep-TLC, eluted with DCM : MeOH = 9 : 1 (0.5% $NH_3.H_2O$) to give **78** (82 mg, 57.3%) as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 6.99 (d, J = 8.4 Hz, 2H), 6.69 – 6.53 (m, 2H), 3.56 (d, J = 5.7 Hz, 2H), 2.90 – 2.87 (m, 1H), 2.29 – 2.11 (m, 1H), 1.77 – 1.13 (m, 17H), 0.95 (d, J = 12 Hz, 6H). Mass (m/z): 315.0$[M+H]^+$.

Compound 79

4-(4,4-dimethylcyclohexyl)-N-(2-(2-methoxyethoxy)ethyl)aniline

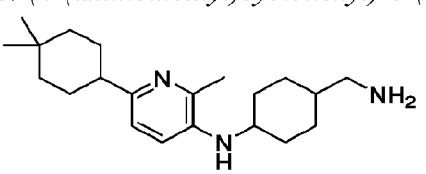


79

The title compound **79** (34.4 mg) was prepared in a yield of 41.9% as a pale yellow powder from 4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.25 mmol), 1-iodo-2-(2-methoxyethoxy)ethane (56 mg, 0.25 mmol) and potassium carbonate (41 mg, 0.3 mmol) according to the procedure for **12**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.19 (s, 2H), 7.00 (s, 2H), 3.65 – 3.39 (m, 5H), 3.24 (s, 3H), 2.35 (s, 1H), 1.98 (dt, J = 13.0, 7.0 Hz, 1H), 1.60 – 1.50 (m, 4H), 1.43 (d, J = 12.9 Hz, 2H), 1.30 (t, J = 8.8 Hz, 2H), 1.23 (s, 2H), 0.95 (s, 3H), 0.92 (s, 3H). Mass (m/z): 306.4 $[M+H]^+$.

Compound 80

N-(4-(aminomethyl)cyclohexyl)-6-(4,4-dimethylcyclohexyl)-2-methylpyridin-3-amine



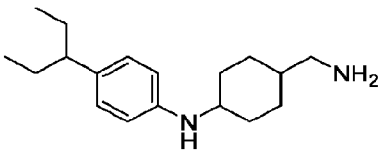
80

The title compound **80** (3.0 mg) was prepared in a total yield of 3.0% as a yellow solid with 1:1 mixture by ^1H NMR. from tert-butyl ((4-((6-(4,4-dimethylcyclohexyl)-2-methylpyridin-3-yl)amino)cyclohexyl)methyl)carbamate (16.0 mg, 37.2 umol) and TFA (3 mL) according to the procedure for **24**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 3H), 7.20 (s, 2H), 2.81 – 2.76 (m, 1H), 2.52 (s, 3H), 2.46 – 2.38 (m, 2H), 1.99 – 1.92 (m, 1H), 1.86 – 1.73 (m, 2H), 1.67 – 1.51 (m, 9H), 1.47– 1.41 (m, 1H), 1.33 – 1.25 (m, 3H), 1.13 – 1.05 (m, 1H), 0.95 (d, J = 9.4 Hz, 6H). Mass (m/z): 330.4 $[M+H]^+$.

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Compound 81

N-(4-(aminomethyl)cyclohexyl)-4-(pentan-3-yl)aniline

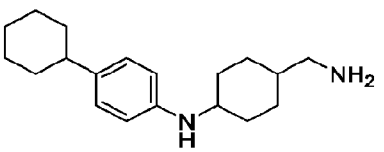


81A
81B

The desired product **81A** (Rt = 9.0 min) as a white solid (8.2 mg, 11.4%) and **81B** (Rt = 10.4 min) as a white solid (34.1 mg, 48.8%) were prepared from tert-butyl ((4-((4-(pentan-3-yl)phenyl)amino)cyclohexyl)methyl)carbamate (96 mg, 0.277 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**, which were purified by prep HPLC (solvent system (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 15%-25%-95%-95%-15%, 0-10 min-10.5 min-11.5 min-13 min). **81A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 2H), 7.21 – 6.93 (m, 4H), 2.69 – 2.58 (m, 2H), 2.25 (s, 1H), 1.90 (d, J = 12.4 Hz, 2H), 1.79 (d, J = 12.8 Hz, 2H), 1.67 – 1.36 (m, 5H), 1.26 (s, 2H), 0.98 (q, J = 12.4 Hz, 2H), 0.66 (t, J = 7.2 Hz, 6H). Mass (m/z): 275.3 $[M+H]^+$. **81B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 2H), 7.21 – 6.93 (m, 4H), 3.44 (td, J = 7.2, 3.6 Hz, 1H), 2.75 (p, J = 6.0 Hz, 2H), 2.25 (dp, J = 9.2, 5.2 Hz, 1H), 1.75 (s, 1H), 1.66 – 1.36 (m, 12H), 0.66 (t, J = 7.2 Hz, 6H). Mass (m/z): 275.3 $[M+H]^+$.

Compound 82

N-(4-(aminomethyl)cyclohexyl)-4-cyclohexylaniline



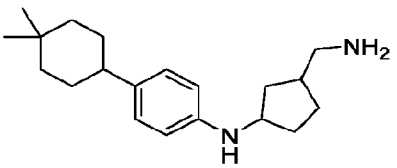
82A
82B

The desired products **82A** (Rt = 8.3 min) as yellow oil (13.4 mg, 10.7%) and **82B** (Rt = 10.7 min) as a white solid (57.6 mg, 46.0%) was prepared from tert-butyl ((4-((4-cyclohexylphenyl)amino)cyclohexyl)methyl)carbamate (169 mg, 0.438 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**, which were purified by prep HPLC (solvent system (ACN/water (0.5% TFA) = 15%-25%-95%-95%-15%, 0-13 min-13.5 min-14.5 min-16 min). **82A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 – 7.67 (m, 3H), 7.16 (s, 2H), 6.99 (s, 2H), 3.19 (s, 1H), 2.63 (p, J = 6.0 Hz, 2H), 2.41 (s, 1H), 1.91 (dd, J = 13.2, 4.0 Hz, 2H), 1.80 – 1.69 (m, 6H), 1.69 – 1.62 (m, 1H), 1.49 (ddh, J = 12.0, 7.9, 4.4 Hz, 1H), 1.32 (dd, J = 12.0, 9.2 Hz, 4H), 1.27 – 1.18 (m, 3H), 0.97 (qd, J = 13.2, 3.2 Hz, 2H). Mass (m/z): 287.3 $[M+H]^+$. **82B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 3H), 7.14 (s, 2H), 6.96 (s, 2H), 3.42 (dq, J = 7.2, 4.0 Hz, 1H), 2.74 (q, J = 5.6, 5.2 Hz, 2H), 2.41 (d, J = 11.6 Hz, 1H), 1.79 – 1.44 (m, 15H), 1.31 (t, J = 10.4 Hz, 4H). Mass (m/z): 287.3 $[M+H]^+$.

Compound 83

N-(3-(aminomethyl)cyclopentyl)-4-(4,4-dimethylcyclohexyl)aniline

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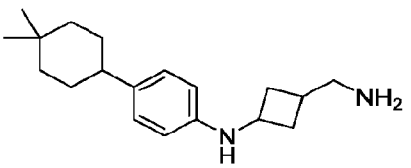


83

The title compound **83** (18.1 mg) was prepared in a yield of 24.5% as a pale yellow powder with 1:1 mixture by ^{1}H NMR from 4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.25 mmol), tert-butyl ((3-oxocyclopentyl)methyl)carbamate (79 mg, 0.37 mmol) and $NaBH(OAc)_3$ (104 mg, 0.49 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 2H), 6.95 (d, J = 7.9 Hz, 2H), 6.49 (s, 2H), 5.54 – 5.27 (m, 1H), 3.78 – 3.64 (m, 1H), 2.77 (dd, J = 12.5, 6.3 Hz, 2H), 2.25 (dq, J = 12.7, 7.1 Hz, 2H), 2.08 – 1.96 (m, 1H), 1.89 (ddd, J = 14.4, 9.2, 5.6 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.53 (dd, J = 10.4, 3.4 Hz, 4H), 1.50 – 1.38 (m, 4H), 1.30 (dd, J = 12.1, 5.2 Hz, 2H), 1.11 (q, J = 8.5 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H). Mass (m/z): 301.6 $[M+H]^+$.

Compound 84

N-(3-(aminomethyl)cyclobutyl)-4-(4,4-dimethylcyclohexyl)aniline

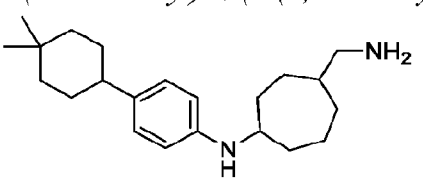


84

The title compound **84** (94 mg, 78.2%) was prepared as an off-white solid with 1:0.43 mixture by ^{1}H NMR from 3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclobutane-1-carboxamide, THF, and $AlLiH_4$ according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 4H), 6.94 (d, J = 8.3 Hz, 3H), 6.45 – 6.36 (m, 3H), 5.68 (dd, J = 6.6, 0.0 Hz, 1H), 5.59 (d, J = 7.1 Hz, 0.43H), 3.89 (h, J = 7.0 Hz, 1H), 3.67 (q, J = 7.4 Hz, 0.43H), 2.96 (d, J = 7.9 Hz, 2H), 2.82 (d, J = 7.3 Hz, 1H), 2.49 – 2.38 (m, 3H), 2.21 (td, J = 11.9, 5.5 Hz, 4H), 2.09 – 1.85 (m, 3H), 1.58 – 1.46 (m, 7H), 1.42 (d, J = 13.8 Hz, 4H), 1.33 – 1.20 (m, 6H), 0.93 (d, J = 8.3 Hz, 9H). Mass (m/z): 287.3 $[M+H]^+$.

Compound 85

4-(aminomethyl)-N-(4-(4,4-dimethylcyclohexyl)phenyl)cycloheptan-1-amine



85

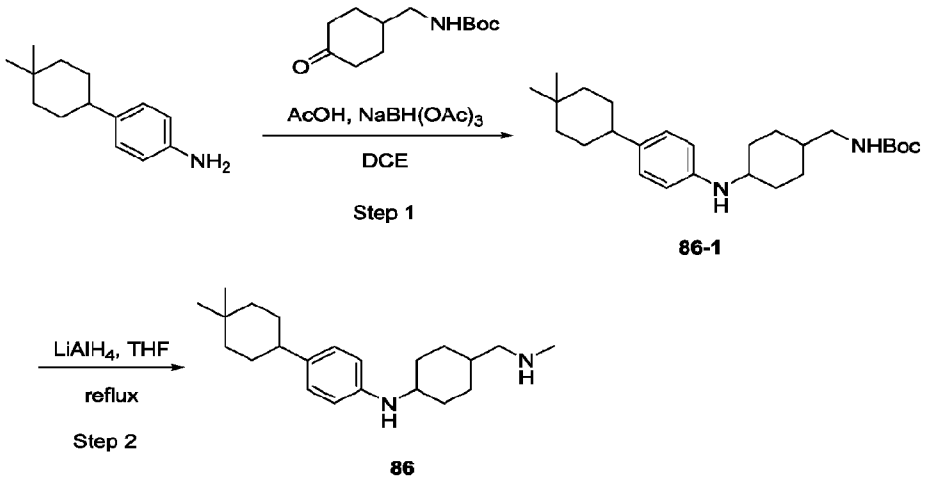
The title compound **85** (15.8 mg) was prepared in a three-step overall yield of 9.78% as a white powder with 1:1 mixture by ^{1}H NMR from 4-(4,4-dimethylcyclohexyl)aniline (100 mg, 0.49 mmol), 4-oxocycloheptane-1-carboxylic acid (92 mg, 0.59 mmol) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (s, 3H), 7.20 (s, 2H), 6.94 (s, 1H), 2.70 – 2.58

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(m, 2H), 2.35 (s, 1H), 2.02 – 1.90 (m, 1H), 1.83 (s, 1H), 1.74 (d, J = 14.5 Hz, 3H), 1.63 – 1.48 (m, 7H), 1.47 – 1.37 (m, 3H), 1.29 (td, J = 12.6, 6.3 Hz, 3H), 1.10 (t, J = 13.6 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H). Mass (m/z): 329.6 $[M+H]^+$.

Compound 86

4-(4,4-dimethylcyclohexyl)-N-(4-((methylamino)methyl)cyclohexyl)aniline



Step 1. Preparation of tert-butyl ((4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)methyl)carbamate **(86-1)**

A mixture of 4-(4,4-dimethylcyclohexyl)aniline (101.5 mg, 0.5 mmol), tert-butyl ((4-oxocyclohexyl)methyl)carbamate (136 mg, 0.6 mmol) and acetic acid (0.029 ml, 0.5 mmol) in DCE (5 mL) was stirred for 1 h at room temperature. Afterwards 211 mg (1 mmol) of sodium triacetoxyborohydride were added and the mixture was stirred overnight. To the mixture, saturated $NaHCO_3$ aq. was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated. The mixture was purified by prep-TLC to afford the intermediate (176 mg, 85%) as a white solid. Mass (m/z): 415.2 $[M+H]^+$.

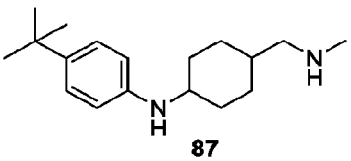
Step 2. Preparation of 4-(4,4-dimethylcyclohexyl)-N-(4-((methylamino)methyl)cyclohexyl)aniline **(86)**

tert-butyl ((4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)methyl)carbamate (41 mg, 0.1 mmol) in THF (1 mL) was slowly added dropwise to a suspension of $LiAlH_4$ (14.8 mg, 0.4 mmol) in THF (1 mL). The mixture was heated to reflux and stirred overnight. To the mixture, saturated $NaHCO_3$ aq. was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated. The mixture was purified by prep-TLC to afford the title compounds (16.2 mg, 49%) as a rosy brown solid with 1:2 mixture by ^{1}H NMR. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.54 (d, J = 8.8 Hz, 2H), 3.41 (s, 1H), 3.36 (s, 3H), 2.78 (m, 1.3H), 2.72 (m, 0.6H), 2.20 (m, 1H), 1.97 (m, 0.6H), 1.81 (m, 1.3H), 1.68 – 1.35 (m, 12H), 1.26 (m, 2H), 1.07 (m, 1H), 0.93 (s, 3H), 0.91 (s, 3H). Mass (m/z): 329.3 $[M+H]^+$.

Compound 87

4-(tert-butyl)-N-(4-((methylamino)methyl)cyclohexyl)aniline

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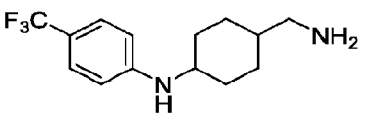


87

The title compound **87** (16.4 mg) was prepared in a total yield of 60% as a yellow solid with 1:3 mixture by ^{1}H NMR from tert-butyl ((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)carbamate (36 mg, 0.1 mmol), and $LiAlH_4$ (14.8 mg, 0.4 mmol) according to the procedure for **86**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.35-7.15 (m, 2H), 6.87 – 6.66 (m, 2H), 3.55 (m, 0.7H), 3.22 (m, 0.3H), 2.96 (d, J = 6.8 Hz, 1.5H), 2.89 (d, J = 6.4 Hz, 0.5H), 2.71 (s, 3H), 2.16 – 1.45 (m, 8H), 1.25 (s, 9H). Mass (m/z): 275.4 $[M+H]^+$.

Compound 88

N-(4-(aminomethyl)cyclohexyl)-4-(trifluoromethyl)aniline

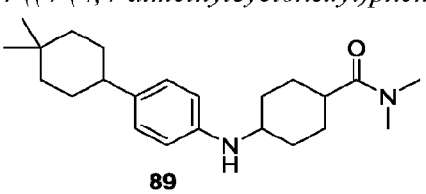


88

The desired product as a white solid (35 mg, 65%) with 1:2 mixture by ^{1}H NMR was prepared from tert-butyl ((4-((4-(trifluoromethyl)phenyl)amino)cyclohexyl)methyl)carbamate (74 mg, 0.2 mmol) and TFA (0.15 mL, 2 mmol) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 3H), 7.34-7.29 (m, 2H), 6.69-6.58 (m, 2H), 3.50 (m, 0.7H), 3.16 (m, 0.3H), 2.68 (d, J = 6.0 Hz, 1.4H), 2.64 (d, J = 6.8 Hz, 0.7H), 1.96 (m, 1H), 1.83 – 1.07 (m, 8H). Mass (m/z): 273.3 $[M+H]^+$.

Compound 89

4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-N,N-dimethylcyclohexane-1-carboxamide



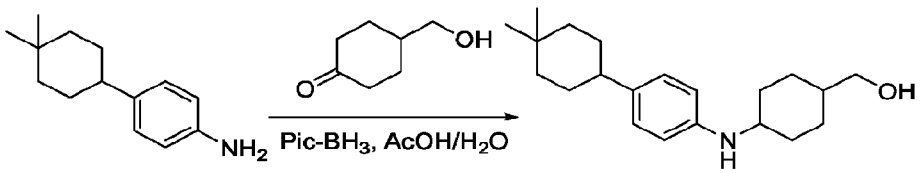
89

The title compound **89** (5.4 mg) was prepared in a total yield of 14% as a white solid with 1:3 mixture by ^{1}H NMR from 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexane-1-carboxylic acid (33 mg, 0.1 mmol), dimethylamine (0.45 mg, 0.15 mmol), DIEA (0.045 mL, 0.26 mmol) and DMT-MM (76 mg, 0.26 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 8.8 Hz, 0.7H), 6.48 (d, J = 8.8 Hz, 1.3H), 3.44 (m, 1H), 3.09 (m, 1H), 3.01 (s, 3H), 2.80 (s, 3H), 1.99 (m, 1H), 1.72 – 1.36 (m, 12H), 1.33 – 1.12 (m, 4H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 357.2 $[M+H]^-$.

Compound 90

N-hydroxy-2-(4-methylpiperazin-1-yl)-N-(4-((4-(1-methylpiperidin-4-yl)phenyl)amino)benzyl)acetamide

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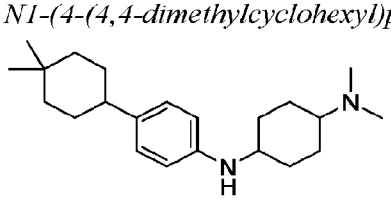


90A
90B

A solution of 4-(4,4-dimethylcyclohexyl)aniline (100 mg, 0.49 mmol), 4-(hydroxymethyl) cyclohexan-1-one (94.55 mg, 0.7377 mmol) and Pic-BH_3 (52-picoline-borane; 3 mg, 0.49 mmol), in AcOH/H_2O (10/1) (22 mL) was stirred 2 hrs at 25 °C. After filtration, the solvent was removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford **90A** (94 mg) as a white solid and **90B** (86 mg) as a white solid. **90A**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.92 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 5.11 (s, 1H), 4.42 (s, 1H), 3.23 (d, J = 5.3 Hz, 2H), 3.06 (s, 1H), 2.21 (s, 2H), 1.98 (d, J = 10.6 Hz, 1H), 1.76 (d, J = 11.6 Hz, 2H), 1.54 – 1.31 (m, 9H), 1.11 – 0.95 (m, 4H), 0.93 (d, J = 8.4 Hz, 6H). Mass (m/z): 316.3[M+H]$^+$. HPLC: Rt = 5.824 min (column-Xbridge 5u C18 150 x 19 mm; Flow Rate: 20 mL/min. Mobile phase: ACN-H_2O (0.1% FA), 35%-60%). **90B**: MS (m/z): 316.3[M+H]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (d, J = 8.4 Hz, 2H), 6.46 (d, J = 8.4 Hz, 2H), 5.16 – 5.04 (m, 1H), 4.38 – 4.30 (m, 1H), 3.42 – 3.34 (m, 1H), 3.23 (d, J =5.2 Hz, 2H), 2.22 – 2.07 (m, 1H), 1.60 – 1.17 (m, 18H), 0.89 (d, J = 8.4 Hz, 6H). MS (m/z): 316.3[M+H]$^+$. HPLC Rt = 7.933 min (column-Xbridge 5u C18 150 x 19 mm; Flow Rate: 20 mL/min. Mobile phase. ACN-H_2O (0.1% FA), 35%-60%).

Compound 91

N1-(4-(4,4-dimethylcyclohexyl)phenyl)-N4,N4-dimethylcyclohexane-1,4-diamine



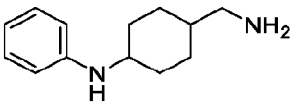
91A
91B

The title compound **91A**, **91B** was prepared according to the procedure for compound **1-1**. The crude residue was purified by preparative TLC (H_2O/MeOH/DCM=0.1/1/5) to afford compound **91A** (R_f value = 0.36) in 19.2% yield as a white solid and **91B** (R_f value = 0.30) in 14.8% yield as a white solid. **91A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 6.94 – 6.87 (m, 2H91), 6.51 (d, J = 8.6 Hz, 2H), 3.55 – 3.46 (m, 1H), 3.17 – 3.06 (m, 1H), 2.65 (s, 6H), 2.23 – 2.14 (m, 1H), 1.88 – 1.81 (m, 2H), 1.77 – 1.66 (m, 4H), 1.57 – 1.46 (m, 6H), 1.41 – 1.35 (m, 2H), 1.27 – 1.19 (m, 2H), 0.89 (d, J = 8.6 Hz, 6H). Mass (m/z):329.3 [M+H]$^+$. **91B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.90 (d, J = 8.0 Hz, 2H), 6.44 (d, J = 8.0 Hz, 2H), 5.19 (s, 1H), 3.10 (t, J = 11.2 Hz, 2H), 2.65 (t, J = 4.8 Hz, 6H), 2.22 – 2.12 (m, 1H), 2.04 – 1.97 (m, 4H), 1.57 – 1.36 (m, 8H), 1.26 – 1.08 (m, 4H), 0.89 (d, J = 8.4 Hz, 6H). Mass (m/z): 329.3 [M+H]$^+$

Compound 92

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N-(4-(aminomethyl)cyclohexyl)aniline



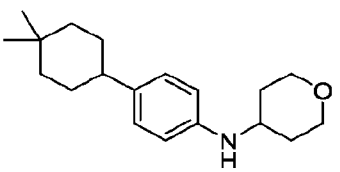
92A

92B

The desired products **92A** (Rt = 7.1 min) as yellow oil (122.2 mg, 67.4%) and **92B** (Rt = 7.9 min) as a white solid (45.5 mg, 25.1%) were prepared from tert-butyl ((4-(phenylamino)cyclohexyl)methyl)carbamate (270 mg, 0.888 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**, which were purified by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; solvent system (ACN/water (0.5% TFA) = 0-90%-50%-50%-100%, 0-10 min-10.5 min-11.5 min-13 min). **92A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 3H), 7.21 (t, J = 7.6 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 6.84 (t, J = 7.6 Hz, 1H), 3.45 (tt, J = 6.8, 3.7 Hz, 1H), 2.74 (p, J = 6.0 Hz, 2H), 1.73 (h, J = 6.0 Hz, 1H), 1.67 – 1.43 (m, 8H). Mass (m/z): 205.3 $[M+H]^+$. **92B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (s, 3H), 7.21 (t, J = 7.7 Hz, 2H), 6.96 – 6.79 (m, 3H), 3.21 (tt, J = 11.3, 3.8 Hz, 1H), 2.64 (p, J = 5.8 Hz, 2H), 1.99 – 1.88 (m, 2H), 1.84 – 1.72 (m, 2H), 1.50 (ttt, J = 10.5, 6.9, 3.4 Hz, 1H), 1.28 – 1.12 (m, 2H), 1.00 (qd, J = 13.2, 3.2 Hz, 2H). Mass (m/z): 205.3 $[M+H]^+$.

Compound 93

N-(4-(4,4-dimethylcyclohexyl)phenyl)tetrahydro-2H-pyran-4-amine

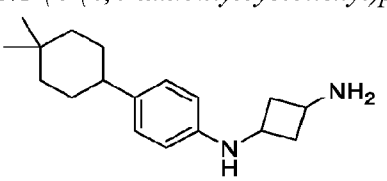


93

The title compound **93** (28.5 mg) was prepared in a yield of 67.2% as a white powder from 4-(4,4-dimethylcyclohexyl)aniline (30 mg, 0.14 mmol), tetrahydro-4H-pyran-4-one (29 mg, 0.29 mmol) and according to the procedure for **4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, J = 8.3 Hz, 2H), 6.51 (d, J = 8.1 Hz, 2H), 5.23 (d, J = 8.2 Hz, 1H), 3.95 – 3.75 (m, 2H), 3.41 – 3.37 (m, 2H), 2.20 (td, J = 10.3, 5.3 Hz, 1H), 1.93 – 1.78 (m, 2H), 1.52 (dd, J = 9.4, 4.4 Hz, 3H), 1.48 – 1.36 (m, 3H), 1.35 – 1.21 (m, 5H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 289.6 $[M+H]^+$.

Compound 94

N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclobutane-1,3-diamine



94

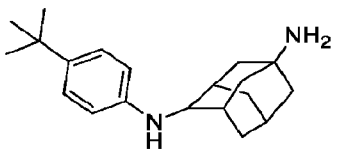
The title compound **94** (46.3 mg) was prepared in a yield of 88.6% as a pale yellow powder with 1:0.1 mixture by ^{1}H NMR from 4-(4,4-dimethylcyclohexyl)aniline (39 mg, 0.19 mmol), and tert-butyl (3-oxocyclobutyl)carbamate (53 mg, 0.29 mmol) according to the

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procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 3H), 7.00 – 6.88 (m, 2H), 6.45 – 6.41 (m, 0.2H), 6.41 – 6.34 (m, 2H), 5.81 (d, J = 6.2 Hz, 1H), 5.73 (d, J = 6.4 Hz, 0.1H), 4.05 (q, J = 7.0 Hz, 1H), 3.72 (tt, J = 8.1, 5.2 Hz, 1H), 2.44 (tt, J = 7.7, 5.2 Hz, 2H), 2.29 – 2.09 (m, 3H), 1.51 (dp, J = 11.7, 3.8 Hz, 4H), 1.41 (dt, J = 14.5, 3.1 Hz, 2H), 1.34 – 1.18 (m, 3H), 0.93 (s, 3H), 0.91 (s, 3H). Mass (m/z): 273.4 $[M+H]^+$.

Compound 95

N^4-(4-(tert-butyl)phenyl)adamantane-1,4-diamine

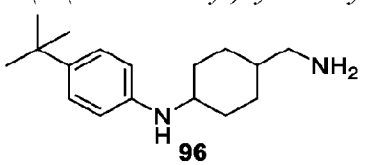


95

The title compound **95** (25.6 mg) was prepared in a total yield of 36.6% as a white solid according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 2H), 7.94 (s, 1H), 7.12 – 7.04 (m, 2H), 6.55 (dd, J = 20.0, 8.4 Hz, 2H), 5.40 – 5.27 (m, 1H), 2.23 – 2.06 (m, 2H), 2.05 – 1.75 (m, 7H), 1.72 – 1.63 (m, 1H), 1.63 – 1.51 (m, 1H), 1.39 – 1.29 (m, 2H), 1.20 (s, 9H). Mass (m/z): 299.3 $[M+H]^+$.

Compound 96

N-(4-(aminomethyl)cyclohexyl)-4-(tert-butyl)aniline

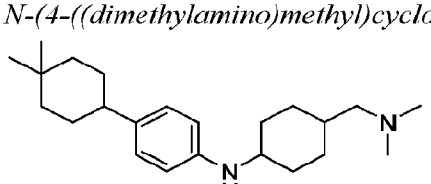


96

The title compound **96** (4.8 mg) was prepared in a total yield of 19 % as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl ((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)carbamate (36 mg, 0.1 mmol), and TFA (0.075 mL, 1 mmol) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 3H), 7.07 (d, J = 8.0 Hz, 2H), 6.47 (d, J = 8.0 Hz, 2H), 3.40 (m, 0.7H), 3.06 (m, 0.3H), 2.63 (m, 2H), 1.95 (m, 0.6H), 1.77 (m, 0.3H), 1.68 – 1.32 (m, 8H), 1.17 (s, 9H). Mass (m/z): 261.2 $[M+H]^+$.

Compound 97

N-(4-((dimethylamino)methyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline



97A
97B

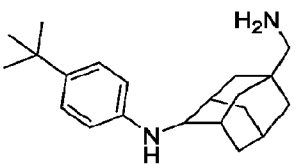
The title compounds **97A** (Rt = 5.48 min; 4.8 mg, 28 %) and **97B** (Rt = 6.22 min; 2.0 mg, 12 %) were prepared from 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-N,N-dimethylcyclohexane-1-carboxamide (36 mg, 0.1 mmol), and $LiAlH_4$ (14.8 mg, 0.4 mmol) according to the procedure for **23**, which

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were purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (5‰TFA = 20%-65%-95%-95%-10%, 0-13 min-13.5 min-14.5 min-16.0 min). **97A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, J = 8.4 Hz, 2H), 6.46 (d, J = 8.4 Hz, 2H), 3.06 (m, 1H), 2.88 (m, 2H), 2.69 (s, 6H), 2.20 (m, 1H), 1.98 – 1.82 (m, 5H), 1.54 – 1.38 (m, 8H), 1.14 – 1.02 (m, 4H), 0.90 (s, 3H), 0.88 (s, 3H). Mass (m/z): 343.4 $[M+H]^+$. **97B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, J = 8.4 Hz, 2H), 6.50 (d, J = 8.4 Hz, 2H), 2.73 (m, 1H), 2.67 (m, 2H), 2.51 (s, 6H), 2.20 (m, 1H), 1.94 – 1.03 (m, 4H), 1.65 – 1.35 (m, 13H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 343.4 $[M+H]^+$.

Compound 98

5-(aminomethyl)-N-(4-(tert-butyl)phenyl)adamantan-2-amine

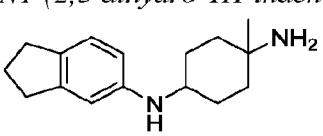


98A
98B

The title compound **98A** and **98B** were prepared according to the procedure for compound **20**. The product was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 0%-0%-30%-95%-95%-0%, 0 min-2 min-9 min-9.5 min-10.5 min-12.0) to afford compound **98A** (Rt = 9.03 min) in 35.6% yield as a white solid and **98B** (Rt = 7.56 min) in 31.2% yield as a white solid. **98A** ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.17 – 7.11 (m, 2H), 6.66 – 6.60 (m, 2H), 3.49 – 3.42 (m, 1H), 2.33 (s, 2H), 2.08 – 2.01 (m, 4H), 1.97 – 1.90 (m, 1H), 1.64– 1.60 (m, 4H), 1.55 – 1.51 (m, 2H), 1.51 – 1.44 (m, 1H), 1.25 (s, 9H). Mass (m/z): 313.3 $[M+H]^+$. **98B** ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.17 – 7.11 (m, 2H), 6.67 – 6.60 (m, 2H), 3.51 – 3.46 (m, 1H), 2.42 (s, 2H), 2.13 – 2.07 (m, 2H), 2.03 – 1.97 (m, 1H), 1.88 – 1.78 (m, 5H), 1.54 – 1.47 (m, 2H), 1.35 – 1.27 (m, 2H), 1.25 (s, 9H). Mass (m/z): 313.3 $[M+H]^+$.

Compound 99

N1-(2,3-dihydro-1H-inden-5-yl)-4-methylcyclohexane-1,4-diamine



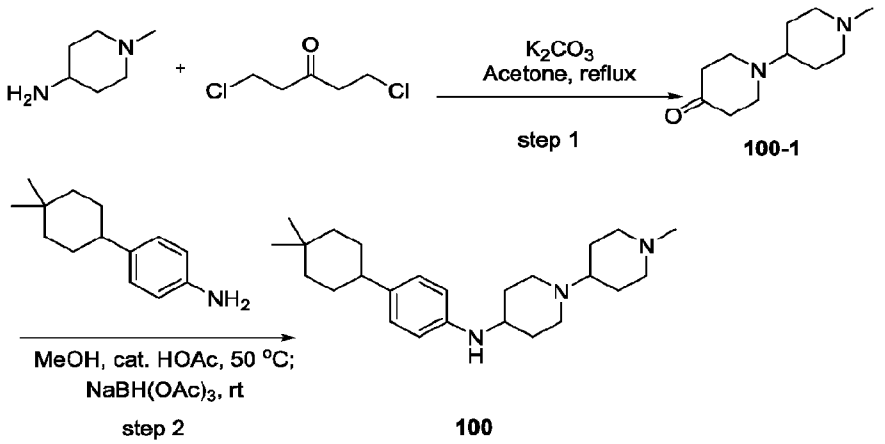
99

The title compound **99** (102.5 mg) was prepared in a total yield of 93.8% as a white solid from tert-butyl (4-((2,3-dihydro-1H-inden-5-yl)amino)-1-methylcyclohexyl)carbamate (168 mg, 0.488 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 36.0 Hz, 3H), 6.90 (d, J = 8.0 Hz, 1H), 6.53 – 6.45 (m, 1H), 6.44 – 6.34 (m, 1H), 5.34 – 4.83 (m, 1H), 3.30 – 3.08 (m, 1H), 2.70 (dt, J = 15.2, 7.2 Hz, 4H), 1.99 – 1.87 (m, 4H), 1.80 – 1.48 (m, 6H), 1.30 (d, J = 8.0 Hz, 3H). Mass (m/z): 245.3 $[M+H]^+$.

Compound 100

N-(4-(4,4-dimethylcyclohexyl)phenyl)-1'-methyl-[1,4'-bipiperidin]-4-amine

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Step 1. Preparation of 1'-methyl-[1,4'-bipiperidin]-4-one **(100-1)**

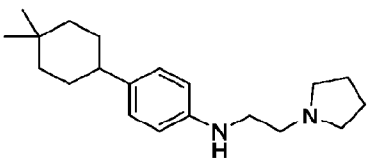
To a solution of 1-methylpiperidin-4-amine (1 g, 8.8 mmol) in acetone (20 mL) was added K_2CO_3 (2.7 g, 19.3 mmol) and 1,5-dichloropentan-3-one (1.5 g, 9.7 mmol) at 25 °C. Then the mixture was stirred at 70 °C for 3 hrs. LCMS showed the reaction was completed. The mixture was filtered and concentrated to give compound 2 (0.5 g, 27% yield) as yellow oil. MS (m/z): 197.1 $[M+H]^+$.

Step 2. Preparation of N-(4-(4,4-dimethylcyclohexyl)phenyl)-1'-methyl-[1,4'-bipiperidin]-4-amine **(100)**

To a solution of compound **100-1** (0.5 g, 2.55 mmol) in MeOH (20 mL) and a drop of AcOH was added 4-(4,4-dimethylcyclohexyl)aniline (570 mg, 2.8 mmol) at 25 °C. Then the mixture was stirred at 50 °C for 1 h. Then the mixture was added $NaBH_3CN$ (480 mg, 7.6 mmol) after cooling to 25 °C. Then the mixture was stirred at 25 °C for 2 hrs. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:0) to afford to give compound 5 (10 mg, 10.2% yield) as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 6.88 (d, J = 8.1 Hz, 2H), 6.52 (d, J = 8.1 Hz, 2H), 3.25 (s, 3H), 2.97 – 2.85 (m, 4H), 2.33 (t, J = 11.5 Hz, 3H), 2.06 – 1.81 (m, 7H), 1.55 – 1.45 (m, 7H), 1.44 – 1.30 (m, 6H), 0.86 (d, J = 12.1 Hz, 6H). MS (m/z) 384.0 $[M+H]^+$.

Compound 101

4-(4,4-dimethylcyclohexyl)-N-(2-(pyrrolidin-1-yl)ethyl)aniline



101

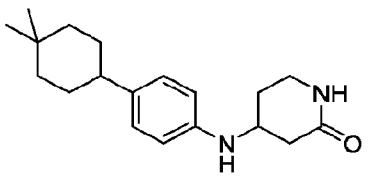
The title compound **101** (8 mg, 9.0%) was prepared from 2-(pyrrolidin-1-yl)acetaldehyde (40 mg, 0.35 mmol), 4-(4,4-dimethylcyclohexyl)aniline (60 mg, 0.30 mmol), MeOH (10 mL), 1 drop of AcOH, and $NaBH_3CN$ (14.2 mg, 0.89 mmol) according to the procedure for **5**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.05 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 3.52 (t, J = 5.6 Hz, 2H), 3.19 (t, J = 5.6 Hz, 6H), 2.32 – 2.26 (m, 1H), 2.02 (t, J = 6.6 Hz, 4H),

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1.69 – 1.42 (m, 6H), 1.30 (td, *J* = 13.1, 4.1 Hz, 2H), 0.96 (t, *J* = 7.9 Hz, 6H). Mass (m/z): 301.0 $[M+H]^+$.

Compound 102

4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)piperidin-2-one

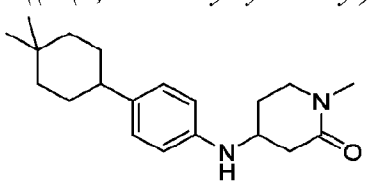


102

The title product **102** (42 mg, 56%) as a yellow solid was prepared from 4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.25 mmol), MeOH (5 mL), piperidine-2,4-dione (30 mg, 0.27 mmol), acetic acid (1.5 mg, 0.025 mmol) and sodium cyanoborohydride (46 mg, 0.75 mmol) according to the procedure for **5**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 6.05 (s, 1H), 3.85 – 3.76 (m, 1H), 3.49 – 3.31 (m, 2H), 2.83 (dd, *J* = 17.4 Hz, 4.5 Hz, 1H), 2.36 – 2.27 (m, 2H), 2.20 – 2.16 (m, 1H), 1.85 – 1.73 (m, 2H), 1.67 – 1.63 (m, 1H), 1.58 – 1.54 (m, 1H), 1.50 – 1.45 (m, 2H), 1.36 – 1.25 (m, 2H), 0.95 (d, *J* = 5.1 Hz, 6H). Mass (m/z): 301.2 $[M+H]^+$.

Compound 103

4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-1-methylpiperidin-2-one



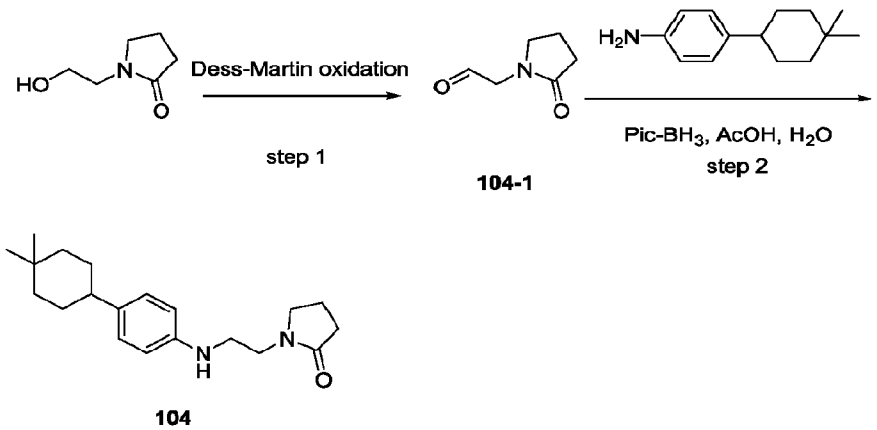
103

The desired product (50 mg, 63.7%) as a white solid was obtained from 4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.25 mmol), MeOH (5 mL), 1-methylpiperidine-2,4-dione (35 mg, 0.27 mmol), acetic acid (1.5 mg, 0.025 mmol)and sodium cyanoborohydride (46 mg, 0.75 mmol) according to the procedure for **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 3.79 – 3.75 (m, 1H), 3.40 – 3.33 (m, 2H), 2.97 (s, 3H), 2.84 (dd, *J* = 17.2 Hz, 4.4 Hz, 1H), 2.33 – 2.27 (m, 2H), 2.22 – 2.19 (m, 1H), 1.84 – 1.80 (m, 2H), 1.66 – 1.60 (m, 1H), 1.57 – 1.54 (m, 1H), 1.49 – 1.44 (m, 2H), 1.31 (td, *J* = 8.8 Hz, 4.0 Hz, 2H), 0.95 (d, *J* = 7.2 Hz, 6H). Mass (m/z): 315.2 $[M+H]^+$.

Compound 104

N-hydroxy-2-(4-methylpiperazin-1-yl)-N-(4-((4-(1-methylpiperidin-4-yl)phenyl)amino)benzyl)acetamide

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Step 1. Preparation of 2-(2-oxopyrrolidin-1-yl)acetaldehyde **(104-1)**

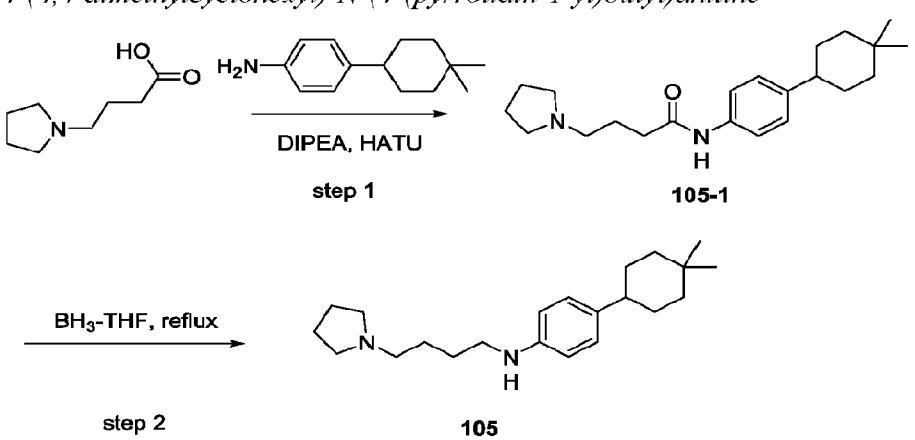
A mixture of 1-(2-hydroxyethyl)pyrrolidin-2-one (2 g, 15.4 mmol) and Dess-Martin reagent (13.06 g, 30.8 mmol in DCM (50 mL) was stirred for 10 mins at rt. The reaction mixture was filtered and evaporated, and the residue was purified by silica gel column (PE/EA = 1:1) to afford the product as yellow oil. (1.54 g, 78.2%).

Step 2. Preparation of 1-(2-((4-(4,4-dimethylcyclohexyl)phenyl)amino)ethyl)pyrrolidin-2-one **(104)**

A mixture solution of 2-(2-oxopyrrolidin-1-yl)acetaldehyde (50 mg, 0.35 mmol), 4-(4,4-dimethylcyclohexyl)aniline (60 mg, 0.3 mmol) and Pic-BH_3 (56 mg, 0.88 mmol) in AcOH/ H_2O=1/9 (5 mL) was stirred 3 hours at rt. The reaction mixture was adjusted to pH 8 with aqueous saturated $NaHCO_3$, exacted with EA (10 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by prep-HPLC to afford the desired product (10 mg, 6.7%) as a white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 3.58 (t, J = 5.7 Hz, 2H), 3.44 (t, J = 7.1 Hz, 2H), 3.35 – 3.27 (m, 2H), 2.39 (t, J = 8.1 Hz, 2H), 2.36 – 2.26 (m, 1H), 2.01 (dt, J = 15.5, 7.6 Hz, 2H), 1.69 – 1.43 (m, 7H), 1.36 – 1.23 (m, 3H), 0.95 (d, J = 7.1 Hz, 6H). Mass (m/z): 314.7 $[M+H]^+$.

Compound 105

4-(4,4-dimethylcyclohexyl)-N-(4-(pyrrolidin-1-yl)butyl)aniline



Step 1. Preparation of N-(4-(4,4-dimethylcyclohexyl)phenyl)-4-(pyrrolidin-1-yl)butanamide **(105-1)**

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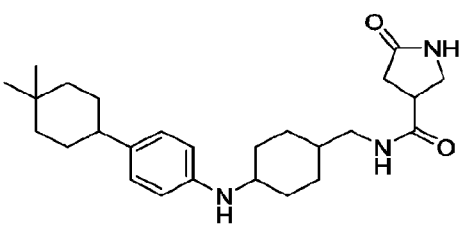
To a solution of 4-(pyrrolidin-1-yl)butanoic acid (46 mg, 0.29 mmol) in DCM (5 ml) was added 4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.25 mmol), DIEA (95 mg, 0.75 mmol) and HATU (140 mg, 0.375 mmol). Then the mixture was stirred at r.t. for 3 h. The reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash to afford the desired product (35 mg, 40.9%) as yellow oil. Mass (m/z): 330.3 $[M+H]^+$.

Step 2. Preparation of 4-(4,4-dimethylcyclohexyl)-N-(4-(pyrrolidin-1-yl)butyl)aniline **(105)**

To a solution of N-(4-(4,4-dimethylcyclohexyl)phenyl)-4-(pyrrolidin-1-yl)butanamide (35 mg, 0.10 mmol) in THF (2 mL) was added BH_3-THF (15 mL) and the mixture was stirred at 70 °C for 2 h. The reaction was quenched with water (10 mL), and extracted by EA (10 mL) for 3 times. The combined organic phase layers were dried over sodium sulfate and concentrated under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford the desired product (13 mg, 41.2%) as a black solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 3.69 (t, J = 5.6 Hz, 1H), 3.15 (t, J = 6.8 Hz, 2H), 2.91 – 2.82 (m, 2H), 2.30 (m, 1H), 2.05 – 1.96 (m, 4H), 1.91 – 1.83 (m, 1H), 1.73 – 1.66 (m, 2H), 1.56 (dd, J = 12.4 Hz, 3.2 Hz, 3H), 1.46 (d, J =12.6, 2H), 1.32 (dd, J = 13.1 Hz, 4.0 Hz, 3H), 0.95 (d, J = 7.4 Hz, 6H). Mass (m/z): 329.3 $[M+H]^+$.

Compound 106

N-((4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)methyl)-5-oxopyrrolidine-3-carboxamide



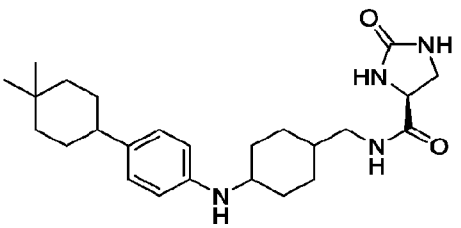
106A
106B

The title compounds **106A** (Rt = 5.28 min; 6.8 mg) in a total yield of 27 % as a white solid and **106B** (Rt = 6.21 min; 5.4 mg) in a total yield of 21 % as a white solid were prepared from N-(4-(aminomethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline (19 mg, 0.06 mmol) according to the procedure for **1**, which were purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (5‰ TFA) = 30%-45%-75%-95%-10%, 0-7 min-7.5 min-8.5 min-10.0 min). **106A**: ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (t, J = 5.6 Hz, 1H), 7.57 (s, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 5.14 (m, 1H), 3.38 (m, 2H), 3.23 – 3.08 (m, 2H), 3.00 (t, J = 6.4 Hz, 2H), 2.31-2.17 (m, 3H), 1.96 (m, 1H), 1.70 (m, 1H), 1.65 – 1.26 (m, 15H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 426.3 $[M+H]^+$. **106B**: ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (t, J = 5.6 Hz, 1H), 7.57 (s, 1H), 6.92 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 5.17 (m, 1H), 3.41 (m, 2H), 3.21 – 3.06 (m, 2H), 2.93 (t, J = 6.4 Hz, 2H), 2.33 – 2.17 (m, 3H), 2.06 – 1.31(m, 17H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 426.3 $[M+H]^+$.

Compound 107

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(S)-N-((4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)methyl)-2-oxoimidazolidine-4-carboxamide

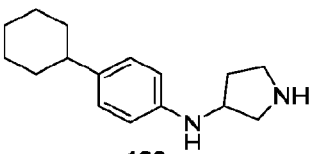


107A
107B

The title compound **107A** (Rt = 4.98 min; 3.7 mg) in a total yield of 15 % as a white solid compound **107B** (Rt = 5.76 min; 5.4 mg) in a total yield of 22 % as a white solid were prepared from N-(4-(aminomethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline (19 mg, 0.06 mmol) according to the procedure for **1** which were purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (5‰ TFA) = 30%-45%-95%-95%-10%, 0-7 min-7.5 min-8.5 min-10.0 min). **107A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (t, J = 5.6 Hz, 1H), 6.91 (d, J = 8.0 Hz, 2H), 6.46 (d, J = 8.0 Hz, 2H), 6.30 (s, 1H), 5.10 (m, 1H), 4.05 (m, 1H), 3.52 (m, 1H), 3.18 (m, 1H), 3.07 – 2.91 (m, 2H), 2.21 (m, 1H), 1.70 (m, 1H), 1.64 – 1.24 (m, 16H), 0.94 (s, 3H), 0.91 (s, 3H). Mass (m/z): 427.2 $[M+H]^+$. **107B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (t, J = 5.6 Hz, 1H), 6.91 (d, J = 8.0 Hz, 2H), 6.51 (d, J = 8.0 Hz, 2H), 6.29 (s, 1H), 5.20 (m, 1H), 4.06 (m, 1H), 3.51 (m, 1H), 3.14 (m, 1H), 3.09 – 2.93 (m, 2H), 2.21 (m, 1H), 1.70 (m, 1H), 1.67 – 1.23 (m, 16H), 0.94 (s, 3H), 0.91 (s, 3H). Mass (m/z): 427.2$[M+H]^+$.

Compound 108

N-(4-cyclohexylphenyl)pyrrolidin-3-amine

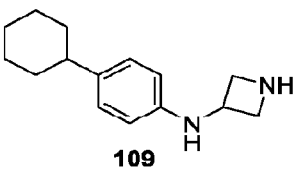


108

The title compound SIR2-1443 (20 mg) was prepared in a total yield of 83% as a white solid from tert-butyl 3-((4-cyclohexylphenyl)amino)pyrrolidine-1-carboxylate (34.1 mg, 0.1 mmol) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.96 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 5.74 (s, 1H), 4.03 (m, 1H), 3.30 – 3.13 (m, 4H), 3.00 (m, 1H), 2.32 (m, 1H), 2.22 – 2.05 (m, 1H), 1.94 – 1.57 (m, 6H), 1.31 (m, 4H). Mass (m/z): 245.2 $[M+H]^+$.

Compound 109

N-(4-cyclohexylphenyl)azetidin-3-amine



109

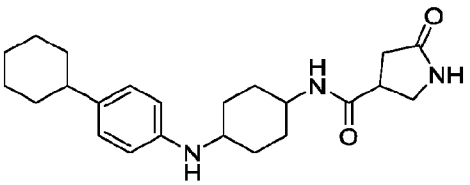
The title compound **109** (18 mg) was prepared in a total yield of 78% as a white solid from tert-butyl 3-((4-cyclohexylphenyl)amino)azetidine-1-carboxylate (33.0 mg, 0.1 mmol)

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according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 6.96 (d, J = 8.4 Hz, 2H), 6.44 (d, J = 8.4 Hz, 2H), 6.21 (s, 1H), 4.28 (m, 1H), 4.20 (m, 2H), 3.77 (m, 2H), 2.32 (m, 1H), 1.80 – 1,63 (m, 4H), 1.36 – 1.17 (m, 6H). Mass (m/z): 231.3[M+H]$^+$.

Compound 110

N-(4-((4-cyclohexylphenyl)amino)cyclohexyl)-5-oxopyrrolidine-3-carboxamide

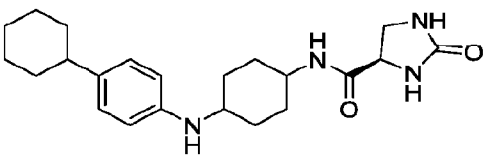


110

The title compound **110** (12.0 mg) was prepared in a total yield of 31 % as a white solid with 2:3 mixture by ^{1}H NMR from N1-(4-cyclohexylphenyl)cyclohexane-1,4-diamine (27.2 mg, 0.1 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 0.6H), 7.84 (s, 0.4H), 7.56 (d, J = 8.4 Hz, 1.2H), 6.90 (d, J = 8.4 Hz, 0.8H), 6.50 (d, J = 8.4 Hz, 1.2H), 6.50 (d, J = 8.4 Hz, 0.8H), 5.16 (s, 0.6H), 5.10 (s, 0.4H), 3.66 (m, 1H), 3.55 – 3.37 (m, 2H), 3.22 – 3.06 (m, 2H), 2.34 – 2.21 (m, 3H), 1.95 – 1.66 (m, 10H), 1.37 – 1.05 (m, 8H). Mass (m/z): 384.3[M+H]$^+$.

Compound 111

(R)-N-(4-((4-cyclohexylphenyl)amino)cyclohexyl)-2-oxoimidazolidine-4-carboxamide

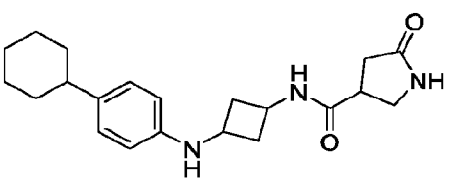


111

The title compound **111** (13.0 mg) was prepared in a total yield of 34 % as a white solid with 1:1 mixture by ^{1}H NMR from N1-(4-cyclohexylphenyl)cyclohexane-1,4-diamine (27.2 mg, 0.1 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (s, 0.5H), 7.72 (s, 0.5H), 6.91 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.51 (m, 2H), 6.29 (s, 1H), 5.16 (s, 0.5H), 5.11 (s, 0.5H), 4.15 – 3.97 (m, 1H), 3.75 – 3.45 (m, 2H), 3.22 – 3.04 (m, 2H), 2.29 (m, 1H), 2.04 – 1.50 (m, 10H), 1.43 – 1.04 (m, 8H). Mass (m/z): 385.2[M+H]$^+$.

Compound 112

N-(3-((4-cyclohexylphenyl)amino)cyclobutyl)-5-oxopyrrolidine-3-carboxamide



112

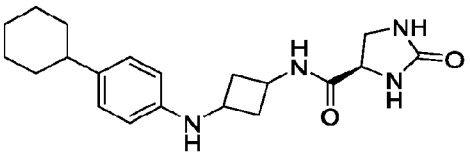
The title compound **112** (11.6 mg) was prepared in a total yield of 33 % as a white solid with 1:4 mixture by ^{1}H NMR from N1-(4-cyclohexylphenyl)cyclobutane-1,3-diamine (24.4 mg, 0.1 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 0.8H), 8.25 (s, 0.2H), 7.58 (s, 1H), 6.92 (d, J = 8.4 Hz, 1.6H), 6.89 (d, J = 8.4 Hz, 0.4H), 6.42 (d, J = 8.4

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Hz, 0.4H), 6.38 (d, J = 8.4 Hz, 1.6H), 5.76 (s, 1H), 4.29 (m, 1H), 3.92 (m, 0.2H), 3.82 (m, 0.8H), 3.41 (m, 1H), 3.26 – 3.04 (m, 2H), 2.35 – 2.17 (m, 5H), 2.11 (m, 2H), 1.78 – 1.64 (m, 4H), 1.37 – 1.11 (m, 6H). Mass (m/z): 356.2$[M+H]^+$.

Compound 113

(R)-N-(3-((4-cyclohexylphenyl)amino)cyclobutyl)-2-oxoimidazolidine-4-carboxamide

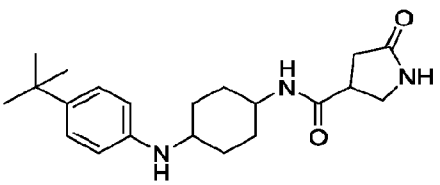


113

The title compound **113** (7.2 mg) was prepared in a total yield of 21% as a white solid with 1:4 mixture by ^{1}H NMR from N1-(4-cyclohexylphenyl)cyclobutane-1,3-diamine (24.4 mg, 0.1 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 8.28 (s, 0.8H), 8.14 (s, 0.2H), 6.95 (d, J = 8.4 Hz, 1.6H), 6.89 (d, J = 8.4 Hz, 0.4H), 6.49 (s, 1H), 6.45(d, J = 8.4 Hz, 0.4H), 6.38 (d, J = 8.4 Hz, 1.6H), 6.33(s, 1H), 5.75 (m, 0.8H), 5.58 (m, 0.2H), 4.32 (m, 1H), 4.06 (m, 0.8H), 3.96 (m, 0.2H), 3.82 (m, 1H), 3.52 (m, 1H), 3.27 – 3.09 (m, 1H), 2.36 – 2.22 (m, 3H), 2.15 – 2.08 (m, 2H), 1.87 – 1.58 (m, 4H), 1.45 – 1.05 (m, 6H). Mass (m/z): 357.4 $[M+H]^+$.

Compound 114

N-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)-5-oxopyrrolidine-3-carboxamide



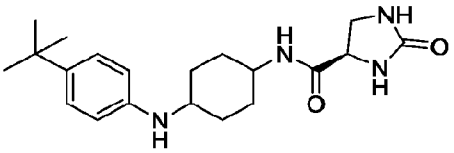
114A
114B

The title compounds **114A** (Rt = 6.00 min; 10.2 mg) in a total yield of 29% as a white solid and **114B** (Rt = 8.03 min; 10.8 mg) was prepared in a total yield of 30% as a white solid were prepared from N1-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine (49.2 mg, 0.2 mmol) according to the procedure for **1** which were purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (5‰ TFA) = 20%-23%-95%-95%-0%, 0-11 min-11.5 min-12.5 min-14.0 min). **114A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 7.2 Hz, 1H), 7.56 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 5.18 (s, 1H), 3.66 (s, 1H), 3.38 (m, 1H), 3.29 (m, 1H), 3.18 (m, 2H), 2.26 (m, 2H), 1.67 – 1.53 (m, 8H), 1.20 (s, 9H). Mass (m/z): 358.3 $[M+H]^+$. **114B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 7.6 Hz, 1H), 7.57 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 8.4 Hz, 2H), 5.12 (s, 1H), 3.51 (m, 1H), 3.37 (m, 1H), 3.24 – 3.14 (m, 1H), 3.14 – 3.04 (m, 2H), 2.26 (m, 2H), 2.04 – 1.89 (m, 2H), 1.85 – 1.73 (m, 2H), 1.35 – 1.22 (m, 4H), 1.20 (s, 9H). Mass (m/z): 358.3 $[M+H]^+$.

Compound 115

(R)-N-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)-2-oxoimidazolidine-4-carboxamide

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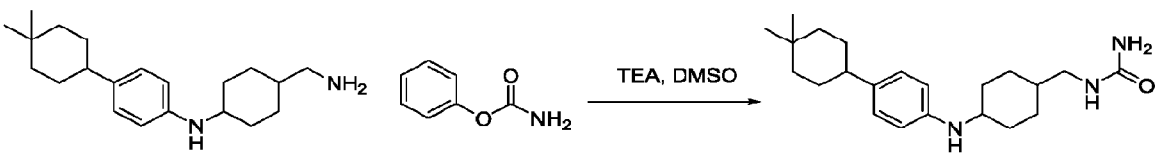


115A
115B

The title compound **115A** (Rt = 5.88 min; 7.0 mg) in a total yield of 20 % as a white solid and **115B** (Rt = 7.52 min; 10.8 mg) in a total yield of 30 % as a white solid were prepared from N1-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine (49.2 mg, 0.2 mmol) according to the procedure for **1,** which were purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (5‰ TFA) = 18%-18%-95%-95%-10%, 0-11 min-11.5 min-12.5 min-10.0 min). **115A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.54 – 6.45 (m, 3H), 6.29 (s, 1H), 5.16 (s, 1H), 4.03 (m, 1H), 3.51 (m, 2H), 3.19 (m, 1H), 3.15-3.03 (m, 1H), 2.04 – 1.89 (m, 2H), 1.84 – 1.75 (m, 2H), 1.43 – 1.26 (m, 4H), 1.20 (s, 9H). Mass (m/z): 359.2 $[M+H]^+$. **115A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 7.2 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.59 – 6.51 (m, 3H), 6.30 (s, 1H), 5.22 (s, 1H), 4.08 (m, 1H), 3.69 (m, 1H), 3.51 (m, 1H), 3.32 (m, 1H), 3.20 (m, 1H), 1.75 – 1.47 (m, 8H), 1.20 (s, 9H). Mass (m/z): 359.2 $[M+H]^+$.

Compound 116

1-((4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)methyl)urea

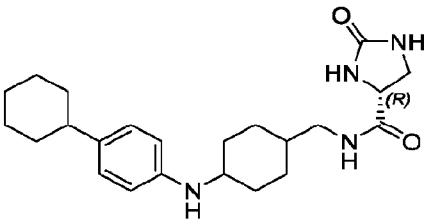


116

The N-(4-(aminomethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline (31.4 mg, 0.1 mmol) and triethylamine (0.028 mL, 0.2 mmol) were both dissolved in 2 mL of DMSO. Then phenylcarbamate (16.4 mg, 0.12 mmol) was added. The resulted solution was stirred overnight. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated. The mixture was purified by prep-TLC to afford the desired product as a white solid (16.8 mg, 48%) with 1:4 mixture by ^{1}H NMR. ^{1}H NMR (400 MHz, DMSO-d_6) 6.95 – 6.86 (m, 2H), 6.50 (d, J = 8.4 Hz, 1.2H), 6.46 (d, J = 8.4 Hz, 0.8 H), 5.96 (m, 1H), 5.34 (s, 2H), 5.16 (m, 0.6H), 5.09 (m, 0.4H), 3.12-2.98 (m, 1H), 2.88 (m, 1.6H), 2.82 (m, 0.8H), 2.20 (m, 1H), 1.98 (m, 1H), 1.75 – 1.25 (m, 16H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 358.4 $[M+H]^+$.

Compound 117

(R)-N-((4-((4-cyclohexylphenyl)amino)cyclohexyl)methyl)-2-oxoimidazolidine-4-carboxamide

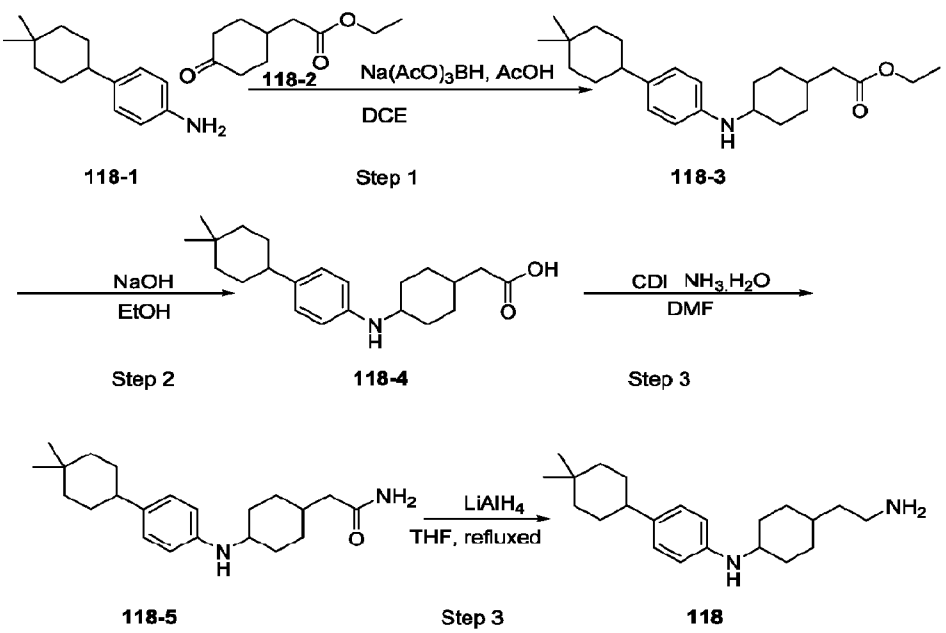


117A
117B

The title products **117A** as a white solid (10.9 mg, 18.6%) and **117B** as a white solid (10.9 mg ,13.7%) were prepared from N-(4-(aminomethyl)cyclohexyl)-4-cyclohexylaniline (57.2 mg, 0.2 mmol), (R)-2-oxoimidazolidine-4-carboxylic acid (33.8 mg, 0.26 mmol), DMF (2.0 mL), DIEA (77.4 mg, 0.6 mmol) and HATU (83.6 mg, 0.22 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 6.94 – 6.87 (m, 2H), 6.51 (d, J = 8.6 Hz, 2H), 3.55 – 3.46 (m, 1H), 3.17 – 3.06 (m, 1H), 2.65 (s, 6H), 2.23 – 2.14 (m, 1H), 1.88 – 1.81 (m, 2H), 1.77 – 1.66 (m, 4H), 1.57 – 1.46 (m, 6H), 1.41 – 1.35 (m, 2H), 1.27 – 1.19 (m, 2H), 0.89 (d, *J* = 8.6 Hz, 6H). Mass (m/z): 329.3 $[M+H]^+$. Rt=4.778 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA) = 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.90 (d, *J* = 8.0 Hz, 2H), 6.44 (d, *J* = 8.0 Hz, 2H), 5.19 (s, 1H), 3.10 (t, *J* = 11.2 Hz, 2H), 2.65 (t, *J* = 4.8 Hz, 6H), 2.22 – 2.12 (m, 1H), 2.04 – 1.97 (m, 4H), 1.57 – 1.36 (m, 8H), 1.26 – 1.08 (m, 4H), 0.89 (d, *J* = 8.4 Hz, 6H). Mass (m/z): 329.3 $[M+H]^-$. Rt=4.456 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA) = 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 118

N-(4-(2-aminoethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline



Step 1. Preparation of ethyl

2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)acetate (**118-3**)

The title compound **118-3** (231 mg) was prepared in a total yield of 62.3% as a yellow solid from 4-(4,4-dimethylcyclohexyl)aniline (203 mg, 1.0 mmol), ethyl 2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)acetate (368 mg, 2.0 mmol) and $NaBH(OAc)_3$ (424 mg, 2.0 mmol) according to the procedure for **1-1**. Mass (m/z): 372.3 $[M+H]^+$.

Step 2. Preparation of 2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)acetic acid (**118-4**)

To a solution of ethyl 2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)acetate (170 mg, 0.5 mmol) in EtOH (10 mL) was added NaOH (100 mg, 2.5 mmol). The mixture was stirred for 3 hours at 65 °C, cooled to room temperature, and acidified with aqueous 2N HCl to adjust the pH to 3. The mixture was extracted with DCM (3x50 mL). The combined organic layers were washed with water, dried with Na_2SO_4, filtered, and concentrated to give a desired product yellow solid (157 mg, 100%). Mass (m/z): 342.3 $[M-H]^+$.

Step 3. Preparation of 2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)acetamide (**118-5**)

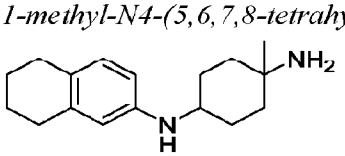
To a solution of 2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)acetic acid (150 mg, 0.44 mmol) in DMF (2.0 mL) was added CDI (78 mg, 0.48 mmol). The mixture was stirred for 3 hours at 100° C, cooled to 0 °C, $NH_3{\cdot}H_2O$ (0.1 mmol) was added. The mixture was stirred for 30 mins at rt. 5 mL of water was added, the mixture was extracted with DCM (3x5 mL). The combined organic layers were washed with water, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by prep-TLC (EA/PE=1/2) to give a desired product yellow solid (60 mg, 40%). Mass (m/z): 343.3 $[M+H]^+$.

Step 4. Preparation of N-(4-(2-aminoethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline (**118**)

A solution of 2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)acetamide (50 mg, 0.15 mol) in THF (10 mL) was added $LiAlH_4$ (24 g, 0.6 mol) at 0 °C, and the mixture was refluxed for 2 h. After cooling to 0 °C, water (24 uL), 10% NaOH (48 uL) and water 972 mL) were added, and the mixture was stirred for 3 min at room temperature. The solid was filtered and the filtered cake was washed with THF (10 mL*2); then the combined filtrates were dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (MeOH/DCM=1/5) to give the desired product (16.2 mg, 34.0%) as a white solid with 7:3 mixture by ^1H NMR. ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 3H), 6.89 (d, J = 7.8 Hz, 2H), 6.49 (s, 2H), 3.40 – 3.35 (m, 0.7H), 3.09 – 3.00 (m, 0.3H) 2.81 – 2.70 (m, 2H), 2.23 – 2.15 (m, 1H), 1.97 – 1.88 (m, 1H), 1.73 – 1.65 (m, 1H), 1.57 – 1.27 (m, 16H), 0.89 (d, J = 8.5 Hz, 6H). Mass (m/z): 329.3 $[M+H]^+$.

Compound 119

1-methyl-N4-(5,6,7,8-tetrahydronaphthalen-2-yl)cyclohexane-1,4-diamine



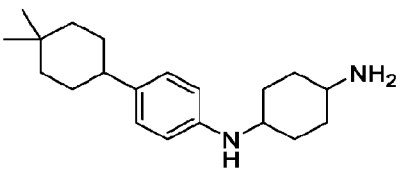
119

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The title compound **119** (86.3 mg) was prepared in a total yield of 97.4% as a white solid from tert-butyl (1-methyl-4-((5,6,7,8-tetrahydronaphthalen-2-yl)amino)cyclohexyl)carbamate (123 mg, 0.344 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 40.0 Hz, 3H), 6.77 (dd, J = 14.8, 7.2 Hz, 1H), 6.55 – 6.26 (m, 2H), 4.98 (s, 1H), 3.25 (dt, J = 8.0, 4.0 Hz, 1H), 2.58 (dd, J = 16.0, 5.6 Hz, 4H), 2.01 – 1.84 (m, 2H), 1.80 – 1.71 (m, 2H), 1.70 – 1.64 (m, 5H), 1.52 (ddd, J – 13.6, 10.0, 4.0 Hz, 2H), 1.29 (d, J = 8.8 Hz, 3H). Mass (m/z): 259.3 $[M+H]^+$.

Compound 120

N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclohexane-1,4-diamine



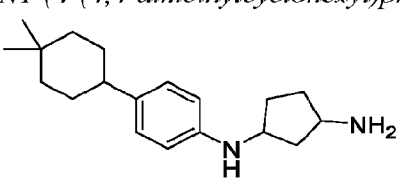
120A

120B

The title compound **120A** (Rt = 5.22 min; 18.3 mg) was prepared in a yield of 24.7% as a pale yellow powder compound **120B** (Rt = 5.87 min; 5.4 mg) was prepared in a yield of 7.31% as a pale yellow powder from 4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.24 mmol), tert-butyl (3-oxocyclobutyl)carbamate (79 mg, 0.37 mmol) and according to the procedure for **20**, which were prepared by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10 min-11 min-15.0 min). **120A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 3H), 7.12 (s, 1H), 6.84 (s, 2H), 6.65 (s, 1H), 3.21 (s, 1H), 2.07 – 1.89 (m, 4H), 1.38 (qd, J = 12.0, 11.3, 6.1 Hz, 2H), 1.31 – 1.16 (m, 11H). Mass(m/z): 301.5 $[M+H]^+$. **120B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 2H), 7.13 – 6.93 (m, 1H), 6.60 (d, J = 84.7 Hz, 3H), 3.47 (s, 1H), 3.14 (s, 1H), 1.88 – 1.56 (m, 7H), 1.24 (d, J = 1.2 Hz, 9H). Mass (m/z): 301.5 $[M+H]^+$.

Compound 121

N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclopentane-1,3-diamine



121A

121B

The title compound **121A** (Rt = 5.76 min; 11.0 mg) was prepared in a yield of 7.8% as a white powder and compound **121B** (Rt = 5.91 mi; 6.8 mg) was prepared in a yield of 4.8% as a white powder from 4-(4,4-dimethylcyclohexyl)aniline (100 mg, 0.49 mmol), tert-butyl (3-oxocyclopentyl)carbamate (146 mg, 0.74 mmol) and according to the procedure for **20** which were prepared by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10 min-11 min-15.0 min). **121A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 3H), 7.01 (d, J = 8.2 Hz, 2H), 6.63 (d, J =

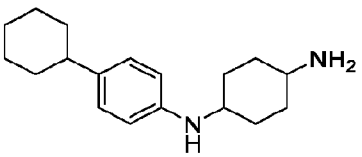
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40.9 Hz, 2H), 3.91 – 3.75 (m, 1H), 3.64 (s, 1H), 2.26 (q, J = 5.7 Hz, 1H), 2.16 – 2.05 (m, 2H), 1.99 (p, J = 6.9, 6.5 Hz, 1H), 1.87 (q, J = 6.0, 5.2 Hz, 2H), 1.57 – 1.48 (m, 5H), 1.43 (d, J = 13.1 Hz, 2H), 1.30 (d, J = 13.8 Hz, 2H), 0.95 (s, 3H), 0.93 (s, 3H). Mass (m/z): 287.3 $[M+H]^+$.

121B: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 3H), 7.00 (d, J = 9.2 Hz, 2H), 6.56 (s, 2H), 3.71 (d, J = 7.1 Hz, 1H),3.54(s, 1H), 2.20-2.32(m, 1H), 1.98 (dt, J = 15.4, 7.8 Hz, 3H), 1.75 – 1.59 (m, 2H), 1.54 (d, J – 8.4 Hz, 4H), 1.43 (d, J – 13.1 Hz, 3H), 1.34 – 1.28 (m, 2H), 0.95 (s, 3H), 0.93 (s, 3H). Mass (m/z): 287.3 $[M+H]^+$.

Compound 122

N1-(4-cyclohexylphenyl)cyclohexane-1,4-diamine

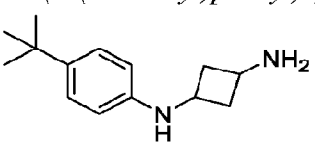


122

The title compound **122** (2.2 mg) was prepared in a yield of 2.8% as a rosy brown solid from 4-cyclohexylaniline (50 mg, 0.27 mmol), tert-butyl (3-oxocyclobutyl)carbamate (91 mg, 0.43 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.20 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 8.1 Hz, 2H), 3.58 (s, 1H), 2.48 (s, 1H), 2.02 (q, J = 6.6 Hz, 1H), 1.95 – 1.77 (m, 12H), 1.74 (d, J = 13.0 Hz, 1H), 1.51 – 1.36 (m, 4H), 1.31 (s, 1H). Mass (m/z): 273.3 $[M+H]^+$.

Compound 123

N1-(4-(tert-butyl)phenyl)cyclobutane-1,3-diamine

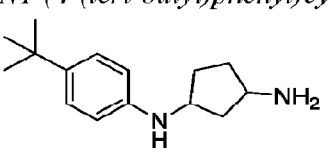


123

The title compound **123** (48.7mg) was prepared in a yield of 33.2% as a white powder with 4:1 mixture by ^{1}H NMR from 4-(tert-butyl)aniline (100 mg, 0.67 mmol), tert-butyl (3-oxocyclobutyl)carbamate (186 mg, 1.1 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 3H), 7.12 – 7.08 (m, 2H), 6.43 – 6.37 (m, 2H), 5.83 (d, J = 6.3 Hz, 1H), 4.07 (h, J = 6.6 Hz, 1H), 3.72 (td, J = 8.2, 4.2 Hz, 1H), 2.45 (td, J = 7.7, 3.8 Hz, 2H), 2.15 (ddd, J = 13.2, 8.1, 5.0 Hz, 2H), 1.20 (d, J = 0.9 Hz, 9H). Mass (m/z): 219.2 $[M+H]^+$.

Compound 124

N1-(4-(tert-butyl)phenyl)cyclopentane-1,3-diamine



124

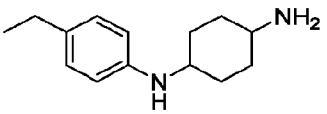
The title compound **124** (40.0 mg) was prepared in a yield of 25.6% as a white powder with

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1:0.3 mixture by ^{1}H NMR from 4-(tert-butyl)aniline (100 mg, 0.67 mmol), tert-butyl (3-oxocyclopentyl)carbamate (200 mg, 1.01 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 4H), 7.11 – 7.03 (m, 3H), 6.49 (dd, J = 8.7, 6.8 Hz, 3H), 5.65 (s, 0.3H), 5.45 (d, J = 7.0 Hz, 1H), 3.88 (h, J = 6.2 Hz, 1H), 3.71 (s, 0.3H), 3.62 – 3.54 (m, 1H), 3.48 (p, J = 7.1 Hz, 0.3H), 2.38 (dt, J = 14.2, 7.3 Hz, 0.3H), 2.09 (tdd, J = 13.0, 10.0, 6.1 Hz, 2H), 2.01 – 1.87 (m, 2H), 1.86 – 1.70 (m, 2H), 1.68 – 1.54 (m, 1H), 1.52 – 1.41 (m, 2H), 1.26 – 1.21 (m, 2H), 1.20 (s, 12H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 125

N1-(4-ethylphenyl)cyclohexane-1,4-diamine

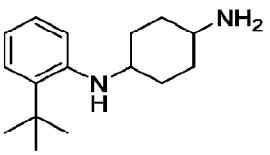


125

The title compound **125** (36.0mg) was prepared in a yield of 19.9% as a white powder with 2:1 mixture by ^{1}H NMR from 4-ethylaniline (100 mg, 0.82 mmol), tert-butyl (4-oxocyclohexyl)carbamate (263 mg, 1.24 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 3H), 6.90 (dd, J = 8.4, 6.3 Hz, 2H), 6.56 – 6.45 (m, 2H), 5.21 – 5.11 (m, 1H), 3.09 (s, 1H), 2.97 (s, 0.46H), 2.43 (qd, J = 7.6, 2.6 Hz, 2H), 1.99 (t, J = 13.8 Hz, 2H), 1.84 – 1.66 (m, 3H), 1.61 (d, J = 11.3 Hz, 1H), 1.44 (q, J = 12.8, 12.2 Hz, 1H), 1.22 – 1.12 (m, 1H), 1.12 – 1.07 (m, 3H). Mass (m/z): 219.4 $[M+H]^+$.

Compound 126

N1-(2-(tert-butyl)phenyl)cyclohexane-1,4-diamine (126)

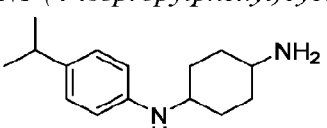


126

The title compound **126** (54.8 mg) was prepared in a yield of 33.1% as a white powder with 8:1 mixture by ^{1}H NMR from 2-(tert-butyl)aniline (93 mg, 0.63 mmol), tert-butyl (4-oxocyclohexyl)carbamate (200 mg, 0.94 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 3H), 7.11 (dd, J = 7.8, 1.6 Hz, 1H), 7.02 (ddd, J = 8.4, 7.2, 1.5 Hz, 1H), 6.71 – 6.65 (m, 1H), 6.55 (tt, J = 7.6, 1.7 Hz, 1H), 3.82 (d, J = 8.0 Hz, 1H), 3.33 – 3.21 (m, 1H), 3.05 – 2.92 (m, 1H), 2.13 – 1.96 (m, 4H), 1.82 (d, J = 9.2 Hz, 1H), 1.50 (qd, J = 12.7, 3.2 Hz, 2H), 1.39 (s, 1H), 1.34 (s, 8H). Mass(m/z): 247.3 $[M+H]^+$.

Compound 127

N1-(4-isopropylphenyl)cyclohexane-1,4-diamine



127

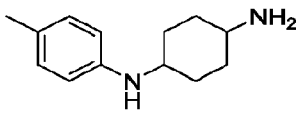
The title compound **127** (56.4 mg) was prepared in a yield of 39.0% as a white powder with 2:1

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mixture by ^{1}H NMR from 4-isopropylaniline (85 mg, 0.63 mmol), tert-butyl (4-oxocyclohexyl)carbamate (200 mg, 0.94 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (d, J = 32.0 Hz, 3H), 6.97 – 6.89 (m, 2H), 6.52 (dd, J = 13.3, 8.3 Hz, 2H), 5.19 (s, 1H), 3.08 (s, 1H), 2.95 (s, 1H), 2.72 (ddd, J = 13.8, 6.9, 2.1 Hz, 1H), 2.05 – 1.93 (m, 2H), 1.75 (tt, J = 10.4, 5.2 Hz, 3H), 1.66 – 1.55 (m, 1H), 1.53 – 1.39 (m, 1H), 1.18 (t, J – 10.9 Hz, 1H), 1.14 (d, J – 1.3 Hz, 3H), 1.12 (d, J – 1.3 Hz, 3H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 128

N1-(p-tolyl)cyclohexane-1,4-diamine

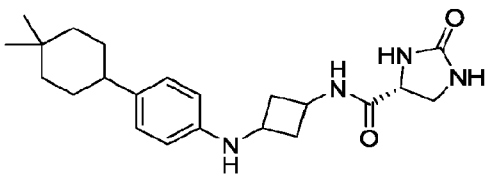


128

The title compound **128** (27.7 mg) was prepared in a yield of 23.0% as a white powder with 3:2 mixture by ^{1}H NMR from p-toluidine (63 mg, 0.59 mmol), tert-butyl (4-oxocyclohexyl)carbamate (188 mg, 0.89 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 – 8.21 (m, 2H), 8.17 (s, 1H), 6.87 (dd, J = 8.1, 4.8 Hz, 2H), 6.56 – 6.43 (m, 2H), 5.15 (s, 1H), 3.08 (s, 1H), 2.95 (s, 1H), 2.13 (d, J = 2.1 Hz, 3H), 2.00 (dd, J = 13.0, 4.1 Hz, 3H), 1.75 (tt, J = 12.3, 10.0, 4.3 Hz, 2H), 1.60 (d, J = 12.8 Hz, 1H), 1.54 – 1.39 (m, 1H), 1.15 (q, J = 12.0 Hz, 1H). Mass (m/z): 205.2 $[M+H]^+$.

Compound 129

(R)-N-(3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclobutyl)-2-oxoimidazolidine-4-carboxamide



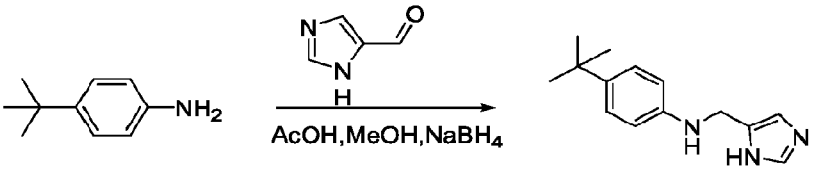
129

The title compound **129** (7.1 mg) was prepared in a yield of 16.77% as a white powder with 1:0.3 mixture by ^{1}H NMR from N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclobutane-1,3-diamine (30 mg, 0.11 mmol), (R)-2-oxoimidazolidine-4-carboxylic acid (19 mg, 0.14 mmol) and according to the procedure for **10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 7.1 Hz, 1H), 6.99 – 6.90 (m, 2H), 6.51 (s, 1H), 6.43 – 6.37 (m, 2H), 6.30 (s, 1H), 5.77 (d, J = 5.9 Hz, 1H), 4.33 (q, J = 7.0 Hz, 1H), 4.05 (ddd, J = 9.7, 6.1, 1.6 Hz, 1H), 3.84 (s, 1H), 2.25 (ddd, J = 20.3, 11.4, 5.3 Hz, 2H), 2.12 (td, J = 8.2, 4.1 Hz, 2H), 2.00 (p, J = 6.9, 6.5 Hz, 2H), 1.59 – 1.50 (m, 4H), 1.50 – 1.38 (m, 4H), 1.13 (dd, J = 6.9, 1.4 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H). Mass (m/z): 385.3 $[M+H]^+$.

Compound 130

N-((1H-imidazol-5-yl)methyl)-4-(tert-butyl)aniline

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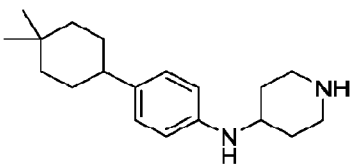


130

To a solution of 4-(tert-butyl)aniline (150 mg, 1.0 mmol) in MeOH (10 mL) and a drop of AcOH was added 1H-imidazole-5-carbaldehyde (201.9 mg, 1.0 mmol) and the mixture was stirred at 50°C for 1 h. Then the mixture was added $NaBH_4$ (76 mg, 2 mmol) after cooling to 25 °C. Then the mixture was stirred at 25 °C for 16 hrs. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to afford to give **130** (0.12 g, 52.0% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 1.2 Hz, 1H), 7.05 – 7.02 (m, 2H), 6.87 (d, J = 0.7 Hz, 1H), 6.54 – 6.51 (m, 2H), 5.54 (d, J = 1.2 Hz, 1H), 4.05 (s, 2H), 1.16 (s, 9H). MS (m/z) 230.2 $[M+H]^+$.

Compound 131

N-(4-(4,4-dimethylcyclohexyl)phenyl)piperidin-4-amine

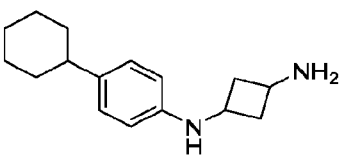


131

The title compound **131** (14.7 mg) was prepared in a yield of 15.4% as a white powder from 4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.25 mmol), tert-butyl 4-oxopiperidine-1-carboxylate (74 mg, 0.37 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.39 (s, 1H), 7.00 (d, J = 8.1 Hz, 2H), 6.62 (d, J = 8.0 Hz, 2H), 3.49 (p, J = 5.8 Hz, 1H), 3.30 (s, 2H), 2.97 (q, J = 11.2 Hz, 2H), 2.25 (tt, J = 10.5, 5.2 Hz, 1H), 2.07 – 1.94 (m, 2H), 1.53 (dt, J = 10.8, 3.4 Hz, 5H), 1.48 – 1.38 (m, 3H), 1.31 – 1.23 (m, 2H), 0.93 (s, 3H), 0.91 (s, 3H). Mass (m/z): 287.5 $[M+H]^+$.

Compound 132

N1-(4-cyclohexylphenyl)cyclobutane-1,3-diamine



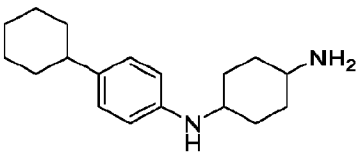
132

The title compound **132** (20.3 mg) was prepared in a yield of 14.5% as a white powder with 9:1 mixture by ^{1}H NMR from 4-cyclohexylaniline (100 mg, 0.57 mmol), tert-butyl (3-oxocyclobutyl)carbamate (158 mg, 0.86 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 2H), 6.97 – 6.87 (m, 2H), 6.41 – 6.36 (m, 2H), 5.81 (d, J = 6.2 Hz, 1H), 4.05 (q, J = 5.9 Hz, 1H), 3.72 (ddd, J = 13.3, 8.2, 5.2 Hz, 1H), 2.44 (tt, J = 7.7,

5.1 Hz, 2H), 2.30 (s, 1H), 2.14 (ddd, *J* = 13.0, 8.0, 4.9 Hz, 2H), 1.80 – 1.63 (m, 5H), 1.29 (d, *J* = 11.7 Hz, 4H), 1.26 – 1.10 (m, 1H). Mass (m/z): 245.3 $[M+H]^+$.

Compound 133

N1-(4-cyclohexylphenyl)cyclohexane-1,4-diamine

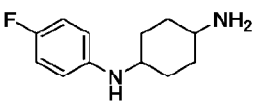


133

The title compound **133** (5.0 mg) was prepared in a yield of 6.1% as a white powder from 4-cyclohexylaniline (50 mg, 0.27 mmol), tert-butyl (3-oxocyclobutyl)carbamate (91 mg, 0.43 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (s, 3H), 7.02 (s, 2H), 6.67 (s, 1H), 3.15(s, 1H), 2.99 (s, 1H), 2.35 (s, 1H), 2.07 – 1.86 (m, 6H), 1.83 – 1.62 (m, 6H), 1.39 – 1.28 (m, 6H). Mass (m/z): 273.3 $[M+H]^+$.

Compound 134

N1-(4-fluorophenyl)cyclohexane-1,4-diamine

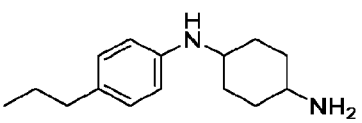


134

The title compound **134** (56.2 mg) was prepared in a total yield of 40.1% as a purple solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((4-fluorophenyl)amino)cyclohexyl)carbamate (207 mg, 0.672 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 3H), 6.98 (t, *J* = 8.9 Hz, 2H), 6.75 (dd, *J* = 8.8, 4.6 Hz, 2H), 3.44 – 3.36 (m, 1H), 3.13 (dp, *J* = 11.5, 6.1, 5.5 Hz, 1H), 1.78 – 1.55 (m, 8H). Mass (m/z): 209.3 $[M+H]^+$.

Compound 135

N1-(4-propylphenyl)cyclohexane-1,4-diamine



135A
135B

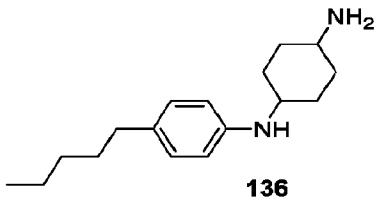
The title compound **135A** (35.5 mg) as a white solid and **135B** (42.8 mg) as a white solid were prepared from tert-butyl (4-((4-cyclopentylphenyl) amino)cyclohexyl) carbamate (170 mg, 5.12 mmol) and HCl in 1,4-dioxane (10 mL, 4 N) according to the literature for **24**. **135A**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 – 7.10 (m, 4H), 3.47 (brs, 1H), 3.14 (brs, 1H), 2.65 – 2.55 (m, 2H), 2.13 (d, *J* = 9.8 Hz, 4H), 1.70 – 1.45 (m, 6H), 0.94 (t, *J* = 7.2 Hz, 3H). MS (m/z): 233$[M+H]^+$. HPLC: Rt = 3.384 min (Column: XBRIDGE 3.5 um 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, Flow rate: 0.8 mL/min). **135B**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 – 7.30 (m, 4 H), 3.66 (br, 1H), 3.46 (br, 1H), 2.64 (dd, *J* = 15.5, 8.2 Hz, 3H), 2.14 – 1.81 (m, 6H), 1.76 – 1.55 (m, 3H), 0.94 (td, *J* = 7.3,

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5.2 Hz, 4H). MS (m/z): 233[M+H]$^+$. HPLC: Rt = 3.580 min (Column: XBRIDGE 3.5 um 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, Flow rate: 0.8 mL/min).

Compound 136

N1-(4-pentylphenyl)cyclohexane-1,4-diamine

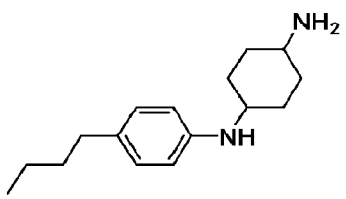


136

The title compound **136** (55 mg, 95.4%) was prepared as a white solid from tert-butyl (4-((4-pentylphenyl)amino)cyclohexyl)carbamate (79 mg, 0.22 mmol) and HCl in 1,4-dioxane (10 mL, 4 N) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.44 – 7.12 (m, 4H), 3.69 – 3.37 (m, 2H), 3.20 – 3.08 (m, 1H), 2.70 – 2.57 (m, 2H), 2.15 (br, 2H), 1.91 (brs, 4H), 1.57 (br, 4H), 1.41 – 1.24 (br, 4H), 0.90 (t, J = 6.9 Hz, 3H). MS (m/z) 261.3[M+H]$^+$.

Compound 137

N1-(4-butylphenyl)cyclohexane-1,4-diamine



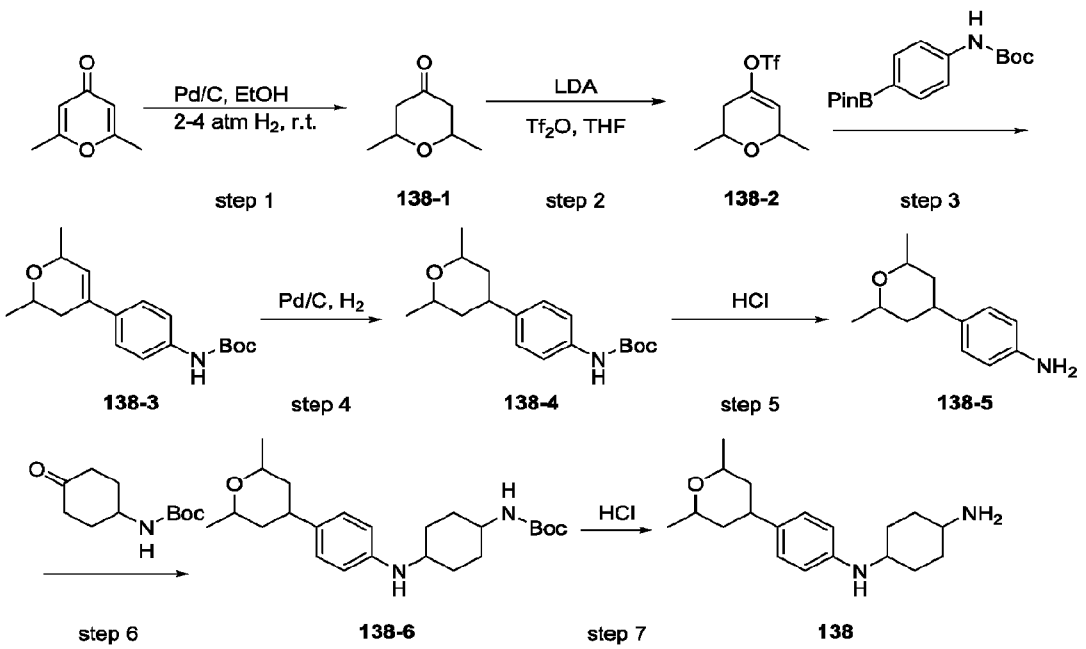
137

The title compound **137** (78 mg ,79.2%) was prepared as a white solid from tert-butyl (4-((4-butylphenyl)amino)cyclohexyl)carbamate (90 mg, 0.26 mmol) and HCl in 1,4-Dioxane (10 mL, 4 N) according to the procedure for **37**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 8.4 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 3.26 (br, 1H), 3.08 (br, 1H), 2.55 – 2.40 (m, 2H), 2.30 – 2.08 (m, 4H), 1.65 – 1.50 (m, 4H), 1.35 – 1.30 (m, 2H), 1.29 – 1.24 (m, 2H), 1.24 – 1.08 (m, 2H), 0.91 (t, J =7.2 Hz, 3H). MS (m/z): 247 [M+H]$^+$.

Compound 138

N1-(4-(2,6-dimethyltetrahydro-2H-pyran-4-yl) phenyl) cyclohexane-1,4-diamine

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Step 1. Preparation of 2,6-dimethyltetrahydro-4H-pyran-4-one **(138-1)**

To a solution of 2,6-dimethyl-4H-pyran-4-one (5 g, 40.3 mmol) in etOH (200 mL) was added Palladium (1 g). Then the mixture was stirred under H_2 in 3 bar at 25 °C for 8 h. After filtrating the Palladium, the organic phase was removed under vacuum and the residue was purified by flash chromatography to afford the desired product (1.4 g, 63.7%) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.76 – 3.64 (m, 2H), 2.22 – 2.18 (m, 4H), 1.20 (d, J = 8 Hz, 6H).

Step 2. Preparation of 2,6-dimethyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate **(138-2)**

To a solution of 2,6-dimethyltetrahydro-4H-pyran-4-one (0.7 g, 5.47 mmol) in THF (20 mL) was added LDA (10 mL, 6.56 mmol) and the mixture was stirred for 30 min at -78 °C under N_2. Then trifluoroacetic anhydride (5.2 g 6.56 mmol) was dripped into the mixture and stirred at 25 °C overnight. The reaction was quenched with water (30 mL), and extracted by EA (10 mL) for 3 times. The combined organic phase was washed 3 times by NaOH aq (10 mL) and dried over sodium sulfate, removed under vacuum to obtain the crude product (0.6 g, 42.1%) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.81 – 6.76 (m, 1H), 3.81 – 3.71 (m, 2H), 3.34 (s, 2H), 2.50 (s, 6H).

Step 3. Preparation of tert-butyl (4-(2,6-dimethyl-3,6-dihydro-2H-pyran-4-yl)phenyl)carbamate **(138-2)**

To a solution of 2,6-dimethyl-3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (0.6 g, 2.3 mmol) in dioxane : H_2O = 4 : 1 (20 mL) was added 4-(N-Boc-amino)phenylboronic acid pinacol ester (733 mg, 2.3 mmol), potassium carbonate (952 mg, 6.9 mmol) and tetrakis(triphenylphosphine)palladium (265 mg, 0.23 mmol). Then the mixture was stirred at 90 °C for 12 h. The reaction was quenched with water (30 mL), and extracted by EA (10 mL) for 3 times. The combined organic phase was dried over sodium sulfate, concentrated under vacuum and the residue was purified by flash chromatography to afford the desired product

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(0.35 g, 50.2%) as yellow oil. Mass (m/z): 248.2 $[M+H]^+$.

Step 4. Preparation of tert-butyl (4-(2,6-dimethyltetrahydro-2H-pyran-4-yl)phenyl)carbamate **(138-3)**

To a solution of tert-butyl (4-((2R,6S)-2,6-dimethyl-3,6-dihydro-2H-pyran-4-yl)phenyl)carbamate (0.35 g, 1.16 mmol) in MeOH (10 mL) was added Palladium (80 mg) . Then the mixture was stirred at 25 °C for 3 h under N_2. After filtrating the Palladium, the organic phase was removed under vacuum and the residue was purified by flash chromatography to afford the desired product as yellow oil (0.33 g, 98.3%). Mass (m/z): 250.2 $[M+H]^+$.

Step 5. Preparation of 4-(2,6-dimethyltetrahydro-2H-pyran-4-yl)aniline **(138-4)**

To a solution of tert-butyl (4-(2,6-dimethyltetrahydro-2H-pyran-4-yl)phenyl)carbamate (0.33 g, 1.08 mmol) in THF (5 mL) was added HCl in dioxane (5 mL) and the mixture was stirred for 2 h. The reaction was quenched with $NaHCO_3$ (10 mL), extracted by EA (10 mL) for 3 times and dried over sodium sulfate. After filtration, the organic phase was removed under vacuum and the residue was purified by flash chromatography to afford the desired product (0.16 g, 72.3%) s white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8 Hz, 2H), 6.65 (d, J = 8 Hz, 2H), 3.58 (m, 3H), 2.69 (m, 1H), 1.78 – 1.74 (m, 2H), 1.35 – 1.26 (m, 2H), 1.24 (d, J = 4 Hz, 6H). Mass m/z): 220.2 $[M+H]^-$

Step 6. Preparation of tert-butyl (4-((4-(2,6-dimethyltetrahydro-2H-pyran-4-yl) phenyl) amino) cyclohexyl) carbamate **(138-5)**

To a solution of 4-(2,6-dimethyltetrahydro-2H-pyran-4-yl)aniline (60 mg, 0.29 mmol) in MeOH (5 mL was added tert-butyl (4-oxocyclohexyl)carbamate (62.3 mg, 0.29 mmol) and acetic acid (1.74 mg, 0.029mmol). Then the mixture was stirred at 60 °C for 3 h. After the reaction was cooled to R.T., sodium cyanoborohydride (54.8 mg, 0.87 mmol) was added. The reaction was stirred for 3 h at R.T. The reaction was quenched with water (10 mL), extracted by EA (10 mL) for 3 times and dried over sodium sulfate. After filtration, the organic phase was removed under vacuum and the residue was purified by flash chromatography to afford the desired product (70 mg, 58.6%) as white solid. Mass (m/z): 402.8 $[M+H]^+$.

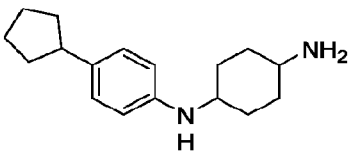
Step 7. Preparation of N1-(4-(2,6-dimethyltetrahydro-2H-pyran-4-yl) phenyl) cyclohexane-1,4-diamine **(138)**

To a solution of 4-(2,6-dimethyltetrahydro-2H-pyran-4-yl)aniline (70 mg, 0.17 mmol) in THF (5 mL) was added HCl in dioxane (4N; 5 mL) and the mixture was stirred for 2 h. The reaction was quenched with $NaHCO_3$ (10 mL), extracted by EA(10 mL) for 3 times and dried over sodium sulfate. After filtration, the organic phase was removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford the desired product (32 mg, 62.3%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 3.57 (m, 3H), 3.19 (s, 1H), 2.66 (m, 1H), 1.95 – 1.58 (m, 10H), 1.37 – 1.13 (m, 9H). Mass (m/z): 303.3 $[M+H]^+$.

Compound 139

N1-(4-cyclopentylphenyl)cyclohexane-1,4-diamine

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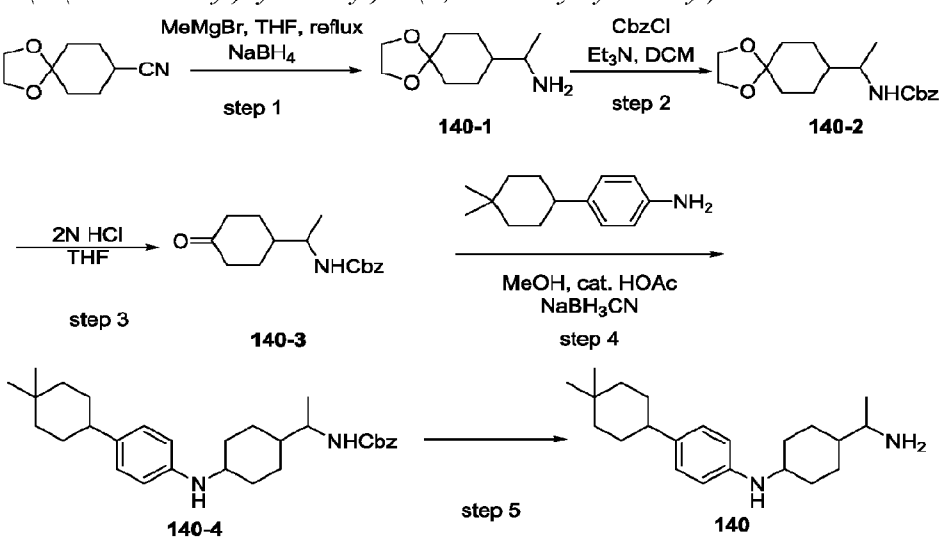


139A
139B

The title compounds **139A** (46.5 mg) as a white solid and **139B** (32.9 mg) as a white solid were prepared from tert-butyl (4-((4-cyclopentylphenyl) amino)cyclohexyl) carbamate (120 mg, 0.33 mmol) and HCl in 1,4-dioxane (10 mL, 4 N) according to the procedure for **24**. **139A**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (br, 2H), 7.20 (br, 2H), 3.58 (br, 1H), 3.39 (br, 1H), 3.19 – 2.97 (m, 1H), 2.13 (br, 2H), 2.00 – 1.34 (m, 14H). MS (m/z) 259 $[M+H]^+$. HPLC: Rt = 3.787 min (Column: XBRIDGE 3.5 um 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, Flow rate: 0.8 mL/min). **139B**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (br, 2H), 7.20 (br, 2H), 3.58 (br, 1H), 3.39 (br, 1H), 3.19 – 2.97 (m, 1H), 2.13 (br, 2H), 2.00 – 1.34 (m, 14H). MS (m/z) 259 $[M+H]^-$. HPLC: Rt = 3.991 min (Column: XBRIDGE 3.5 um 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, Flow rate: 0.8 mL/min).

Compound 140

N-(4-(1-aminoethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline



Step 1. Preparation of 1-(1,4-dioxaspiro[4.5]decan-8-yl)ethan-1-amine **(140-1)**

To a solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (1 g, 6 mmol) in THF (10 mL) was added MeMgBr (2 mL, 6 mmol) at 0 °C under N_2. Then the mixture was stirred at 70 °C for 2 hrs. Then the mixture was added $NaBH_4$ (0.68 g, 18 mmol) after cooling to 25 °C. Then the mixture was stirred at 25 °C for 2 hrs. LCMS showed the reaction was completed. The reaction was quenched with water (20 mL), extracted with EA (20 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:0) to give compound **140-1** (0.2 g, 18.2% yield) as a yellow solid. MS (m/z) 186.2 $[M+H]^+$.

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Step 2. Preparation of benzyl (1-(1,4-dioxaspiro[4.5]decan-8-yl)ethyl)carbamate **(140-2)**

To a solution of compound **140-1** (0.2 g, 1.1 mmol) in DCM (10 mL) was added TEA (218.5 mg, 2.2 mmol) and CbzCl (202.6 mg, 1.2 mmol). Then the mixture was stirred at 25 °C for 2 hrs. LCMS showed the reaction was completed. The mixture was added into H_2O, extracted with EA (20 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to give compound **140-2** (0.2 g, 58% yield) as yellow oil. MS (m/z) 342.2 $[M+Na]^+$.

Step 3. Preparation of benzyl (1-(4-oxocyclohexyl)ethyl)carbamate **(140-3)**

To a solution of **140-2** (0.2 g, 0.62 mmol) in THF (2 mL) was added 2N HCl (2 mL) at 25 °C. Then the mixture was stirred at 25 °C for 10 h. LCMS showed the reaction was completed. The reaction was concentrated. The residue was purified by combi-flash with EA/PE (1:2) to afford compound 4 (0.105 g, 61% yield) as yellow oil. MS (m/z) 275.8 $[M+H]^+$.

Step 4. Preparation of benzyl (1-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)ethyl)carbamate **(140-4)**

To a solution of **140-3** (105 mg, 0.36 mmol) in MeOH (5 mL) and a drop of AcOH was added 4-(4,4-dimethylcyclohexyl)aniline (74 mg, 0.36 mmol) and the mixture was stirred at 50°C for 1 h. Then the mixture was added $NaBH_3CN$ (68.5 mg, 1.1 mmol) after cooling to 25 °C. Then the mixture was stirred at 25 °C for 2 hrs. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to give compound 5 (0.1 g, 59.5% yield) as a yellow solid. MS (m/z) 462.8 $[M+H]^+$.

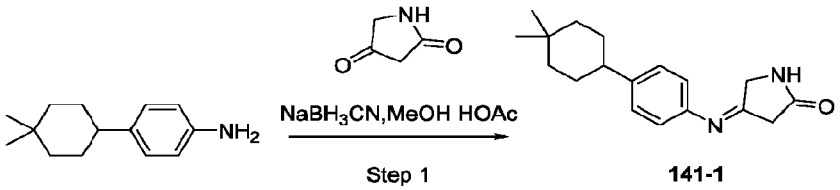
Step 5. Preparation of N-(4-(1-aminoethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline **(140)**

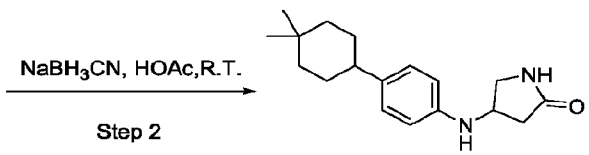
To a solution of compound **140-4** (0.1 g, 0.21 mmol) in DCM (5 mL) was added Et_3SiH (75.4 mg, 0.65 mmol), TEA (44 mg, 0.43 mmol) and $Pd(OAc)_2$ (5 mg, 0.021 mmol) under N_2 at 25 °C. Then the mixture was stirred at 25 °C for 2 h. LCMS showed the reaction was completed. The reaction was quenched by water (20 mL) slowly, extracted with EA (20 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with DCM/MeOH (10:1) to afford compound **140** (10 mg, 13% yield) as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 6.96 – 6.88 (m, 2H), 6.61 – 6.54 (m, 2H), 3.58 – 3.50 (m, 1H), 3.15 – 3.01 (m, 1H), 2.29 – 1.87 (m, 2H), 1.66 – 1.39 (m, 16H), 1.20 (m, 3H), 0.91 (d, J = 12 Hz, 6H). MS (m/z) 329.3 $[M+H]^+$.

Compound 141

4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)pyrrolidin-2-one (141)

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141

Step 1. Preparation of (Z)-4-((4-(4,4-dimethylcyclohexyl)phenyl)imino)pyrrolidin-2-one **(141-1)**

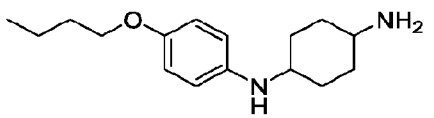
A mixture of 4-(4,4-dimethylcyclohexyl)aniline (100 mg, 0.49 mmol), pyrrolidine-2,4-dione (63.4 mg, 0.64 mmol) and $NaBH_3CN$ (61.8 mg, 0.98 mmol) in MeOH (10 mL) and HOAc (1 drop) was stirred overnight at 50 °C. After cooling, excess MeOH was removed under vacuum, the residual oil was extracted three times with ethyl acetate (20 mL) and water (10 mL). Organic layers were combined, solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE:EA=10:1) to give the imine intermediate (98 mg, 55.7%) as oil. Mass (m/z): 285.2 $[M+H]^+$.

Step 2. Preparation of 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)pyrrolidin-2-one **(141)**

$NaBH_3CN$ (15.5 mg, 0.25 mmol) was added to a solution of (Z)-4-((4-(4,4-dimethylcyclohexyl)phenyl)imino)pyrrolidin-2-one (70 mg, 0.25 mmol) in HOAc (10 mL). The mixture was stirred at 25 °C for overnight. After the reaction was completed, the reaction solution was washed with water, solvent was removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-70%) to afford the desired product **141** (8 mg) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.13 (t, 4H), 7.03 (t, 4H), 3.94 (s, 2H), 3.81 (s, 2H), 3.55 (s, 2H), 2.88 (s, 3H), 2.37 – 2.30 (m, 1H), 1.63 – 1.51 (m, 4H), 1.45 (d, 2H), 1.35 – 1.26 (m, 2H), 0.95 (d, 6H). Mass (m/z): 287.3 $[M+H]^+$.

Compound 142

N1-(4-butoxyphenyl)cyclohexane-1,4-diamine



142A
142B

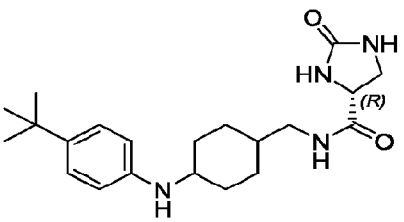
The title compounds **142A** (17.1 mg) as a white solid and **142B** (20.7 mg) as a white solid were prepared from tert-butyl (4-((4-butoxyphenyl)amino)cyclohexyl)carbamate (200 mg, 0.55 mmol) and HCl in 1,4-dioxane (10 mL, 4N) according to the procedure for **24**. **142A**: ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 6.68 (d, J = 8.9 Hz, 2H), 6.50 (d, J = 8.9 Hz, 2H), 3.81 (t, J = 6.5 Hz, 2H), 3.01 (d, J = 11.2 Hz, 1H), 2.87 (d, J = 11.1 Hz, 1H), 1.94 (dd, J = 23.9, 11.9

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Hz, 4H), 1.66 – 1.58 (m, 2H), 1.48 – 1.31 (m, 4H), 1.12 (d, J = 12.7 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H). MS (m/z) 263.2 $[M+H]^+$. HPLC: Rt: 3.789 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **142B**: ^1H NMR (400 MHz, DMSO-d_6)) δ 8.42 (s, 1H), 6.69 (d, J = 8.9 Hz, 2H), 6.54 (d, J = 8.7 Hz, 2H), 3.81 (t, J = 6.5 Hz, 2H), 3.34 (s, 1H), 3.00 (s, 1H), 1.74 – 1.53 (m, 11H), 1.40 (dd, J – 15.0, 7.4 Hz, 2H), 0.91 (t, J = 7.4 Hz, 3H). MS (m/z) 263.2 $[M+H]^+$. HPLC: Rt: 3.887 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 143

(R)-N-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)-2-oxoimidazolidine-4-carboxamide



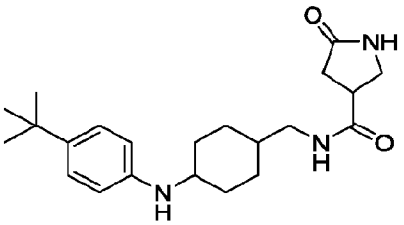
143A
143B

The title compound **143A, 143B** was prepared according to the procedure for compound **1**. The crude residue was purified by preparative TLC (MeOH:Dichloromethane=1:10) to afford 10.4 mg of compound **143A** in 18.6% yield as a light yellow solid and 5.1 mg of **143B** in 5.0% yield as a light yellow solid. **143A**: ^1H NMR (301 MHz, DMSO-d_6) δ 7.94 (t, J = 5.6 Hz, 1H), 7.46 – 6.94 (m, 5H), 6.53 (s, 1H), 6.34 (s, 1H), 4.08 – 4.03 (m, 1H), 3.54 (t, J = 9.3 Hz, 1H), 3.47 – 3.40 (m, 1H), 3.22 – 3.03 (m, 3H), 1.72 – 1.39 (m, 8H), 1.26 (s, 6H). Mass (m/z): 373.3 $[M+H]^+$. HPLC: Rt=0.334 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). **143B**: ^1H NMR (301 MHz, DMSO-d_6) δ 7.89 (t, J = 5.9 Hz, 1H), 7.45 – 6.94 (m, 5H), 6.51 (s, 1H), 6.33 (s, 1H), 4.04 (dd, J = 9.7, 6.3 Hz, 1H), 3.53 (t, J = 9.3 Hz, 1H), 3.30 – 3.14 (m, 2H), 2.94 (t, J = 6.3 Hz, 2H), 1.92 (d, J = 12.0 Hz, 2H), 1.73 (d, J = 12.7 Hz, 2H), 1.50 – 1.32 (m, 2H), 1.26 (s, 6H), 0.95 (q, J = 12.7 Hz, 2H). Mass (m/z): 373.3 $[M+H]^+$. HPLC: Rt=0.238 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 144

N-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)-5-oxopyrrolidine-3-carboxamide

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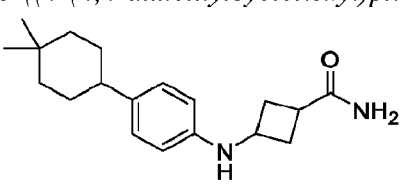


144A
144B

The title compound **144A** and **144B** were prepared according to the procedure for compound 1. The crude residue was purified by preparative TLC (MeOH:Dichloromethane=1:10) to afford 3.7 mg of compound **144A** in 6.6% yield as a light yellow solid and 4.6 mg **of 144B** in 8.3% yield as a light yellow solid. **144A:** ^{1}H NMR (301 MHz, DMSO-d_6) δ 8.01 (t, J = 5.7 Hz, 1H), 7.59 (s, 1H), 7.35 (s, 2H), 7.14 – 6.86 (m, 3H), 3.50 – 3.33 (m, 3H), 3.23 – 3.03 (m, 4H), 2.28 (d, J = 8.3 Hz, 2H), 1.66 – 1.54 (m, 4H), 1.50 – 1.39 (m, 4H), 1.25 (s, 9H). Mass (m/z): 373.3 $[M+H]^+$. HPLC: Rt=0.372 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). **144B**: ^{1}H NMR (301 MHz, DMSO-d_6) δ 7.98 (t, J = 5.7 Hz, 1H), 7.58 (s, 1H), 7.44 – 7.30 (m, 2H), 7.12 – 6.83 (m, 3H), 3.38 (t, J = 8.8 Hz, 1H), 3.27 – 3.08 (m, 4H), 2.92 (t, J = 6.3 Hz, 2H), 2.26 (d, J = 8.4 Hz, 2H), 1.92 (d, J = 12.0 Hz, 2H), 1.73 (d, J = 12.7 Hz, 2H), 1.40 – 1.15 (m, 11H), 1.00 – 0.90 (m, 2H). Mass (m/z): 373.3 $[M+H]^+$. HPLC: Rt=0.173 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 145

3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclobutane-1-carboxamide



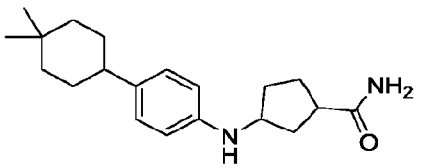
145

The title compound **145** (8.7 mg) was prepared in a total yield of 15.8% as a white solid with 7:3 mixture by ^{1}H NMR from 3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclobutane-1-carboxylic acid (55 mg, 0.18 mmol), CDI (59 mg, 0.36 mmol) and $NH_3{\cdot}H_2O$ (0.5 mL) according to the procedure for **118-5**. ^{1}H NMR (301 MHz, DMSO-d_6) δ 7.24 – 7.19 (m, 1H), 6.97 – 6.90 (m, 2H), 6.78 – 6.72 (m, 1H), 6.43 (d, J = 8.4 Hz, 0.8 H), 6.38 (d, J = 8.4 Hz, 1.2H), 5.66 (d, J = 6.4 Hz, 0.6 H), 5.63 (d, J = 6.4 Hz, 0.4H), 3.89 – 3.82 (m, 0.6H), 3.69 – 3.63 (m, 0.4H), 2.97 – 2.84 (m, 1H), 2.48 – 2.34 (m, 4H), 2.03 – 1.89 (m, 3H), 1.56 – 1.37 (m, 6H), 0.93 (d, J = 6.4 Hz, 6H). Mass (m/z): 301.3 $[M+H]^+$.

Compound 146

3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclopentane-1-carboxamide

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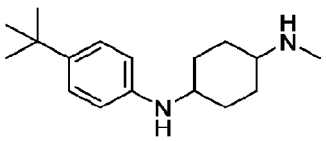


146A
146B

The title compound **146A** and **146B** were prepared according to the procedure for compound **118-5**. The crude residue was purified by preparative TLC (MeOH:Dichloromethane=1:10) to afford compound **146A** in 61.4% yield as a light yellow solid and **146B** in 47.3% yield as a light yellow solid. **146A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (s, 1H), 6.90 (d, J = 8.4 Hz, 2H), 6.67 (s, 1H), 6.43 (d, J = 7.6 Hz, 2H), 5.30 (s, 1H), 3.73 – 3.62 (m, 1H), 2.69 (p, J = 8.1 Hz, 1H), 2.21 – 2.13 (m, 1H), 1.96 – 1.82 (m, 3H), 1.65 – 1.57 (m, 2H), 1.52 – 1.35 (m, 8H), 1.28 – 1.21 (m, 2H), 0.90 (d, J = 8.8 Hz, 6H). Mass (m/z): 315.3 $[M+H]^+$. HPLC: Rt=1.198 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). **146B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 6.67 (s, 1H), 6.43 (d, J = 8.0 Hz, 2H), 5.30 (s, 1H), 3.72 – 3.65 (m, 1H), 2.69 (p, J = 8.0 Hz, 1H),2.10 – 2.20 (m, 2H), 2.01 – 1.82 (m, 3H), 1.66 – 1.57 (m, 2H), 1.49 – 1.35 (m, 7H), 1.27 – 1.20 (m, 2H), 0.90 (d, J = 8.8 Hz, 6H). Mass (m/z): 315.3 $[M+H]^+$. HPLC: Rt=1.807 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 147

N^1-(4-(tert-butyl)phenyl)-N4-methylcyclohexane-1,4-diamine



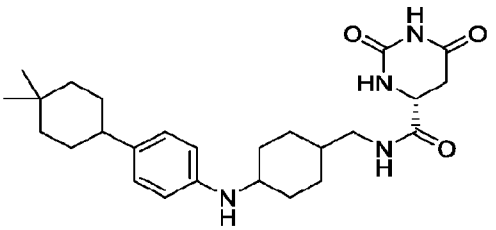
147A
147B

The title compound **147A** and **147B** were prepared according to the procedure for compound **118**. The crude residue was purified by preparative TLC (MeOH:Dichloromethane=1:5) to afford compound **147A** in 27.5% yield as a light yellow solid and **147B** in 7.7% yield as a light yellow solid. **147A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 2H), 7.05 (d, J = 8.6 Hz, 3H), 6.50 (d, J = 8.4 Hz, 2H), 5.19 (d, J = 5.6 Hz, 1H), 3.45 – 3.36 (m, 1H), 3.00 – 2.93 (m, 1H), 2.46 (s, 3H), 1.82 – 1.70 (m, 6H), 1.59 – 1.49 (m, 2H), 1.17 (s, 9H). Mass (m/z): 261.3 $[M+H]^+$. HPLC: Rt=0.423 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). **147B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 – 7.00 (m, 2H), 6.50 – 6.41 (m, 2H), 5.10 (d, J = 8.2 Hz, 1H), 3.44 – 3.27 (m, 2H), 3.12– 3.03 (m, 2H), 6.50 – 6.41 (m, 2H), 2.30 – 2.18 (m, 4H), 1.97 – 1.84 (m, 4H), 1.20 (s, 9H), 1.13 – 0.98 (m, 4H). Mass (m/z): 261.3 $[M+H]^+$. HPLC: Rt=0.318 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

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Compound 148

(R)-N-((4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)methyl)-2,6-dioxohexahydropyrimidine-4-carboxamide

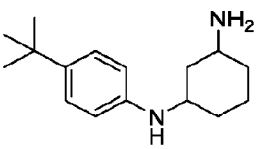


148 A/B

The title compound **148** was prepared from N1-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine (18.6 mg, 0.06 mmol) according to the procedure for compound **1**. The mixture was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 20%-45%-95%-95%-10%, 0 min-12 min-12.5 min-13.5 min-15 min) to afford compound **148A** (Rt = 9.79 min) as a sandy brown solid and compound **148B** (Rt = 10.42 min) as a sandy brown solid. **148A** (7.0 mg, 26%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.00 (s, 1H), 7.54 (s, 1H), 7.29 – 7.03 (m, 4H), 6.95 (s, 1H), 3.92 (m, 1H), 3.17 (m, 1H), 2.88 (m, 2H), 2.66 – 2.54 (m, 2H), 2.29 (m, 1H), 1.97 – 1.85 (m, 3H), 1.68 (m, 2H), 1.56 – 1.22 (m, 12H), 0.92 (s, 3H), 0.89 (s, 3H). Mass (m/z): 455.2 $[M+H]^+$. **148B** (14.1 mg, 53%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.01 (s, 1H), 7.55 (s, 1H), 7.29 – 6.84 (m, 5H), 3.93 (m, 1H), 3.01 (m, 2H), 2.80 (m, 1H), 2.54 (m, 1H), 2.42 (m, 1H), 2.29 (m, 1H), 1.63 – 1.46 (m, 8H), 1.44 – 1.33 (m, 6H), 1.31 – 1.23 (m, 3H), 0.92 (s, 3H), 0.89 (s, 3H). Mass (m/z): 455.2 $[M+H]^+$.

Compound 149

N1-(4-(tert-butyl)phenyl)cyclohexane-1,3-diamine

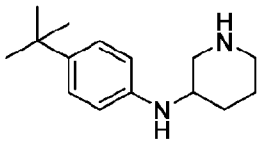


149 A
149 B

The title compound **149** was prepared from tert-butyl (3-((4-(tert-butyl)phenyl)amino)cyclohexyl)carbamate (520 mg, 1.5 mmol) according to the procedure for compound **88**. The mixture was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 10%-32%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13 min) to afford compound **149A** (Rt = 6.88 min) as a white solid and compound **149B** (Rt = 9.25 min) as a white solid. **149A** (79.8 mg, 21%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 3.39 (m, 1H), 3.09 (m, 1H), 2.25 – 1.75 (m, 4H), 1.44 – 1.28 (m, 4H), 1.24 (s, 9H). Mass (m/z): 247.2 $[M+H]^+$. **149B** (188.5 mg, 51%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 3.77 (m, 1H), 3.46 (m, 1H), 2.13-1.32 (m, 8H), 1.23 (s, 9H). Mass (m/z): 247.2 $[M+H]^+$.

Compound 150

N-(4-(tert-butyl)phenyl)piperidin-3-amine

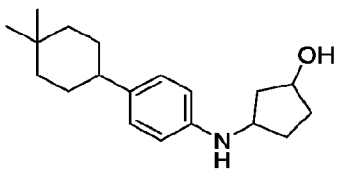


150

The title compound **150** (151.2 mg) was prepared from tert-butyl 3-((4-(tert-butyl)phenyl)amino)piperidine-1-carboxylate (498 mg, 1.5 mmol) according to the procedure for compound **88**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, J = 8.4 Hz, 2H), 6.95 (s, 1H), 6.58 (d, J = 8.4 Hz, 2H), 5.52 (s, 1H), 3.59 (s, 1H), 3.29 – 3.06 (m, 2H), 2.74 – 2.56 (m, 2H), 1.98 – 1.38 (m, 4H), 1.20 (s, 9H). Mass (m/z): 233.4[M+H]$^+$.

Compound 151

3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclopentan-1-ol

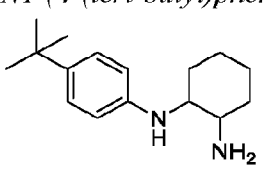


151

The title compound **151** (32.1 mg) was prepared in a total yield of 76 % as a chocolate solid from 4-(4,4-dimethylcyclohexyl)aniline (31 mg, 0.15 mmol) and 3-hydroxycyclopentan-1-one (20 mg, 0.2 mmol) according to the procedure for compound **4**. ^{1}H NMR (400 MHz, DMSO-d6) δ 6.93 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 5.40(s, 1H), 4.49 (s, 1H), 4.19 (m, 1H), 3.79 (m, 1H), 2.20 (m, 1H), 2.12 – 1.83 (m, 3H), 1.55 – 1.27 (m, 11H), 0.93 (s, 3H), 0.91 (s, 3H). Mass (m/z): 288.4[M+H]$^+$.

Compound 152

N1-(4-(tert-butyl)phenyl)cyclohexane-1,2-diamine



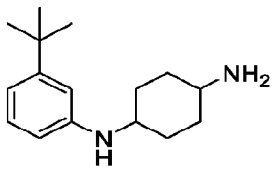
152

The title compound **152** (271.5 mg) was prepared in a total yield of 67% as a yellow solid from 4-(tert-butyl)aniline (223 mg, 1.5 mmol) and tert-butyl (2-oxocyclohexyl)carbamate (426 mg, 2.0 mmol) according to the procedure for compound **24.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.4 Hz, 2H), 3.32 (m, 1H), 2.95 (m, 1H), 2.26 – 1.92 (m, 2H), 1.83 – 1.31 (m, 4H), 1.21 (s, 9H), 1.18 – 1.07 (m, 2H). Mass (m/z): 247.3[M+H]$^+$.

Compound 153

N1-(3-(tert-butyl)phenyl)cyclohexane-1,4-diamine

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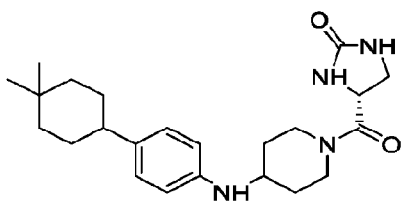
153A

153B

The title compound **153A** (Rt=3.65 min; 45.3 mg) was prepared in a yield of 27.4% as a white powder and compound **153B** (Rt=4.28 min; 36.7 mg) was prepared in a yield of 22.2% as a white powder 3-(tert-butyl)aniline (100 mg, 0.67 mmol), tert-butyl (4-oxocyclohexyl)carbamate (214 mg, 1.01 mmol) and according to the procedure for **20** which were prepared by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10 min-11 min-15.0 min). **153A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 3H), 7.12 (s, 1H), 6.84 (s, 2H), 6.65 (s, 1H), 3.21 (s, 1H), 3.06 – 2.93 (m, 1H), 2.07 – 1.89 (m, 4H), 1.38 (qd, J = 12.0, 11.3, 6.1 Hz, 2H), 1.25 (d, J = 6.3 Hz, 2H), 1.24 – 1.20 (m, 9H). **153**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 2H), 7.13 – 6.93 (m, 1H), 6.60 (d, J = 84.7 Hz, 3H), 3.47 (s, 1H), 3.14 (s, 1H), 1.88 – 1.56 (m, 8H), 1.24 (d, J = 1.2 Hz, 9H). Mass (m/z): 247.6 $[M+H]^+$.

Compound 154

(R)-4-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)piperidine-1-carbonyl)imidazolidin-2-one



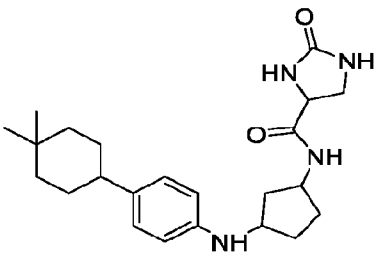
154

The title compound **154** (21.2 mg) was prepared in a yield of 71.2% as a white powder from N-(4-(4,4-dimethylcyclohexyl)phenyl)piperidin-4-amine (21.4 mg, 0.07 mmol), (R)-2-oxoimidazolidine-4-carboxylic acid (11 mg, 0.08 mmol) and according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 (s, 1H), 6.94 (d, J = 8.1 Hz, 2H), 6.67 (s, 1H), 6.52 (d, J = 8.0 Hz, 2H), 6.26 (d, J = 6.6 Hz, 1H), 4.55-4.60(m, 1H), 4.18(s, 1H), 2.40-2.45(m, 2H), 1.90 (s, 2H), 1.52 (s, 4H), 1.49 – 1.37 (m, 9H), 1.08-1.13(m, 1H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 399.3 $[M+H]^+$.

Compound 155

N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclopentane-1,3-diamine

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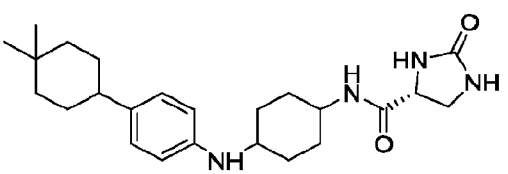


155

The title compound **155** (76.4 mg) was prepared in a yield of 33.0% as a white powder with 2:1 mixture by ^{1}H NMR from N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclopentane-1,3-diamine (166 mg, 0.58 mmol), (R)-2-oxoimidazolidine-4-carboxylic acid (83 mg, 0.64 mmol) and according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.20 (d, J = 63.2 Hz, 4H), 6.37 (d, J = 61.1 Hz, 2H), 4.28 – 4.21 (m, 1H), 4.00 (dd, J = 9.8, 6.2 Hz, 2H), 3.50 (td, J = 9.0, 6.7 Hz, 1H), 3.24 – 3.11 (m, 1H), 2.38 (s, 1H), 2.09 – 1.97 (m, 2H), 1.87 (d, J = 8.7 Hz, 1H), 1.76 (dt, J = 13.8, 7.3 Hz, 1H), 1.57 (d, J = 11.0 Hz, 5H), 1.43 (d, J = 12.5 Hz, 3H), 1.31 (d, J = 14.5 Hz, 1H), 0.95 (s, 3H), 0.92 (s, 3H). Mass (m/z): 399.4 $[M+H]^+$.

Compound 156

(R)-N-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)-2-oxoimidazolidine-4-carboxamide

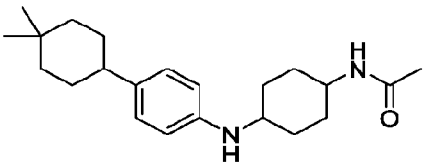


156A
156B

The title compound **156A** (Rt=6.19 min; 4.5 mg) was prepared in a yield of 5.7% as a white powder and compound **156B** (Rt=7.19 min; 10 mg) was prepared in a yield of 12.6% as a white powder from N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclohexane-1,4-diamine (57 mg, 0.19 mmol), (R)-2-oxoimidazolidine-4-carboxylic acid (27 mg, 0.21 mmol) according to the procedure for **1** which were prepared by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 25%-43%-95%-95%-10%, 0 min-10.0 min-10.5 min-11.5 min-13.0 min). **156A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J = 7.8 Hz, 1H), 7.23 (s, 2H), 7.14-6.91(s, 1H), 6.48 (s, 1H), 6.30 (s, 1H), 4.03 (dd, J = 9.7, 6.0 Hz, 2H), 3.55 – 3.48 (m, 2H), 3.17 (dd, J = 8.9, 6.1 Hz, 1H), 2.00 (q, J = 6.8, 6.2 Hz, 1H), 1.93 (d, J = 10.8 Hz, 2H), 1.82 (d, J = 10.8 Hz, 2H), 1.64 – 1.51 (m, 4H), 1.45 (d, J = 12.3 Hz, 3H), 1.32 (t, J = 9.0 Hz, 4H), 0.97 (s, 3H), 0.94 (s, 3H). Mass (m/z): 413.4 $[M+H]^+$. **156B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 – 7.50 (m, 1H), 7.21 (s, 2H), 7.00 (s, 1H), 6.51 (s, 1H), 6.31 (s, 1H), 4.09 (dd, J = 9.7, 5.9 Hz, 1H), 3.72 (s, 1H), 3.52 (t, J = 9.3 Hz, 1H), 3.39 (d, J = 8.5 Hz, 1H), 3.20 (dd, J = 8.9, 5.9 Hz, 1H), 1.98 (p, J = 7.0, 6.5 Hz, 1H), 1.74 (s, 2H), 1.69 – 1.60 (m, 4H), 1.60 – 1.48 (m, 6H), 1.43 (d, J = 12.8 Hz, 2H), 1.31 (d, J = 13.7 Hz, 2H), 0.95 (s, 3H), 0.92 (s, 3H). Mass (m/z):413.4 $[M+H]^+$.

Compound 157

N-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)acetamide

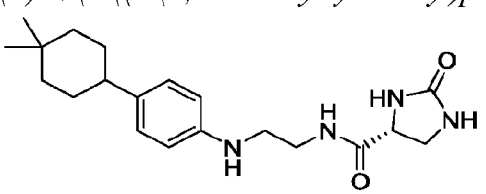


157A
157B

The title compound **157A** (Rt = 6.02 min; 18.7 mg) was prepared in a yield of 16.4% as a white powder and compound **157B** (Rt = 6.34 min; 25.4 mg) was prepared in a yield of 22.8% as a white powder from N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclohexane-1,4-diamine (100 mg, 0.33 mmol), acetic acid (30 mg, 0.50 mmol) and according to the procedure for **1** which were prepared by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10 min-11 min-15.0 min). **175A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (d, J = 7.6 Hz, 1H), 7.29 (s, 2H), 7.13 (s, 2H), 3.53 – 3.39 (m, 1H), 2.40 (s, 1H), 1.99 (q, J = 6.9, 6.4 Hz, 1H), 1.95 – 1.77 (m, 4H), 1.75 (s, 3H), 1.66 – 1.52 (m, 4H), 1.49 – 1.40 (m, 3H), 1.39 – 1.26 (m, 4H), 1.17 (d, J = 12.7 Hz, 1H), 0.95 (s, 3H), 0.92 (s, 3H). Mass (m/z): 343.5 $[M+H]^+$. **175B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 5.9 Hz, 1H), 7.31 (s, 2H), 7.14 (s, 2H), 3.69 (q, J = 4.7 Hz, 1H), 3.40 (d, J = 6.8 Hz, 1H), 2.41 (s, 1H), 1.83 (s, 3H), 1.76 (q, J = 7.3, 5.8 Hz, 2H), 1.67 (q, J = 5.7 Hz, 4H), 1.63 – 1.56 (m, 4H), 1.56 – 1.41 (m, 4H), 1.37 – 1.27 (m, 2H), 0.97 (s, 3H), 0.94 (s, 3H). Mass (m/z): 343.5 $[M+H]^+$.

Compound 158

(R)-N-(2-((4-(4,4-dimethylcyclohexyl)phenyl)amino)ethyl)-2-oxoimidazolidine-4-carboxamide



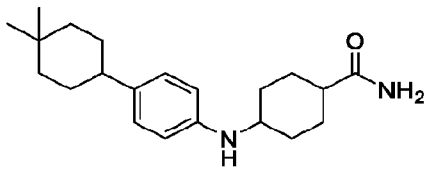
158

The title compound **158** (7.6 mg) was prepared in a yield of 12.7% as a white powder from N1-(4-(4,4-dimethylcyclohexyl)phenyl)ethane-1,2-diamine (41 mg, 0.17 mmol), (R)-2-oxoimidazolidine-4-carboxylic acid (32 mg, 0.25 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (t, J = 5.8 Hz, 1H), 6.98 – 6.93 (m, 2H), 6.55 – 6.48 (m, 3H), 6.37 – 6.30 (m, 1H), 4.06 (ddd, J = 9.8, 6.4, 1.9 Hz, 1H), 3.55 (ddd, J = 9.9, 8.9, 1.1 Hz, 1H), 3.28 – 3.23 (m, 2H), 3.19 (ddd, J = 8.9, 6.4, 1.3 Hz, 1H), 3.06 (q, J = 6.5 Hz, 2H), 2.23 (tt, J = 10.3, 5.1 Hz, 1H), 1.52 (td, J = 12.0, 11.1, 3.3 Hz, 4H), 1.43 (d, J = 13.1 Hz, 3H), 1.30 (dd, J = 12.2, 5.3 Hz, 1H), 0.95 (s, 3H), 0.93 (s, 3H). Mass (m/z): 359.3 $[M+H]^+$.

Compound 159

4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexane-1-carboxamide

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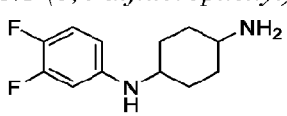


159A
159B

The title compound **159** was prepared from 4-(4,4-dimethylcyclohexyl)aniline (100 mg, 0.493 mmol), 4-oxocyclohexane-1-carboxamide (104 mg, 0.739 mmol), AcOH (0.1 mL), $NaBH(OAc)_3$ (209 mg, 0.986 mmol) and DCE (10 mL) according to the procedure for **1-1**, which was purified by prep HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 25%-50%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13 min) to give the desired product **159A** (Rt = 7.1 min) as a white solid (20.5 mg, 12.7%) and **159B** (Rt = 8.8 min) as a white solid (32.4 mg, 20.0%). **159A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 6.55 (s, 1H), 6.23 (d, J = 7.2 Hz, 2H), 5.22 (s, 1H), 3.72 – 3.62 (m, 1H), 2.71 (p, J = 8.0 Hz, 1H), 2.26 – 2.13 (m, 1H), 1.96 – 1.82 (m, 3H), 1.65 – 1.57 (m, 2H), 1.51 – 1.33 (m, 10H), 1.25 – 1.21 (m, 2H), 0.93 (d, J = 8.0 Hz, 6H). Mass (m/z): 328.3 $[M+H]^+$. **159B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 6.67 (s, 1H), 6.43 (d, J = 8.0 Hz, 2H), 5.28 (s, 1H), 3.72 – 3.65 (m, 1H), 2.67 (p, J = 8.0 Hz, 1H),1.65 – 1.56 (m, 2H), 2.01 – 1.82 (m, 3H), 1.66 – 1.57 (m, 2H), 1.48 – 1.34 (m, 9H), 1.27 – 1.20 (m, 2H), 0.90 (d, J = 8.8 Hz, 6H). Mass (m/z): 328.3 $[M+H]^+$.

Compound 160

N1-(3,4-difluorophenyl)cyclohexane-1,4-diamine

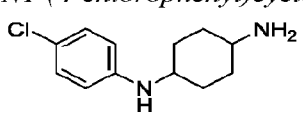


160

The title compound **160** (22.9 mg) was prepared in a total yield of 47.2% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((3,4-difluorophenyl)amino)cyclohexyl)carbamate (73 mg, 0.215 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 – 6.97 (m, 1H), 6.56 (dddd, J = 13.6, 10.0, 6.8, 2.8 Hz, 1H), 6.45 – 6.26 (m, 1H), 5.75 (dd, J = 14.8, 6.8 Hz, 1H), 3.15 – 2.89 (m, 2H), 1.99 (dt, J = 12.8, 4.8 Hz, 2H), 1.75 (tt, J = 8.4, 4.0 Hz, 3H), 1.60 (dq, J = 15.2, 6.4, 5.6 Hz, 1H), 1.48 (qd, J = 13.6, 12.8, 3.6 Hz, 1H), 1.25 – 1.11 (m, 2H). Mass (m/z): 227.3 $[M+H]^+$.

Compound 161

N1-(4-chlorophenyl)cyclohexane-1,4-diamine



161

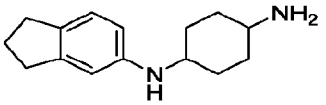
The title compound **161** (28.6 mg) was prepared in a total yield of 48.5% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((4-chlorophenyl)amino)cyclohexyl)carbamate (85 mg, 0.262 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 – 7.00 (m, 2H), 6.62 (dd, J = 9.5, 3.0 Hz, 2H), 3.38 (t, J = 4.0 Hz,

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3H), 3.17 – 3.00 (m, 3H), 2.01 (q, J = 9.9, 9.3 Hz, 2H), 1.76 (q, J = 5.2, 3.9 Hz, 3H), 1.65 – 1.55 (m, 1H), 1.53 – 1.41 (m, 1H). Mass (m/z): 225.3 $[M+H]^+$.

Compound 162

N1-(2,3-dihydro-1H-inden-5-yl)cyclohexane-1,4-diamine

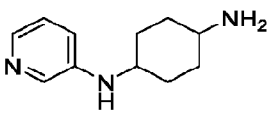


162

The title compound **162** (32.7 mg) was prepared in a total yield of 53.2% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((2,3-dihydro-1H-inden-5-yl)amino)cyclohexyl)carbamate (89 mg, 0.27 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 34.0 Hz, 3H), 6.91 (d, J = 8.0 Hz, 1H), 6.50 (s, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.11 (s, 1H), 3.15 – 2.86 (m, 2H), 2.71 (dt, J = 15.2, 7.2 Hz, 4H), 2.00 (dd, J = 13.2, 4.0 Hz, 2H), 1.92 (q, J = 7.2 Hz, 2H), 1.76 (tt, J = 14.0, 8.0 Hz, 3H), 1.59 (td, J = 10.0, 4.8 Hz, 1H), 1.52 – 1.39 (m, 1H). Mass (m/z): 231.3 $[M+H]^+$.

Compound 163

N1-(pyridin-3-yl)cyclohexane-1,4-diamine

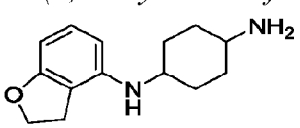


163

The title compound **163** (13.6 mg) was prepared in a total yield of 37.8% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-(pyridin-3-ylamino)cyclohexyl)carbamate (55 mg, 0.189 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (dd, J = 24.4, 2.8 Hz, 1H), 7.69 (ddd, J = 8.0, 4.4, 1.2 Hz, 1H), 7.05 (dt, J = 8.4, 4.8 Hz, 1H), 6.94 (dddd, J = 8.4, 6.0, 2.8, 1.2 Hz, 1H), 5.84 (t, J = 6.4 Hz, 1H), 3.17 – 3.02 (m, 1H), 2.90 (d, J = 13.2 Hz, 1H), 1.97 (ddd, J = 12.4, 7.2, 3.2 Hz, 2H), 1.73 (dq, J = 10.0, 5.2 Hz, 3H), 1.60 (ddd, J = 13.6, 8.0, 4.0 Hz, 1H), 1.50 – 1.37 (m, 1H), 1.24 – 1.09 (m, 2H). Mass (m/z): 192.3 $[M+H]^+$.

Compound 164

N1-(2,3-dihydrobenzofuran-4-yl)cyclohexane-1,4-diamine



164

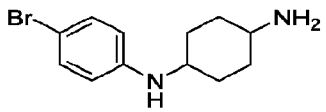
The title compound **164** (64.8 mg) was prepared in a total yield of 89% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((2,3-dihydrobenzofuran-4-yl)amino)cyclohexyl)carbamate (105 mg, 0.316 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.81 (q, J = 7.6 Hz, 1H), 6.07 (d, J = 8.4 Hz, 1H), 5.98 (dd, J = 16.4, 7.6 Hz, 1H), 4.84 – 4.37 (m, 3H), 3.18 – 3.05 (m, 1H), 2.93 (dt, J = 41.2, 8.8 Hz, 3H), 2.02 – 1.90 (m, 2H), 1.84 – 1.74

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(m, 2H), 1.73 – 1.65 (m, 1H), 1.63 – 1.54 (m, 1H), 1.50 – 1.37 (m, 1H), 1.25 (td, J = 12.8, 11.2, 4.0 Hz, 1H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 165

N1-(4-bromophenyl)cyclohexane-1,4-diamine

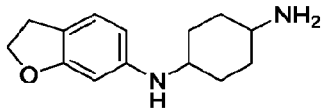


165

The title compound **165** (106.7 mg) was prepared in a total yield of 83.1% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((4-bromophenyl)amino)cyclohexyl)carbamate (176 mg, 0.477 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.13 (t, J = 8.4 Hz, 2H), 6.56 – 6.46 (m, 2H), 5.76 – 5.64 (m, 1H), 3.09 – 2.85 (m, 2H), 2.00 – 1.92 (m, 2H), 1.81 – 1.64 (m, 3H), 1.62 – 1.51 (m, 1H), 1.50 – 1.38 (m, 1H), 1.18 – 1.13 (m, 1H). Mass (m/z): 270.3 $[M+H]^+$.

Compound 166

N1-(2,3-dihydrobenzofuran-6-yl)cyclohexane-1,4-diamine

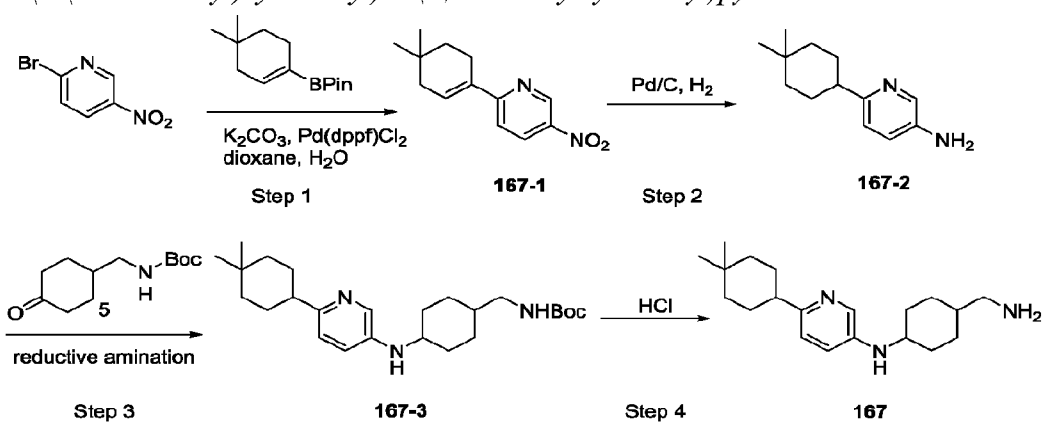


166

The title compound **166** (78.2 mg) was prepared in a total yield of 69.8% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((2,3-dihydrobenzofuran-6-yl)amino)cyclohexyl)carbamate (160 mg, 0.482 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (dd, J = 8.0, 5.6 Hz, 1H), 6.12 – 5.91 (m, 2H), 5.23 (d, J = 7.6 Hz, 1H), 4.37 (td, J = 8.4, 1.2 Hz, 2H), 3.06 – 2.85 (m, 4H), 1.98 – 1.92 (m, 2H), 1.75 – 1.67 (m, 3H), 1.58 – 1.50 (m, 1H), 1.48 – 1.37 (m, 1H), 1.15 – 1.03 (m, 1H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 167

N-(4-(aminomethyl)cyclohexyl)-6-(4,4-dimethylcyclohexyl)pyridin-3-amine



Step 1. Preparation of 2-(4,4-dimethylcyclohex-1-en-1-yl)-5-nitropyridine **(167-1)**

To a solution of 2-bromo-5-nitropyridine (500 mg, 2.46 mmol), 2-(4,4-dimethylcyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (459 mg, 3.69

mmol), K_2CO_3 (1019 mg, 7.39 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was added $Pd(dppf)Cl_2$ (285 mg, 0.25 mmol). The mixture was stirred with refluxing overnight under N_2 atmosphere. After cooling to ambient temperature, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column to provide compound **167-1** (500 mg, 87.3% yield) as a yellow solid. MS (m/z) 233.2 $[M+H]^+$.

Step 2. Preparation of 6-(4,4-dimethylcyclohexyl)pyridin-3-amine **(167-2)**

Pd/C (200 mg , 10%) was added to a solution of 2-(4,4-dimethylcyclohex-1-en-1-yl)-5-nitropyridine (500 mg, 2.15 mmol) in MeOH (10 mL), and the mixture was allowed to react under H_2 for 16 h. Then it was filtered and solvent was removed under vacuum to give compound **167-2** (390 mg, 88.6% yield) as a yellow solid. MS (m/z) 205.1 $[M+H]^+$.

Step 3. Preparation of tert-butyl ((4-((6-(4,4-dimethylcyclohexyl)pyridin-3-yl)amino)cyclohexyl)methyl)carbamate **(167-3)**

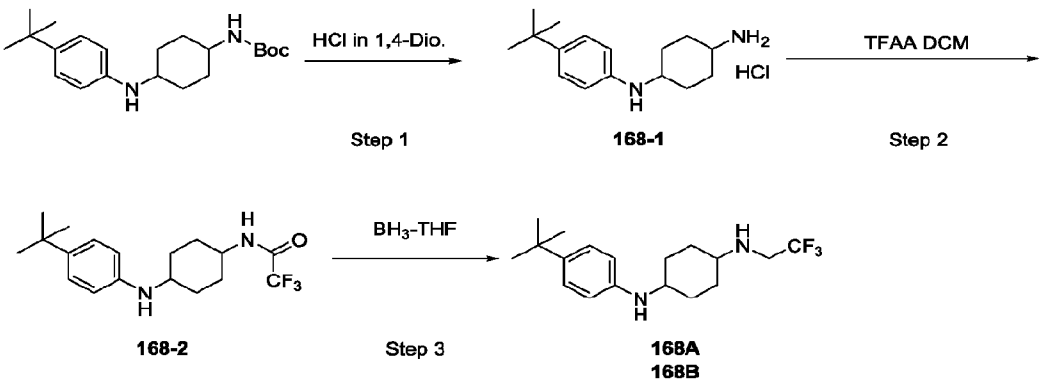
To a solution of compound 4 (200 mg, 0.98 mmol) in MeOH (10 mL) and a drop of AcOH was added compound **167-2** (223 mg, 0.98 mmol). Sodium cyanoborohydride (123 mg, 1.96 mmol) was added and the mixture was stirred at 50 °C for 16 h. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), and extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to afford compound **167-3** (0.4 g, 98.3% yield) as a yellow solid. MS (m/z) 415.9 $[M+H]^+$.

Step 4. Preparation of N-(4-(aminomethyl)cyclohexyl)-6-(4,4-dimethylcyclohexyl)pyridin-3-amine **(167)**

compound **167-3** (200 mg, 0.48 mmol) and HCl in 1,4-dioxane (10 mL, 4N) were placed in a flask stirred at 25 °C for 16 hrs. Excess 1,4-dioxane was distilled under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 2%-20%) to afford **167** (45 mg 29.6%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.86 – 7.60 (m, 3H), 3.35 (s, 1H), 2.85 (dd, J = 15.4, 7.2 Hz, 2H), 2.78 – 2.66 (m, 1H), 2.16 – 2.11 (m, 1H), 1.94 – 1.90 (m, 1H), 1.83 – 1.65 (m, 7H), 1.59 – 1.20 (m, 8H), 1.01 (d, J = 16.8 Hz, 6H). MS (m/z) 316.3 $[M+H]^+$.

Compound 168

N-(4-(tert-butyl)phenyl)-N-(2,2,2-trifluoroethyl)cyclohexane-1,4-diamine



Step 1. Preparation of N-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine hydrochloride **(168-1)**

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tert-Butyl (4-((4-(tert-butyl)phenyl)amino)cyclohexyl)carbamate (1.2 g, 3.5 mmol) and HCl in 1,4-dioxane (20 mL, 4 N) were placed in a flask and stirred at 25 °C for 18 hrs. The solution was concentrated under vacuum to afford 1 g of N-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine hydrochloride (yield: 90%). Mass (m/z): 247.3 $[M+H]^+$.

Step 2. Preparation of N-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)-2,2,2-trifluoroacetamide **(168-2)**

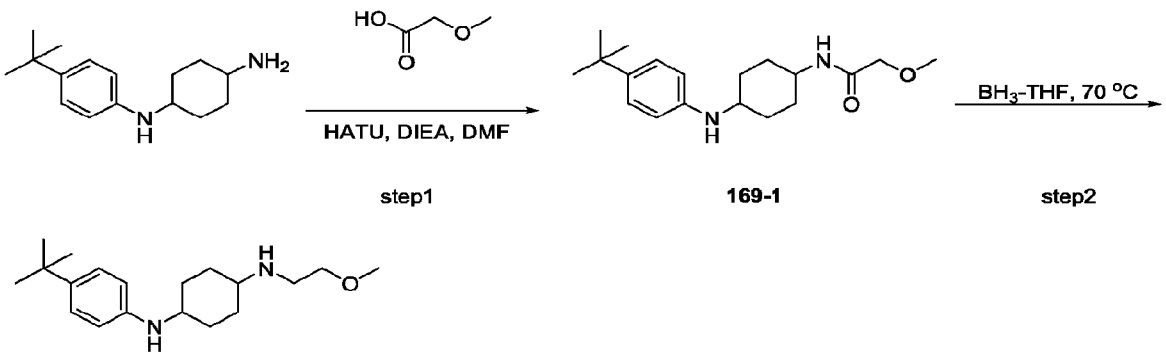
A 100-mL round-bottom flask was charged with **168-1** (400 mg, 1.62 mmol), TFAA (680 mg, 3.2 mg) and DCM (20 mL). The reaction was stirred for 2 hours at 25 °C. The solid were filtered and filtrate was removed under vacuum. The residue was purified through flash column chromatography to provide 200 mg of **168-2** (yield: 36.1%) as an off-white solid. Mass (m/z): 342.8 $[M+H]^+$.

Step 2. Preparation of N-(4-(tert-butyl)phenyl)-N-(2,2,2-trifluoroethyl)cyclohexane-1,4-diamine **(168)**

A solution of **168-2** (200 mg, 0.58 mmol), BH_3-THF (10 ml) in THF (5 ml) was stirred at 70 °C for 18 hours. The solids were filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **168A** (15.4 mg) as a white solid and **168B** (8.3 mg) as a white solid. **168A**: ^1H NMR (400 MHz, CD_3OD) δ 7.15 – 7.11 (m, 2H), 6.62 – 6.58 (m, 2H), 3.45 – 3.37 (m, 1H), 3.20 (q, J = 9.8 Hz, 2H), 2.69 (td, J = 7.4, 3.6 Hz, 1H), 1.76 – 1.68 (m, 2H), 1.68 – 1.60 (m, 4H), 1.59 – 1.50 (m, 2H), 1.23 (s, 9H). Mass (m/z): 329.3 $[M+H]^+$. HPLC: Rt = 4.699 min (Column: XBRIDGE 3.5 um 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, Flow rate: 0.8 mL/min). **168B**: ^1H NMR (400 MHz, CD_3OD) δ 7.13 (d, J = 8.6 Hz, 2H), 6.59 (d, J = 8.6 Hz, 2H), 3.23 – 3.18 (m, 2H), 3.17 (d, J = 3.8 Hz, 1H), 2.52 (dt, J = 9.6, 4.8 Hz, 1H), 2.10 – 1.93 (m, 4H), 1.23 (s, 9H), 1.21 – 1.10 (m, 4H). Mass (m/z): 329.3 $[M+H]^+$. HPLC: Rt = 5.096 min (Column: XBRIDGE 3.5 um 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, Flow rate: 0.8 mL/min).

Compound 169

1-N-(4-(tert-butyl)phenyl)-N4-(2-methoxyethyl)cyclohexane-1,4-diamine (169)



Step 1. Preparation of 1-N-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)-2-methoxy acetamide

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(169-1)

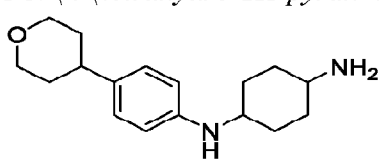
A mixture of 1-N-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine (300 mg, 1.06 mmol), 2-methoxyacetic acid (114 mg, 1.27 mmol), HATU (605 mg, 1.6 mmol), DIEA (685 mg, 5.3 mmol) in DMF (10 mL) was stirred overnight at 25 °C. It was quenched by H_2O (30 mL) and extracted with DCM (3x30 mL). The organic layers were combined, washed with brine NaCl (2x30 mL) and dried with $MgSO_4$, filtered and concentrated. The crude product was applied onto a silica gel column (4 g) eluted with PE:EA (5:1) to give product (100 mg, yield: 90%) as a yellow solid. Mass (m/z): 318.9 $[M+H]^+$.

Step 2. Preparation of 1-N-(4-(tert-butyl)phenyl)-N4-(2-methoxyethyl)cyclohexane-1,4-diamine **(169)**

To a solution of **169-1** (100 mg, 0.31 mmol) in THF (5 mL) was added BH_3-THF (15 mL). Then the mixture was stirred 16 hours at 70 °C. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product (10.8 mg) as a white solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.04 (d, J = 8.4 Hz, 2H), 6.49 (d, J = 8,4 Hz, 2H), 3.49 (t, J = 5.2 Hz, 2H), 3.32 (d, J = 6.6 Hz, 2H), 3.25 (s, 3H), 2.93-2.86 (m, 2H), 1.75-1.45 (m, 8H), 1.16 (d, J = 6.8 Hz, 9H). Mass (m/z): 452.3 $[M+H]^+$.

Compound 170

1-N-(4-(tetrahydro-2H-pyran-4-yl)phenyl)cyclohexane-1,4-diamine

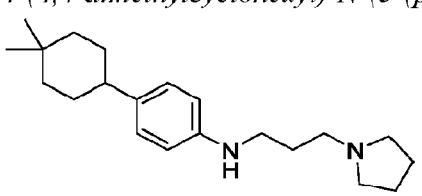


170

The desired product (52.8 mg) as a white solid was prepared from tert-butyl (4-((4-(tetrahydro-2H-pyran-4-yl)phenyl) amino) cyclohexyl) carbamate (300 mg, 0.8 mmol), 1,4-dioxane (5 mL) and HCl/1,4-dioxane (5 mL; 4N) according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.94 (d, J = 8.5 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 5.32 (br, 1H), 3.91 (dd, J = 10.4, 3.1 Hz, 2H), 3.38 (d, J = 3.1 Hz, 2H), 3.00 (br, 1H), 2.52 (br, 1H), 1.76 – 1.52 (m, 12H). Mass (m/z): 275.3 $[M+H]^+$.

Compound 171

4-(4,4-dimethylcyclohexyl)-N-(3-(pyrrolidin-1-yl)propyl)aniline



171

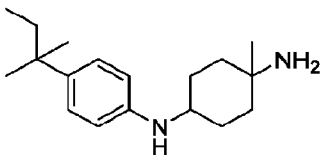
The desired product **171** (45 mg) as a white solid was prepared from N-(4-(4,4-dimethylcyclohexyl)phenyl)-3-(pyrrolidin-1-yl)propanamide (80 mg, 0.24 mmol), THF (1 mL) and BH_3-THF (30 mL) according to the procedure for **169**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.03 (d, 2H), 6.61 (d, 2H), 3.52 (br, 2H), 3.19 (t, 2H), 3.10 (t, 2H), 3.00 (br, 2H), 2.29 – 2.24 (m, 1H), 2.05 – 1.85 (m, 6H), 1.55 – 1.23 (m, 8H), 0.95 (d, 6H). Mass (m/z): 315.3

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$[M+H]^+$.

Compound 172

1-methyl-N4-(4-(tert-pentyl)phenyl)cyclohexane-1,4-diamine

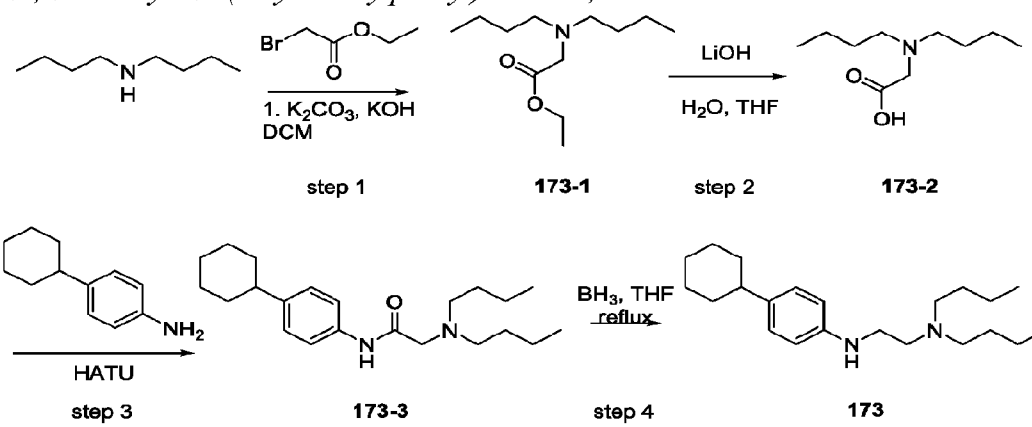


172

The title compound **172** (96.9 mg) was prepared in a total yield of 91.8% as a white solid from tert-butyl (1-methyl-4-((4-(tert-pentyl)phenyl)amino)cyclohexyl)carbamate (144 mg, 0.385 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 36.0 Hz, 3H), 7.02 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 8.4 Hz, 2H), 5.08 (s, 1H), 3.14 (s, 1H), 1.96 (d, J = 14.8 Hz, 2H), 1.81 – 1.61 (m, 4H), 1.52 (q, J = 7.6 Hz, 3H), 1.30 (d, J = 8.0 Hz, 3H), 1.16 (d, J = 1.2 Hz, 6H), 0.61 (t, J = 7.2 Hz, 3H). Mass (m/z): 275.3 $[M+H]^+$.

Compound 173

N1,N1-dibutyl-N2-(4-cyclohexylphenyl)ethane-1,2-diamine



Step 1. Preparation of ethyl dibutylglycinate **(173-1)**

A mixture of dibutylamine (1 g, 7.74 mmol), ethyl 2-bromoacetate (1.55 g, 9.28 mmol), KOH (434 mg, 7.74 mmol), K_2CO_3 (1.07 g, 7.74 mmol) in DCM (40 mL) was stirred overnight at 40°C. After cooling to rt. 40 mL of water was added. The solid was purified by silica gel chromatography. Target product (1.58 g, 95%) was obtained as colorless oil. Mass (m/z): 216.2 $[M+H]^+$.

Step 2. Preparation of dibutylglycine **(173-2)**

A mixture of ethyl dibutylglycinate (1 g, 4.64 mmol), LiOH (334 mg, 14 mmol) in H_2O (10 mL) and THF (10 mL) was stirred overnight at room temperature. The reaction was concentrated under vacuum. The solid (840 mg, 97%) was used in the next step directly. Mass (m/z): 188.2 $[M+H]^+$.

Step 3. Preparation of N-(4-cyclohexylphenyl)-2-(dibutylamino)acetamide **(173-3)**

A mixture of dibutylglycine (840 mg, 4.49 mmol), 4-cyclohexylaniline (943 mg, 5.38 mmol), HATU (2.05 g, 5.38 mmol), DIPEA (870 mg, 6.37 mmol) in DMF (20 mL) was stirred

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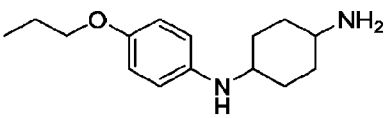
overnight at room temperature. Then 40 mL of water was added. The solid was purified by silica gel chromatography. Target product (1.6 g, 75%) was obtained as a yellow solid. Mass (m/z): 345.2 $[M+H]^+$.

Step 4. Preparation of N1,N1-dibutyl-N2-(4-cyclohexylphenyl)ethane-1,2-diamine **(173)**

N-(4-cyclohexylphenyl)-2-(dibutylamino)acetamide (200 mg, 0.58 mmol) was added to BH_3-THF (20 mL) and the mixture was stirred overnight at 70 °C. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product as a white solid. (20 mg, 10%). ^1H NMR (400 MHz, CD_3OD) δ 7.03 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 3.48 (d, J = 6.0 Hz, 2H), 3.35 (d, J = 5.9 Hz, 2H), 3.22 – 3.13 (m, 4H), 2.44 – 2.33 (m, 1H), 1.86 – 1.72 (m, 4H), 1.72 – 1.61 (m, 4H), 1.49 – 1.33 (m, 8H), 1.33 – 1.26 (m, 2H), 0.98 (t, J = 7.3 Hz, 6H). Mass (m/z): 331.2 $[M+H]^+$.

Compound 174

N1-(4-propoxyphenyl)cyclohexane-1,4-diamine

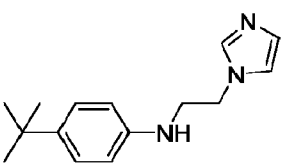


174

The desired product **174** as white solid (82.2 mg, 18.8%) was prepared from tert-butyl (4-((4-propoxyphenyl)amino)cyclohexyl)carbamate (600 mg, 11.73 mmol), 1,4-dioxane (10 mL) and 1,4-dioxane/HCl (10 mL) according to the procedure for **37**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 6.69 (d, 2H), 6.57 (d, 2H), 3.77 (t, 2H), 3.37 (br, 1H), 3.02 (br, 1H), 1.83 – 1.54 (m, 8H), 0.94 (t, 3H). Mass (m/z): 249.3 $[M+H]^+$.

Compound 175

N-(2-(1H-imidazol-1-yl)ethyl)-4-(tert-butyl)aniline

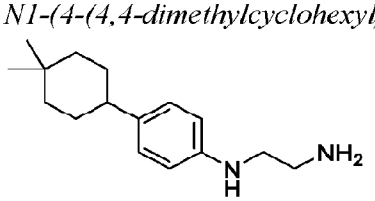


175

The desired product **175** as white solid (34.8 mg, 11.7%) was prepared from N-(4-(tert-butyl)phenyl)-2-(1H-imidazol-1-yl)acetamide (312 mg, 1.21 mmol), THF (1 mL) and BH_3-THF (30 mL) according to the procedure for **169**. ^1H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.11 (d, 2H), 6.54 (d, 2H), 4.33 (br, 2H), 3.48 (br, 2H), 1.21 (s, 9H). Mass (m/z): 244.3 $[M+H]^+$.

Compound 176

N1-(4-(4,4-dimethylcyclohexyl)phenyl)ethane-1,2-diamine



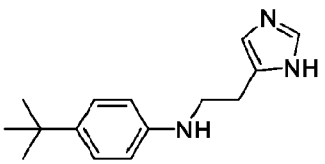
176

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The desired product **176** as a white solid (37.4 mg, 95.3%) was prepared from tert-butyl (2-((4-(4,4-dimethylcyclohexyl)phenyl)amino)ethyl)carbamate (55 mg, 0.16 mmol), 1,4-dioxane (10 mL) and 1,4-dioxane/HCl (10 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.96 (d, 2H), 6.51 (d, 2H), 3.19 (br, 2H), 2.88 (br, 2H), 2.28 – 2.20 (m, 1H), 1.54 – 1.24 (m, 8H), 0.93 (d, 6H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 177

N-(2-(1H-imidazol-5-yl)ethyl)-4-(tert-butyl)aniline

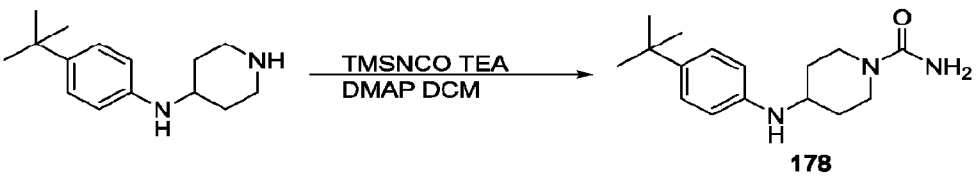


177

The desired product (65.1 mg, 22.9%) as brown oil was prepared from N-(4-(tert-butyl)phenyl)-2-(1H-imidazol-5-yl)acetamide (300 mg, 1.17 mmol), THF (1 mL) and BH_3-THF (30 mL) according to the procedure for **169**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.53 (d, J = 8.6 Hz, 2H), 4.32 (t, J = 5.7 Hz, 2H), 3.47 (t, J = 5.7 Hz, 2H), 1.21 (s, 9H). Mass (m/z): 244.3 $[M+H]^+$.

Compound 178

4-((4-(tert-butyl)phenyl)amino)piperidine-1-carboxamide

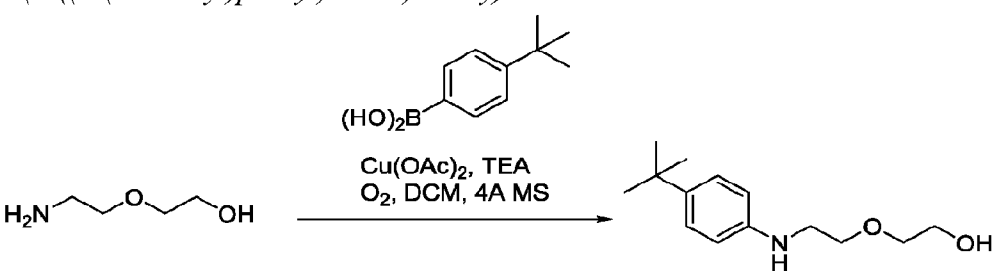


178

A mixture solution of N-(4-(tert-butyl)phenyl)piperidin-4-amine (100 mg, 0.43 mmol), TMSNCO (50 mg, 0.43 mmol), TEA (87 mg, 0.86 mmol) and DMAP (11 mg, 0.086 mmol) in DCM (5 mL) was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **178** (38.2 mg) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.19 – 7.13 (m, 2H), 6.68 – 6.61 (m, 2H), 3.95 (s, 2H), 3.45 (tt, J = 10.2, 4.0 Hz, 1H), 2.97 (d, J = 2.2 Hz, 2H), 2.04 – 1.94 (m, 2H), 1.42 – 1.29 (m, 2H), 1.25 (s, 9H). Mass (m/z): 276.2 $[M+H]^+$.

Compound 179

2-(2-((4-(tert-butyl)phenyl)amino)ethoxy)ethan-1-ol



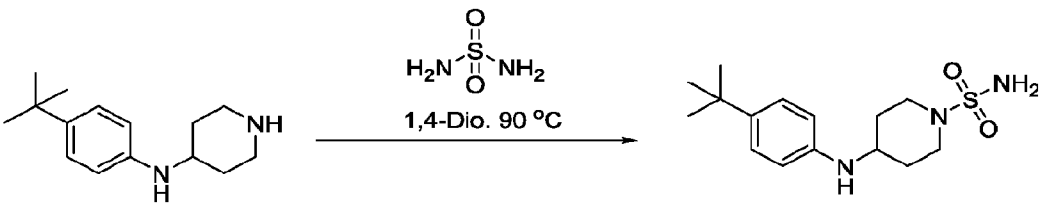
Step 1 **179**

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A 100-mL round-bottom flask was charged with 2-(2-aminoethoxy)ethan-1-ol (400 mg, 3.8 mmol, 1.00 eq), (4-(tert-butyl)phenyl)boronic acid (677 mg, 3.8 mmol, 1.00 eq), $Cu(OAc)_2$ (1382 mg, 7.6 mmol, 2.00 eq) and TEA (1924 mg, 19 mmol, 5.00 eq) and 4Å MS (1 g). The reaction was stirred at R.T. under O_2 atmosphere for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **179** (40.1 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.64 – 7.59 (m, 2H), 7.44 – 7.39 (m, 2H), 3.76 (dd, 3.9 Hz, 2H), 3.71 – 3.67 (m, 2H), 3.64 – 3.60 (m, 2H), 3.58 (d, 2H), 1.34 (d, 9H). Mass (m/z): 238.2 $[M+H]^+$.

Compound 180

4-((4-(tert-butyl)phenyl)amino)piperidine-1-sulfonamide

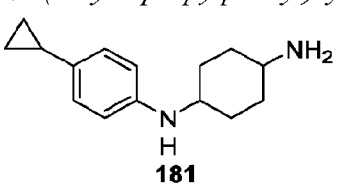


Step 1 **180**

A 10-mL round-bottom flask was charged with N-(4-(tert-butyl)phenyl)piperidin-4-amine (100 mg, 0.43 mmol), 1,4-Dioxane (5 mL) and sulfuric diamide (50 mg, 0.52 mmol). The reaction was stirred for 18 hours at 90 °C. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **180** (21.5 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.19 – 7.14 (m, 2H), 6.63 (d, 2H), 3.60 (d, 2H), 3.37 – 3.32 (m, 1H), 2.78 (td, 2H), 2.08 (d, 2H), 1.55 – 1.45 (m, 2H), 1.25 (s, 9H). Mass (m/z): 311.9 $[M+H]^+$.

Compound 181

N1-(4-cyclopropylphenyl)cyclohexane-1,4-diamine



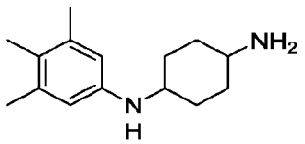
181

The title compound **181** (47 mg, 55.8%) as a white solid was prepared from tert-butyl (4-((4-cyclopropylphenyl) amino)cyclohexyl) carbamate (130 mg) and HCl in 1,4-dioxane (10 mL, 4 N) according to the procedure for **37**. ^1H NMR (400 MHz, CD_3OD) δ 7.24 – 6.98 (m, 4H), 3.15 – 3.07 (m, 2H), 2.20 – 2.00 (m, 4H), 1.97 – 1.81 (m, 1H), 1.58 – 1.35 (m, 4H), 1.02 – 0.88 (m, 2H), 0.71 – 0.56 (m, 2H). MS (m/z): 231.2 $[M+H]^+$.

Compound 182

N1-(3,4,5-trimethylphenyl)cyclohexane-1,4-diamine

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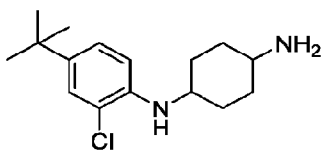
182

Step 2. Preparation of N1-(3,4,5-trimethylphenyl)cyclohexane-1,4-diamine (**182**)

The title compounds **182A** (47.4 mg) as a white solid and **182B** (40.3 mg) as a white solid were prepared from tert-butyl (4-((3,4,5-trimethylphenyl) amino) cyclohexyl) carbamate (110 mg, 0.33 mmol) and HCl in 1,4-dioxane (10 mL, 4 N) according to the procedure for **37**. **182A**: ^{1}H NMR (400 MHz, CD_3OD) δ 6.87 (s, 2H), 3.57 (br, 1H), 3.35 (br, 1H) 2.29 (s, 6H), 2.16 (s, 3H), 1.86 (br, 8H). Mass (m/z): 233.3$[M+H]^+$. HPLC: Rt: 3.206 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **182B**: ^{1}H NMR (400 MHz, CD_3OD) δ 6.93 (s, 2H), 3.56 (s, 1H), 3.28 (s, 1H), 2.20 (s, 6H), 2.11 (s, 3H), 1.49 (br, 8H). Mass (m/z): 233.3 $[M+H]^+$. HPLC: Rt: 3.685 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 183

N1-(4-(tert-butyl)-2-chlorophenyl)cyclohexane-1,4-diamine



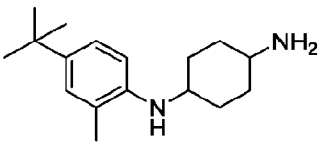
183A
183B

The title compound **183** was prepared from commercial 4-(tert-butyl)-2-chloroaniline (18.3 mg, 0.1 mmol) according to the procedure for compound **24.** The mixture was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-305%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13 min) to afford compound **183A** (Rt = 7.49 min) as a yellow solid and compound **184B** (Rt = 7.26 min) as a yellow solid. **183A** (5.4 mg, 19%): ^{1}H NMR (400 MHz, DMSO-d_6) 8.05 (s, 2H), 7.26 – 7.09 (m, 2H), 6.72 (d, J = 8.8 Hz, 1H), 4.40 (d, J = 7.6 Hz, 1H), 3.59 (s, 1H), 3.25 (s, 1H), 1.82 – 1.62 (m, 8H), 1.21 (s, 9H). Mass (m/z): 281.4$[M+H]^+$. **183B** (18.4 mg, 66%): ^{1}H NMR (400 MHz, DMSO-d_6) 8.06 (s, 2H), 7.28 – 7.11 (m, 2H), 6.74 (d, J = 8.8 Hz, 1H), 4.55 (d, J = 7.6 Hz, 1H), 3.42 (s, 1H), 2.98 (s, 1H), 2.05 – 1.94 (m, 4H), 1.53 – 1.31 (m, 4H), 1.21 (s, 9H). Mass (m/z): 281.4$[M+H]^+$.

Compound 184

N1-(4-(tert-butyl)-2-methylphenyl)cyclohexane-1,4-diamine

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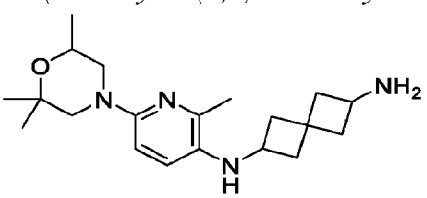


184

The title compound **184** (15.6 mg) was prepared in a total yield of 43% as a yellow solid with 1:2 mixture by ^{1}H NMR from 4-(tert-butyl)-2-methylaniline (16 mg, 0.1 mmol) according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 3H), 7.01 (s, 1H), 6.99 – 6.96 (m, 1H), 6.52 – 6.45 (m, 1H), 3.53 (s, 1 H), 3.20 – 3.05 (m, 0.6 H), 3.02 – 2.84 (m, 0.3H), 2.14 (s, 2H), 2.05 (s, 1H), 2.00 (m, 2H), 1.87 – 1.41 (m, 6H), 1.20 (s, 9H). Mass (m/z): 261.4[M+H]$^+$.

Compound 185

N2-(2-methyl-6-(2,2,6-trimethylmorpholino)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine

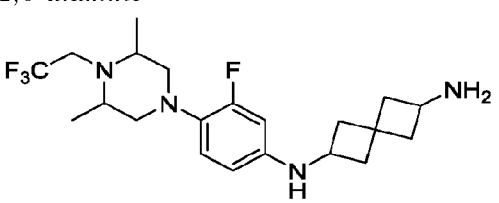


185

The title compound **185** (23.3 mg) was prepared in a total yield of 67.5% as a yellow solid according to the procedure for compound **24**. ^{1}H NM R (400 MHz, DMSO-d_6) δ 6.78 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 8.8 Hz, 1H), 4.02 – 3.80 (m, 2H), 3.77 – 3.63 (m, 2H), 3.53 (m, 1H), 2.43 – 2.31 (m, 2H), 2.27 – 2.14 (m, 5H), 2.10 (m, 1H), 2.01 – 1.87 (m, 2H), 1.22 (s, 3H), 1.16 (s, 3H), 1.07 (d, J = 6.0 Hz, 3H). Mass (m/z): 345.2 [M+H]$^+$

Compound 186

N2-(4-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-3-fluorophenyl)spiro-[3.3]heptane-2,6-diamine



186A

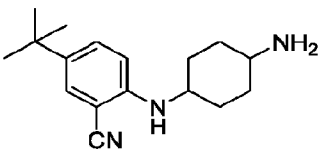
186B

The title compounds **186A** (5.4 mg) as a white solid and **186B** (5.8 mg) as a white solid were prepared according to the procedure for **24**. **186A**: ^{1}HNMR (400 MHz, DMSO-d_6) δ 6.81 (t, J = 8.8 Hz, 1H), 6.31 – 6.26 (m, 2H), 3.76 – 3.59 (m, 2H), 3.34 (q, J = 9.8 Hz, 2H), 3.03 (dd, J = 8.6, 2.2 Hz, 2H), 2.93 (d, J = 6.2 Hz, 2H), 2.54 –2.30 (m, 6H), 2.20 – 2.09 (m, 2H), 1.94 – 1.86 (m, 2H), 1.11 (d, J = 6.2 Hz, 6H). Mass (m/z): 415.3 [M+H]$^+$. HPLC: Rt: 3.919 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA), ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **186B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 (d, J = 8.6 Hz, 1H), 6.32 – 6.21 (m, 2H), 3.68 (d, J = 32.8

Hz, 2H), 3.34 (d, J = 10.0 Hz, 2H), 3.09 –2.94 (m, 4H), 2.61 – 2.48 (m, 2H), 2.40 (t, J = 10.8 Hz, 4H), 2.14 (s, 2H), 1.96 – 1.78 (m, 2H), 1.11 (d, J = 6.2 Hz, 6H). Mass (m/z): 415.3 $[M+H]^+$. HPLC: Rt: 3.921 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA), ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 187

2-((4-aminocyclohexyl)amino)-5-(tert-butyl)benzonitrile

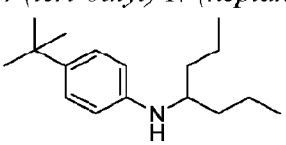


187

The title compound **187** (21.9 mg) was prepared in a total yield of 78 % as a yellow solid with 1:2 mixture by ^{1}H NMR from 2-amino-5-(tert-butyl)benzonitrile (17.4 mg, 0.1 mmol) according to the procedure for compound **88**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 3H), 7.28 – 7.11 (m, 2H), 6.74 (m, 1H), 3.42 (s, 1H), 3.21 – 3.04 (m, 0.6 H), 3.00 – 2.88 (m, 0.3H), 2.98 (m, 1H), 2.10 – 1.93 (m, 4H), 1.56 – 1.33 (m, 4H), 1.22 (s, 9H). Mass (m/z): 272.3$[M+H]^+$

Compound 188

4-(tert-butyl)-N-(heptan-4-yl)aniline

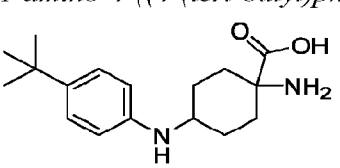


188

The title compound **188** (16.9 mg) was prepared in a total yield of 68 % as a yellow oil from 4-(tert-butyl)aniline (14.9 mg, 0.1 mmol) according to the procedure for compound **4.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 6.54 (d, J = 8.4 Hz, 2H), 3.11 (m, 1H), 1.54 – 1.31 (m, 8H), 1.21 (s, 9H), 0.88 (m, 6H). Mass (m/z): 248.3$[M+H]^+$.

Compound 189

1-amino-4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxylic acid



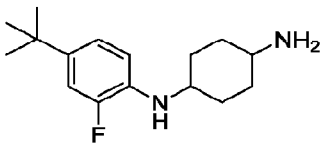
189

The title compound **189** (9.1 mg) was prepared in a total yield of 31% as a white solid with 1:1 mixture by ^{1}H NMR from 4-(tert-butyl)aniline (14.9 mg, 0.1 mmol) according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (s, 3H), 7.07 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 2H), 3.14 (m, 1H), 2.14 – 1.81 (m, 3H), 1.80 – 1.60 (m, 3H), 1.47 – 1.29 (m, 2H), 1.20 (s, 9H). Mass (m/z): 291.3$[M+H]^+$.

Compound 190

N1-(4-(tert-butyl)-2-fluorophenyl)cyclohexane-1,4-diamine

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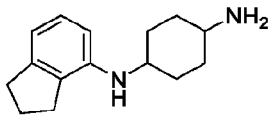


190

The title compound **190** (26.4 mg) was prepared in a total yield of 67 % as a white solid with 1:2 mixture by ^{1}H NMR from 4-(tert-butyl)-2-fluoroaniline (25.1 mg, 0.15 mmol) according to the procedure for compound **88**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 2H), 7.06 – 6.96 (m, 2H), 6.68 (m, 1H), 4.81 (s, 0.6H), 4.53 (s, 0.3H), 3.13 (m, 1.3H), 2.97 – 2.85 (m, 0.7H), 1.98 (m, 3H), 1.87 – 1.56 (m, 3H), 1.47 – 1.23 (m, 2H), 1.19 (s, 9H). Mass (m/z): 265.2[M+H]$^+$.

Compound 191

N1-(2,3-dihydro-1H-inden-4-yl)cyclohexane-1,4-diamine

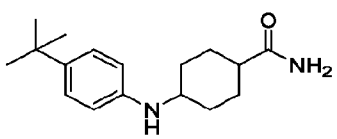


191A
191B

The title compound **191** was prepared from tert-butyl (4-((2,3-dihydro-1H-inden-4-yl)amino)cyclohexyl)carbamate (217 mg, 0.658 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**, which was purified by prep HPLC (solvent system (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 15%-25%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13 min) to give the desired products **191A** (Rt = 8.0 min) as a white solid (47.4 mg, 31.4%) and **191B** (Rt = 9.2 min) as a white solid (38.2 mg, 25.3%). **191A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.96 (s, 1H), 6.56 (d, J = 44.0 Hz, 2H), 3.19 (s, 1H), 2.95 (s, 1H), 2.77 (t, J = 7.6 Hz, 2H), 2.66 (s, 2H), 1.95 (td, J = 15.2, 13.2, 5.6 Hz, 6H), 1.45 – 1.18 (m, 5H). Mass (m/z): 231.3 [M+H]$^+$. **191B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.94 (t, J = 8.8 Hz, 1H), 6.54 (d, J = 57.2 Hz, 2H), 3.50 (d, J = 8.8 Hz, 1H), 3.13 (s, 1H), 2.88 – 2.62 (m, 4H), 1.96 (p, J = 7.2 Hz, 2H), 1.83 – 1.72 (m, 2H), 1.65 (q, J = 14.4, 11.6 Hz, 6H). Mass (m/z): 231.3 [M+H]$^+$.

Compound 192

4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxamide



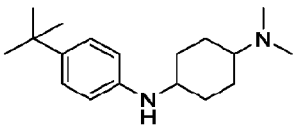
192

The title compound **192** (100.3 mg) was prepared in a total yield of 54.5% as a white solid with 1:2 mixture by ^{1}H NMR with from 4-(tert-butyl)aniline (100 mg, 0.671 mmol), 4-oxocyclohexane-1-carboxamide (142 mg, 1.006 mmol), AcOH (0.1 mL), $NaBH(OAc)_3$ (286 mg, 1.344 mmol) and DCE (10 mL) according to the procedure for **1-1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.18 (d, J = 12.0 Hz, 1H), 7.03 (dd, J = 8.8, 2.8 Hz, 2H), 6.66 (d, J = 8.4 Hz, 1H), 6.49 (t, J = 9.6 Hz, 2H), 3.36 (s, 1H), 2.17 – 1.99 (m, 1H), 1.94 (dd, J = 12.0, 4.0 Hz, 1H), 1.75 (ddd, J = 14.8, 11.6, 5.2 Hz, 2H), 1.63 (d, J = 13.2 Hz, 1H), 1.56 – 1.36 (m, 3H), 1.23 (s, 3H),

1.16 (s, 9H), 1.07 (t, J = 12.0 Hz, 1H). Mass (m/z): 275.3 $[M+H]^+$.

Compound 193

N1-(4-(tert-butyl)phenyl)-N4,N4-dimethylcyclohexane-1,4-diamine

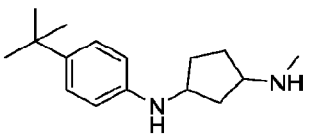


193A
193B

The title compound **193** was prepared from 4-(tert-butyl)aniline (50 mg, 0.336 mmol), 4-(dimethylamino)cyclohexan-1-one (71 mg, 0.503 mmol), AcOH (0.1 mL), $NaBH(OAc)_3$ (143 mg, 0.672 mmol) and DCE (10 mL) according to the procedure for **1-1**, which was purified by prep HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 15%-25%-75%-85%-11%, 0 min-10 min-10.5 min-11.5 min-13 min), to give the desired product **193A** (Rt = 7.5 min) as a white solid (28.7 mg, 31.5%) and **193B** (Rt = 8.8 min) as a white solid (20.2 mg, 21.7%). **193A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (d, J = 8.0 Hz, 2H), 6.85 (s, 2H), 3.33 – 3.08 (m, 2H), 2.73 (d, J = 4.8 Hz, 6H), 2.04 (q, J = 10.8, 8.8 Hz, 4H), 1.51 (dd, J = 13.6, 10.4 Hz, 2H), 1.31 (dd, J = 18.8, 7.6 Hz, 2H), 1.24 (s, 9H). Mass (m/z): 275.3 $[M+H]^+$. **193B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (d, J = 8.0 Hz, 2H), 7.01 (s, 2H), 3.31 (d, J = 22.8 Hz, 1H), 3.24 – 3.12 (m, 1H), 2.73 (d, J = 4.8 Hz, 6H), 2.04 (d, J = 11.2 Hz, 4H), 1.61 – 1.46 (m, 2H), 1.42 – 1.31 (m, 2H), 1.26 (s, 9H). Mass (m/z): 275.3 $[M+H]^+$.

Compound 194

N1-(4-(tert-butyl)phenyl)-N3-methylcyclopentane-1,3-diamine

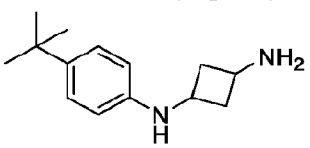


194

The title compound **194** (8.0 mg) was prepared in a total yield of 13.0% as a brown solid from tert-butyl (3-((4-(tert-butyl)phenyl)amino)cyclopentyl)carbamate (83 mg, 0.25 mmol), $LiAlH_4$ (37 mg,1.00 mmol), and THF (5 mL) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 – 7.04 (m, 2H), 6.51 – 6.46 (m, 2H), 3.90 (s, 1H), 3.46 (q, J = 7.2 Hz, 1H), 2.43 (s, 3H), 2.15 – 2.03 (m, 3H), 1.88 – 1.66 (m, 2H), 1.52 – 1.42 (m, 1H), 1.19 (s, 9H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 195

N1-(4-(tert-butyl)phenyl)cyclobutane-1,3-diamine



195

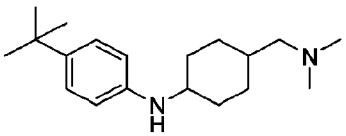
The title compound **195** (12.3 mg) was prepared in a total yield of 15.3% as a yellow oil from tert-butyl (3-((4-(tert-butyl)phenyl)amino)cyclobutyl)carbamate (110 mg, 0.346 mmol), $LiAlH_4$ (51 mg,1.384 mmol) and THF (5 mL) according to the procedure for **23**. ^{1}H NMR (400

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MHz, DMSO-d_6) δ 6.20 (dd, J = 8.8, 2.8 Hz, 2H), 5.60 – 5.50 (m, 2H), 3.21 (q, J = 7.2 Hz, 1H), 2.81 – 2.67 (m, 1H), 1.78 (dtd, J = 9.6, 7.2, 2.8 Hz, 1H), 1.67 (dq, J = 6.8, 2.4 Hz, 1H), 1.63 (h, J = 2.0 Hz, 2H), 1.53 (d, J = 7.8 Hz, 3H), 1.33 – 1.12 (m, 2H), 0.31 (s, 9H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 196

4-(tert-butyl)-N-(4-((dimethylamino)methyl)cyclohexyl)aniline

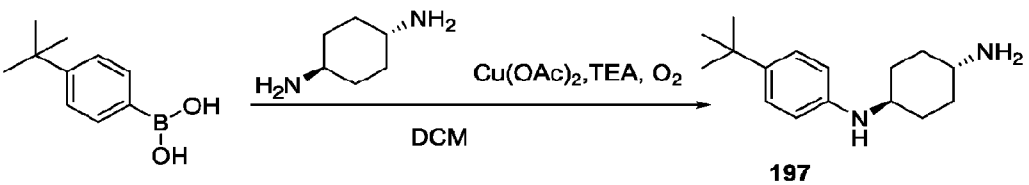


196

The title compound **196** (62.2 mg) was prepared in a total yield of 43.5% as a brown oil from 4-((4-(tert-butyl)phenyl)amino)-N,N-dimethylcyclohexane-1-carboxamide (150 mg, 0.497 mmol), $LiAlH_4$ (74 mg,1.987 mmol) and THF (10 mL) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.07 – 7.01 (m, 2H), 6.55 – 6.44 (m, 2H), 5.19 (s, 1H), 3.45 – 3.33 (m, 2H), 3.05 (s, 1H), 2.61 (d, J = 27.2 Hz, 2H), 2.48 (s, 6H), 1.96 (dd, J = 13.2, 3.6 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.64 – 1.49 (m, 3H), 1.19 (s, 9H). Mass (m/z): 289.3 $[M+H]^+$.

Compound 197

(1r,4r)-N1-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine

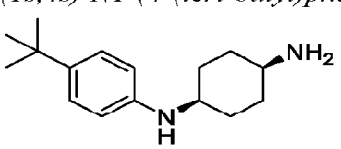


197

A suspension of 4-(tert-butyl)aniline (178.1 mg, 1.0 mmol), $Cu(OAc)_2$ (185.4 mg, 1.5 mmol), TEA (0.28 mL, 2.0 mmol) and powdered 4 Å MS (0.75 g) in CH_2Cl_2 (10.0 mL) was stirred for 5 min at room temperature. To this mixture was added (1r,4r)-cyclohexane-1,4-diamine (22.2 mg, 0.2 mmol). The reaction mixture stirred at room temperature under O_2 for 24 h. The reaction mixture was then filtered through a plug of Celite, the resulting solution was extracted with 3x10 mL of ethyl acetate. The organic layers were combined, washed with water (30 mL), dried and concentrated under vacuum. The residue was purified by prep-TLC (MeOH/DCM = 1:5) to afford the desired product as a white solid. (70.4 mg, 28.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 3.22 (m, 1H), 2.99 (m, 1H), 2.04 – 1.92 (m, 4H), 1.45 – 1.27 (m, 4H), 1.23 (s, 9H). Mass (m/z): 247.2 $[M+H]^+$.

Compound 198

(1s,4s)-N1-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine



198

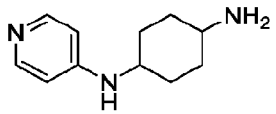
The title compound **198** (76.1 mg) was prepared in a total yield of 30.8% as a white solid from 4-(tert-butyl)aniline (178.1 mg, 1.0 mmol), (1s,4s)-cyclohexane-1,4-diamine (171 mg, 1.5

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mmol) according to the procedure for compound **197**. ^{1}H NMR (400 MHz, DMSO-d_6) δ7.19 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 3.43 (m, 1H), 3.15 (m, 1H), 1.86 – 1.54 (m, 8H), 1.22 (s, 9H). Mass (m/z): 247.2 $[M+H]^+$.

Compound 199

N1-(pyridin-4-yl)cyclohexane-1,4-diamine

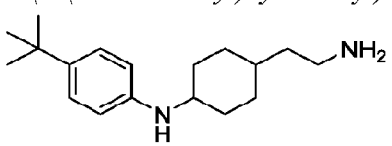


199

The title compound **199** (6.1 mg) was prepared in a yield of 1.97% as a white powder with 1:1 mixture by ^{1}H NMR from pyridin-4-amine (100 mg, 1.06 mmol), tert-butyl (4-oxocyclohexyl)carbamate (339 mg, 1.59 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 – 8.08 (m, 2H), 8.03 (s, 3H), 6.83 – 6.71 (m, 2H), 3.76 (s, 1H), 2.97 (s, 1H), 2.26 (q, J = 2.6, 2.0 Hz, 1H), 2.23 (t, J = 2.7 Hz, 1H), 2.14 (dh, J = 12.9, 3.3 Hz, 2H), 1.74 (ddd, J = 12.7, 11.0, 4.5 Hz, 2H), 1.50 – 1.37 (m, 2H). Mass (m/z): 192.4 $[M+H]^+$.

Compound 200

N-(4-(2-aminoethyl)cyclohexyl)-4-(tert-butyl)aniline



200A

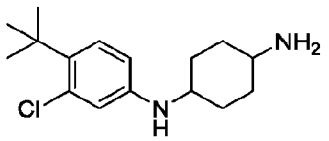
200B

The title compound **200A** (Rt = 7.31 min; 53.2 mg) was prepared in a three-step overall yield of 9.8% as a white powder and compound **200B** (Rt = 8.47 min; 50.2 mg) was prepared in a three-step overall yield of 9.1% as a white powder from 4-(tert-butyl)aniline (300 mg, 2.01 mmol), ethyl 2-(4-oxocyclohexyl)acetate (555 mg, 3.02 mmol) according to the procedure for **84** which were prepared by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-33%-95%-95%-5%, 0 min-10.0 min-10.5 min-11.5 min-13.0 min). **200A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (s, 3H), 7.01 – 7.32(br, 2H), 6.41 – 6.82 (br, 2H), 3.46 (s, 1H), 2.82 (s, 2H), 1.61 (s, 4H), 1.49 (d, J = 10.8 Hz, 7H), 1.23 (s, 9H). Mass (m/z): 275.6 $[M+H]^+$. **200B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (s, 3H), 6.94 – 7.38(br, 2H), 6.43 – 6.72(br, 2H), 2.78 (s, 2H), 1.88 – 1.97(m, 2H), 1.73 (d, J = 12.4 Hz, 2H), 1.46 – 1.36 (m, 2H), 1.36 – 1.23(br, 2H), 1.22 (s, 9H), 0.98 (d, J = 12.8 Hz, 2H). Mass (m/z): 275.6 $[M+H]^+$.

Compound 201

N1-(4-(tert-butyl)-3-chlorophenyl)cyclohexane-1,4-diamine

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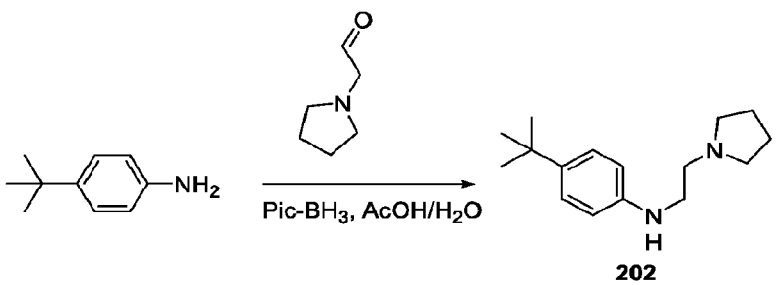


201

The title compound **201** (68.1 mg) was prepared in a yield of 44.54% as a white powder with 5:4 mixture by 1H NMR from 4-(tert-butyl)-3-chloroaniline (100 mg, 0.54 mmol), tert-butyl (4-oxocyclohexyl)carbamate (174 mg, 0.82 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 2H), 7.13 (dd, J = 8.7, 5.7 Hz, 1H), 6.61 (dd, J = 20.6, 2.5 Hz, 1H), 6.48 (ddd, J = 11.5, 8.7, 2.6 Hz, 1H), 5.64 (dd, J = 15.8, 6.9 Hz, 1H), 3.08 (q, J = 6.9 Hz, 1H), 3.01 – 2.89 (m, 1H), 2.04 – 1.93 (m, 2H), 1.80 – 1.69 (m, 3H), 1.61 (d, J = 8.6 Hz, 1H), 1.54 – 1.41 (m, 1H), 1.36 (d, J = 1.5 Hz, 9H), 1.21 – 1.10 (m, 1H). Mass (m/z): 281.5 $[M+H]^+$.

Compound 202

2-(pyrrolidin-1-yl)acetaldehyde--4-(tert-butyl)-N-(2-(pyrrolidin-1-yl)ethyl)aniline--4-(tert-butyl)aniline



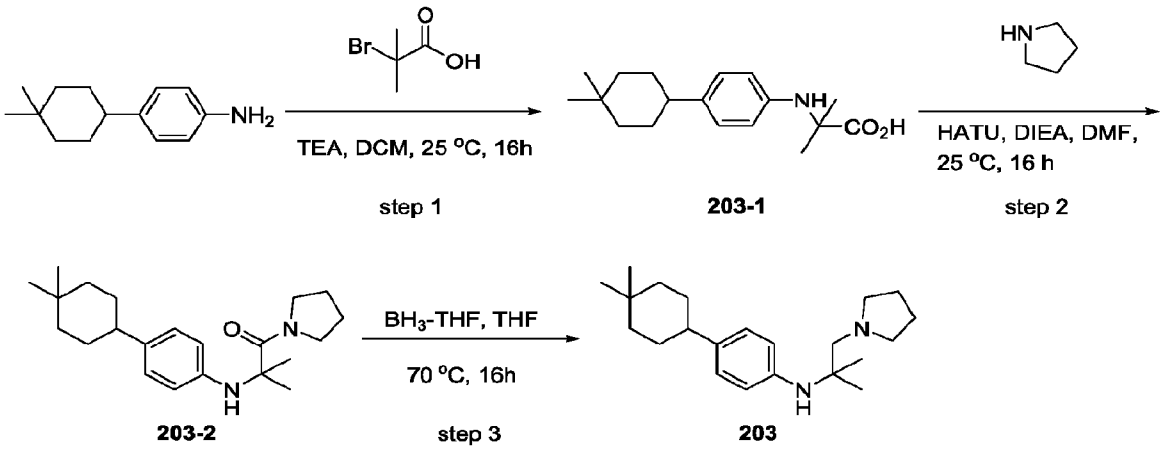
202

The compound **202** (32 mg, 19%) as a yellow solid was prepared from 4-(tert-butyl)aniline (100mg, 0.67 mmol), AcOH/H_2O (10:1;11 mL), 2-(pyrrolidin-1-yl)acetaldehyde (76 mg, 0.67 mmol) and Pic-BH_3 (108 mg, 1.0 mmol) according to the procedure for **90**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.20 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 3.47 (t, J = 6.0 Hz, 2H), 3.37 (t, J = 6.0 Hz, 2H), 3.32 (s, 2H), 3.28 (dt, J = 3.2, 1.6 Hz, 2H), 2.06 (br, 4H), 1.26 – 1.21 (m, 10H). Mass (m/z): 274.2$[M+H]^+$.

Compound 203

1-N-(4-(tert-butyl)phenyl)-N4-(2-methoxyethyl)cyclohexane-1,4-diamine

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Step 1. 2-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-2-methylpropanoic acid **(203-1)**

A mixture of 4-(4,4-dimethylcyclohexyl)aniline (100 mg, 0.49 mmol), 2-methoxy- acetic acid (123 mg, 0.73 mmol), TEA (100 mg, 0.98 mmol) in DCM (5 mL) was stirred overnight at 25 °C. It was quenched by H_2O (30 mL) and extracted with DCM (3x30 mL). The organic layers were combined, washed with brine NaCl (2x30 mL) and dried with $MgSO_4$, filtered and concentrated to afford target product as yellow oil. (200 mg, yield: 80%). Mass (m/z): 289.9 $[M+H]^+$.

Step 2. 2-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-2-methyl-1-(pyrrolidin-1-yl) propan-1-one **(203-2)**

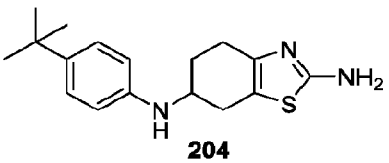
To a solution of **203-1** (100 mg, 0.34 mmol), pyrrolidine (29.49 mg, 0.41 mmol) in DMF (5 mL) was added HATU (197 mg, 0.52 mmol) and DIEA (134 mg, 1.03 mmol). Then the mixture was stirred overnight at 25 °C. It was quenched by H_2O (30 mL) and extracted with EA (3x30 mL). The organic layers were combined, washed with brine NaCl (2x30 mL) and dried with $MgSO_4$, filtered and concentrated. The crude product was applied onto a silica gel column (4 g) eluted with PE:EA (10:1) to give product (40 mg, yield: 27%). Mass (m/z): 342.9 $[M+H]^+$.

Step 3. Preparation of 4-(4,4-dimethylcyclohexyl)-N-(2-methyl-1-(pyrrolidin-1-yl)propan-2-yl)aniline **(203)**

To a solution of **203-2** (50 mg, 0.15 mmol), 2-(4-methylpiperazin-1-yl)acetic acid (66 mg, 0.42 mmol) in THF (5 mL) was added BH_3-THF (10 mL). Then the mixture was stirred overnight at rt. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product (15.5 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.09 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 3.67 (br, 2H), 3.49 (br, 2H), 3.30 (br, 2H), 2.38-2.30 (m, 1H), 2.07 (br, 4H), 1.65 – 1.57 (m, 4H), 1.49 (d, J = 11.2 Hz, 2H), 1.39 – 1.31 (m, 8H), 0.97 (d, J = 15.8 Hz, 6H). Mass (m/z): 329.0 $[M+H]^+$.

Compound 204

4- N-(4-(tert-butyl)phenyl)-4,5,6,7-tetrahydrobenzo[d]thiazole-2,6-diamine

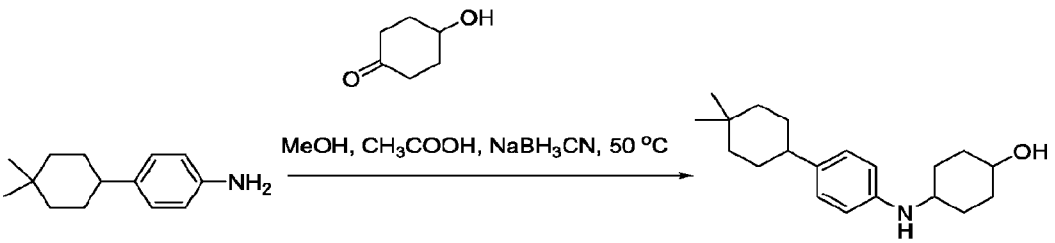


204

The title compound **204** (31.6 mg) as a white solid was prepared from 4-(tert-butyl)aniline (90 mg, 0.6 mmol), 2-amino-4,7-dihydrobenzo[d]thiazol-6(5H)-one (101 mg, 0.6 mmol), Pic-BH_3 (98 mg, 0.9 mmol), H_2O (9 mL) and HOAc (1 mL) according to the procedure for **90**. ^1H NMR (400 MHz, CD_3OD) δ 7.20 – 7.14 (m, 2H), 6.69 – 6.64 (m, 2H), 3.77 (dddd, J = 10.6, 8.0, 5.0, 2.8 Hz, 1H), 2.92 (dd, J = 15.8, 4.4 Hz, 1H), 2.65 – 2.55 (m, 2H), 2.46 – 2.39 (m, 1H), 2.18 – 2.10 (m, 1H), 1.82 – 1.72 (m, 1H), 1.26 (s, 9H). Mass (m/z): 302.2 $[M+H]^+$.

Compound 205

4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexan-1-ol



205A

205B

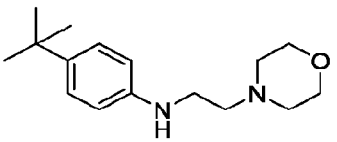
A mixture of 4-(4,4-dimethylcyclohexyl)aniline (80 mg, 0.39 mmol), 4-hydroxycyclohexan-1-one (53.9 mg, 0.47 mmol) and $NaBH_3CN$ (49.5 mg, 0.79 mmol) in MeOH (10 mL) and CH_3COOH (1 drop) was stirred overnight at 50 °C. After cooling, excess MeOH was distilled under vacuum and the residual oil was distilled under vacuum. Then the reaction solution was extracted three times with ethyl acetate (20 mL) and water (20 mL). Then solvent was removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 32%-37%) to afford the desired products **205A**: (30.3 mg, 24.6%) as a white solid and **205B** (38.1 mg, 30.9%) as a white solid. **205A**: ^1H NMR (400 MHz, DMSO-d_6) δ 6.93 (d, 2H), 6.50 (d, 2H), 4.54 (br, 1H), 3.39 (br, 1H), 3.08 (br, 1H), 2.26 – 2.16 (m, 1H), 1.86 (dd, 4H), 1.56 – 1.46 (m, 4H), 1.42 (d, 2H), 1.31 – 1.20 (m, 4H), 1.18 – 1.07 (m, 2H), 0.93 (d, 6H). Mass (m/z): 301.9 $[M+H]^+$. HPLC: Rt: 5.674 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

205B: ^1H NMR (400 MHz, DMSO-d_6) δ 6.90 (d, 2H), 6.49 (d, 2H), 5.16 (br, 1H), 4.37 (br, 1H), 3.68 (br, 1H), 3.18 (br, 1H), 2.20 (br, 1H), 1.58 – 1.10 (m, 14H), 0.93 (d, 6H). Mass (m/z): 301.9 $[M+H]^+$. HPLC: Rt: 5.919 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 206

U4-(tert-butyl)-N-(2-morpholinoethyl)aniline

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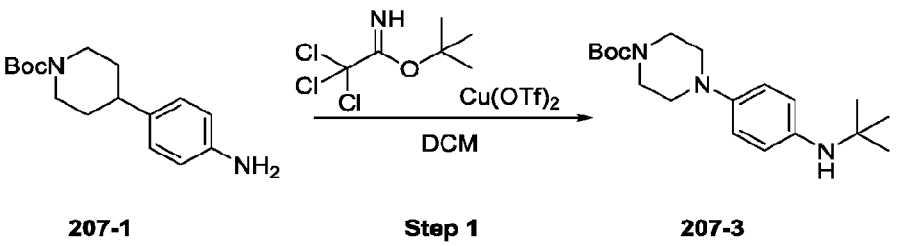
206

The desired product **206** (10.1 mg, 7.1%) as a white oil was prepared from 4-tert-butylaniline (80 mg, 0.54 mmol), 2-morpholinoacetaldehyde (83.1 mg, 0.64 mmol), borane-2-picoline complex (86.0 mg, 0.80 mmol), CH_3COOH (1 mL) and H_2O (9 mL) according to the procedure for **90**. ^1H NMR (400 MHz, CD_3OD) δ 7.19 – 7.14 (m, 2H), 6.64 – 6.57 (m, 2H), 3.73 – 3.67 (m, 4H), 3.21 (t, J = 6.6 Hz, 2H), 2.59 (t, J = 6.6 Hz, 2H), 2.50 (m, 4H), 1.25 (s, 9H). Mass (m/z): 263.0 $[M+H]^+$.

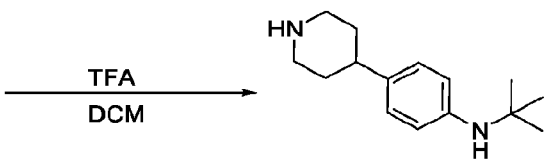
Compound 207

N-(tert-butyl)-4-(piperidin-4-yl)aniline

207-2



207-1 **Step 1** **207-3**



Step 2 **207**

Step 1. Preparation of tert-butyl 4-(4-(tert-butylamino)phenyl)piperazine-1-carboxylate (**207-3**)

The title compound **207-3** (33.0 mg) was prepared in a total yield of 10.0% as a white solid from tert-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (276mg, 1.0 mmol), tert-butyl 2,2,2-trichloroacetimidate (545 mg, 2.5 mmol) and $Cu(OTf)_2$ (18.1 mg, 50 umol) according to the procedure for **11**. Mass (m/z): 333.3 $[M+H]^+$.

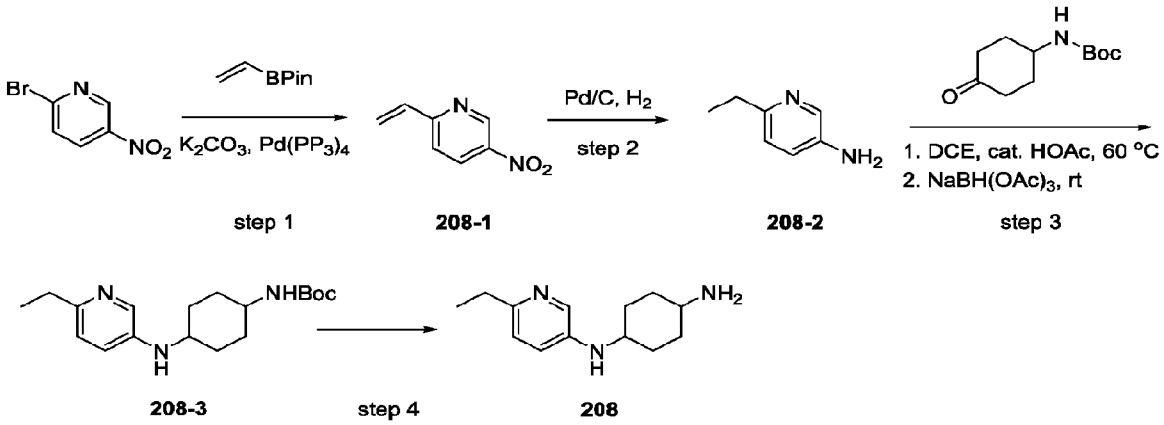
Step 2. Preparation of N-(tert-butyl)-4-(piperidin-4-yl)aniline (**207**)

The title compound **207** (6.8 mg) was prepared in a total yield of 30.6% as a yellow solid from tert-butyl 4-(4-(tert-butylamino)phenyl)piperazine-1-carboxylate (33 mg, 0.1 mmol) and TFA (1.0 mL) according to the procedure for **24**. ^1H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H), 8.48 (d, J = 83.7 Hz, 1H), 7.35 (s, 4H), 3.36 (d, J = 12.5 Hz, 2H), 3.04 – 2.79 (m, 3H), 1.92 (d, J = 13.7 Hz, 2H), 1.73 (qd, J = 13.0, 4.0 Hz, 2H), 1.25 (s, 9H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 208

N1-(6-ethylpyridin-3-yl)cyclohexane-1,4-diamine

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Step 1. Preparation of 5-nitro-2-vinylpyridine **(208-1)**

To a solution of 2-bromo-5-nitropyridine (500 mg, 2.46 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (569 mg, 3.69 mmol), K_2CO_3 (1019 mg, 7.39 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was added $Pd(PPh_3)_4$ (285 mg, 0.24 mmol). The mixture was stirred with refluxing overnight under N_2 atmosphere. After cooling to ambient temperature, concentrated under reduced pressure. The residue was purified by silica gel column to provide compound **208-1** (370 mg, 100% yield) as a yellow solid. MS (m/z): 150.9 $[M+H]^+$.

Step 2. Preparation of 6-ethylpyridin-3-amine **(208-2)**

Pd/C (35 mg, 10%) was added to a solution of 2-(4,4-dimethylcyclohex-1-en-1-yl)-5-nitropyridine (350 mg, 2.33 mmol) in MeOH (10 mL), and the mixture was allowed to react under H_2 for 16h. Then the reaction was filtered and solvent was removed under vacuum to give compound **208-2** (260 mg, 91.2% yield) as a yellow solid. MS (m/z): 123.0 $[M+H]^+$.

Step 3. Preparation of tert-butyl (4-((6-ethylpyridin-3-yl)amino)cyclohexyl)carbamate **(208-3)**

To a solution of compound **208-2** (260 mg, 2.13 mmol) in MeOH (10 mL) and a drop of AcOH was added tert-butyl (4-oxocyclohexyl)carbamate (501 mg, 2.34 mmol). Then the mixture was added $NaBH_4$ (160 mg, 4.26mmol) and the mixture was stirred at 25 °C for 16 h. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to afford to give compound **208-3** (0.4 g, 58.8% yield) as a yellow solid. MS (m/z): 319.9 $[M+H]^+$.

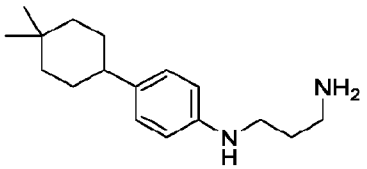
Step 4. Preparation of N1-(6-ethylpyridin-3-yl)cyclohexane-1,4-diamine **(208)**

Compound **208-3** (200 mg, 0.63 mmol) and HCl in 1,4-dioxane (10 mL, 4N) were placed in a flask stirred at 25 °C for 16 hrs. Excess 1,4-dioxane was distilled under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 20%-40%) to afford **208** (7.7 mg 5.61%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 2.5 Hz, 1H), 7.83 (s, 2H), 7.53 (s, 2H), 6.58 (s, 1H), 3.30 – 3.26 (m, 1H), 3.04 (s, 1H), 2.77 (dd, J = 15.2, 7.3 Hz, 2H), 2.52 (d, J = 1.9 Hz, 2H), 2.10 – 1.86 (m, 4H), 1.44 (d, J = 11.8 Hz, 2H), 1.21 (t, J = 7.6 Hz, 3H). MS (m/z) 220.2 $[M-H]^+$.

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Compound 209

1-N-(4-(4,4-dimethylcyclohexyl)phenyl)propane-1,3-diamine

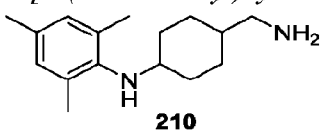


209

The title compound **209** (19.8 mg) as a white solid was prepared from tert-butyl (3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)propyl)carbamate (50 mg, 0.14 mmol), 1,4-dioxane (5 mL) and HCl/1,4-dioxane (5 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.17 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 3.06 – 3.02 (m, 2H), 2.41 – 2.34 (m, 1H), 2.01 – 1.96 (m, 2H), 1.65 – 1.35 (m, 10H), 0.99 (s, 3H), 0.95 (s, 3H). Mass (m/z): 260.9 $[M+H]^+$.

Compound 210

N-[4-(aminomethyl)cyclohexyl]-2,4,6-trimethylaniline

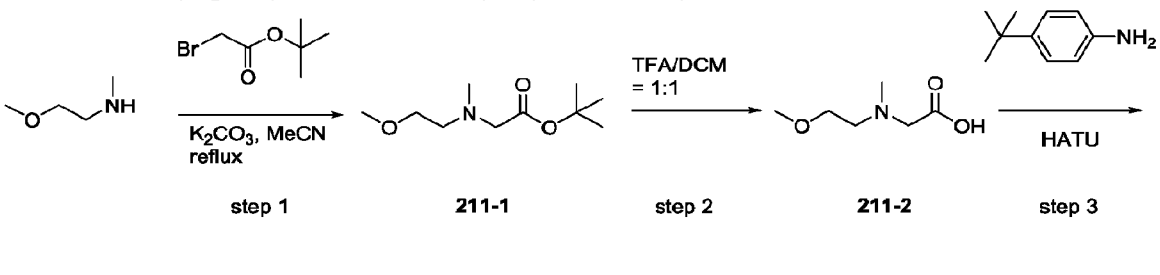


210

The title compound **210** (16.2 mg) as a yellow oil was prepared from tert-butyl N-({4-[(2,4,6-trimethylphenyl)amino]cyclohexyl}methyl)carbamate (160 mg, 0.46 mmol) and HCl in MeOH (10 mL, 4N) according to the procedure for **37**. ^{1}H NMR (300 MHz, CD_3OD) δ 6.72 (s, 2H), 3.11 (br, 1H), 2.64 (br, 2H), 2.13 (s, 6H), 2.12 (br, 3H), 1.55 (br, 9H). MS (m/z) 247.0 $[M+H]^+$.

Compound 211

N1-(4-(tert-butyl)phenyl)-N2-(2-methoxyethyl)-N2-methylethane-1,2-diamine



Step 1. Preparation of tert-butyl N-(2-methoxyethyl)-N-methylglycinate **(211-1)**

A mixture of 2-methoxy-N-methylethan-1-amine (800 mg, 9.00 mmol), tert-butyl 2-bromoacetate (2.45 mg, 12.6 mmol), K_2CO_3 (2.48 g, 18 mmol) in MeCN (50 mL) was stirred

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overnight at 80 °C. After cooling to rt., 40 mL of water was added. The solid was purified by silica gel chromatography. Target product was obtained as colorless oil. Mass (m/z): 204.0 $[M+H]^+$.

Step 2. Preparation of N-(2-methoxyethyl)-N-methylglycine (**211-2**)

A mixture of tert-butyl N-(2-methoxyethyl)-N-methylglycinate (572 mg, 2.81 mmol) in TFA (20 mL) and DCM (2 mL) was stirred overnight at room temperature. The reaction was concentrated under vacuum. The solid was used in the next step directly. Mass (m/z): 148.2 $[M+H]^+$.

Step 3. Preparation of N-(4-(tert-butyl)phenyl)-2-((2-methoxyethyl)(methyl)amino)acetamide (**211-3**)

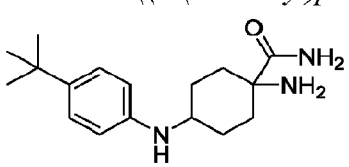
A mixture of N-(2-methoxyethyl)-N-methylglycine (402 mg, 273 mmol), 4-(tert-butyl)aniline (489 mg, 3.28 mmol), HATU (1.25 g, 3.28 mmol), DIPEA (530 mg, 4.1 mmol) in DMF (20 mL) was stirred overnight at room temperature. Then 40 ml of water was added. The solid was purified by silica gel chromatography. Target product (543 mg, 71%) was obtained as a yellow solid. Mass (m/z): 279.2 $[M+H]^+$.

Step 4. Preparation of N1-(4-(tert-butyl)phenyl)-N2-(2-methoxyethyl)-N2-methylethane-1,2-diamine (**211**)

N-(4-(tert-butyl)phenyl)-2-((2-methoxyethyl)(methyl)amino)acetamide (200 mg, 0.72 mmol) was added to BH_3-THF (20 mL) and the mixture was stirred overnight at 70 °C. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product (11 mg, 6%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.21 (d, J = 8.8 Hz, 2H), 6.66 (d, J = 8.7 Hz, 2H), 3.71 – 3.63 (m, 2H), 3.47 (t, J = 6.1 Hz, 2H), 3.33 (s, 3H), 3.28 (d, J = 4.9 Hz, 4H), 2.85 (s, 3H), 1.26 (s, 9H). Mass (m/z): 365.2 $[M+H]^+$.

Compound 212

1-amino-4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxamide



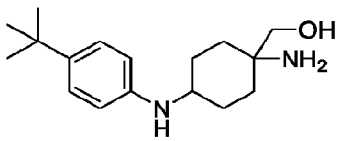
212

The title compound **212** (8.0 mg) was prepared in a total yield of 57% as a white solid with 1:1 mixture by ^{1}H NMR from 1-amino-4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxylic acid (14.5 mg, 0.05 mmol) according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 3H), 7.95 (s, 1H), 7.67 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 3.28 (m, 0.5H), 2.67 (m, 0.5H), 2.23 – 2.15 (m, 2H), 2.03 – 1.86 (m, 4H), 1.63 – 1.45 (m, 2H), 1.21 (s, 9H). Mass (m/z): 290.1$[M+H]^+$.

Compound 213

(1-amino-4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methanol

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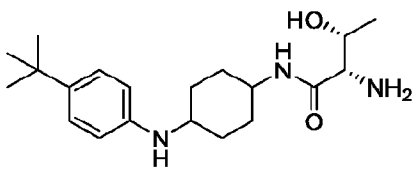


213A
213B

The title compound **213** from 1-amino-4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxylic acid (14.5 mg, 0.05 mmol) according to the procedure for compound **86**. The mixture was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-30%-95%-95%-5%, 0 min-10 min-10.5 min-11.5 min-13 min) to afford compound **213A** (Rt = 3.16 min) as a white solid and compound **213B** (Rt = 3.57 min) as a white solid. **213A** (4.6 mg, 17%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 2H), 7.36 (s, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 3.43 (s, 2H), 2.64 (m, 1H), 1.95 – 1.51(m, 4H), 1.22 (s, 9H). Mass (m/z): 277.3 $[M+H]^+$. **213B** (6.8 mg, 25%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (s, 2H), 7.34 (s, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.50 (d, J = 8.4 Hz, 2H), 3.55 (s, 2H), 2.66 (m, 1H), 2.05-1.87 (m, 4H), 1.63-1.41(m, 4H), 1.22 (s, 9H). Mass (m/z): 277.3$[M+H]^+$.

Compound 214

(2S,3R)-2-amino-N-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)-3-hydroxybutanamide

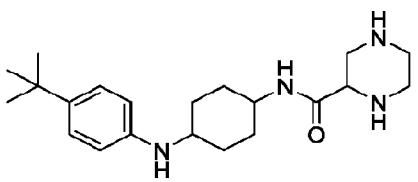


214

The title compound **214** (11.6 mg) was prepared in a total yield of 68% as a white solid with 1:1 mixture by ^{1}H NMR from tert-butyl ((2S,3R)-1-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)-3-hydroxy-1-oxobutan-2-yl)carbamate (22.4 mg, 0.05 mmol) according to the procedure for compound **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.05 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.65 (s, 3H), 6.49 (d, J = 8.4 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 5.19 (s, 2H), 4.06-3.43 (m, 2H), 3.37 (s, 1H), 3.27 (s, 1H), 1.94 (m, 1H), 1.78 (m, 1H), 1.58 (m, 4H), 1.31 (m, 2H), 1.16 (s, 9H), 1.08 (d, J = 3.2 Hz, 1.5H), 1.06 (d, J = 3.2 Hz, 1.5H). Mass (m/z): 348.2 $[M+H]^+$.

Compound 215

N-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)piperazine-2-carboxamide



215

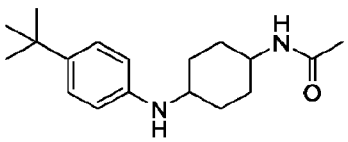
The title compound **215** (7.8 mg) was prepared in a total yield of 43 % as a white solid with 1:1 mixture by ^{1}H NMR from tert-butyl di-tert-butyl 2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)carbamoyl)piperazine-1,4-dicarboxylate (27.9

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mg, 0.05 mmol) according to the procedure for compound **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.47 (d, J = 8.4 Hz, 1H), 5.16 (s, 1H), 3.68 (m, 0.5H), 3.50 (m, 0.5H), 3.31 (s, 1H), 3.10 (m, 2H), 2.92-2.53 (m, 4H), 2.46 (s, 1H), 1.95 (m, 1H), 1.76 (m, 1H), 1.65-1.50 (m, 4H), 1.27 (m, 2H), 1.19 (s, 9H). Mass (m/z): 359.3 $[M+H]^+$.

Compound 216

N-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)acetamide



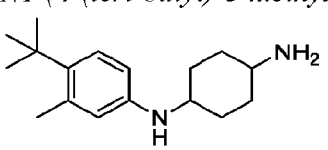
216A

216B

The title compound **216A** (Rt = 4.57 min; 3 mg) was prepared in a yield of 7.0% as a white powder compound **216B** (Rt =4.72 min; 18.2 mg) was prepared in a yield of 18.2% as a white powder from N1-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine (100 mg, 0.41 mmol), acetic acid (49 mg, 0.81 mmol) according to the procedure for **1** which were prepared by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10 min-11 min-15.0 min). **216A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 7.6 Hz, 1H), 7.40 (s, 2H), 7.08 (s, 2H), 3.56 – 3.42 (m, 1H), 3.31 (s, 1H), 1.95 – 1.80 (m, 4H), 1.77 (s, 3H), 1.40 – 1.32 (m, 2H), 1.27 (s, 9H), 1.22 – 1.16 (m, 2H). Mass (m/z): 289.2 $[M+H]^+$. **216B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 6.1 Hz, 1H), 7.39 (s, 2H), 7.07 (s, 2H), 3.67 (d, J = 5.4 Hz, 1H), 3.38 (dd, J = 9.2, 3.7 Hz, 1H), 1.81 (s, 3H), 1.73 (t, J = 9.6 Hz, 2H), 1.65 (q, J = 6.4, 5.5 Hz, 4H), 1.54 – 1.42 (m, 2H), 1.25 (s, 9H). Mass (m/z): 289.2 $[M+H]^+$.

Compound 217

N1-(4-(tert-butyl)-3-methylphenyl)cyclohexane-1,4-diamine



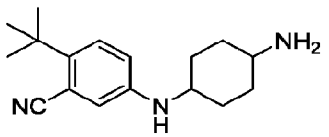
217

The title compound **217** (47.9 mg) was prepared in a yield of 30.0% as a white powder with 1:1 mixture by ^{1}H NMR from 4-(tert-butyl)-3-methylaniline (110 mg, 0.67 mmol), tert-butyl (4-oxocyclohexyl)carbamate (215 mg, 1.01 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 3H), 7.08 (d, J = 8.5 Hz, 1H), 6.50 (s, 2H), 3.41 (s, 1H), 3.13 (s, 1H), 2.38 (s, 3H), 1.82 – 1.65 (m, 6H), 1.62 (d, J = 10.1 Hz, 2H), 1.29 (s, 9H). Mass (m/z): 261.3 $[M+H]^+$.

Compound 218

5-((4-aminocyclohexyl)amino)-2-(tert-butyl)benzonitrile

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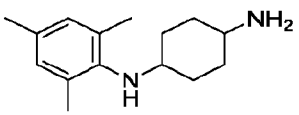


218

The title compound **218** (96.2 mg) was prepared in a yield of 61.7% as a white powder with 1:0.7 mixture by ^{1}H NMR from 5-amino-2-(tert-butyl)benzonitrile (100 mg, 0.57 mmol), tert-butyl (4-oxocyclohexyl)carbamate (183 mg, 0.86 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 5H), 7.21 (t, J = 8.5 Hz, 2H), 6.94 (d, J = 2.7 Hz, 1H), 6.91 (d, J = 2.6 Hz, 1H), 6.83 (dd, J = 8.9, 2.7 Hz, 1H), 6.79 (dd, J = 8.8, 2.7 Hz, 1H), 5.92 (d, J = 5.9 Hz, 1H), 5.87 (d, J = 8.0 Hz, 1H), 3.42 (s, 1H), 3.20 – 3.01 (m, 2H), 2.94 (ddt, J = 11.7, 7.5, 3.6 Hz, 1H), 2.03 – 1.92 (m, 4H), 1.74 (dq, J = 8.8, 5.7 Hz, 5H), 1.67 – 1.56 (m, 2H), 1.54 – 1.42 (m, 2H), 1.37 (d, J = 1.6 Hz, 16H), 1.27 – 1.08 (m, 4H). Mass (m/z): 272.7 $[M+H]^+$.

Compound 219

N1-mesitylcyclohexane-1,4-diamine

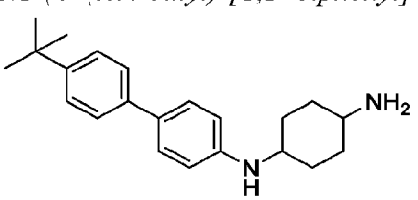


219

The title compound **219** (23.7 mg) was prepared in a total yield of 35.7% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-(mesitylamino)cyclohexyl)carbamate (95 mg, 0.286 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.69 (s, 2H), 3.04 (d, J = 39.6 Hz, 1H), 2.91 – 2.59 (m, 1H), 2.16 – 2.08 (m, 9H), 1.95 – 1.89 (m, 1H), 1.77 (d, J = 9.2 Hz, 2H), 1.64 (dt, J = 10.0, 6.4 Hz, 2H), 1.49 (td, J = 9.6, 4.4 Hz, 1H), 1.25 (dt, J = 23.2, 11.2 Hz, 2H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 220

N1-(4'-(tert-butyl)-[1,1'-biphenyl]-4-yl)cyclohexane-1,4-diamine



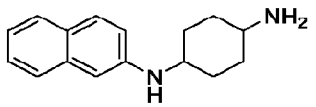
220

The title compound **220** (72.6 mg) was prepared in a total yield of 35.7% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-(mesitylamino)cyclohexyl)carbamate (149 mg, 0.353 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (dq, J = 8.8, 2.4 Hz, 2H), 7.35 – 7.31 (m, 4H), 6.68 – 6.57 (m, 2H), 5.60 (s, 1H), 3.46 – 2.84 (m, 3H), 2.06 – 1.68 (m, 5H), 1.64 – 1.40 (m, 2H), 1.24 (s, 9H). Mass (m/z): 323.3 $[M+H]^+$.

Compound 221

N1-(naphthalen-2-yl)cyclohexane-1,4-diamine

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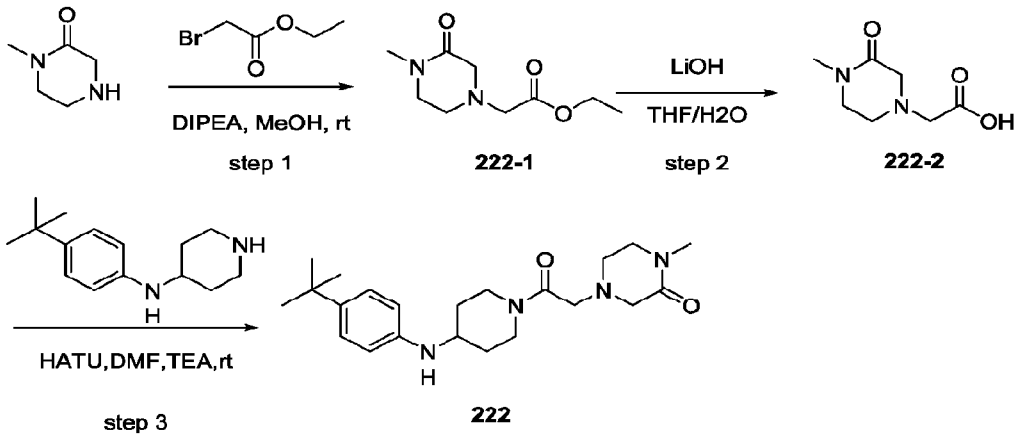


221

The title compound **221** (87.2 mg) was prepared in a total yield of 70.7% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-(naphthalen-2-ylamino)cyclohexyl)carbamate (174 mg, 0.512 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 – 7.47 (m, 3H), 7.24 (dddd, J = 8.0, 6.8, 3.2, 1.2 Hz, 1H), 7.09 – 6.86 (m, 2H), 6.68 (dd, J = 12.4, 2.4 Hz, 1H), 5.80 – 5.74 (m, 1H), 3.56 – 3.17 (m, 3H), 3.12 – 2.92 (m, 1H), 2.12 – 2.03 (m, 1H), 2.03 – 1.95 (m, 1H), 1.85 (dd, J = 12.4, 4.0 Hz, 1H), 1.74 (q, J = 5.6 Hz, 2H), 1.69 – 1.59 (m, 1H), 1.56 – 1.43 (m, 1H). Mass (m/z): 241.3 $[M+H]^+$.

Compound 222

4-(2-{4-[(4-tert-butylphenyl)amino]piperidin-1-yl}-2-oxoethyl)-1-methylpiperazin-2-one



Step 1. Preparation of ethyl 2-(4-methyl-3-oxopiperazin-1-yl)acetate **(222-1)**

To a solution of 1-methylpiperazin-2-one (400 mg, 3.50 mmol), ethyl 2-bromoacetate (878 mg, 5.25 mmol) and N,N-diisopropylethylamine (906 mg, 7.00 mmol) in MeOH (30 mL) was stirred overnight at 25 °C. LCMS showed the reaction was completed. The reaction was quenched with water (50 mL), extracted with EA (50 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to afford to give compound **222-1** (550 mg, 76.8% yield) as a yellow solid. MS (m/z): 200.9 $[M+H]^+$.

Step 2. Preparation of (4-methyl-3-oxopiperazin-1-yl)acetic acid **(222-2)**

A solution of product **222-1** (200 mg, 0.99 mmol) and LiOH (101 mg, 19.9 mmol) in THF/H_2O (1:1) (30 mL) was stirred overnight at 25 °C. LCMS showed the reaction was completed. The reaction was concentrated and freeze-drying to afford compound **222-2** (50 mg, 85.47% yield) as yellow oil. Mass (m/z): 173.2 $[M+H]^+$.

Step 3. Preparation of 4-(2-{4-[(4-tert-butylphenyl)amino]piperidin-1-yl}-2-oxoethyl)-1-methylpiperazin-2-one **(222)**

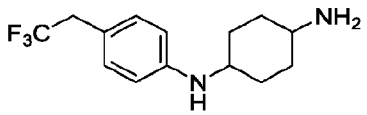
A solution of compound **222-2** (100 mg, 0.58 mmol), N-(4-tert-butylphenyl)piperidin-4-amine (135 mg, 0.58 mmol), HATU (331 mg, 0.87 mmol) and triethylamine (117 mg, 1.16 mmol) in DMF (30 mL) was stirred overnight at 25 °C. LCMS showed the reaction was completed. The

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reaction was quenched with water (50 mL), extracted with EA (50 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (2:3) to afford to give compound **222** (50 mg, 21.1%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 4.59 (br, 1h), 4.12 (br, 1H), 3.84 (s, 3H), 3.78 – 3.62 (m, 2H), 3.49 (s, 3H), 3.31 – 3.13 (m, 2H), 3.02 (s, 3H), 2.06 (d, J – 11.6 Hz, 2H), 1.86 – 1.47 (m, 3H), 1.31 (s, 12H). Mass (m/z): 386.9 $[M+H]^+$.

Compound 223

N1-(4-(2,2,2-trifluoroethyl)phenyl)cyclohexane-1,4-diamine

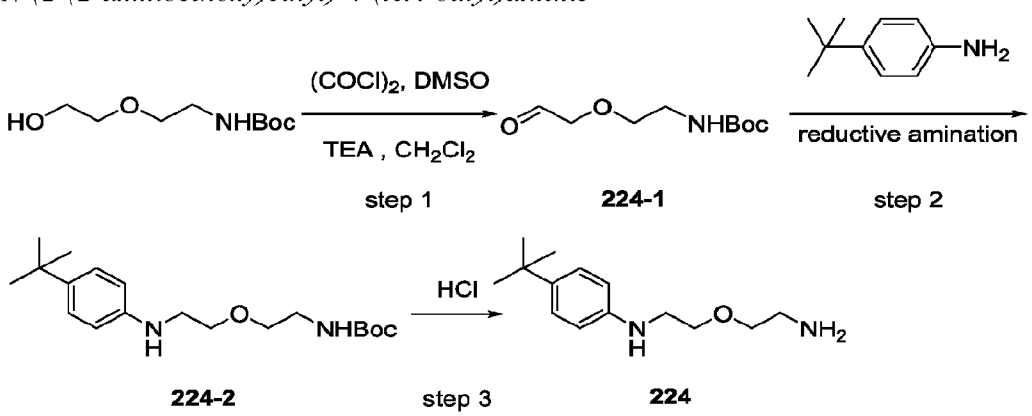


223

The desired product **223** (50.8 mg, 24.5%) as white solid was prepared from tert-butyl (4-((4-(2,2,2-trifluoroethyl)phenyl)amino)cyclohexyl)carbamate (278 mg, 0.74 mmol), 1,4-dioxane (10 mL) and 1,4-dioxane/HCl (10 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 3H), 7.05 (d, 2H), 6.62 (d, 2H), 3.44 – 3.36 (m, 3H), 3.13 (br, 1H), 1.89 – 1.39 (m, 8H). Mass (m/z): 273.1 $[M+H]^+$.

Compound 224

N-(2-(2-aminoethoxy)ethyl)-4-(tert-butyl)aniline



Step 1. Preparation of tert-butyl (2-(2-oxoethoxy)ethyl)carbamate **(224-1)**

A mixture of $(COCl)_2$ (2.13 g, 16.8 mmol) in CH_2Cl_2 (15 mL) was added dropwise DMSO (2.85 g, 36.5 mmol) in CH_2Cl_2 (15 mL) at -78 °C under nitrogen. After the addition, the solution was stirred for 30 min and a solution of tert-butyl (2-(2-hydroxyethoxy)ethyl)carbamate (1.5 g, 7.31 mmol) in CH_2Cl_2 (15 mL) was then added. After the addition of TEA (6.66 g, 65.8 mmol), the reaction was stirred for 30 min at -78 °C and then was stirred for overnight at room temperature. 100 ml of water was added. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated to afford the product. Target product (1.3 g, 88%) was obtained as a yellow solid. Mass (m/z): 225.9 $[M+H]^+$.

Step 2. Preparation of tert-butyl (2-(2-((4-(tert-butyl)phenyl)amino)ethoxy)ethyl)carbamate **(224-2)**

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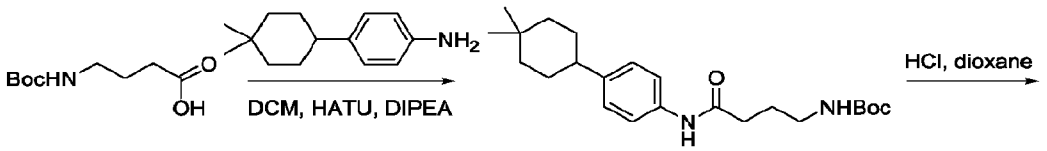
A mixture of tert-butyl (2-(2-oxoethoxy)ethyl)carbamate (100 mg, 0.49 mmol), 4-(tert-butyl)aniline (73 mg, 0.49 mmol), Pic-BH_3 (63 mg, 0.59 mmol) in H_2O (9 mL) and CH_3COOH (1 mL) was stirred 5 h at room temperature. Then the reaction was quenched with aqueous $NaHCO_3$. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The target product (122 mg, 74%) was obtained by silica gel chromatography. Mass (m/z): 336.9 $[M+H]^+$.

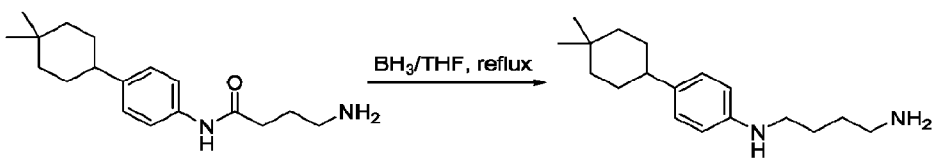
Step 3. Preparation of N-(2-(2-aminoethoxy)ethyl)-4-(tert-butyl)aniline **(224)**

To a solution of tert-butyl (2-(2-((4-(tert-butyl)phenyl)amino)ethoxy)ethyl)carbamate (122 mg, 0.36 mmol) in HCl in dioxane (3 mL) and in CH_2Cl_2 (3 mL). Then the mixture was stirred for overnight at rt. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product (23 mg, 27%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.19 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 3.69 (dt, J = 12.8, 5.2 Hz, 4H), 3.30 – 3.27 (m, 2H), 3.14 – 3.04 (m, 2H), 1.26 (s, 9H). Mass (m/z): 236.9 $[M+H]^+$.

Compound 225

N1-(4-(4,4-dimethylcyclohexyl)phenyl)propane-1,3-diamine





Step 1. Preparation of tert-butyl (3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-3-oxopropyl)carbamate **(225-1)**

A mixture of 4-((tert-butoxycarbonyl)amino)butanoic acid (600 mg, 2.95 mmol), 4-(4,4-dimethylcyclohexyl)aniline (500 mg, 2.45 mmol), HATU (1.12 g, 2.95 mmol), and DIPEA (955 mg, 7.4 mmol in DCM (20 mL) was stirred for 2 hours at rt. The reaction was washed with water, dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by prep-TLC to afford the product as light yellow solid (500 mg, 44.7%). Mass (m/z): 288.7 $[M-Boc+H]^+$.

Step 2. Preparation of 3-amino-N-(4-(4,4-dimethylcyclohexyl)phenyl)propanamide **(225-2)**

To a solution of tert-butyl (3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-3-oxopropyl)carbamate (300 mg, 0.772 mmol) in dioxane/HCl (20 mL, 4M) stirred at rt for 2 hours. The reaction was concentrated under vacuum. The residue was adjusted to pH 8 with aqueous Na_2CO_3 (sat.), exacted with EA (20 mL), dried over Na_2SO_4, filtered and purified by prep-TLC to afford the product as a yellow solid (80 mg, 34.1%). Mass (m/z): 288.7 $[M+H]^+$.

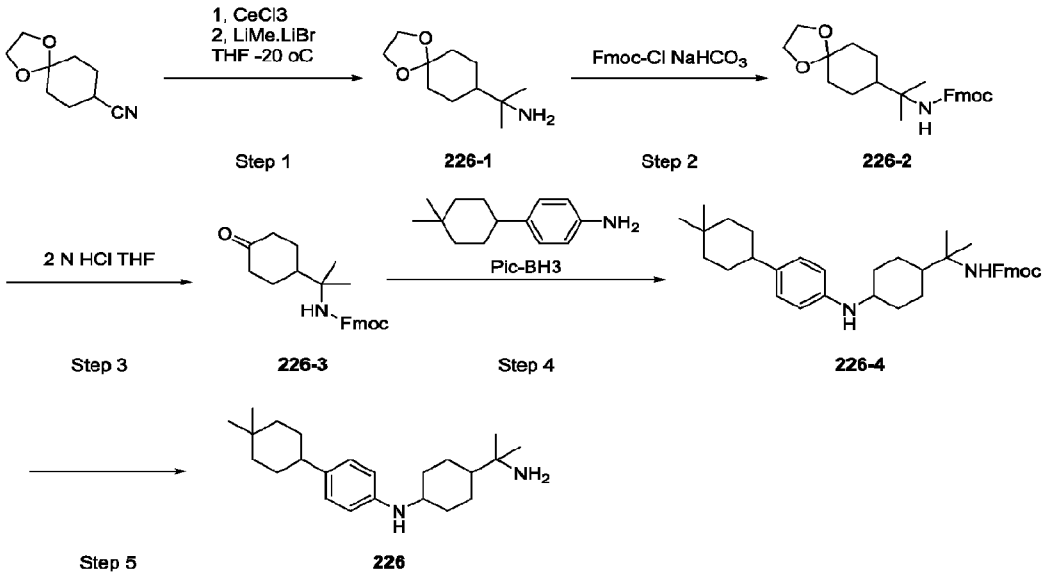
Step 3. Preparation of N1-(4-(4,4-dimethylcyclohexyl)phenyl)butane-1,4-diamine **(225)**

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To a solution of 3-amino-N-(4-(4,4-dimethylcyclohexyl)phenyl)propanamide (80 mg, 0.28 mmol) in BH_3-THF (20 mL, 1M) was ad stirred 16 hours at 80 °C. The reaction was concentrated under vacuum, washed with water, exacted with EA, dried over Na_2SO_4. The residue was purified by prep-HPLC to afford the desired product as a white solid. (17.8 mg, 23.3%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.3 Hz, 2H), 6.56 (d, J = 8.3 Hz, 2H), 3.11 (t, J – 6.6 Hz, 2H), 2.77 (t, J – 6.7 Hz, 2H), 2.35 – 2.25 (m, 1H), 1.70 – 1.46 (m, 11H), 1.38 – 1.19 (m, 3H), 0.95 (d, J = 7.3 Hz, 6H). Mass (m/z): 274.7 $[M+H]^+$.

Compound 226

N-(4-(2-aminopropan-2-yl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline



Step 1. Preparation of 2-(1,4-dioxaspiro[4.5]decan-8-yl)propan-2-amine **(226-1)**

To a solution of 1,4-dioxaspiro[4.5]decane-8-carbonitrile (500 mg, 2.87 mmol), $CeCl_3$ (1474 mg, 5.74 mmol) and LiMe-LiBr (3 mL, 3 N in THF) in THF (10 mL). The reaction was stirred at -20 °C for 18 hours under N_2 atmosphere. Ethyl acetate was added to the reaction mixture and filtered through Celite, and the filtrate was washed with water and saturated brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column to provide 215 mg (yield: 37.5%) of **226-1** as a yellow oil. Mass (m/z): 200.2 $[M+H]^+$.

Step 2. Preparation of (9H-fluoren-9-yl)methyl (2-(1,4-dioxaspiro[4.5]decan-8-yl)propan-2-yl)carbamate **(226-2)**

To a solution of **226-1** (100 mg, 0.5 mmol) and $NaHCO_3$ (84 mg, 1 mmol) in H_2O (10 mL) was added Fmoc-Cl (143 mg, 0.55 mmol). The mixture was stirred at 25 °C overnight. Ethyl acetate was added to the reaction mixture and the mixture was filtered through celite. The filtrate was washed with water and saturated brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column to provide 230 mg of **226-3** (yield: 90%) as a yellow solid. Mass (m/z): 444.2 $[M+Na]^+$.

Step 3. Preparation of (9H-fluoren-9-yl)methyl (2-(4-oxocyclohexyl)propan-2-yl)carbamate **(226-3)**

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226-2 (700 mg, 1.67 mmol) and HCl in THF (10 mL, 2 N) were placed in a flask stirred at 25 °C for 18 hrs. Excess THF was distilled under vacuum and the residue was purified by silica gel column to provide 400 mg of **226-4** (yield: 63.4%) as a yellow solid. Mass (m/z): 378.0 $[M+H]^+$.

Step 4. Preparation of (9H-fluoren-9-yl)methyl (2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)propan-2-yl)carbamate **(226-4)**

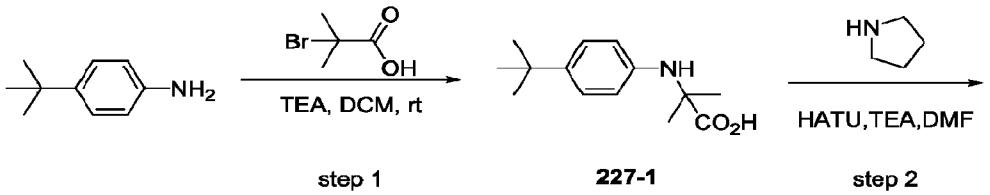
To a solution of **226-3** (212 mg, 0.6 mmol), 4-(4,4-dimethylcyclohexyl)aniline (113 mg, 0.6 mmol) and Pic-BH_3 (98 mg, 0.9 mmol) in H_2O (9 ml) and HOAc (1 mL). The reaction was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 250 mg of **226** (yield: 74.0%) as a yellow solid. Mass (m/z): 565.3 $[M+H]^+$.

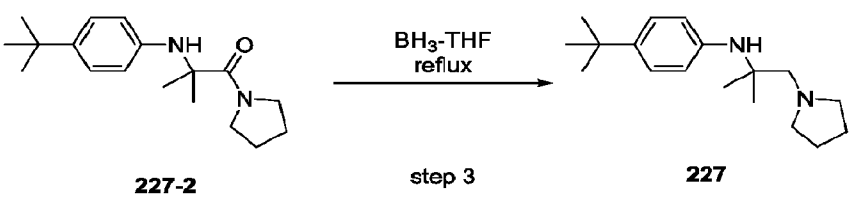
Step 5. Preparation of N-(4-(2-aminopropan-2-yl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline **(226)**

To a solution of **226-4** (190 mg, 0.34 mmol) and Piperidine (1 mL) in MeOH (5 mL). The reaction was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford **226** (15.4 mg) as a white solid. Mass (m/z): 343.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 6.98 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.4 Hz, 2H), 3.64 (s, 1H), 2.31 – 2.23 (m, 1H), 2.04 (d, J = 12.8 Hz, 2H), 1.66 – 1.42 (m, 13H), 1.39 – 1.33 (m, 2H), 1.31 (s, 6H), 0.96 (d, J = 16.0 Hz, 6H).

Compound 227

4-(tert-butyl)-N-(2-methyl-1-(pyrrolidin-1-yl)propan-2-yl)aniline





Step 1. Preparation of 2-((4-(tert-butyl)phenyl)amino)-2-methylpropanoic acid **(227-1)**

A solution of 4-(tert-butyl)aniline (500 mg, 3.35 mmol), 2-bromo-2-methylpropanoic acid (671 mg, 4.02 mmol) and TEA (677 mg, 6.7 mmol) in DCM (30 mL) was stirred overnight at 25 °C. LCMS showed the reaction was completed. The reaction was quenched with water (30 mL), extracted with DCM (30 mL*3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:1) to afford to give compound 3 (700 mg, 79.9% yield) as a yellow solid. Mass (m/z): 235.9 $[M+H]^+$.

Step 2. Preparation of 2-((4-(tert-butyl)phenyl)amino)-2-methyl-1-(pyrrolidin-1-yl)propan-1-one **(227-2)**

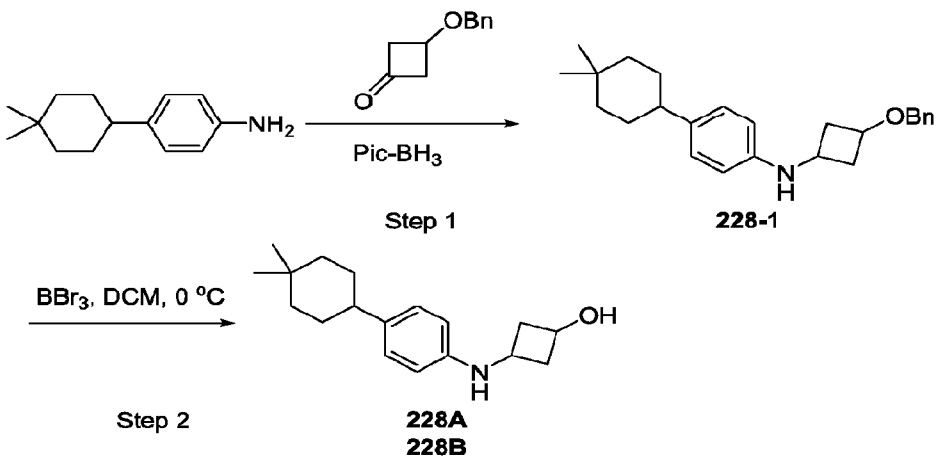
A solution of **227-1** (700 mg, 2.97 mmol), pyrrolidine (211 mg, 2.97 mmol), HATU (262 mg, 5.95 mmol) and TEA (600 mg, 5.95 mmol) in DMF (30 mL) was stirred overnight at 25 °C. LCMS showed the reaction was completed. The reaction was quenched with water (50 mL), extracted with EA (50 mL*3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (4:1) to afford to give compound 5 (800 mg, 81.6% yield) as yellow oil. Mass (m/z): 289.3 $[M+H]^+$.

Step 3. Preparation of 4-(tert-butyl)-N-(2-methyl-1-(pyrrolidin-1-yl)propan-2-yl)aniline **(227)**

A solution of **227-2** (100 mg) in BH_3-THF (20 mL) was stirred 2 h at reflux, quenched with MeOH, concentrated under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 20%-40%) to afford **227-2** (42 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.30 (br, 2H), 6.83 (br, 2H), 3.94 – 3.44 (m, 4H), 3.30 (br, 2H), 2.08 (br, 4H), 1.40 (br, 6H), 1.28 (s, 9H). MS (m/z) 275$[M+H]^+$.

Compound 228

3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclobutan-1-ol



Step 1. Preparation of N-(3-(benzyloxy)cyclobutyl)-4-(4,4-dimethylcyclohexyl)aniline **(228-1)**

To a solution of 4-(4,4-dimethylcyclohexyl)aniline (200 mg, 1 mmol), 3-(benzyloxy)cyclobutan-1-one (176 mg, 1 mmol), Pic-BH_3 (87 mg, 0.86 mmol) in H_2O (9 mL) and HOAc (1 mL). The reaction was stirred at R.T. for 18 hours. The reaction mixture was filtered and the filtrate was purified by silica gel column to provide 300 mg of **228-1** (yield: 82.4%) as a yellow solid. Mass (m/z): 364.3 $[M+H]^+$.

Step 2. Preparation of 3-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclobutan-1-ol **(228)**

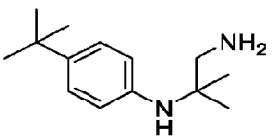
To a solution of **228-1** (300 mg, 0.83 mmol) in DCM (10 mL) was added BBr_3 (1 mL) at -10 °C and stirred at -10 °C for 18 hours. The reaction mixture was concentrated and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **228A** (32.8 mg) as a white solid & **228B** (31.7 mg) as a white solid. **228A**: ^1H NMR (400 MHz, CD_3OD) δ 6.97 (d, J = 8.4 Hz, 2H), 6.50 (d, J =

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8.4 Hz, 2H), 4.42 (d, *J* = 5.4 Hz, 1H), 3.93 (t, *J* = 4.2 Hz, 1H), 2.32 – 2.28 (m, 1H), 2.27 – 2.21 (m, 2H), 2.23 – 2.14 (m, 2H), 1.69 – 1.54 (m, 4H), 1.47 (d, *J* = 11.4 Hz, 2H), 1.39 – 1.26 (m, 2H), 0.96 (d, *J* = 16.4 Hz, 6H). Mass (m/z): 274.3 $[M+H]^+$. HPLC: Rt=5.555 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min). **228B**: ^1H NMR (400 MHz, CD_3OD) δ 6.97 (d, *J* – 8.4 Hz, 2H), 6.50 (d, *J* – 8.4 Hz, 2H), 4.43 (t, *J* = 5.4 Hz, 1H), 3.93 (t, *J* = 4.2 Hz, 1H), 2.34 – 2.13 (m, 5H), 1.66 – 1.55 (m, 4H), 1.47 (d, *J* = 11.8 Hz, 2H), 1.36 – 1.23 (m, 2H), 0.96 (d, *J* = 16.4 Hz, 6H). HPLC: Rt=5.570 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min).

Compound 229

N-(4-(tert-butyl)phenyl)-2-methylpropane-1,2-diamine

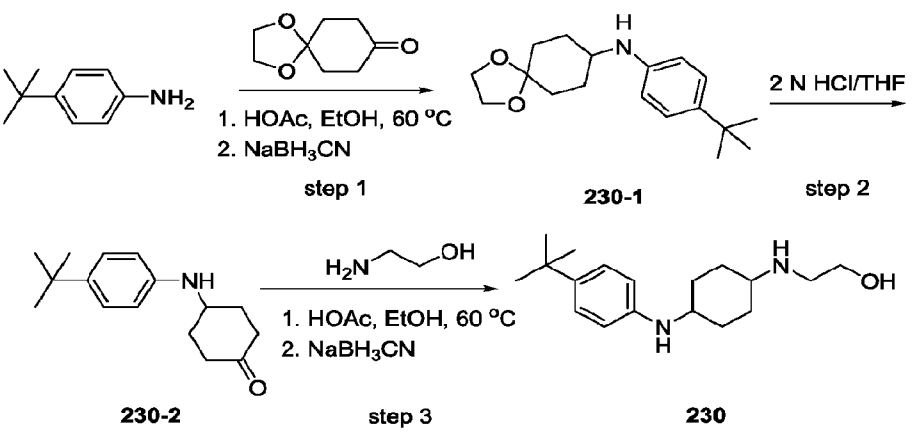


229

The title compound **229** (34.7 mg) as a white solid was prepared from 2-((4-(tert-butyl)phenyl)amino)-2-methylpropanamide (150 mg, 0.64 mmol), BH_3-THF (10 mL) and THF (5 mL) according to the procedure for **105**. ^1H NMR (400 MHz, CD_3OD) δ 7.23 (d, 2H), 6.80 (d, 2H), 3.07 (s, 2H), 1.28 (d, 15H). Mass (m/z): 221.0 $[M+H]^+$.

Compound 230

2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)ethan-1-ol



Step 1. Preparation of N-(4-(tert-butyl)phenyl)-1,4-dioxaspiro[4.5]decan-8-amine **(230-1)**

To a solution of 4-(tert-butyl)aniline (1 g, 6.71 mmol) in MeOH (10 mL) was added 1,4-dioxaspiro[4.5]decan-8-one (1.04 g, 6.71 mmol) and the mixture was stirred at 60 °C for 1 h. Then Sodium cyanoborohydride (1.27 g, 20.13 mmol) was added to the mixture. The reaction was stirred for 3 h at R.T. Quenched with water (50 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, concentrated under vacuum and the residue was purified by flash chromatography to afford the

desired product (1.6 g, 82.6%) as a white solid. Mass (m/z): 289.9 $[M+H]^+$.

Step 2. Preparation of 4-((4-(tert-butyl)phenyl)amino)cyclohexan-1-one **(230-2)**

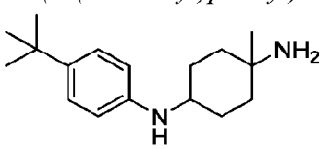
To a solution of N-(4-(tert-butyl)phenyl)-1,4-dioxaspiro[4.5]decan-8-amine (1.6 g, 5.54 mmol) in THF (5 mL) was added HCl in THF (2 N, 5 mL) and the mixture was stirred for 2 h. Quenched with $NaHCO_3$ (10 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, concentrated under vacuum to afford the product (0.9 g, 66.2%) as a white solid. Mass (m/z): 246.2 $[M+H]^+$.

Step 3. Preparation of 2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)ethan-1-ol **(230)**

The desired product **230** (113 mg, 95%) as a yellow solid was prepared from 4-((4-(tert-butyl)phenyl)amino)cyclohexan-1-one (100 mg, 0.41mmol), MeOH (5 mL), 2-aminoethan-1-ol (25 mg, 0.41 mmol), acetic acid (2.46 mg, 0.041 mmol) and sodium cyanoborohydride (77.49 mg, 12.3 mmol) according to the procedure for **5**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, J = 8.8 Hz, 2H), 6.49 (dd, J = 13.6 Hz, 8.4 Hz, 2H), 5.13 (s, 1H), 3.49 (s, 3H), 3.20 (m, 1H), 2.67 (m, 2H), 2.51 (s, 1H), 1.95 (t, J = 14.0 Hz, 2H), 1.69 – 1.49 (m, 3H), 1.20 (s, 12H). Mass (m/z): 290.9 $[M+H]^+$.

Compound 231

N^1-(4-(tert-butyl)phenyl)-4-methylcyclohexane-1,4-diamine



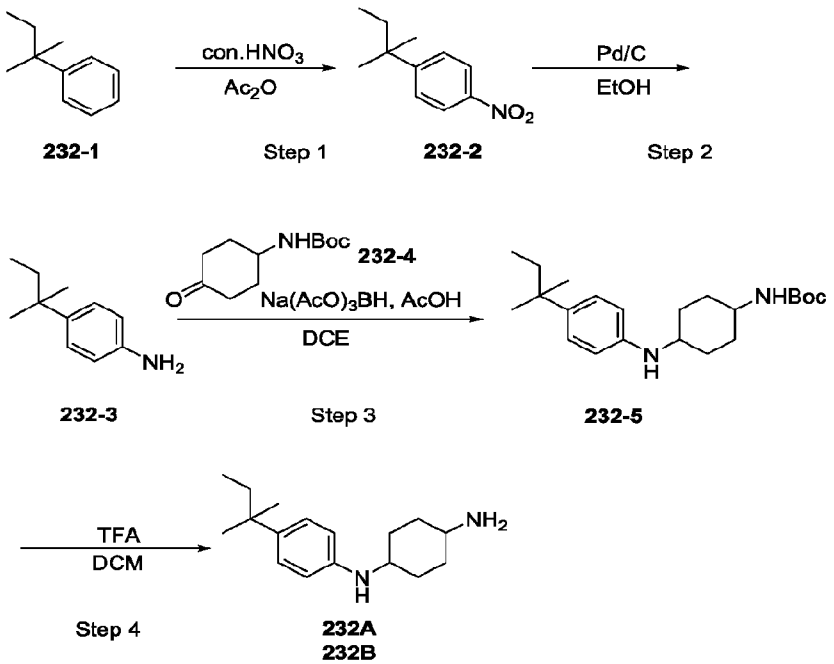
231A
231B

The title compound **231A** and **231B** were prepared according to the procedure for compound **24**. The crude residue was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 10%-30%-95%-95%-0, 0 min-7 min-7.5 min-8.5 min-10 min) to afford compound **231A** (Rt = 6.49 min) in 5.7% yield as a white solid and **231B** (Rt = 5.60 min) in 8.7% yield as a white solid. **231A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 2H), 7.06 (d, J = 7.4 Hz, 2H), 6.61 – 6.36 (m, 2H), 5.06 (s, 1H), 3.26 – 3.18 (m, 1H), 1.86 – 1.71 (m, 4H), 1.57 – 1.49 (m, 4H), 1.23 (s, 3H), 1.17 (s, 9H). Mass (m/z): 261.3$[M+H]^+$. **231B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.72 (m, 3H), 7.28 – 7.03 (m, 2H), 6.90 – 6.61 (m, 2H), 3.26 – 3.11 (m, 1H), 1.87 – 1.78 (m, 2H), 1.75 – 1.66 (m, 2H), 1.60 – 1.50 (m, 2H), 1.45 – 1.33 (m, 2H), 1.24 (s, 3H), 1.20 (s, 9H). Mass (m/z): 261.3$[M+H]^+$.

Compound 232

N^1-(4-(tert-pentyl)phenyl)cyclohexane-1,4-diamine

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Step 1. Preparation of 1-nitro-4-(tert-pentyl)benzene (**232-2**)

To a stirred solution of tert-pentylbenzene (388 mg, 2.0 mol) in acetic anhydride (5.0 mL) at -5°C was added con. HNO_3 (0.3 mL) slowly. The reaction was maintained at 0 °C for 1 hour and then room temperature for 18 hours. Water (10 mL) was added. The reaction was extracted with EtOAc (3x10 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-TLC (DCM/PE=1/10) to afford the title compound (230 mg, 60%).

Step 2. Preparation of 4-(tert-pentyl)aniline (**232-3**)

To a solution of 1-nitro-4-(tert-pentyl)benzene (230 mg, 1.2 mmol) in EtOH (10 mL) was added 10% Pd/C (12.6 mg, 12 umol). Then the reaction was stirred overnight at room temperature (RT) under an atmosphere of hydrogen. Pd/C was filtrated out. The filtrate was concentrated under vacuum. The residue was purified by prep-TLC (EA/PE=1/3) to afford the desired product as a yellow solid (1.8 g, 81.8%). Mass (m/z): 164.3 $[M+H]^+$.

Step 3. Preparation of tert-butyl (4-((4-(tert-pentyl)phenyl)amino)cyclohexyl)carbamate (**232-5**)

The title compound **232-5** (120 mg) was prepared in a total yield of 50.0% as a crude yellow solid from 4-(tert-pentyl)aniline (110 mg, 0.67 mmol), tert-butyl (4-oxocyclohexyl)carbamate (285 mg, 1.34 mmol) and $Na(AcO)_3BH$ (283 mg, 1.34 mmol) according to the procedure for **24-1**. Mass (m/z): 361.3 $[M+H]^+$.

Step 4. N^1-(4-(tert-pentyl)phenyl)cyclohexane-1,4-diamine (**232**)

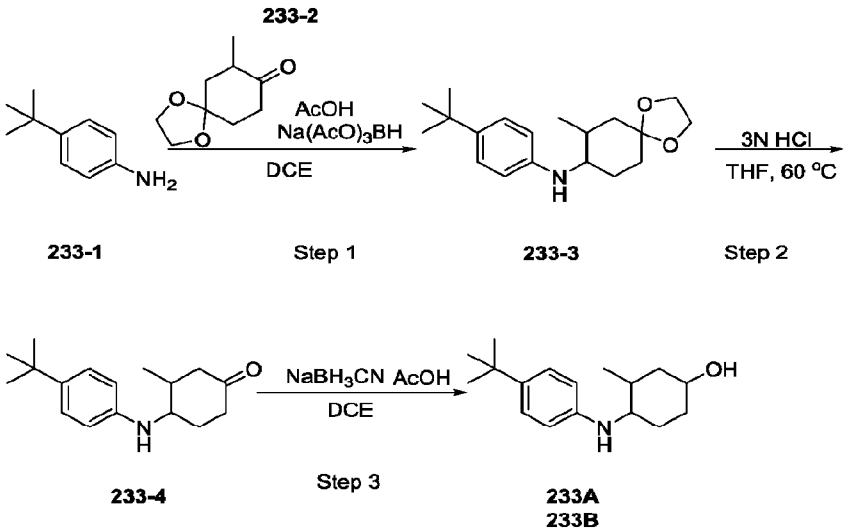
The title compound **232A**, **232B** was prepared according to the procedure for compound **28**. The crude residue was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 10%-33%-95%-95%-10%, 0 min-7 min-7.5 min-8.5 min-10 min) to afford compound **232A** (Rt = 6.23 min) in 14.9% yield as a white solid and **232B** (Rt = 5.05 min) in 34.7% yield as a white solid. **231A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 3H), 7.04 (d, J = 8.0 Hz, 2H), 6.59 (s, 2H), 3.41 – 3.32 (m, 1H), 3.16 – 3.03 (m, 1H),

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1.78 – 1.57 (m, 8H), 1.50 (q, J = 7.4 Hz, 2H), 1.13 (s, 6H), 0.57 (t, J = 7.4 Hz, 3H). Mass (m/z): 261.3[M+H]$^+$. **231B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79 (s, 3H), 7.32 – 7.04 (m, 2H), 6.92 – 6.50 (m, 2H), 3.28 – 3.09 (m, 1H), 3.03 – 2.90 (m, 1H), 1.93 (t, J = 10.8 Hz, 4H), 1.52 (q, J = 7.6 Hz, 2H), 1.40 – 1.12 (m, 10H), 0.57 (t, J = 7.4 Hz, 3H). Mass (m/z): 261.3[M+H]$^+$.

Compound 233

4-((4-(tert-butyl)phenyl)amino)-3-methylcyclohexan-1-ol



Step 1. Preparation of N-(4-(tert-butyl)phenyl)-7-methyl-1,4-dioxaspiro[4.5]decan-8-amine (**233-3**)

The title compound **233-3** (350 mg) was prepared in a total yield of 92.3% as a yellow solid from 4-(tert-pentyl)aniline (1.86 mg, 1.25 mmol), 7-methyl-1,4-dioxaspiro[4.5]decan-8-one (319 mg, 1.88 mmol) and Na(AcO)$_3$BH (399 mg, 1.88 mmol) according to the procedure for **1-1**. Mass (m/z): 304.3 [M+H]$^-$.

Step 2. Preparation of 4-((4-(tert-butyl)phenyl)amino)-3-methylcyclohexan-1-one (**233-4**)

A solution of N-(4-(tert-butyl)phenyl)-7-methyl-1,4-dioxaspiro[4.5]decan-8-amine (350 mg, 1.16 mmol) in 10 mL tetrahydrofuran and 10 mL of 1 M hydrochloric acid was heated to 60 °C for 30 min. After cooling to 0 °C, the PH of the solution was adjusted to 8-9 with sodium carbonate solution. Then the mixture was extracted by DCM (20 mL x 3). The combined organic layers were washed with water (20 mL), dried over Na_2SO_4 and concentrated to afford the desired product as a yellow solid (280 mg, 93.6%). Mass (m/z): 260.3 [M+H]$^+$.

Step 3. Preparation of 4-((4-(tert-butyl)phenyl)amino)-3-methylcyclohexan-1-ol (**233**)

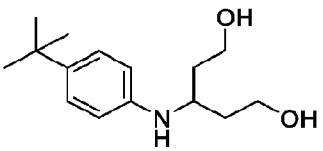
To a solution of 4-((4-(tert-butyl)phenyl)amino)-3-methylcyclohexan-1-one (130 mg, 0.6 mmol) in DCE (10 mL) was added $NaBH_3CN$ (62 g, 1 mmol) and 5 drops of AcOH. The mixture was stirred at rt for 3 h. Then the reaction was washed with water (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC (MeOH/DCM=1/10) to afford compound **233A** in 15.9% yield as a light yellow solid and **233B** in 11.4% yield as a light yellow solid. **233A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 – 7.03 (m, 2H), 6.96 – 6.61 (m, 2H), 5.31 (s, 2H), 3.50 – 3.36 (m, 2H), 1.81 – 1.68 (m, 2H), 1.56 – 1.28

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(m, 5H), 1.19 (s, 10H), 0.93 (d, J = 6.9 Hz, 3H). Mass (m/z): 262.3 $[M+H]^+$. HPLC: Rt=6.485 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). **233B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 – 6.30 (m, 5H), 3.41 – 3.32 (m, 1H), 2.90 (qd, J = 13.4, 12.2, 6.8 Hz, 1H), 2.03 – 1.43 (m, 5H), 1.20 (s, 9H), 1.15 – 0.93 (m, 7H). Mass (m/z): 262.3 $[M+H]^+$. HPLC: Rt–5.229 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)– 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 234

3-((4-(tert-butyl)phenyl)amino)pentane-1,5-diol

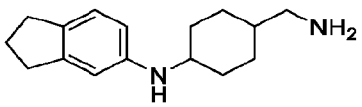


234

The title compound **234** (72.7 mg) was prepared in a total yield of 58% as a white solid from 4-(tert-butyl)aniline (75 mg, 0.5 mmol) according to the procedure for compound **4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 5.07 (s, 1H), 4.39 (s, 2H), 3.46 (t, J = 68.4 Hz, 4H), 3.35 (m, 1H), 1.59 (m, 4H), 1.20 (s, 9H). Mass (m/z): 252.3 $[M+H]^+$.

Compound 235

N-(4-(aminomethyl)cyclohexyl)-2,3-dihydro-1H-inden-5-amine

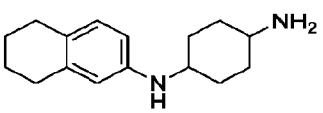


235

The title compound **235** (131.4 mg) was prepared in a total yield of 90.3% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((2,3-dihydro-1H-inden-5-yl)amino)cyclohexyl)carbamate (205 mg, 0.596 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (dd, J = 8.0, 3.2 Hz, 1H), 6.47 – 6.25 (m, 2H), 5.06 (d, J = 24.0 Hz, 1H), 3.35 (d, J = 27.2 Hz, 1H), 2.73 – 2.53 (m, 6H), 1.98 – 1.73 (m, 3H), 1.61 – 1.35 (m, 6H), 1.01 (q, J = 9.6 Hz, 1H). Mass (m/z): 245.3 $[M+H]^+$.

Compound 236

N1-(5,6,7,8-tetrahydronaphthalen-2-yl)cyclohexane-1,4-diamine



236

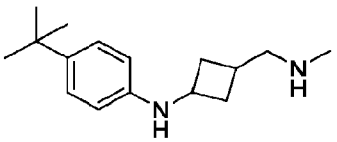
The title compound **236** (93.7 mg) was prepared in a total yield of 73.4% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((5,6,7,8-tetrahydronaphthalen-2-yl)amino)cyclohexyl)carbamate (180 mg, 0.523 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz,

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DMSO-d_6) δ 6.74 (d, J = 8.0 Hz, 1H), 6.46 – 6.20 (m, 2H), 5.03 (s, 1H), 3.00 (d, J = 54.4 Hz, 2H), 2.57 (d, J = 18.4 Hz, 4H), 1.99 (d, J = 11.6 Hz, 2H), 1.75 (d, J = 15.2 Hz, 3H), 1.66 (p, J = 3.2 Hz, 4H), 1.59 (d, J = 12.4 Hz, 1H), 1.46 (q, J = 12.4 Hz, 1H), 1.18 (t, J = 18.8 Hz, 1H). Mass (m/z): 245.3 $[M+H]^+$.

Compound 237

4-(tert-butyl)-N-(3-((methylamino)methyl)cyclobutyl)aniline

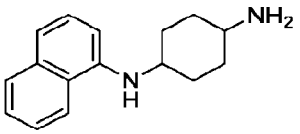


237

The title compound **237** (17.9 mg) was prepared in a total yield of 25.3% as an orange solid from 3-((4-(tert-butyl)phenyl)amino)-N-methylcyclobutane-1-carboxamide (75 mg, 0.288 mmol), $LiAlH_4$ (43 mg,1.152 mmol) and THF (10 mL) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (s, 1H),7.09 – 6.96 (m, 2H), 6.46 – 6.30 (m, 2H), 5.65 (dd, J = 13.6, 7.2 Hz, 1H), 3.74 (dq, J = 84.4, 8.0, 7.6 Hz, 1H), 2.69 – 2.56 (m, 1H), 2.53 (dd, J = 10.8, 4.4 Hz, 3H), 2.42 – 2.32 (m, 2H), 1.98 – 1.83 (m, 2H), 1.16 (s, 9H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 238

N1-(naphthalen-1-yl)cyclohexane-1,4-diamine

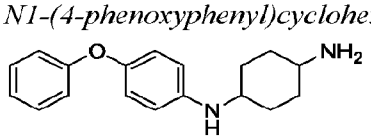


238

The title compound **238** (119.1 mg) was prepared in a total yield of 85% as a pink solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-(naphthalen-1-ylamino)cyclohexyl)carbamate (198 mg, 0.582 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 8.32 – 8.24 (m, 1H), 8.19 (dd, J = 20.8, 8.0 Hz, 1H), 7.70 (td, J = 8.4, 1.6 Hz, 1H), 7.42 – 7.30 (m, 2H), 7.23 (td, J = 8.0, 5.6 Hz, 1H), 7.06 (dd, J = 17.2, 8.0 Hz, 1H), 6.52 (t, J = 7.2 Hz, 1H), 5.89 – 5.39 (m, 1H), 3.17 – 2.88 (m, 1H), 2.13 – 2.01 (m, 2H), 1.95 (dq, J = 8.8, 4.4 Hz, 1H), 1.84 (t, J = 10.0 Hz, 1H), 1.78 – 1.72 (m, 1H), 1.70 – 1.61 (m, 1H), 1.59 – 1.46 (m, 1H), 1.44 – 1.31 (m, 1H). Mass (m/z): 241.3 $[M+H]^+$.

Compound 239

N1-(4-phenoxyphenyl)cyclohexane-1,4-diamine



239

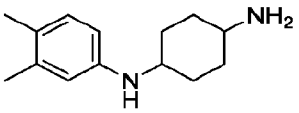
The title compound **239** (93.2 mg) was prepared in a total yield of 70.6% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((4-phenoxyphenyl)amino)cyclohexyl)carbamate (179 mg, 0.469 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (tt, J = 7.2, 2.0 Hz, 2H), 7.04 – 6.94 (m, 1H), 6.89 – 6.77

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(m, 4H), 6.71 – 6.55 (m, 2H), 5.32 (d, J = 5.0 Hz, 1H), 3.09 (s, 1H), 2.95 (s, 1H), 2.01 (d, J = 11.2 Hz, 3H), 1.78 (qd, J = 12.0, 10.8, 7.2 Hz, 3H), 1.61 (dt, J = 13.6, 7.2 Hz, 1H), 1.54 – 1.40 (m, 1H). Mass (m/z): 283.3 $[M+H]^+$.

Compound 240

N1-(3,4-dimethylphenyl)cyclohexane-1,4-diamine

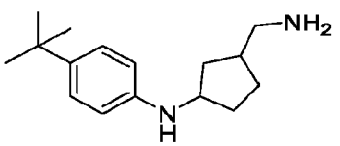


240

The title compound **240** (80.2 mg) was prepared in a total yield of 65.6% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((3,4-dimethylphenyl)amino)cyclohexyl)carbamate (178 mg, 0.560 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.76 (dd, J = 8.0, 5.2 Hz, 1H), 6.36 (dd, J = 18.0, 2.4 Hz, 1H), 6.27 (ddd, J = 15.6, 8.0, 2.4 Hz, 1H), 4.98 (d, J = 7.6 Hz, 1H), 3.37 – 2.75 (m, 2H), 2.05 (d, J = 2.0 Hz, 3H), 2.00 (d, J = 2.4 Hz, 3H), 1.97 – 1.86 (m, 2H), 1.73 – 1.47 (m, 4H), 1.36 (qd, J = 13.6, 12.4, 3.6 Hz, 1H), 1.15 – 1.02 (m, 1H). Mass (m/z): 219.3 $[M+H]^+$.

Compound 241

N-(3-(aminomethyl)cyclopentyl)-4-(tert-butyl)aniline

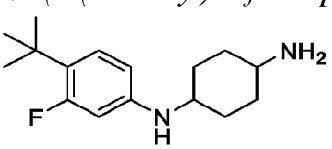


241

The title compound **241** (4.2 mg) was prepared in a total yield of 5.4% as a pink solid from 3-((4-(tert-butyl)phenyl)amino)cyclopentane-1-carboxamide (83 mg, 0.319 mmol), $LiAlH_4$ (47 mg, 1.276 mmol) and THF (10 mL) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, J = 8.0 Hz, 2H), 6.50 (s, 2H), 3.67 (dt, J = 12.8, 6.3 Hz, 1H), 2.71 (d, J = 16.8 Hz, 2H), 2.29 – 1.91 (m, 3H), 1.84 (ddd, J = 14.0 9.2, 5.6 Hz, 1H), 1.77 – 1.66 (m, 1H), 1.46 – 1.35 (m, 2H), 1.17 (s, 9H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 242

N1-(4-(tert-butyl)-3-fluorophenyl)cyclohexane-1,4-diamine 2,2,2-trifluoroacetate



242A
242B

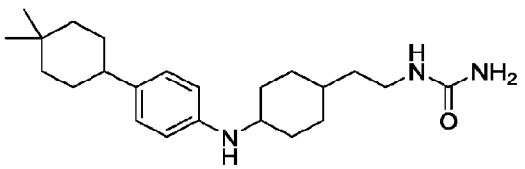
The title compound **242A** and **242B** were prepared according to the procedure for compound **20**. The residue was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 25%-30%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13 min) to afford compound **242A** (Rt = 8.13 min) in 19.0% yield as a white solid and **242B** (Rt = 8.63 min) in 18.1% yield as a white solid. **242A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 3H), 6.97 (dd, J = 10.2, 8.2 Hz, 1H), 6.37 – 6.21 (m, 2H), 3.09 (d, J =

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22.1 Hz, 1H), 2.99 (d, J = 5.1 Hz, 1H), 2.06 – 1.87 (m, 4H), 1.51 – 1.33 (m, 2H), 1.24 (d, J = 0.8 Hz, 9H), 1.15 (q, J = 11.4 Hz, 2H). Mass (m/z): 265.3 $[M+H]^+$. **242B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (s, 3H), 7.09 (dt, J = 8.7, 1.1 Hz, 1H), 6.56 (q, J = 2.5 Hz, 1H), 6.44 (dt, J = 8.7, 2.2 Hz, 1H), 3.07 (dd, J = 14.5, 7.3 Hz, 1H), 2.97 (d, J = 4.8 Hz, 1H), 2.00 – 1.84 (m, 4H), 1.44 – 1.34 (m, 2H), 1.32 (s, 9H), 1.13 (q, J = 11.6 Hz, 2H). Mass (m/z): 265.3 $[M+H]^+$.

Compound 243

1-(2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)ethyl)urea

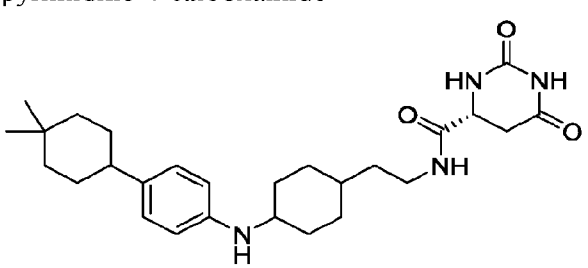


243

The desired product **243** (10.1 mg) as a white powder with 1:1 mixture by ^{1}H NMR in a yield of 24.8% was prepared from of N-(4-(2-aminoethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline (36 mg, 0.11 mmol), DMSO (5 mL), phenyl carbamate (18 mg, 0.13 mmol) according to the procedure for **116**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.91 (d, J = 8.0 Hz, 2H), 6.49 (dd, J = 19.6, 7.9 Hz, 2H), 5.86 (s, 1H), 5.34 (s, 2H), 5.13 (d, J = 27.3 Hz, 1H), 2.97 (d, J = 6.7 Hz, 2H), 2.20 (d, J = 6.4 Hz, 1H), 1.97 (t, J = 14.1 Hz, 2H), 1.73 (d, J = 12.5 Hz, 1H), 1.60 – 1.49 (m, 6H), 1.49 – 1.36 (m, 6H), 1.30 (dd, J = 14.1, 8.1 Hz, 5H), 1.03 (dt, J = 21.9, 11.7 Hz, 2H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 372.6 $[M+H]^+$.

Compound 244

(R)-N-(2-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)ethyl)-2,6-dioxohexahydropyrimidine-4-carboxamide



244A
244B

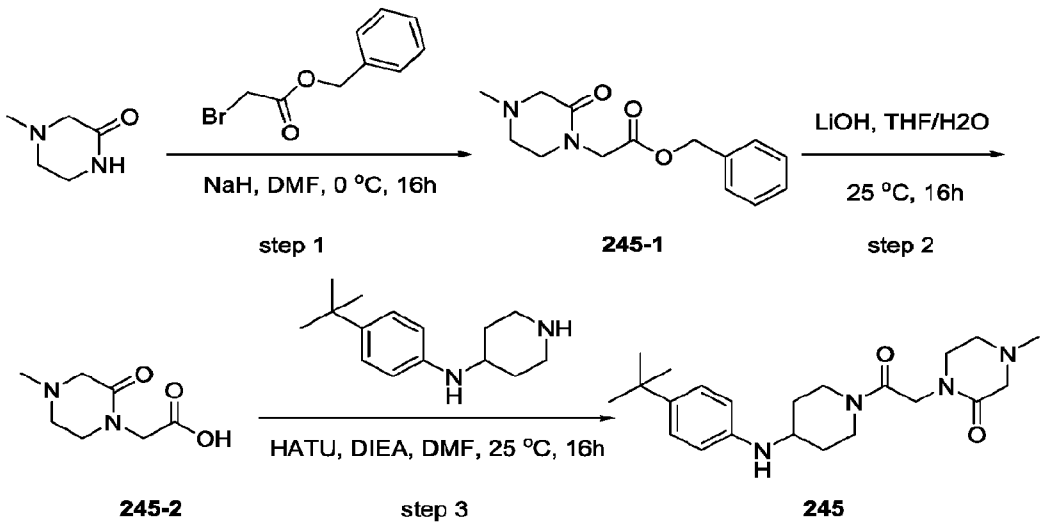
The title compound **244** (**244A** and **244B**) was prepared in a yield of 18.6% as a white powder from N-(4-(2-aminoethyl)cyclohexyl)-4-(4,4-dimethylcyclohexyl)aniline (50 mg, 0.15 mmol), (R)-2,6-dioxohexahydropyrimidine-4-carboxylic acid (29 mg, 0.18 mmol) according to the procedure for **1**. The mixture was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-5%-95%-95%-5%, 0 min-1 min-10 min-11 min-15.0 min) afford compound **244A** (Rt = 6.11 min) as a white solid and compound **244B** (Rt = 5.90 min) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (d, J = 1.9 Hz, 1H), 8.02 (t, J = 5.6 Hz, 1H), 7.64 – 7.51 (m, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.52 (d, J = 8.1 Hz, 2H), 5.18 (s, 1H), 3.93 (dt, J = 7.1, 3.5 Hz, 1H), 3.39 (s, 1H), 3.15 – 3.03 (m,

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2H), 2.83 (dd, J = 16.6, 7.2 Hz, 1H), 2.43 (dd, J = 16.2, 3.2 Hz, 1H), 2.21 (dq, J = 10.5, 5.8, 5.4 Hz, 1H), 1.53 (dt, J = 8.0, 3.3 Hz, 7H), 1.49 – 1.42 (m, 4H), 1.42 – 1.34 (m, 5H), 1.29 (dd, J = 12.3, 5.2 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H). Mass (m/z): 469.3 $[M+H]^+$.

Compound 245

1-(2-(4-((4-(tert-butyl)phenyl)amino)piperidin-1-yl)-2-oxoethyl)-4-methylpiper-azin-2-one



Step 1. benzyl 2-(4-methyl-2-oxopiperazin-1-yl)acetate **(245-1)**

A mixture of 4-methylpiperazin-2-one (500 mg, 4.38 mmol), NaH (210.26 mg, 5.25 mmol) in THF (5 mL) was stirred 1 hours at 0 °C. Then it was added benzyl 2-bromoacetate (1.1 g, 4.81 mmol). It was quenched by H_2O (30 mL) and extracted with DCM (3x30 mL). The organic layers were combined, washed with brine NaCl (2x30 mL) and dried with $MgSO_4$, filtered and concentrated to give product (800 mg, yield: 55.7%) as yellow oil. Mass (m/z): 262.9 $[M+H]^+$.

Step 2. 2-(4-methyl-2-oxopiperazin-1-yl)acetic acid **(245-2)**

To a solution of **245-1** (300 mg, 1.14 mmol), LiOH (273.89 mg, 11.43 mmol) in THF/H_2O=1:1 (5 mL). Then the mixture was stirred overnight at 25 °C. It was quenched by H_2O (300 mL) and extracted with EA (3x300 mL). The organic layers were combined, washed with brine NaCl (2x300 mL) and dried with $MgSO_4$, filtered and concentrated to afford the target product (100 mg, yield: 40.6%) as yellow oil.

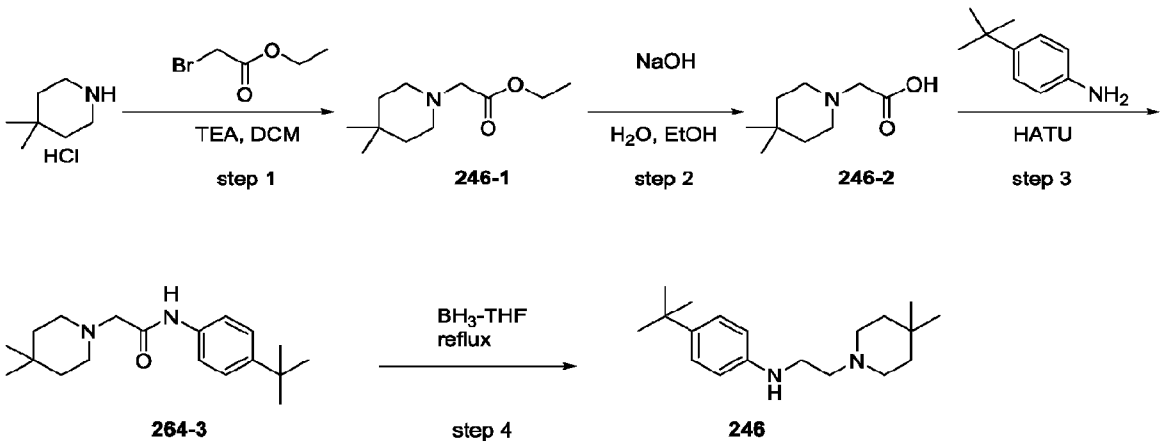
Step 3. Preparation of 1-(2-(4-((4-(tert-butyl)phenyl)amino)piperidin-1-yl)-2-oxoethyl) -4-methylpiperazin-2-one **(245)**

To a solution of **245-2** (80 mg, 0.46 mmol), N-(4-(tert-butyl)phenyl)piperidin-4-amine (107.96 mg, 0.46 mmol) in DMF (5 ml) was added HATU (88.33 mg, 0.23 mmol), and DIEA (600.45 mg, 4.64 mmol). Then the mixture was stirred overnight at rt. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product **245** (19.8 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.16 (d, J = 9.2 Hz, 2H), 6.63 (dd, J = 9.2 Hz, 2H), 4.34 (d, J = 16.0 Hz, 2H), 4.20 (d, J = 16.4 Hz, 1H), 3.85 (d, J = 14.0 Hz, 1H), 3.59 – 3.47 (m, 1H), 3.41 (t, J – 5.4 Hz, 2H), 3.18 (s, 2H), 2.90 (t, J – 12.4 Hz, 1H), 2.79 (s, 2H), 2.38 (d, J = 1.6 Hz, 3H), 2.03 (dd, J = 19.4, 14.8 Hz, 2H), 1.45 – 1.26 (m, 2H), 1.23 (s, 9H). Mass(m/z): 315.2 $[M+H]^+$.

Compound 246

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4-(tert-butyl)-N-(2-(4,4-dimethylpiperidin-1-yl)ethyl)aniline



Step 1. ethyl 2-(4,4-dimethylpiperidin-1-yl)acetate **(246-1)**

A mixture of 4,4-dimethylpiperidine (500 mg, 4.41 mmol) and TEA (1.78 g, 17.66 mmol) in DCM (10 mL) was stirred overnight at 25 °C. Then it was added ethyl 2-bromoacetate (811.39 mg, 4.85 mmol). It was quenched by H_2O (300 mL) and extracted with DCM (3x300 mL). The organic layers were combined, washed with brine NaCl (2x300 mL) and dried with $MgSO_4$, filtered and concentrated to give the target product (600 mg, 61.3%) as a yellow oil.

Step 2. 2-(4,4-dimethylpiperidin-1-yl)acetic acid **(246-2)**

To a solution of **246-1** (600 mg, 3.01 mmol), NaOH (361.26 mg, 9.03 mmol) in H_2O/EtOH=2:1 (15 ml). Then the mixture was stirred overnight at 50 °C. It was quenched by H_2O (300 mL) and extracted with EA (3x300 mL). The organic layers were combined, washed with brine NaCl (2x300 mL) and dried with $MgSO_4$, filtered and concentrated to give the target product (300 mg, 52.3%) as yellow oil.

Step 3. N-(4-(tert-butyl)phenyl)-2-(4,4-dimethylpiperidin-1-yl)acetamide **(246-3)**

To a solution of **246-2** (150 mg, 0.87 mmol), and 4-(tert-butyl)aniline (130.73 mg, 0.87 mmol) in DMF (5 mL) was added HATU (499.62 mg, 1.31 mmol), TEA (433.21 mg, 4.38 mmol). Then the mixture was stirred overnight at rt. It was quenched by H_2O (100mL) and extracted with EA (3x100mL). The organic layers were combined, washed with brine NaCl (2x100mL) and dried with $MgSO_4$, filtered and concentrated. The crude product was applied onto a silica gel column (12 g) eluted with PE:EA (5:1) to give the product (300 mg, 90.5%) as a yellow solid. Mass (m/z): 302.9 $[M+H]^+$.

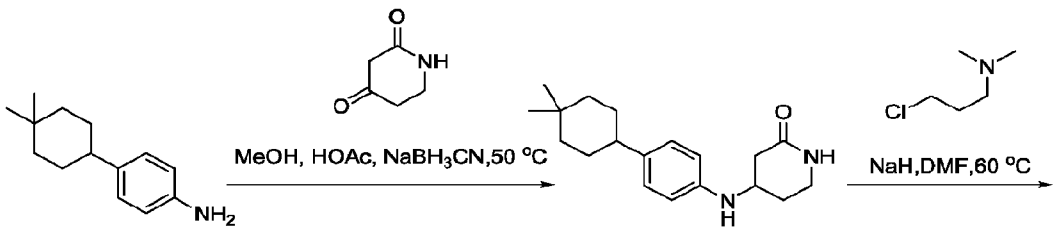
Step 4. Preparation of 4-(tert-butyl)-N-(2-(4,4-dimethylpiperidin-1-yl)ethyl)aniline **(246)**

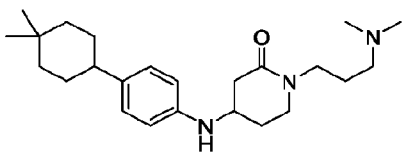
To a solution of **246-3** (160 mg, 0.53 mmol) in THF (5 mL) was added BH_3-THF(5 mL). Then the mixture was stirred overnight at 25 °C. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product **246** (39.5 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.40 (s, 1H), 7.17 (t, J = 5.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 3.49 (t, J = 5.6 Hz, 2H), 3.29 (dd, J = 4.8, 3.2 Hz, 4H), 3.28 (s, 2H), 1.64 (d, J = 5.0 Hz, 4H), 1.27 1.18 (m, 9H), 1.03 (d, J = 7.0 Hz, 6H). Mass (m/z): 289.0 $[M+H]^+$.

Compound 247

1-(3-(dimethylamino)propyl)-4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)piperidin-2-one

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247

Step 1. Preparation of 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)piperidin-2-one **(247-1)**

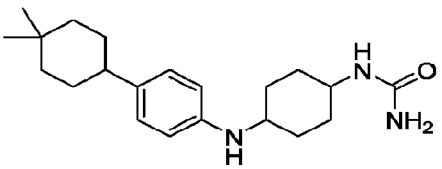
A mixture of 4-(4,4-dimethylcyclohexyl)aniline (200 mg, 0.98 mmol), 1λ2-piperidine-2,4-dione (133.5 mg, 1.18 mmol) and $NaBH_3CN$ (123.6 mg, 1.97 mmol) in MeOH (10 mL) and AcOH (1 drop) was stirred overnight at 50 °C. After cooling, the reaction solution was washed with water, and excess MeOH was distilled under vacuum and the residual oil was distilled under vacuum. Then the reaction solution was extracted three times with ethyl acetate (30 mL) and water (30 mL). The organic layers were combined, the solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE:EA=5:1) to give the desired product as oil (220 mg, 44.7%). Mass (m/z): 300.9 $[M+H]^+$.

Step 2. Preparation of 1-(3-(dimethylamino)propyl)-4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)piperidin-2-one **(247)**

The mixture of 4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)piperidin-2-one (132 mg, 0.44 mmol), 3-chloro-N,N-dimethylpropan-1-amine (80.2 mg, 0.66 mmol) and NaH (21.1 mg, 0.88 mmol) in DMF (3 mL) was stirred for 16 hours at 60 °C. After reaction was completed, solution was quenched with water and removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford the desired product **247** (22.2 mg, 12.7%) as brown oil. ^1H NMR (400 MHz, DMSO-d_6) δ 6.95 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 5.39 (br, 1H), 3.65 (br, 1H), 3.34 – 3.24 (m, 4H), 2.58 – 2.54 (m, 1H), 2.36 – 2.24 (m, 3H), 2.20 (s, 6H), 2.15 – 2.03 (m, 2H), 1.67 –1.23 (m, 11H), 0.93 (d, J = 8.6 Hz, 6H). Mass (m/z): 386.3 $[M+H]^+$.

Compound 248

1-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)urea

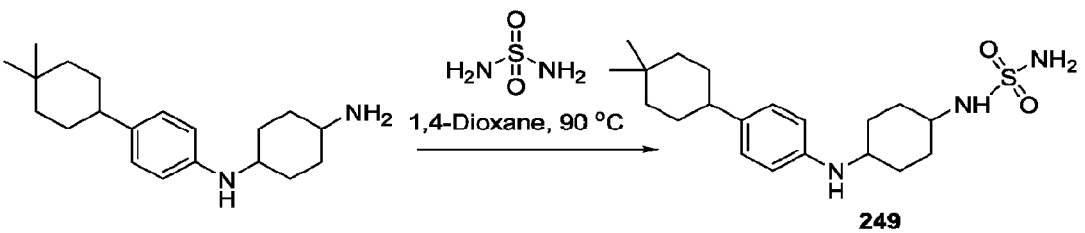


248

The desired product **248** (15.7 mg, 12.0%) as a white solid was prepared from N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclohexane-1,4-diamine (105 mg, 0.34 mmol), TMSNCO (40.25 mg, 0.35 mmol), TEA (70.7 mg, 0.70 mmol), DMAP (8.5 mg, 0.07 mmol) and DCM (10 mL) according to the procedure for **178**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, J = 8.3 Hz, 2H), 6.50 (d, J = 8.3 Hz, 2H), 5.96 (br, 1H), 5.37 (br, 2H), 5.16 (br, 1H), 3.25 (br, 1H), 2.20 (br, 1H), 1.64-1.23 (m, 17H), 0.93 (d, J = 8.4 Hz, 6H). Mass(m/z): 343.9 $[M+H]^+$.

Compound 249

N-(4-{[4-(4,4-dimethylcyclohexyl)phenyl]amino}cyclohexyl)aminosulfonamide

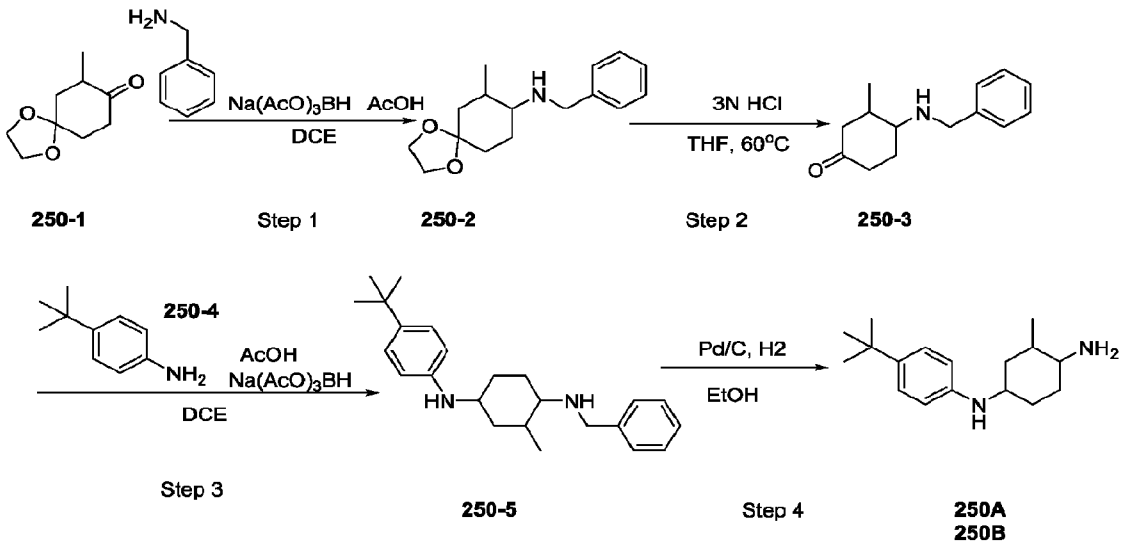


249

To a solution of 1-N-[4-(4,4-dimethylcyclohexyl)phenyl]cyclohexane-1,4-diamine (95 mg, 0.32 mmol), and sulfamoylamine (36.5 mg, 0.38 mmol) in 1,4-dioxane (10 mL) was stirred overnight at 90 °C under N_2. After cooling to rt., the reaction was concentrated under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 30%-50%) to afford the desired product **249** (13.2 mg, 10.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92 (d, J = 8.3 Hz, 2H), 6.49 (d, J = 8.4 Hz, 2H), 6.45 (s, 2H), 6.39 (d, J = 5.7 Hz, 1H), 5.09 (br, 1H), 3.25 (br, 2H), 2.28 – 2.16 (m, 1H), 1.67 –1 .24 (m, 16H), 0.93 (d, J = 8.6 Hz, 6H). Mass (m/z): 380.3 $[M+H]^+$.

Compound 250

N^1-(4-(tert-butyl)phenyl)-3-methylcyclohexane-1,4-diamine



Step 1. Preparation of N-benzyl-7-methyl-1,4-dioxaspiro[4.5]decan-8-amine (**250-2**)

The title compound **250-2** (420 mg) was prepared in a total yield of 53.6% as a light-yellow oil from 7-methyl-1,4-dioxaspiro[4.5]decan-8-one (510 mg, 3.0 mmol) phenylmethanamine (321 mg, 3.0 mmol) and $Na(AcO)_3BH$ (954 mg, 4.5 mmol) according to the procedure for **24-1**. Mass (m/z): 262.2 $[M+H]^+$.

Step 2. Preparation of 4-(benzylamino)-3-methylcyclohexan-1-one (**250-3**)

The title compound **250-3** (185 mg) was prepared in a total yield of 74.0% as a light-yellow oil from 7-methyl-1,4-dioxaspiro[4.5]decan-8-one (300 mg, 1.15 mmol) and 3N HCl (1.0 mL) according to the procedure for **233-4**. Mass (m/z): 217.3 $[M+H]^+$.

Step 3. Preparation of N1-benzyl-N4-(4-(tert-butyl)phenyl)-2-methylcyclohexane-1,4-diamine (**250-5**)

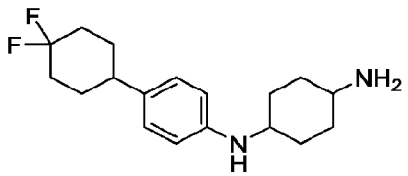
The title compound **250-5** (120 mg) was prepared in a total yield of 50.0% as a light-yellow oil from 4-(benzylamino)-3-methylcyclohexan-1-one (150 mg, 0.69 mmol), 4-(tert-butyl)aniline (103 mg, 0.69 mmol) and $Na(AcO)_3BH$ (293 mg, 1.38 mmol) according to the procedure for **24-1**. Mass (m/z): 351.3 $[M+H]^+$.

Step 4. Preparation of N1-(4-(tert-butyl)phenyl)-3-methylcyclohexane-1,4-diamine (**250**)

The title compound **250A** and **250B** were prepared according to the procedure for compound **232-3**. The crude residue was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 10%-27%-95%-95%-10%, 0 min-12 min-12.5 min-13.5 min-15 min) to afford compound **250A** (Rt = 10.17 min) in 4.0% yield as a white solid and **250B** (Rt = 5.05 min) in 15.3% yield as a white solid. **250A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.15 – 7.10 (m, 2H), 6.61 – 6.57 (m, 2H), 3.62 – 3.58 (m, H), 2.47 (td, J = 10.0, 4.0 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.73 – 1.55 (m, 3H), 1.37 – 1.29 (m, 2H), 1.23 (s, 9H), 0.98 (d, J = 6.4 Hz, 3H). Mass (m/z): 261.3 $[M+H]^+$. **250B**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.16 – 7.10 (m, 2H), 6.61 – 6.57 (m, 2H), 3.25 – 3.18 (m, 1H), 2.95 – 2.89 (m, 1H), 1.86 – 1.62 (m, 5H), 1.32 – 1.20 (m, 11H), 0.94 (d, J = 6.8 Hz, 3H). Mass (m/z): 261.3 $[M+H]^+$.

Compound 251

N^1-(4-(4,4-difluorocyclohexyl)phenyl)cyclohexane-1,4-diamine

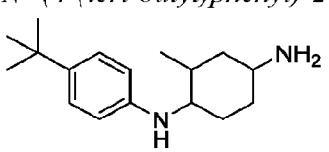


251A
251B

The title compound **251A** and **251B** were prepared according to the procedure for compound **24**. The crude residue was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 10%-30%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13 min) to afford compound **251A** (Rt = 8.29 min) in 17.7% yield as a white solid and **251B** (Rt = 6.36 min) in 8.8% yield as a white solid. **251A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (d, J = 8.6 Hz, 2H), 6.47 (d, J = 8.6 Hz, 2H), 5.16 (d, J = 7.6 Hz, 1H), 3.26 – 3.16 (m, 1H), 2.80 – 2.71 (m, 1H), 2.04 – 1.72 (m, 7H), 1.62 – 1.42 (m, 10H). Mass (m/z): 309.3 $[M+H]^+$. **251B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.87 (d, J = 8.5 Hz, 2H), 6.43 (d, J = 8.6 Hz, 2H), 5.11 (d, J = 8.2 Hz, 1H), 3.07 – 2.94 (m, 1H), 2.48 – 2.49 (m, 1H), 2.07 – 1.67 (m, 11H), 1.57 – 1.48 (m, 3H), 1.11 – 0.99 (m, 4H). Mass(m/z): 309.3 $[M+H]^+$.

Compound 252

N^1-(4-(tert-butyl)phenyl)-2-methylcyclohexane-1,4-diamine



252A
252B
252C
252D

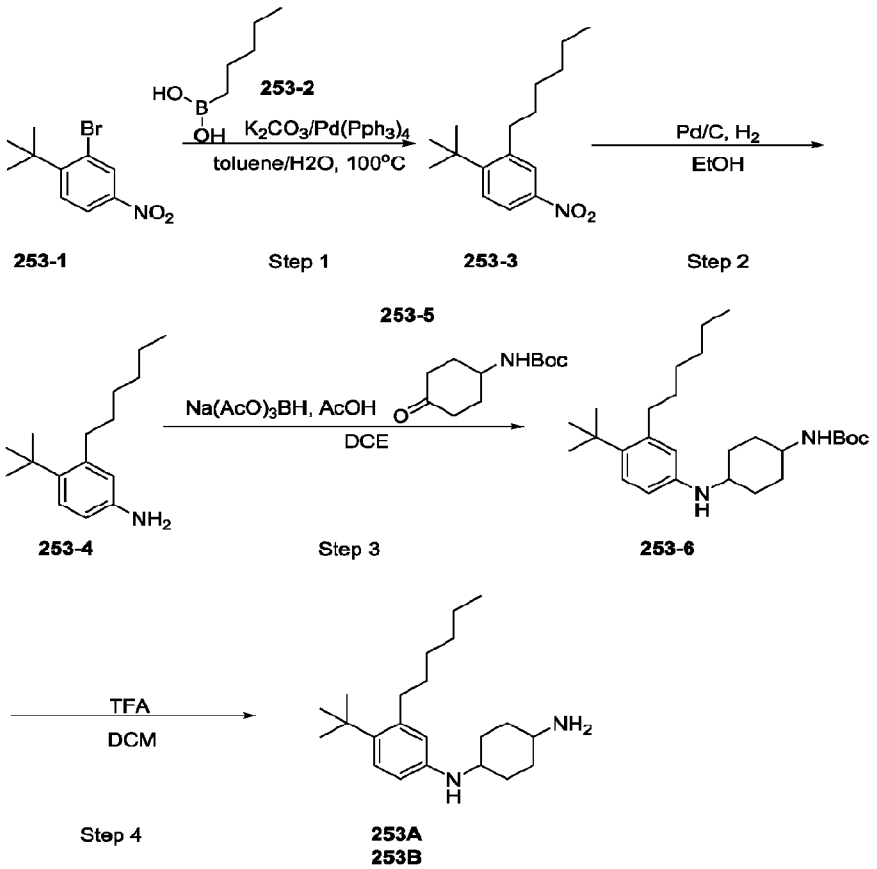
The title compound **252A**, **252B**, **252C**, **252D** were prepared according to the procedure for compound **250**. The crude residue was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 10%-43%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13 min) to afford compound **252A** (Rt = 9.55 min) in 1.1% yield as a white solid, **252B** (Rt = 7.47 min) in 2.8% yield as a white solid, **252C** (Rt = 6.45 min) in 2.7% yield as a white solid and **252D** (Rt = 5.88 min) in 7.3% yield as a white solid. **252A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.12 – 7.07 (m, 2H), 6.61 – 6.54 (m, 2H), 3.51 – 3.45 (m, 1H), 2.77 – 2.63 (m, 1H), 1.98 – 1.91 (m, 1H), 1.86 – 1.74 (m, 1H), 1.67 – 1.56 (m, 2H), 1.47 – 1.36 (m, 1H), 1.33 – 1.26 (m, 2H), 1.23 (s, 9H), 0.97 (d, J = 7.0 Hz, 3H). Mass (m/z): 261.3 $[M+H]^+$. **252B**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.16 – 7.05 (m, 2H), 6.57 – 6.46 (m, 2H), 3.14 – 2.92 (m, 2H), 1.89 – 1.77 (m, 2H), 1.75 – 1.54 (m, 3H), 1.52 – 1.39 (m, 3H), 1.23 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H). Mass (m/z): 261.3 $[M+H]^+$. **252C**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.10 – 7.06 (m, 2H), 6.53 – 6.48 (m, 2H), 2.81 – 2.67 (m, 2H), 2.11 – 1.81 (m, 4H), 1.51 – 1.41 (m, 1H), 1.22 (s, 9H), 1.14 – 1.02 (m, 2H), 1.00 (d, J = 6.4 Hz, 3H). Mass (m/z): 261.3 $[M+H]^+$. **252D**: ^{1}H NMR (400 MHz, Methanol-d_4) δ

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7.14 – 7.09 (m, 2H), 6.62 – 6.55 (m, 2H), 3.44 – 3.37 (m, 1H), 2.94 – 2.84 (m, 1H), 2.32 – 2.24 (m, 1H), 1.91 – 1.84 (m, 1H), 1.79 – 1.66 (m, 2H), 1.59 – 1.51 (m, 1H), 1.45 – 1.35 (m, 1H), 1.30 – 1.19 (m, 10H), 0.88 (d, J = 7.2 Hz, 3H). Mass (m/z): 261.3 $[M+H]^+$.

Compound 253

N^1-(4-(tert-butyl)-3-hexylphenyl)cyclohexane-1,4-diamine



Step 1. Preparation of 1-(tert-butyl)-2-hexyl-4-nitrobenzene (**253-3**)

The title compound **253-3** (150 mg) was prepared in a total yield of 46.2% as a light-yellow oil from 2-bromo-1-(tert-butyl)-4-nitrobenzene (193 mg, 0.74 mmol), pentylboronic acid (593 mg, 4.5 mmol), K_2CO_3 (153 mg, 1.11 mmol) and $Pd(PPh_3)_4$ (177 mg, 0.15 mmol) according to the procedure for **208-1**.

Step 2. Preparation of 4-(tert-butyl)-3-hexylaniline (**253-4**)

The title compound **253-4** (50 mg) was prepared in a total yield of 63.1% as a yellow solid from 1-(tert-butyl)-2-hexyl-4-nitrobenzene (150 mg, 0.57 mmol) and 10% Pd/C (3.6 mg, 3.4 umol) according to the procedure for **208-2**. Mass (m/z): 234.3 $[M+H]^+$.

Step 3. Preparation of tert-butyl (4-((4-(tert-butyl)-3-hexylphenyl)amino)cyclohexyl)carbamate (**253-6**)

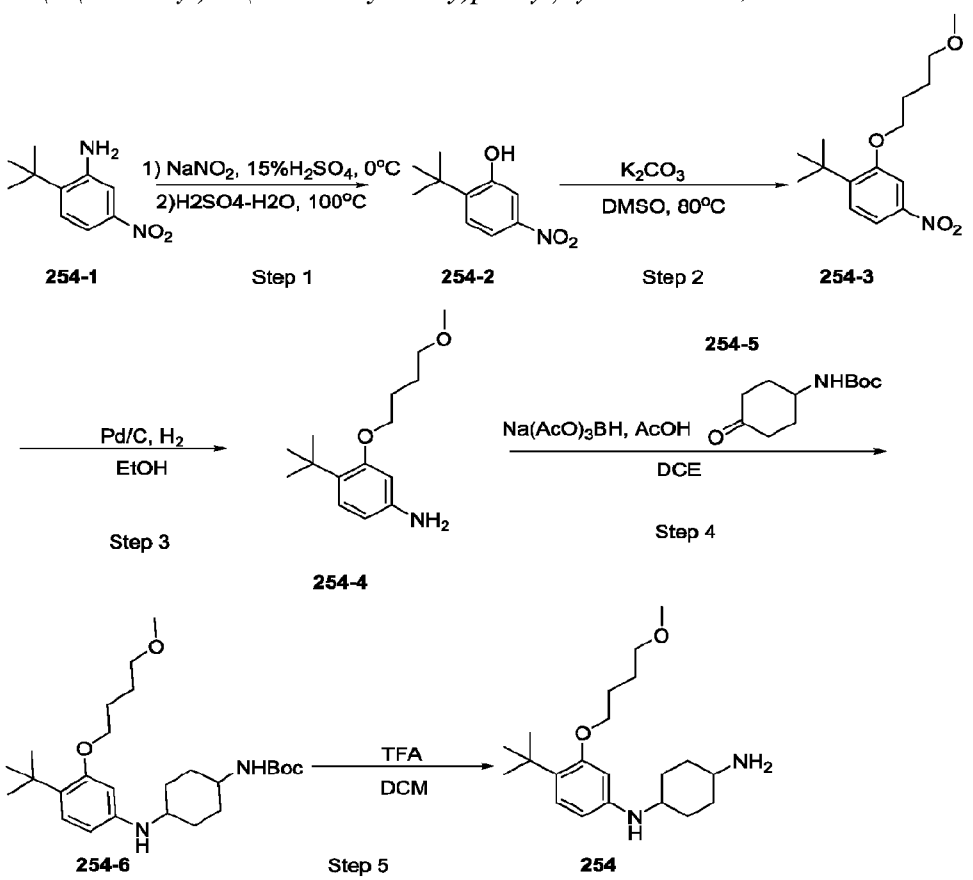
The title compound **253-6** (35 mg) was prepared in a total yield of 38.8% as a yellow solid from 4-(tert-butyl)-3-hexylaniline (50 mg, 0.21 mmol), tert-butyl (4-oxocyclohexyl)carbamate (89 mg, 0.42 mmol) and $Na(AcO)_3BH$ (89 mg, 0.42 mmol) according to the procedure for **24-1**. Mass (m/z): 431.4 $[M+H]^+$.

Step 4. Preparation of N1-(4-(tert-butyl)-3-hexylphenyl)cyclohexane-1,4-diamine (**253**)

The title compound **253A** and **253B** were prepared according to the procedure for compound **24**. The crude residue was purified by preparative TLC (H_2O/MeOH/DCM=0.1/1/5) to afford compound **253A** (Rf value = 0.40) in 57.4% yield as a white solid and **253B** (Rf value = 0.36) in 15.3% yield as a white solid. **253A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.08 (d, J = 8.8 Hz, 1H), 6.49 (d, J – 2.8 Hz, 1H), 6.39 (dd, J – 8.6, 2.8 Hz, 1H), 3.56 – 3.49 (m, 1H), 3.24 – 3.15 (m, 1H), 2.74 – 2.67 (m, 2H), 1.88 – 1.71 (m, 8H), 1.61 – 1.52 (m, 2H), 1.46 – 1.36 (m, 2H), 1.36 – 1.31 (m, 13H), 0.94 – 0.86 (m, 3H). Mass (m/z): 331.3 $[M+H]^+$. **253B**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.08 (d, J = 8.6 Hz, 1H), 6.49 (d, J = 2.8 Hz, 1H), 6.40 (dd, J = 8.6, 2.7 Hz, 1H), 3.24 – 3.17 (m, 1H), 3.11 – 3.04 (m, 1H), 2.74 – 2.67 (m, 2H), 2.17 – 2.10 (m, 2H), 2.09 – 1.99 (m, 2H), 1.57 – 1.26 (m, 21H), 0.93 – 0.85 (m, 3H). Mass (m/z): 331.3 $[M+H]^+$.

Compound 254

N^1-(4-(tert-butyl)-3-(4-methoxybutoxy)phenyl)cyclohexane-1,4-diamine



Step 1. Preparation of 2-(tert-butyl)-5-nitrophenol (**254-2**)

To a mixture of 2-tert-butyl-5-nitroaniline (582 g, 3.0 mmol) in 10 mL of 15% H_2SO_4 was added dropwise a solution of $NaNO_2$ (217 mg, 3.15 mmol) in water (3 mL) at 0 °C. The resulting mixture was stirred at 0-5 °C for 20 min. Then the solution was added dropwise to a solution of 5 mL of H_2SO_4 –H_2O (V/V=1/2) stirred at 100°C. The resulting mixture was stirred at 100 °C for 20 min. After cooling to rt, and extracted by DCM (20 mL x 3), the combined organic layers were washed with water (20 mL), dried over Na_2SO_4 and concentrated. The

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residue was purified by prep-TLC (DCM/PE=1/3) to afford the title compound as a yellow oil (300 mg, 51.5%). Mass(m/z):194.0 $[M-H]^-$.

Step 2. Preparation of 1-(tert-butyl)-2-(4-methoxybutoxy)-4-nitrobenzene (**254-3**)

To a mixture of 2-(tert-butyl)-5-nitrophenol (150 mg, 0.77 mmol), KI (12.8 mg, 77 ummol) and K_2CO_3 (212 mg, 1.54 mmol) in DMSO (2.0 mL) was added 1-bromo-4-methoxybutane (190 mg, 1.15 mmol). Then the mixture was stirred overnight at 80 °C. After cooling to rt, 5 mL was added, and extracted by DCM (10 mL x 3). The combined organic layers were washed with water (10 mL x 3), dried over Na_2SO_4 and concentrated to afford the title compound as a crude yellow oil (216 mg, 100%).

Step 3. Preparation of 4-(tert-butyl)-3-(4-methoxybutoxy)aniline (**254-4**)

The title compound **254-4** (193 mg) was prepared in a total yield of 100% as a yellow solid from 1-(tert-butyl)-2-(4-methoxybutoxy)-4-nitrobenzene (216 mg, 0.77 mmol) and 10% Pd/C (81.6 mg, 77 umol) according to the procedure for **208-2**. Mass (m/z): 252.4 $[M+H]^+$.

Step 4. Preparation of N1-(4-(tert-butyl)-3-(4-methoxybutoxy)phenyl)cyclohexane-1,4-diamine (**254-6**)

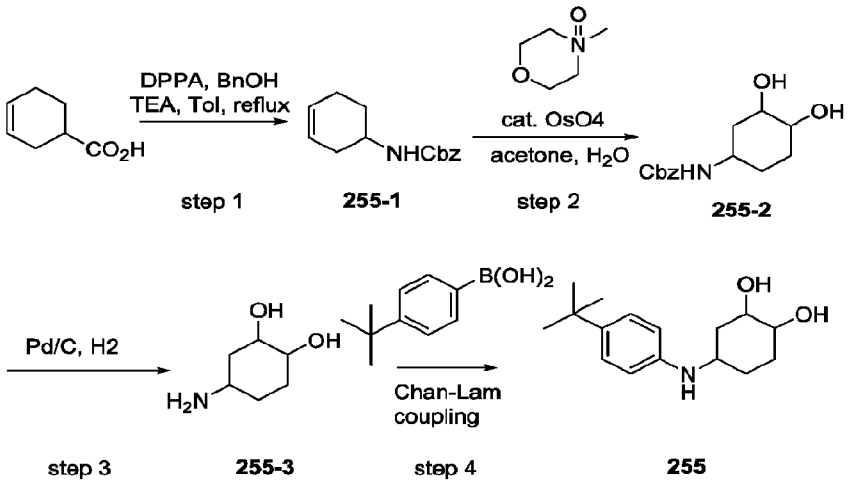
The title compound **254-6** (62 mg) was prepared in a total yield of 18.0% as a yellow solid from 4-(tert-butyl)-3-(4-methoxybutoxy)aniline (193 mg, 0.77 mmol), tert-butyl (4-oxocyclohexyl)carbamate (328 mg, 1.54 mmol) and $Na(AcO)_3BH$ (326 mg, 1.54 mmol) according to the procedure for **24-1**. Mass (m/z): 449.4 $[M+H]^+$.

Step 5. Preparation of N1-(4-(tert-butyl)-3-(4-methoxybutoxy)phenyl)cyclohexane-1,4-diamine (**254**)

The title compound **254** (32.2 mg) was prepared in a total yield of 66.1% as a white solid with 1:1 mixture by ^1H NMR from N1-(4-(tert-butyl)-3-(4-methoxybutoxy)phenyl)cyclohexane-1,4-diamine (62 mg, 0.14 mmol) and TFA (2.0 mL) according to the procedure for **24**. ^1H NMR (400 MHz, Methanol-d_4) δ 6.99 (dd, J = 10.4, 8.4 Hz, 1H), 6.30 (t, J = 2.6 Hz, 1H), 6.20 (dd, J = 8.4, 2.3 Hz, 0.5H), 6.15 (dd, J = 8.4, 2.3 Hz, 0.5H), 3.93 (t, J = 6.0 Hz, 2H), 3.56 – 3.49 (m, 0.5H), 3.46 (t, J = 6.2 Hz, 2H), 3.33 (s, 3H), 3.26 – 3.19 (m, 1H), 3.12 – 3.04 (m, 0.5H), 2.19 – 2.11 (m, 1H), 2.10 – 2.04 (m, 0.5H), 1.95 – 1.65 (m, 8H), 1.56 – 1.45 (m, 1H), 1.37 – 1.12 (m, 11H). Mass (m/z): 349.3 $[M+H]^+$.

Compound 255

4-((4-(tert-butyl)phenyl)amino)cyclohexane-1,2-diol



Step 1. Preparation of benzyl cyclohex-3-en-1-ylcarbamate **(255-1)**

A mixture of cyclohex-3-ene-1-carboxylic acid (1 g, 7.93 mmol), TEA (882 mg, 8.72 mmol) and DPPA (2.18 g, 7.93 mmol) in toluene (40 mL) was refluxed for 2 hours. After BnOH (857 mg, 7.93 mmol), the mixture was refluxed for 10 hours. The mixture was evaporated in vacuo and the obtained residue was diluted with ethyl acetate. The organic layer was washed successively with 1N hydrochloric acid, an aqueous saturated sodium hydrogen carbonate solution and brine. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated to afford the product (1.56 g, 85%) as a yellow solid. Mass (m/z): 232.1 $[M+H]^+$.

Step 2. Preparation of benzyl (3,4-dihydroxycyclohexyl)carbamate **(255-2)**

To a solution of benzyl (3,4-dihydroxycyclohexyl)carbamate (1.56 g, 6.74 mmol) in a mixture of tetrahydrofuran (40 mL) and water (5 mL) was added 4-methylmorpholine 4-oxide(1.19 g, 10.1 mmol) and OsO_4 (500 mg, 1.97 mmol). The mixture was stirred at ambient temperature for 30 minutes. The resulting mixture was quenched with $Na_2S_2O_3$ aqueous and the obtained residue was diluted with ethyl acetate. The organic phases were combined, dried over Na_2SO_4, filtered and concentrated to afford the product (1.1 g, 62%) as a white solid. Mass (m/z): 266.1 $[M+H]^+$.

Step 3. Preparation of 4-aminocyclohexane-1,2-diol **(255-3)**

A mixture of benzyl (3,4-dihydroxycyclohexyl)carbamate (700 mg, 2.64 mmol) and Pd/C (281 mg, 0.26 mmol) in ethanol (10 mL) was stirred at ambient temperature under hydrogen atmosphere for overnight. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo. The target product (288 mg, 83%) was obtained as a white solid. Mass (m/z): 132.1 $[M+H]^+$.

Step 4. Preparation of 4-((4-(tert-butyl)phenyl)amino)cyclohexane-1,2-diol **(255)**

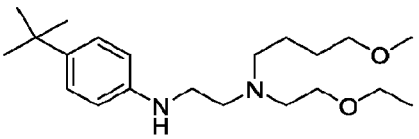
To a solution of 4-aminocyclohexane-1,2-diol (288 mg, 2.20 mmol), (4-(tert-butyl)phenyl)boronic acid (391 mg, 2.20 mmol) and TEA (1.11 g, 11 mmol) in CH_2Cl_2 (20 ml) was added $Cu(OAc)_2$ (877 mg, 4.39 mmol). Then the mixture was stirred for overnight at rt. The reaction was filtered through celite and the filtrate was evaporated in vacuo. The residue was purified by prep-TLC to afford the desired product **255** (11.4 mg, 4%) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 7.15 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 4.01 – 3.94 (m, 1H), 3.70 – 3.56 (m, 2H), 2.21 – 2.12 (m, 1H), 2.06 – 1.97 (m, 1H), 1.86 – 1.75 (m,

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1H), 1.75 – 1.65 (m, 1H), 1.44 – 1.35 (m, 1H), 1.26 (s, 9H). Mass (m/z): 263.9 $[M+H]^+$.

Compound 256

N1-(4-(tert-butyl)phenyl)-N2-(2-ethoxyethyl)-N2-(4-methoxybutyl)ethane-1,2-diamine

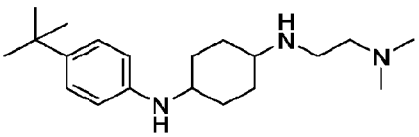


256

The title compound **256** (44 mg, 33%) as a white solid was prepared from N-(4-(tert-butyl)phenyl)-2-((2-ethoxyethyl)(4-methoxybutyl)amino)acetamide (139 mg, 0.38 mmol), and BH_3-THF (20 mL) according to the procedure for **105**. ^1H NMR (400 MHz, CD_3OD) δ 7.22 (d, J = 8.7 Hz, 2H), 6.67 (dd, J = 8.6, 2.0 Hz, 2H), 3.70 (s, 2H), 3.48 (q, J = 7.0 Hz, 4H), 3.39 (dt, J = 4.3, 3.7 Hz, 6H), 3.32 (s, 3H), 3.27 – 3.18 (m, 2H), 1.85 – 1.74 (m, 2H), 1.64 – 1.56 (m, 3H), 1.28 – 1.25 (m, 9H), 1.15 (t, J = 7.0 Hz, 3H). Mass (m/z): 350.9 $[M+H]^+$.

Compound 257

N-(4-cyclohexylphenyl)-1-ethylpiperidin-4-amine

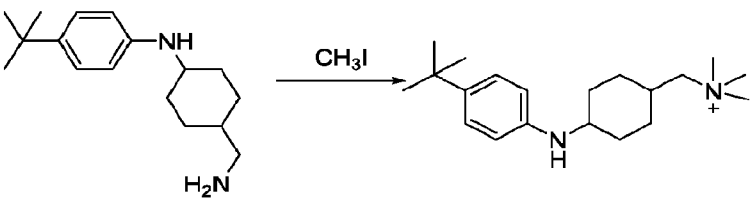


257

The title compound **257** (17.2 mg, 13.2%) as a yellow solid was prepared from 4-((4-(tert-butyl)phenyl)amino)cyclohexan-1-one (100 mg, 0.41mmol), MeOH (5 ml), N1,N1-dimethylethane-1,2-diamine (36 mg, 0.41 mmol) and acetic acid (2.46 mg, 0.041 mmol) according to the procedure for **5**. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 6.52 (d, J = 8.0 Hz, 2H), 3.26 – 2.95 (m, 5H), 2.52 (s, 6H), 2.22 (m, 4H), 1.62 (s, 2H), 1.25 (s, 9H), 1.21 – 1.04 (m, 2H). Mass (m/z): 318.3 $[M+H]^+$.

Compound 258

1-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)-N,N,N-trimethylmethanaminium



258

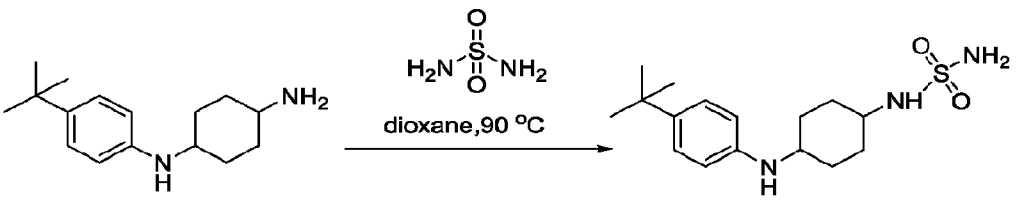
To a solution of N-(4-(aminomethyl)cyclohexyl)-4-(tert-butyl)aniline (120 mg, 0.46mmol) in MeOH (5 mL) was added K_2CO_3 (180 mg, 1.30 mmol) and iodomethane (327 mg, 2.3 mmol). Then the mixture was stirred at 25 °C for 12 h. Quenched with water (20 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, concentrated under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford the desired product **258** (10.1 mg, 7.2%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 3.37 (s, 1H), 3.24

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(s, 2H), 3.07 (s, 9H), 2.07 (s, 1H), 1.67 (d, J = 12 Hz, 2H), 1.55 (s, 6H), 1.20 (s, 9H). Mass (m/z): 303.3 $[M+H]^+$.

Compound 259

N-(4-{[4-(4,4-dimethylcyclohexyl)phenyl]amino}cyclohexyl)aminosulfonamide



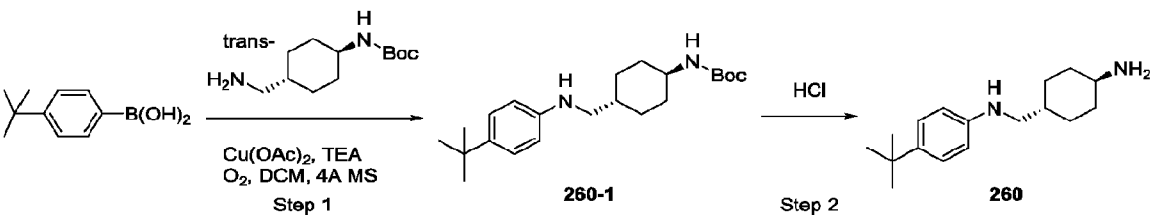
259A

259B

A solution of N1-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine (70 mg, 0.28 mmol), and sulfamoylamine (32.8 mg, 0.34 mmol) in 1,4-dioxane (10 mL) was stirred overnight at 90 °C under N_2. After cooling to rt., the reaction was concentrated under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 20%-40%) to afford the desired product **295A** (19.3 mg, 20.6%) as a white solid and **295B** (11.0 mg, 11.7%) as a white solid. **259A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, J = 8.6 Hz, 2H), 6.51 (d, J = 8.6 Hz, 2H), 6.45 (s, 2H), 6.38 (d, J = 5.8 Hz, 1H), 5.11 (br, 1H), 3.57 (br, 1H), 2.54 (br, 1H), 1.76–1.56 (m, 8H), 1.20 (s, 9H). Mass (m/z): 326.2 $[M+H]^+$. HPLC: Rt=3.384 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min). **259B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (br, 2H), 7.17 (br, 2H), 6.57 (d, J = 6.7 Hz, 1H), 6.50 (br, 2H), 3.25 (br, 1H), 3.03 (br, 1H), 1.96 (t, J = 15.2 Hz, 4H), 1.42 (br, 2H), 1.26 (s, 9H), 1.21-1.18 (m, 2H). Mass (m/z): 326.2 $[M+H]^+$. HPLC: Rt=3.273 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min).

Compound 260

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(tert-butyl)aniline



Step 1. Preparation of tert-butyl ((1r,4r)-4-(((4-(tert-butyl)phenyl)amino)methyl)cyclohexyl)carbamate (**260-1**)

A 100-mL round-bottom flask was charged with tert-butyl ((1r,4r)-4-(aminomethyl)cyclohexyl)carbamate (232 mg,1.01 mmol, 1.1 eq), (4-(tert-butyl)phenyl)boronic acid (150 mg, 0.84 mmol, 1.00 eq), $Cu(OAc)_2$ (306 mg,1.7 mmol, and 2.00 eq) and TEA (426 mg, 4.2 mmol, 5.00 eq) and 4Å MS (1 g). The reaction was stirred at R.T. under O_2 atmosphere for 18 hours. The solids were filtered and solvent was removed

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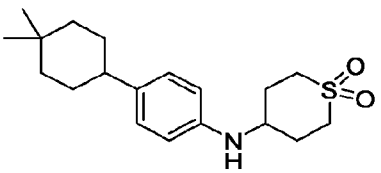
under vacuum. The residue was purified by Flash Chromatography to give 260-1 (0.2 g, 65.6% yield) as a yellow solid. MS (m/z) 361.3 $[M+H]^+$.

Step 2. Preparation of N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(tert-butyl)aniline (**260**)

260-1 (200 mg, 0.28 mmol) and HCl in 1,4-dioxane (10 mL, 4N) were placed in a flask stirred at 25 °C for 16 hrs. Excess 1,4-dioxane was distilled under vacuum and the residue was purified by Flash Chromatography to afford **260** (68.2 mg 47.3%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, J = 8.6 Hz, 2H), 6.46 (d, J = 8.6 Hz, 2H), 5.36 (t, J = 5.5 Hz, 1H), 2.79 (t, J = 6.2 Hz, 2H), 1.76 (s, 4H), 1.42 (s, 1H), 1.20 (s, 9H), 0.94 (d, J = 8.4 Hz, 4H). MS (m/z) 261.3 $[M+H]^+$.

Compound 261

4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)tetrahydro-2H-thiopyran 1,1-dioxide

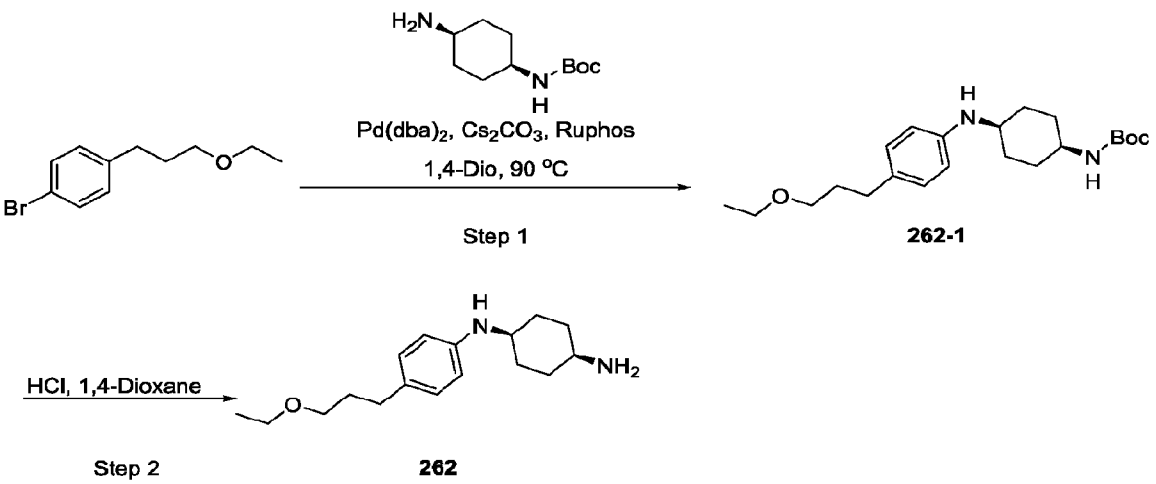


261

The desired product **261** (5.4 mg, 4.5%) as a white solid was prepared from 4-(4,4-dimethylcyclohexyl)aniline (70 mg, 0.34 mmol), tetrahydro-4H-thiopyran-4-one 1,1-dioxide (61.2 mg, 0.41 mmol), borane-2-picoline complex (55.2 mg, 0.52 mmol), CH_3COOH (1 mL) and H_2O (9 mL) according to the procedure for **90**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.96 (d, J = 8.3 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 5.46 (d, J = 8.7 Hz, 1H), 3.60 (d, J = 8.7 Hz, 1H), 3.23 – 3.10 (m, 4H), 2.23 – 2.13 (m, 3H), 1.92 – 1.83 (m, 2H), 1.59 – 1.37 (m, 6H), 1.31 – 1.23 (m, 2H), 0.93 (d, J = 8.8 Hz, 6H). Mass (m/z): 336.3 $[M+H]^+$.

Compound 262

(1s,4s)-N1-(4-(3-ethoxypropyl)phenyl)cyclohexane-1,4-diamine



Step 1. Preparation of tert-butyl ((1s,4s)-4-((4-(3-ethoxypropyl)phenyl)amino)cyclohexyl)carbamate **(262-1)**

A mixture of 1-bromo-4-(3-ethoxypropyl)benzene (200 mg, 0.82 mmol), tert-butyl ((1s,4s)-4-aminocyclohexyl)carbamate (352.6 mg, 1.65 mmol), $Pd_2(dba)_3$ (75.3 mg, 0.08

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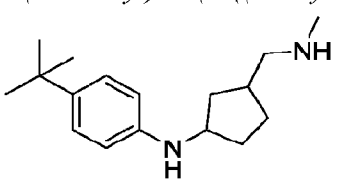
mmol), Ruphos (76.8 mg, 0.16 mmol), Cs_2CO_3 (536.0 mg, 1.65 mmol) in 1,4-dioxane (10 mL) was stirred overnight at 90 °C under N_2 atmosphere. After cooling to rt, the reaction solution was washed with water, and the reaction solution was extracted three times with ethyl acetate (20 mL) and water (20 mL). Organic layers were combined, the solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE:EA=5:1) to give the desired product (300 mg, 58.1%) as an oil. Mass (m/z): 377.3 $[M+H]^+$.

Step 2. Preparation of (1s,4s)-N1-(4-(3-ethoxypropyl)phenyl)cyclohexane-1,4-diamine **(262)**

The mixture of tert-butyl ((1s,4s)-4-((4-(3-ethoxypropyl)phenyl)amino)cyclohexyl)carbamate (300 mg, 0.79 mmol) in 1,4-dioxane (10 mL) and 1,4-dioxane/HCl (10 mL) was stirred for 16 hour at 25 °C. After reaction was completed, solvent was removed under vacuum and the residue was purified by prep-HPLC(column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 5%-20%) to afford the desired product **262** as a white solid. (23.6 mg, 10.7%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (d, J = 8.3 Hz, 2H), 6.54 (d, J = 8.3 Hz, 2H), 5.36 (br, 1H), 3.41– 3.35 (m, 3H), 3.31 (t, J = 6.5 Hz, 2H), 3.02 (br, 1H), 2.43 (t, J = 7.6 Hz, 2H), 1.93 – 1.53 (m, 10H), 1.10 (t, J = 7.0 Hz, 3H). Mass (m/z): 277.3 $[M+H]^+$.

Compound 263

4-(tert-butyl)-N-(3-((methylamino)methyl)cyclopentyl)aniline

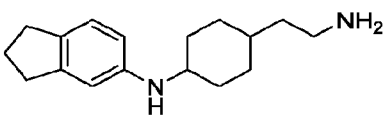


263

The title compound **263** (18.8 mg) was prepared in a total yield of 22.0% as a yellow solid from 3-((4-(tert-butyl)phenyl)amino)-N-methylcyclopentane-1-carboxamide (90 mg, 0.328 mmol), $LiAlH_4$ (49 mg,1.314 mmol) and THF (10 mL) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 – 6.96 (m, 2H), 6.45 (d, J = 8.2 Hz, 2H), 5.63 – 5.22 (m, 1H), 3.64 (s, 1H), 2.82 (s, 2H), 2.43 (s, 3H), 2.26 – 2.19 (m, 2H), 1.89 – 1.69 (m, 3H), 1.47 – 1.43 (m, 1H), 1.16 (s, 9H). Mass (m/z): 261.3 $[M+H]^+$.

Compound 264

N-(4-(2-aminoethyl)cyclohexyl)-2,3-dihydro-1H-inden-5-amine



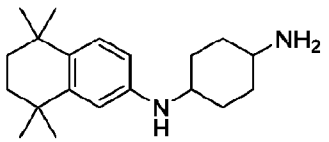
264

The title compound **264** (47.1 mg) was prepared in a total yield of 34.2% as a brown solid from 2-(4-((2,3-dihydro-1H-inden-5-yl)amino)cyclohexyl)acetamide (145 mg, 0.533 mmol), $LiAlH_4$ (79 mg,2.132 mmol) and THF (10 mL) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.90 (dd, J = 8.0, 4.2 Hz, 1H), 6.55 – 6.38 (m, 2H), 5.65 – 4.98 (m, 1H), 2.71 (dq, J = 14.8, 8.8, 7.2 Hz, 6H), 1.93 (p, J = 7.2 Hz, 3H), 1.76 – 1.33 (m, 11H). Mass (m/z): 259.3 $[M+H]^+$.

Compound 265

N1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclohexane-1,4-diamine

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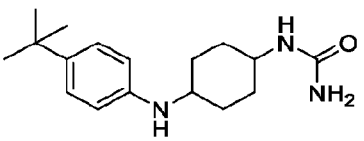


265

The title compound **265** (21.8 mg) was prepared in a yield of 29.5% as a white powder with 1:0.41 mixture by ^{1}H NMR from 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-amine (50 mg, 0.25 mmol), tert-butyl (4-oxocyclohexyl)carbamate (78 mg, 0.37 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 4H), 7.00 (dd, J = 8.5, 4.7 Hz, 1H), 6.51 (d, J = 2.5 Hz, 0.40H), 6.45 (d, J = 2.5 Hz, 1H), 6.37 (td, J = 8.6, 8.0, 2.4 Hz, 1H), 5.14 (d, J = 5.4 Hz, 0.41H), 5.08 (d, J = 8.0 Hz, 1H), 3.40 (s, 0.41H), 3.17 (d, J = 4.9 Hz, 1H), 3.08 (d, J = 8.3 Hz, 1H), 2.98 (tt, J = 11.5, 3.7 Hz, 1H), 1.99 (td, J = 10.4, 5.3 Hz, 4H), 1.85 – 1.67 (m, 2H), 1.58 (s, 6H), 1.44 (qd, J = 13.5, 12.4, 3.8 Hz, 2H), 1.21 – 1.13 (m, 18H). Mass (m/z): 301.6 $[M+H]^+$.

Compound 266

1-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)urea



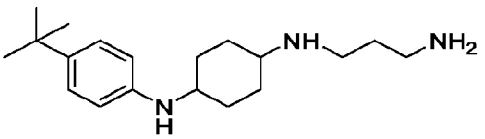
266A
266B

The title compounds **266A** (26.94 mg) as white solid and **266B** (25.46 mg) as a white solid were prepared from 1-N-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine (100 mg, 0.4 mmol), DCM (7 mL), TMSNCO (46.76 mg, 0.4 mmol), TEA (104.92 mg, 0.81 mmol) and DMAP (9.92 mg, 0.08 mmol) according to the procedure for **178**. **266A**: ^{1}HNMR (400 MHz, CD_3OD) δ 7.15 – 7.12 (m, 2H), 6.62 – 6.59 (m, 2H), 3.50 – 3.37 (m, 1H), 3.19 – 3.13 (m, 1H), 2.05 (dd, J = 7.0, 3.6 Hz, 2H), 1.98 – 1.92 (m, 2H), 1.25 – 1.21 (m, 13H). Mass (m/z): 289.9 $[M+H]^+$. HPLC: Rt=4.262 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min). **266B**: ^{1}HNMR (400 MHz, CD_3OD) δ 7.15 – 7.12 (m, 2H), 6.62 – 6.58 (m, 2H), 3.64 (s, 1H), 3.36 (tt, J = 7.0, 3.6 Hz, 1H), 1.80 – 1.72 (m, 2H), 1.65 (dd, J = 10.8, 5.4 Hz, 4H), 1.61 – 1.53 (m, 2H), 1.23 (s, 9H). Mass (m/z): 289.9 $[M+H]^+$. HPLC: Rt=4.328 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min).

Compound 267

1-N-(3-aminopropyl)-4-N-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine

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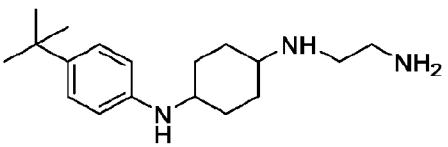


267

The desired product **267** (24.8 mg) as a white solid was prepared from tert-butyl (3-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)propyl)carba-mate (100 mg, 0.25 mmol), 1,4-dioxane (5 mL) and HCl /1,4-Dioxane (10 mL) according to the procedure for **224**. ^{1}HNMR (400 MHz, CD_3OD) δ 7.24 – 7.17 (m, 2H), 6.76 (t, *J* = 9.2 Hz, 2H), 3.46 – 3.38 (m, 1H), 3.24 – 3.19 (m, 01H), 3.17 – 3.13 (m, 1H), 3.03 (t, *J* = 3.6 Hz, 0.5H), 2.68 – 2.62 (m, 2H), 2.59 (dd, *J* = 9.6, 5.6 Hz, 0.5H), 1.94 – 1.88 (m, 1H), 1.82 – 1.70 (m, 3H), 1.67 – 1.59 (m, 3H), 1.59 – 1.26 (m, 3H), 1.25 (s, 9H). Mass (m/z): 304.0 $[M+H]^+$.

Compound 268

1-N-(2-aminoethyl)-N4-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine

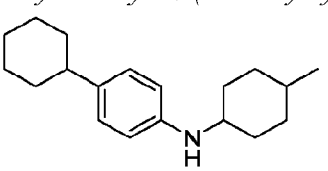


268

The title compound **268** (6 mg) as a white solid was prepared from tert-butyl (2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)ethyl)carba-mate (100 mg, 0.25 mmol), 1,4-dioxane (5 mL) and HCl /1,4-dioxane (10 mL) according to the procedure for **224**. ^{1}HNMR (400 MHz, CD_3OD) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 3.23 (dd, *J* = 6.2, 2.4 Hz, 4H), 3.07 (m, 1H), 2.17 (d, *J* = 11.0 Hz, 4H), 1.56 – 1.45 (m, 2H), 1.40 – 1.18 (m, 12H). Mass (m/z): 290.0 $[M+H]^+$.

Compound 269

4-cyclohexyl-N-(4-methylcyclohexyl)aniline



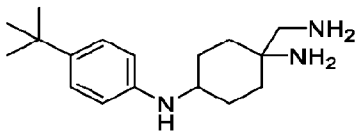
269

The title compound **269** (10.2 mg) was prepared in a total yield of 74% as a white solid with 1:4 mixture by ^{1}H NMR from 4-cyclohexylaniline (9 mg, 0.05 mmol) according to the procedure for compound **4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (d, *J* = 8.4 Hz, 2H), 6.51(d, *J* = 8.4 Hz, 1.6H), 6.46 (d, *J* = 8.4 Hz, 0.4H), 5.26 (br s, 1H), 3.17 (m, 0.8H), 3.04 (m, 0.2H), 2.28 (m, 1H), 1.80 – 1.11 (m, 19H), 0.89 (m, 3H). Mass (m/z): 272.1 $[M+H]^+$.

Compound 270

1-(aminomethyl)-N4-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine

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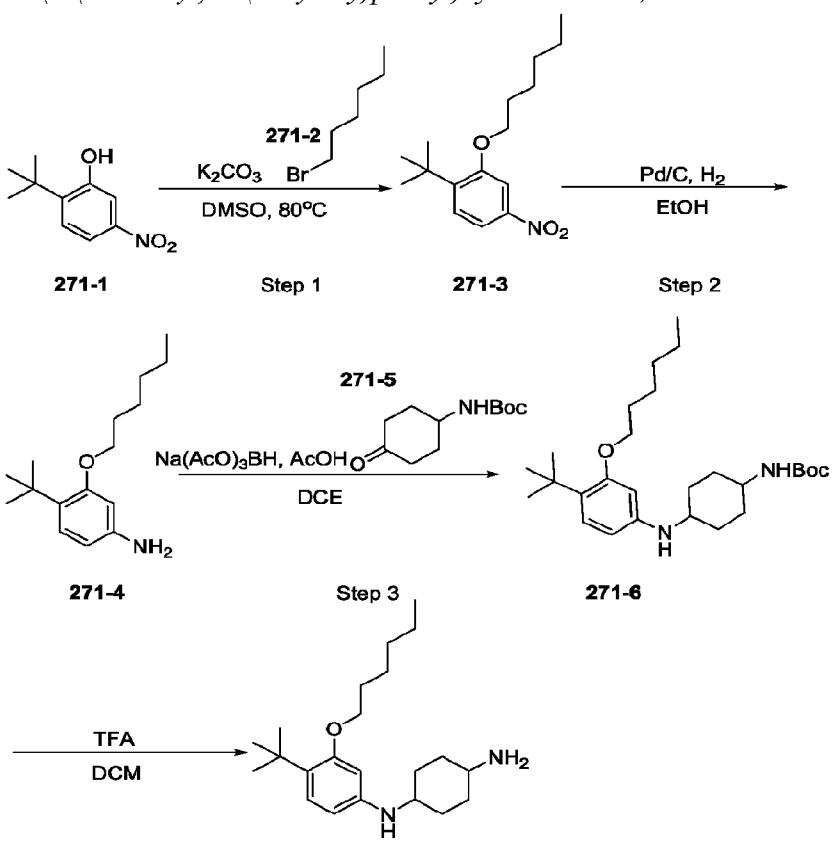


270

The title compound **270** (6.4 mg) was prepared in a total yield of 46% as a light yellow solid with 1:1 mixture by ^{1}H NMR from 1-amino-4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxamide (15 mg, 0.05 mmol) according to the procedure for compound **86**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (br s, 4H), 7.12 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 5.31 (br s, 1H), 3.27 (s, 2H), 3.20 (m, 0.5H), 3.04 (m, 0.5H), 2.11-1.38 (m, 8H), 1.21 (s, 9H). Mass (m/z): 276.1 $[M+H]^+$.

Compound 271

N^1-(4-(tert-butyl)-3-(hexyloxy)phenyl)cyclohexane-1,4-diamine



Step 1. Preparation of 1-(tert-butyl)-2-(hexyloxy)-4-nitrobenzene (**271-3**)

The title compound **271-3** (215 mg) was prepared in a total yield of 100% as a yellow solid from 2-(tert-butyl)-5-nitrophenol (150 mg, 0.77 mmol), 1-bromohexane (165 mg, 1.14 mmol) and K_2CO_3 (212 mg, 1.54 mmol) according to the procedure for **254-3**.

Step 2. Preparation of 4-(tert-butyl)-3-(hexyloxy)aniline (**271-4**)

The title compound **271-4** (60 mg) was prepared in a total yield of 31.3% as a yellow solid from 1-(tert-butyl)-2-(hexyloxy)-4-nitrobenzene (215 mg, 0.77 mmol) and 10% Pd/C (81.6 mg,

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77 umol) according to the procedure for **208-2**. Mass (m/z):250.4 $[M+H]^+$.

Step 3. tert-butyl (4-((4-(tert-butyl)-3-(hexyloxy)phenyl)amino)cyclohexyl)carbamate (**271-6**)

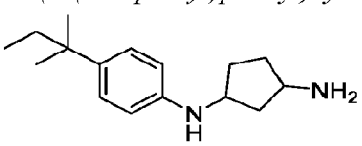
The title compound **271-6** (43 mg) was prepared in a total yield of 40.2% as a yellow solid from 4-(tert-butyl)-3-(hexyloxy)aniline (60 mg, 0.24 mmol), tert-butyl (4-oxocyclohexyl)carbamate (102 mg, 0.48 mmol) and $Na(AcO)_3BH$ (102 mg, 0.48 mmol) according to the procedure for **24-1**. Mass(m/z):447.4 $[M+H]^+$.

Step 4. N1-(4-(tert-butyl)-3-(hexyloxy)phenyl)cyclohexane-1,4-diamine (**271**)

The title compound **271** (18.0 mg) was prepared in a total yield of 54.2% as a white solid 1:1 mixture by ^1H NMR from tert-butyl (4-((4-(tert-butyl)-3-(hexyloxy)phenyl)amino)cyclohexyl)carbamate (43 mg, 96 umol) and TFA (2.0 mL) according to the procedure for **24**. ^1H NMR (400 MHz, Methanol-d_4) δ 7.12 – 7.01 (m, 0.5H), 6.98 (d, J = 8.4 Hz, 0.5H), 6.40 – 6.10 (m, 2H), 4.06 – 3.84 (m, 4H), 3.61 – 3.50 (m, 0.5H), 3.25 – 3.17 (m, 1H), 3.12 – 3.02 (m, 0.5H), 2.15 (d, J = 12.8 Hz, 1H), 2.06 (d, J = 12.6 Hz, 1H), 1.91 – 1.70 (m, 6H), 1.58 – 1.44 (m, 4H), 1.38 – 1.34 (m, 4H), 1.30 (d, J = 3.6 Hz, 9H), 0.96 – 0.85 (m, 3H). Mass (m/z): 347.4 $[M+H]^+$.

Compound 272

N^1-(4-(tert-pentyl)phenyl)cyclopentane-1,3-diamine

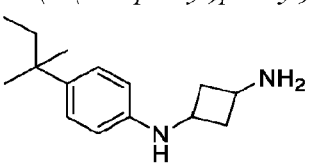


272

The title compound **272** (10.3 mg) was prepared in a total yield of 57.8% as a white solid 1 : 1 mixture by ^1H NMR from tert-butyl (3-((4-(tert-pentyl)phenyl)amino)cyclopentyl)carbamate (25 mg, 70 umol) and TFA (2.0 mL) according to the procedure for **24**. ^1H NMR (400 MHz, Methanol-d_4) δ 8.53 – 8.39 (m, 2H), 8.06 – 7.95 (m, 2H), 5.38 (p, J = 6.0 Hz, 0.5H), 5.24 (p, J = 6.5 Hz, 0.5H), 5.11 (p, J = 7.2 Hz, 0.5H), 5.05 – 4.96 (m, 0.5H), 3.98 – 3.31 (m, 4H), 3.26 – 2.88 (m, 4H), 2.58 (s, 6H), 2.02 (td, J = 7.4, 1.0 Hz, 3H).Mass(m/z):247.3 $[M+H]^+$.

Compound 273

N^1-(4-(tert-pentyl)phenyl)cyclobutane-1,3-diamine



273

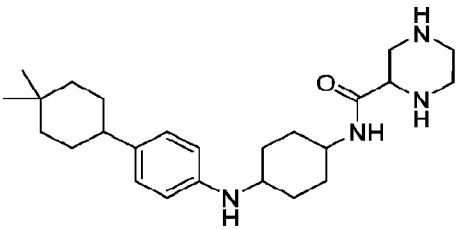
The title compound **273** (5.0 mg) was prepared in a total yield of 28.4% as a white solid with 3 : 2 mixture by ^1H NMR from tert-butyl (3-((4-(tert-pentyl)phenyl)amino)cyclobutyl)carbamate (25 mg, 80 umol) and TFA (2.0 mL) according to the procedure for **24**. ^1H NMR (400 MHz, Methanol-d_4) δ 7.13 – 7.02 (m, 2H), 6.57 – 6.48 (m, 2H), 4.16 – 4.04 (m, 0.6H), 3.93 – 3.83 (m, 0.6H), 3.78 – 3.67 (m, 0.4H), 3.60 – 3.49 (m, 0.4 H), 2.95 – 2.78 (m, 0.4H), 2.57 – 2.39 (m, 1.6H), 2.39 – 2.27 (m, 1.6H), 2.03 –

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1.85 (m, 0.4H), 1.67 – 1.45 (m, 2H), 0.62 (t, J = 7.4 Hz, 3H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 274

N-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)piperazine-2-carboxamide

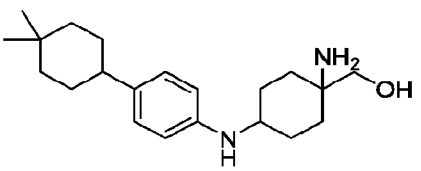


274

The title compound **274** (28.1 mg) was prepared in a yield of 40.93% as a white powder with 1:1 mixture by ^{1}H NMR from N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclohexane-1,4-diamine (50 mg, 0.17 mmol), 1,4-bis(tert-butoxycarbonyl)piperazine-2-carboxylic acid (82 mg, 0.25 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (dd, J = 24.8, 7.9 Hz, 1H), 6.92 (dd, J = 8.4, 3.7 Hz, 2H), 6.48 (dd, J = 16.2, 8.1 Hz, 2H), 5.14 (dd, J = 25.0, 7.8 Hz, 1H), 3.69 (s, 1H), 3.51 (s, 1H), 3.15 – 3.00 (m, 2H), 2.87 (d, J = 11.9 Hz, 1H), 2.79 – 2.62 (m, 2H), 2.20 (s, 1H), 1.95 (d, J = 12.8 Hz, 1H), 1.82 – 1.71 (m, 1H), 1.57 (d, J = 37.1 Hz, 8H), 1.41 (d, J = 13.3 Hz, 3H), 1.28 (q, J = 12.8, 11.7 Hz, 4H), 1.15 (d, J = 12.4 Hz, 1H), 0.94 (s, 3H), 0.92 (s, 3H). Mass (m/z): 413.5 $[M+H]^+$.

Compound 275

1-amino-4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)methanol



275A

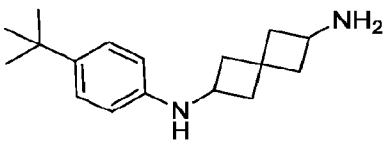
275B

The title compound **275A** and **275B** were prepared according to the procedure for compound **20**. The residue was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 0%-40%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13.0 min) to afford compound 275A (Rt = 5.25 min) in 3.34% yield as a white solid and 275B (Rt = 5.53min) in 13.5% yield as a white solid. **275A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.91 (d, J = 8.2 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 5.12 (d, J = 8.0 Hz, 1H), 4.67 (s, 1H), 3.19 (s, 1H), 2.21 (dt, J = 11.0, 5.4 Hz, 1H), 2.00 (q, J = 7.0, 6.3 Hz, 1H), 1.79 (s, 2H), 1.63 (d, J = 10.6 Hz, 2H), 1.50 (dd, J = 12.9, 9.3 Hz, 4H), 1.42 (d, J = 14.0 Hz, 3H), 1.33 – 1.26 (m, 5H), 0.94 (s, 3H), 0.92 (s, 3H), 0.85 (t, J = 6.7 Hz, 1H). Mass (m/z): 331.5 $[M+H]^+$. **275B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.91 (d, J = 7.9 Hz, 2H), 6.46 (d, J = 8.1 Hz, 2H), 5.07 (s, 1H), 4.58 (s, 1H), 3.11 (s, 2H), 3.03 (s, 1H), 2.20 (s, 1H), 2.01 (s, 2H), 1.69 (s, 3H), 1.51 (s, 6H), 1.35 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.85 (s, 1H). Mass (m/z): 331.5 $[M+H]^+$.

Compound 276

N2-(4-(tert-butyl)phenyl)spiro[3.3]heptane-2,6-diamine

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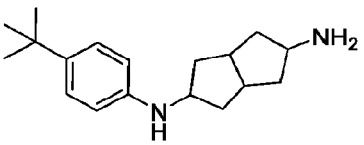


276

The title compound **276** (45.2 mg) was prepared in a yield of 34.8% as a white powder with 1:1 mixture by ^{1}H NMR from 4-(tert-butyl)aniline (75 mg, 0.50 mmol), tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (170 mg, 0.75 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 2H), 7.11 – 7.00 (m, 2H), 6.45 – 6.35 (m, 2H), 5.59 (s, 1H), 3.66 (t, J = 7.6 Hz, 1H), 3.54 (s, 1H), 2.43 – 2.29 (m, 2H), 2.22 – 2.06 (m, 3H), 1.82 (td, J = 11.1, 7.7 Hz, 2H), 1.23 (s, 1H), 1.19 (s, 9H). Mass (m/z): 259.2 $[M+H]^+$.

Compound 277

N2-(4-(tert-butyl)phenyl)octahydropentalene-2,5-diamine

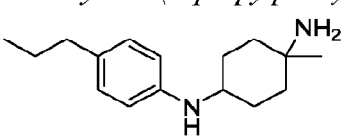


277

The title compound **277** (24.0 mg) was prepared in a four-step total yield of 13.1% as a white solid with 1:1 mixture by ^{1}H NMR from 4-(tert-butyl)aniline (100 mg, 0.67 mmol), (3as,6as)-tetrahydropentalene-2,5(1H,3H)-dione (278 mg, 2.0 mmol) and $NaBH(OAc)_3$ (284 mg, 1.34 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 18.4 Hz, 3H), 7.07 (d, J = 8.1 Hz, 2H), 6.53 (s, 2H), 5.42 (s, 1H), 3.66 (d, J = 6.6 Hz, 1H), 3.51 (s, 1H), 2.36 (q, J = 8.2, 7.5 Hz, 1H), 2.29 – 2.14 (m, 3H), 1.74 (dd, J = 12.8, 7.1 Hz, 1H), 1.46 – 1.33 (m, 2H), 1.19 (s, 9H). Mass (m/z): 273.1 $[M+H]^+$.

Compound 278

1-methyl-N4-(4-propylphenyl)cyclohexane-1,4-diamine



278

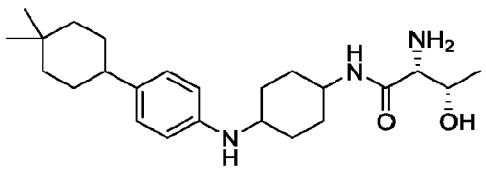
The title compound **278** (60.6 mg) was prepared in a yield of 66.5% as a white powder with 1:1 mixture by ^{1}H NMR from 4-propylaniline (50 mg, 0.37 mmol), tert-butyl (1-methyl-4-oxocyclohexyl)carbamate (100 mg, 0.44 mmol) and according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 26.1 Hz, 3H), 6.87 (d, J = 7.9 Hz, 2H), 6.51 (d, J = 8.3 Hz, 2H), 5.12 (d, J = 50.3 Hz, 1H), 3.12 (s, 1H), 2.37 (t, J = 7.5 Hz, 2H), 1.88 (td, J = 11.0, 9.5, 5.7 Hz, 2H), 1.82 – 1.70 (m, 2H), 1.65 (td, J = 12.6, 3.5 Hz, 1H), 1.55 (d, J = 9.9 Hz, 2H), 1.49 (q, J = 7.4 Hz, 2H), 1.27 (d, J = 7.5 Hz, 4H), 0.85 (t, J = 7.3 Hz, 3H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 279

(2R,3S)-2-amino-N-(4-((4-(4,4-dimethylcyclohexyl)phenyl)amino)cyclohexyl)-3-hydroxybutana

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mide

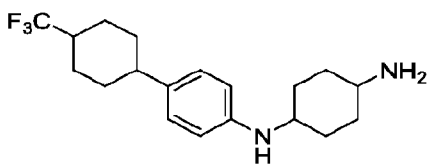


279

The title compound **279** (9.1 mg) was prepared in a yield of 36.37% as a white powder with 1:1 mixture by ^{1}H NMR from N1-(4-(4,4-dimethylcyclohexyl)phenyl)cyclohexane-1,4-diamine (100 mg, 0.33 mmol), (tert-butoxycarbonyl)-D-threonine (109 mg, 0.50 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 3H), 6.94 (s, 2H), 6.60 (s, 2H), 4.07 (s, 2H), 2.75 (s, 1H), 2.61 (s, 2H), 2.28 (s, 3H), 1.96 (s, 1H), 1.83 (s, 2H), 1.77 – 1.35 (m, 8H), 1.20 (d, J = 26.6 Hz, 4H), 1.02 (d, J = 11.7 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H). Mass (m/z): 402.3 $[M+H]^+$.

Compound 280

N1-(4-(4-(trifluoromethyl)cyclohexyl)phenyl)cyclohexane-1,4-diamine

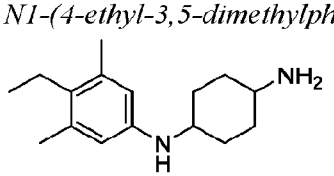


280

The title compound **280** (53.4 mg) was prepared in a total yield of 91.4% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((4-(4-(trifluoromethyl)cyclohexyl)phenyl)amino)cyclohexyl)carbamate (75 mg, 0.17 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.00 – 6.87 (m, 2H), 6.63 – 6.43 (m, 2H), 5.29 (d, J = 26.8 Hz, 1H), 3.00 (d, J = 55.2 Hz, 2H), 2.59 (s, 1H), 2.44 (t, J = 6.8 Hz, 1H), 2.06 – 1.90 (m, 3H), 1.73 (dq, J = 23.2, 13.6, 9.6 Hz, 10H), 1.51 – 1.35 (m, 2H), 1.20 – 1.10 (m, 1H). Mass (m/z): 341.3 $[M+H]^+$.

Compound 281

N1-(4-ethyl-3,5-dimethylphenyl)cyclohexane-1,4-diamine



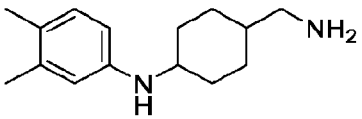
281

The title compound **281** (66.8 mg) was prepared in a total yield of 91.2% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((4-ethyl-3,5-dimethylphenyl)amino)cyclohexyl)carbamate (103 mg, 0.298 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.24 (d, J = 16.8 Hz, 2H), 3.13 – 2.88 (m, 2H), 2.44 (q, J = 7.6 Hz, 2H), 2.15 (s, 6H), 2.12 (d, J = 1.8 Hz, 1H), 1.98 (d, J = 11.2 Hz, 2H), 1.76 (d, J = 14.8 Hz, 3H), 1.63 – 1.53 (m, 1H), 1.49 (dd, J = 12.8, 9.2 Hz, 1H), 0.98 (t, J = 7.2 Hz, 3H). Mass (m/z): 247.3 $[M+H]^+$.

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Compound 282

N-(4-(aminomethyl)cyclohexyl)-3,4-dimethylaniline

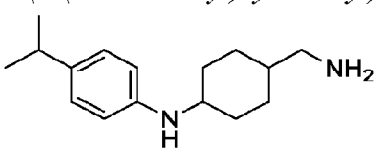


282

The title compound **282** (64.1 mg) was prepared in a total yield of 93.4% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl ((4-((3,4-dimethylphenyl)amino)cyclohexyl)methyl)carbamate (98 mg, 0.295 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (dd, J = 8.4, 2.8 Hz, 1H), 6.50 – 6.24 (m, 2H), 5.05 (dd, J = 30.4, 8.0 Hz, 1H), 3.48 – 2.99 (m, 1H), 2.64 (dd, J = 23.6, 6.8 Hz, 2H), 2.09 (d, J = 2.0 Hz, 3H), 2.04 (s, 3H), 2.00 – 1.92 (m, 1H), 1.83 (dd, J = 8.8, 4.8 Hz, 1H), 1.70 (d, J = 9.6 Hz, 1H), 1.64 – 1.58 (m, 1H), 1.49 (pd, J = 14.0, 10.8, 4.0 Hz, 4H). Mass (m/z): 233.3 $[M+H]^+$.

Compound 283

N-(4-(aminomethyl)cyclohexyl)-4-isopropylaniline

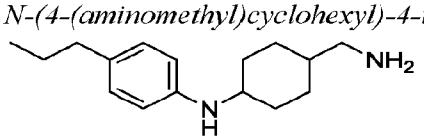


283

The title compound **283** (52.7 mg) was prepared in a total yield of 70.2% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl ((4-((4-isopropylphenyl)amino)cyclohexyl)methyl)carbamate (105 mg, 0.303 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.02 – 6.88 (m, 2H), 6.60 (d, J = 9.7 Hz, 2H), 3.51 – 3.04 (m, 2H), 2.75 – 2.59 (m, 3H), 2.03 – 1.42 (m, 8H), 1.13 (d, J = 6.8 Hz, 6H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 284

N-(4-(aminomethyl)cyclohexyl)-4-isopropylaniline



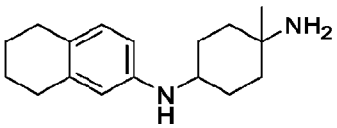
284

The title compound **284** (20.7 mg) was prepared in a total yield of 40.9% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl ((4-((4-propylphenyl)amino)cyclohexyl)methyl)carbamate (85 mg, 0.246 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 (dd, J = 8.4, 2.8 Hz, 2H), 6.50 (dd, J = 27.6, 8.0 Hz, 2H), 5.19 (dd, J = 26.4, 8.0 Hz, 1H), 3.43 (s, 1H), 3.07 (s, 1H), 2.66 (dd, J = 22.0, 6.8 Hz, 2H), 2.36 (t, J = 7.6 Hz, 2H), 2.02 – 1.77 (m, 2H), 1.53 (tdt, J = 25.2, 15.6, 8.8 Hz, 8H), 0.86 (t, J = 7.2 Hz, 3H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 285

1-methyl-N4-(5,6,7,8-tetrahydronaphthalen-2-yl)cyclohexane-1,4-diamine

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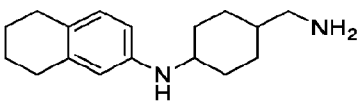


285

The title compound **285** (66.8 mg) was prepared in a total yield of 91% as a white solid with 1:2 mixture by ^{1}H NMR from tert-butyl (1-methyl-4-((5,6,7,8-tetrahydronaphthalen-2-yl)amino)cyclohexyl)carbamate (101 mg, 0.282 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (dd, J = 8.4, 3.2 Hz, 1H), 6.47 – 6.22 (m, 2H), 3.31 – 3.04 (m, 1H), 2.62 – 2.53 (m, 4H), 2.00 – 1.83 (m, 2H), 1.81 – 1.46 (m, 10H), 1.30 (d, J = 7.2 Hz, 3H). Mass (m/z): 259.3 $[M+H]^+$.

Compound 286

N-(4-(aminomethyl)cyclohexyl)-5,6,7,8-tetrahydronaphthalen-2-amine

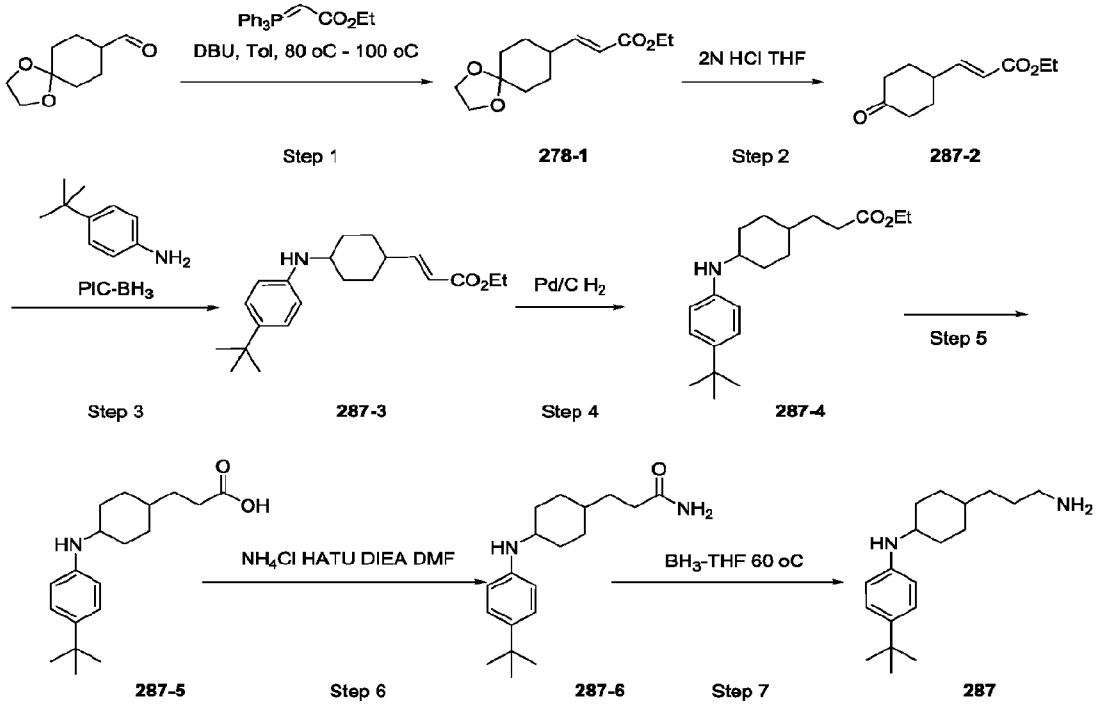


286

The title compound **286** (33.5 mg) was prepared in a total yield of 50% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl ((4-((5,6,7,8-tetrahydronaphthalen-2-yl)amino)cyclohexyl)methyl)carbamate (93 mg, 0.26 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (dd, J = 8.4, 3.2 Hz, 1H), 6.45 – 6.14 (m, 2H), 5.03 (dd, J = 27.2, 8.4 Hz, 1H), 3.51 – 2.98 (m, 1H), 2.64 (d, J = 6.8 Hz, 1H), 2.61 – 2.51 (m, 5H), 1.97 (d, J = 9.6 Hz, 1H), 1.80 (dd, J = 13.2, 8.0 Hz, 1H), 1.66 (p, J = 2.8 Hz, 5H), 1.56 – 1.35 (m, 4H), 1.04 (q, J = 11.2 Hz, 1H). Mass(m/z): 259.3 $[M+H]^+$.

Compound 287

N-(4-(3-aminopropyl)cyclohexyl)-4-(tert-butyl)aniline



Step 1. Preparation of ethyl (E)-3-(1,4-dioxaspiro[4.5]decan-8-yl)acrylate **(287-1)**

A solution of 1,4-dioxaspiro[4.5]decane-8-carbaldehyde (1 g, 5.8 mmol), DBU (1.07 g, 7.1 mmol) and ethyl 2-(triphenyl-l5-phosphaneylidene)acetate (3 g, 8.8 mmol) in toluene (20 mL) was stirred at 100 °C under N2 atmosphere for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 1 g of **287-1** (yield: 71.5%) as a yellow solid. Mass (m/z): 241.2 $[M+H]^+$.

Step 2. Preparation of ethyl (E)-3-(4-oxocyclohexyl)acrylate **(287-2)**

287-1 (1 g, 4.1 mmol) and HCl in THF (20 mL, 2 N) were placed in a flask and stirred at 25oC for 18 hrs. Excess THF was removed under vacuum and the residue was purified by silica gel column to provide 500 mg of **287-2** (yield: 61.9%) as a yellow oil. Mass (m/z): 197.2 $[M+H]^+$.

Step 3. Preparation of ethyl (E)-3-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)acrylate **(287-3)**

To a solution of **287-2** (200 mg, 1 mmol), 4-(tert-butyl)aniline (150 mg, 1 mmol) and $NaBH_3CN$ (120 mg, 2 mmol) in MeOH (10 mL). The reaction was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 220 mg of **287-3** (yield: 66.7%) as a yellow solid. Mass (m/z): 330.3 $[M+H]^+$.

Step 4. Preparation of ethyl 3-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)propanoate **(287-4)**

A solution of **287-3** (220 mg, 0.67 mmol), Pd/C (20 mg) in MeOH (10 mL) was stirred at 25 °C under H2 atmosphere for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 150 mg of **287-4** (yield: 67.4%) as a yellow solid. Mass (m/z): 332.3 $[M+H]^+$.

Step 5. Preparation of 3-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)propanoic acid **(287-5)**

To a solution of **287-4** (150 mg, 0.45 mmol) in H_2O (5 mL) and THF (5 mL) was added NaOH (90 mg, 2.25 mmol). The mixture was stirred at 25 °C overnight. Ethyl acetate was added to the

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reaction mixture and the mixture was filtered through Celite. The filtrate was washed with water and saturated brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column to provide 100 mg of **287-5** (yield: 73.1%) as yellow oil. Mass (m/z): 304.2 $[M+H]^+$.

Step 6. Preparation of 3-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)propenamide **(287-6)**

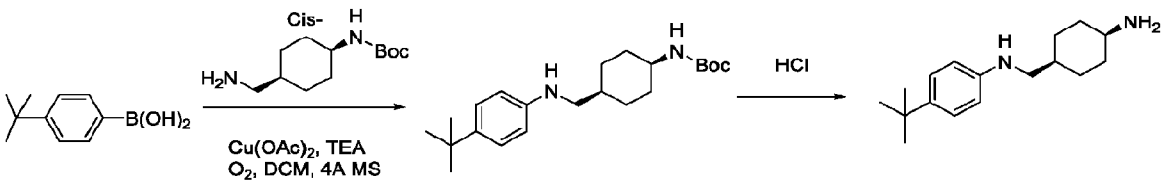
A solution of **287-5** (150 mg, 0.5 mmol), NH_4Cl (80 mg, 1.5 mmol), HATU (281 mg, 0.75 mmol) and DIEA (191 mg, 1.5 mmol) in DMF (10 mL) was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 200 mg of **287-6** (yield: 90.1%) as a yellow solid. Mass (m/z): 302.9 $[M+H]^+$.

Step 7. Preparation of N-(4-(3-aminopropyl)cyclohexyl)-4-(tert-butyl)aniline (**287**)

A solution of **287-6** (60 mg, 0.2 mmol), BH_3-THF (10 mL) in THF (5 mL) was stirred at 70 oC for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **287** (7.0 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.14 (d, J = 8.6 Hz, 2H), 6.62 (d, J = 8.6 Hz, 2H), 3.49 – 3.43 (m, 1H), 2.64 (t, J = 7.4 Hz, 2H), 1.79 – 1.61 (m, 4H), 1.58 – 1.47 (m, 4H), 1.40 (s, 3H), 1.31 (m, 2H), 1.25 (s, 9H). Mass (m/z): 289.0 $[M+H]^+$.

Compound 288

N-(((1s,4s)-4-aminocyclohexyl)methyl)-4-(tert-butyl)aniline



Step 1. Preparation of tert-butyl ((1s,4s)-4-(((4-(tert-butyl)phenyl)amino)methyl)cyclohexyl)carbamate **(288-1)**

A 100-mL round-bottom flask was charged with tert-butyl ((1s,4s)-4-(aminomethyl)cyclohexyl)carbamate (155 mg, 0.67 mmol, 1.1 eq), (4-(tert-butyl)phenyl)boronic acid (100 mg, 0.56 mmol, 1.00 eq), $Cu(OAc)_2$ (204 mg,1.1 mmol, and 2.00 eq) and TEA (284 mg, 2.8 mmol, 5.00 eq) and 4Å MS (1 g),. The reaction was stirred at R.T. under O_2 atmosphere for 18 hours. The solids were filtered and solvent was removed under vacuum. The residue was purified by Flash Chromatography to give **288-1** (0.1 g, 49.2% yield) as a yellow solid. MS (m/z) 361.3 $[M+H]^+$.

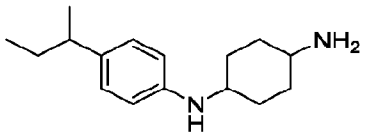
Step 2. Preparation of N-(((1s,4s)-4-aminocyclohexyl)methyl)-4-(tert-butyl)aniline **(288)**

288-1 (100 mg, 0.28 mmol) and HCl in 1,4-dioxane (10 mL, 4N) were placed in a flask stirred at 25 °C for 16 hrs. Excess 1,4- dioxane was distilled under vacuum and the residue was purified by Flash Chromatography to afford **288** (59.1 mg 82.0%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.55 – 7.52 (m, 2H), 7.30 – 7.26 (m, 2H), 3.35 – 3.30 (m, 3H), 1.97 (dd, J = 7.1, 3.6 Hz, 1H), 1.85 – 1.71 (m, 6H), 1.65 – 1.57 (m, 2H), 1.31 (s, 9H). MS (m/z) 261.2 $[M+H]^+$.

Compound 289

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1-N-(4-(sec-butyl)phenyl)cyclohexane-1,4-diamine

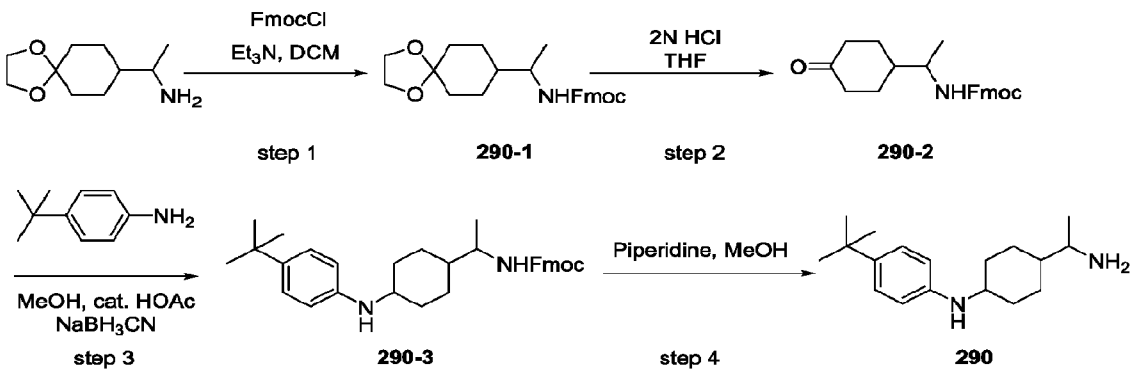


289A
289B

The title compounds **289A** (64.1 mg) as a white solid and **289B** (51.4 mg) as a white solid were prepared from tert-butyl (4-((4-(sec-butyl)phenyl)amino)cyclohexyl)carbamate (100 mg, 0.28 mmol), 1,4-dioxane (5 mL) and HCl /1,4-dioxane (10 mL) according to the procedure for **37**. **289A**: ^{1}HNMR (400 MHz, CD_3OD) δ 6.93 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.6 Hz, 2H), 3.22 – 3.11 (m, 1H), 2.70 – 2.60 (m, 1H), 2.43 (dd, *J* = 14.2, 7.0 Hz, 1H), 2.06 (d, *J* = 11.8 Hz, 2H), 1.91 (d, *J* = 11.8 Hz, 2H), 1.59 – 1.47 (m, 2H), 1.31 – 1.21 (m, 3H), 1.16 (d, *J* = 7.0 Hz, 4H), 0.78 (t, *J* = 7.4 Hz, 3H). Mass (m/z): 247.2 $[M+H]^+$. HPLC: Rt=3.770 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min). **289B**: ^{1}HNMR (400 MHz, CD_3OD) δ 6.93 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 2H), 3.44 (s, 1H), 2.83 (d, *J* = 8.2 Hz, 1H), 2.46-2.41 (m, 1H), 1.77 – 1.49 (m, 10H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H). Mass (m/z): 247.2 $[M+H]^+$. HPLC: Rt=3.962 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min).

Compound 290

N-(4-(1-aminoethyl)cyclohexyl)-4-(tert-butyl)aniline



Step 1. Preparation of (9H-fluoren-9-yl)methyl (1-(1,4-dioxaspiro[4.5]decan-8-yl)ethyl)carbamate (**290-1**)

To a solution of 1-(1,4-dioxaspiro[4.5]decan-8-yl)ethan-1-amine (0.5 g, 2.7 mmol) in DCM (10 mL) was added DIEA (697 mg, 5.4 mmol) and FmocCl (600 mg, 2.7 mmol). Then the mixture was stirred at 25 °C for 2 hrs. LCMS showed the reaction was completed. The mixture was added into H_2O, extracted with EA (20 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:1) to give **290-1** (0.5 g, 45.4% yield) as a yellow oil. MS (m/z) 407.8 $[M+H]^+$.

Step 2. Preparation of (9H-fluoren-9-yl)methyl(1-(4-oxocyclohexyl)ethyl)carbamate (**290-2**)

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To a solution of **290-1** (0.25 g, 0.61 mmol) in THF (4 mL) was added 2N HCl (4 mL) at 25 °C. Then the mixture was stirred at 25 °C for 10 h. LCMS showed the reaction was completed. The reaction was concentrated. The residue was purified by combi-flash with EA/PE (1:2) to afford **290-2** (0.17 g, 76.2% yield) as yellow oil. MS (m/z) 364.2 $[M+H]^+$.

Step 3. Preparation of (9H-fluoren-9-yl)methyl(1-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)ethyl)carbamate (**290-3**)

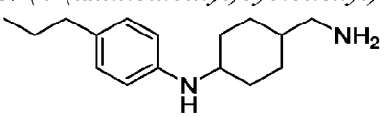
To a solution of **290-2** (100 mg, 0.27 mmol) in MeOH (5 mL) and a drop of AcOH was added 4-(tert-butyl)aniline (41 mg, 0.27 mmol) and the mixture was stirred at 50 °C for 1 h. Then the mixture was added $NaBH_3CN$ (51 mg, 0.81 mmol) after cooling to 25 °C. Then the mixture was stirred at 25 °C for 2 hrs. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:2) to give **290-3** (0.1 g, 73.5% yield) as a yellow solid. MS (m/z) 496.8 $[M+H]^+$.

Step 4. Preparation of N-(4-(1-aminoethyl)cyclohexyl)-4-(tert-butyl)aniline (**290**)

To a solution of **290-3** (0.1 g, 0.20 mmol) in MeOH (2 mL) was added piperidine (2 mL) at 25 °C. Then the mixture was stirred at 25 °C for 4 h. LCMS showed the reaction was completed. The reaction was concentrated. The residue was purified by prep-HPLC to afford **290** (10 mg, 13% yield) as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 7.63 (d, J = 7.2 Hz, 2H), 7.46 – 7.36 (m, 2H), 3.53 – 3.38 (m, 1H), 3.20 – 3.10 (m, 1H), 2.10 (d, J = 11.2 Hz, 1H), 2.00 – 1.42 (m, 8H), 1.35 (s, 9H), 1.27 – 1.22 (m, 3H). MS (m/z) 275.3 $[M+H]^+$.

Compound 291

N-(4-(aminomethyl)cyclohexyl)-4-propylaniline

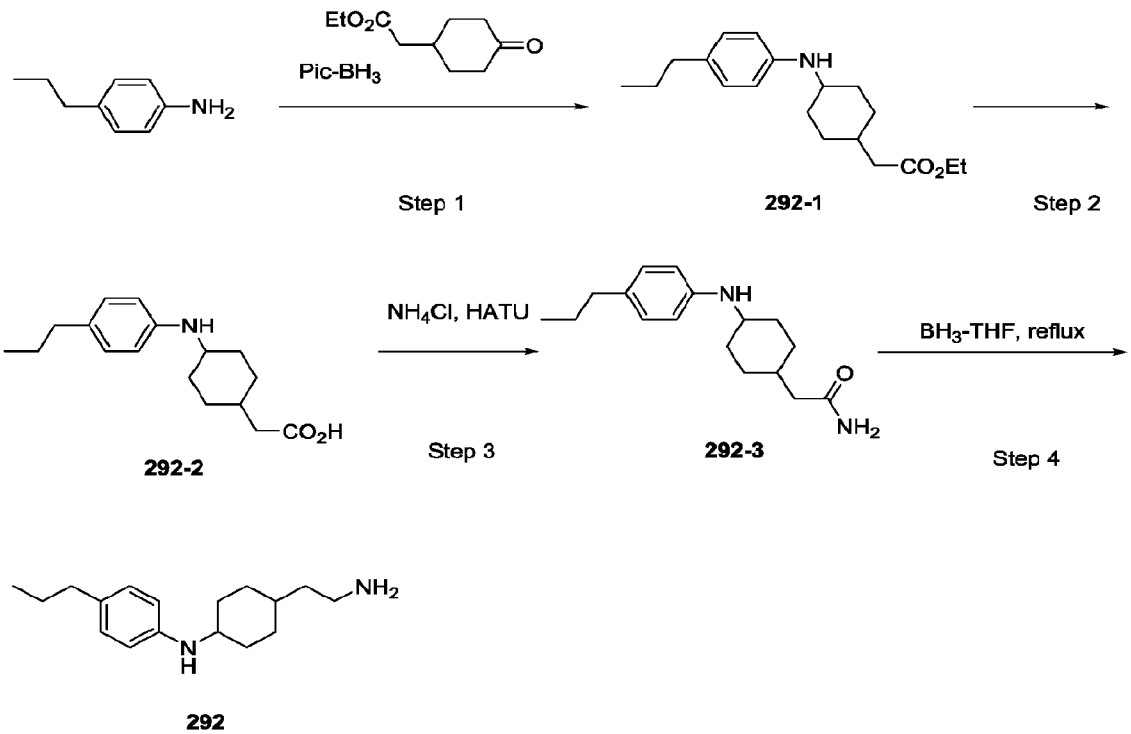


291

The title compound **291** (30.6 mg, 28.8%) as a white solid was prepared from tert-butyl ((4-((4-propylphenyl)amino)cyclohexyl)methyl)carbamate (150 mg, 0.43 mmol), 1,4-dioxane (10 mL) and 1,4-dioxane/HCl (10 mL) according to the procedure for **224**. ^1H NMR (400 MHz, DMSO-d_6) δ 6.86 (d, J = 7.6 Hz, 2H), 6.46 (d, J = 7.7 Hz, 2H), 5.13 (br, 1H), 3.07 (br, 1H), 2.63 (br, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.97 (br, 2H), 1.81 (br, 2H), 1.50 – 1.45 (m, 3H), 1.10 – 0.95 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 292

N-(4-(2-aminoethyl)cyclohexyl)-4-propylaniline



Step 1. Preparation of ethyl 2-(4-((4-propylphenyl)amino)cyclohexyl)acetate **(292-1)**

A solution of 4-propylaniline (500 mg, 3.7 mmol), ethyl 2-(4-oxocyclohexyl)acetate (681 mg, 3.7 mmol) and Pic-BH_3 (474 mg, 4.44 mmol) in H_2O (9 mL) and HOAc (1 mL) was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 600 mg of **292-1** (yield: 53.3%) as a yellow solid. Mass (m/z): 304.3 $[M+H]^+$.

Step 2. Preparation of 2-(4-((4-propylphenyl)amino)cyclohexyl)acetic acid **(292-2)**

To a solution of **292-1** (600 mg, 2 mmol) in H_2O (5 mL) and THF (5 mL) was added LiOH (780 mg, 20 mmol). The mixture was stirred at 25 °C overnight. Ethyl acetate was added to the reaction mixture and the mixture was filtered through Celite. The filtrate was washed with water and saturated brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column to provide 200 mg of **292-2** (yield: 36.2%) as a yellow oil. Mass (m/z): 276.2 $[M+H]^+$.

Step 3. Preparation of 2-(4-((4-propylphenyl)amino)cyclohexyl)acetamide **(292-3)**

A solution of **292-2** (300 mg, 1.1 mmol), NH_4Cl (70 mg, 1.3 mmol), HATU (621 mg, 1.6 mmol) and DIEA (281 mg, 2.2 mmol) in DMF (10 mL) was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 200 mg of **292-3** (yield: 66.1%) as a yellow solid. Mass(m/z): 275.2 $[M+H]^+$.

Step 4. Preparation of N-(4-(2-aminoethyl)cyclohexyl)-4-propylaniline **(292)**

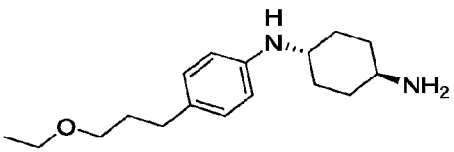
A solution of **292-3** (200 mg, 0.73 mmol), BH_3-THF (10 mL) in THF (5 mL) was stirred at 70 °C for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase:

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ACN-H_2O (0.1% FA), 25%-40%) to afford **292** (13.4 mg) as a white solid. Mass (m/z): 261.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.81 (d, J = 8.4 Hz, 2H), 6.42 (d, J = 8.4 Hz, 2H), 3.09 – 2.97 (m, 1H), 2.80 – 2.68 (m, 2H), 2.36 – 2.28 (m, 2H), 1.92 (d, J = 11.6 Hz, 2H), 1.68 (d, J = 12.0 Hz, 2H), 1.51 – 1.36 (m, 4H), 1.34 – 1.20 (m, 1H), 1.11 – 0.89 (m, 4H), 0.81 (t, J = 7.4 Hz, 3H).

Compound 293

(1r,4r)-N1-(4-(3-ethoxypropyl)phenyl)cyclohexane-1,4-diamine

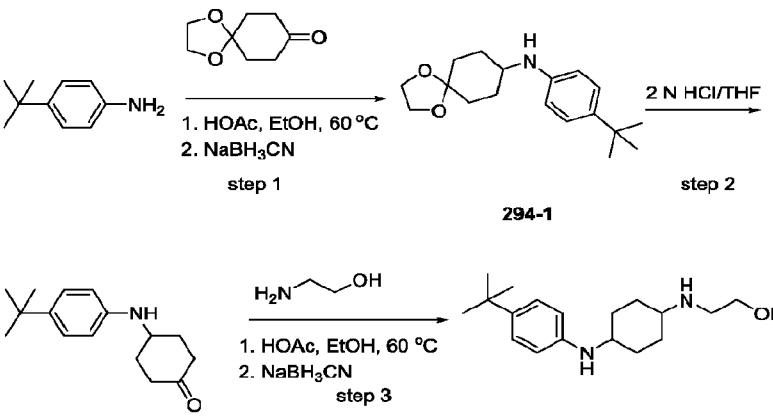


293

The mixture of tert-butyl ((1r,4r)-4-((4-(3-ethoxypropyl)phenyl)amino)cyclohexyl)carbamate (300 mg, 0.79 mmol) in 1,4-dioxane (10 mL) and 1,4-dioxane/HCl (10 mL) was stirred for 16 hour at 25 °C. After reaction was completed, solvent was removed under vacuum, and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 2%-10%) to afford the desired product as a white solid. (30.5 mg, 13.7%). ^1H NMR (400 MHz, DMSO-d_6) δ 6.87 (d, J = 8.2 Hz, 2H), 6.48 (d, J = 8.3 Hz, 2H), 3.41 – 3.35 (m, 2H), 3.31 (t, J = 6.5 Hz, 2H), 3.08 (br, 1H), 2.90 (br, 1H), 2.45 – 2.41 (m, 2H), 2.02 – 1.91 (m, 4H), 1.73 – 1.64 (m, 2H), 1.42 – 1.36 (m, 2H), 1.24 – 1.12 (m, 2H), 1.09 (d, J = 7.0 Hz, 3H). Mass (m/z): 277.3 $[M+H]^+$.

Compound 294

2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)ethan-1-ol



Step 1. Preparation of N-(4-(tert-butyl)phenyl)-1,4-dioxaspiro[4.5]decan-8-amine (**294-1**)

To a solution of 4-(tert-butyl)aniline (1 g, 6.71 mmol) in MeOH (10 mL) was added 1,4-dioxaspiro[4.5]decan-8-one (1.04 g, 6.71 mmol) and the mixture was stirred at 60 °C for 1 h. Then sodium cyanoborohydride (1.27 g, 20.13 mmol) was added to the mixture. The reaction was stirred for 3 h at R.T. Quenched with water (50 mL), the reaction was extracted by EA (10 mL) for 3 times. The organic phase was dried over sodium sulfate. removed under vacuum and the residue was purified by flash chromatography to afford the desired product (1.6 g, 82.6%) as a white solid. Mass(m/z): 289.9 $[M+H]^+$.

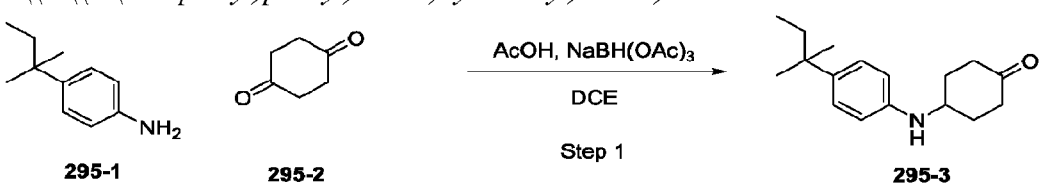
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Step 2. Preparation of 4-((4-(tert-butyl)phenyl)amino)cyclohexan-1-one **(294-2)**
To a solution of N-(4-(tert-butyl)phenyl)-1,4-dioxaspiro[4.5]decan-8-amine (1.6 g, 5.54 mmol) in THF (5 mL) was added HCl in THF (2 N, 5 mL) and the mixture was stirred for 2 h. Quenched with $NaHCO_3$ (10 mL), the reaction was extracted by EA (10 mL) for 3 times. The organic phase was dried over sodium sulfate, removed under vacuum and the product (0.9 g, 66.2%) as a white solid. Mass (m/z): 246.2 $[M+H]^+$.

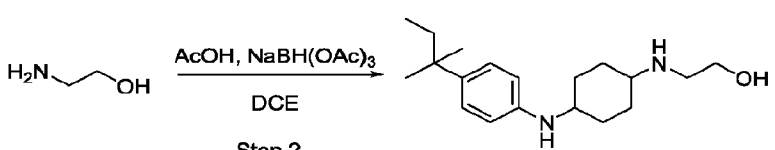
Step 3. Preparation of 2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)ethan-1-ol **(294)**
To a solution of 4-((4-(tert-butyl)phenyl)amino)cyclohexan-1-one (100 mg, 0.41 mmol) in MeOH (5 mL) was added 2-aminoethan-1-ol (25 mg, 0.41 mmol) and acetic acid (2.46 mg, 0.041 mmol). Then the mixture was stirred at 60 °C for 1 h. After reaction was cooled to R.T., Sodium cyanoborohydride (77.49 mg, 12.3 mmol) was added. The reaction was stirred for 3 h at R.T. Quenched with water (10 mL), the reaction was extracted by EA (10 mL) for 3 times. The organic phase was dried over sodium sulfate, removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford the desired product (mixture; 113 mg, 95%) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, J = 8.8 Hz, 2H), 6.49 (dd, J = 13.6 Hz, 8.4 Hz, 2H), 5.13 (s, 1H), 3.49 (s, 3H), 3.20 (m, 1H), 2.67 (m, 2H), 2.51 (s, 1H), 1.95 (t, J = 14.0 Hz, 2H), 1.69 – 1.49 (m, 3H), 1.20 (s, 12H). Mass (m/z): 290.9 $[M+H]^+$. HPLC: Rt: 3.505 min, 3.849 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 295

2-((4-((4-(tert-pentyl)phenyl)amino)cyclohexyl)amino)ethan-1-ol



295-1 295-2 295-3



295-4 295A 295B

Step 1. Preparation of 4-((4-(tert-pentyl)phenyl)amino)cyclohexan-1-one **(295-3)**
The compound **295-3** (99 mg) was prepared in a total yield of 77% as a white solid from 4-(tert-pentyl)aniline (26 mg, 0.1 mmol) and cyclohexane-1,4-dione (66 mg, 0.6 mmol) according to the procedure for compound **4**. Mass (m/z): 260.2 $[M+H]^+$.

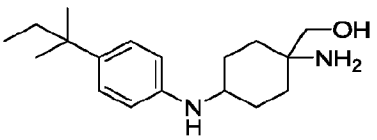
Step 2. Preparation of 2-((4-((4-(tert-pentyl)phenyl)amino)cyclohexyl)amino)ethan-1-ol **(295)**
A mixture of 4-((4-(tert-pentyl)phenyl)amino)cyclohexan-1-one (26 mg, 0.1 mmol), 2-aminoethan-1-ol (4.4 mg, 0.12 mmol) and acetic acid (0.06 ml, 0.1 mmol) in DCE (5 mL) was stirred for 1 h at room temperature. Afterwards sodium triacetoxyborohydride (42 mg, 0.2

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mmol) was added and the mixture was stirred overnight. To the mixture, saturated $NaHCO_3$ aq. was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated. The mixture was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 5%-40%-95%-95%-5%, 0 min-10 min-10.5 min-11.5 min-13 min) to afford compound **295A** (Rt = 6.58 min) as a white solid and compound **295B** (Rt = 7.83 min) as a white solid. **295A** (7.1 mg, 24%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 5.29 (s, 1H), 5.18 (s, 1H), 3.68 (m, 2H), 3.45 (m, 1H), 3.09 (m, 1H), 2.99 (m, 2H), 1.90-1.75 (m, 6H), 1.63-1.48 (m, 4H), 1.16 (s, 6H), 0.60 (t, J =7.2 Hz, 3H). Mass (m/z): 305.1 $[M+H]^+$. **295B** (10.2 mg, 34%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 5.28 (s, 1H), 5.18 (s, 1H), 3.68 (m, 2H), 3.44 (m, 1H), 3.09 (m, 1H), 2.97 (m, 2H), 2.17 – 1.73 (m, 4H), 1.58 – 1.41 (m, 4H), 1.22 (m, 2H), 1.15 (s, 6H), 0.59 (t, J =7.2 Hz, 3H). Mass (m/z): 305.1 $[M+H]^+$.

Compound 296

(1-amino-4-((4-(tert-pentyl)phenyl)amino)cyclohexyl)methanol



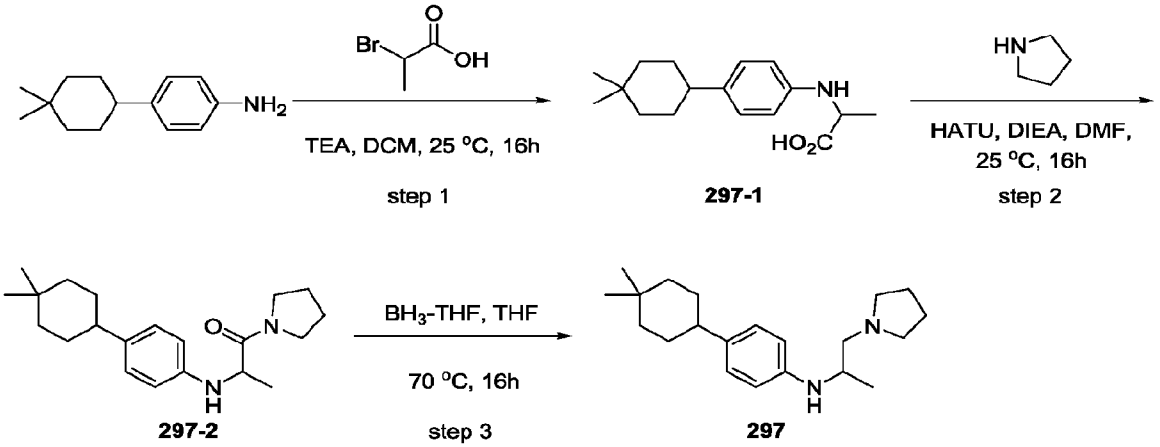
296A
296B

The title compound **296** was prepared from 1-amino-4-((4-(tert-pentyl)phenyl)amino)cyclohexane-1-carboxylic acid (31 mg, 0.1 mmol) according to the procedure for compound **4.** The mixture was purified by preparative HPLC (ACN/water (5‰TFA = 5-30-95-95-5, 0-10-10.5-11.5-13.0min) to afford compound **296A** (Rt = 4.33 min) as a rosy brown solid and compound **296B** (Rt = 3.95 min) as a rosy brown solid. **296A** (15.6 mg, 54%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 5.47 (s, 1H), 5.07 (s, 1H), 3.46 (s, 2H), 3.23 (m, 1H), 1.95 – 1.68 (m, 4H), 1.65 – 1.40 (m, 6H), 1.16 (s, 6H), 0.61 (t, J =7.2 Hz, 3H). Mass (m/z): 291.2$[M+H]^+$. **296B** (10.2 mg, 35%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.4 Hz, 2H), 5.48 (s, 1H), 5.27 (s, 1H), 3.46 (s, 2H), 3.15 (m, 1H), 1.95 – 1.80 (m, 4H), 1.65 – 1.48 (m, 4H), 1.35 – 1.23 (m, 3H), 1.15 (s, 6H), 0.60 (t, J =7.2 Hz, 3H). Mass (m/z): 291.2$[M+H]^+$.

Compound 297

4-(4,4-dimethylcyclohexyl)-N-(1-(pyrrolidin-1-yl)propan-2-yl)aniline

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Step 1. (4-(4,4-dimethylcyclohexyl)phenyl)alanine **(297-1)**

A mixture of 4-(4,4-dimethylcyclohexyl)aniline (100 mg, 0.49 mmol), 2-bromopro-panoic acid (112.85 mg, 0.74 mmol), TEA (99.53 mg, 0.98 mmol) in DCM (5 mL) was stirred overnight at 25°C. It was quenched by H_2O (30 mL) and extracted with DCM (3x30 mL). The organic layers were combined, washed with brine NaCl (2x30 mL) and dried with $MgSO_4$, filtered and concentrated to afford target product (100 mg, 59%) as yellow oil. Mass (m/z): 276.0 $[M+H]^+$.

Step 2. 2-((4-(4,4-dimethylcyclohexyl)phenyl)amino)-1-(pyrrolidin-1-yl)propan-1-one **(297-2)**

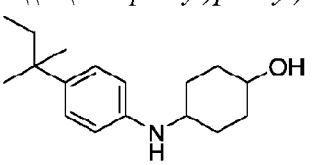
To a solution of **297-1** (100 mg, 0.36 mmol), pyrrolidine (51.65 mg, 0.72 mmol) in DMF (7 ml) was added HATU (207.1 mg, 0.54 mmol) and DIEA (93.86 mg, 0.72 mmol). Then the mixture was stirred overnight at 25 °C. It was quenched by H_2O (30 mL) and extracted with EA (3x30 mL). The organic layers were combined, washed with brine NaCl (2x30 mL) and dried with $MgSO_4$, filtered and concentrated. The crude product was applied onto a silica gel column (4 g) eluted with PE:EA (10:1) to give product (50 mg, 13.4 %). Mass (m/z): 329.3 $[M+H]^+$.

Step 3. Preparation of 4-(4,4-dimethylcyclohexyl)-N-(1-(pyrrolidin-1-yl)propan-2-yl)aniline **(297)**

To a solution of **297-2** (50 mg, 0.15 mmol), 2-(4-methylpiperazin-1-yl)acetic acid (66 mg, 0.42 mmol) in THF (5 mL) was added BH_3-THF (10 mL). Then the mixture was stirred overnight at rt. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product **297** (19.8 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.06 – 6.96 (m, 2H), 6.72 – 6.59 (m, 2H), 3.90 – 3.79 (m, 1H), 3.27 – 3.17 (m, 3H), 3.10 (d, J = 6.6 Hz, 2H), 2.34 – 2.21 (m, 1H), 2.01 (d, J = 6.6 Hz, 4H), 1.67 – 1.30 (m, 9H), 1.15 (d, J = 6.4 Hz, 3H), 0.96 (s, 3H), 0.92 (s, 3H). Mass (m/z): 315.2 $[M+H]^+$.

Compound 298

4-((4-(tert-pentyl)phenyl)amino)cyclohexan-1-ol



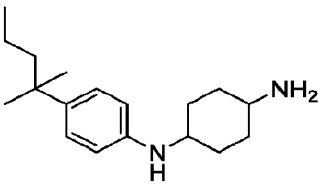
298

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The title compound **298** (47.8 mg) was prepared in a total yield of 61.0% as a light-yellow solid from 4-(tert-pentyl)aniline (49.2 mg, 0.3 mmol), 4-hydroxycyclohexan-1-one (68.4 mg, 0.6 mmol) and $Na(AcO)_3BH$ (127 mg, 0.6 mmol) according to the procedure for **4**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.06 – 6.80 (m, 2H), 6.59 – 6.27 (m, 2H), 5.12 (d, J = 8.0 Hz, 0.5H), 5.04 (d, J = 8..0 Hz, 0.5H), 4.50 (d, J = 4.4 Hz, 0.5H), 4.34 (d, J = 3.0 Hz, 0.5H), 3.71 – 3.59 (m, 0.5H), 3.36 (s, 0.5H), 3.21 – 3.10 (m, 0.5H), 3.02 (s, 0.5H), 1.87 (d, J – 12.8 Hz, 0.5H), 1.78 (d, J = 12.4 Hz, 0.5H), 1.62 – 1.41 (m, 10H), 1.12 (s, 6H), 0.57 (td, J = 7.4, 2.0 Hz, 3H). Mass (m/z): 262.3 $[M+H]^+$.

Compound 299

N^1-(4-(tert-pentyl)phenyl)cyclohexane-1,4-diamine

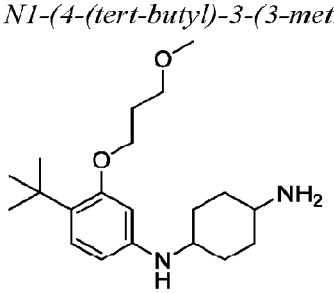


299A
299B

The title compound **299A** and **299B** were prepared according to the procedure for compound **232**. The crude residue was purified by preparative TLC (H_2O/MeOH/DCM=0.1/1/5) to afford compound **299A** in 30.9% yield as a white solid and **299B** in 25.3% yield as a white solid. **299A**: ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (s, 2H), 7.05 – 6.98 (m, 2H), 6.56 – 6.48 (m, 2H), 5.20 (d, J = 5.6 Hz, 1H), 3.43 – 3.36 (m, 1H), 3.07 (p, J = 6.4 Hz, 1H), 1.85 – 1.56 (m, 6H), 1.51 – 1.36 (m, 2H), 1.17 (s, 6H), 1.07 – 0.95 (m, 2H), 0.77 (t, J = 7.3 Hz, 3H). Mass (m/z): 275.3 $[M+H]^+$. HPLC: Rt=1.816 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA) = 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). **299B**: ^1H NMR (400 MHz, DMSO-d_6) δ 7.04 – 6.96 (m, 2H), 6.67 – 6.45 (m, 4H), 5.15 (d, J = 8.0 Hz, 1H), 3.13 – 3.01 (m, 1H), 2.90 – 2.79 (m, 1H), 2.07 – 1.84 (m, 4H), 1.51 – 1.41 (m, 2H), 1.38 – 1.28 (m, 2H), 1.21 – 1.11(m, 7H), 1.02 – 0.96 (m, 1H), 0.77 (t, J = 7.2 Hz, 3H). Mass (m/z): 275.3 $[M+H]^+$. HPLC: Rt=1.561 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 300

N1-(4-(tert-butyl)-3-(3-methoxypropoxy)phenyl)cyclohexane-1,4-diamine



300A
300B

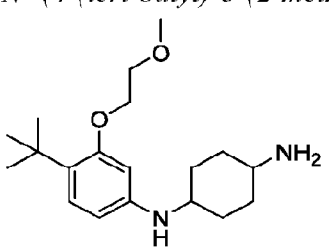
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The title compound **300A** and **300B** were prepared according to the procedure for compound **254**. The crude residue was purified by preparative TLC (H_2O/MeOH/DCM=0.1/1/5) to afford compound **300A** in 33.4% yield as a white solid and **300B** in 25.3% yield as a white solid. **300A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.98 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 6.16 (dd, J = 8.4, 2.3 Hz, 1H), 3.99 (t, J = 6.2 Hz, 2H), 3.60 (t, J = 6.2 Hz, 2H), 3.55 – 3.50 (m, 1H), 3.33 (s, 3H), 3.23 – 3.17 (m, 1H), 2.04 (q, J – 6.2 Hz, 2H), 1.88 – 1.73 (m, 8H), 1.30 – 1.29 (m, 9H). Mass (m/z):335.3 $[M+H]^+$. HPLC: Rt=4.800 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA) = 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

300B: ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.99 (d, J = 8.4 Hz, 1H), 6.30 (d, J = 2.3 Hz, 1H), 6.18 (dd, J = 8.4, 2.3 Hz, 1H), 3.99 (t, J = 6.2 Hz, 2H), 3.60 (t, J = 6.2 Hz, 2H), 3.33 (s, 3H), 3.28 – 3.17 (m, 4H), 3.16 – 3.02 (m, 1H), 2.18 – 2.12 (m, 2H), 2.10 – 2.02 (m, 4H), 1.49 (td, J = 12.5, 3.3 Hz, 2H), 1.30 (s, 9H), 1.28 – 1.21 (m, 2H). Mass (m/z): 335.3 $[M+H]^+$. HPLC: Rt=4.284 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 301

N^1-(4-(tert-butyl)-3-(2-methoxyethoxy)phenyl)cyclohexane-1,4-diamine



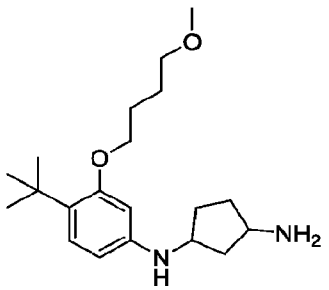
301A
301B

The title compound **301A** and **301B** were prepared according to the procedure for compound **254**. The crude residue was purified by preparative TLC (H_2O/MeOH/DCM=0.1/1/5) to afford compound **301A** in 31.2% yield as a white solid and **301B** in 21.3% yield as a white solid. **301A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.07 (d, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.25 (d, J = 8.4 Hz, 1H), 5.15 – 5.08 (m, 2H), 4.88 – 4.81 (m, 2H), 4.70 – 4.54 (m, 1H), 4.49 (s, 3H), 4.34 – 4.25 (m, 1H), 2.97 – 2.77 (m, 8H), 2.38 (s, 9H). Mass (m/z): 321.3 $[M+H]^+$. HPLC: Rt=4.678 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). **301B**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.98 (d, J = 8.4 Hz, 1H), 6.27 (d, J = 2.3 Hz, 1H), 6.17 (dd, J = 8.4, 2.3 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.79 – 3.71 (m, 2H), 3.40 (s, 3H), 3.23 – 3.10 (m, 1H), 3.10 – 2.98 (m, 1H), 2.19 – 2.01 (m, 4H), 1.56 – 1.44 (m, 2H), 1.30 (s, 9H), 1.28 – 1.19 (m, 2H). Mass (m/z):321.3 $[M+H]^-$. HPLC: Rt=4.231 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 302

N1-(4-(tert-butyl)-3-(4-methoxybutoxy)phenyl)cyclopentane-1,3-diamine

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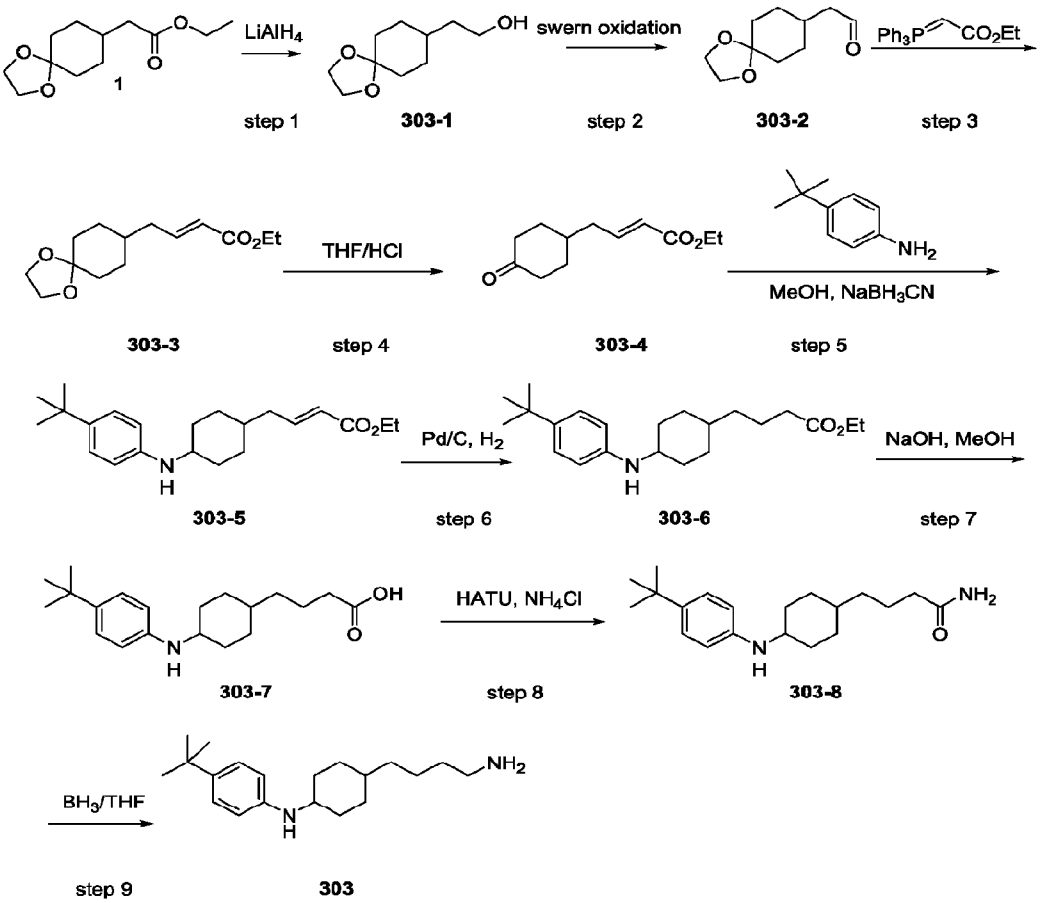


302

The title compound **302** (12.5 mg) was prepared in a total yield of 28.2% as a yellow solid with 7:3 mixture by ^{1}H NMR from tert-butyl (3-((4-(tert-butyl)-3-(4-methoxybutoxy)phenyl)amino)cyclopentyl)carbamate (58 mg, 0.13 mmol) and TFA (2.0 mL) according to the procedure for **254**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.00 (dd, J = 8.4, 4.1 Hz, 1H), 6.29 (d, J = 11.8 Hz, 1H), 6.18 (t, J = 10.5 Hz, 1H), 4.02 – 3.97 (m, 0.7H), 3.97 – 3.92 (m, 2H), 3.87 – 3.83 (m, 2H), 3.76 – 3.68 (m, 0.7H), 3.64 – 3.59 (m, 0.3H) , 3.46 (t, J = 6.2 Hz, 2H), 3.33 (s, 3H), 2.55 – 1.77 (m, 10H), 1.69 – 1.57 (m, 2H), 1.30 (s, 9H). Mass (m/z): 335.3 $[M+H]^+$.

Compound 303

N-(4-(4-aminobutyl)cyclohexyl)-4-(tert-butyl)aniline



Step 1. Preparation of 2-(1,4-dioxaspiro[4.5]decan-8-yl)ethan-1-ol **(303-1)**

To a solution of ethyl 2-(1,4-dioxaspiro[4.5]decan-8-yl)acetate (2 g, 8.76 mmol) in THF (30 mL) stirred 0 °C was added $LiAlH_4$ (998 mg, 26.28 mmol) in 3 min. 1 mL of H_2O was added into the mixture after stirred at 25 °C for 16 hrs. The mixture was filtered, diluted with H_2O, extracted with EA, dried over Na_2SO_4, filtered and evaporated to give the product (1.5 g, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 4H), 3.70 (t, J = 6.6 Hz, 2H), 1.75 (d, J = 9.8 Hz, 4H), 1.62 – 1.40 (m, 7H), 1.27 (dd, J = 22.2, 11.3 Hz, 2H).

Step 2. Preparation of 2-(1,4-dioxaspiro[4.5]decan-8-yl)acetaldehyde **(303-2)**

To a solution of oxalyl dichloride (1.23 g, 9.66 mmol) in THF (20 mL) was cooled to -78 °C was added DMSO (1.05 g, 13.42 mmol) and stirred at -78 °C for 30 min. Then a solution of 2-(1,4-dioxaspiro[4.5]decan-8-yl)ethan-1-ol (1.5 g, 8.05 mmol) was added into the mixture dropwise. After 1.5h stirring, triethylamine (6.52 g, 64.43 mmol) was added dropwise. Then the reaction was allowed to warm to rt and stirred for 12h. The mixture was filtered, evaporated and the residue was applied on silica gel column with EA/PE (0: 1-1: 5) to afford the product (930 mg, 94%). ^1H NMR (301 MHz, $CDCl_3$) δ 9.77 (s, 1H), 3.94 (s, 4H), 2.36 (d, J = 6.6 Hz, 2H), 1.94 (s, 1H), 1.75 (d, J = 11.1 Hz, 4H), 1.58 (t, J = 12.2 Hz, 2H), 1.43 – 1.18 (m, 2H).

Step 3. Preparation of ethyl (E)-4-(1,4-dioxaspiro[4.5]decan-8-yl)but-2-enoate **(303-3)**

To a solution of 2-(1,4-dioxaspiro[4.5]decan-8-yl)acetaldehyde (800 mg, 4.34 mmol) in Tol (20 mL) stirred at 80 °C was added DBU (4.54 g, 13.03 mmol) and ethyl

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2-(triphenyl-l5-phosphanylidene)acetate (1.98 g, 13.03 mmol) . The reaction mixture was stirred at 80°C for 16h. The residue was applied on to silica gel column with EA:PE (0:1-1:5) to afford the product as yellow oil (800 mg, 72.4%). Mass(m/z): 254.7 $[M+H]^+$.

Step 4. Preparation of ethyl (E)-4-(4-oxocyclohexyl)but-2-enoate **(303-4)**

To a solution of (E)-4-(1,4-dioxaspiro[4.5]decan-8-yl)but-2-enoate (800 mg, 3.15 mmol) in THF (20 mL) was added 2N HCl (10 mL). Then the mixture was stirred 16 hours at rt. The reaction was concentrated under vacuum. The residue was applied on to silica gel column with EA:PE (0:1-1:5) to afford the desired product as a colorless oil. (615 mg, 92.98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 – 6.87 (m, 1H), 5.85 (d, J = 15.5 Hz, 1H), 4.14 (dq, J = 21.0, 6.9 Hz, 2H), 2.49 – 2.29 (m, 4H), 2.23 (t, J = 7.0 Hz, 2H), 2.14 – 2.00 (m, 2H), 2.00 – 1.81 (m, 1H), 1.53 – 1.36 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H).

Step 5. Preparation of ethyl (E)-4-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)but-2-enoate **(303-5)**

To a solution of ethyl (E)-4-(4-oxocyclohexyl)but-2-enoate (615 mg, 2.92 mmol) and 4-(tert-butyl)aniline (524 mg, 3.51 mmol) in THF (20 mL) was stirred at 50 °C for 2 hours. Then the mixture was cooled to rt and $NaBH_3CN$ (551 mg, 8.77 mmol) was added. The mixture was stirred 16 hours at rt. The reaction was concentrated under vacuum. The residue was applied on to silica gel column with EA:PE (0:1-1:5) to afford the desired product as colorless oil (530 mg, 52.7%). Mass(m/z): 343.7 $[M+H]^+$.

Step 6. Preparation of ethyl 4-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)butanoate **(303-6)**

To a solution of ethyl (E)-4-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)but-2-enoate (530 mg, 1.54 mmol) in THF (20 ml) was added Pd/C (50 mg). Then the mixture was stirred 16 hours at rt under H_2 atmosphere. The crude mixture was filtered, concentrated under vacuum to afford the desired product as a colorless oil. (520 mg, 97.5%). Mass (m/z): 345.7 $[M+H]^+$.

Step 7. Preparation of 4-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)butanoic acid **(303-7)**

To a solution of ethyl 4-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)butanoate (520 mg, 1.50 mmol) in MeOH (15 mL) was added 4 N NaOH (1.1 mL). Then the mixture was stirred 16 hours at 50°C. The reaction was adjusted to pH 4 with 2 N HCl, exacted with EA (30 mL × 3), dried over Na_2SO_4, filtered, concentrated under vacuum. The residue was used directly as a colorless oil (455 mg, 95.2%).

Step 8. Preparation of 4-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)butanamide **(303-8)**

To a solution of 4-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)butanoic acid (120 mg, 0.378 mmol), NH_4Cl (61 mg, 1.134 mmol), HATU (287 mg, 0.756 mmol) and TEA (115 mg, 1.134 mmol) in DCM (10 mL) stirred 2 hours at rt. The reaction was washed with water, exacted with EA (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was applied on to silica gel column with EA:PE (0:1-2:1) to afford the desired product (100 mg, 83.5%) as a white solid. Mass (m/z): 316.7 $[M+H]^+$.

Step 9. Preparation of ethyl N-(4-(4-aminobutyl)cyclohexyl)-4-(tert-butyl)aniline **(303)**

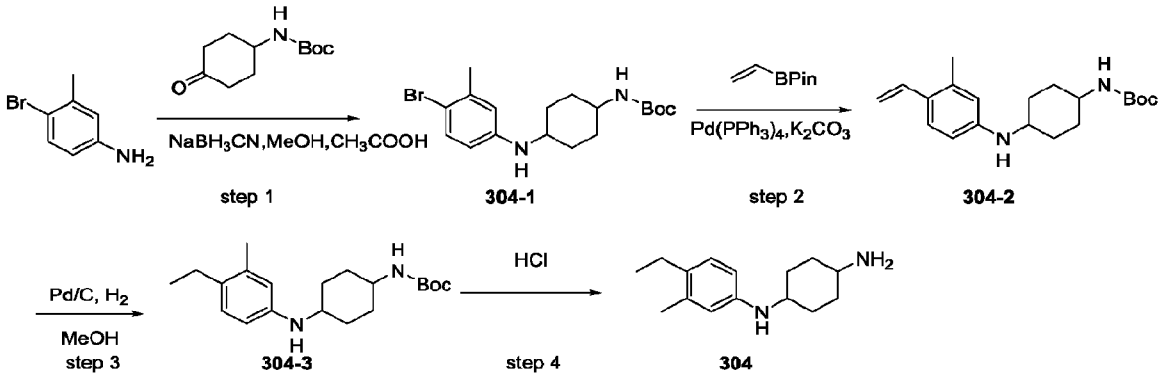
4-(4-((4-(tert-Butyl)phenyl)amino)cyclohexyl)butanamide (100 mg, 0.32 mmol) in BH_3-THF (30 mL) was stirred at 50 °C for 16 hours. The mixture was quenched with methanol, evaporated and purified by prep-HPLC to afford the product (29.2 mg, 30.2%) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.16 – 7.11 (m, 2H), 6.63 – 6.58 (m, 2H), 3.17 – 3.07 (m, 1H), 2.93 – 2.84 (m, 2H), 1.71 – 1.51 (m, 6H), 1.44 – 1.32 (m, 6H), 1.23 (s, 9H), 1.16 – 0.99

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(m, 3H). Mass (m/z): 303.2 $[M+H]^+$.

Compound 304

N1-(4-ethyl-3-methylphenyl)cyclohexane-1,4-diamine



Step 1. Preparation of tert-butyl (4-((6-ethylpyridin-3-yl)amino)cyclohexyl)carbamate **(304-1)**

To a solution of 4-bromo-3-methylaniline (1g, 5.4 mmol) in MeOH (10 mL) and a drop of AcOH was added tert-butyl (4-oxocyclohexyl)carbamate (1.4g, 6.5 mmol). Then the mixture was added NaBH3CN (680 mg, 10.8mmol) and the mixture was stirred at 25 °C for 16 h. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to afford to give **304-1** (1.5 g, 72.2% yield) as a yellow solid. MS (m/z) 383.1 $[M+H]^+$.

Step 2. Preparation of tert-butyl (4-((3-methyl-4-vinylphenyl)amino)cyclohexyl)carbamate **(304-2)**

To a solution of **304-1** (400 mg, 1.04 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (240 mg, 1.56 mmol), K_2CO_3 (430 mg, 3.12 mmol) in 1,4-dioxane (20 mL) and water (2 mL) was added $Pd(PPh_3)_4$ (120 mg, 0.10 mmol). The mixture was stirred with refluxing overnight under N_2 atmosphere. After cooling to ambient temperature, concentrated under reduced pressure. The residue was purified by silica gel column to provide **304-2** (240 mg, 69.5% yield) as a yellow solid. MS (m/z) 330.9 $[M+H]^+$.

Step 3. Preparation of tert-butyl (4-((4-ethyl-3-methylphenyl)amino)cyclohexyl)carbamate **(304-3)**

Pd/C (50 mg , 10%) was added to a solution of 2-(4,4-dimethylcyclohex-1-en-1-yl)-5-nitropyridine (240 mg, 0.72 mmol) in MeOH (10 mL), the mixture was allowed to react under H_2 for 16h , then filtered and solvent was removed under vacuum to give **304-3** (140 mg, 57.9% yield) as a yellow solid. MS (m/z) 332.9 $[M+H]^+$.

Step 4. Preparation of N1-(4-ethyl-3-methylphenyl)cyclohexane-1,4-diamine **(304)**

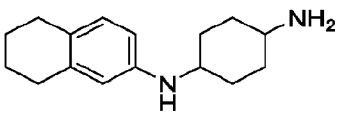
304-3 (140 mg, 0.42 mmol) and HCl in 1,4-dioxane (10 mL, 4N) were placed in a flask stirred at 25 °C for 16 hrs. Excess 1,4-dioxane. was distilled under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 20%-40%) to afford **304** (36 mg 36.9%) as a white solid. ^1H NMR (400 MHz,CD_3OD) δ 7.28 (dd, J = 23.3, 8.0 Hz, 1H), 7.14 (d, J = 9.3 Hz, 1H), 7.07 (d, J = 9.2 Hz,

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1H), 3.65 – 3.37 (m, 1H), 3.24 – 3.06 (m, 1H), 2.65 (dd, J = 9.6, 7.6 Hz, 2H), 2.34 (d, J = 9.4 Hz, 3H), 2.14 – 2.07 (m, 2H), 1.89 (dd, J = 10.6, 6.6 Hz, 4H), 1.58 – 1.44 (m, 2H), 1.18 (td, J = 7.6, 3.7 Hz, 3H). MS (m/z) 233.2 $[M+H]^+$.

Compound 305

N1-(5,6,7,8-tetrahydronaphthalen-2-yl)cyclohexane-1,4-diamine

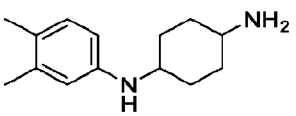


305A
305B

The title compound **305** was prepared from tert-butyl (4-((5,6,7,8-tetrahydronaphthalen-2-yl)amino)cyclohexyl)carbamate (88 mg, 0.256 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**, which was purified by prep HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 10%-25%-85%-95%-15%, 0 min-10 min-10.5 min-11.5 min-13 min) to give the desired product **305A** (Rt = 5.9 min) as a white solid (2.7 mg, 4.3%) and **305B** (Rt = 7.0 min) as yellow oil (8.9 mg, 14.2%). **305A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, J = 8.0 Hz, 1H), 6.46 – 6.20 (m, 2H), 5.03 (s, 1H), 3.00 (d, J = 54.8 Hz, 2H), 2.57 (d, J = 18.8 Hz, 4H), 1.99 (d, J = 11.6 Hz, 2H), 1.75 (d, J = 15.2 Hz, 3H), 1.66 (p, J = 3.2 Hz, 4H), 1.59 (d, J = 12.4 Hz, 1H), 1.46 (q, J = 12.0 Hz, 1H), 1.18 (t, J = 20.0 Hz, 1H). Mass(m/z): 245.3 $[M+H]^+$. **305B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, J = 8.0 Hz, 1H), 6.46 – 6.20 (m, 2H), 5.03 (s, 1H), 3.00 (d, J = 54.8 Hz, 2H), 2.57 (d, J = 18.8 Hz, 4H), 1.99 (d, J = 11.6 Hz, 2H), 1.75 (d, J = 15.2 Hz, 3H), 1.66 (p, J = 3.2 Hz, 4H), 1.59 (d, J = 12.4 Hz, 1H), 1.46 (q, J = 12.0 Hz, 1H), 1.18 (t, J = 20.0 Hz, 1H). Mass (m/z): 245.3 $[M+H]^+$.

Compound 306

N1-(3,4-dimethylphenyl)cyclohexane-1,4-diamine



306A
306B

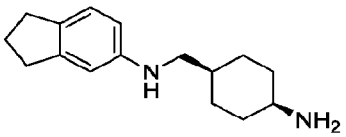
The title compound **306** was prepared from tert-butyl (4-((3,4-dimethylphenyl)amino)cyclohexyl)carbamate (128 mg, 0.402 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**, which was purified by prep HPLC (solvent system (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 15%-25%-95%-95%-15%, 0 min-9 min-9.5 min-10.5 min-13 min) to give the desired product **306A** (Rt = 6.6 min) as a white solid (4.8 mg, 5.4%) and **306B** (Rt = 7.5 min) as a white solid (5.5 mg, 6.3%). **306A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.76 (dd, J = 8.0, 5.2 Hz, 1H), 6.36 (dd, J = 18.4, 2.4 Hz, 1H), 6.27 (ddd, J = 15.6, 8.0, 2.4 Hz, 1H), 4.98 (d, J = 7.6 Hz, 1H), 3.37 – 2.75 (m, 2H), 2.05 (d, J = 2.4 Hz, 3H), 2.00 (d, J = 2.4 Hz, 3H), 1.97 – 1.86 (m, 2H), 1.73 – 1.47 (m, 4H), 1.36 (qd, J = 13.6, 12.4, 3.6 Hz, 1H), 1.15 – 1.02 (m, 1H). Mass (m/z): 219.3 $[M+H]^+$. **306B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.76 (dd, J = 8.0, 5.2 Hz, 1H),

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6.36 (dd, J = 18.4, 2.4 Hz, 1H), 6.27 (ddd, J = 15.6, 8.0, 2.4 Hz, 1H), 4.98 (d, J = 7.6 Hz, 1H), 3.37 – 2.75 (m, 2H), 2.05 (d, J = 2.4 Hz, 3H), 2.00 (d, J = 2.4 Hz, 3H), 1.97 – 1.86 (m, 2H), 1.73 – 1.47 (m, 4H), 1.36 (qd, J = 13.6, 12.4, 3.6 Hz, 1H), 1.15 – 1.02 (m, 1H). Mass (m/z): 219.3 $[M+H]^+$.

Compound 307

N-(((1s,4s)-4-aminocyclohexyl)methyl)-2,3-dihydro-1H-inden-5-amine

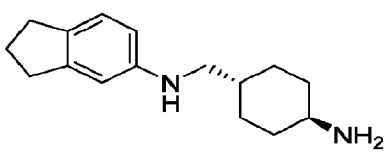


307

The title compound **307** (48.2 mg) was prepared in a total yield of 74.7% as a yellow solid from tert-butyl ((1s,4s)-4-((E)-((2,3-dihydro-1H-inden-5-yl)imino)methyl)cyclohexyl)carbamate (91 mg, 0.264 mmol), TFA(1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 (d, J = 8.0 Hz, 1H), 6.49 – 6.29 (m, 2H), 5.43 (dt, J = 21.6, 5.6 Hz, 1H), 3.15 (tt, J = 7.2, 3.2 Hz, 1H), 2.86 (dt, J = 46.0, 5.6 Hz, 2H), 2.70 (dt, J = 14.8, 7.2 Hz, 4H), 2.03 – 1.84 (m, 3H), 1.78 – 1.44 (m, 7H), 1.41 – 1.26 (m, 1H). Mass (m/z): 245.3 $[M+H]^+$.

Compound 308

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2,3-dihydro-1H-inden-5-amine (308)

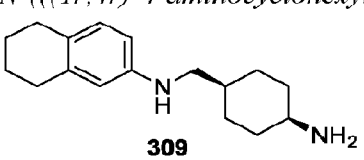


308

The title compound **308** (43.9 mg) was prepared in a total yield of 54.9% as a yellow solid from tert-butyl ((1r,4r)-4-((E)-((2,3-dihydro-1H-inden-5-yl)imino)methyl)cyclohexyl)carbamatetert-butyl (113 mg, 0.328 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (d, J = 8.0 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.33 (dd, J = 8.0, 2.0 Hz, 1H), 5.39 (q, J = 6.0 Hz, 1H), 2.91 (td, J = 12.0, 10.0, 6.0 Hz, 1H), 2.81 (t, J = 5.6 Hz, 2H), 2.70 (dt, J = 14.8, 7.4 Hz, 4H), 2.02 – 1.90 (m, 4H), 1.90 – 1.81 (m, 2H), 1.72 – 1.40 (m, 2H), 1.36 – 1.19 (m, 2H), 0.98 (qd, J = 13.2, 3.1 Hz, 2H). Mass (m/z): 245.3 $[M+H]^+$.

Compound 309

N-(((1r,4r)-4-aminocyclohexyl)methyl)-5,6,7,8-tetrahydronaphthalen-2-amine



309

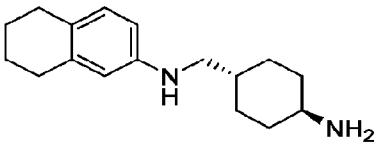
The title compound **309** (15.1 mg) was prepared in a total yield of 27.8% as a yellow solid from tert-butyl tert-butyl

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((1s,4s)-4-((E)-((5,6,7,8-tetrahydronaphthalen-2-yl)imino)methyl)cyclohexyl)carbamate (75 mg, 0.209 mmol), TFA(1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (d, J = 8.2 Hz, 1H), 6.38 – 6.27 (m, 1H), 6.22 (dd, J = 8.2, 2.4 Hz, 1H), 5.32 (dt, J = 17.5, 5.8 Hz, 1H), 3.14 (tt, J = 7.2, 3.3 Hz, 1H), 2.84 (dt, J = 44.0, 6.1 Hz, 2H), 2.57 (d, J = 5.1 Hz, 4H), 1.96 (td, J = 12.3, 11.4, 5.7 Hz, 1H), 1.84 (d, J = 13.4 Hz, 1H), 1.75 – 1.54 (m, 9H), 1.51 (q, J – 4.4, 4.0 Hz, 1H), 1.30 (tt, J – 12.7, 6.7 Hz, 1H), 1.10 – 0.89 (m, 1H). Mass (m/z): 259.3 $[M+H]^+$.

Compound 310

N-(((1r,4r)-4-aminocyclohexyl)methyl)-5,6,7,8-tetrahydronaphthalen-2-amine

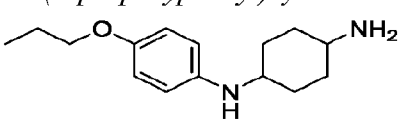


310

The title compound **310** (37 mg) was prepared in a total yield of 27.8% as a yellow solid from tert-butyl tert-butyl ((1s,4s)-4-((E)-((5,6,7,8-tetrahydronaphthalen-2-yl)imino)methyl)cyclohexyl)carbamate (82 mg, 0.229 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.70 (d, J = 8.4 Hz, 1H), 6.31 (dd, J = 8.4, 2.4 Hz, 1H), 6.20 (d, J = 2.4 Hz, 1H), 5.30 (s, 1H), 2.87 (ddt, J = 12.0, 7.6, 4.0 Hz, 1H), 2.77 (d, J = 6.4 Hz, 2H), 2.56 (dd, J = 14.0, 8.8 Hz, 4H), 1.98 (dd, J = 12.8, 4.0 Hz, 2H), 1.89 – 1.77 (m, 2H), 1.64 (h, J = 4.0, 3.6 Hz, 4H), 1.52 – 1.40 (m, 1H), 1.32 (qd, J = 12.4, 3.2 Hz, 2H), 0.96 (qd, J = 13.2, 3.1 Hz, 2H). Mass (m/z): 259.3 $[M+H]^+$.

Compound 311

N1-(4-propoxyphenyl)cyclohexane-1,4-diamine

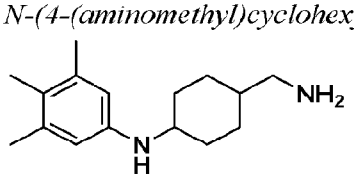


311

The title compound **311** (89.7 mg) was prepared in a total yield of 65.2% as a yellow oil with 1:2 mixture by ^{1}H NMR from tert-butyl (4-((4-propoxyphenyl)amino)cyclohexyl)carbamate (193 mg, 0.554 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 12.4 Hz, 2H), 5.43 (dd, J = 48.0, 7.6 Hz, 1H), 4.05 (td, J = 6.8, 1.6 Hz, 2H), 2.43 (d, J = 5.6 Hz, 2H), 2.20 (d, J = 3.6 Hz, 2H), 1.72 (dd, J = 12.8, 4.3 Hz, 4H), 1.63 (d, J = 6.4 Hz, 4H), 0.89 (t, J = 7.6 Hz, 3H). Mass (m/z):249.3 $[M+H]^+$.

Compound 312

N-(4-(aminomethyl)cyclohexyl)-3,4,5-trimethylaniline



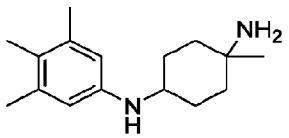
312

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The title compound **312** (59.6 mg) was prepared in a total yield of 61.2% as a yellow solid with 1:2 mixture by ^{1}H NMR from tert-butyl ((4-((3,4,5-trimethylphenyl)amino)cyclohexyl)methyl)carbamate (137 mg, 0.369 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.21 (d, J = 28.0 Hz, 2H), 4.86 (d, J = 30.8 Hz, 1H), 3.16 – 2.67 (m, 1H), 2.54 (dd, J = 26.4, 6.8 Hz, 2H), 2.06 (d, J – 2.0 Hz, 6H), 1.91 (d, J – 1.2 Hz, 3H), 1.83 – 1.66 (m, 1H), 1.56 (dq, J = 9.2, 4.2 Hz, 2H), 1.51 – 1.31 (m, 4H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 313

1-methyl-N4-(3,4,5-trimethylphenyl)cyclohexane-1,4-diamine

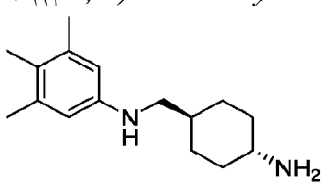


313

The title compound **313A** (13.6 mg) was prepared in a yield of 14.9% as a brown solid by ^{1}H NMR compound **313B** (14.9 mg) was prepared in a yield of 16.35% as a brown solid from 3,4,5-trimethylaniline (50 mg, 0.37 mmol) and tert-butyl (1-methyl-4-oxocyclohexyl)carbamate (50 mg, 0.22 mmol)according to the procedure for **20**. **313A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 31.5 Hz, 2H), 6.26 (d, J = 11.9 Hz, 2H), 4.84 (d, J = 69.4 Hz, 1H), 3.19 (d, J = 42.5 Hz, 1H), 2.11 (s, 6H), 1.96 (s, 3H), 1.92 – 1.83 (m, 2H), 1.80 – 1.70 (m, 2H), 1.70 – 1.61 (m, 1H), 1.55 (t, J = 8.4 Hz, 2H), 1.31 (s, 1H), 1.28 (d, J = 6.6 Hz, 3H). Mass(m/z): 247.5 $[M+H]^+$. **313B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 2H), 6.25 (s, 1H), 6.22 (s, 1H), 5.02 – 4.61 (m, 1H), 3.17 (d, J = 45.2 Hz, 1H), 2.09 (s, 6H), 1.94 (d, J = 2.1 Hz, 3H), 1.89 – 1.81 (m, 2H), 1.71 (s, 2H), 1.64 (s, 1H), 1.53 (d, J = 9.7 Hz, 1H), 1.31 – 1.20 (m, 5H). Mass(m/z): 247.5 $[M+H]^+$.

Compound 314

N-(((1r,4r)-4-aminocyclohexyl)methyl)-3,4,5-trimethylaniline



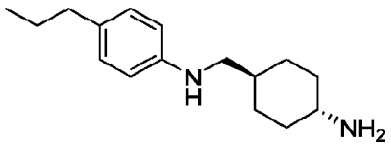
314

The title compound **314** (34.2 mg) was prepared in a yield of 47.3% as a white powder from 3,4,5-trimethylaniline (40 mg, 0.29 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (80 mg, 0.35 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 – 7.95 (m, 2H), 6.22 (d, J = 8.3 Hz, 2H), 5.18 (s, 1H), 2.90 (d, J = 7.4 Hz, 1H), 2.83 – 2.74 (m, 2H), 2.10 (s, 6H), 1.95 (s, 3H), 1.84 (dd, J = 13.9, 3.6 Hz, 2H), 1.64 (d, J = 6.9 Hz, 1H), 1.57 – 1.38 (m, 2H), 1.39 – 1.19 (m, 2H), 1.06 – 0.91 (m, 2H). Mass (m/z): 247.2 $[M+H]^+$.

Compound 315

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-propylaniline

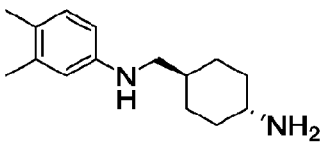
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The title compound 315 (12.3 mg) was prepared in a yield of 17.02% as a white powder from 4-propylaniline (40 mg, 0.29 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (80 mg, 0.35 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 19.6 Hz, 2H), 6.87 (dd, J = 8.5, 2.1 Hz, 2H), 6.47 (dd, J = 8.9, 7.2 Hz, 2H), 5.43 (s, 1H), 2.93 (q, J = 7.8, 6.7 Hz, 1H), 2.81 (t, J = 6.2 Hz, 1H), 2.37 (t, J = 7.5 Hz, 2H), 2.00 – 1.81 (m, 3H), 1.66 (s, 1H), 1.61 – 1.37 (m, 4H), 1.29 (dd, J = 26.4, 13.7 Hz, 2H), 1.09 – 0.95 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). Mass (m/z): 247.6 $[M+H]^+$.

Compound 316

N-(((1r,4r)-4-aminocyclohexyl)methyl)-3,4-dimethylaniline

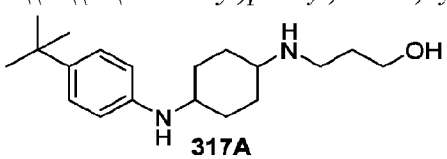


316

The title compound **316** (34.9 mg) was prepared in a yield of 52.0% as a white powder from 3,4-dimethylaniline (35 mg, 0.29 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (80 mg, 0.35 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 2H), 6.81 (d, J = 8.2 Hz, 1H), 6.38 (s, 1H), 6.29 (d, J = 8.1 Hz, 1H), 5.29 (s, 1H), 2.81 (d, J = 6.6 Hz, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 2.00 – 1.90 (m, 2H), 1.90 – 1.81 (m, 2H), 1.64 (t, J = 6.2 Hz, 1H), 1.54 (q, J = 5.7 Hz, 1H), 1.33 – 1.23 (m, 2H), 1.06 – 0.93 (m, 2H). Mass(m/z): 233.2 $[M+H]^+$.

Compound 317

3-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)propan-1-ol



317A
317B

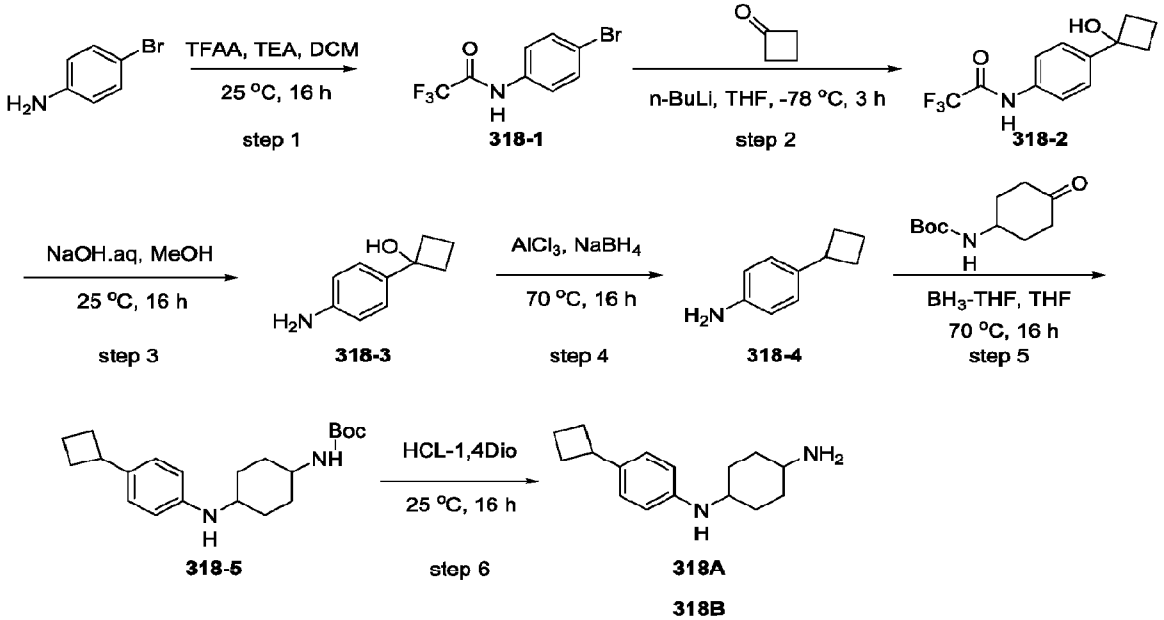
The title compound **317A** (21.1 mg) was prepared in a yield of 34.0% as a white powder and compound **317B** (22.3 mg) was prepared in a yield of 35.9% as a white powder from 4-((4-(tert-butyl)phenyl)amino)cyclohexan-1-one (50 mg, 0.20 mmol), methyl 3-aminopropan-1-ol (46 mg, 0.61 mmol) and $NaBH(OAc)_3$ (86 mg, 0.40 mmol) according to the procedure for **20**. **317A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 7.13 – 6.99 (m, 2H), 6.59 – 6.46 (m, 2H), 5.22 (d, J = 5.6 Hz, 1H), 4.76 (s, 1H), 3.48 (t, J = 6.0 Hz, 2H), 3.46 – 3.41 (m, 1H), 3.07 (s, 1H), 2.95 (s, 2H), 1.88 – 1.67 (m, 8H), 1.57 (ddd, J = 13.9, 9.5, 3.6 Hz, 2H), 1.20 (s, 9H). Mass (m/z): 305.6 $[M+H]^+$. HPLC: Rt=2.070 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1%)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min). **317B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12 – 7.02 (m, 2H), 6.55 – 6.46 (m, 2H), 5.20 (d, J = 8.1 Hz, 1H), 3.49 (t, J = 6.0 Hz, 2H), 3.16 – 3.05 (m, 1H), 2.96 (q, J

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= 7.9 Hz, 3H), 2.15 – 1.98 (m, 4H), 1.85 – 1.74 (m, 2H), 1.48 (q, *J* = 12.2, 11.7 Hz, 2H), 1.21 (s, 9H), 1.19 – 1.12 (m, 2H). Mass (m/z): 305.6 $[M+H]^+$. HPLC: Rt=1.944 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1%)= 5%-5%-95%-95%-95%-5%, 0-0.5 min-10 min-10.5 min-12.0 min).

Compound 318

1-N-(4-cyclobutylphenyl)cyclohexane-1,4-diamine



Step 1. N-(4-bromophenyl)-2,2,2-trifluoroacetamide **(318-1)**

A mixture of 4-bromoaniline (1 g, 5.8 mmol), TFAA (2.35 ml), TEA (1.23 ml) in DCM (10 mL) was stirred overnight at 25°C. The pH of the water phase was adjusted to 8 by 1N NaOH. It was quenched by H_2O (300 mL) and extracted with EA (3x300 mL), dried over Na_2SO_4, concentrated to afford target product (600 mg, yield: 30.7%) as a yellow solid.

Step 2. 2,2,2-trifluoro-N-(4-(1-hydroxycyclobutyl)phenyl)acetamide **(318-2)**

To a solution of **318-1** (600 mg, 2.23 mmol), cyclobutanone (156.3 mg, 2.23 mmol) in THF (10 ml) was added n-BuLi (5.3 mL) at -78 °C. Then the mixture was stirred overnight at rt. The reaction was quenched by adding aq. NH_4Cl. It was quenched by H_2O (100 mL) and extracted with DCM (3x100 mL). The organic layers were combined, washed with brine NaCl (2x100 mL) and dried with $MgSO_4$, filtered and concentrated. The crude product was applied onto a silica gel column (12 g) eluted with PE:EA (5:1) to give product (400 mg, yield: 90%) as a yellow solid. Mass (m/z): 241.9/262.9 $[M+H]^+$.

Step 3. 1-(4-aminophenyl)cyclobutan-1-ol **(318-3)**

To a solution of **318-2** (400 mg, 1.53 mmol) in MeOH (5 ml) was added 1N NaOH (10 mL) at 25 °C. Then the mixture was stirred overnight at rt. The reaction was concentrated under vacuum. It was quenched by H_2O (100 mL) and extracted with DCM (3x100 mL), dried with $MgSO_4$, filtered and concentrated to afford target product (200 mg, yield: 63.8%) as a yellow solid. Mass (m/z): 164.2 $[M+H]^+$.

Step 4. 4-cyclobutylaniline **(318-4)**

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To a solution of **318-3** (200 mg, 1.22 mmol) in THF (5 mL) was added $NaBH_4$ (254.96 mg, 6.74 mmol) at 0 °C. Then $AlCl_3$ (490.18 mg, 3.67 mmol) was added in portions. Then the mixture was stirred overnight at rt. The reaction was concentrated under vacuum. It was quenched by H_2O (100 mL) and extracted with EA (3x100 mL). The crude product was applied onto a silica gel column (12 g) eluted with PE:EA (5:1) to give the product (200 mg, yield: 63.8%) as a yellow solid. Mass (m/z): 148.2 $[M+H]^+$.

Step 5. tert-butyl (4-((4-cyclobutylphenyl)amino)cyclohexyl)carbamate **(318-5)**

To a solution of **318-4** (80 mg, 0.31 mmol), Pic-BH_3 (87.22 mg, 0.81 mmol) in AcOH/H_2O=1:10 (5.5 mL) was stirred overnight at 25°C. The pH of the water phase was adjusted to 8 by aq. $NaHCO_3$. It was quenched by H_2O (30 mL) and extracted with EA (3x30 mL), dried with $MgSO_4$, filtered and concentrated to afford the target product (100 mg, yield: 17.2%) as a yellow solid. Mass (m/z): 345.3 $[M+H]^+$.

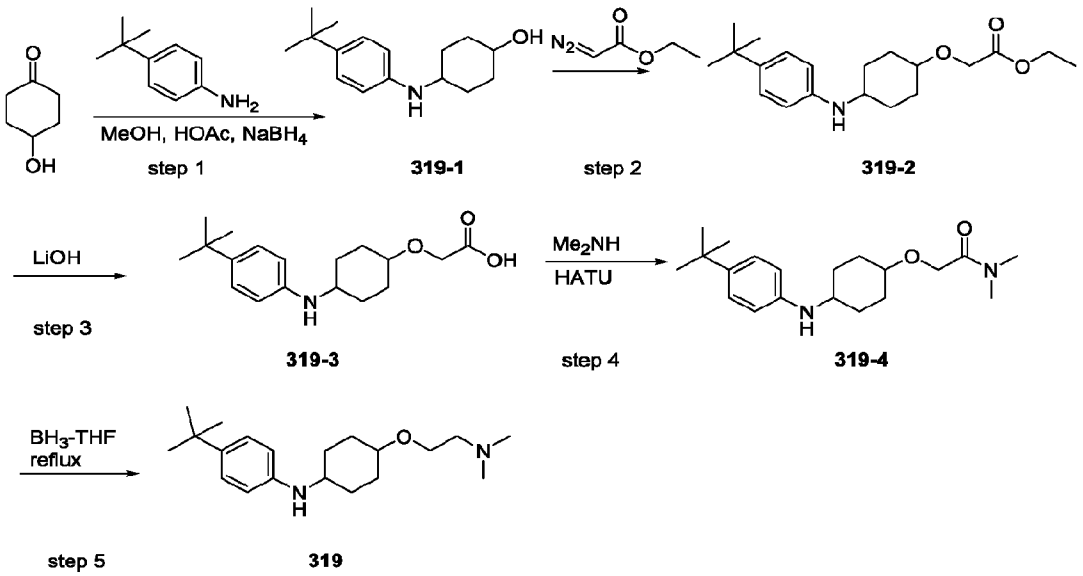
Step 6. Preparation of N1-(4-cyclobutylphenyl)cyclohexane-1,4-diamine **(318)**

To a solution of **318-5** (200 mg, 0.57 mmol) in 1,4-dioxane (5 ml) was added HCl /1,4-dioxane (10 mL). Then the mixture was stirred overnight at 25 °C. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired products **318A** (5.4 mg) as a white solid and **318B** (17.8 mg) as a white solid. **318A**: ^1H NMR (400 MHz, CD_3OD) δ 7.01 – 6.94 (m, 2H), 6.64 – 6.52 (m, 2H), 3.47 – 3.31 (m, 2H), 3.27 – 3.15 (m, 0.5H), 3.10 – 3.02 (m, 0.5H), 2.29 – 2.20 (m, 2H), 2.17 – 2.10 (m, 2H), 2.09 – 1.96 (m, 5H), 1.83 – 1.75 (m, 1H), 1.49 (qd, J = 13.0, 3.6 Hz, 2H), 1.34 – 1.17 (m, 2H). Mass (m/z): 452.3 $[M+H]^+$. HPLC: Rt=3.582 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min). **318B**: ^1H NMR (400 MHz, CD_3OD) δ 7.06 – 6.91 (m, 2H), 6.67 – 6.52 (m, 2H), 3.52 (s, 1H), 3.44 – 3.32 (m, 1H), 3.25 – 3.09 (m, 1H), 2.29 – 2.16 (m, 2H), 2.10 – 1.91 (m, 3H), 1.90 – 1.58 (m, 9H). Mass (m/z): 452.3 $[M+H]^+$. HPLC: Rt=3.757 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min).

Compound 319

4-(tert-butyl)-N-(4-(2-(dimethylamino)ethoxy)cyclohexyl)aniline

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Step 1. Preparation of 4-((4-(tert-butyl)phenyl)amino)cyclohexan-1-ol **(319-1)**

To a solution of 4-hydroxycyclohexan-1-one (2000 mg, 17.52 mmol) in MeOH (50 mL) and a drop of AcOH was added 4-(tert-butyl)aniline (3138 mg, 21.03 mmol) and the mixture was stirred at 50 °C for 1 h. Then the mixture was added $NaBH_4$ (1325 mg, 35.04 mmol) after cooling to 25 °C. Then the mixture was stirred at 25 °C for 16 hrs. LCMS showed the reaction was completed. The reaction was quenched with water (10 mL), extracted with EA (10 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:3) to afford to give **319-1** (1500 mg, 34.6% yield) as a yellow solid. MS (m/z) 247.9 $[M+H]^+$.

Step 2. ethyl 2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)oxy)acetate **(319-2)**

Ethyl 2-diazoacetate (276.7 mg, 2.43 mmol), Rhodium(II) acetate dimer (89.34 mg, 0.20 mmol) was added to a solution of 4-[(4-tert-butylphenyl)amino]cyclohexan-1-ol(500 mg, 2.02 mmol) in DCM (10 mL), the mixture was removed under vacuum. The residue was purified through flash column chromatography to give **319-2** (400 mg, 59.3% yield) as a yellow solid. MS (m/z): 333.8 $[M+H]^+$.

Step 3. Preparation of 2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)oxy)acetic acid **(319-3)**

To a solution of **319-2** (400 mg, 1.20 mmol) in THF (4 mL) and water (4 mL) was added LiOH (172.3 mg, 7.2 mmol) and the mixture was stirred at 25 °C for 2 h. the solvent was removed under vacuum. Dissolved in water (20 mL) and adjusted pH=2 with 1NHCl, extracted with EA (20 mL*3). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated to give **319-3** (200 mg, 54.6% yield) as a yellow solid. MS (m/z) 306.2 $[M+H]^+$.

Step 4. Preparation of 2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)oxy)-N,N-dimethylacetamide **(319-4)**

To a solution of 2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)oxy)acetic acid (200 mg, 0.66 mmol) in DMF (5 mL) was added 2N Me_2NH (0.7 mL, 1.31 mmol), triethylamine (9198.8 mg, 1.96 mmol) and HATU (373.5 mg, 0.98 mmol). Then the mixture was stirred at rt. for 2 h. The

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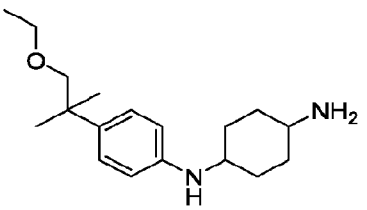
reaction was extracted by EA (10 mL) for 3 times. The organic layers were dried over sodium sulfate, concentrated under vacuum and the residue was purified by flash to afford the desired product (100 mg, 45.9%) as yellow oil. MS (m/z) 332.9 $[M+H]^+$.

Step 5. Preparation of 4-(tert-butyl)-N-(4-(2-(dimethylamino)ethoxy)cyclohexyl)aniline **(319)**

To a solution of 2-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)oxy)-N,N-dimethylacetamide (70 mg, 0.21 mmol) in THF (2 mL) was added $LiAlH_4$ (16.8 mg, 0.42 mmol) and the mixture was stirred at 50 °C for 16 h. The reaction was quenched with water (1 mL), 1N NaOH (1 mL) and water (3 mL). The residue was filtered and the filtrate was removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 40%-60%) to afford **319A** (10.4 mg) as a white solid and **319B** (15.5 mg) as a white solid. **319A**: ^1H NMR (400 MHz, CD_3OD) δ 7.61 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 3.83 – 3.79 (m, 2H), 3.46 (d, J = 3.8 Hz, 1H), 2.91 (s, 6H), 2.68 (s, 4H), 2.20 (d, J = 10.2 Hz, 2H), 2.09 (s, 1H), 1.55 (d, J = 12.5 Hz, 2H), 1.36 (s, 9H). MS (m/z) 319.3 $[M+H]^+$. HPLC: Rt: 3.843 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **319B**: ^1H NMR (400 MHz, CD_3OD) δ 7.51 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 3.68 – 3.64 (m, 2H), 3.58 (s, 1H), 3.43 – 3.36 (m, 1H), 3.30 – 3.26 (m, 2H), 2.85 (s, 6H), 1.99 (d, J = 15.0 Hz, 2H), 1.78 – 1.66 (m, 4H), 1.46 (d, J = 16.7 Hz, 2H), 1.25 (s, 9H). MS (m/z) 319.3 $[M+H]^+$. HPLC: Rt: 3.977 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 320

N1-(4-(1-ethoxy-2-methylpropan-2-yl)phenyl)cyclohexane-1,4-diamine



320A
320B

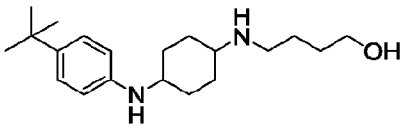
The title compound **320** was prepared from tert-butyl (4-((4-(1-ethoxy-2-methylpropan-2-yl)phenyl)amino)cyclohexyl)carbamate (120 mg, 0.3 mmol) according to the procedure for compound **24**. The mixture was purified by preparative HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 15%-33%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13.0 min) to afford compound **320A** (Rt = 7.46 min) as a white solid and compound **320B** (Rt = 9.14 min) as a white solid. **320A** (33.1 mg, 38%): ^1H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 5.25 (s, 1H), 3.33 (m, 2H), 3.27 (s, 2H), 3.07 (m, 2H), 1.84 – 1.68 (m, 6H), 1.65 – 1.50 (m, 2H), 1.17 (s, 6H), 1.06 (t, J = 7.2Hz, 3H). Mass (m/z): 291.3$[M+H]^+$. **320B** (34.1 mg, 39%): ^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 5.29 (s, 1H), 3.34 (m, 2H), 3.27 (s, 2H), 3.07 (m, 1H), 2.93 (m, 1H), 2.10 – 1.88 (m, 4H), 1.55 – 1.39 (m, 2H), 1.21 (m, 2H), 1.16 (s, 6H), 1.05 (t, J = 7.2Hz, 3H).

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Mass (m/z): 291.3$[M+H]^+$.

Compound 321

4-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)butan-1-ol

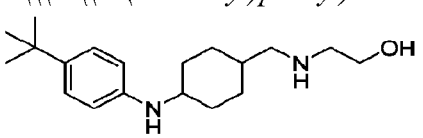


321

The title compound **321** (60.9 mg) was prepared in a yield of 93.8% as a white powder with 1:1 mixture by ^{1}H NMR from 4-((4-(tert-butyl)phenyl)amino)cyclohexan-1-one (50 mg, 0.20 mmol), methyl 4-aminobutan-1-ol (54 mg, 0.61 mmol) and $NaBH(OAc)_3$ (86 mg, 0.41 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.67 (s, 1H), 7.08 (dd, J = 8.5, 5.9 Hz, 2H), 6.52 (dd, J = 15.8, 8.5 Hz, 2H), 5.21 (s, 1H), 4.60 (q, J = 5.2, 3.9 Hz, 1H), 3.42 (q, J = 5.8 Hz, 2H), 2.98 (s, 2H), 2.90 (s, 2H), 2.15 – 1.97 (m, 3H), 1.87 – 1.73 (m, 2H), 1.68 (dq, J = 15.5, 7.9, 7.5 Hz, 2H), 1.56 (t, J = 13.6 Hz, 1H), 1.51 – 1.39 (m, 3H), 1.21 (d, J = 1.5 Hz, 11H). Mass (m/z): 319.2 $[M+H]^+$.

Compound 322

2-(((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)amino)ethan-1-ol

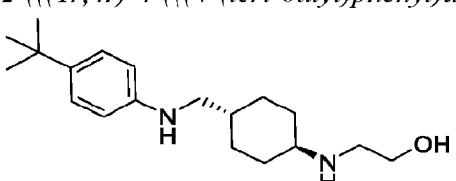


322

The title compound **322** (18 mg) was prepared in a yield of 30.79% as a white powder with 1:1 mixture by ^{1}H NMR from N-(4-(aminomethyl)cyclohexyl)-4-(tert-butyl)aniline (50 mg, 0.19 mmol), 2-bromoethan-1-ol (24 mg, 0.19 mmol) and potassium carbonate (40 mg, 0.29 mmol) according to the procedure for **12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.00 (s, 2H), 7.41 (s, 3H), 3.68 (dt, J = 11.4, 5.4 Hz, 1H), 3.45 (s, 1H), 3.27 (s, 1H), 2.91 (s, 1H), 2.77 (s, 1H), 2.63 (t, J = 6.3 Hz, 1H), 1.97 (d, J = 11.9 Hz, 1H), 1.83 (d, J = 14.4 Hz, 1H), 1.77 – 1.45 (m, 6H), 1.26 (d, J = 3.6 Hz, 9H), 0.98 (d, J = 12.5 Hz, 1H). Mass (m/z): 305.2 $[M+H]^+$.

Compound 323

2-(((1r,4r)-4-(((4-(tert-butyl)phenyl)amino)methyl)cyclohexyl)amino)ethan-1-ol



323

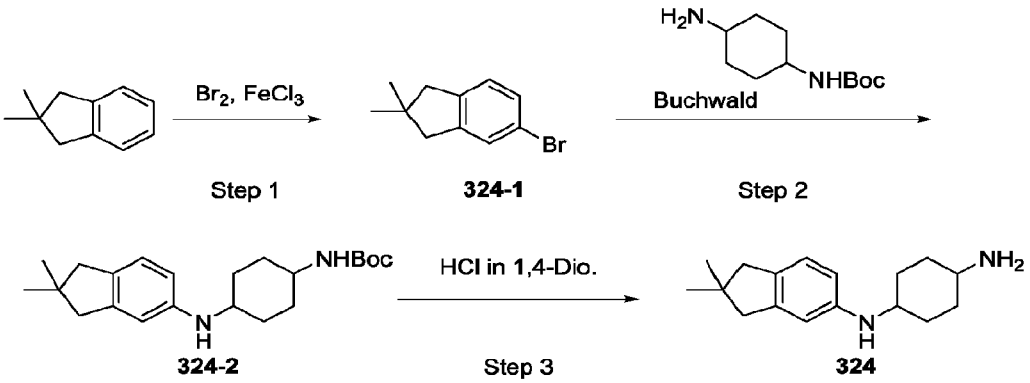
The title compound **323** (25.9 mg) was prepared in a yield of 44.31% as a white powder from N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(tert-butyl)aniline (50 mg, 0.19 mmol), 2-bromoethan-1-ol (24 mg, 0.19 mmol) and potassium carbonate (40 mg, 0.29 mmol) according to the procedure for **12**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.01 (s, 1H), 7.08 (d, J = 8.2 Hz, 2H), 6.49 (s, 2H), 5.52 – 5.15 (m, 2H), 3.67 (s, 1H), 2.98 (s, 2H), 2.82 (d, J = 6.4 Hz, 2H), 2.09 (d, J = 12.0 Hz, 1H), 2.01 – 1.83 (m, 3H), 1.47 (s, 1H), 1.40 – 1.22 (m, 4H),

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1.20 (s, 9H), 1.00 (q, J = 12.4 Hz, 2H). Mass (m/z): 305.2 $[M+H]^+$.

Compound 324

N-(2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)cyclohexane-1,4-diamine



Step 1. Preparation of 5-bromo-2,2-dimethyl-2,3-dihydro-1H-indene **(324-1)**

A solution of 2,2-dimethyl-2,3-dihydro-1H-indene (500 mg, 2.87 mmol), $FeCl_3$ (3.4 mg, 0.021 mmol) and Br_2 (460 mg, 2.87 mmol) in DCM (10 mL) was stirred at 0 °C for 18 hours. The mixture was concentrated under vacuum to afforded 300 mg(crude) of **324-1** (yield: 46.7 %) as yellow oil.

Step 2. Preparation of tert-butyl (4-((2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)amino)cyclohexyl)carbamate **(324-2)**

To a solution of **324-1** (300 mg, 1.33 mmol), tert-butyl (4-aminocyclohexyl)carbamate (314 mg, 1.33 mmol), Cs_2CO_3 (868 mg, 2.66 mmol) and Ruphos (124 mg, 0.26 mmol) in 1,4-dioxane (15 mL) was added $Pd_2(dba)_3$ (122 mg, 0.13 mmol). The mixture was stirred with refluxing overnight under N_2 atmosphere. After cooling to ambient temperature, ethyl acetate was added to the reaction mixture and the mixture was filtered through Celite. The filtrate was washed with water and saturated brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column to provide 100 mg of **324-2** (yield: 20.7%) as a yellow solid. Mass (m/z): 364.3 $[M+H]^+$.

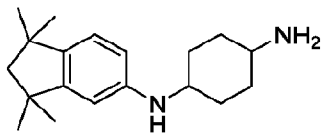
Step 3. Preparation of N-(2,2-dimethyl-2,3-dihydro-1H-inden-5-yl)cyclohexane-1,4-diamine **(324)**

324-2 (100 mg, 0.28 mmol) and HCl in 1,4-dioxane (10 mL, 4 N) were placed in a flask and stirred at 25 °C for 18 hrs. Excess 1,4-Dio. was removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **324** (11.4 mg) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 6.83 (d, J = 8.0 Hz, 1H), 6.38 (s, 1H), 6.31 (d, J = 8.0 Hz, 1H), 5.06 (s, 1H), 3.06 (s, 1H), 2.87 (s, 1H), 2.53 (s, 4H), 1.95 (dd, J = 22.8, 12.8 Hz, 4H), 1.36 (dd, J = 22.0, 12.2 Hz, 2H), 1.22 – 1.09 (m, 2H), 1.07 (s, 6H). Mass (m/z): 259.3 $[M+H]^+$.

Compound 325

N1-(1,1,3,3-tetramethyl-2,3-dihydro-1H-inden-5-yl)cyclohexane-1,4-diamine

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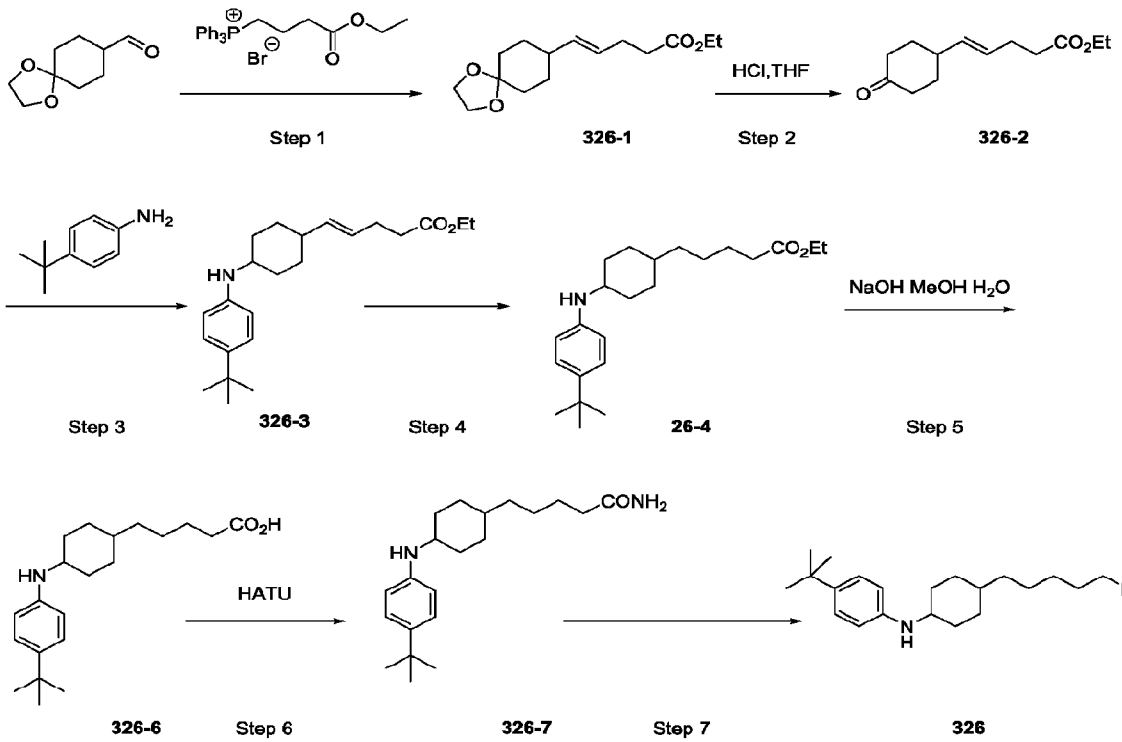


325A
325B

The title compounds **325A** (45.7 mg) as a white solid and **325B** (54.8 mg) as a white solid were prepared from tert-butyl (4-((1,1,3,3-tetramethyl-2,3-dihydro-1H-inden-5-yl)amino) cyclohexyl)carbamate (400 mg, 0.25 mmol), 1,4-dioxane (5 mL) and HCl /1,4-dioxane (10 mL) according to the procedure for **324**. **325A**: ^{1}NMR (400 MHz, CD_3OD) δ 6.85 (d, J = 8.0 Hz, 1H), 6.50 (dd, J = 8.2, 2.2 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 3.53 (s, 1H), 3.24 – 3.14 (m, 1H), 1.88 – 1.66 (m, 10H), 1.22 (d, J = 7.4 Hz, 12H). Mass (m/z): 452.3 $[M+H]^+$. HPLC: Rt=4.180 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min). **325B**: ^{1}H NMR (400 MHz, CD_3OD) δ 6.85 (d, J = 8.0 Hz, 1H), 6.50 (dd, J = 8.2, 2.2 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 3.53 (s, 1H), 3.24 – 3.14 (m, 1H), 1.88 – 1.66 (m, 10H), 1.22 (d, J = 7.4 Hz, 12H). Mass (m/z): 452.3 $[M+H]^+$. HPLC: Rt=4.480 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min).

Compound 326

N-(4-(5-aminopentyl)cyclohexyl)-4-(tert-butyl)aniline



Step 1. Preparation of ethyl (E)-5-(1,4-dioxaspiro[4.5]decan-8-yl)pent-4-enoate **(326-1)**

A solution of 1,4-dioxaspiro[4.5]decane-8-carbaldehyde (1000 mg, 5.9 mmol), NaH (940 mg,

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23.6 mmol) and (4-ethoxy-4-oxobutyl)triphenylphosphonium bromide (5380 mg, 11.8 mmol) in THF (10 mL) was stirred at 0 °C under N_2 atmosphere for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 1 g of **326-1** (yield: 63.4%) as a yellow solid.

Step 2. Preparation of ethyl (E)-5-(4-oxocyclohexyl)pent-4-enoate **(326-2)**

326-1 (370 mg, 1.4 mmol) and HCl in THF (20 mL, 2 N) were placed in a flask and stirred at 25 °C for 18 hrs. Excess THF was removed under vacuum and the residue was purified by silica gel column to provide 320 mg of **326-2** (yield: 86.4%) as yellow oil.

Step 3. Preparation of ethyl (E)-5-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)pent-4-enoate **(326-3)**

A solution of **326-2** (320 mg, 1.42 mmol), 4-(tert-butyl)aniline (214 mg, 1.42 mmol) and $NaBH_3CN$ (179 mg, 2.84 mmol) in MeOH (10 mL) was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 225 mg of **326-3** (yield: 44.3%) as a yellow solid. Mass (m/z): 358.2 $[M+H]^+$.

Step 4. Preparation of ethyl 5-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)pentanoate **(326-4)**

A solution of **326-3** (225 mg, 0.63 mmol), Pd/C (20 mg) in MeOH (10 mL) was stirred at 25 °C under H_2 atmosphere for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 120 mg of **326-4** (yield: 52.9%) as a yellow solid. Mass (m/z): 360.3 $[M+H]^+$.

Step 5. Preparation of 5-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)pentanoic acid **(326-5)**

To a solution of **326-4** (120 mg, 0.33 mmol) in H_2O (5 mL) and THF (5 ml) was added NaOH (66 mg, 1.65 mmol). The mixture was stirred at 25 °C overnight. Ethyl acetate was added to the reaction mixture and the mixture was filtered through celite. The filtrate was washed with water and saturated brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column to provide 60 mg of **326-5** (yield: 56.3%) as a yellow oil. Mass (m/z): 332.3 $[M+1]^+$.

Step 6. Preparation of 5-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)pentanamide **(326-6)**

A solution of **326-5** (87 mg, 0.26 mmol), NH_4Cl (56 mg, 1 mmol), HATU (149 mg, 0.39 mmol) and DIEA (169 mg, 1.3 mmol) in DMF(10 mL) was stirred at R.T. for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 40 mg of **326-6** (yield: 46.4%) as a yellow solid. Mass (m/z): 331.3 $[M+H]^+$.

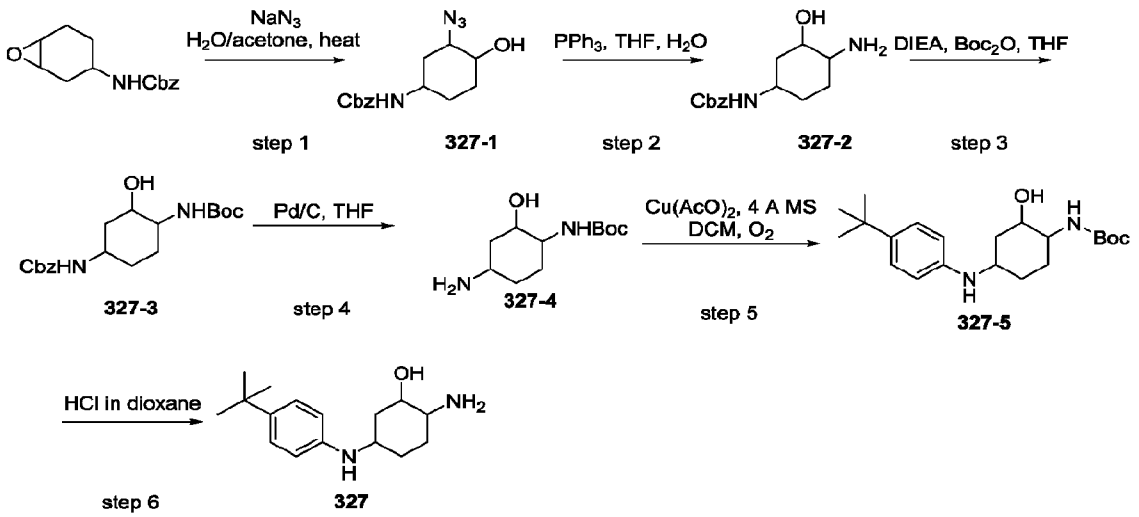
Step 7. Preparation of N-(4-(5-aminopentyl)cyclohexyl)-4-(tert-butyl)aniline **(326)**

A solution of **326-6** (40 mg, 0.12 mmol), BH_3-THF (10 mL) in THF (5 mL) was stirred at 70 °C for 18 hours. The solid was filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **326** (5.3 mg) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.05 (d, J = 8.8 Hz, 2H), 6.46 (d, J = 8.8 Hz, 2H), 5.09 (s, 1H), 3.05 (s, 2H), 2.70 (t, J = 7.2 Hz, 2H), 1.96 (d, J = 12.0 Hz, 2H), 1.73 (d, J = 12.0 Hz, 2H), 1.49 (s, 2H), 1.25 (d, J = 15.6 Hz, 6H), 1.16 (d, J = 30.8 Hz, 9H), 1.01 (dd, J = 24.8, 11.9 Hz, 5H). Mass (m/z): 317.3 $[M+H]^+$.

Compound 327

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2-amino-5-((4-(tert-butyl)phenyl)amino)cyclohexan-1-ol



Step 1. Preparation of benzyl (3-azido-4-hydroxycyclohexyl)carbamate (**327-1**)

To a solution of benzyl (7-oxabicyclo[4.1.0]heptan-3-yl)carbamate (0.9 g, 3.6 mmol) in Acetone (10 mL) and H_2O (1 mL) was added NaN_3 (0.26 g, 4 mmol) at 25 °C. Then the mixture was stirred at 70 °C for 4 hrs. LCMS showed the reaction was completed. The reaction was quenched with water (20 mL), extracted with EA (20 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated to give **327-1** (0.7 g, 66.3% yield) as yellow oil. MS (m/z): 313.1 $[M+Na]^+$.

Step 2. Preparation of benzyl (4-amino-3-hydroxycyclohexyl)carbamate (**327-2**)

To a solution of **327-1** (0.7 g, 2.4 mmol) in THF (10 mL) and H_2O (2 mL) was added PPh_3 (500 mg, 1.90 mmol) under N_2 at 25 °C. Then the mixture was stirred at 25 °C overnight. LCMS showed the reaction was completed. The mixture was added into H_2O and wash with EA. The water phase was concentrated to give **327-2** (700 mg, 100% yield) as a yellow solid. MS (m/z): 265.2 $[M+H]^+$.

Step 3. Preparation of benzyltert-butyl(2-hydroxycyclohexane-1,4-diyl)dicarbamate (**327-3**)

To a solution of **327-2** (0.7 g, 2.6 mmol) in THF (10 mL) was added Boc_2O (630 mg, 2.9 mmol) and DIEA (513 mg, 4 mmol) at 25 °C. Then the mixture was stirred at 25 °C for 4 h. LCMS showed the reaction was completed. The reaction was quenched by water (20 mL) slowly, extracted with EA (20 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:2) to afford **327-3** (0.5 g, 60% yield) as a white solid. MS (m/z): 387.2 $[M+Na]^+$.

Step 4. Preparation of tert-butyl (4-amino-2-hydroxycyclohexyl)carbamate (**327-4**)

To a solution of **327-3** (550 mg, 1.51 mmol) in THF (10 mL) was added wet Pd/C (80 mg) and the mixture was stirred at 25°C for 8 hrs. LCMS showed the reaction was completed. The reaction was filtered and concentrated to give **327-4** (120 mg, 34.6% yield) as a yellow solid. MS (m/z): 230.2 $[M+H]^+$.

Step 5. Preparation of tert-butyl(4-((4-(tert-butyl)phenyl)amino)-2-hydroxycyclo hexyl)carbamate (**327-5**)

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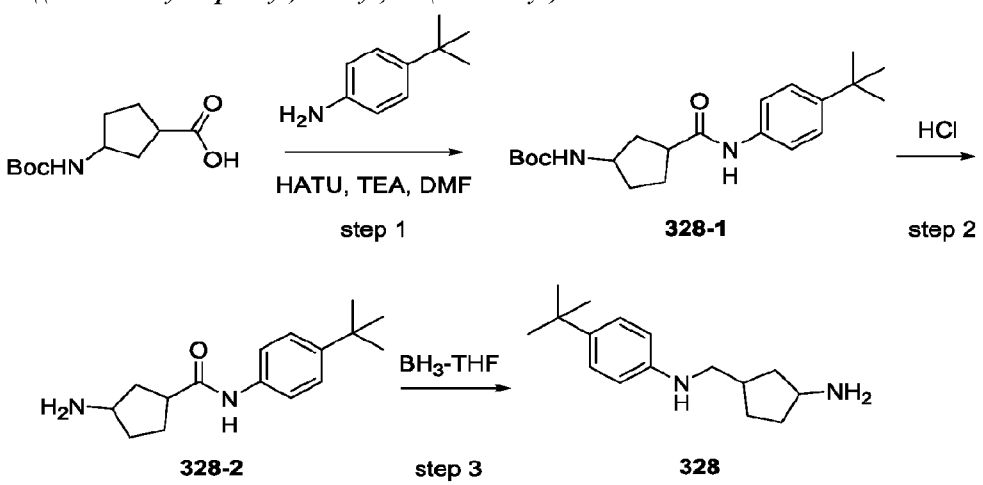
To a solution of **327-4** (0.12 g, 0.52 mmol) in DCM (10 mL) was added (4-(tert-butyl)phenyl)boronic acid (92.8 mg, 0.52 mmol), $Cu(AcO)_2$ (10 mg, 0.052 mmol) and 4 A MS(100 mg) under O_2 at 25 °C. Then the mixture was stirred at 25 °C overnight. LCMS showed the reaction was completed. The reaction was quenched by water (20 mL) slowly, extracted with EA (20 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:1) to afford **327-5** (0.11 g, 58.5% yield) as a yellow solid. MS (m/z): 362.9 $[M+H]^+$.

Step 6. Preparation of 2-amino-5-((4-(tert-butyl)phenyl)amino)cyclohexan-1-ol (**327**)

To a solution of **327-5** (110 mg, 0.30 mmol) in DCM (4 mL) was added HCl in dioxane (4 mL), and the mixture was stirred at 25 °C for 2 hrs. LCMS showed the reaction was completed. The residue was concentrated. The residue was purified by Prep-HPLC to give **327** (15 mg, 18.8% yield) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 7.60 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 3.97 - 3.85 (m, 1H), 3.75 - 3.65 (m, 1H), 3.52 - 3.42 (m, 1H), 2.42 - 2.25 (m, 1H), 2.09 - 1.75 (m, 5H), 1.32 (s, 9H). MS (m/z): 263.0 $[M+H]^+$.

Compound 328

N-((3-aminocyclopentyl)methyl)-4-(tert-butyl)aniline



Step 1. Preparation of tert-butyl (3-((4-(tert-butyl)phenyl)carbamoyl)cyclopentyl)carbamate **(328-1)**

A mixture of 3-((tert-butoxycarbonyl)amino)cyclopentane-1-carboxylic acid (300 mg, 1.31 mmol), 4-(tert-butyl)aniline (234 mg, 1.57mmol), HATU (597 mg, 1.57 mmol), DIPEA (254 mg, 1.96 mmol) in DMF (5 mL) was stirred overnight at room temperature. Then 40 mL of water was added. The solid was purified by silica gel chromatography. Target product (430 mg, 91%) was obtained as a yellow solid. Mass (m/z): 383.3 $[M+H]^+$.

Step 2. Preparation of 3-amino-N-(4-(tert-butyl)phenyl)cyclopentane-1-carboxamide **(328-2)**

To a solution of tert-butyl (3-((4-(tert-butyl)phenyl)carbamoyl)cyclopentyl)carbamate (430 mg, 1.92 mmol) in HCl in dioxane (5 ml) and in CH_2Cl_2 (5 mL). Then the mixture was stirred for overnight at rt. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product (305 mg, 97%) as a white solid. Mass (m/z): 261.3 $[M+H]^+$.

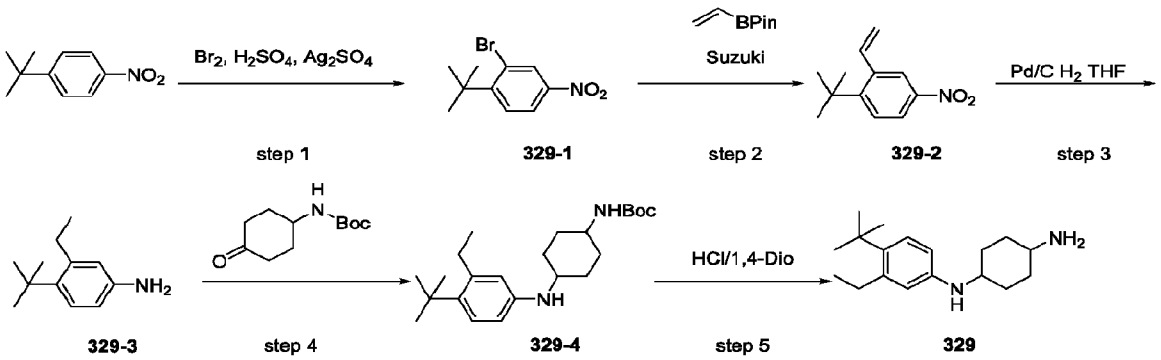
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Step 3. Preparation of N-((3-aminocyclopentyl)methyl)-4-(tert-butyl)aniline **(328)**

To a solution of 3-amino-N-(4-(tert-butyl)phenyl)cyclopentane-1-carboxamide (305 mg, 1.17 mmol) in BH_3-THF (20 mL). Then the mixture was stirred overnight at 70 °C. The reaction was concentrated under vacuum. The residue was purified by prep-HPLC to afford the desired product (45.2 mg, 16%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.15 (d, J = 8.8 Hz, 2H), 6.60 (d, J – 8.7 Hz, 2H), 3.49 – 3.36 (m, 1H), 3.07 (d, J – 6.6 Hz, 1H), 2.34 – 2.16 (m, 2H), 2.08 – 1.80 (m, 2H), 1.61 – 1.46 (m, 2H), 1.34 – 1.29 (m, 1H), 1.25 (s, 9H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 329

1-N-(4-(tert-butyl)-3-ethylphenyl)cyclohexane-1,4-diamine



Step 1. Preparation of 2-bromo-1-(tert-butyl)-4-nitrobenzene **(329-1)**

A mixture of 1-(tert-butyl)-4-nitrobenzene (1 g, 5.6 mmol), Ag_2SO_4 (2.97 g, 9.5 mmol) in H_2SO_4 (10 mL) was added Br_2 (0.89 g, 5.6 mmol) and stirred at rt for 16 hours. Pour the mixture into a diluted $NaHSO_3$ solution and extract with ethyl acetate (3x100 mL). It was quenched by H_2O (300 mL) and extracted with EA (3x300 mL), dried with $MgSO_4$, filtered and concentrated to afford target product (600 mg, yield: 33.3%) as a black solid.

Step 2. Preparation of 1-(tert-butyl)-4-nitro-2-vinylbenzene **(329-2)**

To a solution of **329-1** (600 mg, 2.32 mmol) in 1,4-dioxane (10 mL) was added $Pd(PPh_3)_4$ (268.62 mg, 0.23 mmol), K_2CO_3 (962.38 mg, 6.97 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (999.75 mg, 5.814 mmol). Then the mixture was stirred overnight at 90°C. It was quenched by H_2O (100 mL) and extracted with EA (3x100 mL). The crude product was applied onto a silica gel column (12 g) eluted with PE:EA (10:1) to give product (300 mg, yield: 50.3%) as a yellow solid.

Step 3. Preparation of 4-(tert-butyl)-3-ethylaniline **(329-3)**

To a solution of **329-2** (300 mg, 1.46 mmol) in THF (10 mL) was added Pd/C (15.55 mg, 0.14 mmol). Then the mixture was stirred overnight at rt. It was quenched by H_2O (100 mL) and extracted with EA (3x100 mL). The organic layers were combined, washed with brine NaCl (2x100 mL) and dried with $MgSO_4$, filtered and concentrated to afford target product (150 mg, yield: 46.3%) was obtained as a yellow solid. Mass (m/z): 178.2 $[M+H]^+$.

Step 4. Preparation of 4-cyclobutylaniline **(329-4)**

A mixture of 1-N-(4-(tert-butyl)phenyl)cyclohexane-1,4-diamine (150 mg, 0.84 mmol), tert-butyl (3-oxopropyl)carbamate (181.3 mg, 0.84 mmol), Pic-BH_3 (135.75 mg, 1.27 mmol) in AcOH/H_2O=1:10 (5.5 mL) was stirred overnight at 25 °C. The pH of the water phase was

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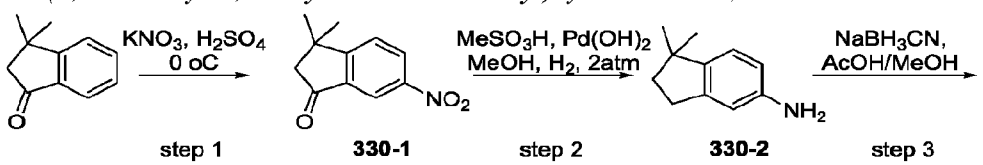
adjusted to 8 by aq. $NaHCO_3$. It was quenched by H_2O (30mL) and extracted with EA (3x30 mL), dried with $MgSO_4$, filtered and concentrated to afford the target product (200 mg, yield: 37.8%) as a yellow solid. Mass (m/z): 375.3 $[M+H]^+$.

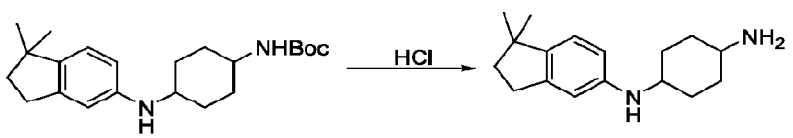
Step 5. Preparation of 1-N-(4-(tert-butyl)-3-ethylphenyl)cyclohexane-1,4-diamine **(329)**

To a solution of **329-4** (200 mg, 0.53 mmol) in 1,4-dioxane (5 mL) was added 4 N HCl in 1,4-dioxane (10 mL). Then the mixture was stirred overnight at 25 °C. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product **329** (22.8 mg) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.07 (d, J = 8.6 Hz, 1H), 6.50 (d, J = 2.8 Hz, 1H), 6.38 (dd, J = 8.6, 2.8 Hz, 1H), 3.52 (s, 1H), 3.25 – 3.12 (m, 1H), 2.77 (q, J = 7.6 Hz, 2H), 1.91 – 1.70 (m, 8H), 1.32 (s, 9H), 1.20 (t, J = 7.4 Hz, 3H). Mass (m/z): 275.0 $[M+H]^+$.

Compound 330

N1-(1,1-dimethyl-2,3-dihydro-1H-inden-5-yl)cyclohexane-1,4-diamine





330-3 step 4 **330A** **330B**

Step 1. Preparation of 3,3-dimethyl-6-nitro-2,3-dihydro-1H-inden-1-one (**330-1**)

To a solution of 3,3-dimethyl-2,3-dihydro-1H-inden-1-one (2 g, 12.5 mmol) in H_2SO_4 (10 mL) was added KNO_3 (1.39 g, 13.7 mmol) at 0 °C. Then the mixture was stirred at 0 °C for 2 hrs. LCMS showed the reaction was completed. The reaction was quenched with ice-water (20 mL). The mixture was filtered to give **330-1** (1.6 g, 62.5% yield) as a yellow solid. MS (m/z): 206.1 $[M+H]^+$.

Step 2. Preparation of 1,1-dimethyl-2,3-dihydro-1H-inden-5-amine (**330-2**)

To a solution of 3,3-dimethyl-6-nitro-2,3-dihydro-1H-inden-1-one (0.2 g, 0.97 mmol) in MeOH (10 mL) was added $MeSO_3H$ (93 mg, 0.97 mmol) and $Pd(OH)_2/C$ (50 mg) under H_2 at 25 °C. Then the mixture was stirred at 25 °C and 2 atm overnight. LCMS showed the reaction was completed. The mixture was filtered and concentrated to give **330-2** (0.15 g, 95.5% yield) as a brown oil. MS (m/z) 162.2 $[M+H]^+$.

Step 3. Preparation of tert-butyl (4-((1,1-dimethyl-2,3-dihydro-1H-inden-5-yl)amino)cyclohexyl)carbamate **(330-3)**

To a solution of 1,1-dimethyl-2,3-dihydro-1H-inden-5-amine (0.15 g, 0.93 mmol) in MeOH (10 mL) and AcOH (0.1 mL) was added tert-butyl (4-oxocyclohexyl)carbamate (218 mg, 1.02 mmol) at 25 °C. Then the mixture was stirred at 50 °C for 2 h. Then the mixture was added $NaBH_3CN$ (175 mg, 2.79 mmol) after cooling to 25 °C. The mixture was stirred at 25 °C for 6 h. LCMS showed the reaction was completed. The reaction was quenched by ice water (20

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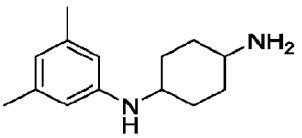
mL) slowly, extracted with EA (20 mL*3). The combined organic layers were washed with brine (40 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by combi-flash with EA/PE (1:1) to afford **330-3** (0.14 g, 42% yield) as a yellow solid. MS (m/z) 359.2 $[M+H]^+$.

Step 4. Preparation of N1-(1,1-dimethyl-2,3-dihydro-1H-inden-5-yl)cyclohexane-1,4-diamine (**330**)

To a solution of tert-butyl (4-((1,1-dimethyl-2,3-dihydro-1H-inden-5-yl)amino)cyclohexyl)carbamate (140 mg, 0.39 mmol) in DCM (5 mL) was added HCl in dioxane (5 mL), and the mixture was stirred at 25°C for 2 hrs. LCMS showed the reaction was completed. The residue was concentrated. The residue was purified by Prep-HPLC to give **330A** (16 mg, 15.8% yield) as a white solid and **330B** (21.2 mg, 21% yield) as a white solid. **330A**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.30 (d, J = 8.0 Hz, 1H), 7.27 – 7.16 (m, 2H), 3.55 – 3.40 (m, 1H), 3.20 – 3.05 (m, 1H), 2.92 (t, J = 7.2 Hz, 2H), 2.20 – 2.05 (m, 4H), 1.95 (t, J = 7.2 Hz, 2H), 1.65 – 1.37 (m, 4H), 1.23 (s, 6H). MS (m/z): 259.3 $[M+H]^+$. HPLC: Rt: 3.807 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **330B**: ^{1}H NMR (300 MHz, CD_3OD) δ 7.39 – 7.25 (m, 3H), 3.70 – 3.50 (m, 1H), 3.45 – 3.35 (m, 1H), 2.92 (t, J = 7.2 Hz, 2H), 2.10 – 1.80 (m, 10H), 1.23 (s, 6 H). MS (m/z): 259.3 $[M+H]^+$. HPLC: Rt: 3.915 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 331

N1-(3,5-dimethylphenyl)cyclohexane-1,4-diamine

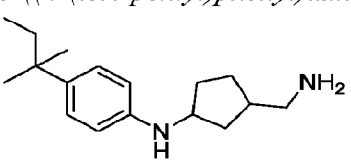


331

The title compound **331** (81.1 mg) was prepared in a yield of 90.0% as a white powder from 3,5-dimethylaniline (50 mg, 0.41 mmol), tert-butyl (4-oxocyclohexyl)carbamate (132 mg, 0.61 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (d, J = 22.4 Hz, 2H), 6.20 (s, 1H), 6.19 – 6.11 (m, 2H), 5.18 (s, 1H), 3.40 (s, 1H), 3.08 (d, J = 11.5 Hz, 1H), 2.97 (s, 1H), 2.12 (d, J = 2.0 Hz, 6H), 2.05 – 1.91 (m, 2H), 1.81 – 1.65 (m, 2H), 1.51 – 1.35 (m, 1H), 1.21 – 1.08 (m, 1H). Mass (m/z): 219.4 $[M+H]^+$.

Compound 332

3-((4-(tert-pentyl)phenyl)amino)cyclopentane-1-carboxamide



332

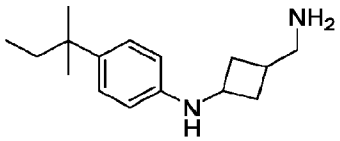
The title compound **332** (15.6 mg) was prepared in a total yield of 20.0% as a white solid with 3:2 mixture by ^{1}H NMR from 3-((4-(tert-pentyl)phenyl)amino)cyclopentane-1-carboxamide

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(82 mg, 0.3 mmol) and $LiAlH_4$ (34 mg, 0.9 mmol) according to the procedure for **118**. ^1H NMR (400 MHz, Methanol-d_4) δ 7.10 – 7.03 (m, 2H), 6.62 – 6.56 (m, 2H), 3.88 – 3.76 (m, 1H), 2.76 (dd, J = 12.7, 7.3 Hz, 2H), 2.34 – 1.75 (m, 4H), 1.65 – 1.33 (m, 4H), 1.19 (s, 6H), 0.63 (t, J = 7.4 Hz, 3H). Mass (m/z): 276.3 $[M+H]^+$.

Compound 333

N-(3-(aminomethyl)cyclobutyl)-4-(tert-pentyl)aniline

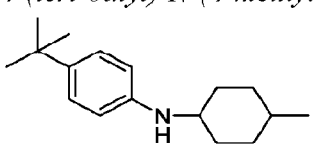


333

The title compound **333** (30.5 mg) was prepared in a total yield of 38.8% as a white solid with 3:2 mixture by ^1H NMR from 3-((4-(tert-pentyl)phenyl)amino)cyclobutane-1-carboxamide (83 mg, 0.32 mmol) and $LiAlH_4$ (36 mg, 0.96 mmol) according to the procedure for **118**. ^1H NMR (301 MHz, Methanol-d_4) δ 7.07 – 7.00 (m, 2H), 6.46 – 6.58 (m, 2H), 4.00 – 3.86 (m, 0.4H), 3.84 – 3.68 (m, 0.6H), 95 (d, J = 7.2 Hz, 0.8H), 2.84 (d, J = 7.2 Hz, 1.2H), 2.60 – 2.47 (m, 2H), 2.28 – 2.13 (m, 1.2 H), 2.09 – 1.97 (m, 0.8H), 1.60 – 1.47 (m, 2H), 0.59 (t, J = 7.4 Hz, 3H). Mass (m/z): 247.3 $[M+H]^+$.

Compound 334

4-(tert-butyl)-N-(4-methylcyclohexyl)aniline



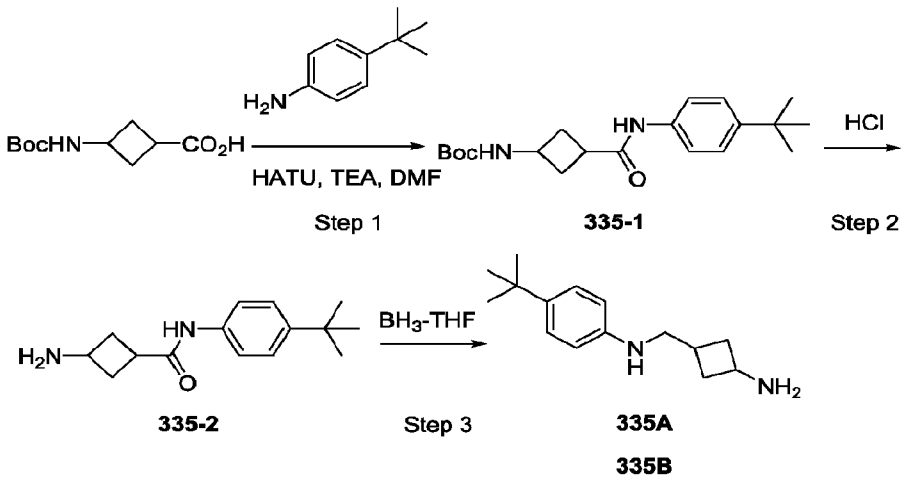
334

The title compound **334** (565 mg, 86.1%) as a yellow oil was prepared from 4-(tert-butyl)aniline (400 mg, 2.68 mmol), 4-methylcyclohexan-1-one (361 mg, 3.22 mmol), DCM (5 mL), and sodium triacetoxyborohydride (1.14 g, 5.36 mmol) according to the procedure for **1-1**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.10 – 7.00 (m, 2H), 6.54 – 6.44 (m, 2H), 5.12 (dd, J = 35.9, 8.0 Hz, 1H), 3.37 (s, 1H), 1.93 (d, J = 11.6 Hz, 1H), 1.69 – 1.28 (m, 7H), 1.20 (d, J = 1.3 Hz, 9H), 1.05 (t, J = 9.2 Hz, 1H), 0.89 (dd, J = 8.2, 6.5 Hz, 3H). Mass (m/z): 246.2 $[M+H]^+$

Compound 335

N-((3-aminocyclobutyl)methyl)-4-(tert-butyl)aniline

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Step 1. Preparation of tert-butyl (3-((4-(tert-butyl)phenyl)carbamoyl)cyclobutyl)carbamate **(335-1)**

A mixture of 3-((tert-butoxycarbonyl)amino)cyclopentane-1-carboxylic acid (300 mg, 1.31 mmol), 4-(tert-butyl)aniline (250 mg, 1.67mmol), HATU (636 mg, 1.67 mmol), DIPEA (270 mg, 2.09 mmol) in DMF (5 mL) was stirred overnight at room temperature. Then 40 mL of water was added. The solid was purified by silica gel chromatography. The target product (451 mg, 93%) was obtained as a yellow solid. Mass (m/z): 346.9 $[M+H]^+$.

Step 2. Preparation of 3-amino-N-(4-(tert-butyl)phenyl)cyclobutane-1-carboxamide **(335-2)**

To a solution of tert-butyl (3-((4-(tert-butyl)phenyl)carbamoyl)cyclobutyl)carbamate (451 mg, 1.30 mmol) in CH_2Cl_2 (5 mL) was added HCl in dioxane (4N; 5 mL). Then the mixture was stirred for overnight at rt. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired product (303 mg, 92%) as a white solid. Mass (m/z): 247.2 $[M+H]^+$.

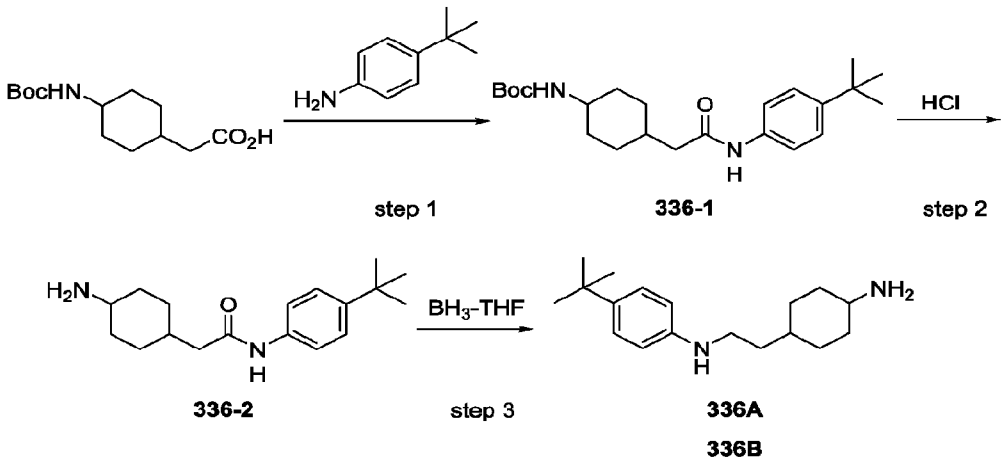
Step 3. Preparation of N-((3-aminocyclobutyl)methyl)-4-(tert-butyl)aniline **(335)**

To a solution of 3-amino-N-(4-(tert-butyl)phenyl)cyclobutane-1-carboxamide (303 mg, 1.23 mmol) in BH_3-THF (20 mL). Then the mixture was stirred overnight at 70°C. The reaction was concentrated under vacuum. The residue was purified by prep-HPLC to afford the desired product **335A** (27.2 mg, 7%) as a white solid and **335B** (9.8 mg, 4%) as a white solid. **335A**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.15 (d, J = 8.7 Hz, 2H), 6.59 (d, J = 8.7 Hz, 2H), 3.43 – 3.37 (m, 1H), 3.09 (d, J = 6.5 Hz, 2H), 2.47 – 2.40 (m, 2H), 2.30 – 2.21 (m, 1H), 1.69 – 1.60 (m, 2H), 1.25 (s, 9H). Mass (m/z): 233.3 $[M+H]^+$. HPLC: Rt: 3.621 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **335B**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.15 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 8.7 Hz, 2H), 3.81 – 3.66 (m, 1H), 3.17 (d, J = 7.6 Hz, 2H), 2.67-2.60 (m, 1H), 2.27 – 2.03 (m, 4H), 1.25 (s, 9H). Mass (m/z): 233.3 $[M+H]^+$. HPLC: Rt: 3.714 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 336

N-(2-(4-aminocyclohexyl)ethyl)-4-(tert-butyl)aniline

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Step 1. Preparation of tert-butyl (4-(2-((4-(tert-butyl)phenyl)amino)-2-oxoethyl)cyclohexyl)carbamate **(336-1)**

To a solution of 2-(4-((tert-butoxycarbonyl)amino)cyclohexyl)acetic acid (0.2 g, 0.78 mmol) in DMF (10 mL) was added 4-(tert-butyl)aniline (0.14 g, 0.94 mmol), HATU (0.44 mg, 1.17 mmol), DIEA (0.3 g, 2.34 mmol) the mixture was stirred at 25 °C for 2 h. Diluting with water (30 mL), the reaction was extracted by EA (20 mL) for 3 times. The organic phase was washed 3 times by NaCl aq. (20 mL), dried over sodium sulfate, concentrated under vacuum and the residue was purified by flash chromatography to afford the desired product (0.15 g, 49.5%) as colorless oil. Mass (m/z): 333.2 $[M+H]^+$.

Step 2. Preparation of 2-(4-aminocyclohexyl)-N-(4-(tert-butyl)phenyl)acetamide **(336-2)**

To a solution of tert-butyl (4-(2-((4-(tert-butyl)phenyl)amino)-2-oxoethyl)cyclohexyl)carbamate (0.15 g, 0.39 mmol) in THF (5 mL) was added HCl in dioxane (5 mL) and the mixture was stirred for 2 h. Quenched with $NaHCO_3$ (10 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, concentrated under vacuum and the residue was purified by flash chromatography to afford the desired product (0.1 g, 88.9%) as colorless oil. Mass (m/z): 289.2 $[M+H]^+$.

Step 3. Preparation of N-(2-(4-aminocyclohexyl)ethyl)-4-(tert-butyl)aniline **(336)**

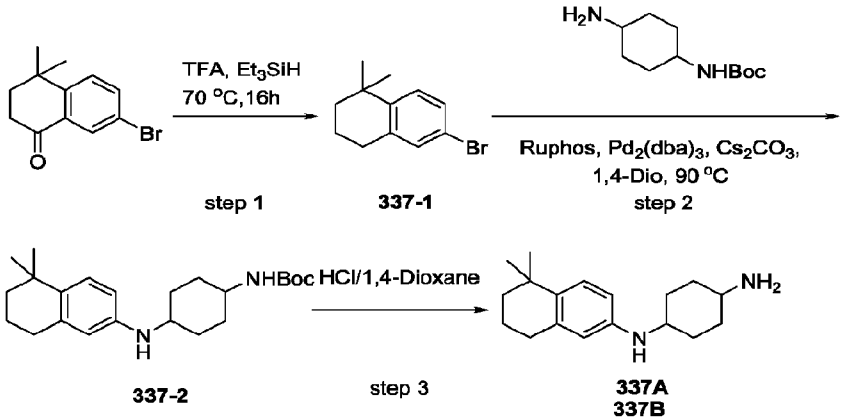
To a solution of 2-(4-aminocyclohexyl)-N-(4-(tert-butyl)phenyl)acetamide (0.2 g, 0.5 mmol) in THF (2 mL) was added BH_3-THF (15 mL) and the mixture was stirred at 70 ℃ for 2 h. Quenched with water (10 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, concentrated under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5um; Mobile phase: ACN-H_2O (0.1%FA), 40%-60%) to afford the desired product **336A** (11.1 mg) as a black solid and **336B** (3.4 mg) as a black solid. **336A**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4, 2H), 6.54 (d, J = 8.4, 2H), 3.09 (t, J = 6.8, 2H), 2.98 (s, 1H), 2.08 (s, 2H), 1.86 (d, J = 11.6, 2H), 1.51 – 1.42 (m, 5H), 1.27 (s, 9H), 1.01 (d, J=12.0, 2H). Mass (m/z): 274.9 $[M+H]^+$. HPLC: Rt=3.801 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min). **336B**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4, 2H), 6.72

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(d, J = 8.4, 2H), 3.42 (s, 1H), 3.12 (s, 2H), 1.92 (s, 2H), 1.72 (s, 4H), 1.60 (s, 5H), 1.27 (s, 9H). Mass (m/z): 274.9 $[M+H]^+$. HPLC: Rt=4.110 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min).

Compound 337

1-N-(5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclohexane-1,4-diamine



Step 1. 6-bromo-1,1-dimethyl-1,2,3,4-tetrahydronaphthalene **(337-1)**

A mixture of 7-bromo-4,4-dimethyl-3,4-dihydronaphthalen-1(2H)-one (500 mg, 1.97 mmol) in TFA (7 mL) was added Et_3SiH (2.3 g, 19.8 mmol). It was quenched by H_2O (30 mL) and extracted with DCM (3x30 mL). The organic layers were combined, washed with brine NaCl (2x30 mL) and dried with $MgSO_4$, filtered and concentrated to afford the target product (500 mg, yield: 95.2%) as a yellow oil.

Step 2. tert-butyl (4-((5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)amino)cyclo-hexyl)carbamate **(337-2)**

To a solution of **337-1** (300 mg, 1.25 mmol) in 1,4-dioxane (15 mL) was added tert-butyl (4-aminocyclohexyl)carbamate (268.82 mg, 1.25 mmol), $Pd_2(dba)_3$ (144.87 mg, 0.13 mmol), Ruphos (117 mg, 0.25 mmol) and Cs_2CO_3 (817.42 mg, 2.5 mmol). Then the mixture was stirred 16 hours at 90 °C. It was quenched by H_2O (300 mL) and extracted with EA (3x300 mL). The organic layers were combined, washed with brine NaCl (2x300 mL) and dried with $MgSO_4$, filtered and concentrated. The crude product was applied onto a silica gel column (24 g) eluted with PE:EA (10:1) to give product (200 mg, yield: 38.5 %) as a white solid. Mass (m/z): 373.3 $[M+H]^+$.

Step 3. Preparation of 1-N-(5,5-dimethyl-5,6,7,8-tetrahydronaphthalen-2-yl)cyclo-hexane-1,4-diamine **(337)**

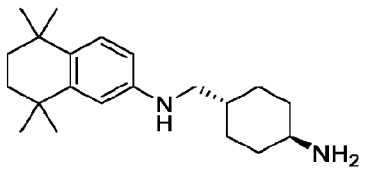
To a solution of **337-2** (200 mg, 0.54 mmol) in 1,4-dioxane (5 mL) was added 4 N HCl in 1,4-dioxane (10 mL). Then the mixture was stirred overnight at 25 °C. The reaction was concentrated under vacuum. The residue was purified by prep-TLC to afford the desired products **337A** (56.1 mg) as a white solid and **337B** (24.7 mg) as a white solid. **337A**: ^1H NMR (400 MHz, CD_3OD) δ 7.47 (dd, J = 8.4, 5.2 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 9.8 Hz, 1H), 3.44 (m, 1H), 3.11 (m, 1H), 2.92 – 2.70 (m, 2H), 2.11 (d, J = 10.0 Hz, 4H), 1.87 – 1.76 (m, 2H), 1.71 – 1.64 (m, 2H), 1.58 – 1.41 (m, 4H), 1.27 – 1.24 (m, 6H). Mass (m/z): 373.0

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$[M+H]^+$. HPLC: Rt=4.141 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min). **337B**: ^1H NMR (400 MHz, CD_3OD) δ 7.47 (d, J = 8.4 Hz, 1H), 7.17 – 7.08 (m, 1H), 7.02 (s, 1H), 3.59 (s, 1H), 3.39 (s, 1H), 2.77 (t, J = 6.2 Hz, 2H), 2.03 – 1.77 (m, 10H), 1.72 – 1.59 (m, 2H), 1.25 (d, J = 14.8 Hz, 6H). Mass (m/z): 373.0 $[M+H]^+$. HPLC: Rt=4.266 min (Column: XBRIDGE 3.5 um, 2.1*50 mm, Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%, Flow rate: 0.8 mL/min).

Compound 338

N-(((1r,4r)-4-aminocyclohexyl)methyl)-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-amine

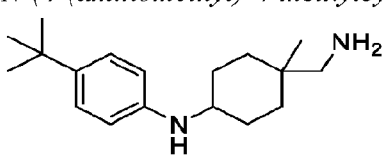


338

The title compound **338** (25.7 mg, 21.1%) as yellow oil was prepared from tert-butyl ((1r,4r)-4-(((5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)amino)methyl)cyclohexyl)carbamate, DCM (6 mL) and 2,2,2-trifluoroacetic acid (3 mL) according to the procedure for **24**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.79 – 7.59 (m, 3H), 6.96 (d, J = 8.5 Hz, 1H), 6.46 – 6.26 (m, 2H), 2.91 (d, J = 5.0 Hz, 1H), 2.78 (d, J = 6.5 Hz, 2H), 1.97 – 1.77 (m, 4H), 1.54 (d, J = 2.1 Hz, 4H), 1.42 (s, 1H), 1.30 – 1.17 (m, 2H), 1.15 (s, 6H), 1.12 (s, 6H), 1.04 – 0.90 (m, 2H). Mass (m/z): 315.3 $[M+H]^+$.

Compound 339

N-(4-(aminomethyl)-4-methylcyclohexyl)-4-(tert-butyl)aniline



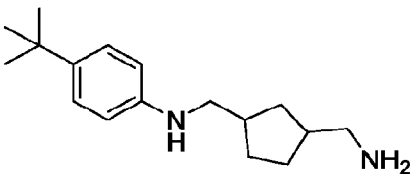
339

The title compound **339** (57.1 mg) was prepared in a two-step overall yield of 44.9% as a white powder from 4-(tert-butyl)aniline (70 mg, 0.47 mmol) and 1-methyl-4-oxocyclohexane-1-carbonitrile (77 mg, 0.56 mmol) according to the procedure for **84**. ^1H NMR (300 MHz, DMSO-d_6) δ 7.81 (s, 3H), 7.06 (d, J = 8.0 Hz, 2H), 6.49 (s, 2H), 3.17 (d, J = 12.1 Hz, 1H), 2.75 (d, J = 5.7 Hz, 2H), 1.84 – 1.53 (m, 5H), 1.43 (s, 1H), 1.27 (s, 2H), 1.19 (s, 9H), 0.96 (d, J = 5.1 Hz, 3H). Mass (m/z): 275.3 $[M+H]^+$.

Compound 340

N-((3-(aminomethyl)cyclopentyl)methyl)-4-(tert-butyl)aniline

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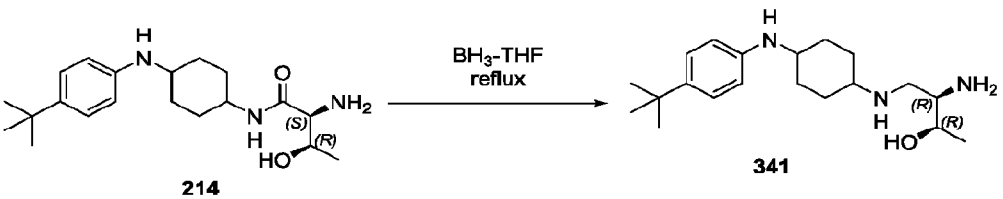


340

The title compound **340** (57.1 mg) was prepared in a two-step overall yield of 44.9% as a white powder from 4-(tert-butyl)aniline (100 mg, 0.67 mmol) and cyclopentane-1,3-dicarboxylic acid (318 mg, 2.01 mmol) according to the procedure for **84**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 2H), 7.13 – 7.00 (m, 2H), 6.54 – 6.41 (m, 2H), 5.36 (s, 1H), 2.89 (dd, J = 7.0, 4.6 Hz, 2H), 2.74 (d, J = 7.2 Hz, 2H), 2.24 – 2.04 (m, 2H), 2.00 (dt, J = 13.8, 7.0 Hz, 1H), 1.82 – 1.63 (m, 2H), 1.41 – 1.27 (m, 2H), 1.19 (s, 9H), 0.89 (dt, J = 12.5, 9.6 Hz, 1H). Mass (m/z): 261.4 $[M+H]^+$.

Compound 341

(2R,3R)-3-amino-4-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)butan-2-ol

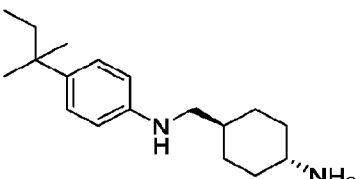


214 **341**

To a solution of (2S,3R)-2-amino-N-(4-((4-(tert-butyl)phenyl)amino)cyclohexyl)-3-hydroxybutanamide (230 mg, 0.66 mmol) in THF (5 mL) was added BH_3-THF (10 mL). The reaction was stirred at 70 °C for 18 hours. The solids were filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **341** (80.2 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (s, 2H), 7.06 (d, J = 8.6 Hz, 2H), 6.48 (d, J = 8.6 Hz, 2H), 3.73 – 3.63 (m, 1H), 3.09 (t, J = 10.4 Hz, 1H), 2.83 (t, J = 9.6 Hz, 2H), 2.63 (m, 1H), 1.96 (s, 4H), 1.28 (d, J = 9.4 Hz, 1H), 1.20 (s, 9H), 1.14 (dd, J = 18.6, 6.8 Hz, 6H). Mass (m/z): 334.3 $[M+H]^+$.

Compound 342

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(tert-pentyl)aniline



342

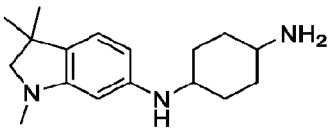
The title compound **342** (7.5 mg) was prepared in a total yield of 14.2% as a white solid from tert-butyl ((1r,4r)-4-(((4-(tert-pentyl)phenyl)amino)methyl)cyclohexyl)carbamate (72 mg, 0.193 mmol), TFA (1 mL) and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 3H), 7.00 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 8.4 Hz, 2H), 5.44 (q, J = 8.8, 5.6 Hz, 1H), 2.94 – 2.74 (m, 3H), 2.02 – 1.79 (m, 4H), 1.52 (q, J = 7.2 Hz, 3H), 1.30

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(qd, J = 12.8, 3.6 Hz, 2H), 1.16 (s, 5H), 1.07 – 0.91 (m, 2H), 0.60 (t, J = 7.2 Hz, 3H). Mass (m/z): 275.3 $[M+H]^+$.

Compound 343

N1-(1,3,3-trimethylindolin-6-yl)cyclohexane-1,4-diamine

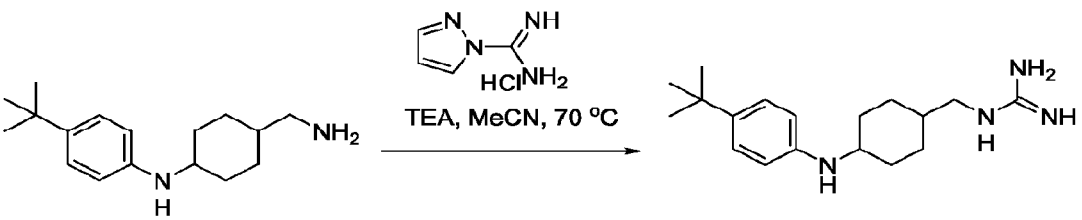


343

The title compound **343** (21.7 mg) as a yellow solid was prepared from tert-butyl (4-((1,3,3-trimethylindolin-6-yl)amino)cyclohexyl)carbamate (200 mg, 0.53 mmol), 1,4-dioxane (5 mL) and HCl /1,4-dioxane (5 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.68 – 6.62 (m, 1H), 6.02 – 5.93 (m, 1H), 5.85 (dd, J = 13.8, 1.8 Hz, 1H), 3.34 (s, 1H), 3.21 (dt, J = 3.2, 1.6 Hz, 2H), 2.75 – 2.66 (m, 1H), 2.62 – 2.52 (m, 3H), 1.59 (tdd, J = 11.6, 10.4, 4.8 Hz, 6H), 1.42 (dt, J = 10.8, 7.0 Hz, 2H), 1.12 (s, 6H). Mass (m/z): 274.3 $[M+H]^+$.

Compound 344

1-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)guanidine



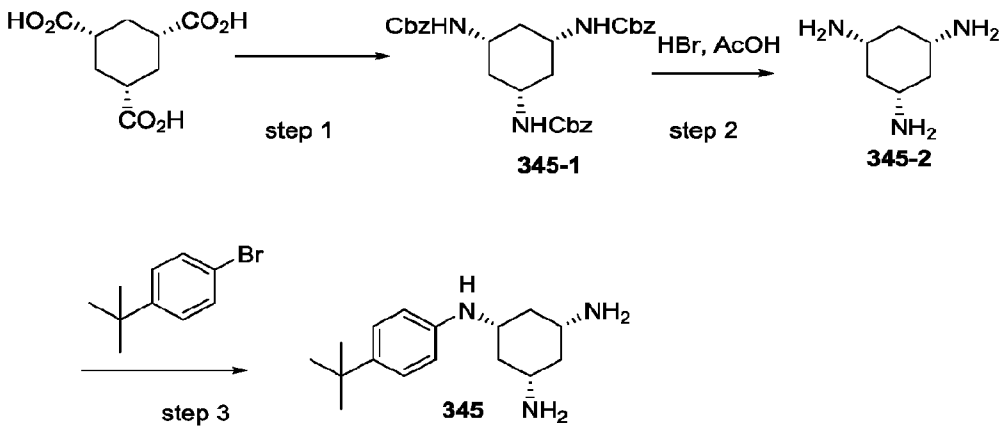
344

A 10-mL round-bottom flask was charged with N-(4-(aminomethyl)cyclohexyl)-4-(tert-butyl)aniline (120 mg, 0.46 mmol), 1H-pyrazole-1-carboximidamide hydrochloride (76 mg, 0.69 mmol), TEA (93 mg, 0.92 mmol) and 1,4-dioxane (5 mL). The reaction was stirred for 18 hours at 70 °C. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **344** (18.3 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.40 (s, 1H), 7.73 (s, 2H), 7.07 (d, J = 8.8 Hz, 2H), 6.53 (d, J = 8.8 Hz, 2H), 3.45 (s, 1H), 2.98 (t, J = 5.8 Hz, 2H), 1.68 – 1.39 (m, 9H), 1.20 (s, 9H). Mass (m/z): 303.3 $[M+H]^+$.

Compound 345

(1s,3R,5S)-N1-(4-(tert-butyl)phenyl)cyclohexane-1,3,5-triamine

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Step 1. Preparation of (1s,3s,5s)-cyclohexane-1,3,5-triamine **(345-1)**

Add cis-1,3,5-cyclohexane tricarboxylic acid (1.0 g, 4.6 mmol), triethylamine (1.4 g, 13.8 mmol), and diphenyl phosphoryl azide (3.8 g, 13.8 mmol) in toluene (30 mL), then stirred at room temperature for 30 minutes. The mixture was stirred at 80 °C for 90 minutes, then add benzyl alcohol (1.99 g, 18.4 mmol) to the mixture, reflux the solution for 24 hours. Cool the solution to ambient temperature. Collect the white precipitate by filtration, wash the precipitate with cold toluene to give the product (1.7 g, 69.5%). Mass (m/z): 532.3 $[M+H]^+$.

Step 2. Preparation of (1s,3s,5s)-cyclohexane-1,3,5-triamine **(345-2)**

Dissolve tris-benzyl carbamate (1.4 g, 2.63 mmol) in 33% HBr/glacial acetic acid (5 mL). Allow the mixture to stand for 90 minutes under stirring. Add diethyl ether (100 mL) to the mixture, filter off the product, wash the product with diethyl ether to give the product (300 mg, 88.2%). Mass (m/z): 130.1 $[M+H]^+$.

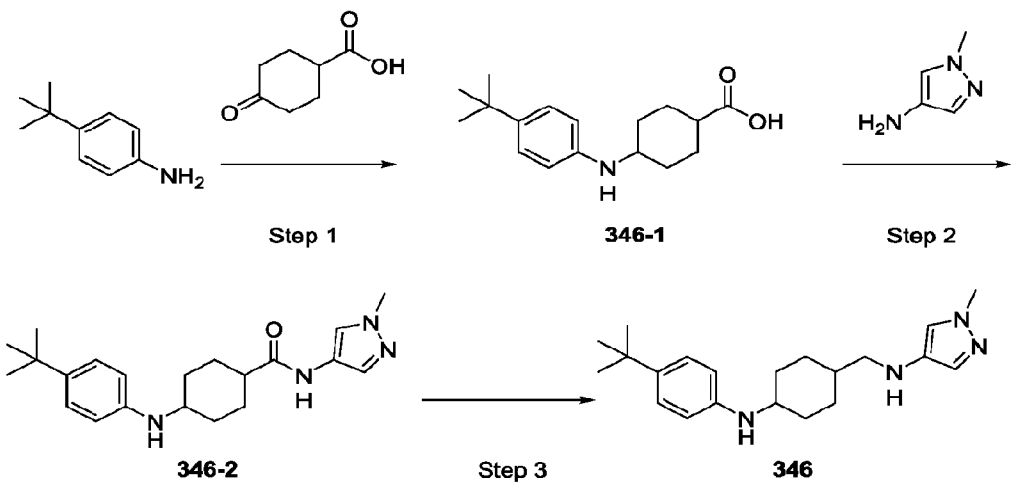
Step 3. Preparation of (1s,3R,5S)-N1-(4-(tert-butyl)phenyl)cyclohexane-1,3,5-triamine **(345)**

$Pd_2(dba)_3$ (43 mg, 0.047 mmol), Cs_2CO_3 (611 mg, 1.88 mmol), and RuPhos (22 mg, 0.047 mmol) were added to a solution of cyclohexane-1,3,5-triamine trihydrobromide (174 mg, 0.47 mmol), 1-bromo-4-tert-butylbenzene (50 mg, 0.23 mmol) in toluene (10 mL), and the mixture was heated to 110 °C for 16 hrs, then cooled to rt, the solvent was removed in vacuo. The residue was purified by prep-HPLC (column-Gemini -C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 5%-20%) to afford the desired product **345** as a yellow solid (12.2 mg, 19.9%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.16 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 8.3 Hz, 2H), 3.47 (s, 1H), 3.17 (s, 1H), 2.54 (s, 2H), 2.22 (d, J = 10.8 Hz, 3H), 1.45 – 1.37 (m, 1H), 1.22 (s, 9H), 1.19 (s, 1H). Mass (m/z): 262.3 $[M+H]^-$.

Compound 346

N-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)-1-methyl-1H-pyrazol-4-amine

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Step 1. Preparation of 4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxylic acid **(346-1)**

A mixture of 4-(tert-butyl)aniline (1 g, 0.0067 mmol), 4-oxocyclohexane-1-carboxylic acid (1.14 g, 0.0080 mmol) and $NaBH_3CN$ (0.84 g, 0.0134 mmol) in MeOH (10 mL) and HOAc (1 drop) was stirred overnight at 50 °C. After cooling, the excess MeOH was removed under vacuum and the residual was diluted with water (20 mL), extracted three times with ethyl acetate (20 mL). Organic layers were combined, solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE: EA=3:1) to give the desired product as an oil (1.5 g, 49.2%). Mass (m/z): 276.3 $[M+H]^+$.

Step 2. Preparation of 4-((4-(tert-butyl)phenyl)amino)-N-(1-methyl-1H-pyrazol-4-yl)cyclohexane-1-carboxamide **(346-2)**

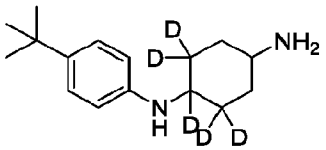
A mixture of 4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxylic acid (100 mg, 0.3631 mmol), 1-methyl-1H-pyrazol-4-amine (42.3 mg, 0.4357 mmol), HATU (207.1 mg, 0.5447 mmol) and DIEA (140.8 mg, 1.0893 mmol) in DMF (10 mL) was stirred overnight at rt. Then the reaction solution was diluted with water (30 mL), extracted three times with ethyl acetate (20 mL). Organic layers were combined, solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE/EA=2:1) to give the desired product as an oil (200 mg, 77.7%). Mass (m/z): 355.5 $[M+H]^+$.

Step 3. Preparation of N-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)-1-methyl-1H-pyrazol-4-amine **(346)**

To a solution of N-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)-1-methyl-1H-pyrazol-4-amine (200 mg, 0.5642 mmol) in THF (1 mL) was added BH_3-THF (30 mL). Then the mixture was stirred overnight at 70 °C. After the reaction was completed, solvent was removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 21.2 mm, 5um; Mobile phase: ACN-H_2O (0.1%FA), 2%-20%) to afford the desired product **346** (6 mg, 3%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.15 (dd, J = 11.9, 9.2 Hz, 4H), 6.65 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.53 (s, 1H), 2.89 (d, J = 6.8 Hz, 2H), 1.74 – 1.44 (m, 9H), 1.28 (s, 9H). Mass (m/z): 341.2 $[M+H]^+$.

Compound 347

N1-(4-(tert-butyl)phenyl)cyclohexane-1,2,2,6,6-d5-1,4-diamine

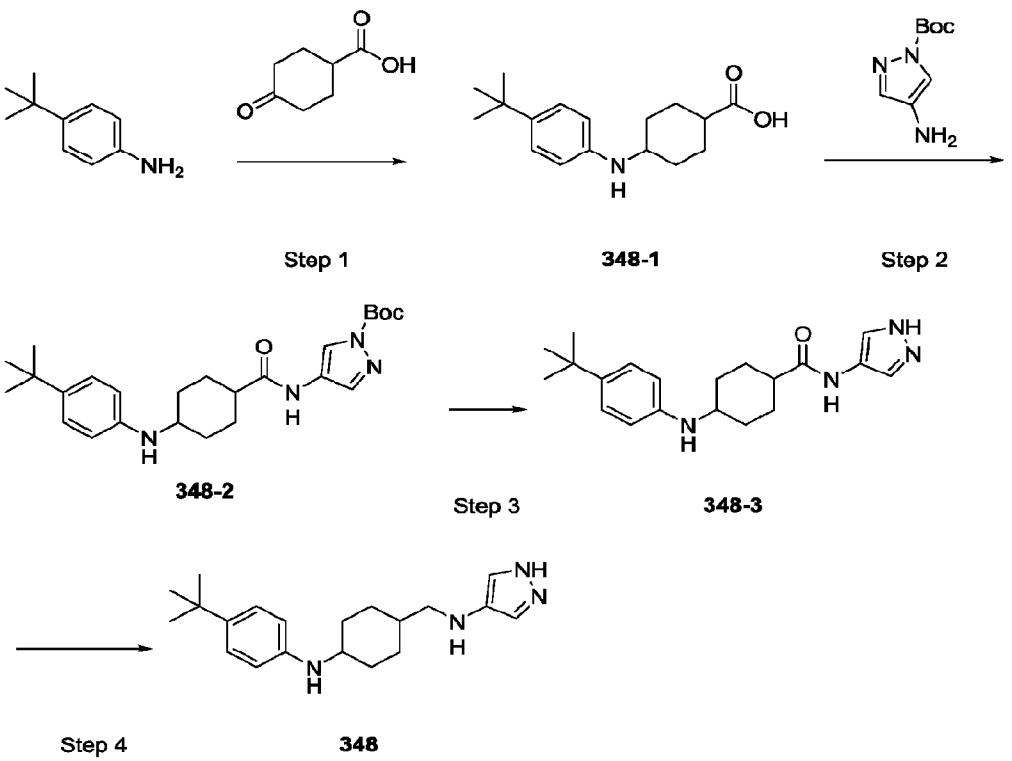


347

The title compound **347** (105.7 mg) was prepared in a total yield of 83.9 % as a white solid from tert-butyl (4-((4-(tert-butyl)phenyl)amino)cyclohexyl-3,3,4,5,5-d5)carbamate (176 mg, 0.5 mmol), and TFA according to the procedure for compound **24**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.16 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 3.19 - 2.95 (m, 1H), 2.07 – 1.98 (m, 1H), 1.85 – 1.67 (m, 2H), 1.52 – 1.40 (m, 1H), 1.25 (s, 9H). Mass (m/z): 252.3 $[M+H]^+$.

Compound 348

N-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)-1H-pyrazol-4-amine



Step 1. Preparation of 4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxylic acid (348-1)

A mixture of 4-(tert-butyl)aniline (1 g, 0.0067 mmol), 4-oxocyclohexane-1-carboxylic acid (1.14 g, 0.0080 mmol) and $NaBH_3CN$ (0.84 g, 0.0134 mmol) in MeOH (10 mL) and HOAc (1 drop) was stirred overnight at 50 °C. After cooling, the excess MeOH was removed under vacuum and the residue was diluted with water (20 mL), extracted three times with ethyl acetate (20 mL). Organic layers were combined, solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE: EA=3:1) to give the desired product as oil (1.5 g, 49.2%). Mass (m/z): 276.3 $[M+H]^+$.

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Step 2. tert-butyl 4-(4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxamido)-1H-pyrazole-1-carboxylate **(348-2)**

A mixture of 4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxylic acid (300 mg, 1.0894 mmol), tert-butyl 4-amino-1H-pyrazole-1-carboxylate (301.03 mg, 1.6341 mmol), EDCI (313.26 mg, 1.6341 mmol), DIEA (281.59 mg, 2.1788 mmol) and HOBT (220.80 mg, 1.6341 mmol) in DMF (10 mL) was stirred overnight at rt. Then the reaction solution was diluted with water (30 mL), extracted three times with ethyl acetate (20 mL). Organic layers were combined, solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE/EA=5:1) to give the desired product as oil (376 mg, 46.4%). Mass (m/z): 441.5 $[M+H]^+$.

Step 3. Preparation of 4-((4-(tert-butyl)phenyl)amino)-N-(1H-pyrazol-4-yl)cyclohexane-1-carboxamide **(348-3)**

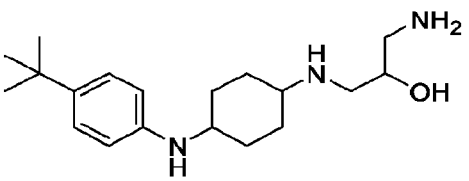
The mixture of 4-(4-((4-(tert-butyl)phenyl)amino)cyclohexane-1-carboxamido)-1H-pyrazole-1-carboxylate (376 mg, 0.8515 mmol) in 1,4-dioxane (10 mL) and 1,4-dioxane/HCl (10 mL) was stirred for 16 hours at 25 °C. After the reaction was completed, the solvent was removed under vacuum to give the desired product as oil (200 mg, 38.6%). Mass (m/z): 340.9 $[M+H]^+$.

Step 4. Preparation of N-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)-1H-pyrazol-4-amine **(348)**

To a solution of N-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)methyl)-1-methyl-1H-pyrazol-4-amine (200 mg, 0.5874 mmol) in THF (1 mL) was added BH_3-THF (30 mL). Then the mixture was stirred overnight at 25 °C. After the reaction was completed, solvent was removed under vacuum and the residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5 um; Mobile phase: ACN-H_2O (0.05%NH_3), 55%-60%) to afford the desired product **348** (9.7 mg, 5.0%) as a purple solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 7.06 (d, J = 8.6 Hz, 2H), 7.01 (s, 2H), 6.47 (d, J = 8.6 Hz, 2H), 5.10 (d, J = 7.8 Hz, 1H), 4.26 (brs, 1H), 3.08 (brs, 1H), 2.69 (d, J = 6.5 Hz, 2H), 1.98 (m, 2H), 1.84 (m, 2H), 1.47 (brs, 1H), 1.20 (s, 9H), 1.05 (q, J = 10.9 Hz, 4H). Mass (m/z): 327.5 $[M+H]^+$.

Compound 349

1-amino-3-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)propan-2-ol



349A
349B

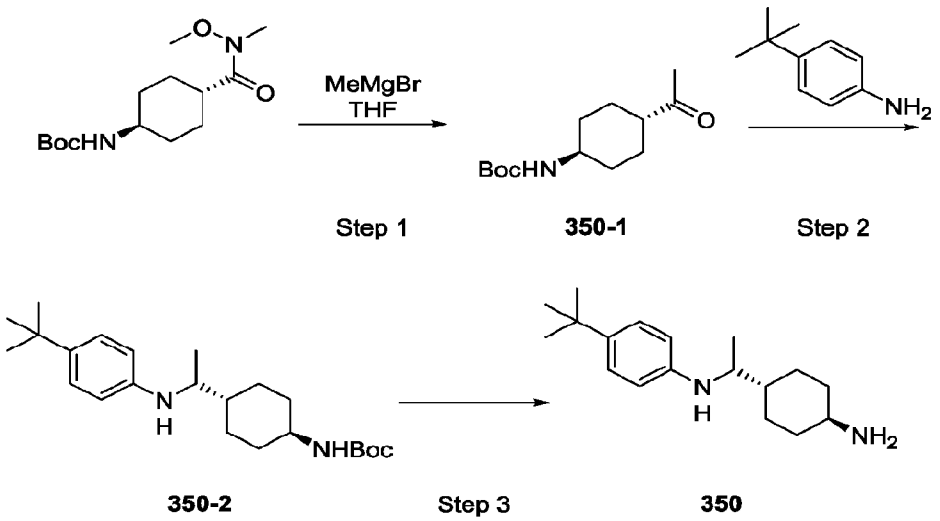
The title compound **349A** (68.7 mg, 29.8%) as a yellow solid and compound **349B** (62 mg, 27.4%) as a yellow solid were prepared from tert-butyl (3-((4-((4-(tert-butyl)phenyl)amino)cyclohexyl)amino)-2-hydroxypropyl)carbamate (300 mg, 0.68 mmol), and 4M HCl/dioxane (20 mL) according to the procedure for **37**. **349A**: ^{1}H NMR

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(400 MHz, CD_3OD) δ 7.37 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 4.14 (tt, J = 9.3, 3.3 Hz, 0H), 3.41 – 3.32 (m, 0H), 3.23 – 3.00 (m, 2H), 2.94 (d, J = 8.6 Hz, 1H), 2.18 (s, 2H), 1.65 – 1.34 (m, 2H), 1.28 (s, 5H). Mass (m/z): 320.8 $[M+H]^+$. HPLC: Rt: 2.996 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA), ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **349B**: ^1H NMR (400 MHz, CD_3OD) δ 7.14 (d, J – 8.7 Hz, 2H), 6.60 (d, J – 8.7 Hz, 2H), 4.19 – 4.11 (m, 1H), 3.63 – 3.56 (m, 0H), 3.23 – 2.99 (m, 2H), 2.92 (dd, J = 13.0, 8.6 Hz, 1H), 2.02-1.67 (m, 8H), 1.23 (d, J = 1.7 Hz, 9H). Mass (m/z): 320.8 $[M+H]^+$. HPLC: Rt: 3.380 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA) ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 350

N-((S)-1-((1r,4S)-4-aminocyclohexyl)ethyl)-4-(tert-butyl)aniline



Step 1. Preparation of tert-butyl ((1r,4r)-4-acetylcyclohexyl)carbamate **(350-1)**

A mixture of tert-butyl ((1r,4r)-4-(methoxy(methyl)carbamoyl)cyclohexyl)carbamate (500 mg, 1.746 mmol), and CH_3MgBr (1.46 mL, 4.365 mmol) in THF (10 mL) was stirred overnight at 0 °C under N_2. After cooling, diluted, extracted three times with ethyl acetate (20 mL). The organic layers were combined, solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE: EA=2:1) to give the desired product as white solid (350 mg, 46.5%). Mass (m/z): 242.17 $[M+H]^+$.

Step 2. Preparation of tert-butyl ((1S,4r)-4-((S)-1-((4-(tert-butyl)phenyl)amino)ethyl)cyclohexyl)carbamate **(350-2)**

A mixture of 4-(tert-butyl)aniline (200 mg, 1.3402 mmol), tert-butyl ((1r,4r)-4-acetylcyclohexyl)carbamate (485.4 mg, 2.0103 mmol) and $NaBH(OAc)_3$ (852.13 mg, 4.0206 mmol) in DCM (20 mL) was stirred overnight at 25 °C. After cooling, the excess DCM was removed under vacuum and the residue was extracted three times with DCM (20 mL) and water (20 mL). Organic layer was combined, solvent was removed under vacuum and the crude was purified through silica gel chromatography (PE: EA=7:1) to give the desired product (150 mg, 14.9%) as oil. Mass (m/z): 375.3 $[M+H]^+$.

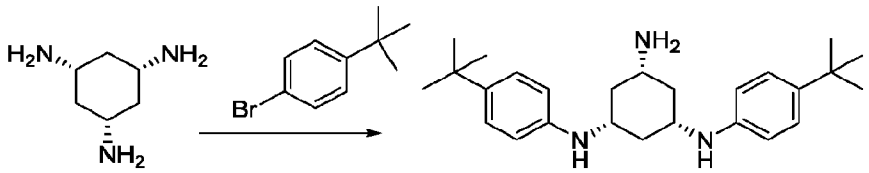
Step 3. Preparation of N-((S)-1-((1r,4S)-4-aminocyclohexyl)ethyl)-4-(tert-butyl)aniline **(350)**

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The crude product was purified by prep-HPLC (column-Gemini -C18 150 x 21.2 mm, 5um; Mobile phase: ACN-H_2O (0.1%FA), 10%-30%) to afford the desired product **350** (30.1 mg, 26.2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (d, J = 8.7 Hz, 2H), 6.46 (d, J = 8.7 Hz, 2H), 5.10 (s, 1H), 3.18 (m, 1H), 2.81 (m, 1H), 2.00 – 1.69 (m, 4H), 1.39 – 1.22 (m, 2H), 1.20 (s, 10H), 1.13 – 1.03 (m, 2H), 1.01 (d, J = 6.5 Hz, 3H). Mass (m/z): 275.3 $[M+H]^+$.

Compound 351

(1R,3S,5r)-N1,N3-bis(4-(tert-butyl)phenyl)cyclohexane-1,3,5-triamine

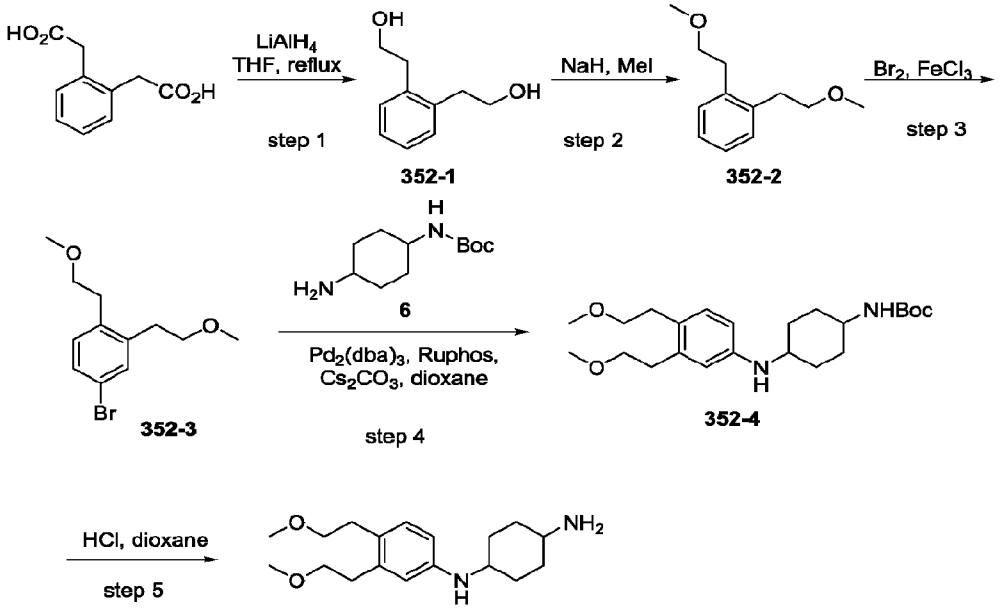


351

$Pd_2(dba)_3$ (49 mg, 0.054 mmol), Cs_2CO_3 (701 mg, 2.15 mmol), and RuPhos (25 mg, 0.054 mmol) were added to a solution of cyclohexane-1,3,5-triamine trihydrobromide, and 1-bromo-4-tert-butylbenzene (100 mg, 0.27 mmol) in toluene (10 mL), and the mixture was heated to 110 °C for 16 hrs, then cooled to room, the solvent was removed in vacuo, the residue was purified by prep-HPLC (column-Gemini -C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 5%-20%) to afford the desired product as yellow solid (8 mg, 7.5%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (d, J = 8.4 Hz, 4H), 6.73 (d, J = 7.6 Hz, 4H), 3.58 (brs, 2H), 3.37 (brs, 2H), 2.68 (s, 1H), 2.45 (d, J = 11.5 Hz, 4H), 1.28 (s, 16H). Mass (m/z): 394.4 $[M+H]^+$.

Compound 352

N-(4-(4-aminocyclohexyl)phenyl)-3,4-bis(2-methoxyethyl)aniline



352

Step 1. Preparation of 2,2'-(1,2-phenylene)bis(ethan-1-ol) **(352-1)**

A mixture of 2,2'-(1,2-phenylene)diacetic acid (5 g, 25.7 mmol) in THF (80 mL) was added

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$LiAlH_4$ (3.9 g, 10.28 mmol) at 25 °C. The reaction was stirred at 70 °C for 16 h. The reaction was quenched with water. The mixture was diluted with EA (20 mL) and washed with water (20 mL x 3). The organic phase was concentrated to give **352-1** as a pale solid (4 g, 84%). Mass (m/z): 167.2 $[M+H]^+$.

Step 2. Preparation of 1,2-bis(2-methoxyethyl)benzene (**352-2**)

To a solution of **352-1** (4 g, 24.1 mmol) in THF (100 mL) was added NaH (1.21 g, 50.6 mmol) at 0 °C. The reaction was stirred at 0 °C for 0.5 h. Then the reaction was added MeI (6.84 g, 48.2 mmol). The reaction was stirred at 25 °C for 2 h. The reaction was quenched with water. The mixture was diluted with EA (20 mL) and washed with water (20 mL x 3). The organic phase was concentrated and purification by a silica gel column chromatography (PE : EA = 4 : 1) to give **352-2** as a pale solid (3 g, 58%). Mass (m/z): 195.2 $[M+H]^+$.

Step 3. Preparation of 4-bromo-1,2-bis(2-methoxyethyl)benzene (**352-3**)

To a solution of **353-2** (2 g, 10.3 mmol) in DCE (20 mL) was added $FeCl_3$ (5.01 g, 30.9 mmol) and Br_2 (3.29 g, 20.6 mmol) at 25 °C. The reaction was stirred at 70 °C for 16 h. The reaction was quenched with water. The mixture was diluted with EA (20 mL), washed with water (20 mL x 3) and washed with aq.$Na_2S_2SO_3$. The organic phase was concentrated and purification by a silica gel column chromatography (PE : EA = 10 : 1) to give **353-3** as a white solid (0.5 g, 15.5%). Mass (m/z): 273.1 $[M+H]^+$.

Step 4. Preparation of tert-butyl (4-((3,4-bis(2-methoxyethyl)phenyl)amino) cyclohexyl)carbamate (**352-4**)

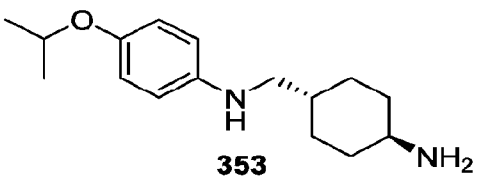
A mixture of **353-3** (0.1 g, 0.4 mmol), tert-butyl (4-aminocyclohexyl)carbamate (85.6 mg, 0.4 mmol), Ruphos (0.04 g, 0.08 mmol), Cs_2CO_3 (260 mg, 0.8 mmol) and $Pd_2(dba)_3$ (36.6 mg, 0.04 mmol) in dioxane (2 mL) was stirred under nitrogen at 90 °C for 16 hrs. The mixture was filtered, concentrated and purification by Prep-TLC (PE : EA = 1 : 1) to give **352-4** as a yellow solid (0.01 g, 5.6%). Mass (m/z): 406.8 $[M+H]^+$.

Step 5. Preparation of N1-(3,4-bis(2-methoxyethyl)phenyl)cyclohexane-1,4-diamine (**352**)

To a solution of **352-4** (0.01 g, 0.0245 mmol) in DCM (5 mL) was added HCl in dioxane (1 mL). The reaction was stirred at 25 °C for 2 h. The mixture was concentrated and purification by Prep-TLC (DCM : MeOH = 10 : 1) to give **352** (5 mg, 60%) as a yellow solid. ^1H NMR (300 MHz, CD_3OD) δ 7.25 (d, J = 9 Hz, 1H), 7.12 – 6.98 (m, 1H), 6.96 – 6.76 (m, 1H), 3.75 – 3.30 (m, 8H), 3.29 – 2.66 (m, 6H), 2.12 (s, 2H), 1.85 – 1.49 (m, 8H). Mass (m/z): 307.3 $[M+H]^+$.

Compound 353

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-isopropoxyaniline



353

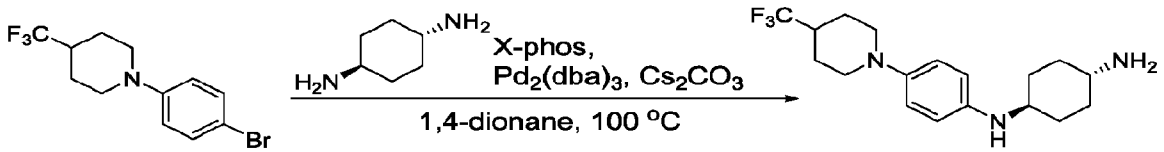
The title compound **353** (26.1 mg, 17.0%) as white solid was prepared from tert-butyl ((1r,4r)-4-(((4-isopropoxyphenyl)amino)methyl)cyclohexyl)carbamate (201 mg, 0.5777 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^1H NMR (400 MHz, CD_3OD) δ 6.76 – 6.70 (m, 2H), 6.62 – 6.56 (m, 2H), 4.35 (dt, J = 12.1, 6.1 Hz, 1H), 2.87 (d, J

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= 6.7 Hz, 2H), 2.56 (tt, *J* = 10.9, 3.5 Hz, 1H), 1.88 (d, *J* = 10.1 Hz, 4H), 1.58 – 1.47 (m, 1H), 1.24 (d, *J* = 6.1 Hz, 6H), 1.15 – 0.98 (m, 4H). Mass (m/z): 263.20 $[M+H]^+$.

Compound 354

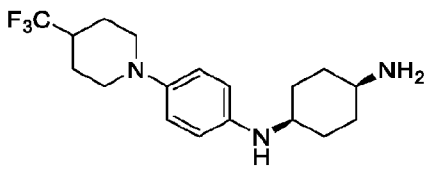
(1r,4r)-N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



A mixture of 1-(4-bromophenyl)-4-(trifluoromethyl)piperidine (46.1 mg, 0.15 mmol), (1r,4r)-cyclohexane-1,4-diamine (22.2 mg, 0.2 mmol), $Pd_2(dba)_3$ (4.6 mg, 5 umol), X-phos (12 mg, 25 umol), and Cs_2CO_3 (65.6 mg, 0.2 mmol) in 1,4-dioxane (3.0 mL) was stirred overnight at 100 °C under nitrogen atmosphere. After cooling to rt. 5 mL of water was added. The resulting solution was extracted with 3x10 mL of ethyl acetate. The organic layers were combined, washed with water (30 mL), dried and concentrated under vacuum. The residue was purified by prep-TLC (MeOH/DCM = 1:5) to afford the desired product (16.1 mg, 31.4%) as a rosy brown solid. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 6.81 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 3.55 – 3.42 (m, 2H), 3.07 (m, 1H), 2.94 (m, 1H), 2.68 – 2.55 (m, 2H), 2.16 – 1.96 (m, 4H), 1.93 – 1.77 (m, 4H), 1.58 (m, 1H), 1.54 – 1.36 (m, 2H), 1.27 – 1.11 (m, s 2H). Mass (m/z): 342.3 $[M+H]^+$.

Compound 355

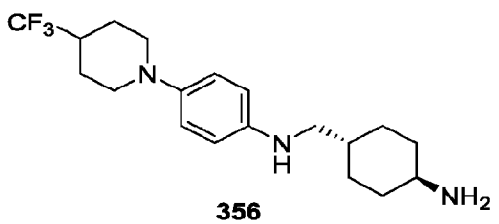
(1s,4s)-N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



The title compound **355** (26.1 mg) was prepared in a total yield of 50.8% as a rosy brown solid from 1-(4-bromophenyl)-4-(trifluoromethyl)piperidine (46.1 mg, 0.15 mmol), (1s,4s)-cyclohexane-1,4-diamine (22.2 mg, 0.2 mmol) according to the procedure for compound **354**. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 6.76 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.50 – 3.37 (m, 2H), 3.33 (m, 1H), 3.06 (m, 1H), 2.62 – 2.53 (m, 2H), 1.92 – 1.83 (m, 2H), 1.80 – 1.67 (m, 6H), 1.64 – 1.48 (m, 5H). Mass (m/z): 342.3 $[M+H]^+$.

Compound 356

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(4-(trifluoromethyl)piperidin-1-yl)aniline



356

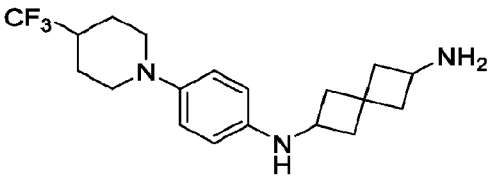
The desired product (29.4 mg, 47.7%) as a purple solid was prepared from tert-butyl ((1r,4r)-4-(((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)methyl)cyclohexyl)carbamate (79 mg, 0.174 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H

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NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 3H), 6.79 (s, 2H), 6.53 (s, 2H), 3.42 (s, 2H), 2.84 (d, J = 33.6 Hz, 3H), 2.05 – 1.79 (m, 7H), 1.51 (d, J = 38.4 Hz, 4H), 1.32 (d, J = 13.6 Hz, 2H), 0.99 (s, 3H). Mass (m/z): 356.3 $[M+H]^+$.

Compound 357

N2-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)spiro[3.3]heptane-2,6-diamine

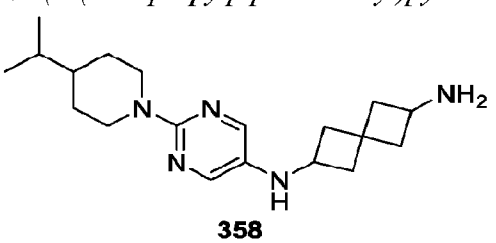


357

The title compound **357** (47.0 mg) was prepared in a yield of 55.9% as a white powder with 1: 0.2 mixture by ^{1}H NMR from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (54.2 mg, 0.22 mmol) and tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (60 mg, 0.27 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (s, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.49 – 6.32 (m, 2H), 5.37 (d, J = 6.8 Hz, 1H), 3.63 (q, J = 7.2 Hz, 1H), 3.54 (p, J = 8.1 Hz, 1H), 3.42 (d, J = 11.9 Hz, 2H), 2.55 (d, J = 2.5 Hz, 3H), 2.42 – 2.27 (m, 3H), 2.25 – 2.09 (m, 3H), 1.91 – 1.70 (m, 4H), 1.56 (qd, J = 12.5, 4.0 Hz, 2H). Mass (m/z): 354.3 $[M+H]^+$.

Compound 358

N2-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)spiro[3.3]heptane-2,6-diamine

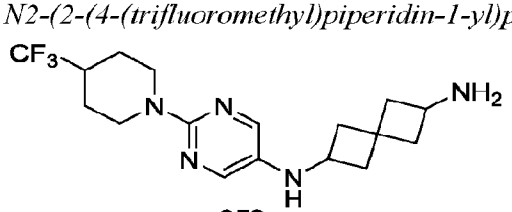


358

The title compound **358** (55.2 mg) was prepared in a yield of 75.4% as a white powder with 1: 0.2 mixture by ^{1}H NMR from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (49.3 mg, 0.22 mmol) and tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (60 mg, 0.27 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 3H), 7.79 (s, 2H), 5.29 (d, J = 7.4 Hz, 1H), 4.47 (dt, J = 12.7, 2.8 Hz, 2H), 3.63 (p, J = 7.4 Hz, 1H), 3.52 (p, J = 8.1 Hz, 1H), 2.61 (td, J = 12.6, 2.5 Hz, 2H), 2.41 – 2.28 (m, 2H), 2.15 (ddt, J = 11.5, 8.4, 4.5 Hz, 3H), 1.79 (dt, J = 11.3, 8.2 Hz, 2H), 1.63 (dd, J = 12.9, 3.2 Hz, 2H), 1.38 (hept, J = 6.6 Hz, 1H), 1.26 – 1.14 (m, 1H), 1.06 (qd, J = 12.4, 4.2 Hz, 2H), 0.84 (d, J = 6.8 Hz, 6H). Mass (m/z): 330.3 $[M+H]^+$.

Compound 359

N2-(2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)spiro[3.3]heptane-2,6-diamine



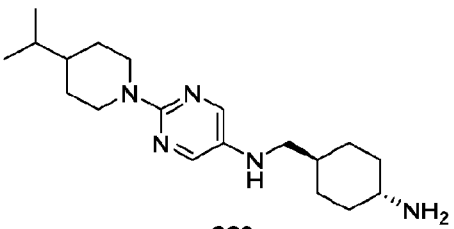
359

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The title compound **359** (17.2 mg) was prepared in a yield of 21.8% as a white powder with 1: 0.2 mixture by ^{1}H NMR from 2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-amine (55.1 mg, 0.22 mmol) and tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (60 mg, 0.27 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 3H), 7.82 (s, 2H), 5.41 (d, J = 7.2 Hz, 1H), 4.65 – 4.44 (m, 2H), 3.64 (h, J = 7.4 Hz, 1H), 3.53 (p, J = 8.1 Hz, 1H), 2.76 (td, J – 12.9, 2.5 Hz, 2H), 2.56 (td, J – 8.7, 3.8 Hz, 1H), 2.42 – 2.28 (m, 2H), 2.26 – 2.12 (m, 3H), 1.81 (td, J = 11.5, 9.6, 5.9 Hz, 4H), 1.34 (qd, J = 12.6, 4.2 Hz, 2H). Mass (m/z): 356.2 $[M+H]^+$.

Compound 360

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine

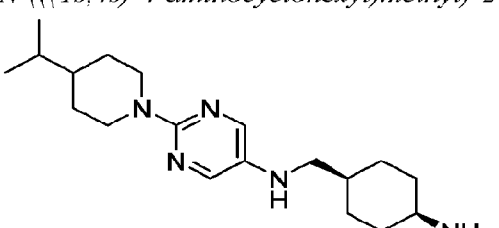


360

The desired product **360** as a white solid (38.8 mg, 42.3%) was prepared from tert-butyl ((1r,4r)-4-(((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)methyl)cyclohexyl)carbamate (crude), DCM (6 mL) and 2,2,2-trifluoroacetic acid (3 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 2H), 5.05 (t, J = 6.0 Hz, 1H), 4.47 (d, J = 12.9 Hz, 2H), 2.78 (t, J = 6.4 Hz, 2H), 2.70 – 2.54 (m, 4H), 1.77 (d, J = 9.8 Hz, 4H), 1.64 (d, J = 12.8 Hz, 2H), 1.40 (dd, J = 13.0, 6.6 Hz, 2H), 1.26 – 0.91 (m, 7H), 0.85 (d, J = 6.8 Hz, 6H). Mass (m/z): 332.3 $[M+H]^+$

Compound 361

N-(((1s,4s)-4-aminocyclohexyl)methyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine



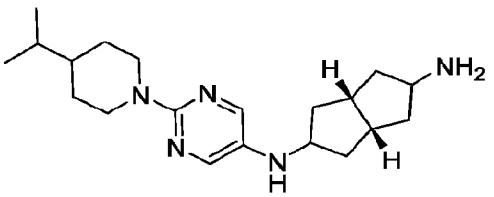
361

The desired product **361** (10.8 mg, 11.9%) as a yellow solid was prepared from tert-butyl ((1s,4s)-4-(((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)methyl)cyclohexyl)carbamate according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.87 (d, J = 4.9 Hz, 1H), 5.07 (t, J = 5.9 Hz, 1H), 4.57 – 4.41 (m, 2H), 2.97 – 2.79 (m, 2H), 2.70 – 2.56 (m, 2H), 2.41 – 2.34 (m, 1H), 1.82 – 1.56 (m, 3H), 1.43 (dt, J = 13.2, 10.2 Hz, 6H), 1.17 (d, J = 32.5 Hz, 2H), 1.16 – 0.97 (m, 2H), 0.85 (d, J = 6.8 Hz, 6H). Mass (m/z): 332.3 $[M+H]^+$

Compound 362

(3aR,6aS)-N2-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)octahydropentalene-2,5-diamine

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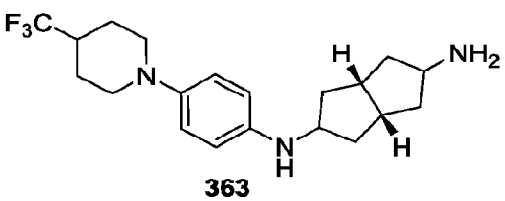


362

The title compound **362** (16.7 mg) was prepared in a three-step overall yield of 21.8% as a white powder with 1: 0.8 mixture by ^{1}H NMR from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (106 mg, 0.48 mmol) and (3as,6as)-tetrahydropentalene-2,5(1H,3H)-dione (200 mg, 1.45 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 3H), 7.91 (s, 2H), 5.12 (d, J = 5.9 Hz, 1H), 4.48 (d, J = 12.8 Hz, 2H), 2.62 (t, J = 12.2 Hz, 1H), 2.38 (s, 4H), 2.21 (td, J = 15.6, 14.1, 6.9 Hz, 5H), 1.64 (d, J = 12.7 Hz, 2H), 1.40 (dq, J = 13.7, 8.2, 6.6 Hz, 4H), 1.09 (td, J = 12.2, 4.0 Hz, 2H), 0.85 (d, J = 6.7 Hz, 6H). Mass (m/z): 344.4 $[M+H]^+$.

Compound 363

(3aR,6aS)-N2-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)octahydropentalene-2,5-diamine

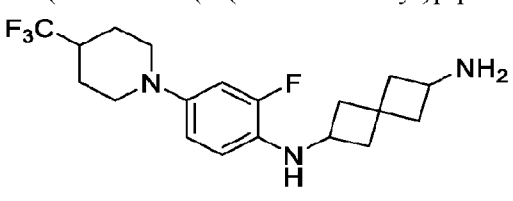


363

The title compound **363** (30.8 mg) was prepared in a three-step overall yield of 17.5% as a white powder with 1: 0.8 mixture by ^{1}H NMR from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (118 mg, 0.48 mmol) and (3as,6as)-tetrahydropentalene-2,5(1H,3H)-dione (200 mg, 1.45 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (s, 3H), 6.76 (dd, J = 8.7, 6.5 Hz, 2H), 6.50 (dd, J = 8.6, 6.2 Hz, 2H), 5.17 (d, J = 40.9 Hz, 1H), 3.84 – 3.50 (m, 1H), 3.42 (d, J = 12.3 Hz, 2H), 2.38 (s, 2H), 2.22 (td, J = 13.8, 12.2, 6.4 Hz, 3H), 1.86 (d, J = 11.9 Hz, 2H), 1.74 (tt, J = 16.3, 7.1 Hz, 1H), 1.63 – 1.50 (m, 2H), 1.50 – 1.34 (m, 2H), 1.35 – 1.14 (m, 3H). Mass (m/z): 368.7 $[M+H]^+$.

Compound 364

N2-(2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)spiro[3.3]heptane-2,6-diamine



364

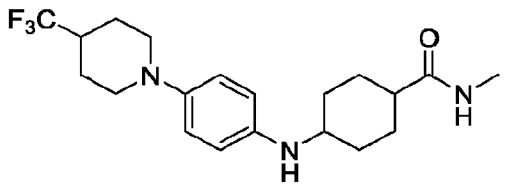
The title compound **364** (14.5 mg) was prepared in a yield of 11.5% as a white powder with 1: 0.2 mixture by ^{1}H NMR from 2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (70 mg, 0.27 mmol) and tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (90 mg, 0.40 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 3H), 6.73 (dd, J =

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14.5, 2.6 Hz, 1H), 6.58 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.54 – 6.42 (m, 1H), 5.01 (d, *J* = 7.1 Hz, 1H), 3.67 (h, *J* = 7.3 Hz, 1H), 3.50 (d, *J* = 12.3 Hz, 3H), 2.56 (dd, *J* = 12.2, 2.5 Hz, 3H), 2.42 – 2.26 (m, 3H), 2.24 – 2.07 (m, 3H), 1.96 – 1.79 (m, 4H), 1.53 (qd, *J* = 12.5, 4.0 Hz, 2H). Mass (m/z): 472.4 $[M+H]^+$.

Compound 365

N-methyl-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxamide

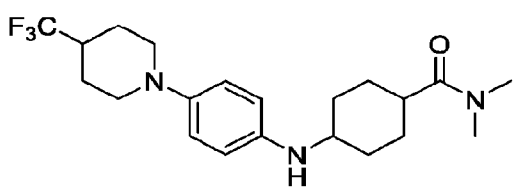


365

The title compound **365** (10.1 mg) was prepared in a yield of 9.7% as a white powder from 4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylic acid (100 mg, 0.27 mmol) and methanamine hydrochloride (73 mg, 1.08 mmol) according to the procedure for **10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, *J* = 4.7 Hz, 1H), 6.79 – 6.69 (m, 2H), 6.50 – 6.44 (m, 2H), 4.87 (d, *J* = 8.5 Hz, 1H), 3.41 (d, *J* = 12.0 Hz, 2H), 3.04 (d, *J* = 7.8 Hz, 1H), 2.55 (t, *J* = 4.3 Hz, 5H), 2.42 – 2.34 (m, 1H), 2.09 – 1.93 (m, 3H), 1.85 (d, *J* = 12.5 Hz, 2H), 1.78 – 1.67 (m, 2H), 1.57 (td, *J* = 12.5, 4.0 Hz, 2H), 1.45 (qd, *J* = 13.5, 3.7 Hz, 3H), 1.11 – 0.97 (m, 2H). Mass (m/z): 384.3 $[M+H]^+$.

Compound 366

N,N-dimethyl-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxamide



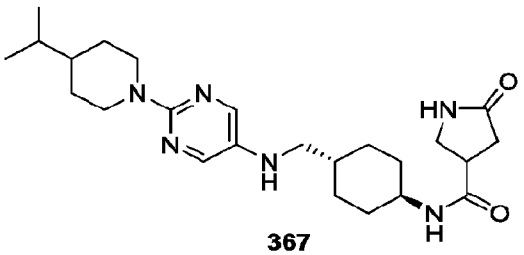
366

The title compound **366** (31.9 mg) was prepared in a yield of 29.8% as a white powder from 4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylic acid (100 mg, 0.27 mmol) and dimethylamine (36 mg, 0.80 mmol) according to the procedure for **10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, *J* = 8.2 Hz, 2H), 6.51 (s, 2H), 4.89 (s, 1H), 3.42 (d, *J* = 11.6 Hz, 2H), 3.06 (s, 1H), 3.00 (s, 3H), 2.79 (s, 3H), 2.04 – 1.92 (m, 3H), 1.85 (d, *J* = 12.5 Hz, 2H), 1.68 (d, *J* = 13.1 Hz, 2H), 1.56 (d, *J* = 12.4 Hz, 3H), 1.44 (q, *J* = 13.3 Hz, 3H), 1.13 (q, *J* = 12.4 Hz, 3H). Mass (m/z): 398.4 $[M+H]^+$.

Compound 367

N-((1r,4r)-4-(((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)methyl)cyclohexyl)-5-oxopyrrolidine-3-carboxamide

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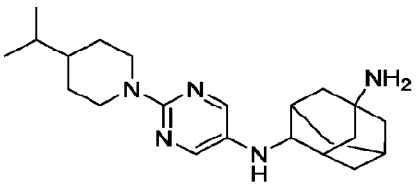


367

The desired product **367** (32.7 mg, 49.0%) as yellow solid was prepared from N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (50 mg, 0.151 mmol), 5-oxopyrrolidine-3-carboxylic acid (25 mg, 0.196 mmol), HATU (75 mg,0.196 mmol), DIEA (58 mg,0.453 mmol) and DMF (5 mL) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (dt, J = 12.8, 5.6 Hz, 1H), 7.94 (s, 1H), 7.88 (s, 1H), 7.59 (s, 1H), 4.91 (dd, J = 71.2, 8.4 Hz, 1H), 4.58 – 4.41 (m, 2H), 3.44 – 3.38 (m, 2H), 3.25 – 3.16 (m, 2H), 2.96 (dt, J = 30.0, 6.4 Hz, 3H), 2.61 (td, J = 12.5, 2.4 Hz, 2H), 2.27 (dd, J = 8.4, 4.0 Hz, 2H), 1.94 (d, J = 11.2 Hz, 1H), 1.74 – 1.55 (m, 4H), 1.54 – 1.45 (m, 2H), 1.44 – 1.36 (m, 3H), 1.14 – 0.96 (m, 4H), 0.85 (d, J = 6.8 Hz, 6H). Mass (m/z): 443.3 $[M+H]^+$.

Compound 368

N4-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)adamantane-1,4-diamine

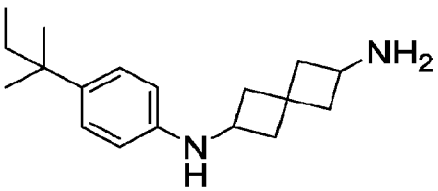


368

The title compound **368** (4.6 mg) was prepared in a yield of 2.16% as a white powder with 1: 0.3 mixture by ^{1}H NMR from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (100 mg, 0.45 mmol) and tert-butyl (4-oxoadamantan-1-yl)carbamate (180 mg, 0.34 mmol) according to the procedure for **20**. ^{1}H NMR (301 MHz, Methanol-d_4) δ 7.97 (s, 1H), 7.95 (s, 1H), 6.80 (s, 3H), 4.99 (d, J = 6.9 Hz, 2H), 2.73 (s, 2H), 2.60 (s, 3H), 2.28 – 2.10 (m, 5H), 1.98 (d, J = 28.3 Hz, 5H), 1.73 (d, J = 12.5 Hz, 4H), 1.60 (s, 3H), 0.90 (d, J = 3.0 Hz, 6H). Mass (m/z): 470.4 $[M+H]^+$.

Compound 369

N2-(4-(tert-pentyl)phenyl)spiro[3.3]heptane-2,6-diamine



369

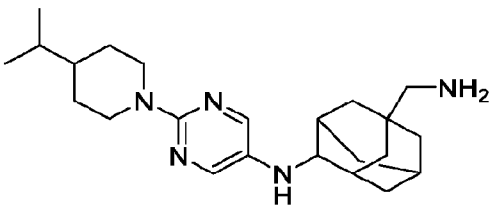
The title compound **369** (44.3 mg) was prepared in a yield of 38.5% as a white powder from 4-(tert-pentyl)aniline (100 mg, 0.43 mmol) and tert-butyl

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(6-oxospiro[3.3]heptan-2-yl)carbamate (116 mg, 0.50 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.03 – 6.95 (m, 2H), 6.44 – 6.33 (m, 2H), 5.50 (d, J = 6.7 Hz, 1H), 3.63 (h, J = 7.3 Hz, 1H), 3.22 – 3.10 (m, 1H), 2.39 (ddd, J = 11.3, 7.1, 4.7 Hz, 1H), 2.35 – 2.21 (m, 2H), 2.11 (ddd, J = 11.8, 7.1, 5.2 Hz, 1H), 1.75 (td, J = 11.0, 7.8 Hz, 2H), 1.65 (ddd, J = 18.9, 10.8, 8.4 Hz, 2H), 1.51 (q, J = 7.4 Hz, 2H), 1.14 (s, 6H), 0.59 (t, J = 7.3 Hz, 3H). Mass (m/z): 273.1 $[M+H]^+$.

Compound 370

N-(5-(aminomethyl)adamantan-2-yl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine

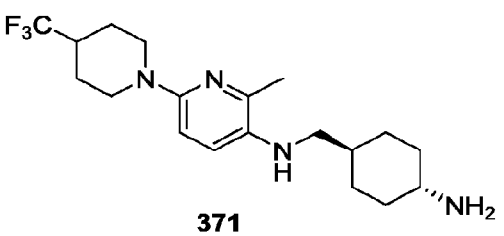


370

The title compound **370** (8.6 mg) was prepared in a two-step overall yield of 6.8% as a white powder from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (200 mg, 0.90 mmol) and 4-oxoadamantane-1-carboxylic acid (260 mg, 1.36 mmol) according to the procedure for **84**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 2.3 Hz, 1H), 7.19 (s, 1H), 6.65 (s, 1H), 5.31 (t, J = 4.8 Hz, 1H), 4.46 (d, J = 12.2 Hz, 1H), 1.99 (q, J = 6.8, 6.2 Hz, 7H), 1.66 (s, 5H), 1.42 (d, J = 18.3 Hz, 6H), 1.06 – 1.01 (m, 3H), 0.84 (dd, J = 6.9, 3.8 Hz, 8H). Mass (m/z): 399.8 $[M+H]^+$.

Compound 371

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine



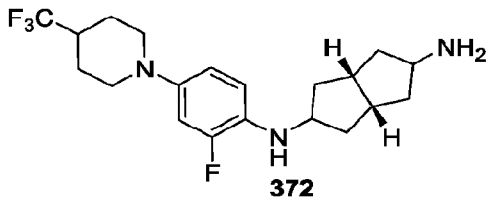
371

The title compound **371** (23.6 mg) was prepared in a yield of 23.6% as a white powder from 2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (70 mg, 0.27 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (114 mg, 0.54 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (s, 1H), 7.33 (s, 1H), 7.20 (s, 1H), 6.90 (s, 1H), 6.61 (s, 1H), 4.10 (d, J = 12.7 Hz, 2H), 3.03 – 2.77 (m, 3H), 2.64 (s, 2H), 2.25 (s, 3H), 2.05 – 1.92 (m, 2H), 1.86 (d, J = 15.5 Hz, 4H), 1.48 (s, 3H), 1.36 – 1.26 (m, 2H), 1.10 – 0.91 (m, 2H). Mass (m/z): 371.3 $[M+H]^+$.

Compound 372

(3aR,6aS)-N2-(2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)octahydropentalene-2,5-diamine

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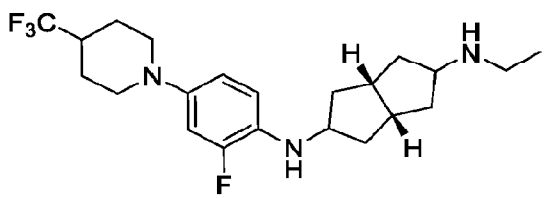


372

The title compound **372** (11.2 mg) was prepared in a three-step overall yield of 8.1% as a white powder with 1: 0.8 mixture by ^{1}H NMR from 2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (150 mg, 0.57 mmol) and (3as,6as)-tetrahydropentalene-2,5(1H,3H)-dione (237 mg, 1.72 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.87 – 6.63 (m, 3H), 3.81 (d, J = 11.7 Hz, 1H), 3.52 (ddt, J = 15.2, 6.6, 3.6 Hz, 2H), 2.75 – 2.50 (m, 4H), 2.46 – 2.32 (m, 3H), 2.25 (dtt, J = 17.2, 8.7, 4.5 Hz, 1H), 2.03 – 1.87 (m, 3H), 1.70 (qd, J = 12.6, 4.1 Hz, 3H), 1.48 (td, J = 11.8, 7.9 Hz, 1H), 1.39 – 1.26 (m, 2H). Mass (m/z): 386.2 $[M+H]^+$.

Compound 373

(3aR,6aS)-N2-ethyl-N5-(2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)octahydropentalene-2,5-diamine

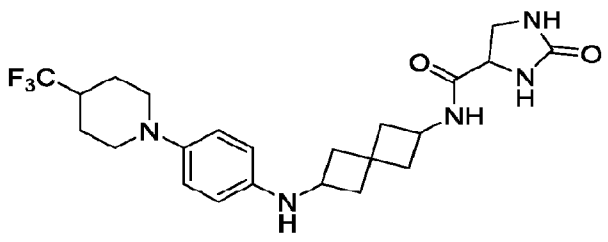


373

The title compound **373** (7.8 mg) was prepared in a three-step overall yield of 6.5% as a white powder with 1: 0.8 mixture by ^{1}H NMR from 2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (150 mg, 0.57 mmol) and (3as,6as)-tetrahydropentalene-2,5(1H,3H)-dione (237 mg, 1.72 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (s, 1H), 6.84 – 6.49 (m, 3H), 3.76 (d, J = 12.5 Hz, 1H), 3.50 (t, J = 9.9 Hz, 2H), 2.90 (d, J = 7.3 Hz, 1H), 2.70 – 2.62 (m, 3H), 2.26 (d, J = 8.5 Hz, 2H), 1.99 (q, J = 6.9, 6.4 Hz, 2H), 1.88 (d, J = 17.5 Hz, 2H), 1.64 – 1.38 (m, 4H), 1.23 – 1.13 (m, 4H), 0.95 (s, 1H), 0.87 – 0.80 (m, 1H). Mass (m/z): 414.5 $[M+H]^+$.

Compound 374

2-oxo-N-(6-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)spiro[3.3]heptan-2-yl)imidazolidine-4-carboxamide



374

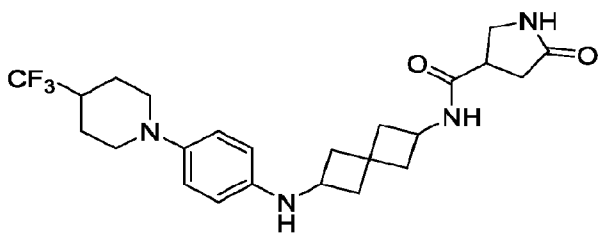
The title compound **374** (33.4 mg) was prepared in a yield of 50.7% as a white powder from N2-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)spiro[3.3]heptane-2,6-diamine (50 mg, 0.14

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mmol) and 2-oxoimidazolidine-4-carboxylic acid (22 mg, 0.17 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 7.7 Hz, 1H), 6.78 – 6.70 (m, 2H), 6.41 (dd, J = 8.8, 6.7 Hz, 3H), 6.27 (s, 1H), 5.31 (d, J = 6.8 Hz, 1H), 4.10 (h, J = 8.0 Hz, 1H), 3.98 (ddd, J = 9.7, 6.1, 1.6 Hz, 1H), 3.62 (h, J = 7.4 Hz, 1H), 3.49 (t, J = 9.3 Hz, 1H), 3.41 (d, J = 12.1 Hz, 2H), 3.16 (ddd, J = 9.0, 6.1, 1.3 Hz, 1H), 2.40 – 2.25 (m, 4H), 2.16 (q, J = 5.5 Hz, 1H), 1.96 (ddd, J – 19.9, 12.8, 9.1 Hz, 3H), 1.90 – 1.71 (m, 5H), 1.55 (qd, J – 12.4, 4.1 Hz, 2H). Mass (m/z): 466.5 $[M+H]^+$.

Compound 375

5-oxo-N-(6-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)spiro[3.3]heptan-2-yl)pyrrolidine-3-carboxamide

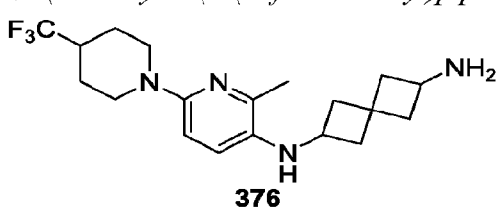


375

The title compound **375** (45.1 mg) was prepared in a yield of 68.6% as a white powder from N2-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)spiro[3.3]heptane-2,6-diamine (50 mg, 0.14 mmol) and 5-oxopyrrolidine-3-carboxylic acid (22 mg, 0.17 mmol) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 7.5 Hz, 1H), 7.54 (s, 1H), 6.80 – 6.69 (m, 2H), 6.46 – 6.34 (m, 2H), 5.31 (d, J = 6.8 Hz, 1H), 4.06 (h, J = 8.0 Hz, 1H), 3.62 (h, J = 7.4 Hz, 1H), 3.40 (d, J = 12.4 Hz, 2H), 3.36 (dd, J = 8.9, 1.9 Hz, 1H), 3.16 (ddd, J = 9.6, 6.5, 3.5 Hz, 1H), 3.04 (qd, J = 8.6, 6.5 Hz, 1H), 2.54 (d, J = 2.5 Hz, 2H), 2.39 – 2.27 (m, 3H), 2.27 – 2.20 (m, 2H), 2.16 (dt, J = 11.9, 6.2 Hz, 1H), 2.03 – 1.69 (m, 7H), 1.55 (qd, J = 12.5, 4.1 Hz, 2H). Mass (m/z): 465.7 $[M+H]^+$.

Compound 376

N2-(2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine



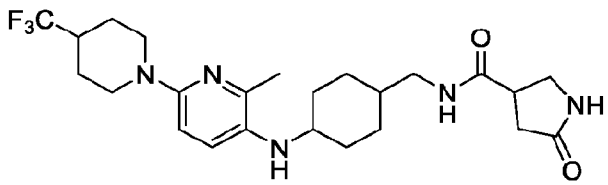
376

The title compound **376** (19.3 mg) was prepared in a yield of 19.4% as a white powder from 2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (70 mg, 0.27 mmol) and tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (79 mg, 0.35 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.91 (d, J = 9.5 Hz, 1H), 6.62 (s, 1H), 4.04 (s, 2H), 3.69 (p, J = 8.1 Hz, 2H), 2.83 – 2.52 (m, 4H), 2.47 (dt, J = 11.7, 6.0 Hz, 1H), 2.41 – 2.10 (m, 7H), 2.10 – 1.79 (m, 4H), 1.72 – 1.55 (m, 2H). Mass (m/z): 369.7 $[M+H]^+$.

Compound 377

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N-((4-((2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)amino)cyclohexyl)methyl)-5-oxopyrrolidine-3-carboxamide

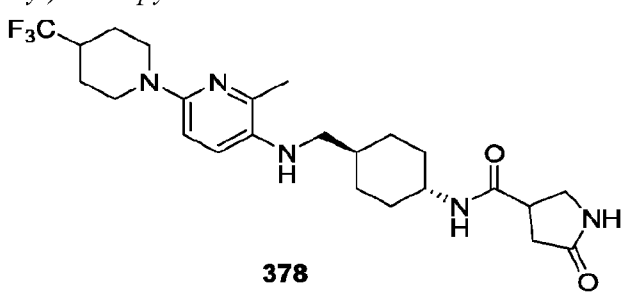


377

The title compound **377** (10.6 mg) was prepared in a yield of 16.3% as a white powder from N-(4-(aminomethyl)cyclohexyl)-2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (50 mg, 0.13 mmol) and 5-oxopyrrolidine-3-carboxylic acid (21 mg, 0.16 mmol) according to the procedure for 10. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.05 (s, 1H), 4.06 (s, 2H), 3.58 (dd, J = 9.9, 8.8 Hz, 2H), 3.46 (dd, J = 9.9, 6.4 Hz, 2H), 3.35 (s, 1H), 3.18 (d, J = 7.1 Hz, 2H), 3.08 (dd, J = 6.8, 1.2 Hz, 1H), 2.60 – 2.43 (m, 4H), 1.93 (s, 3H), 1.80 – 1.51 (m, 6H), 1.45 – 1.35 (m, 2H), 1.16 – 1.01 (m, 1H). Mass (m/z): 482.4 $[M+H]^+$.

Compound 378

N-((1r,4r)-4-(((2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)amino)methyl)cyclohexyl)-5-oxopyrrolidine-3-carboxamide

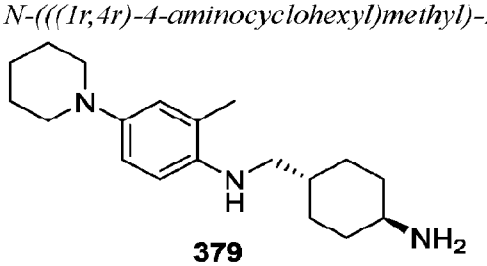


378

The title compound **378** (12.0 mg) was prepared in a yield of 16.3% as a white powder from N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-methyl-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (40 mg, 0.11 mmol) and 5-oxopyrrolidine-3-carboxylic acid (17 mg, 0.13 mmol) according to the procedure for **10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 7.9 Hz, 1H), 7.56 (s, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 8.7 Hz, 1H), 4.41 (t, J = 6.0 Hz, 1H), 4.11 (d, J = 12.7 Hz, 2H), 3.50 (tt, J = 7.4, 3.8 Hz, 1H), 3.41 – 3.34 (m, 1H), 3.19 (dd, J = 9.3, 6.4 Hz, 1H), 3.12 – 3.00 (m, 1H), 2.84 (t, J = 6.3 Hz, 2H), 2.60 (td, J = 12.5, 2.5 Hz, 3H), 2.38 – 2.23 (m, 3H), 2.22 (s, 3H), 1.88 – 1.74 (m, 6H), 1.46 (qd, J = 12.5, 4.4 Hz, 3H), 1.20 – 1.05 (m, 2H), 1.05 – 0.92 (m, 2H). Mass (m/z): 482.2 $[M+H]^+$.

Compound 379

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-methyl-4-(piperidin-1-yl)aniline



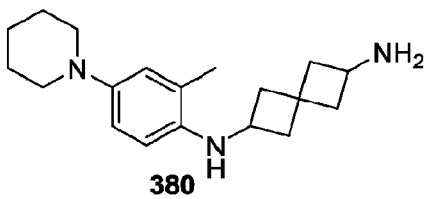
379

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The title compound **379** (21 mg) was prepared in a yield of 49.5% as a white powder from 2-methyl-4-(piperidin-1-yl)aniline (40 mg, 0.23 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (54 mg, 0.33 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (s, 3H), 6.67 (s, 2H), 6.38 (s, 1H), 4.37 (s, 1H), 2.88 (d, J = 25.2 Hz, 5H), 2.04 (s, 3H), 1.96 (t, J = 8.3 Hz, 2H), 1.85 (d, J = 12.8 Hz, 2H), 1.54 (d, J = 58.9 Hz, 7H), 1.35 – 1.20 (m, 3H), 0.98 (q, J – 12.7 Hz, 2H). Mass (m/z): 302.6 $[M+H]^+$.

Compound 380

N2-(2-methyl-4-(piperidin-1-yl)phenyl)spiro[3.3]heptane-2,6-diamine

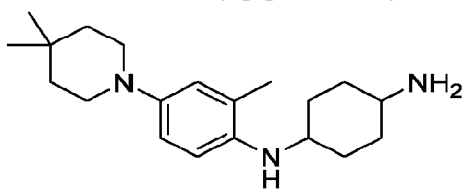


380

The title compound **380** (26 mg) was prepared in a yield of 59.2% as a white powder from 2-methyl-4-(piperidin-1-yl)aniline (40 mg, 0.2 mmol) and tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (51 mg, 0.32 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 – 8.05 (m, 3H), 7.51 – 7.07 (m, 1H), 6.38 (s, 1H), 3.71 (s, 1H), 3.55 (s, 1H), 3.24 – 2.93 (m, 2H), 2.39 (dd, J = 12.4, 6.7 Hz, 2H), 2.17 (q, J = 10.4, 9.6 Hz, 3H), 2.06 (s, 3H), 2.02 – 1.87 (m, 3H), 1.74 (s, 3H), 1.48 (d, J = 30.5 Hz, 2H), 1.32 – 1.17 (m, 3H). Mass (m/z): 300.6 $[M+H]^+$.

Compound 381

N1-(4-(4,4-dimethylpiperidin-1-yl)-2-methylphenyl)cyclohexane-1,4-diamine

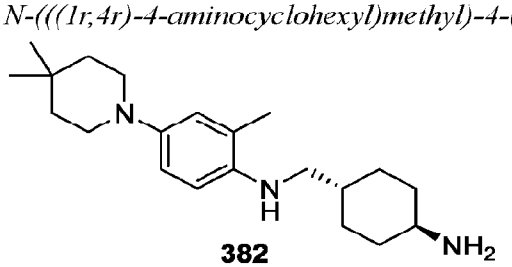


381

The title compound **381** (22 mg) was prepared in a yield of 43.2% as a white powder from 4-(4,4-dimethylpiperidin-1-yl)-2-methylaniline (40 mg, 0.18 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (45 mg, 0.24 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 3H), 6.55 (s, 2H), 3.04 (d, J = 63.1 Hz, 5H), 2.23 – 1.88 (m, 6H), 1.75 (d, J = 41.8 Hz, 4H), 1.45 (s, 5H), 0.96 (d, J = 4.2 Hz, 6H). Mass (m/z): 316.4 $[M+H]^+$.

Compound 382

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(4,4-dimethylpiperidin-1-yl)-2-methylaniline



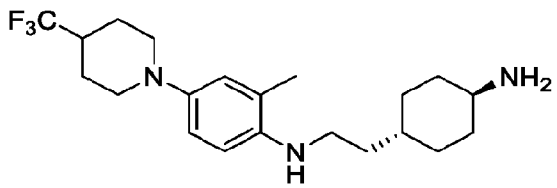
382

CA 03227251 2024-1-26

The title compound **382** (38 mg) was prepared in a yield of 64.2% as a white powder from 4-(4,4-dimethylpiperidin-1-yl)-2-methylaniline (55 mg, 0.23 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (64 mg, 0.31 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 3H), 7.38 – 7.02 (m, 1H), 6.61 (d, J = 48.8 Hz, 2H), 3.04 (d, J = 63.1 Hz, 5H), 2.04 (dd, J = 43.5, 19.9 Hz, 6H), 1.75 (d, J = 41.8 Hz, 4H), 1.56 – 1.35 (m, 5H), 1.28 (s, 1H), 0.96 (d, J – 4.2 Hz, 6H). Mass (m/z): 330.5 $[M+H]^+$.

Compound 383

N-(2-((1r,4r)-4-aminocyclohexyl)ethyl)-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline

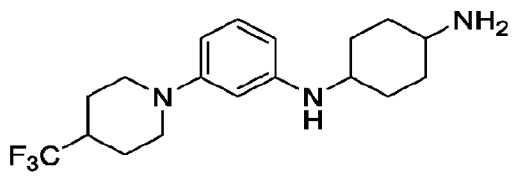


383

The title compound **383** (18 mg) was prepared in a yield of 23.5% as a white powder from 2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (70 mg, 0.32 mmol) and tert-butyl ((1r,4r)-4-(2-oxoethyl)cyclohexyl)carbamate (95 mg, 0.46 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 3H), 6.70 (s, 1H), 6.65 (d, J = 8.8 Hz, 1H), 6.42 (d, J = 8.6 Hz, 1H), 4.27 (s, 1H), 3.46 (t, J = 12.0 Hz, 2H), 3.01 (s, 2H), 2.93 (s, 1H), 2.37 (d, J = 10.7 Hz, 1H), 2.04 (s, 3H), 1.93 (d, J = 12.3 Hz, 3H), 1.83 (t, J = 16.9 Hz, 4H), 1.56 (d, J = 12.1 Hz, 2H), 1.47 (d, J = 7.0 Hz, 2H), 1.36 – 1.25 (m, 3H), 1.07 – 0.92 (m, 2H). Mass (m/z): 384.3 $[M+H]^+$.

Compound 384

N1-(3-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



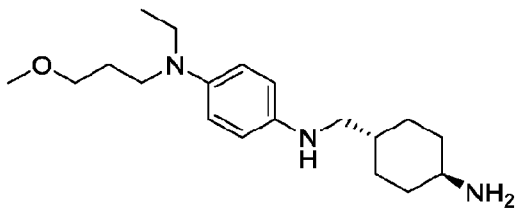
384

The title compound **384** (64 mg, 55.8%) as a yellow solid was prepared from tert-butyl (4-((3-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 12.0, 1H), 7.13 – 7.02 (m, 1H), 6.59 – 6.32 (m, 2H), 3.81 – 3.62 (m, 2H), 3.46 (s, 1H), 3.25 (s, 1H), 3.19 – 3.08 (m, 1H), 2.95 (d, J = 4.0, 2H), 2.63 – 2.54 (m, 2H), 2.05 – 1.85 (m, 4H), 1.85 – 1.51 (m, 6H), 1.33 (m, 2H). Mass (m/z): 341.9 $[M+H]^+$.

Compound 385

N1-(((1r,4r)-4-aminocyclohexyl)methyl)-N4-ethyl-N4-(3-methoxypropyl)benzene-1,4-diamine

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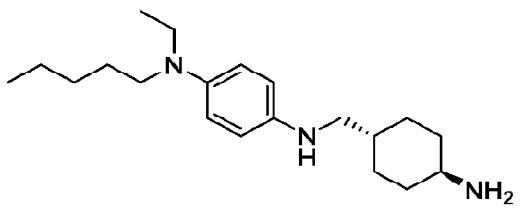


385

The title compound **385** (24.8 mg) was prepared in a total yield of 47.9% as a purple solid from tert-butyl ((1r,4r)-4-(((4-(ethyl(3-methoxypropyl)amino)phenyl)amino)methyl)cyclohexyl)carbamate (68 mg, 0.162 mmol), TFA (1 mL) and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.88 – 6.39 (m, 4H), 3.23 – 3.20 (m, 3H), 3.18 (d, J = 2.4 Hz, 2H), 2.82 (q, J = 7.2 Hz, 3H), 2.00 – 1.90 (m, 3H), 1.86 – 1.77 (m, 3H), 1.69 – 1.59 (m, 4H), 1.30 (t, J = 12.0 Hz, 2H), 1.16 (t, J = 7.2 Hz, 2H), 1.08 – 0.93 (m, 7H). Mass (m/z): 320.3 $[M+H]^+$.

Compound 386

N1-(((1r,4r)-4-aminocyclohexyl)methyl)-N4-ethyl-N4-pentylbenzene-1,4-diamine

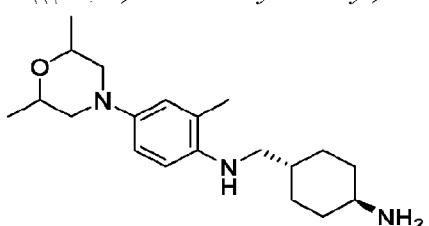


386

The title compound **386** (41.8 mg) was prepared in a total yield of 71.5% as a purple solid from tert-butyl ((1r,4r)-4-(((4-(ethyl(pentyl)amino)phenyl)amino)methyl)cyclohexyl)carbamate (77 mg, 0.185 mmol), TFA(1 mL), and DCM (10 mL) according to the procedure for **1-2**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.70 – 6.47 (m, 4H), 3.25 – 3.17 (m, 3H), 2.92 – 2.73 (m, 4H), 1.94 (d, J = 12.4 Hz, 3H), 1.83 (d, J = 12.8 Hz, 2H), 1.49 – 1.38 (m, 4H), 1.28 – 1.25 (m, 3H), 0.97 – 0.91 (m, 4H), 0.86 – 0.75 (m, 8H). Mass (m/z): 318.3 $[M+H]^+$.

Compound 387

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2-methylaniline



387

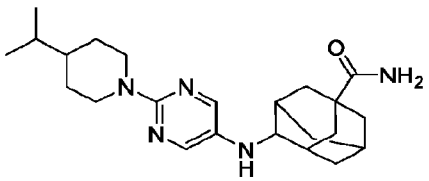
The title compound **387** (38.5 mg) was prepared in a total yield of 57.0% as a purple solid from tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)-2-methylphenyl)amino)methyl)cyclohexyl)carbamate (88 mg, 0.204 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 3H), 6.63 (d, J = 2.8 Hz, 1H), 6.57 (dd, J = 8.8, 2.8 Hz,

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1H), 6.35 (d, J = 8.8 Hz, 1H), 4.33 (s, 1H), 3.62 (dqd, J = 12.4, 6.0, 2.0 Hz, 2H), 3.23 (dt, J = 10.8, 2.0 Hz, 2H), 2.85 (s, 1H), 2.83 – 2.77 (m, 2H), 2.09 – 2.04 (m, 2H), 2.01 (s, 3H), 1.96 (dt, J = 13.2, 3.2 Hz, 2H), 1.82 (dd, J = 13.6, 3.6 Hz, 2H), 1.55 – 1.43 (m, 1H), 1.30 (qd, J = 12.4, 3.2 Hz, 2H), 1.07 (d, J = 6.0 Hz, 6H), 1.00 – 0.88 (m, 2H). Mass (m/z): 332.3 $[M+H]^+$.

Compound 388

4-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)adamantane-1-carboxamide

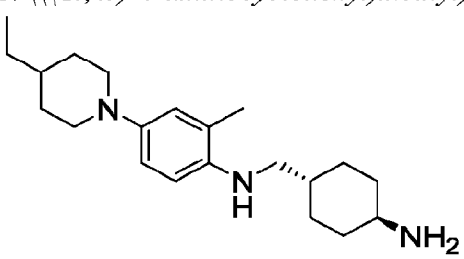


388

The title compound **388** (34 mg) was prepared in a yield of 47.8% as a white powder from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (70 mg, 0.27 mmol) and 4-oxoadamantane-1-carboxamide (73 mg, 0.34 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 4.0 Hz, 2H), 6.97 (s, 1H), 6.72 (s, 1H), 5.00 (dd, J = 8.2, 4.6 Hz, 1H), 4.47 (dt, J = 12.9, 2.8 Hz, 2H), 2.61 (td, J = 12.8, 2.4 Hz, 2H), 2.03 – 1.89 (m, 4H), 1.89 – 1.79 (m, 4H), 1.72 (dd, J = 12.1, 4.0 Hz, 3H), 1.67 – 1.60 (m, 2H), 1.43 – 1.33 (m, 3H), 1.18 (ddd, J = 12.1, 6.0, 3.0 Hz, 1H), 1.07 (qd, J = 12.3, 4.0 Hz, 2H), 0.85 (d, J = 6.7 Hz, 6H). Mass (m/z): 398.4 $[M+H]^+$.

Compound 389

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(4-ethylpiperidin-1-yl)-2-methylaniline



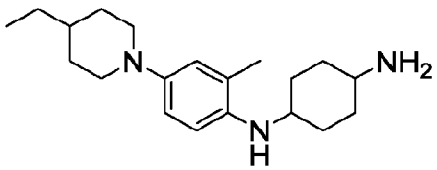
389

The title compound **389** (18 mg) was prepared in a yield of 28.4% as a pale rosy powder from 4-(4-ethylpiperidin-1-yl)-2-methylaniline (70 mg, 0.23 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (83 mg, 0.32 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 3H), 6.47 (s, 1H), 2.92 (s, 4H), 2.08 (s, 3H), 1.99 (d, J = 22.8 Hz, 3H), 1.85 (s, 4H), 1.55 (s, 2H), 1.29 (q, J = 14.1, 13.6 Hz, 5H), 1.00 (d, J = 13.2 Hz, 2H), 0.90 (t, J = 7.3 Hz, 4H). Mass (m/z): 330.3 $[M+H]^+$.

Compound 390

N1-(4-(4-ethylpiperidin-1-yl)-2-methylphenyl)cyclohexane-1,4-diamine

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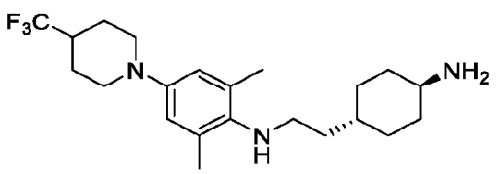


390

The title compound **390** (29 mg) was prepared in a yield of 54.6% as a pale rosy powder from 4-(4-ethylpiperidin-1-yl)-2-methylaniline (70 mg, 0.23 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (75 mg, 0.32 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 3H), 6.65 (s, 2H), 6.48 (s, 1H), 3.70 (s, 1H), 3.48 (s, 1H), 3.36 (d, J = 11.3 Hz, 2H), 3.13 (d, J = 22.8 Hz, 1H), 2.95 (s, 1H), 2.11 (s, 1H), 2.01 (d, J = 19.5 Hz, 3H), 1.75 (d, J = 32.9 Hz, 6H), 1.44 (q, J = 12.1 Hz, 1H), 1.25 (dd, J = 12.3, 5.4 Hz, 6H), 0.88 (t, J = 7.2 Hz, 3H). Mass (m/z): 316.4 $[M+H]^+$.

Compound 391

N-(2-((1r,4r)-4-aminocyclohexyl)ethyl)-2,6-dimethyl-4-(4-(trifluoromethyl)piperidin-1-yl)anilin e

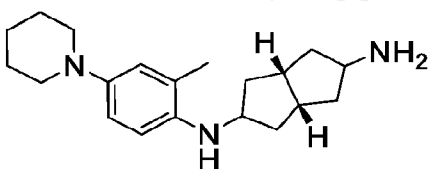


391

The title compound **391** (11 mg) was prepared in a yield of 17.5% as a pale yellow powder from 2,6-dimethyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (100 mg, 0.35 mmol) and tert-butyl ((1r,4r)-4-(2-oxoethyl)cyclohexyl)carbamate (83 mg, 0.43 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (s, 3H), 6.56 (s, 2H), 4.09 (d, J = 5.2 Hz, 1H), 3.58 (d, J = 12.4 Hz, 2H), 3.16 (d, J = 5.2 Hz, 2H), 2.75 (d, J = 6.5 Hz, 2H), 2.16 (s, 6H), 1.95 – 1.80 (m, 5H), 1.75 (d, J = 12.9 Hz, 2H), 1.52 (d, J = 9.1 Hz, 3H), 1.37 (s, 2H), 0.96 (d, J = 12.6 Hz, 2H). Mass (m/z): 398.5 $[M+H]^+$.

Compound 392

(3aR,6aS)-N2-(2-methyl-4-(piperidin-1-yl)phenyl)octahydropentalene-2,5-diamine



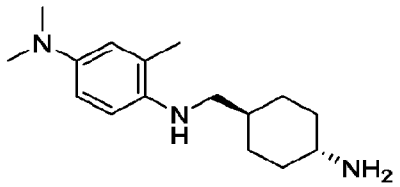
392

The title compound **392** (32 mg) was prepared in a three-step total yield of 15.3% as a white solid with 1:1 mixture by ^{1}H NMR from 2-methyl-4-(piperidin-1-yl)aniline (100 mg, 0.63 mmol) and (3as,6as)-tetrahydropentalene-2,5(1H,3H)-dione (278 mg, 2.0 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 3H), 7.65 – 7.21 (m, 3H), 6.62 (s, 1H), 3.83 (d, J = 68.0 Hz, 2H), 2.39 (s, 2H), 2.31 – 2.16 (m, 3H), 2.11 (s, 4H), 1.77 (s, 4H), 1.58 (s, 2H), 1.46 (q, J = 11.9, 11.1 Hz, 3H), 1.36 (s, 2H). Mass (m/z): 314.6 $[M+H]^+$.

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Compound 393

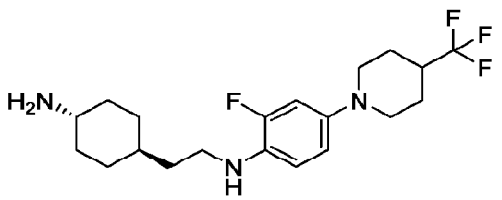
N^1-(((1r,4r)-4-aminocyclohexyl)methyl)-N4,N4,2-trimethylbenzene-1,4-diamine



The title compound **393** (15.2 mg) was prepared in a total yield of 50.2% as a Purple solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (s, 3H), 7.27 – 7.12 (m, 2H), 6.64 – 6.48 (m, 1H), 3.60 – 3.50 (m, 2H), 3.38 (s, 6H), 2.96 – 2.93 (m, 1H), 2.12 (s, 3H), 1.99 – 1.85 (m, 4H), 1.63 – 1.51 (m, 1H), 1.32 – 1.19 (m, 4H). Mass (m/z): 262.2 $[M+H]^+$.

Compound 394

N-(2-((1r,4r)-4-aminocyclohexyl)ethyl)-2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)aniline

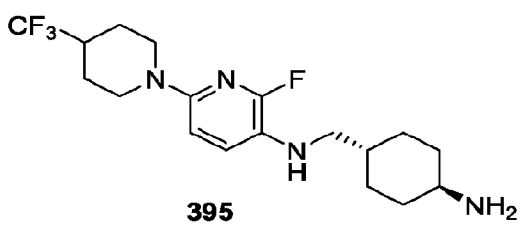


394

The desired product **394** as a white solid (19.7 mg, 26.6%) was prepared from tert-butyl ((1r,4r)-4-(2-((2-fluoro-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)ethyl)cyclohexyl)carbamate according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (s, 3H), 6.75 – 6.66 (m, 1H), 6.61 – 6.50 (m, 2H), 4.73 (s, 1H), 3.54 – 3.42 (m, 2H), 2.98 (q, J = 6.8 Hz, 2H), 2.94 – 2.79 (m, 1H), 2.41 – 2.32 (m, 1H), 1.94 – 1.71 (m, 6H), 1.51 (qd, J = 12.5, 4.1 Hz, 2H), 1.40 (q, J = 7.0 Hz, 2H), 1.24 (q, J = 13.0, 11.9 Hz, 4H), 1.01 – 0.86 (m, 2H). Mass (m/z): 388.2 $[M+H]^+$.

Compound 395

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-fluoro-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine



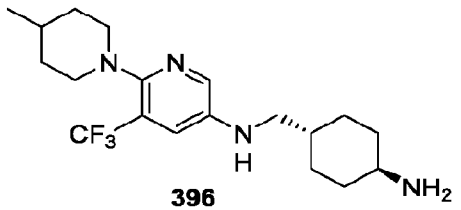
395

The title compound **395** (9.5 mg, 8.5%) as a yellow solid was prepared from tert-butyl ((1r,4r)-4-(((2-fluoro-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)amino)methyl)cyclohexyl)carbamate (140 mg, 0.3 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.17 – 7.01 (m, 1H), 6.50 (d, J=7.6, 1H), 4.04 – 4.01 (m, 2H), 2.99 – 2.89 (m, 3H), 2.68 – 2.61 (m, 1H), 2.29 – 2.63 (m, 1H), 1.98 – 1.81 (m, 6H), 1.52 – 1.44 (m, 3H), 1.34 – 1.19 (m, 2H), 1.09 – 0.99 (m, 2H). Mass (m/z): 375.2$[M+H]^+$.

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Compound 396

N-(((1r,4r)-4-aminocyclohexyl)methyl)-6-(4-methylpiperidin-1-yl)-5-(trifluoromethyl)pyridin-3-amine

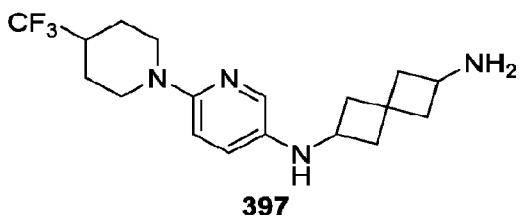


396

The title compound 396 (28.1 mg, 17.8%) To a solution of tert-butyl ((1r,4r)-4-(((6-(4-methylpiperidin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)amino)methyl)cyclohexyl)carbamate (200 mg, 0.52 mmol), 1,4-dioxane (2 mL) and HCl /1,4-Dioxane (5 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 2.8 Hz, 1H), 7.14 (d, J = 2.8 Hz, 1H), 6.09 (t, J = 5.6 Hz, 1H), 2.91 – 2.86 (m, 4H), 2.75 (m, 3H), 1.86 (br, 4H), 1.64 (d, J = 10.4 Hz, 2H), 1.49 – 1.41 (m, 2H), 1.26 – 1.16 (m, 4H), 1.06 – 0.98 (m, 2H), 0.94 (d, J = 6.4 Hz, 3H). Mass (m/z): 371.3 $[M+H]^+$.

Compound 397

N2-(6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine

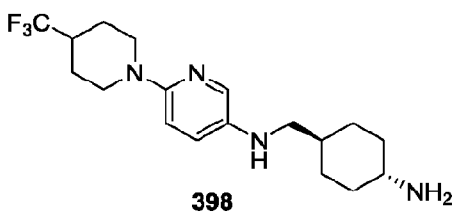


397

The title compound **397** (42.9 mg) was prepared in a yield of 47.4% as a white powder from 6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (70 mg, 0.22 mmol) and tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (77 mg, 0.31 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 – 8.14 (m, 3H), 7.46 (d, J = 2.9 Hz, 1H), 6.97 (d, J = 9.6 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 4.11 (d, J = 12.8 Hz, 2H), 3.66 (p, J = 7.4 Hz, 1H), 3.54 (s, 1H), 3.34 (s, 1H), 2.79 – 2.65 (m, 2H), 2.47 (dd, J = 5.5, 3.2 Hz, 1H), 2.42 – 2.29 (m, 2H), 2.24 – 2.13 (m, 3H), 1.83 (q, J = 8.2, 7.8 Hz, 4H), 1.45 (qd, J = 12.5, 4.1 Hz, 2H). Mass (m/z): 355.2 $[M+H]^+$.

Compound 398

N-(((1r,4r)-4-aminocyclohexyl)methyl)-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine



398

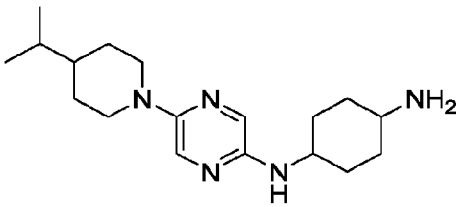
The title compound **398** (50 mg) was prepared in a yield of 56.8% as a white powder from 6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine (80 mg, 0.29 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (85 mg, 0.37 mmol) according to the procedure for **20**.

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^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 – 7.84 (m, 3H), 7.52 (s, 1H), 7.02 (s, 1H), 6.79 (d, J = 9.0 Hz, 1H), 5.31 (s, 1H), 4.08 (d, J = 12.8 Hz, 2H), 2.92 (d, J = 4.9 Hz, 1H), 2.80 (d, J = 6.6 Hz, 2H), 2.69 (t, J = 12.1 Hz, 2H), 1.99 – 1.89 (m, 2H), 1.89 – 1.76 (m, 4H), 1.44 (qd, J = 12.6, 4.2 Hz, 3H), 1.27 (dt, J = 14.9, 11.2 Hz, 2H), 1.09 – 0.90 (m, 2H). Mass (m/z): 357.5 $[M+H]^+$.

Compound 399

N1-(5-(4-isopropylpiperidin-1-yl)pyrazin-2-yl)cyclohexane-1,4-diamine

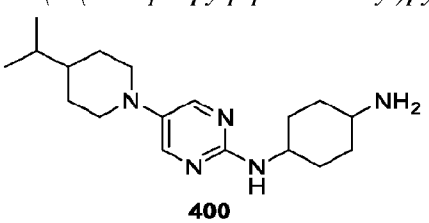


399

The title compound **399** (29.0 mg) was prepared in a total yield of 29.3% as a yellow solid from tert-butyl (4-((5-(4-isopropylpiperidin-1-yl)pyrazin-2-yl)amino)cyclohexyl)carbamate (130 mg, 0.312 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **1-2**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 – 7.54 (m, 2H), 6.11 (dd, J = 6.8, 3.2 Hz, 1H), 3.89 (d, J = 12.0 Hz, 2H), 2.89 (2, J = 13.0 Hz, 1H), 2.50 (d, J = 1.6 Hz, 2H), 1.95 (t, J = 12.0 Hz, 4H), 1.70 (d, J = 6.4 Hz, 2H), 1.64 (d, J = 12.0 Hz, 3H), 1.55 (s, 1H), 1.46 – 1.35 (m, 4H), 1.16 – 1.11 (m, 3H), 0.83 (s, 3H), 0.82 (s, 3H). Mass (m/z): 318.3 $[M+H]^+$.

Compound 400

N1-(5-(4-isopropylpiperidin-1-yl)pyrimidin-2-yl)cyclohexane-1,4-diamine



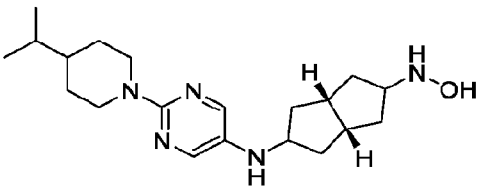
400

The title compound **400** (11.2 mg) was prepared in a total yield of 30.7% as a white solid from tert-butyl (4-((5-(4-isopropylpiperidin-1-yl)pyrimidin-2-yl)amino)cyclohexyl)carbamate (48 mg, 0.115 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 2H), 8.04 (d, J = 8.4 Hz, 2H), 3.36 (d, J = 9.6 Hz, 2H), 2.50 (s, 2H), 2.41 (s, 2H), 1.90 (d, J = 18.0 Hz, 3H), 1.71 – 1.49 (m, 4H), 1.40 (dd, J = 13.2, 7.2 Hz, 3H), 1.26 (td, J = 12.4, 3.6 Hz, 4H), 1.03 (s, 1H), 0.84 (d, J = 6.8 Hz, 6H). Mass (m/z): 318.3 $[M+H]^+$.

Compound 401

N-((3aR,6aS)-5-(hydroxyamino)octahydropentalen-2-yl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine

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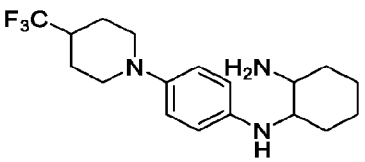


401

The title compound **401** (6.9 mg) was prepared in a total yield of 38.3 % as a yellow solid according to the procedure for compound **1**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (s, 2H), 4.55 – 4.46 (m, 2H), 2.78 – 2.67 (m, 2H), 2.62 (m, 1H), 2.52 (m, 1H), 2.36 – 2.13 (m, 3H), 1.85 (m, 1H), 1.77 – 1.68 (m, 3H), 1.61 (m, 1H), 1.48 – 1.31 (m, 4H), 1.27 – 1.13 (m, 4H), 0.91 (d, J = 6.4 Hz, 6H). Mass (m/z): 360.3 $[M+H]^+$.

Compound 402

N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,2-diamine

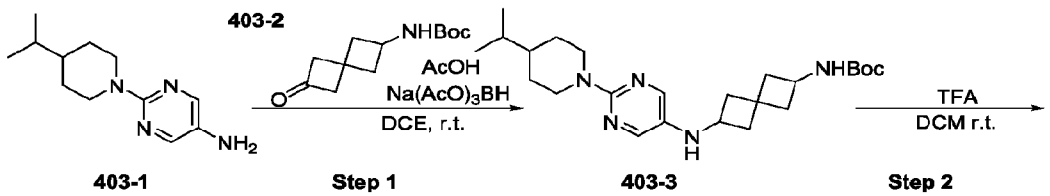


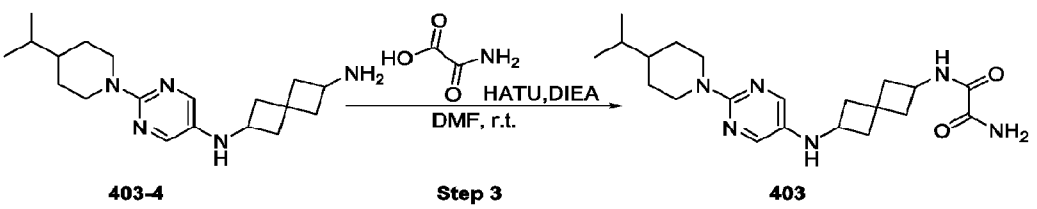
402

The title compound **402** (24.2 mg) was prepared in a total yield of 70.7 % as a rosy brown solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.91 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 3.57 – 3.46 (m, 2H), 3.21 (m, 1H), 2.95 (m, 1H), 2.68 – 2.57 (m, 2H), 2.25 (m, 1H), 2.17 – 2.06 (m, 2H), 1.98 – 1.91 (m, 2H), 1.87 – 1.63 (m, 4H), 1.56 – 1.24 (m, 4H). Mass (m/z): 342.2 $[M+H]^+$.

Compound 403

N1-(6-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptan-2-yl)oxalamide





Step 1. Preparation of tert-butyl (6-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptan-2-yl)carbamate **(403-3)**

To a solution of 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (220 mg, 1.0 mmol),

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tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (225 mg, 1.0 mmol) in DCE (15 mL) was added a drop of AcOH. Then the mixture stirred for 30 mins at r.t. $Na(AcO)_3BH$ (424 mg, 2.0 mmol) was added. The reaction was stirred overnight at rt. The reaction mixture was washed with water (20 mL x 3), dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (EA/PE=1/2) to afford the desired product (235 mg, 54.8%) as a yellow solid. Mass (m/z): 430.3 $[M+H]^+$.

Step 2. Preparation of N^2-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)spiro[3.3]heptane-2,6-diamine **(403-4)**

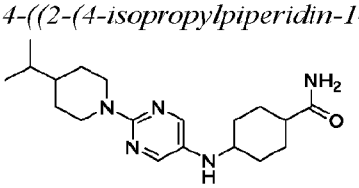
To a solution of tert-butyl (6-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptan-2-yl)carbamate (235 mg, 0.58 mmol) in DCM (3.0 mL) was added TFA (3.0 mL). Then the solution was stirred for 30 mins at r.t. and concentrated. 5 mL of water was added. The pH of the filtration was adjusted to 8-9 with sodium carbonate solution. Then the mixture was extracted by DCM (5 mL x 3). The combined organic layers were washed with water (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by prep-TLC (MeOH/DCM=1/5) to afford the desired product (176 mg, 92.2%) as a yellow solid. Mass (m/z): 330.2 $[M+H]^+$.

Step 3. Preparation of N^1-(6-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptan-2-yl)oxalamide **(403)**

To a solution of 2-amino-2-oxoacetic acid (8.9 mg, 0.1 mmol) and HATU (38.0 mg, 0.1 mmol) in DMF (1.0 ml) was added DIEA (38.7 mg, 0.3 mmol). Followed by the addition of N^2-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)spiro[3.3]heptane-2,6-diamine (33.0 mg, 0.1 mmol) then the reaction mixture was stirred for 10 hours at r.t. 5.0 mL of water was added. Then the mixture was extracted by DCM (5.0 mL x 3). The combined organic layers were washed with water (5.0 mL x 3), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by prep-TLC (MeOH/DCM=1/10) to give the desired products **403** (10.9 mg, 18.6%) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 8.3 Hz, 1H), 8.01 (s, 1H), 7.79 (s, 2H), 7.74 (s, 1H), 5.24 (d, J = 7.4 Hz, 1H), 4.51 – 4.45 (m, 2H), 4.16 – 4.05 (m, 1H), 3.66 – 3.59 (m, 1H), 2.66 – 2.59 (m, 2H), 2.35 – 2.10 (m, 6H), 1.84 – 1.72 (m, 2H), 1.67 – 1.60 (m, 2H), 1.46 – 1.36 (m, 1H), 1.22 – 1.17 (m, 1H), 1.12 – 1.01 (m, 2H), 0.85 (d, J = 6.8 Hz, 6H). Mass (m/z): 401.2 $[M+H]^+$.

Compound 404

4-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)cyclohexane-1-carboxamide



404

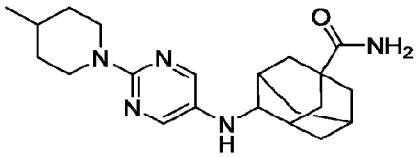
The title compound **404** (32.1 mg) was prepared in a yield of 34.7% as a white powder from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (70 mg, 0.23 mmol) and 4-oxocyclohexane-1-carboxamide (73 mg, 0.35 mmol) according to the procedure for **20**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.89 (s, 1H), 7.17 (d, J = 13.3 Hz, 1H), 6.68 (d, J =

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11.6 Hz, 1H), 4.93 (d, J = 8.0 Hz, 1H), 4.53 – 4.42 (m, 2H), 2.62 (td, J = 12.5, 2.4 Hz, 2H), 2.17 (dq, J = 9.3, 5.2, 4.5 Hz, 1H), 2.00 – 1.94 (m, 1H), 1.77 (dd, J = 12.5, 9.3 Hz, 2H), 1.64 (d, J = 12.6 Hz, 3H), 1.59 – 1.44 (m, 3H), 1.40 (dt, J = 13.3, 6.6 Hz, 1H), 1.25 – 1.17 (m, 1H), 1.15 – 1.02 (m, 3H), 0.86 (d, J = 6.8 Hz, 6H). Mass (m/z): 346.5 $[M+H]^+$.

Compound 405

4-((2-(4-methylpiperidin-1-yl)pyrimidin-5-yl)amino)adamantane-1-carboxamide

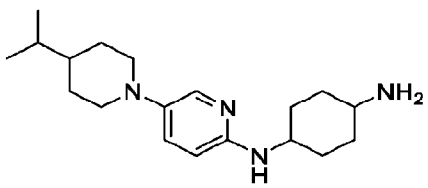


405

The title compound **405** (6.5 mg) was prepared in a yield of 13.5% as a white powder from 2-(4-methylpiperidin-1-yl)pyrimidin-5-amine (40 mg, 0.17 mmol) and 4-oxoadamantane-1-carboxamide (46 mg, 0.24 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 4.0 Hz, 2H), 6.93 (s, 1H), 6.68 (s, 1H), 4.97 (d, J = 8.0 Hz, 1H), 4.36 (d, J = 12.9 Hz, 2H), 2.73 – 2.61 (m, 3H), 1.94 (dd, J = 26.9, 14.2 Hz, 5H), 1.82 (d, J = 13.7 Hz, 4H), 1.71 (s, 2H), 1.57 (d, J = 13.2 Hz, 2H), 1.34 (d, J = 12.3 Hz, 2H), 1.04 – 0.93 (m, 2H), 0.87 (d, J = 6.4 Hz, 3H). Mass (m/z): 370.3 $[M+H]^+$.

Compound 406

N^1-(5-(4-isopropylpiperidin-1-yl)pyridin-2-yl)cyclohexane-1,4-diamine

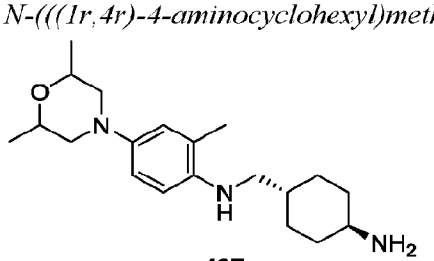


406

The title compound **406** (21.1 mg, 18.5%) as a light brown solid was prepared from tert-butyl (4-((5-(4-isopropylpiperidin-1-yl)pyridin-2-yl)amino)cyclohexyl)carbamate (150 mg, 0.36 mmol), DCM (2 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (t, J = 2.8 Hz, 1H), 7.10 (dt, J = 9.0, 3.0 Hz, 1H), 6.44 – 6.29 (m, 1H), 5.73 (dd, J = 17.8, 7.6 Hz, 1H), 3.74 – 3.30 (m, 1H), 2.43 – 2.35 (m, 2H), 1.91 – 1.56 (m, 7H), 1.54 – 1.34 (m, 3H), 1.32 – 1.17 (m, 3H), 1.17 – 0.97 (m, 4H), 0.84 (d, J = 6.8 Hz, 6H). MS (m/z): 317.3$[M+H]^+$.

Compound 407

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2-methylaniline



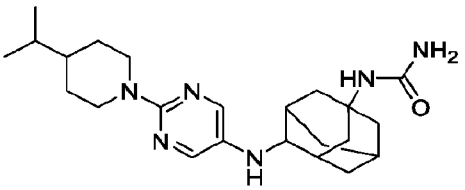
407

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The title compound **407** (61.2 mg) was prepared in a total yield of 65.3% as a white solid from tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)-2-methylphenyl)amino)methyl)cyclohexyl)carbamate (122 mg, 0.283 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 – 8.15 (m, 3H), 6.74 (d, J = 8.4 Hz, 1H), 6.36 (s, 2H), 3.70 – 3.59 (m, 2H), 2.85 (s, 1H), 2.72 (dd, J – 22.0, 8.8 Hz, 4H), 2.19 (t, J – 10.8 Hz, 2H), 2.11 (s, 3H), 1.98 – 1.90 (m, 2H), 1.81 (d, J = 12.8 Hz, 2H), 1.41 (s, 1H), 1.35 – 1.23 (m, 2H), 1.04 (d, J = 6.4 Hz, 6H), 1.00 – 0.88 (m, 2H). Mass (m/z): 332.3 $[M+H]^+$.

Compound 408

1-(4-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)adamantan-1-yl)urea

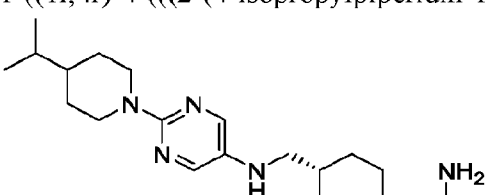


408

The title compound **408** (6.5 mg) was prepared in a yield of 13.5% as a white powder from N^4-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)adamantane-1,4-diamine (46 mg, 0.18 mmol) and phenyl carbamate (24 mg, 0.17 mmol) according to the procedure for **243**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 4.3 Hz, 2H), 5.89 (s, 1H), 5.72 (s, 1H), 4.48 (d, J = 12.9 Hz, 2H), 2.62 (td, J = 12.8, 2.2 Hz, 2H), 2.40 (d, J = 3.8 Hz, 3H), 2.20 – 2.09 (m, 6H), 2.11 – 2.04 (m, 4H), 1.68 – 1.59 (m, 3H), 1.47 – 1.31 (m, 2H), 1.08 (qd, J = 12.2, 4.1 Hz, 2H), 0.86 (d, J = 6.7 Hz, 6H). Mass (m/z): 413.5 $[M+H]^+$.

Compound 409

1-((1r,4r)-4-(((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)methyl)cyclohexyl)urea



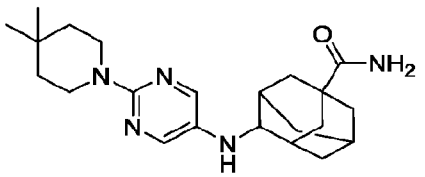
409

The title compound **409** (6.9 mg) was prepared in a yield of 14.2% as a white powder from N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (51 mg, 0.19 mmol) and phenyl carbamate (25 mg, 0.17 mmol) according to the procedure for **243**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 2H), 5.76 (d, J = 8.0 Hz, 1H), 5.06 (t, J = 6.1 Hz, 1H), 4.46 (d, J = 13.2 Hz, 2H), 3.23 (s, 1H), 2.78 (t, J = 6.3 Hz, 2H), 2.61 (t, J = 12.1 Hz, 2H), 1.78 (d, J = 11.6 Hz, 4H), 1.63 (d, J = 11.9 Hz, 2H), 1.39 (dd, J = 13.0, 6.7 Hz, 2H), 1.16 (s, 1H), 1.08 (td, J = 12.3, 4.0 Hz, 2H), 0.99 (q, J = 11.8, 11.0 Hz, 4H), 0.84 (d, J = 6.8 Hz, 6H). Mass (m/z): 375.4 $[M+H]^+$

Compound 410

4-((2-(4,4-dimethylpiperidin-1-yl)pyrimidin-5-yl)amino)adamantane-1-carboxamide

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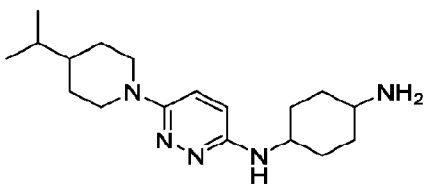


410

The title compound **410** (8.2 mg) was prepared in a yield of 12.09% as a white powder from 2-(4,4-dimethylpiperidin-1-yl)pyrimidin-5-amine (68 mg, 0.18 mmol) and 4-oxoadamantane-1-carboxamide (41 mg, 0.25 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 4.1 Hz, 2H), 6.98 (s, 1H), 6.73 (s, 1H), 5.01 (d, J = 7.8 Hz, 1H), 3.60 – 3.50 (m, 4H), 2.89 (s, 2H), 2.73 (s, 1H), 2.03 – 1.91 (m, 2H), 1.89 – 1.79 (m, 3H), 1.75 (d, J = 2.9 Hz, 3H), 1.38 (d, J = 12.4 Hz, 2H), 1.33 – 1.25 (m, 4H), 0.94 (s, 6H). Mass (m/z): 384.2 $[M+H]^+$.

Compound 411

N^1-(6-(4-isopropylpiperidin-1-yl)pyridazin-3-yl)cyclohexane-1,4-diamine

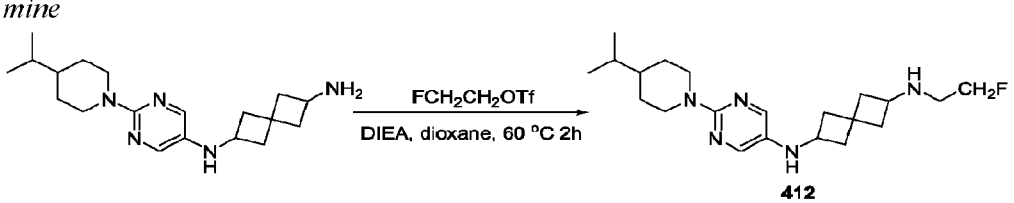


411

The title compound **411** (8.4 mg, 17.5%) as an off-white solid was prepared from tert-butyl (4-((6-(4-isopropylpiperidin-1-yl)pyridazin-3-yl)amino)cyclohexyl)carbamate (60 mg, 0.14 mmol), DCM (2 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.08 (dd, J = 9.7, 2.3 Hz, 1H), 6.72 (dd, J = 39.5, 9.6 Hz, 1H), 5.93 (dd, J = 12.3, 7.2 Hz, 1H), 4.00 (d, J = 12.3 Hz, 2H), 3.90 – 3.51 (m, 1H), 3.04 – 2.72 (m, 1H), 2.64 – 2.57 (m, 2H), 2.00 – 1.96 (m, 1H), 1.80 – 1.76 (m, 1H), 1.75 – 1.61 (m, 3H), 1.61 – 1.48 (m, 1H), 1.46 – 1.37 (m, 2H), 1.28 – 1.05 (m, 6H), 0.87 (d, J = 6.8 Hz, 6H). MS (m/z): 318.3$[M+H]^+$.

Compound 412

N2-(2-fluoroethyl)-N6-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)spiro[3.3]heptane-2,6-diamine



412

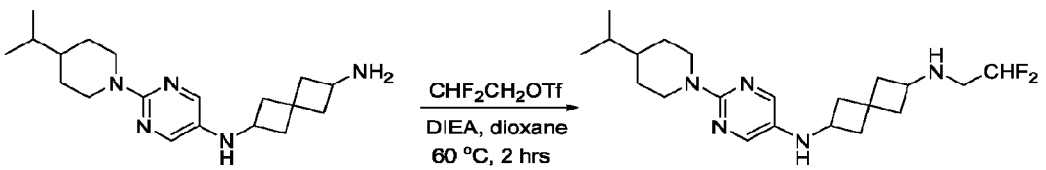
TEA (92mg, 0.91 mmol), 2-fluoroethyl trifluoromethanesulfonate (119 mg, 0.61 mmol) was added to a solution of 2-N-[2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl]spiro[3.3]heptane-2,6-diamine hydrochloride (100mg, 0.31 mmol) in dioxane (20 mL), the mixture was heated to 60 °C for 2 hrs, then the mixture was removed in vacuo. The residue was purified by prep-HPLC (column-Gemini -C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 5%-20%) to afford the desired product **412** (6.7 mg, 5.8%) as yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (s, 2H), 4.73

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– 4.70 (m, 1H), 4.62 – 4.57 (m, 1H), 4.47 (d, J = 13.2 Hz, 2H), 3.69 (dt, J = 11.8, 7.8 Hz, 2H), 3.22 (s, 1H), 3.18 – 3.14 (m, 1H), 2.71 (dd, J = 18.0, 7.2 Hz, 2H), 2.60 – 2.51 (m, 2H), 2.45 – 2.33 (m, 2H), 2.23 – 2.14 (m, 2H), 1.97 – 1.89 (m, 2H), 1.70 (d, J = 11.9 Hz, 2H), 1.45 – 1.37 (m, 1H), 1.26 – 1.11 (m, 3H), 0.88 (d, J = 6.8 Hz, 6H). MS (m/z): 376.3[M+H]$^+$

Compound 413

N2-(2,2-difluoroethyl)-N6-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)spiro[3.3]heptane-2,6-diamine

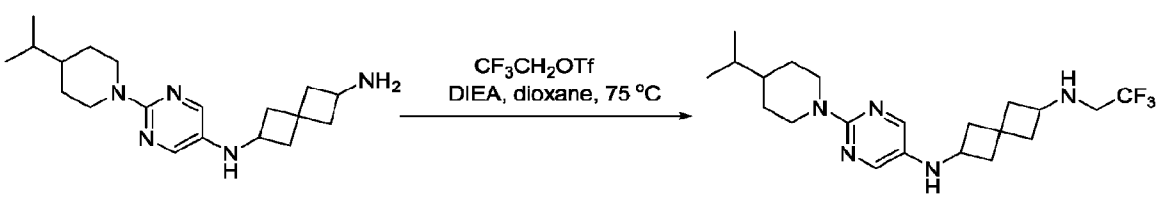


413

DIEA(118 mg, 0.91 mmol), 2,2-Difluoroethyl trifluoromethanesulfonate (130 mg, 0.61 mmol), was added to a solution of 2-N-[2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl]spiro[3.3]heptane-2,6-diamine hydrochloride (100 mg, 0.31 mmol) in MeOH (20 mL), the mixture was stirred at rt for 2 hrs, then the mixture was removed in vacuo. The residue was purified by prep-HPLC (column-Gemini -C18 150 x 21.2 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 5%-20%) to afford the desired product as yellow solid (8.7 mg, 7.2%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (s, 2H), 6.13 (dd, J = 55.6, 52.9 Hz, 1H), 4.47 (d, J = 13.2 Hz, 2H), 3.73 – 3.55 (m, 2H), 3.28 – 3.19 (m, 2H), 2.71 (dd, J = 18.0, 7.2 Hz, 2H), 2.57 – 2.47 (m, 2H), 2.43 – 2.30 (m, 2H), 2.17 – 2.08 (m, 2H), 1.91 (dt, J = 11.2, 8.3 Hz, 2H), 1.70 (d, J = 11.8 Hz, 2H), 1.44 – 1.37 (m, 1H), 1.18 (m, 3H), 0.88 (d, J = 6.8 Hz, 6H). MS (m/z): 394.2[M+H]$^+$

Compound 414

N2-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)-N6-(2,2,2-trifluoroethyl)spiro[3.3]heptane-2,6-diamine



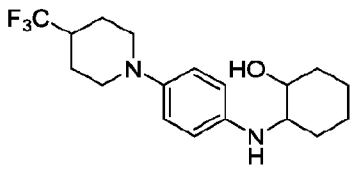
414

DIEA (106 mg, 0.82 mmol), 2,2,2-trifluoroethyl triflate (127 mg, 0.55 mmol), was added to a solution of 2-N-[2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl]spiro[3.3]heptane-2,6-diamine hydrochloride (100 mg, 0.27 mmol), in dioxane (20 mL), and the mixture was stirred at rt for 2 hrs, and then the mixture was removed in vacuo. The residue was purified by prep-HPLC (column-Gemini-C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 5%-20%) to afford the desired product (3.3 mg, 2.9%) as yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 0.7 Hz, 2H), 4.49 – 4.44 (m, 2H), 3.66 (t, J = 7.5 Hz, 1H), 3.21 (d, J = 7.5 Hz, 1H), 3.09 (d, J = 9.9 Hz, 2H), 2.74 – 2.67 (m, 2H), 2.48 (ddd, J = 11.3, 6.3, 2.8 Hz, 1H), 2.41 – 2.29 (m, 2H), 2.22 – 2.16 (m, 1H), 1.87 – 1.78 (m, 4H), 1.73 – 1.68 (m, 2H), 1.45 – 1.38 (m, 1H), 1.19 (m, 3H), 0.88 (d, J = 6.8 Hz, 6H). MS (m/z): 412.3[M+H]$^+$.

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Compound 415

2-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexan-1-ol

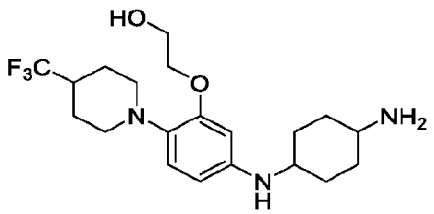


415

The title compound **415** (20.6 mg) was prepared in a total yield of 60.1% as a white solid according to the procedure for compound **4**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 8.0 Hz, 2H), 4.48 (m, 1H), 3.47 – 3.36 (m, 2H), 3.23 (m, 1H), 2.42 – 2.30 (m, 2H), 1.96 (m, 1H), 1.90 – 1.81 (m, 2H), 1.75 – 1.43 (m, 6H), 1.35 – 1.23 (m, 4H). Mass (m/z): 343.2 $[M+H]^+$.

Compound 416

(5-((4-aminocyclohexyl)amino)-2-(4-(trifluoromethyl)piperidin-1-yl)phenoxy)ethan-1-ol

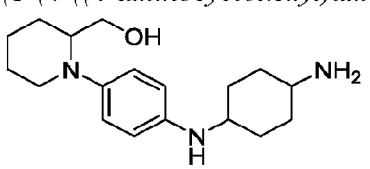


416

The title compound **416** (43.7 mg) was prepared in a total yield of 72.5% as a white solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.66 (s, 1H), 6.23 (d, J = 8.8 Hz, 1H), 6.09 (d, J = 8.4 Hz, 1H), 3.90 (m, 2H), 3.67 (m, 2H), 3.30 – 3.21 (m, 2H), 3.06 (m, 1H), 2.96 (m, 1H), 2.42 – 2.31 (m, 2H),2.05 – 1.90 (m, 2H), 1.87 – 1.34 (m, 10H), 1.26 – 1.09 (m, 1H). Mass (m/z): 402.2 $[M+H]^+$.

Compound 417

(1-(4-((4-aminocyclohexyl)amino)phenyl)piperidin-2-yl)methanol



417A
417B

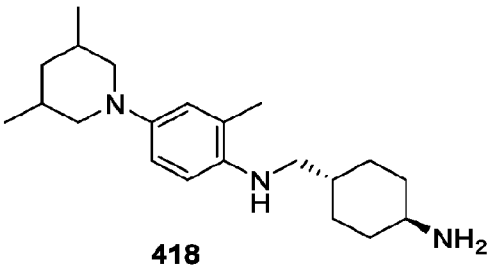
The title compound **417** was prepared according to the procedure for compound **24**. The mixture was purified by prep HPLC (XSelect-CSH-Prep 5 μm OBD, 19*150 mm column; ACN/water (0.5% TFA) = 10%-35%-95%-95%-0%, 0 min-10 min-10.5 min-11.5 min-13 min) to afford compound **417A** (Rt = 8.52 min) in 37.8% yield as a gray solid and **417B** (Rt = 9.64 min) in 12.2% yield as a gray solid. **417A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.01 (d, J = 8.8 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 3.61 – 3.40 (m, 2H), 3.22 – 2.93 (m, 3H), 2.85 (m, 1H), 2.76 (m, 1H), 2.05 – 1.80 (m, 4H), 1.63 – 1.54 (m, 2H), 1.50 – 1.20 (m, 6H), 1.18 – 1.03 (m, 2H). Mass (m/z): 304.2 $[M+H]^+$. **417B**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.02 (d, J = 8.8 Hz,

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2H), 6.74 (d, J = 8.8 Hz, 2H), 3.50 – 3.35 (m, 2H), 3.21 – 2.95 (m, 3H), 2.84 (m, 1H), 2.76 (m, 1H), 2.05 – 1.91 (m, 3H), 1.85 – 1.63 (m, 4H), 1.60 – 1.53 (m, 3H), 1.23 – 1.05 (m, 4H). Mass (m/z): 304.2 $[M+H]^+$.

Compound 418

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-fluoro-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine

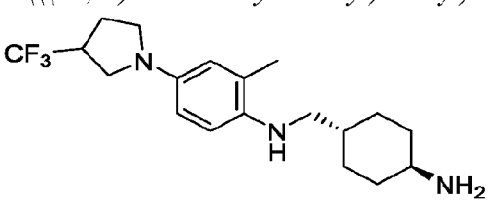


418

The title compound **418** (14.1 mg, 22%) as a yellow solid was prepared from ((1r,4r)-4-(((4-(3,5-dimethylpiperidin-1-yl)-2-methylphenyl)amino)methyl)cyclohexyl)carbamate (100 mg, 0.23 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.65 (s, 2H), 6.38 (s, 1H), 4.25 (s, 1H), 3.30 (s, 9H), 2.83 (s, 2H), 2.04 - 1.97 (m, 3H), 1.80 – 1.71 (m, 4H), 1.48 (s, 1H), 1.24 (s, 2H), 1.08 (s, 1H), 0.87 (s, 6H). Mass (m/z): 329.9 $[M+H]^+$.

Compound 419

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-methyl-4-(3-(trifluoromethyl)pyrrolidin-1-yl)aniline

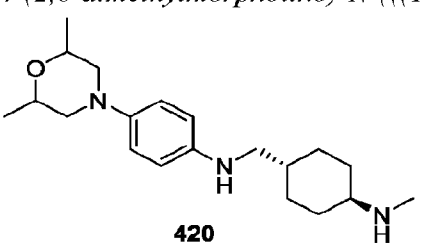


419

The title compound **419** (45.1 mg, 35.8%) as a purple solid was prepared from tert-butyl ((1r,4r)-4-(((2-methyl-4-(3-(trifluoromethyl)pyrrolidin-1-yl)phenyl)amino)methyl)cyclohexyl)carbamate (160 mg, 0.35 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.40 (m, 3H), 3.43 – 3.28 (m, 2H), 3.23 – 3.11 (m, 3H), 2.91 (m, 1H), 2.83 (d, J = 6.6 Hz, 2H), 2.25 – 2.18 (m, 1H), 2.06 (s, 3H), 2.02 – 1.84 (m, 5H), 1.52 (s, 1H), 1.30 – 1.20 (m, 2H), 1.00 (m, 2H). Mass (m/z): 356.22 $[M+H]^+$.

Compound 420

4-(2,6-dimethylmorpholino)-N-(((1r,4r)-4-(methylamino)cyclohexyl)methyl)aniline



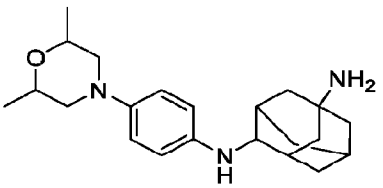
420

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The title compound **420** (4.2 mg, 5%) as a white solid was prepared from tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)phenyl)amino)methyl)cyclohexyl)carbamate (100 mg, 0.24 mmol), THF (3 mL) and LAH (0.3 mL, 0.71 mmol) according to the procedure for **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.73 – 6.64 (m, 2H), 6.48 – 6.39 (m, 2H), 5.06 (s, 1H), 3.69 – 3.57 (m, 2H), 3.25 – 3.17 (m, 2H), 2.74 (t, J = 5.4 Hz, 2H), 2.27 (s, 3H), 2.12 – 2.02 (m, 2H), 1.91 – 1.83 (m, 2H), 1.82 – 1.75 (m, 2H), 1.43 – 1.39 (m, 1H), 1.22 – 1.18 (m, 1H), 1.08 (d, J – 6.3 Hz, 6H), 1.01 – 0.78 (m, 4H). MS (m/z): 332.3[M+H]$^-$.

Compound 421

N^4-(4-(2,6-dimethylmorpholino)phenyl)adamantane-1,4-diamine

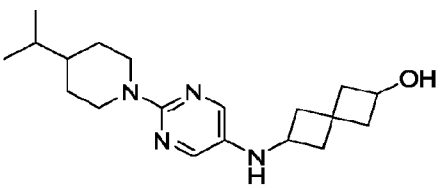


421A
421B

The title compound **421A** (Rt = 7.5 min) (17 mg, 21.7%) as a white solid and compound **421B** (Rt = 8.76 min) (11.4 mg, 14.6%) as a white solid were prepared from tert-butyl (4-((4-(2,6-dimethylmorpholino)phenyl)amino)adamantan-1-yl)carbamate (100 mg, 0.22 mmol), DCM (3 mL), and TFA (1 mL) according to the procedure for **24**, which were purified by Prep-HPLC (XSelect-CSH-Prep 5 μm OBD, 19*150 mm column; ACN/water (0.5% TFA) = 0%-30%-95%-95%-0%, 0 min-10 min-10.5 min-11.5 min-13 min). **421A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 – 6.64 (m, 2H), 6.55 – 6.47 (m, 2H), 4.94 (d, J = 7.5 Hz, 1H), 3.69 – 3.57 (m, 2H), 3.27 – 3.19 (m, 3H), 2.12 – 2.02 (m, 2H), 1.93 – 1.85 (m, 5H), 1.74 – 1.45 (m, 7H), 1.27 – 1.18 (m, 3H), 1.08 (d, J = 6.2 Hz, 6H). MS (m/z): 356.3[M+H]$^+$. **421B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 – 6.64 (m, 2H), 6.56 – 6.47 (m, 2H), 4.88 (d, J = 7.3 Hz, 1H), 3.69 – 3.57 (m, 2H), 3.25 – 3.15 (m, 3H), 2.12 – 2.02 (m, 2H), 2.00 – 1.89 (m, 3H), 1.77 (d, J = 12.2 Hz, 2H), 1.68 – 1.51 (m, 5H), 1.46 – 1.40 (m, 2H), 1.23 – 1.16 (m, 3H), 1.08 (d, J = 6.3 Hz, 6H). MS (m/z): 356.3[M+H]$^+$.

Compound 422

6-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptan-2-ol



422

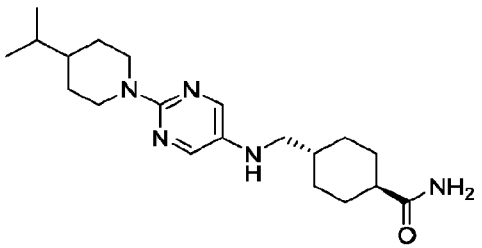
The title compound **422** (32.3 mg) was prepared in a yield of 43.07% as a white powder from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (50 mg, 0.23 mmol) and 6-hydroxyspiro[3.3]heptan-2-one (34 mg, 0.27 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 2H), 5.22 (d, J = 7.5 Hz, 1H), 4.88 (d, J = 6.4 Hz, 1H), 4.47 (dt, J = 12.4, 3.0 Hz, 2H), 3.99 – 3.90 (m, 1H), 3.61 (q, J = 7.5 Hz, 1H), 2.61 (td, J = 12.6, 2.5 Hz, 2H), 2.53 (dd, J = 7.7, 1.9 Hz, 1H), 2.40 – 2.31 (m, 2H), 2.27 (ddd, J = 11.5, 7.1, 4.7

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Hz, 1H), 2.15 (dt, J = 11.7, 6.2 Hz, 1H), 1.85 – 1.78 (m, 2H), 1.74 (ddd, J = 11.2, 7.9, 3.3 Hz, 2H), 1.67 – 1.60 (m, 2H), 1.44 – 1.33 (m, 1H), 1.20 (ddt, J = 14.7, 6.1, 3.0 Hz, 1H), 1.06 (qd, J = 12.3, 4.2 Hz, 2H), 0.85 (d, J = 6.8 Hz, 6H). Mass (m/z): 331.4 $[M+H]^+$.

Compound 423

(1r,4r)-4-(((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)methyl)cyclohexane-1-carboxamide

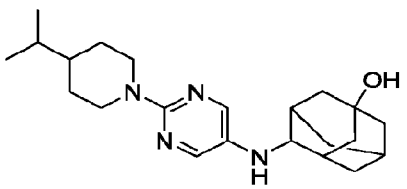


423

The title compound **423** (8.5 mg) was prepared in a yield of 17.0% as a white powder from (1r,4r)-4-(((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)methyl)cyclohexane-1-carboxylic acid (50 mg, 0.14 mmol) and ammonia (0.500 mL) according to the procedure for **10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 1H), 7.16 (s, 1H), 6.64 (s, 1H), 4.54 (dd, J = 53.1, 13.4 Hz, 2H), 2.79 (t, J = 6.4 Hz, 1H), 2.66 – 2.57 (m, 2H), 2.01 (t, J = 6.1 Hz, 1H), 1.74 (ddd, J = 46.9, 30.3, 12.6 Hz, 8H), 1.41 (dt, J = 13.4, 6.6 Hz, 3H), 1.24 (s, 7H), 1.16 – 1.00 (m, 1H), 0.96 – 0.81 (m, 6H). Mass (m/z): 360.5 $[M+H]^+$.

Compound 424

4-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)adamantan-1-ol



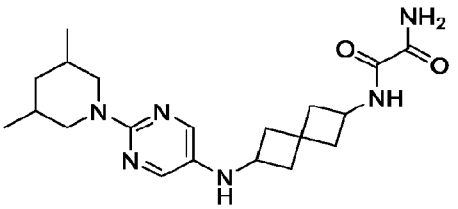
424

The title compound **424** (28.6 mg) was prepared in a yield of 34.01% as a white powder from 2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (50 mg, 0.23 mmol) and 5-hydroxyadamantan-2-one (45 mg, 0.27 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 1.9 Hz, 2H), 4.92 (dd, J = 12.4, 7.7 Hz, 1H), 4.44 (dt, J = 12.7, 2.7 Hz, 2H), 4.33 (d, J = 18.2 Hz, 1H), 2.58 (td, J = 12.6, 2.5 Hz, 2H), 1.98 (d, J = 30.4 Hz, 3H), 1.86 (d, J = 12.7 Hz, 2H), 1.69 (d, J = 11.6 Hz, 1H), 1.65 – 1.49 (m, 7H), 1.40 – 1.33 (m, 1H), 1.33 – 1.13 (m, 2H), 1.04 (qd, J = 12.2, 4.1 Hz, 2H), 0.82 (d, J = 6.8 Hz, 6H). Mass (m/z): 371.4 $[M+H]^+$.

Compound 425

N1-(6-((2-(3,5-dimethylpiperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptan-2-yl)oxalamide

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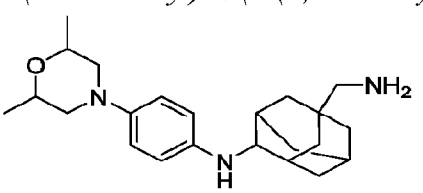


425

The title compound **425** (4.8 mg) was prepared in a yield of 21.7% as a white powder from N2-(2-(3,5-dimethylpiperidin-1-yl)pyrimidin-5-yl)spiro[3.3]heptane-2,6-diamine (18 mg, 0.057 mmol) and 2-amino-2-oxoacetic acid (6 mg, 0.068 mmol) according to the procedure for **10**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J = 8.3 Hz, 1H), 8.01 (s, 1H), 7.78 (s, 1H), 7.73 (s, 1H), 4.42 (d, J = 13.8 Hz, 2H), 3.68 – 3.54 (m, 3H), 3.17 – 3.08 (m, 3H), 2.25 – 2.09 (m, 2H), 1.73 (d, J = 10.5 Hz, 2H), 1.19 (d, J = 6.7 Hz, 6H), 0.85 (dd, J = 6.7, 3.5 Hz, 6H). Mass (m/z): 387.4 $[M+H]^+$.

Compound 426

5-(aminomethyl)-N-(4-(2,6-dimethylmorpholino)phenyl)adamantan-2-amine

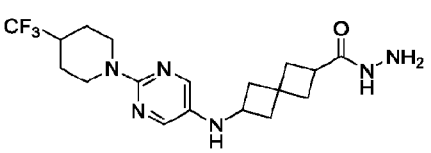


426

The title compound **426** (28.2 mg) was prepared in a two-step overall yield of 26.7% as a white powder from 4-(2,6-dimethylmorpholino)aniline (70 mg, 0.34 mmol) and 4-oxoadamantane-1-carboxylic acid (99 mg, 0.51 mmol) according to the procedure for **84**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 2H), 6.75 (s, 2H), 6.58 (s, 2H), 5.08 (s, 1H), 3.68 (s, 2H), 2.12 (s, 2H), 1.98 (s, 4H), 1.91 (d, J = 6.6 Hz, 2H), 1.72 (d, J = 17.9 Hz, 2H), 1.63 (s, 3H), 1.53 (s, 2H), 1.49 (s, 1H), 1.35 (d, J = 12.2 Hz, 1H), 1.25 (d, J = 7.8 Hz, 1H), 1.12 (d, J = 6.0 Hz, 6H). Mass (m/z): 389.3 $[M+H]^+$.

Compound 427

6-((2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptane-2-carbohydrazide



427

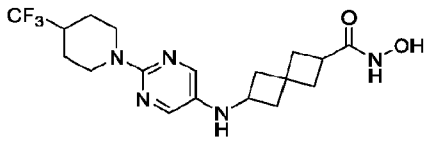
The title compound **427** (5.1 mg) was prepared in a total yield of 16.4% as a yellow solid from 6-((2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptane-2-carboxylic acid (30 mg, 0.078 mmol), hydrazinium hydroxide solution (23 mg, 0.468 mmol), HATU(45 mg,0.117 mmol) and DIEA(30 mg,0.234 mmol) and DMF (5 mL) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.92 (s, 1H), 7.78 (s, 2H), 4.54 – 4.11 (m, 7H), 3.63 – 3.51 (m, 2H), 2.80 (t, J = 8.4 Hz, 1H), 2.72 (td, J = 12.8, 2.5 Hz, 2H), 2.25 (td, J =

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6.8, 3.4 Hz, 1H), 2.18 – 2.03 (m, 3H), 1.93 – 1.87 (m, 1H), 1.77 (dd, *J* = 12.4, 3.8 Hz, 3H), 1.71 (s, 3H), 1.67 (dd, *J* = 11.2, 7.8 Hz, 1H), 1.28 (tt, *J* = 12.0, 5.2 Hz, 8H), 0.86 – 0.78 (m, 1H). Mass (m/z): 399.3 $[M+H]^+$.

Compound 428

N-hydroxy-6-((2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptane-2-carboxamide

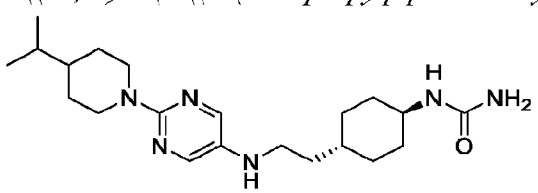


428

The title compound **428** (7.0 mg) was prepared in a total yield of 22.4% as a yellow solid from 6-((2-(4-(trifluoromethyl)piperidin-1-yl)pyrimidin-5-yl)amino)spiro[3.3]heptane-2-carboxylic acid (30 mg, 0.078 mmol), hydroxylamine hydrochloride (11 mg, 0.156 mmol), HATU (45 mg, 0.117 mmol) and DIEA (30 mg,0.234 mmol) and DMF (5 mL) according to the procedure for **1**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.65 (d, *J* = 1.6 Hz, 1H), 7.78 (s, 2H), 5.36 (d, *J* = 7.2 Hz, 1H), 4.49 (d, *J* = 13.2 Hz, 2H), 3.57 (q, *J* = 7.2 Hz, 1H), 2.78 – 2.68 (m, 3H), 2.26 (q, *J* = 5.6, 5.2 Hz, 1H), 2.11 (ddd, *J* = 22.0, 11.2, 8.4 Hz, 3H), 1.89 (ddd, *J* = 12.0, 8.0, 4.0 Hz, 1H), 1.77 (dd, *J* = 12.0, 4.0 Hz, 3H), 1.67 (dd, *J* = 11.2, 8.0 Hz, 1H), 1.30 (qd, *J* = 12.4, 4.0 Hz, 4H). Mass (m/z): 400.3 $[M+H]^+$.

Compound 429

1-((1r,4r)-4-(2-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)ethyl)cyclohexyl)urea



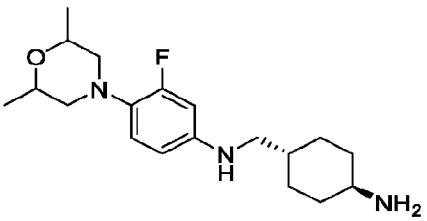
429

The title compound **429** (4.4 mg, 3.7%) was prepared from of N-(2-((1r,4r)-4-aminocyclohexyl)ethyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine (100 mg, 0.2894 mmol), DCM (10 mL), TMSNCO (33.34 mg, 0.2894 mmol), TEA (87.85 mg, 0.8682 mmol) and DMAP (7.07 mg, 0.0579 mmol) according to the procedure for **178**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 2H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.28 (s, 2H), 4.94 (s, 1H), 4.48 (d, *J* = 13.0 Hz, 2H), 3.25 – 3.19 (m, 1H), 2.94 (t, *J* = 6.9 Hz, 2H), 2.67 – 2.58 (m, 2H), 1.83 – 1.61 (m, 6H), 1.46 – 1.36 (m, 3H), 1.13 (m, 8H), 0.85 (d, *J* = 6.8 Hz, 6H). Mass (m/z): 389.30 $[M+H]^+$.

Compound 430

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-3-fluoroaniline

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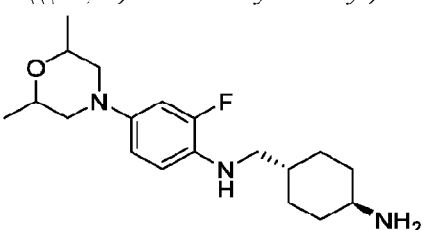


430

The title compound **430** (10 mg, 12.9%) as a white solid was prepared from tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)-3-fluorophenyl)amino)methyl)cyclohexyl)carbamate (100 mg, 0.23 mmol), DCM (3 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (dd, J = 10.0, 8.6 Hz, 1H), 6.33 (dd, J = 15.0, 2.5 Hz, 1H), 6.28 (dd, J = 8.6, 2.7 Hz, 1H), 5.56 (t, J = 5.8 Hz, 1H), 3.75 – 3.63 (m, 2H), 3.00 – 2.92 (m, 2H), 2.77 (t, J = 6.2 Hz, 2H), 2.53 – 2.52 (m, 1H), 2.29 – 2.20 (m, 2H), 1.80 – 1.73 (m, 4H), 1.42 – 1.37 (m, 1H), 1.08 (d, J = 6.2 Hz, 6H), 1.03 – 0.86 (m, 4H). MS (m/z): 336.3[M+H]$^+$.

Compound 431

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2-fluoroaniline

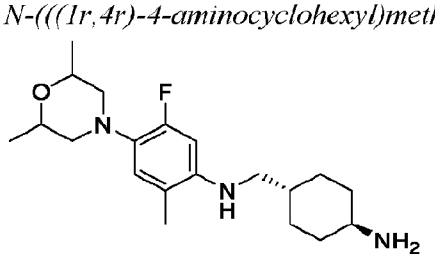


431

The title compound **431** (20.9 mg, 27.1%) as a white solid was prepared tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)-2-fluorophenyl)amino)methyl)cyclohexyl)carbamate (100 mg, 0.23 mmol), DCM (3 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77 – 6.68 (m, 1H), 6.63 – 6.52 (m, 2H), 4.82 – 4.75 (m, 1H), 3.72 – 3.60 (m, 2H), 3.37 – 3.29 (m, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.29 – 2.25 (m, 1H), 2.16 – 2.06 (m, 2H), 1.79 – 1.72 (m, 4H), 1.53 – 1.37 (m, 1H), 1.12 (d, J = 6.3 Hz, 6H), 1.04 – 0.84 (m, 4H). MS (m/z): 336.3[M+H]$^+$.

Compound 432

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-5-fluoro-2-methylaniline



433

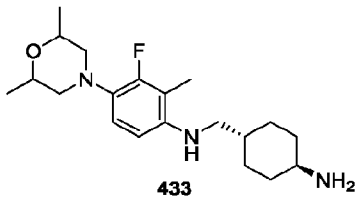
The title compound **432** (41.2 mg) was prepared in a total yield of 66.1% as a pink solid from tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)-5-fluoro-2-methylphenyl)amino)methyl)cyclohexyl)carbamate (80 mg, 0.178 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for

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24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.22 (m, 3H), 6.71 (d, J = 10.0 Hz, 1H), 6.28 (d, J = 15.2 Hz, 1H), 4.83 (s, 1H), 3.76 – 3.63 (m, 2H), 2.98 (d, J = 11.2 Hz, 2H), 2.87 (t, J = 12.0 Hz, 3H), 2.27 (t, J = 10.8 Hz, 2H), 2.06 – 1.93 (m, 5H), 1.89 – 1.80 (m, 2H), 1.52 (s, 1H), 1.34 (qd, J = 12.4, 3.2 Hz, 2H), 1.09 (d, J = 6.4 Hz, 6H), 1.03 – 0.92 (m, 2H). Mass (m/z): 350.3 $[M+H]^+$.

Compound 433

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-3-fluoro-2-methylaniline

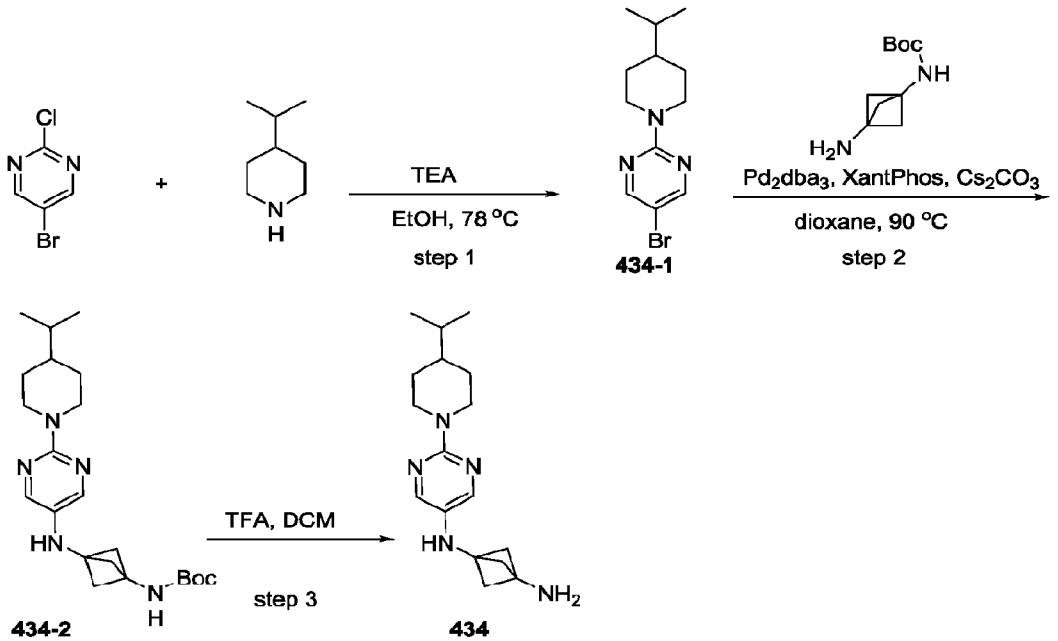


433

The title compound **433** (23.5 mg) was prepared in a total yield of 43.1% as a green solid from tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)-3-fluoro-2-methylphenyl)amino)methyl)cyclohexyl)carbamate (70 mg, 0.156 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 3H), 6.70 (t, J = 9.2 Hz, 1H), 6.23 (d, J = 8.8 Hz, 1H), 4.84 (d, J = 5.6 Hz, 1H), 3.77 – 3.64 (m, 2H), 3.03 – 2.95 (m, 2H), 2.86 (t, J = 5.6 Hz, 3H), 2.23 (t, J = 10.8 Hz, 2H), 2.05 – 1.93 (m, 5H), 1.90 – 1.80 (m, 2H), 1.53 (d, J = 9.2 Hz, 1H), 1.35 (qd, J = 12.4, 3.6 Hz, 2H), 1.09 (d, J = 6.4 Hz, 6H), 1.04 – 0.91 (m, 2H). Mass (m/z): 350.3 $[M+H]^+$.

Compound 434

N1-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)bicyclo[1.1.1]pentane-1,3-diamine



434-2 434

Step 1. Preparation of 5-bromo-2-(4-isopropylpiperidin-1-yl)pyrimidine **(434-1)**

A mixture of 5-bromo-2-chloropyrimidine (200 mg, 1.04 mmol), trimethylamine (202 mg, 2.00

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mmol) and 4-isopropylpiperidine (127 mg, 1.00 mmol) in ethanol (2 mL) was stirred under nitrogen at 78 °C overnight. The resulting mixture was concentrated under vacuum and purified by a fast silica gel column chromatography (petroleum ether/ethyl acetate 5/1) to give the desired product 5-bromo-2-(4-isopropylpiperidin-1-yl)pyrimidine (125 mg, 44.2%) as a white solid. MS (m/z): 284, 286 $[M+H]^+$.

Step 2. Preparation of tert-butyl (3-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (**434-2**)

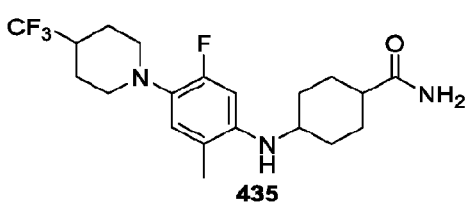
A mixture of 5-bromo-2-(4-isopropylpiperidin-1-yl)pyrimidine (110 mg, 0.41 mmol), tert-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (100 mg, 0.51 mmol), Cs_2CO_3 (200 mg, 0.62 mmol), Pd_2dba_3 (18 mg, 0.02 mmol) and XantPhos (40 mg, 0.07 mmol) in dioxane (3 mL) was bubbled with nitrogen for 3 min and then stirred overnight at 90 °C. Additional tert-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (30 mg), Cs_2CO_3 (50 mg), Pd_2dba_3 (9 mg) and XantPhos (20 mg) were added and the mixture was stirred for 16 h. Starting materials still remained a little and the reaction was cooled and diluted with water. The resulting mixture was extracted with ethyl acetate twice and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC (DCM/MeOH 20/1) to afford tert-butyl (3-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (46 mg, 28%) as a yellow solid. MS (m/z): 402 $[M+H]^+$.

Step 3. Preparation of N1-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)bicyclo[1.1.1]pentane-1,3-diamine (**434**)

To a solution of tert-butyl (3-((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)bicyclo[1.1.1]pentan-1-yl)carbamate (45 mg, 0.11 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.2 mL) and stirred overnight at room temperature. The resulting mixture was diluted with ethyl acetate and washed with sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC (dichloromethane/methanol 15/1) to afford the title compound N1-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)bicyclo[1.1.1]pentane-1,3-diamine **434** (1.5 mg, 4.5%) as colorless oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.12 (s, 2H), 4.69 (d, J = 13.1 Hz, 2H), 2.82 – 2.68 (m, 2H), 2.59 (s, 2H), 2.42 (s, 2H), 1.76 – 1.65 (m, 2H), 1.39 (dt, J = 13.3, 6.7 Hz, 1H), 1.29 – 1.05 (m, 9H), 0.83 (d, J = 6.7 Hz, 6H). MS (m/z): 302 $[M+H]^+$.

Compound 435

4-((5-fluoro-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxamide



435

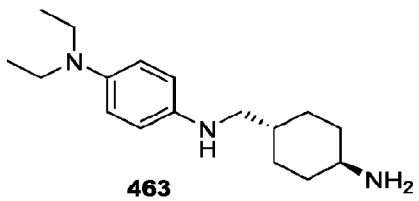
The title compound **435** (37.9 mg, 26.1%) was prepared from

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5-fluoro-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline (100 mg, 0.36 mmol), 4-oxocyclohexane-1-carboxamide (50 mg, 0.36 mmol), $NaBH(OAc)_3$ (76.3 mg, 0.36 mmol), and DCE (10 mL) according to the procedure for **4**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.15 (s, 1H), 6.71 (d, J = 10.0 Hz, 2H), 6.30 (d, J = 15.0 Hz, 1H), 4.11 (d, J = 6.4 Hz, 1H), 3.33 (d, J = 3.0 Hz, 1H), 3.13 (d, J = 11.6 Hz, 2H), 2.58 (dd, J = 11.8, 10.2 Hz, 2H), 2.39 – 2.28 (m, 1H), 2.18 (tt, J = 7.8, 4.0 Hz, 1H), 2.00 (s, 3H), 1.82 (d, J = 12.0 Hz, 2H), 1.74 – 1.54 (m, 10H). Mass (m/z): 401.8 $[M+H]^+$.

Compound 436

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-fluoro-6-(4-(trifluoromethyl)piperidin-1-yl)pyridin-3-amine

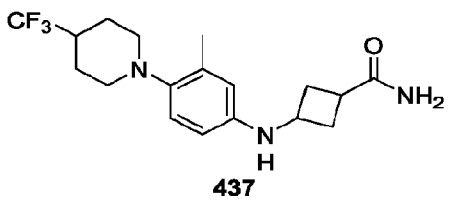


463

The title compound **463** (14.1 mg, 22%) as a yellow solid was prepared from tert-butyl((1r,4r)-4-(((4-(diethylamino)phenyl)amino)methyl)cyclohexyl) carbamate (190 mg, 0.5 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^1H NMR (400 MHz, DMSO-d_6) δ = 6.59 (d, J = 8.8, 2H), 6.46 (d, J = 8.8, 2H), 4.90 (s, 1H), 3.08 (q, J = 7.2, 4H), 2.75 (d, J = 4.4, 2H), 2.47 – 2.43 (m, 1H), 1.86 – 1.66 (m, 4H), 1.49 – 1.34 (m, 2H), 1.00 – 0.88 (m, 9H). Mass (m/z): 276.3$[M+H]^+$.

Compound 437

3-((3-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclobutane-1-carboxamide



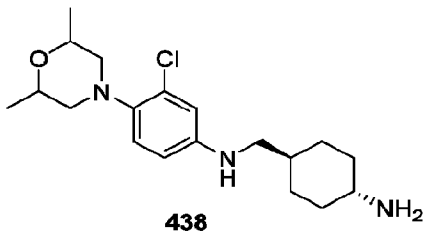
437

The title compound **437** (27.5 mg, 27.5%) was prepared as a yellow solid from 3-({3-methyl-4-[4-(trifluoromethyl)piperidin-1-yl]phenyl}amino)cyclobutane-1-carboxylic acid (100 mg, 0.28 mmol), ammonium chloride (30 mg, 0.56 mmol), triethylamine (85 mg, 0.84 mmol), and HATU (160 mg, 0.42 mmol) according to the procedure for **1**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.17 (s, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.71 (s, 1H), 6.27 (d, J = 2.6 Hz, 1H), 6.21 (dd, J = 8.5, 2.7 Hz, 1H), 5.48 (d, J = 6.7 Hz, 1H), 3.81 (dd, J = 13.9, 6.8 Hz, 1H), 2.89 (m, 3H), 2.51 (t, J = 3.3 Hz, 1H), 2.42 – 2.36 (m, 3H), 2.31 – 2.28 (m, 1H), 2.10 (s, 3H), 1.95 – 1.89 (m, 2H), 1.82 (d, J = 12.3 Hz, 2H), 1.54 (dd, J = 12.3, 3.7 Hz, 2H). Mass (m/z): 356.3$[M+H]^+$.

Compound 438

N-(((1r,4r)-4-aminocyclohexyl)methyl)-3-chloro-4-(2,6-dimethylmorpholino)aniline

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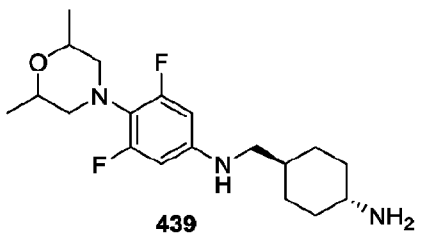


438

The title compound **438** (41.0 mg) was prepared in a yield of 40.07% as a white powder from 3-chloro-4-(2,6-dimethylmorpholino)aniline (70 mg, 0.29 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (99 mg, 0.44 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 – 7.84 (m, 3H), 6.92 (d, J = 8.7 Hz, 1H), 6.60 (d, J = 2.6 Hz, 1H), 6.48 (dd, J = 8.7, 2.6 Hz, 1H), 5.70 (s, 1H), 3.69 (dqd, J = 12.6, 6.2, 2.0 Hz, 2H), 3.00 – 2.88 (m, 3H), 2.81 (d, J = 6.5 Hz, 2H), 2.26 (dd, J = 11.4, 9.9 Hz, 2H), 1.98 – 1.80 (m, 4H), 1.44 (s, 1H), 1.31 – 1.20 (m, 2H), 1.09 (d, J = 6.3 Hz, 6H), 1.00 (q, J = 11.8 Hz, 2H). Mass (m/z): 352.5 $[M+H]^+$.

Compound 439

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-3,5-difluoroaniline

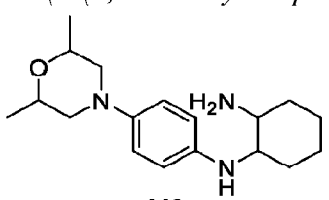


439

The title compound **439** (46.2 mg) was prepared in a yield of 31.67% as a white powder from 4-(2,6-dimethylmorpholino)-3,5-difluoroaniline (100 mg, 0.41 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (175 mg, 0.83 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (s, 2H), 6.22 – 5.98 (m, 3H), 3.61 (dtd, J = 8.6, 6.1, 2.3 Hz, 2H), 2.96 – 2.86 (m, 1H), 2.84 – 2.72 (m, 4H), 2.68 – 2.61 (m, 2H), 2.01 – 1.77 (m, 4H), 1.42 (d, J = 3.5 Hz, 1H), 1.36 – 1.22 (m, 2H), 1.04 (d, J = 6.2 Hz, 6H), 1.01 – 0.91 (m, 2H). Mass (m/z): 354.5 $[M+H]^+$.

Compound 440

N1-(4-(2,6-dimethylmorpholino)phenyl)cyclohexane-1,2-diamine



440

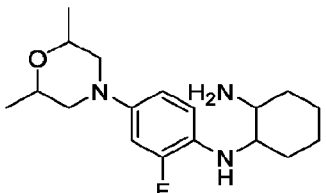
The title compound **440** (20.9 mg) was prepared in a yield of 20.9% as a white powder from 4-(2,6-dimethylmorpholino)aniline (64 mg, 0.31 mmol) and tert-butyl (2-oxocyclohexyl)carbamate (100mg, 0.47 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 2H), 6.82 – 6.75 (m, 2H), 6.67 – 6.57 (m, 2H), 4.90 (s, 1H), 3.67 (ddt, J = 13.2, 6.9, 3.4 Hz, 2H), 3.33 – 3.28 (m, 2H), 3.15 (s, 1H), 2.88 (d, J = 9.4 Hz, 1H),

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2.12 (ddd, *J* = 11.9, 10.3, 1.7 Hz, 2H), 2.00 (dd, *J* = 34.1, 12.8 Hz, 2H), 1.68 (d, *J* = 23.8 Hz, 2H), 1.41 (q, *J* = 12.3, 11.8 Hz, 1H), 1.25 (q, *J* = 11.1, 10.7 Hz, 2H), 1.12 (d, *J* = 6.2 Hz, 6H), 1.10 – 1.00 (m, 1H). Mass (m/z): 304.5 $[M+H]^+$.

Compound 441

N1-(4-(2,6-dimethylmorpholino)-2-fluorophenyl)cyclohexane-1,2-diamine

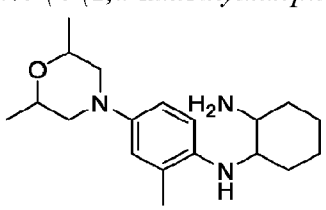


441

The title compound **441** (10.1 mg) was prepared in a yield of 10.6% as a white powder from 4-(2,6-dimethylmorpholino)-2-fluoroaniline (71 mg, 0.31 mmol) and tert-butyl (2-oxocyclohexyl)carbamate (100mg, 0.47 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 2H), 6.84 – 6.71 (m, 2H), 6.63 (d, *J* = 9.2 Hz, 1H), 4.67 (d, *J* = 10.4 Hz, 1H), 3.72 – 3.59 (m, 2H), 3.39 (d, J = 11.4 Hz, 2H), 3.18 (s, 1H), 3.05 (s, 1H), 2.13 (t, J = 10.8 Hz, 2H), 2.04 (d, *J* = 12.6 Hz, 1H), 1.90 (d, *J* = 7.0 Hz, 1H), 1.68 (d, *J* = 29.5 Hz, 2H), 1.40 (d, *J* = 12.5 Hz, 1H), 1.28 – 1.17 (m, 2H), 1.13 (d, *J* = 6.3 Hz, 6H). Mass (m/z): 322.3 $[M+H]^+$.

Compound 442

N1-(4-(2,6-dimethylmorpholino)-2-methylphenyl)cyclohexane-1,2-diamine

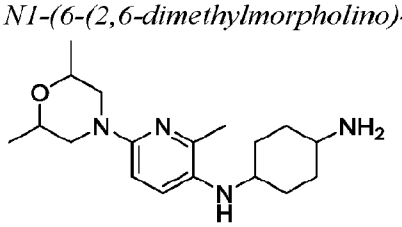


442

The title compound **442** (33.3 mg) was prepared in a yield of 34.5% as a white powder from 4-(2,6-dimethylmorpholino)-2-methylaniline (69 mg, 0.31 mmol) and tert-butyl (2-oxocyclohexyl)carbamate (100 mg, 0.47 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (s, 2H), 6.79 – 6.50 (m, 3H), 4.14 (s, 1H), 3.67 (s, 2H), 3.15 (d, *J* = 37.6 Hz, 2H), 2.17 (s, 1H), 2.12 (s, 6H), 1.96 (d, *J* = 12.6 Hz, 1H), 1.80 – 1.59 (m, 2H), 1.55 1.32 (m, 2H), 1.23 (s, 2H), 1.12 (d, *J* = 6.2 Hz, 6H). Mass (m/z): 318.4 $[M+H]^+$.

Compound 443

N1-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)cyclohexane-1,4-diamine



443

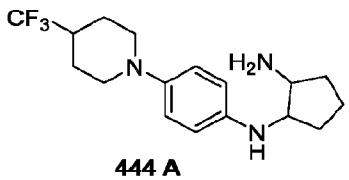
The title compound **443** (17.7 mg) was prepared in a yield of 24.6% as a white powder from

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6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine (50 mg, 0.22 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (72 mg, 0.34 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 21.0 Hz, 3H), 6.99 (s, 1H), 6.59 (s, 1H), 3.88 (d, J = 11.7 Hz, 2H), 3.60 (d, J = 8.6 Hz, 2H), 3.45 (s, 1H), 3.10 (s, 1H), 2.94 (s, 1H), 2.38 – 2.12 (m, 5H), 2.05 – 1.91 (m, 2H), 1.85 – 1.67 (m, 3H), 1.60 (s, 1H), 1.43 (d, J = 12.2 Hz, 1H), 1.14 (d, J = 6.2 Hz, 6H). Mass (m/z): 319.3 $[M+H]^+$.

Compound 444

(1R,2R)-N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclopentane-1,2-diamine



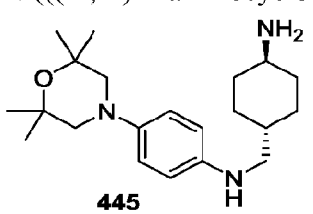
444 A

444 B

The title compound **444A** (12 mg) was prepared in a yield of 17.9% as a white powder and compound **444B** (23 mg) was prepared in a yield of 36% as a white powder from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (50 mg, 0.20 mmol) and tert-butyl (2-oxocyclopentyl)carbamate (61 mg, 0.30 mmol) according to the procedure for **20**. **444A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.14 (d, J = 8.3 Hz, 2H), 5.91 (d, J = 8.1 Hz, 2H), 2.98 (dq, J = 11.1, 6.3, 5.6 Hz, 2H), 2.69 (d, J = 12.1 Hz, 2H), 1.85 (t, J = 12.1 Hz, 2H), 1.52 – 1.37 (m, 2H), 1.37 – 1.28 (m, 1H), 1.22 – 1.12 (m, 2H), 1.05 (q, J = 8.1 Hz, 2H), 0.99 – 0.82 (m, 4H). Mass (m/z): 328.3 $[M+H]^+$. **444B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.12 (d, J = 8.4 Hz, 2H), 5.86 (d, J = 8.2 Hz, 2H), 2.93 (t, J = 7.1 Hz, 1H), 2.68 (d, J = 11.9 Hz, 2H), 2.58 (d, J = 7.2 Hz, 1H), 1.85 (t, J = 12.1 Hz, 2H), 1.41 (tt, J = 13.9, 7.1 Hz, 3H), 1.16 (d, J = 13.0 Hz, 2H), 1.04 (q, J = 7.4 Hz, 2H), 0.91 (dp, J = 21.7, 8.2 Hz, 3H), 0.69 (dd, J = 13.7, 7.3 Hz, 1H). Mass(m/z): 328.3 $[M+H]^+$.

Compound 445

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,2,6,6-tetramethylmorpholino)aniline



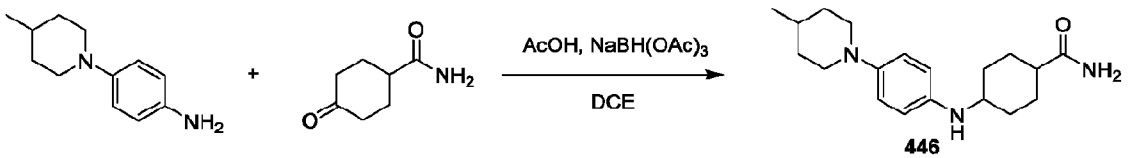
445

The title compound **445** (31.5 mg) was prepared in a total yield of 60.9% as a dark blue solid according to the procedure for compound **354**. ^{1}H NMR (400 MHz, Pyridine-d_5) δ 7.04 – 6.96 (m, 2H), 6.92 – 6.84 (m, 2H), 5.19 (s, 3H), 3.44 – 3.35 (m, 1H), 2.99 – 2.95 (m, 2H), 2.52 – 2.42 (m, 2H), 1.95 – 1.88 (m, 2H), 1.85 – 1.74 (m, 2H), 1.66 – 1.57 (m, 1H), 1.43 – 1.15 (m, 16H), 1.07 – 0.95 (m, 2H). Mass (m/z): 346.3 $[M+H]^+$.

Compound 446

4-((4-(4-methylpiperidin-1-yl)phenyl)amino)cyclohexane-1-carboxamide

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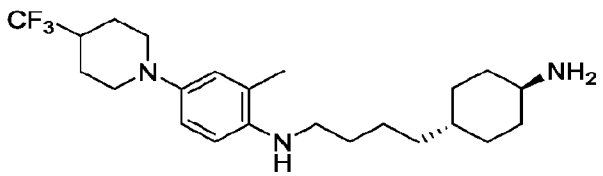


446

A solution of 4-(4-methylpiperidin-1-yl)aniline (50 mg, 0.240 mmol), 4-oxocyclohexane-1-carboxamide (51 mg, 0.360 mmol) and AcOH (0.1 mL) in DCE (10 mL) was stirred at r.t. for 30 min before $NaBH(OAc)_3$ (130 mg, 0.614 mmol) was added. The mixture was stirred at room temperature for 2 h. The mixture was extracted by DCM (25 mL x 3). The combined organic layers were washed with brine (15 mL x 3), dried over Na_2SO_4 and concentrated to give the crude product, which was purified by prep HPLC (XSelect-CSH-Prep 5 μm OBD, 19*150 mm column; ACN/water ($0.5\%NH_3H_2O$) = 50%-77%-95%-95%-0%, 0 min-8 min-8.5 min-9.5 min-11 min), to give the desired product **446A** (Rt = 6.1 min) as white solid (24.6 mg, 31.1%) and **446B** (Rt = 7.1 min) as white solid (27.1 mg, 33.3%). **446A** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 – 7.17 (m, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.69 – 6.63 (m, 1H), 6.38 (d, J = 2.8 Hz, 1H), 6.32 (dd, J = 8.4, 2.8 Hz, 1H), 4.89 (d, J = 8.4 Hz, 1H), 3.04 (tdt, J = 11.2, 7.2, 3.6 Hz, 1H), 2.83 (dt, J = 12.0, 3.2 Hz, 2H), 2.46 (dd, J = 11.6, 2.4 Hz, 2H), 2.11 (s, 3H), 2.01 (ddq, J = 27.2, 12.0, 3.6 Hz, 3H), 1.76 (dt, J = 14.4, 3.6 Hz, 2H), 1.69 – 1.60 (m, 2H), 1.43 (qd, J = 13.0, 3.6 Hz, 3H), 1.25 (qd, J = 12.0, 3.6 Hz, 2H), 1.13 – 0.99 (m, 2H), 0.94 (d, J = 6.4 Hz, 3H). **446B** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 (s, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.69 (s, 1H), 6.43 (d, J = 2.8 Hz, 1H), 6.36 (dd, J = 8.4, 2.8 Hz, 1H), 5.00 (d, J = 7.6 Hz, 1H), 2.83 (dt, J = 12.0, 3.6 Hz, 2H), 2.46 (dd, J = 11.6, 2.4 Hz, 2H), 2.12 (s, 4H), 1.83 – 1.71 (m, 2H), 1.70 – 1.60 (m, 4H), 1.59 – 1.35 (m, 5H), 1.25 (qd, J = 11.6, 3.6 Hz, 2H), 0.94 (d, J = 6.4 Hz, 3H). Mass (m/z): 330.3 $[M+H]^+$.

Compound 447

N-(4-((1r,4s)-4-aminocyclohexyl)butyl)-2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)aniline



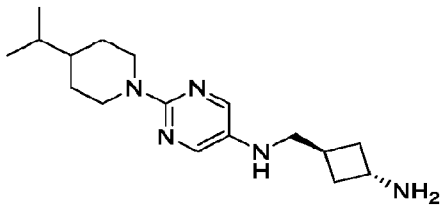
447

The title compound **447** (17.4 mg, 23.2%) as a white solid was prepared from 4-((1r,4s)-4-aminocyclohexyl)-N-(2-methyl-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)butanamide (100 mg, 0.18 mmol) in BH_3-THF (20 mL) according to the procedure for **105**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.80 (s, 2H), 6.58 (d, J = 8.7 Hz, 1H), 3.47 (d, J = 11.8 Hz, 2H), 3.10 (dd, J = 14.9, 7.8 Hz, 2H), 2.86 – 2.77 (m, 1H), 2.60 (t, J = 11.2 Hz, 2H), 2.31 – 2.22 (m, 1H), 2.12 (s, 3H), 1.95 (d, J = 11.9 Hz, 4H), 1.84 (d, J = 12.1 Hz, 2H), 1.78 – 1.68 (m, 2H), 1.61 (dt, J = 15.0, 7.5 Hz, 2H), 1.41 (d, J = 15.5 Hz, 2H), 1.32 – 1.19 (m, 6H), 1.07 – 0.95 (m, 2H). Mass (m/z): 412.3 $[M+H]^+$.

Compound 448

N-(((1r,3r)-3-aminocyclobutyl)methyl)-2-(4-isopropylpiperidin-1-yl)pyrimidin-5-amine

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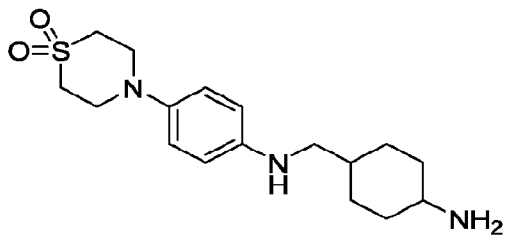


448

The title compound **448** (28.2 mg) as a yellow solid was prepared from tert-butyl ((1r,3r)-3-(((2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)amino)methyl)cyclobutyl)carbamate (100 mg, 0.24 mmol), 1,4-dioxane (3 mL) and HCl /1,4-dioxane (1 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.89 (s, 2H), 4.47 (d, J = 13.2 Hz, 2H), 3.83 (d, J = 7.4 Hz, 1H), 3.12 (d, J = 7.4 Hz, 2H), 2.70 (s, 2H), 2.25 (d, J = 5.6 Hz, 4H), 1.70 (d, J = 11.6 Hz, 2H), 1.41 (qd, J = 13.2, 6.6 Hz, 1H), 1.22 – 1.13 (m, 4H), 0.88 (d, J = 6.8 Hz, 6H). Mass (m/z): 304.3 $[M+H]^+$.

Compound 449

4-(4-(((4-aminocyclohexyl)methyl)amino)phenyl) thiomorpholine 1,1-dioxide

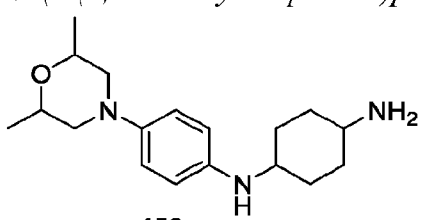


449

The title compound **449** (122 mg, 66.7%) as a yellow solid was prepared from tert-butyl (4-(((4-(1,1-dioxidothiomorpholino phenyl)amino)methyl)cyclohexyl)carbamate (200 mg, 0.46 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 8.4, 2H), 6.55 (d, J = 8.4, 2H), 3.58 (s, 4H), 3.11 (s, 4H), 2.92 (d, J = 6.4, 2H), 2.62 (s, 1H), 1.90 – 1.83 (m, 4H), 1.51 (s, 1H), 1.38 (s, 1H), 1.20 – 0.94 (m, 4H). Mass (m/z): 337.9 $[M+H]^+$.

Compound 450

N^1-(4-(2,6-dimethylmorpholino)phenyl)cyclohexane-1,4-diamine



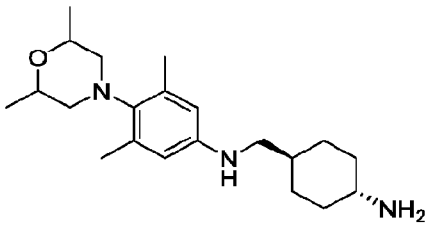
450

The desired product **450** as a yellow solid (21.5 mg, 24.4%) was prepared from tert-butyl (4-((4-(2,6-dimethylmorpholino)phenyl)amino)cyclohexyl)carbamate according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (s, 1H), 7.07 (d, J = 8.5 Hz, 2H), 6.94 (t, J = 10.7 Hz, 2H), 3.5 – 3.2 (m, 6H), 1.6 – 1.5 (m, 2H), 1.20 (d, J = 4.9 Hz, 6H), 0.71 – 0.64 (m, 2H). Mass (m/z): 304.2 $[M+H]^+$

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Compound 451

(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-3,5-dimethylaniline

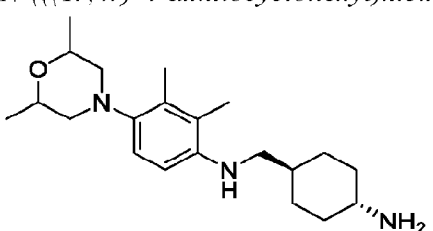


451

The title compound **451** (14.2 mg) was prepared in a total yield of 41.0% as a white solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.20 (d, J = 2.8 Hz, 1H), 6.08 (d, J = 2.8 Hz, 1H), 3.73 – 3.58 (m, 2H), 2.90 – 2.72 (m, 5H), 2.65 – 2.57 (m, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 2.02 – 1.75 (m, 4H), 1.64 - 1.42 (m, 2H), 1.36 – 1.23 (m, 3H), 1.05 (d, J = 6.4 Hz, 6H), 1.00 – 0.87 (m, 2H). Mass (m/z): 346.3 $[M+H]^+$

Compound 452

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2,3-dimethylaniline

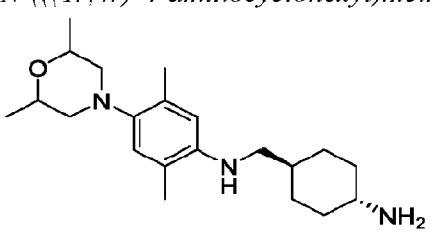


452

The title compound **452** (22.5 mg) was prepared in a total yield of 65.2% as a white solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.21 (d, J = 2.8 Hz, 1H), 6.09 (d, J = 2.8 Hz, 1H), 3.72 – 3.61 (m, 2H), 2.95 – 2.74 (m, 5H), 2.63 – 2.56 (m, 2H), 2.14 (s, 3H), 2.13 (s, 3H), 2.02 – 1.92 (m, 2H), 1.88 – 1.80 (m, 2H), 1.36 – 1.22 (m, 3H), 1.06 (d, J = 6.4 Hz, 6H), 1.02 – 0.88 (m, 2H). Mass (m/z): 346.3 $[M+H]^+$

Compound 453

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2,5-dimethylaniline



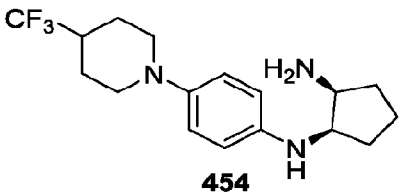
453

The title compound **453** (18.1 mg) was prepared in a total yield of 52.7% as a white solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.69 (s, 1H), 6.30 (s, 1H) ,3.76 – 3.62 (m, 2H), 3.01 – 2.83 (m, 3H), 2.78 – 2.67 (m, 2H), 2.35 – 2.21 (m, 2H), 2.17 (s, 3H), 2.02 (s, 3H), 2.00 - 1.91 (m, 2H), 1.91 – 1.82 (m, 2H), 1.39 – 1.17 (m, 3H), 1.08 (d, J = 6.4 Hz, 6H), 1.01 – 0.89 (m, 2H). Mass(m/z): 346.3 $[M+H]^+$.

Compound 454

CA 03227251 2024-1-26

(1R,2S)-N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclopentane-1,2-diamine

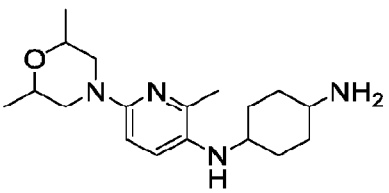


454

The title compound **454** (23 mg) was prepared in a yield of 36% as a white powder from 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (50 mg, 0.20 mmol) and tert-butyl (2-oxocyclopentyl)carbamate (61 mg, 0.30 mmol) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.12 (d, J = 8.4 Hz, 2H), 5.86 (d, J = 8.2 Hz, 2H), 2.93 (t, J = 7.1 Hz, 1H), 2.68 (d, J = 11.9 Hz, 2H), 2.58 (d, J = 7.2 Hz, 1H), 1.85 (t, J = 12.1 Hz, 2H), 1.41 (tt, J = 13.9, 7.1 Hz, 3H), 1.16 (d, J = 13.0 Hz, 2H), 1.04 (q, J = 7.4 Hz, 2H), 0.91 (dp, J = 21.7, 8.2 Hz, 3H), 0.69 (dd, J = 13.7, 7.3 Hz, 1H). Mass (m/z): 328.3 $[M+H]^+$.

Compound 455

(1s,4s)-N1-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)cyclohexane-1,4-diamine



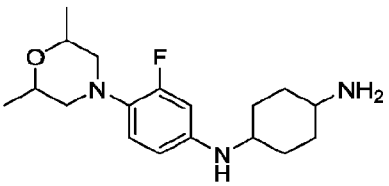
455A
455B

The title compound **455A** (4.6 mg) was prepared in a yield of 6.5% as a white powder and compound **455B** (1.4 mg) was prepared in a yield of 1.7% as a white powder from 6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine (Rt=7.62 min; 50 mg, 0.22 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (Rt= 8.07; 72 mg, 0.34 mmol) according to the procedure for **20**, which were prepared by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 0%-20%-95%-95%-10%, 0 min-10 min-10.5 min-11.5 min-13.0 min). **455A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (d, J = 8.9 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 3.88 (d, J = 8.3 Hz, 1H), 3.85 – 3.79 (m, 2H), 3.60 (ddd, J = 10.4, 6.2, 2.4 Hz, 2H), 2.98 (s, 1H), 2.18 (s, 2H), 2.14 (dd, J = 12.3, 10.4 Hz, 2H), 1.82 (dd, J = 46.2, 11.3 Hz, 4H), 1.25 – 1.15 (m, 4H), 1.13 (d, J = 6.2 Hz, 6H). Mass (m/z): 319.3 $[M+H]^+$. **455B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.85 (d, J = 8.9 Hz, 1H), 6.57 (d, J = 8.7 Hz, 1H), 3.85 (d, J = 8.3 Hz, 1H), 3.85 – 3.75 (m, 2H), 3.61 (ddd, J = 10.4, 6.3, 2.2 Hz, 2H), 2.96 (s, 1H), 2.18 (s, 2H), 2.14 (dd, J = 12.3, 10.4 Hz, 2H), 1.82 (dd, J = 46.2, 11.3 Hz, 4H), 1.23 – 1.11 (m, 4H), 0.94 (d, J = 6.5 Hz, 6H). Mass (m/z): 319.3 $[M+H]^+$.

Compound 456

N1-(4-(2,6-dimethylmorpholino)-3-fluorophenyl)cyclohexane-1,4-diamine

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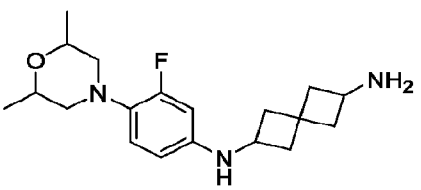


456

The title compound **456** (24.3 mg) was prepared in a yield of 33.9% as a white powder from 4-(2,6-dimethylmorpholino)-3-fluoroaniline (50 mg, 0.22 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (71mg, 0.33 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 2H), 6.80 (s, 1H), 6.48 – 6.27 (m, 2H), 5.43 (s, 1H), 3.69 (ddd, J = 8.6, 6.4, 2.1 Hz, 2H), 3.07 (s, 1H), 2.97 (d, J = 11.1 Hz, 3H), 2.25 (t, J = 10.7 Hz, 2H), 1.98 (d, J = 11.4 Hz, 4H), 1.73 (s, 1H), 1.59 (s, 1H), 1.45 (q, J = 12.0 Hz, 2H), 1.09 (d, J = 6.2 Hz, 6H). Mass (m/z): 322.5 $[M+H]^+$.

Compound 457

N2-(4-(2,6-dimethylmorpholino)-3-fluorophenyl)spiro[3.3]heptane-2,6-diamine

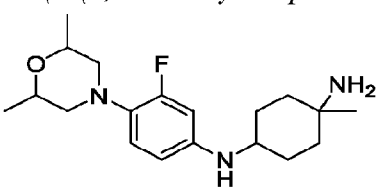


457

The title compound **457** (22.8 mg) was prepared in a yield of 30.7% as a white powder from 4-(2,6-dimethylmorpholino)-3-fluoroaniline (50 mg, 0.22 mmol) and tert-butyl (6-oxospiro[3.3]heptan-2-yl)carbamate (75mg, 0.34 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 2H), 6.80 (t, J = 9.2 Hz, 1H), 6.33 – 6.17 (m, 2H), 5.83 (s, 1H), 3.67 (ddd, J = 20.7, 11.2, 6.1 Hz, 3H), 3.54 (d, J = 7.0 Hz, 1H), 2.97 (d, J = 11.1 Hz, 2H), 2.43 – 2.29 (m, 3H), 2.25 (t, J = 10.7 Hz, 2H), 2.21 – 2.10 (m, 3H), 1.86 – 1.73 (m, 2H), 1.08 (d, J = 6.2 Hz, 6H). Mass (m/z): 334.6 $[M+H]^+$.

Compound 458

N1-(4-(2,6-dimethylmorpholino)-3-fluorophenyl)-4-methylcyclohexane-1,4-diamine



458

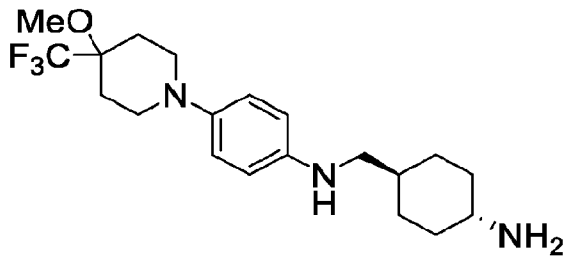
The title compound **458** (51.7 mg) was prepared in a yield of 69.1% as a white powder from 4-(2,6-dimethylmorpholino)-3-fluoroaniline (50 mg, 0.22 mmol) and tert-butyl (1-methyl-4-oxocyclohexyl)carbamate (61mg, 0.27 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (d, J = 32.3 Hz, 2H), 6.80 (t, J = 9.3 Hz, 1H), 6.50 – 6.25 (m, 2H), 5.39 (d, J = 50.6 Hz, 1H), 3.69 (ddt, J = 13.9, 7.5, 3.8 Hz, 2H), 3.15 (d, J = 42.1 Hz, 1H), 2.97 (d, J = 11.0 Hz, 2H), 2.25 (t, J = 10.7 Hz, 2H), 1.98 – 1.83 (m, 2H), 1.71 (p, J = 12.0, 11.1 Hz, 3H), 1.63 – 1.47 (m, 2H), 1.28 (d, J = 6.8 Hz, 4H), 1.08 (d, J = 6.2 Hz, 6H).

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Mass (m/z): 336.3 $[M+H]^+$.

Compound 459

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(4-methoxy-4-(trifluoromethyl)piperidin-1-yl)aniline

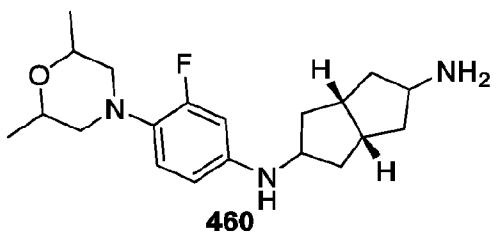


459

The title compound **459** (42.3 mg) was prepared in a yield of 60.2% as a white powder from 4-(4-methoxy-4-(trifluoromethyl)piperidin-1-yl)aniline (50 mg, 0.18 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (62mg, 0.27 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.47 (d, J = 8.4 Hz, 2H), 5.21 (s, 1H), 3.37 (d, J = 1.5 Hz, 3H), 3.25 (d, J = 12.0 Hz, 2H), 2.91 (s, 1H), 2.78 (s, 2H), 2.71 – 2.63 (m, 2H), 1.96 (d, J = 12.7 Hz, 4H), 1.82 (q, J = 12.0, 10.9 Hz, 4H), 1.44 (s, 1H), 1.27 (q, J = 13.2, 12.8 Hz, 2H), 0.98 (q, J = 12.5 Hz, 2H). Mass (m/z): 386.8 $[M+H]^+$.

Compound 460

(3aR,6aS)-N2-(4-(2,6-dimethylmorpholino)-3-fluorophenyl)octahydropentalene-2,5-diamine



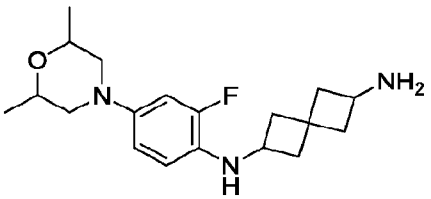
460

The title compound **460** (19.7 mg) was prepared in a three-step total yield of 24.5% as a white solid with 1:0.1 mixture by ^{1}H NMR from 4-(2,6-dimethylmorpholino)-3-fluoroaniline (100 mg, 0.45 mmol) and (3as,6as)-tetrahydropentalene-2,5(1H,3H)-dione (198 mg, 0.86 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.53 – 7.38 (m, 2H), 6.85 (t, J = 9.2 Hz, 1H), 6.41 (d, J = 15.0 Hz, 2H), 4.11 (s, 1H), 3.81 (p, J = 6.9, 5.5 Hz, 2H), 3.70 (dt, J = 16.0, 6.4 Hz, 1H), 3.49 (tt, J = 11.2, 6.5 Hz, 1H), 3.06 (d, J = 11.3 Hz, 2H), 2.67 (d, J = 10.3 Hz, 1H), 2.61 – 2.50 (m, 2H), 2.43 – 2.28 (m, 5H), 1.98 – 1.73 (m, 2H), 1.46 (td, J = 11.9, 8.2 Hz, 1H), 1.17 (d, J = 6.3 Hz, 6H). Mass (m/z): 347.3 $[M+H]^+$.

Compound 461

N2-(4-(2,6-dimethylmorpholino)-2-fluorophenyl)spiro[3.3]heptane-2,6-diamine

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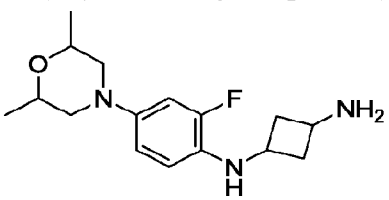


461

The title compound **461** (7.2 mg) was prepared in a total yield of 19.1% as a purple solid from tert-butyl (6-((4-(2,6-dimethylmorpholino)-2-fluorophenyl)amino)spiro[3.3]heptan-2-yl)carbamate (49 mg, 0.113 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 2H), 6.72 (dd, J = 14.8, 2.4 Hz, 1H), 6.59 – 6.45 (m, 2H), 4.98 (d, J = 7.2 Hz, 1H), 3.73 – 3.60 (m, 3H), 3.51 (q, J = 8.0 Hz, 1H), 3.34 (dt, J = 10.8, 2.0 Hz, 2H), 2.46 (td, J = 6.8, 3.2 Hz, 1H), 2.34 (dddd, J = 22.8, 11.6, 7.2, 3.6 Hz, 2H), 2.26 – 2.15 (m, 3H), 2.11 (dd, J = 11.6, 10.0 Hz, 2H), 1.91 (dt, J = 11.2, 7.2 Hz, 2H), 1.12 (d, J = 6.4 Hz, 6H). Mass (m/z): 334.3 $[M+H]^+$.

Compound 462

N1-(4-(2,6-dimethylmorpholino)-2-fluorophenyl)cyclobutane-1,3-diamine

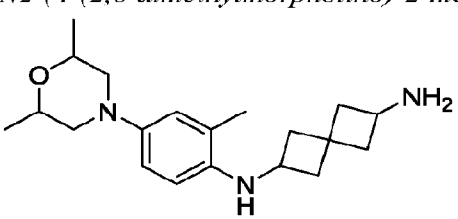


462

The title compound **462** (7.8 mg) was prepared in a total yield of 20.9% as a green solid from tert-butyl (3-((4-(2,6-dimethylmorpholino)-2-fluorophenyl)amino)cyclobutyl)carbamate (50 mg, 0.127 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 9.31 – 9.15 (m, 2H), 8.19 – 8.01 (m, 1H), 7.15 (t, J = 9.2 Hz, 1H), 7.01 – 6.91 (m, 1H), 6.86 (dd, J = 8.8, 2.8 Hz, 1H), 5.23 (dd, J = 12.0, 1.6 Hz, 1H), 3.73 – 3.60 (m, 4H), 2.46 (s, 3H), 2.31 (dd, J = 12.0, 10.0 Hz, 2H), 1.16 (d, J = 6.0 Hz, 6H). Mass (m/z): 294.3 $[M+H]^+$.

Compound 463

N2-(4-(2,6-dimethylmorpholino)-2-methylphenyl)spiro[3.3]heptane-2,6-diamine



463

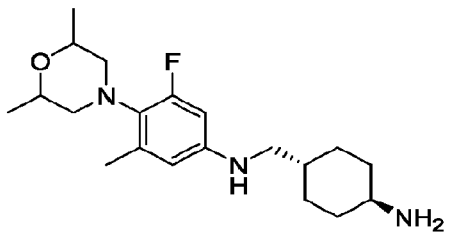
The title compound **463** (33.8 mg) was prepared in a total yield of 50.0% as a purple solid from tert-butyl (6-((4-(2,6-dimethylmorpholino)-2-methylphenyl)amino)spiro[3.3]heptan-2-yl)carbamate (88

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mg, 0.205 mmol), TFA (1 mL) and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (s, 3H), 6.62 (d, J = 2.8 Hz, 1H), 6.54 (dd, J = 8.8, 2.8 Hz, 1H), 6.26 (d, J = 8.8 Hz, 1H), 4.41 (d, J = 6.8 Hz, 1H), 3.62 (dqd, J = 10.4, 6.0, 2.4 Hz, 3H), 3.51 – 3.44 (m, 1H), 3.23 (dt, J = 10.4, 2.0 Hz, 2H), 2.32 (dtd, J = 16.8, 7.2, 4.0 Hz, 2H), 2.19 (dd, J = 11.2, 8.4 Hz, 1H), 2.13 (dd, J = 8.0, 4.0 Hz, 2H), 2.09 – 2.02 (m, 2H), 2.00 (s, 3H), 1.86 (ddd, J – 11.2, 8.0, 5.6 Hz, 2H), 1.07 (d, J – 6.0 Hz, 6H). Mass(m/z): 330.3 $[M+H]^+$.

Compound 464

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-3-fluoro-5-methylaniline

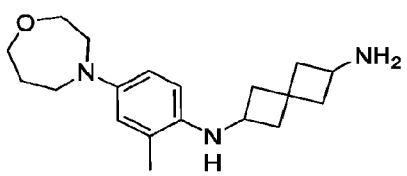


464

The title compound **464** (15.2 mg) was prepared in a total yield of 7.1% as a light-yellow solid according to the procedure for compound **354**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.26 – 6.21 (m, 1H), 6.15 – 6.07 (m, 1H), 3.79 – 3.71 (m, 2H), 3.08 – 3.00 (m, 1H), 2.93 – 2.87 (m, 2H), 2.82 – 2.75 (m, 2H), 2.69 – 2.64 (m, 2H), 2.21 (s, 3H), 2.10 – 1.94 (m, 4H), 1.65 – 1.57 (m, 1H), 1.43 – 1.33 (m, 2H), 1.18 – 1.02 (m, 8H). Mass (m/z): 350.2 $[M+H]^+$.

Compound 465

N^2-(2-methyl-4-(1,4-oxazepan-4-yl)phenyl)spiro[3.3]heptane-2,6-diamine



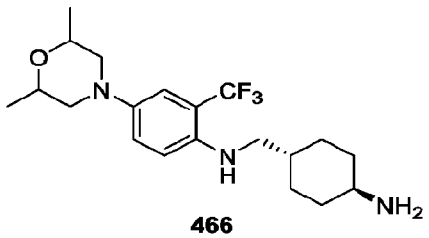
465

The desired product **465** (45 mg, 31.4%) as oil was prepared from tert-butyl (6-((2-methyl-4-(1,4-oxazepan-4-yl)phenyl)amino)spiro[3.3]heptan-2-yl)carbamate (180 mg, 0.4321 mmol), 1,4-dioxane (10 mL) and HCl/1,4-dioxane (10 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.49 (s, 1H), 6.42 (d, J = 8.4 Hz, 1H), 6.28 (d, J = 8.6 Hz, 1H), 4.14 (brs, 1H), 3.72 – 3.65 (m, 2H), 3.59 (s, 1H), 3.54 (t, J = 5.5 Hz, 2H), 3.38 – 3.24 (m, 2H), 3.19 – 3.13 (m, 1H), 2.43 – 2.37 (m, 1H), 2.33 – 2.23 (m, 2H), 2.14 – 2.09 (m, 1H), 2.03 (s, 3H), 1.83 (m, 5H), 1.69 – 1.59 (m, 2H). Mass (m/z): 316.23 $[M+H]^+$.

Compound 466

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2-(trifluoromethyl)aniline

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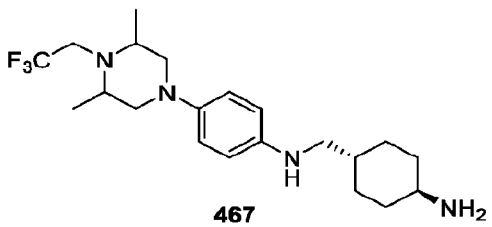


466

The title compound **466** (16.2 mg, 16.7%) as a yellow solid was prepared from tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)-2-(trifluoromethyl)phenyl)amino)methyl)cyclohexyl) carbamate (120 mg, 0.2461 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, J = 9.1 Hz, 1H), 6.95 (d, J = 2.5 Hz, 1H), 6.75 (d, J = 9.0 Hz, 1H), 3.73 – 3.62 (m, 3H), 3.36 (brs, 7H), 2.96 (d, J = 6.2 Hz, 2H), 2.85 (s, 1H), 2.14 (s, 1H), 1.89 (s, 2H), 1.78 (d, J = 11.0 Hz, 2H), 1.13 (d, J = 6.2 Hz, 6H). Mass (m/z): 386.23 $[M+H]^+$.

Compound 467

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(3,5-dimethyl-4-(2,2,2-trifluoroethyl) piperazin-1-yl)aniline

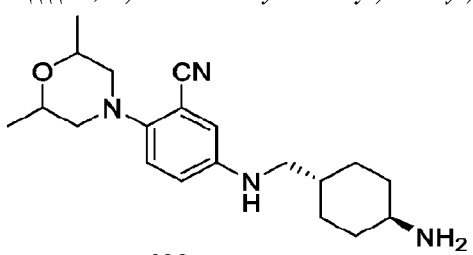


467

The title compound **467** as a yellow solid (10 mg, 20%) was prepared from tert-butyl ((1r,4r)-4-(((4-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)phenyl)amino)methyl)cyclohexyl)carbamate (0.06 g, 0.3 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 3.54 – 3.52 (m, 4H), 3.26 (s, 2H), 3.16 – 2.91 (m, 5H), 2.04 – 2.02 (m, 4H), 1.69 (s, 1H), 1.40 – 1.38 (m, 2H), 1.32 – 1.04 (m, 8H). Mass (m/z): 398.8$[M+H]^+$.

Compound 468

5-((((1r,4r)-4-aminocyclohexyl)methyl)amino)-2-(2,6-dimethylmorpholino)-benzonitrile



468

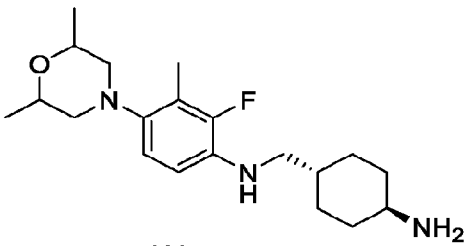
The title compound **468** (84 mg) as a white solid was prepared from tert-butyl ((1r,4r)-4-(((3-cyano-4-(2,6-dimethylmorpholino)phenyl)amino)-methyl)cyclohexyl)carbamate (200 mg, 0.45 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.99 (d, J = 8.8 Hz, 1H), 6.84 (dd, J = 8.8, 2.8 Hz, 1H), 6.79 (d, J = 2.8 Hz, 1H), 3.89 – 3.77 (m, 2H), 3.11 (d, J = 10.8 Hz, 2H), 3.05 (td, J = 8.0, 4.0 Hz, 1H),

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2.94 (d, J = 6.6 Hz, 2H), 2.46 – 2.37 (m, 2H), 2.02 (dd, J = 31.0, 11.8 Hz, 4H), 1.65 – 1.53 (m, 1H), 1.40 (m, 2H), 1.18 (d, J = 6.2 Hz, 6H), 1.10 (dd, J = 19.2, 8.8 Hz, 2H). Mass (m/z): 343.3 $[M+H]^+$.

Compound 469

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2-fluoro-3-methylaniline

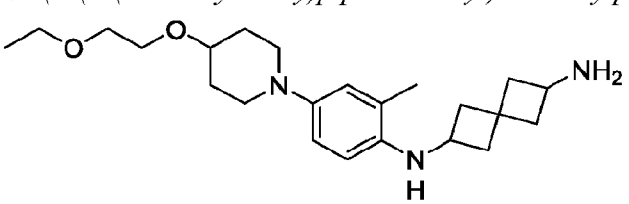


469

The title compound **469** (141 mg) as a white solid was prepared from tert-butyl ((1r,4r)-4-(((4-(2,6-dimethylmorpholino)-2-fluoro-3-methylphenyl)-amino)methyl)cyclohexyl) carbamate (200 mg, 0.44 mmol), DCM (10 mL), and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.70 (dd, J = 8.6, 1.2 Hz, 1H), 6.52 (t, J = 9.2 Hz, 1H), 3.81 (brs, 2H), 3.05 (ddd, J = 15.8, 7.8, 3.8 Hz, 1H), 3.00 (t, J = 6.6 Hz, 2H), 2.81 (d, J = 10.8 Hz, 2H), 2.39 – 2.26 (m, 2H), 2.17 (d, J = 2.8 Hz, 3H), 2.01 (dd, J = 31.0, 11.6 Hz, 4H), 1.67 – 1.53 (m, 1H), 1.37 (qd, J = 12.6, 3.0 Hz, 2H), 1.16 (d, J = 6.2 Hz, 6H), 1.14 – 1.03 (m, 2H). Mass (m/z): 350.3 $[M+H]^+$.

Compound 470

N2-(4-(4-(2-ethoxyethoxy)piperidin-1-yl)-2-methylphenyl)spiro[3.3]heptane-2,6-diamine



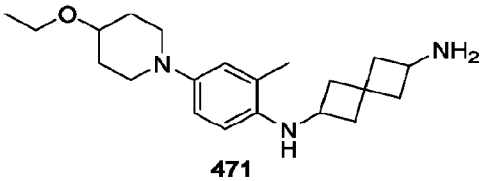
470

The title compound **470** (40 mg) as a yellow solid (40 mg, 33.5%) was prepared from tert-butyl (6-((4-(4-(2-ethoxyethoxy)piperidin-1-yl)-2-methylphenyl)amino)spiro[3.3]heptan-2-yl)carba mate (150 mg, 0.24 mmol), 1,4-dioxane (3 mL) and HCl /1,4-dioxane (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.66 (d, J = 2.5 Hz, 1H), 6.59 (dd, J = 8.5, 2.6 Hz, 1H), 6.27 (d, J = 8.6 Hz, 1H), 4.36 (d, J = 6.0 Hz, 1H), 3.66 – 3.59 (m, 1H), 3.55 – 3.51 (m, 2H), 3.47 (dd, J = 4.4, 2.3 Hz, 2H), 3.44 – 3.41 (m, 2H), 3.20 (s, 3H), 2.65 – 2.57 (m, 2H), 2.45 – 2.38 (m, 1H), 2.30 (dt, J = 11.5, 4.5 Hz, 2H), 2.15 – 2.09 (m, 1H), 2.02 (s, 3H), 1.93 – 1.81 (m, 4H), 1.68 (dd, J = 14.3, 6.0 Hz, 2H), 1.55 – 1.47 (m, 2H), 1.10 (t, J = 7.0 Hz, 3H). Mass (m/z): 388.3 $[M+H]^+$.

Compound 471

N2-(4-(4-ethoxypiperidin-1-yl)-2-methylphenyl)spiro[3.3]heptane-2,6-diamine

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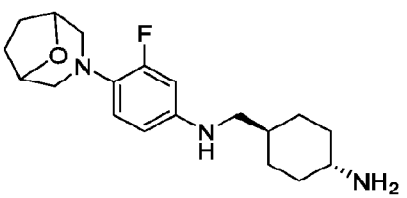


471

The title compound **471** (47.7 mg, 19%) as a white solid was prepared from tert-butyl (6-((4-(4-ethoxypiperidin-1-yl)-2-methylphenyl)amino)spiro[3.3]heptan-2-yl)carbamate (319 mg, 0.72 mmol), HCl in dioxane (5 mL) and DCM (5 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.83 – 6.73 (m, 2H), 6.47 (d, J = 8.5 Hz, 1H), 3.81 – 3.73 (m, 1H), 3.56 (q, J = 7.0 Hz, 2H), 3.49 – 3.40 (m, 1H), 3.29 – 3.22 (m, 2H), 2.78 – 2.69 (m, 2H), 2.57-2.50 (m, 1H), 2.48 – 2.41 (m, 1H), 2.40 – 2.32 (m, 1H), 2.28-2.21 (m, 1H), 2.11 (s, 3H), 2.06 – 1.96 (m, 2H), 1.94 – 1.76 (m, 4H), 1.74 – 1.62 (m, 2H), 1.19 (t, J = 7.0 Hz, 3H). Mass (m/z): 344.3$[M+H]^+$.

Compound 472

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-3-fluoroanilin e

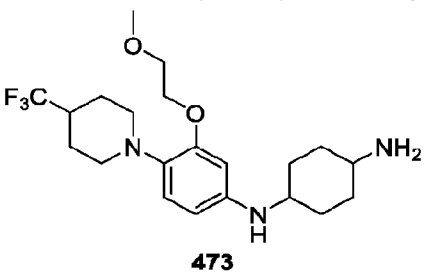


472

The title compound **472** (19.5 mg) was prepared in a total yield of 58.4% as a gray solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.75 (m, 1H), 6.45 – 6.20 (m, 2H), 4.32 – 4.26 (m, 2H), 2.91 (m, 1H), 2.85 – 2.71 (m, 6H), 2.05 – 1.93 (m, 4H), 1.89 – 1.70 (m, 4H), 1.44 – 1.24 (m, 3H), 1.05 – 0.92 (m, 2H). Mass (m/z): 334.2 $[M+H]^+$.

Compound 473

N1-(3-(2-methoxyethoxy)-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,4-diamine



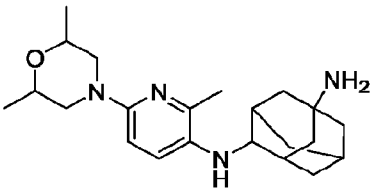
473

The title compound **473** (18.1 mg) was prepared in a total yield of 43.5% as a white solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.66 (s, 1H), 6.35 – 6.05 (m, 2H), 4.10 - 3.95 (m, 2H), 3.72 - 3.57 (m, 2H), 3.28 (s, 3H), 3.30 – 3.22 (m, 2H), 3.07 (m, 1H), 2.95 (m, 1H), 2.47 – 2.38 (m, 2H), 2.33 (m, 1H), 2.06 – 1.93 (m, 2H), 1.89 – 1.65 (m, 5H), 1.62 – 1.36 (m, 4H), 1.14 (m, 1H). Mass(m/z): 416.3 $[M+H]^+$

Compound 474

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N^4-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)adamantane-1,4-diamine



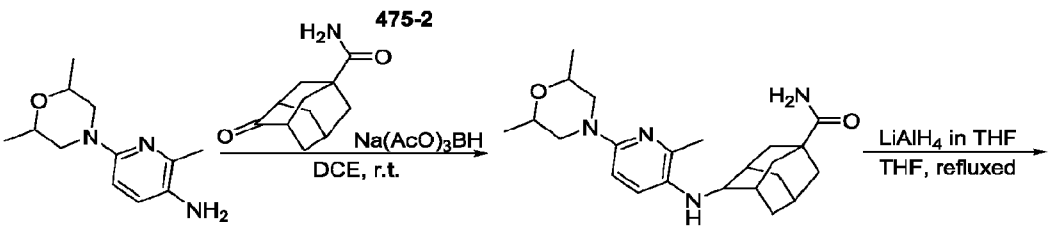
474A

474B

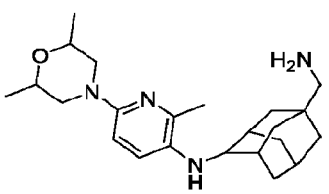
The title compound **474A** and **474B** were prepared according to the procedure for compound **24**. The residue was purified by preparative HPLC (XSelect-CSH-Prep 5 μm OBD, 19*150 mm column; ACN/water (0.5% TFA) = 0%-0%-30%-95%-95%-0%, 0 min-2 min-9 min-9.5 min-10.5 min-12.0 min) to afford compound **474A** (Rt = 7.35 min) in a 22.6% yield as a white solid and **474B** (Rt = 7.86 min) in a 14.0% yield as a white solid. **474A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, J = 8.9 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 3.83 – 3.78 (m, 3H), 3.61 – 3.54 (m, 2H), 3.41 (br, 3H), 3.31 – 3.28 (m, 1H), 2.24 (s, 3H), 2.12 (dd, J = 12.4, 10.4 Hz, 2H), 1.97 – 1.85 (m, 5H), 1.69 – 1.62 (m, 2H), 1.61 – 1.53 (m, 4H), 1.31 – 1.25 (m, 2H), 1.10 (d, J = 6.3 Hz, 6H). Mass (m/z): 374.2 $[M+H]^+$. **474B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (br, 3H), 6.90 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.8 Hz, 1H), 3.91 – 3.81 (m, 3H), 3.65 – 3.57 (m, 2H), 3.30 (d, J = 3.1 Hz, 1H), 2.31 (s, 3H), 2.21 – 2.12 (m, 4H), 2.11 – 2.04 (m, 3H), 1.80 – 1.63 (m, 6H), 1.54 – 1.46 (m, 2H), 1.14 (d, J = 6.2 Hz, 6H). Mass (m/z): 374.2 $[M+H]^+$.

Compound 475

N-(5-(aminomethyl)adamantan-2-yl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine



475-1 Step 1 **475-3** Step 2



475A

475B

Step 1. Preparation of 4-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)adamantane-1-carboxamide (**475-3**)

The title compound **475-3** (16.0 mg) was prepared in a total yield of 68.7% as a yellow solid from 6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine (150 mg, 0.68 mmol),

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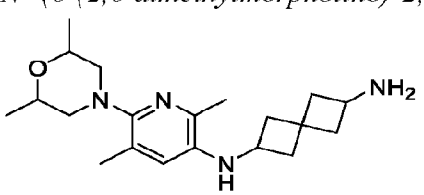
4-oxoadamantane-1-carboxamide (131 mg, 0.68 mmol) and $Na(AcO)_3BH$ (288 mg, 1.36 mmol) in DCE (5.0 mL) according to the procedure for **403-3**. Mass (m/z): 399.2 $[M+H]^+$.

Step 2. Preparation of *N*-(5-(aminomethyl)adamantan-2-yl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine (**475**)

A solution of 4-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)adamantane-1-carboxamide (186 mg, 0.47 mol) in THF (10 mL) was added 0.39 mL of a solution of $LiAlH_4$ (35.7 mg, 0.6 mol) in THF at 0 °C, and the mixture was refluxed for 2 h. After cooling to 0 °C, water (35.7 uL), 10% NaOH (71.4 uL) and water 107.1 uL) were added, and the mixture was stirred for 3 min at room temperature. The solid was filtered and the filtered gray cake was washed with THF (10 mL*2); then the combined filtrates were dried over Na_2SO_4 and concentrated. The residue was purified by preparative HPLC (XSelect-CSH-Prep 5 μm OBD, 19*150 mm column; ACN/water (0.5% TFA) = 0%-0%-40%-95%-95%-0%, 0 min-2 min-9 min-9.5 min-10.5 min-12 min) to afford compound **475A** (Rt = 7.89 min) in 14.5% yield as a white solid and **475B** (Rt = 8.56 min) in 6.3% yield as a white solid. **475A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 3H), 6.87 (d, J = 8.6 Hz, 1H), 6.54 (d, J = 8.8 Hz, 1H), 3.98 – 3.79 (m, 3H), 3.67 – 3.55 (m, 2H), 3.35 – 3.30 (m, 2H), 2.30 (s, 3H), 2.22 – 2.13 (m, 2H), 2.04 – 1.90 (m, 5H), 1.64 – 1.58 (m, 2H), 1.55 – 1.50 (m, 2H), 1.40 – 1.33 (m, 2H), 1.14 (d, J = 6.2 Hz, 6H). Mass (m/z): 385.2 $[M+H]^+$. **475B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (s, 3H), 6.91 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 3.88 – 3.82 (m, 2H), 3.81 – 3.76 (m, 1H), 3.66 – 3.57 (m, 2H), 3.40 – 3.35 (m, 2H), 2.29 (s, 3H), 2.20 – 2.13 (m, 2H), 2.02 – 1.95 (m, 3H), 1.81 – 1.73 (m, 4H), 1.71 – 1.66 (m, 2H), 1.51 – 1.47 (m, 2H), 1.29 – 1.22 (m, 2H), 1.14 (d, J = 6.2 Hz, 6H). Mass (m/z): 385.2 $[M+H]^+$.

Compound 476

N^2-(6-(2,6-dimethylmorpholino)-2,5-dimethylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



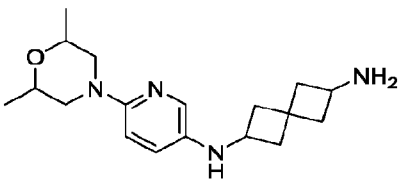
476

The title compound **476** (18.0 mg) was prepared in a total yield of 60.9% as a dark blue solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 6.87 (s, 1H), 3.83 – 3.73 (m, 2H), 3.69 – 3.59 (m, 2H), 2.98 (d, J = 12.2 Hz, 2H), 2.51 – 2.39 (m, 4H), 2.37 – 2.30 (m, 1H), 2.26 – 2.18 (m, 1H), 2.14 – 2.03 (m, 8H), 1.88 – 1.79 (m, 2H), 1.06 (d, J = 6.3 Hz, 6H). Mass (m/z): 345.2$[M+H]^+$.

Compound 477

N2-(6-(2,6-dimethylmorpholino)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine

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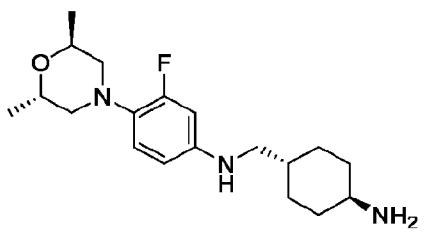


477

The title compound **477** (55.2 mg) was prepared in a total yield of 53.1% as a green solid from tert-butyl (6-((6-(2,6-dimethylmorpholino)pyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (125 mg, 0.300 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 3H), 7.49 (d, J = 2.8 Hz, 1H), 6.92 (dd, J = 8.8, 2.8 Hz, 1H), 6.71 (d, J = 9.2 Hz, 1H), 3.89 – 3.80 (m, 2H), 3.70 – 3.57 (m, 3H), 3.51 (d, J = 8.4 Hz, 2H), 2.47 (td, J = 6.8, 3.6 Hz, 1H), 2.35 (tdt, J = 11.6, 6.8, 4.0 Hz, 2H), 2.27 – 2.15 (m, 5H), 1.82 (dt, J = 11.2, 8.0 Hz, 2H), 1.13 (d, J = 6.0 Hz, 6H). Mass (m/z): 317.3 $[M+H]^+$.

Compound 478

N-(((1r,4S)-4-aminocyclohexyl)methyl)-4-((2S,6S)-2,6-dimethylmorpholino)-3-fluoroaniline

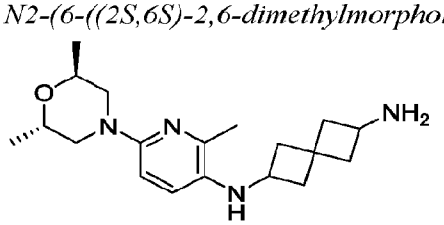


478

The title compound **478** (41.9 mg) was prepared in a total yield of 39.6% as a white solid from tert-butyl ((1S,4r)-4-(((4-((2S,6S)-2,6-dimethylmorpholino)-3-fluorophenyl)amino)methyl)cyclohexyl)carbamate (138 mg, 0.317 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 3H), 6.77 (dd, J = 10.0, 8.8 Hz, 1H), 6.39 – 6.26 (m, 2H), 5.68 (t, J = 6.0 Hz, 1H), 3.99 (pd, J = 6.4, 3.2 Hz, 2H), 2.93 – 2.75 (m, 5H), 2.58 – 2.52 (m, 2H), 2.05 – 1.94 (m, 2H), 1.90 – 1.78 (m, 2H), 1.51 – 1.27 (m, 3H), 1.20 (d, J = 6.4 Hz, 6H), 0.98 (tdd, J = 15.2, 11.2, 4.8 Hz, 2H). Mass (m/z): 336.3 $[M+H]^+$.

Compound 479

N2-(6-((2S,6S)-2,6-dimethylmorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



479

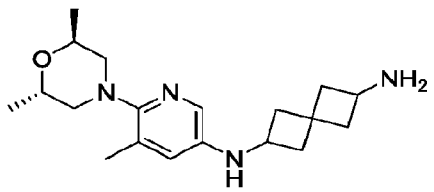
The title compound **479** (51.5 mg) was prepared in a total yield of 61.6% as a yellow solid from tert-butyl (6-((6-((2S,6S)-2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (109 mg, 0.253 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure

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for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 3H), 6.76 (s, 1H), 6.50 (d, J = 8.4 Hz, 1H), 4.60 (s, 1H), 3.99 (tt, J = 10.0, 4.8 Hz, 2H), 3.71 – 3.59 (m, 1H), 3.53 (s, 1H), 3.30 (dd, J = 12.4, 3.2 Hz, 2H), 2.92 (dd, J = 12.0, 6.0 Hz, 2H), 2.47 (t, J = 5.6 Hz, 1H), 2.36 (dddd, J = 20.0, 11.6, 7.2, 4.0 Hz, 2H), 2.26 – 2.15 (m, 6H), 1.92 (p, J = 6.4 Hz, 2H), 1.17 (d, J = 6.4 Hz, 6H). Mass (m/z): 331.3 $[M+H]^+$.

Compound 480

N2-(6-((2S,6S)-2,6-dimethylmorpholino)-5-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

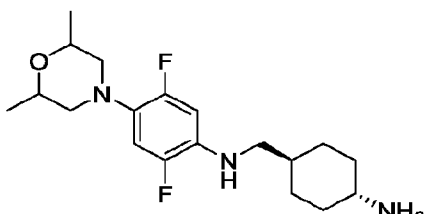


480

The title compound **480** (47.4 mg) was prepared in a total yield of 55.6% as a yellow solid from tert-butyl (6-((6-((2S,6S)-2,6-dimethylmorpholino)-5-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (111 mg, 0.258 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 3H), 7.42 (d, J = 2.8 Hz, 1H), 6.75 (d, J = 2.8 Hz, 1H), 5.71 (s, 1H), 3.73 – 3.64 (m, 3H), 3.00 – 2.89 (m, 2H), 2.51 – 2.46 (m, 1H), 2.37 (qd, J = 11.6, 6.4 Hz, 4H), 2.24 – 2.16 (m, 3H), 2.15 (s, 3H), 1.82 (dt, J = 11.2, 8.4 Hz, 2H), 1.08 (d, J = 6.0 Hz, 6H). Mass (m/z): 331.3 $[M+H]^+$.

Compound 481

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2,5-difluoroaniline



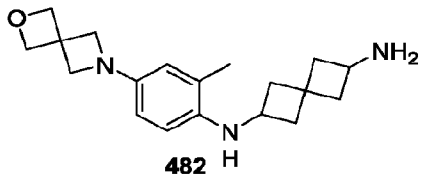
481

The title compound **481** (4 mg) as a white solid was prepared according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (dd, J = 13.3, 8.0 Hz, 1H), 6.51 (dd, J = 14.2, 8.0 Hz, 1H), 5.35 – 5.24 (m, 1H), 3.69 (ddt, J = 12.7, 6.5, 3.2 Hz, 2H), 3.05 – 2.95 (m, 2H), 2.84 (t, J = 6.4 Hz, 2H), 2.25 (t, J = 10.8 Hz, 2H), 1.99 (p, J = 7.0, 6.5 Hz, 1H), 1.76 (dd, J = 22.6, 10.2 Hz, 4H), 1.45 (d, J = 12.5 Hz, 1H), 1.31 – 1.18 (m, 4H), 1.09 (d, J = 6.2 Hz, 6H). Mass (m/z): 354.2 $[M+H]^+$.

Compound 482

N^2-(2-methyl-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)spiro[3.3]heptane-2,6-diamine

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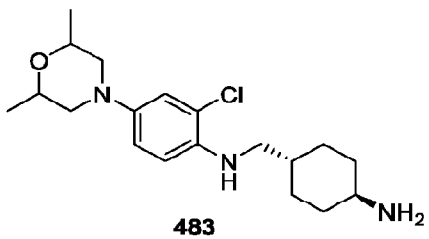


482

The title compound **482** (24.1 mg, 16.8%) as oil was prepared from tert-butyl (6-((2-methyl-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)amino)spiro[3.3]heptan-2-yl)carbamate (160 mg, 0.39 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.46 (m, 1H), 6.33 (m, 2H), 4.79 (s, 4H), 3.88 (brs, 4H), 3.74 (brs, 1H), 3.42 (t, J = 7.6 Hz, 1H), 2.57 – 2.50 (m, 1H), 2.51 – 2.44 (m, 1H), 2.38 (m, 1H), 2.30 – 2.22 (m, 1H), 2.10 (s, 3H), 1.92 (m, 4H). Mass (m/z): 314.22 $[M+H]^+$.

Compound 483

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-chloro-4-(2,6-dimethylmorpholino)aniline

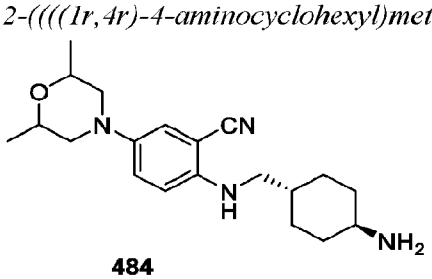


483

The title compound **483** (29.8 mg, yield: 75.9%) as black oil was prepared from tert-butyl ((1r,4r)-4-(((2-chloro-4-(2,6-dimethylmorpholino)phenyl)amino)methyl)cyclohexyl)carbamate (90 mg, 0.2 mmol), DCM (20 mL) and TFA (4 mL) according to the procedure for **24**. 1H NMR (400 MHz, CD_3OD) δ 7.18 (dd, J = 9.2, 2.9 Hz, 1H), 6.96 (d, J = 2.8 Hz, 1H), 6.73 (d, J = 9.2 Hz, 1H), 3.77 (ddd, J = 10.2, 6.3, 2.2 Hz, 2H), 3.30 – 3.24 (m, 2H), 3.04 (d, J = 6.8 Hz, 2H), 2.64 (s, 1H), 2.28 – 2.19 (m, 2H), 1.96 – 1.83 (m, 4H), 1.64 – 1.50 (m, 1H), 1.24 – 0.99 (m, 10H). Mass (m/z): 351.8 $[M+H]^+$.

Compound 484

2-((((1r,4r)-4-aminocyclohexyl)methyl)amino)-5-(2,6-dimethylmorpholino)benzonitrile



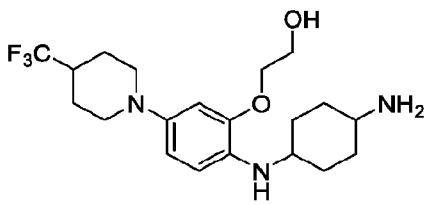
484

The title compound **484** (29 mg, yield: 37.2%) as a blue solid was prepared from tert-butyl ((1r,4r)-4-(((2-cyano-4-(2,6-dimethylmorpholino)phenyl)amino)methyl)cyclohexyl)carbamate (100 mg, 0.21 mmol), DCM (20 mL) and TFA (4 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.92 (d, J = 2.7 Hz, 1H), 6.84 (dd, J = 8.9, 2.7 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H), 3.77 (ddd, J = 10.2, 6.3, 2.2 Hz, 2H), 3.27 (d, J = 10.6 Hz, 2H), 3.00 (d, J = 6.8 Hz, 2H), 2.67 (tt, J = 11.2, 3.8 Hz, 1H), 2.29 – 2.19 (m, 2H), 1.99 – 1.83 (m, 4H), 1.56 (ddd, J = 11.1, 7.7, 4.0 Hz, 1H), 1.16 (dd, J = 32.3, 17.3 Hz, 10H). Mass (m/z): 342.9 $[M+H]^+$.

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Compound 485

2-(2-((4-aminocyclohexyl)amino)-5-(4-(trifluoromethyl)piperidin-1-yl)phenoxy)ethan-1-ol

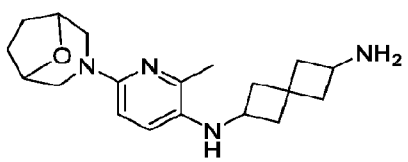


485

The desired product as a yellow solid (4.7 mg, 5.8%) was prepared from tert-butyl (4-((2-(2-hydroxyethoxy)-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (100 mg, 0.20 mmol), 1,4-dioxane (3 mL) and HCl /1,4-Dioxane (1 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 2H), 6.64 (d, J = 8.3 Hz, 2H), 6.57 (s, 1H), 4.06 (s, 2H), 3.92 – 3.88 (m, 2H), 3.50 (dd, J = 13.8, 6.7 Hz, 3H), 3.34 (s, 1H), 2.97 (s, 1H), 2.65 (s, 3H), 2.24 (s, 1H), 1.96 (d, J = 11.9 Hz, 2H), 1.72 (m, 10H). Mass (m/z): 402.2 $[M+H]^+$.

Compound 486

N2-(6-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

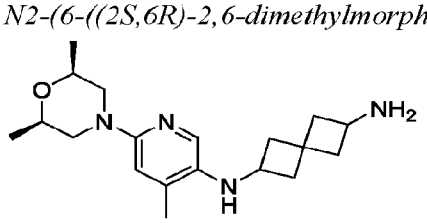


486

The title compound **486** (50.2 mg) was prepared in a total yield of 76.3% as a purple solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 8.8 Hz, 1H), 4.41 – 4.30 (m, 2H), 3.69 – 3.46 (m, 3H), 3.16 (m, 1H), 2.78 – 2.67 (m, 2H), 2.43 – 2.30 (m, 2H), 2.25 – 2.06 (m, 7H), 1.96 – 1.84 (m, 2H), 1.80 – 1.68 (m, 4H). Mass (m/z): 329.2 $[M+H]^+$.

Compound 487

N2-(6-((2S,6R)-2,6-dimethylmorpholino)-4-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



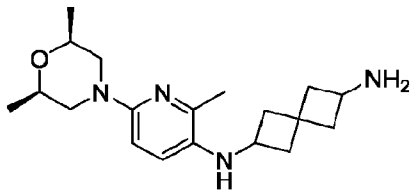
487

The title compound **487** (52.1 mg) was prepared in a total yield of 52.4% as a white solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 (s, 1H), 6.69 (s, 1H), 3.95 – 3.82 (m, 2H), 3.76 – 3.47 (m, 5H), 3.16 (m, 1H), 2.44 – 2.30 (m, 2H), 2.27 – 2.12 (m, 4H), 2.09 (s, 3H), 1.97 – 1.86 (m, 2H), 1.12 (d, J = 6.4 Hz, 6H). Mass (m/z): 331.2 $[M+H]^+$.

Compound 488

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N2-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

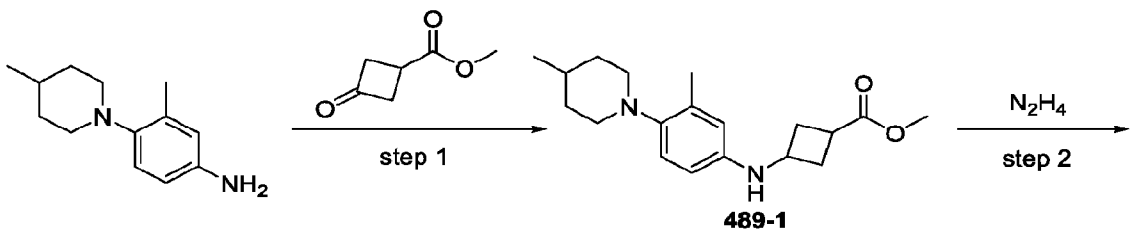


488A
488B

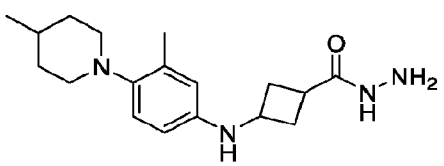
The title compound **488** was prepared according to the procedure for compound **24**. The mixture was purified by CHIRALPAK IG-3, 4.6*50 mm, 3 μm (solvent system (MTBE (3‰ isopropylamine):EtOH=80:20) to afford compound **488A** (Rt = 1.614 min) in 13.6 % yield as a light yellow solid and **488B** (Rt = 2.177 min) in 14.5% yield as a light yellow solid. **488A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.86 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 3.85 – 3.64 (m, 5H), 3.27 (m, 1H), 2.56 – 2.39 (m, 2H), 2.35 (m, 1H), 2.31 – 2.22 (m, 6H), 1.96 – 1.75 (m, 4H), 1.21 (d, J = 6.0 Hz, 6H). Mass (m/z): 331.2 $[M+H]^+$. **488B**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.87 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 8.8 Hz, 1H), 3.85 – 3.64 (m, 5H), 3.27 (m, 1H), 2.62 – 2.40 (m, 2H), 2.38 – 2.32 (m, 2H), 2.28 (s, 3H), 2.26 – 2.19 (m, 2H), 1.97 – 1.72 (m, 4H), 1.21 (d, J = 6.0 Hz, 6H). Mass (m/z): 331.2 $[M+H]^+$.

Compound 489

3-((3-methyl-4-(4-methylpiperidin-1-yl)phenyl)amino)cyclobutane-1-carbohydrazide



489-1



489

Step 1. Preparation of methyl 3-((3-methyl-4-(4-methylpiperidin-1-yl)phenyl)amino)cyclobutane-1-carboxylate (**489-1**)

To a solution of 3-methyl-4-(4-methylpiperidin-1-yl)aniline (0.2 g, 0.98 mmol) in DCE (5 ml) was added methyl 3-oxocyclobutane-1-carboxylate (125 mg, 0.98 mmol) and $NaBH(OAc)_3$ (623 mg, 2.94 mmol). The reaction was stirred for 3 h at R.T. Quenched with water (10 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, concentrated and purified by flash, eluted with PE/EA = 10:1 to 1:1 to give the desired product as yellow oil (0.22 g, 60%). Mass (m/z): 316.9 $[M+H]^+$.

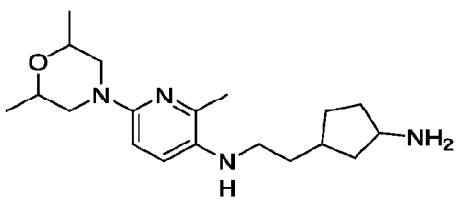
Step 2. Preparation of 3-((3-methyl-4-(4-methylpiperidin-1-yl)phenyl)amino)cyclobutane-1-carbohydrazide (**489**)

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To a solution of methyl 3-((3-methyl-4-(4-methylpiperidin-1-yl)phenyl)amino)cyclobutane-1-carboxylate (220 mg, 0.7 mmol) in EtOH (10 mL) was added N_2H_4 (50 mg) and the mixture was stirred at 80 °C for 2 h . Quenched with water (30 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, removed under vacuum and the residue was purified by preparative HPLC (column-Gemini-C18 150 x 21.2 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 10%-40%) to afford compound **489** (83 mg, 42.9%) as a yellow solid. Mass (m/z): 316.8 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 6.79 (dd, *J*=8.4, 3.6, 1H), 6.35 – 6.22 (m, 2H), 5.55 – 5.50 (m, 1H), 3.91 – 3.68 (m, 1H), 3.64 (s, 1H), 3.59 (s, 2H), 2.84 – 2.81 (m, 2H), 2.55 – 2.52 (m, 1H), 2.47 – 2.44 (m, 1H), 2.12 – 2.04 (m, 4H), 1.98 – 1.91 (m, 1H), 1.65 – 1.63 (m, 2H), 1.42 – 1.37 (m, 1H), 1.29 – 1.20 (m, 2H), 0.94 (d, *J* = 6.4, 3H). Mass (m/z): 317.3 $[M+H]^+$.

Compound 490

N-(2-(3-aminocyclopentyl)ethyl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine

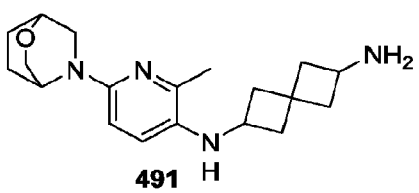


490

The title compound **490** (40.4 mg, 9.4% yield) as a yellow solid was prepared from N-(4-aminophenyl)-2,2,2-trifluoro-N-methylacetamide (0.45 g, 1.3 mmol), BH_3-THF (10 mL) and THF (5 mL) according to the procedure for **150**. ^1H NMR (400 MHz, DMSO-d_6) δ = 6.83 (d, *J* = 8.8, 1H), 6.51 (d, *J* = 8.8, 1H), 4.30 (s, 1H), 3.83 (d, *J*=11.2, 2H), 3.63 – 3.60 (m, 2H), 3.29 – 3.14 (m, 1H), 2.94 (t, *J* = 7.2, 2H), 2.21 (s, 3H), 2.09 – 1.94 (m, 1H), 1.89 – 1.79 (m, 2H), 1.78 – 1.65 (m, 1H), 1.65 – 1.40 (m, 3H), 1.39 – 1.17 (m, 2H), 1.14 (d, *J* = 6.4, 7H). Mass (m/z): 332.9 $[M+H]^+$.

Compound 491

N2-(6-(2-oxa-5-azabicyclo[2.2.2]octan-5-yl)-2-methylpyridin-3-yl)spiro[3.3]-heptane-2,6-diamine



491

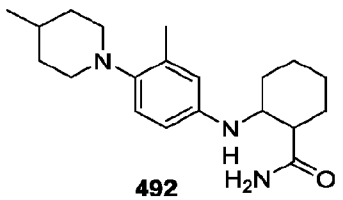
The title compound (35 mg) as a white solid was prepared from tert-butyl (6-((6-(2-oxa-5-azabicyclo[2.2.2]octan-5-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (400 mg, 0.84 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^1HNMR (400 MHz, DMSO-d_6) δ 6.71 (d, *J* = 8.8 Hz, 1H), 6.18 (d, *J* = 8.8 Hz, 1H), 4.37 (s, 1H), 3.90 – 3.88 (m, 1H), 3.86 (t, *J* = 5.6 Hz, 2H), 3.79 – 3.75 (m, 0.4H), 3.53 (br, 2H), 3.31 (d, *J* = 10.4 Hz, 1H), 3.15 (m, 1H), 2.44 – 2.32 (m, 1H), 2.31 – 2.25 (m, 1H), 2.24 – 2.17

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(m, 1H), 2.16 – 2.12 (m, 3H), 2.12 – 2.05 (m, 1H), 2.00 – 1.91 (m, 1H), 1.89 – 1.70 (m, 5H), 1.68 – 1.57 (m, 2H). Mass (m/z): 329.3 $[M+H]^+$.

Compound 492

2-((3-methyl-4-(4-methylpiperidin-1-yl)phenyl)amino)cyclohexane-1-carboxamide

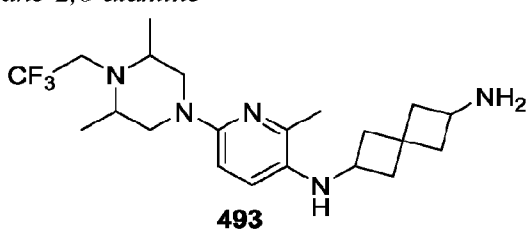


492

The title compound (141 mg) as a white solid was prepared from 2-((3-methyl-4-(4-methylpiperidin-1-yl)phenyl)amino)cyclohexane-1-carbox-ylic acid (100 mg, 0.3 mmol), DMF (15 mL), NH_4Cl (19.42 mg, 0.36 mmol), HATU (172.59 mg, 0.45 mmol) and DIEA (117.32 mg, 0.9 mmol) according to the procedure for **1**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.18 (s, 1H), 6.74 (d, J = 8.6 Hz, 1H), 6.71 (s, 1H), 6.41 (d, J = 2.6 Hz, 1H), 6.35 (dd, J = 8.4, 2.7 Hz, 1H), 3.63 (d, J = 3.2 Hz, 1H), 2.79 (d, J = 11.6 Hz, 2H), 2.46 – 2.39 (m, 3H), 2.08 (s, 3H), 1.79 (br, 2H), 1.64 –1.21 (m, 12H), 0.90 (d, J = 6.6 Hz, 3H). Mass (m/z): 330.3 $[M+H]^+$.

Compound 493

N2-(6-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

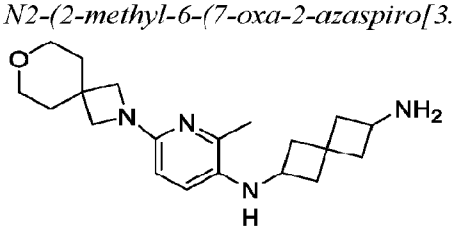


493

The title compound **493** (40 mg, 25%) as a yellow oil was prepared from tert-butyl (6-((6-(3,5-dimethyl-4-(2,2,2-trifluoroethyl) piperazin-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (0.2 g, 0.4 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^1H NMR (400 MHz, CD_3OD) δ 6.84 (d, J = 8.6 Hz, 1H), 6.52 (d, J = 8.6 Hz, 1H), 3.74 – 3.68 (m, 3H), 3.41 – 3.30 (m, 3H), 2.87 – 2.83 (m, 2H), 2.57 – 2.32 (m, 5H), 2.28 – 2.22 (m, 4H), 1.94 – 1.83 (m, 4H), 1.14 (d, J = 6.2 Hz, 6H). Mass (m/z): 411.8$[M+H]^-$.

Compound 494

N2-(2-methyl-6-(7-oxa-2-azaspiro[3.5]nonan-2-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine



494

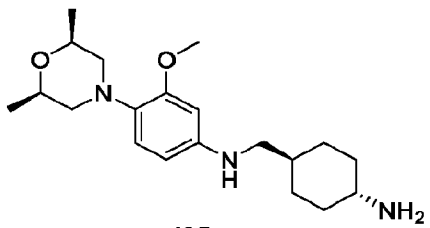
The title compound **494** (4.1 mg, 3.1%) as a yellow solid was prepared from

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(4-((2-(2-hydroxyethoxy)-4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (170 mg, 0.38 mmol), 1,4-dioxane (3 mL) and HCl /1,4-dioxane (1 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.15 (d, J = 8.4 Hz, 1H), 6.41 (d, J = 8.3 Hz, 1H), 3.69 (m, 5H), 2.64 2.00 (m, 7H), 1.86 – 1.79 (m, 4H), 1.70-1.60 (m, 4H). Mass (m/z): 342.8 $[M+H]^+$.

Compound 495

N-(((1r,4R)-4-aminocyclohexyl)methyl)-4-((2S,6R)-2,6-dimethylmorpholino)-3-methoxyaniline

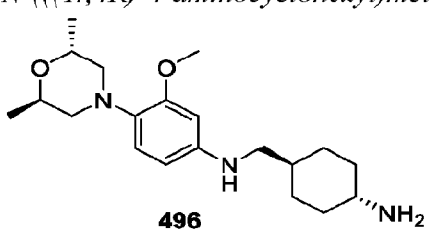


495

The title compound **495** (57.2 mg) was prepared in a yield of 55.6% as a white powder from 4-(2,6-dimethylmorpholino)-3-methoxyaniline (70 mg, 0.30 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (101 mg, 0.44 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 2H), 6.65 (s, 1H), 6.25 (s, 1H), 6.05 (s, 1H), 5.34 (s, 1H), 3.71 (s, 3H), 2.96 (d, J = 39.4 Hz, 3H), 2.81 (s, 2H), 2.17 (s, 2H), 2.02 – 1.93 (m, 2H), 1.86 (d, J = 13.0 Hz, 2H), 1.46 (s, 1H), 1.31 (td, J = 13.4, 10.1 Hz, 3H), 1.08 (d, J = 6.3 Hz, 6H), 1.01 (d, J = 12.8 Hz, 2H). Mass (m/z): 348.3 $[M+H]^+$.

Compound 496

N-(((1r,4R)-4-aminocyclohexyl)methyl)-4-((2S,6R)-2,6-dimethylmorpholino)-3-methoxyaniline



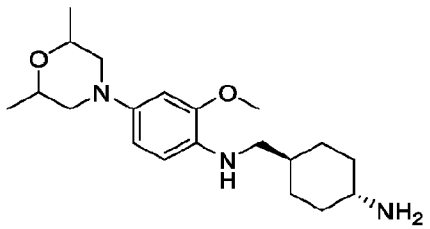
496

The title compound **496** (13.7 mg) was prepared in a yield of 14.1% as a white powder from 4-(2,6-dimethylmorpholino)-3-methoxyaniline (70 mg, 0.30 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (101mg, 0.44 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 2H), 6.64 (s, 1H), 6.24 (s, 1H), 6.04 (s, 1H), 3.70 (s, 5H), 2.95 (d, J = 39.1 Hz, 3H), 2.81 (s, 2H), 2.16 (s, 1H), 1.95 (d, J = 12.0 Hz, 2H), 1.85 (d, J = 12.9 Hz, 2H), 1.45 (s, 1H), 1.35 – 1.21 (m, 3H), 1.07 (d, J = 6.3 Hz, 6H), 1.03 – 0.93 (m, 2H). Mass (m/z): 348.3 $[M+H]^+$.

Compound 497

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(2,6-dimethylmorpholino)-2-methoxyaniline

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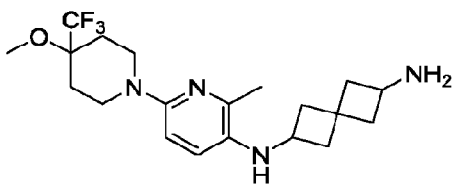


497

The title compound **497** (46.7 mg) was prepared in a yield of 45.4% as a white powder from 4-(2,6-dimethylmorpholino)-2-methoxyaniline (70 mg, 0.30 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (101 mg, 0.44 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 3H), 6.55 (s, 1H), 6.37 (d, J = 22.1 Hz, 2H), 4.36 (s, 1H), 3.78 (d, J = 6.0 Hz, 3H), 3.68 (s, 2H), 2.88 (d, J = 24.0 Hz, 3H), 2.14 (s, 2H), 1.95 (s, 2H), 1.82 (d, J = 12.7 Hz, 2H), 1.50 (s, 1H), 1.28 (q, J = 13.3, 12.7 Hz, 3H), 1.19 – 1.08 (m, 6H), 0.99 (s, 2H). Mass (m/z): 348.7 $[M+H]^+$.

Compound 498

N2-(6-(4-methoxy-4-(trifluoromethyl)piperidin-1-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

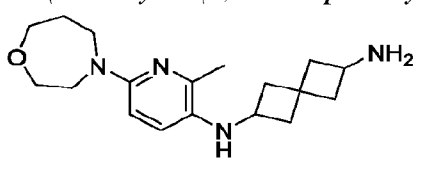


498

The title compound **498** (6.0 mg) was prepared in a total yield of 11.0% as a white solid from tert-butyl (6-((6-(4-methoxy-4-(trifluoromethyl)piperidin-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (68 mg, 0.137 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (dd, J = 8.8, 4.0 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 4.52 (d, J = 7.2 Hz, 1H), 3.94 (d, J = 12.8 Hz, 2H), 3.84 (q, J = 8.0 Hz, 1H), 3.61 (q, J = 7.4 Hz, 1H), 3.38 (s, 3H), 2.74 (td, J = 12.8, 2.4 Hz, 2H), 2.46 – 2.40 (m, 1H), 2.27 (td, J = 10.4, 6.0 Hz, 2H), 2.20 (s, 3H), 2.10 (dd, J = 11.2, 6.0 Hz, 1H), 1.97 – 1.64 (m, 8H). Mass (m/z): 399.3 $[M+H]^+$.

Compound 499

N2-(2-methyl-6-(1,4-oxazepan-4-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine



499

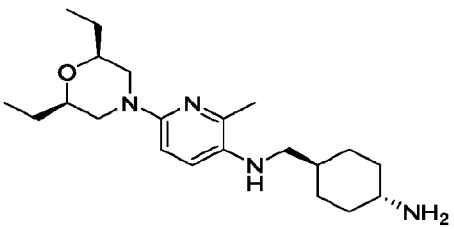
The title compound **499** (41.1 mg) was prepared in a total yield of 31.2% as a yellow solid from tert-butyl (6-((2-methyl-6-(1,4-oxazepan-4-yl)pyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (158 mg, 0.380 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR

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(400 MHz, DMSO-d_6) δ 8.44 (s, 3H), 6.86 (s, 1H), 6.40 (d, J = 8.4 Hz, 1H), 3.70 – 3.58 (m, 8H), 3.55 (t, J = 5.6 Hz, 3H), 2.49 – 2.42 (m, 1H), 2.35 (dddd, J = 19.6, 11.2, 7.2, 2.8 Hz, 3H), 2.25 (d, J = 8.0 Hz, 4H), 2.21 – 2.14 (m, 3H), 1.96 (s, 2H), 1.84 (p, J = 5.6 Hz, 2H). Mass (m/z): 317.3 $[M+H]^+$.

Compound 500

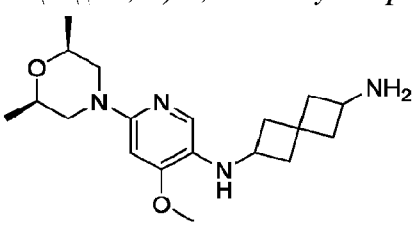
N-(((1r,4R)-4-aminocyclohexyl)methyl)-6-((2R,6S)-2,6-diethylmorpholino)-2-methylpyridin-3-amine



The title compound **500** (30.8 mg) was prepared in a total yield of 53.1% as a light yellow solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 2H), 6.83 (d, J = 8.7 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 4.44 (s, 1H), 3.84 (d, J = 11.9 Hz, 2H), 3.41 – 3.36 (m, 2H), 2.98 – 2.91 (m, 1H), 2.88 – 2.79 (m, 2H), 2.22 (s, 3H), 2.21 – 2.14 (m, 2H), 1.97 – 1.84 (m, 4H), 1.51 – 1.45 (m, 4H), 1.30 – 1.25 (m, 2H), 1.06 – 0.90 (m, 8H). Mass (m/z): 361.3 $[M+H]^+$.

Compound 501

N^2-(6-((2R,6S)-2,6-dimethylmorpholino)-4-methoxypyridin-3-yl)spiro[3.3]heptane-2,6-diamine

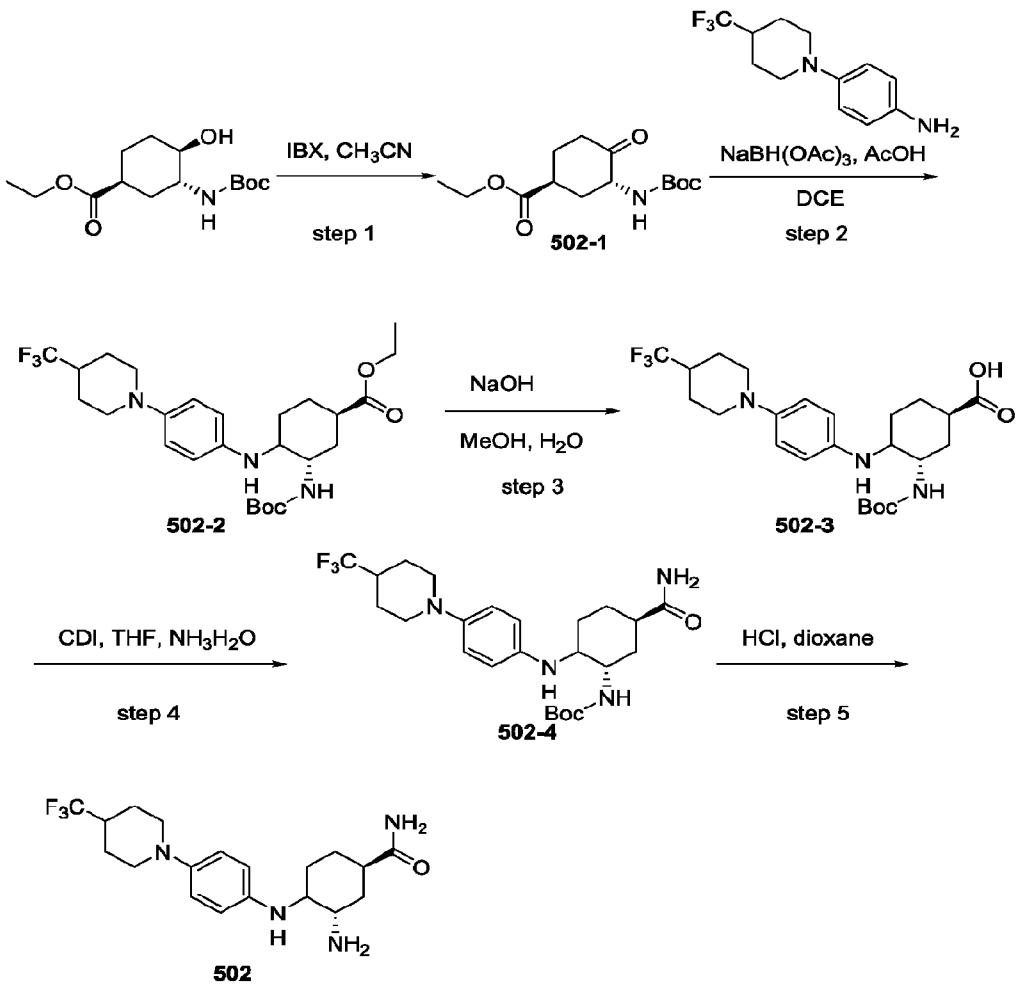


The title compound **501** (28.8 mg) was prepared in a total yield of 16.6% as a light yellow solid according to the procedure for compound **34**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 3H), 7.06 (s, 1H), 6.51 (s, 1H), 4.04 – 3.97 (m, 2H), 3.90 (s, 3H), 3.69 – 3.58 (m, 3H), 3.56 – 3.50 (m, 1H), 3.41 – 3.29 (m, 2H), 2.50 – 2.45 (m, 2H), 2.42 – 2.30 (m, 4H), 2.23 – 2.13 (m, 3H), 1.96 – 1.86 (m, 2H). Mass (m/z): 347.2$[M+H]^+$.

Compound 502

(1R,3S)-3-amino-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxamide

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Step 1. Preparation of ethyl (1S,3R)-3-((tert-butoxycarbonyl)amino)-4-oxocyclohexane-1-carboxylate (**502-1**)

A mixture of ethyl (1S,3R,4R)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclohexane-1-carboxylate (3 g, 10.5 mmol) and IBX (6 g, 21.4 mmol) in acetonitrile (80 mL) was refluxed overnight. Additional IBX (3 g, 10.7 mmol) was added and stirred for another 5 h. The reaction was cooled and filtered. The filtrate was concentrated to obtain ethyl (1S,3R)-3-((tert-butoxycarbonyl)amino)-4-oxocyclohexane-1-carboxylate (3.2 g crude, quant) as a white solid. The crude product was used directly without further purification.

Step 2. Preparation of ethyl (1R,3S)-3-((tert-butoxycarbonyl)amino)-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylate (**502-2**)

A solution of 4-(4-(trifluoromethyl)piperidin-1-yl)aniline (500 mg, 2.05 mmol), ethyl (1S,3R)-3-((tert-butoxycarbonyl)amino)-4-oxocyclohexane-1-carboxylate (800 mg, 2.81 mmol), and a drop of AcOH in DCE (10 mL) was stirred for 10 min before $NaBH(OAc)_3$ (600 mg, 2.84 mmol) was added and stirred at room temperature overnight. The reaction was quenched with sodium bicarbonate aqueous solution and extracted with DCM. The combined

organic layers were washed with brine, dried over sodium sulfate and concentrated under vacuum. The residue was purified by silica gel Flash chromatography (PE/EA 90/10 to 70/30) to obtain 500 mg (47.5%) of the title compound as a grey solid. Mass (m/z): 514.5 $[M+H]^+$.

Step 3. Preparation of (1R,3S)-3-((tert-butoxycarbonyl)amino)-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylic acid **(502-3)**

A mixture of ethyl (1R,3S)-3-((tert-butoxycarbonyl)amino)-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylate (300 mg, 0.584 mmol) and sodium hydroxide (300 mg, 7.5 mmol) in THF (1 mL), MeOH (1 mL) and water (0.5 mL) was stirred for 2 h. The reaction was concentrated under vacuum, adjusted pH to 5-6 with 2N HCl and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated under vacuum to obtain the crude product (280 mg, 98.8%) as black syrup. Mass (m/z): 486.5 $[M+H]^+$.

Step 4. Preparation of tert-butyl ((1S,5R)-5-carbamoyl-2-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carba mate **(502-4)**

A mixture of (1R,3S)-3-((tert-butoxycarbonyl)amino)-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxylic acid (200 mg, 0.412 mmol) and CDI (150 mg, 2.42 mmol) in THF (2 mL) was refluxed overnight and added slowly to NH_3H_2O (5 mL). The resulting mixture was stirred for 10 min and then extracted with EtOAc twice. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC (EtOAc) to obtain 180 mg (90.2%) of the product as a grey solid. Mass (m/z): 485.5 $[M+H]^+$.

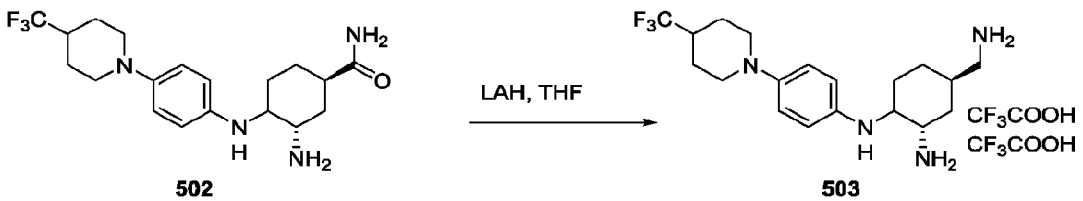
Step 5. Preparation of (1R,3S)-3-amino-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carbox amide **(502)**

A solution of tert-butyl ((1S,5R)-5-carbamoyl-2-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carba mate (89 mg, 0.18 mmol) in 4N HCl in dioxane (1.5 mL) was stirred for 0.5 h at rt. The reaction was concentrated, basified with sodium bicarbonate and extracted with EA/EtOH (10/1) for 3 times. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The residue was purified by Prep-TLC (DCM/MeOH/NH_4OH 100/20/1, R_f=0.1) to obtain the title compound **502** (50.7 mg, 73.1%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.30 – 7.14 (m, 1H), 6.83 – 6.67 (m, 3H), 6.66 – 6.48 (m, 2H), 5.04 – 4.79 (m, 1H), 3.50 – 3.38 (m, 2H), 2.95 – 2.83 (m, 1H), 2.76 – 2.65 (m, 1H), 2.39 – 2.30 (m, 1H), 2.21 – 2.12 (m, 1H), 2.03 – 1.76 (m, 5H), 1.76 – 1.50 (m, 3H), 1.45 – 1.21 (m, 2H), 1.09 – 0.90 (m, 1H). Mass (m/z): 385.4 $[M+H]^+$.

Compound 503

(2S,4R)-4-(aminomethyl)-N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,2-dia mine bis(2,2,2-trifluoroacetate)

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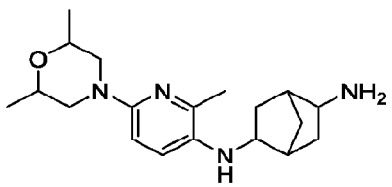


502 503

A solution of (1R,3S)-3-amino-4-((4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexane-1-carboxamide (30 mg, 0.08 mmol) and $LiAlH_4$ (1N in THF, 0.2 mL) in THF (2 mL) was refluxed for 2 h. The reaction was cooled and quenched with $Na_2SO_4 10H_2O$, filtered and the filtrate was concentrated and purified by Prep-HPLC to obtain (2S,4R)-4-(aminomethyl)-N1-(4-(4-(trifluoromethyl)piperidin-1-yl)phenyl)cyclohexane-1,2-diamine bis(2,2,2-trifluoroacetate) **502** (5.2 mg, 10.8%) as a grey solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.03 – 7.70 (m, 6H), 7.15 – 6.93 (m, 2H), 6.67 (d, J = 8.5 Hz, 2H), 3.65 – 3.47 (m, 6H), 3.03 – 2.85 (m, 1H), 2.85 – 2.65 (m, 2H), 2.15 – 1.89 (m, 4H), 1.84 – 1.50 (m, 4H), 1.30 – 0.93 (m, 2H). Mass (m/z): 371.3 $[M+H]^+$.

Compound 504

N2-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)bicyclo[2.2.1]heptane-2,5-diamine

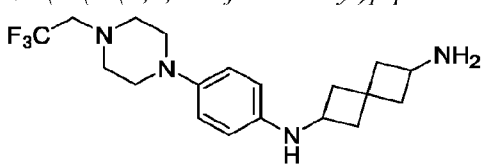


504

The title compound **504** (14.8 mg) was prepared in a total yield of 44.8% as a white solid according to the procedure for compound **24**. ^1H NMR (400 MHz, DMSO-d_6) δ 6.94 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 3.95 – 3.50 (m, 5H), 3.17 (m, 1H), 2.46 – 2.10 (m, 7H), 2.02 – 1.76 (m, 3H), 1.67 – 1.45 (m, 2H), 1.36 (m, 1H), 1.12 (d, J = 6.0 Hz, 6H). Mass (m/z): 331.2 $[M+H]^+$.

Compound 505

N2-(4-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)phenyl)spiro[3.3]heptane-2,6-diamine



505

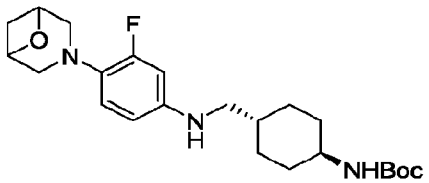
The title compound **505** (25.1 mg) was prepared in a total yield of 68.0% as a gray solid according to the procedure for compound **24**. ^1H NMR (400 MHz, DMSO-d_6) δ 6.85 – 6.68 (m, 2H), 6.57 – 6.44 (m, 2H), 3.37 (s, 2H), 3.27 – 3.15 (m, 2H), 2.83 – 2.67 (m, 6H), 2.05 – 1.98 (m, 2H), 1.89 – 1.77 (m, 2H), 1.52 – 1.24 (m, 4H), 1.05 – 0.93 (m, 2H). Mass (m/z): 369.2 $[M+H]^+$.

Compound 506

tert-butyl

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((1r,4r)-4-(((4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-3-fluorophenyl)amino)methyl)cyclohexyl)carbamate

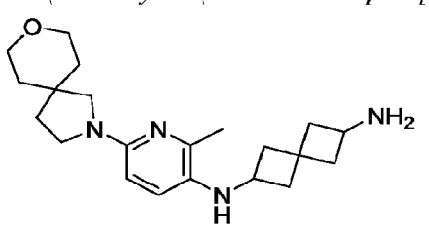


506

The title compound **506** (14.8 mg) was prepared in a total yield of 14.7% as a white solid from 4-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-3-fluoroaniline (50 mg, 0.240 mmol), tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (82 mg, 0.360 mmol), AcOH (0.1 mL), $NaBH(OAc)_3$ (102 mg, 0.480 mmol) and DCE (10 mL) according to the procedure for **24-1**. ^1H NMR (400 MHz, DMSO-d_6) δ 6.87 (dd, J = 10.4, 8.8 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.41 – 6.25 (m, 2H), 5.46 (t, J = 5.6 Hz, 1H), 4.53 (d, J = 6.0 Hz, 2H), 3.38 (d, J = 11.2 Hz, 2H), 3.31 (s, 2H), 3.17 (d, J = 8.0 Hz, 1H), 2.99 (dt, J = 8.0, 6.4 Hz, 1H), 2.78 (t, J = 6.0 Hz, 2H), 2.23 (d, J = 8.0 Hz, 1H), 1.80 (d, J = 11.6 Hz, 4H), 1.37 (s, 9H), 1.16 – 1.05 (m, 2H), 1.01 – 0.89 (m, 2H). Mass (m/z): 420.3 $[M+H]^+$.

Compound 507

N2-(2-methyl-6-(8-oxa-2-azaspiro[4.5]decan-2-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine

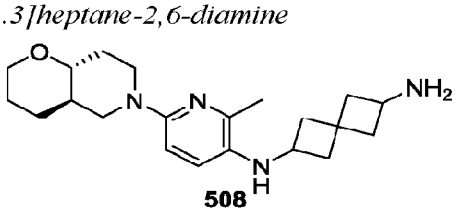


507

The title compound **507** (12.7 mg) was prepared in a total yield of 29.5% as a yellow solid from tert-butyl (6-((2-methyl-6-(8-oxa-2-azaspiro[4.5]decan-2-yl)pyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (55 mg, 0.121 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.42 (s, 1H), 3.71 – 3.49 (m, 4H), 3.43 (s, 1H), 3.32 (s, 2H), 3.21 – 3.14 (m, 1H), 3.12 – 3.07 (m, 1H), 2.45 (d, J = 8.0 Hz, 2H), 2.42 – 2.30 (m, 2H), 2.19 (d, J = 8.5 Hz, 1H), 1.94 (d, J = 20.0 Hz, 1H), 1.86 (t, J = 7.2 Hz, 1H), 1.53 (d, J = 5.2 Hz, 2H). Mass (m/z): 357.3 $[M+H]^+$.

Compound 508

N2-(6-((4aR,8aR)-hexahydro-2H-pyrano[3,2-c]pyridin-6(5H)-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



508

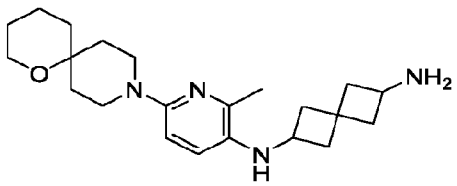
The title compound **508** (48.8 mg) was prepared in a total yield of 86.7% as a yellow solid

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from tert-butyl (6-((6-((4aR,8aR)-hexahydro-2H-pyrano[3,2-c]pyridin-6(5H)-yl)-2-methylpyridin-3-yl)amino) spiro[3.3]heptan-2-yl)carbamate (72 mg, 0.158 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 3H), 6.82 – 6.68 (m, 1H), 6.54 (d, J = 8.8 Hz, 1H), 4.60 (s, 1H), 4.07 (d, J = 12.8 Hz, 1H), 3.88 (dd, J = 16.8, 11.4 Hz, 2H), 3.71 – 3.46 (m, 3H), 3.00 (td, J = 10.4, 4.2 Hz, 1H), 2.61 (t, J = 13.2 Hz, 2H), 2.41 – 2.30 (m, 2H), 2.22 (td, J = 15.6, 13.2, 8.0 Hz, 7H), 1.93 (d, J = 11.2 Hz, 2H), 1.73 (dd, J = 32.0, 12.0 Hz, 2H), 1.57 (qd, J = 7.6, 5.2, 3.2 Hz, 2H), 1.50 – 1.28 (m, 2H), 1.26 – 1.11 (m, 1H). Mass (m/z): 357.3 $[M+H]^+$.

Compound 509

N2-(2-methyl-6-(1-oxa-9-azaspiro[5.5]undecan-9-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine

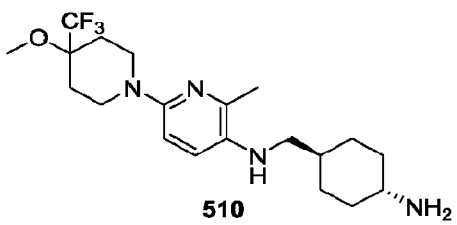


509

The title compound **509** (48.4 mg) was prepared in a total yield of 89.0% as a yellow solid from tert-butyl (6-((2-methyl-6-(1-oxa-9-azaspiro[5.5]undecan-9-yl)pyridin-3-yl)amino)spiro[3.3]heptan-2-yl) carbamate (69 mg, 0.147 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, J = 39.6 Hz, 6H), 7.11 (s, 1H), 6.43 (s, 1H), 3.71 – 3.50 (m, 8H), 3.43 (s, 2H), 3.32 (s, 1H), 3.19 – 3.14 (m, 2H), 3.11 – 3.06 (m, 2H), 2.45 (d, J = 8.0 Hz, 5H), 2.40 – 2.30 (m, 4H), 2.22 (dd, J = 21.6, 8.4 Hz, 3H), 1.96 (s, 1H), 1.86 (t, J = 7.2 Hz, 2H), 1.53 (d, J = 5.2 Hz, 4H). Mass (m/z): 371.3 $[M+H]^+$.

Compound 510

N-(((1r,4r)-4-aminocyclohexyl)methyl)-6-(4-methoxy-4-(trifluoromethyl)piperidin-1-yl)-2-methylpyridin-3-amine



510

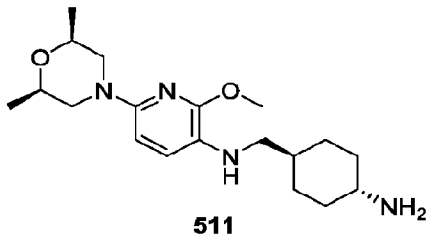
The title compound **510** (24.8 mg) was prepared in a total yield of 35.2% as a white solid from tert-butyl ((1r,4r)-4-(((6-(4-methoxy-4-(trifluoromethyl)piperidin-1-yl)-2-methylpyridin-3-yl)amino)methyl)cyclohexyl)carbamate (88 mg, 0.176 mmol), TFA (1 mL) and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 – 8.18 (m, 3H), 7.20 – 6.71 (m, 2H), 4.83 (s, 1H), 3.52 (s, 2H), 3.12 (s, 3H), 2.88 (d, J = 6.8 Hz, 3H), 2.32 (s, 3H), 2.05 – 1.95 (m, 2H), 1.87 (d, J = 12.8 Hz, 2H), 1.74 (d, J = 13.2 Hz, 2H), 1.53 (s, 2H), 1.42 – 1.27 (m, 2H),

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1.00 (dd, J = 13.6, 10.4 Hz, 2H). Mass (m/z): 401.3 $[M+H]^+$.

Compound 511

N-(((1r,4R)-4-aminocyclohexyl)methyl)-6-((2S,6R)-2,6-dimethylmorpholino)-2-methoxypyridin-3-amine

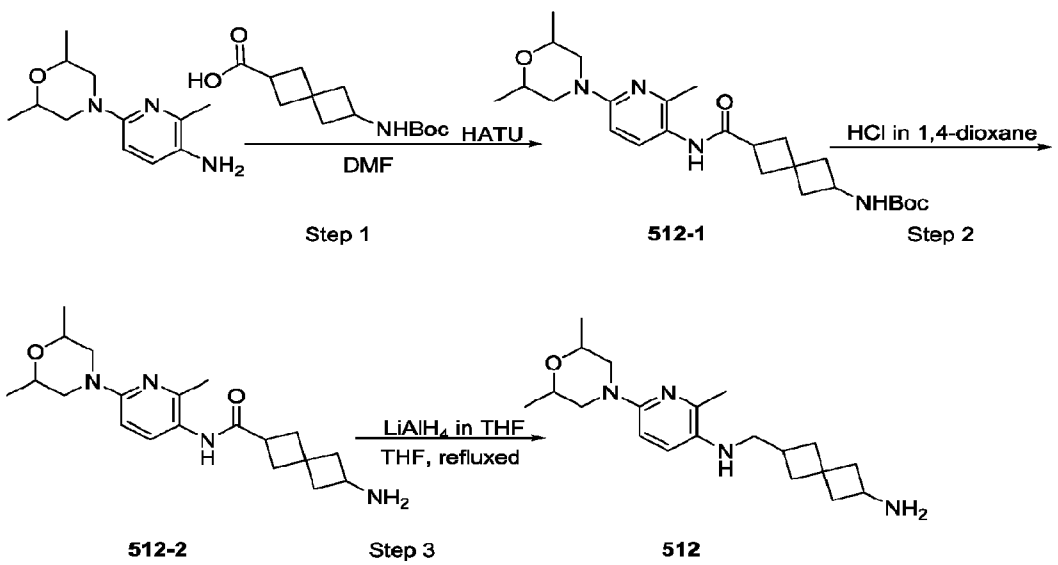


511

The title compound **511** (14.5 mg) was prepared in a total yield of 28.3% as a purple solid from tert-butyl ((1R,4r)-4-(((6-((2S,6R)-2,6-dimethylmorpholino)-2-methoxypyridin-3-yl)amino)methyl)cyclohexyl)carbamate (66 mg, 0.147 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 2H), 6.75 (d, J = 8.0 Hz, 1H), 6.16 (d, J = 8.0 Hz, 1H), 4.33 (s, 1H), 3.99 (td, J = 6.4, 3.2 Hz, 1H), 3.79 (d, J = 2.4 Hz, 1H), 3.63 (ddd, J = 10.4, 6.4, 2.4 Hz, 2H), 3.27 (dd, J = 12.0, 3.2 Hz, 1H), 2.96 – 2.79 (m, 4H), 2.23 – 2.12 (m, 3H), 1.96 (d, J = 12.0 Hz, 2H), 1.81 (d, J = 12.8 Hz, 2H), 1.47 (s, 1H), 1.29 (d, J = 13.6 Hz, 2H), 1.17 (s, 1H), 1.17 – 1.12 (m, 6H), 0.97 (q, J = 12.8, 12.4 Hz, 2H). Mass (m/z): 349.3 $[M+H]^+$.

Compound 512

N-((6-aminospiro[3.3]heptan-2-yl)methyl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine



Step 1. Preparation of tert-butyl (6-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)carbamoyl)spiro[3.3]heptan-2-yl)carbamate **(512-1)**

The title compound **512-1** (360 mg) was prepared in a total yield of 78.6% as a yellow solid

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from 6-((tert-butoxycarbonyl)amino)spiro[3.3]heptane-2-carboxylic acid (338 mg, 1.5 mmol), 6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine (219 mg, 1.0 mmol), DIEA (387 mg, mmol) and HATU (456 mg, 1.2 mmol) according to the procedure for **403.** Mass(m/z): 381.3 $[M+H]^+$.

Step 2. Preparation of 6-amino-N-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2-carboxamide **(512-2)**

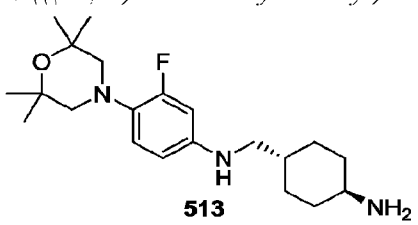
The title compound **512-2** (260 mg) was prepared in a total yield of 92.5% as a light yellow solid from tert-butyl (6-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)carbamoyl)spiro[3.3]heptan-2-yl)carbamate (360 mg, 0.79 mmol) and 5.0 mL of HCl in 1,4 dioxane according to the procedure for compound **37**. Mass (m/z): 359.2 $[M+H]^+$.

Step 3. Preparation of *N*-((6-aminospiro[3.3]heptan-2-yl)methyl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine **(512)**

The title compound **512** (9.4 mg) was prepared in a total yield of 4.9% as a purple solid from 6-amino-N-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2-carboxamide (200 mg, 0.56 mmol) and 1.16 mL of $LiAlH_4$ in THF (2.4 M, 2.78 mmol) according to the procedure for compound **23**. ^1H NMR (400 MHz, DMSO-d_6) δ 7.87 (s, 3H), 6.82 (d, J = 8.8 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.28 (t, J = 5.8 Hz, 1H), 3.87 – 3.79 (m, 2H), 3.67 – 3.47 (m, 4H), 2.97 (t, J = 6.4 Hz, 2H), 2.39 (s, 1H), 2.22 – 2.01 (m, 9H), 1.81 – 1.68 (m, 2H), 1.14 (d, J = 6.2 Hz, 6H). Mass (m/z): 345.2$[M+H]^+$.

Compound 513

N-(((1r,4r)-4-aminocyclohexyl)methyl)-3-fluoro-4-(2,2,6,6-tetramethylmorpholino)aniline



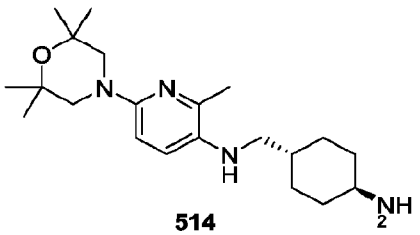
513

The title compound **513** (22.0 mg) was prepared in a total yield of 40.2% as a white solid according to the procedure for compound **24**. ^1H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 3H), 6.79 (dd, J = 10.0, 8.6 Hz, 1H), 6.35 (dd, J = 14.7, 2.5 Hz, 1H), 6.29 (dd, J = 8.6, 2.6 Hz, 1H), 2.96 – 2.85 (m, 1H), 2.80 (t, J = 6.1 Hz, 2H), 2.01– 1.93 (m, 2H), 1.88 – 1.78 (m, 2H), 1.49 – 1.39 (m, 1H), 1.34 – 1.24 (m, 2H), 1.21 (s, 12H), 1.04 – 0.91 (m, 2H). Mass (m/z): 364.2 $[M+H]^+$.

Compound 514

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-methyl-6-(2,2,6,6-tetramethylmorpholino)pyridin-3-amine

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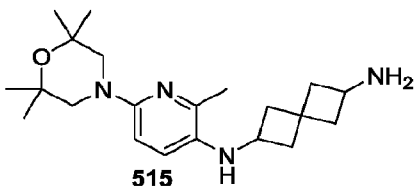


514

The title compound **514** (13.0 mg) was prepared in a total yield of 24.1% as a yellow solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 3H), 7.10 – 6.76 (m, 1H), 6.69 – 6.37 (m, 1H), 4.63 – 4.32 (m, 1H), 3.23 – 3.07 (m, 3H), 2.97 – 2.72 (m, 3H), 2.27 (s, 3H), 2.03 – 1.80 (m, 4H), 1.63 – 1.44 (m, 1H), 1.36 – 1.27 (m, 2H), 1.18 (s, 12H), 1.06 – 0.93 (m, 2H). Mass (m/z): 361.3 $[M+H]^+$.

Compound 515

N^2-(2-methyl-6-(2,2,6,6-tetramethylmorpholino)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine

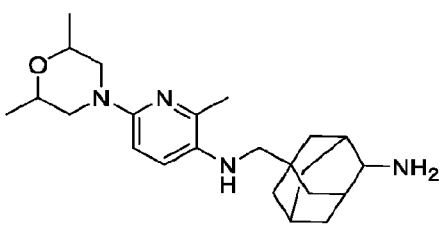


515

The title compound **515** (15.2 mg) was prepared in a total yield of 28.3% as a white solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 3H), 6.76 (s, 1H), 6.53 (d, J = 8.1 Hz, 1H), 4.61 – 4.45 (m, 1H), 3.61 (d, J = 35.7 Hz, 2H), 3.14 – 3.06 (m, 4H), 2.45 – 2.34 (m, 2H), 2.27 – 2.05 (m, 7H), 1.98 – 1.87 (m, 7H), 1.18 (s, 12H). Mass (m/z): 359.2 $[M+H]^+$.

Compound 516

N-(((1s,4r)-4-aminoadamantan-1-yl)methyl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine



516A
516B

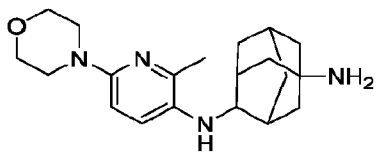
The title compound **516A** (Rt=8.59 min; 5.4 mg) was prepared in a three-step total yield of 7.2% as a white solid and compound **516B** (Rt=9.96 min; 1.4 mg) was prepared in a three-step total yield of 2.5% as a white solid ^{1}H NMR from 6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine (300 mg, 1.36 mmol) and 4-oxoadamantane-1-carboxylic acid (316 mg, 1.63 mmol) according to the procedure for **20**. The target products were purified by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 0%-25%-95%-95%-10%, 0 min-13 min-13.5 min-14.5 min-16.0 min). **516A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93 (d, J = 8.8 Hz, 1H), 6.50 (d, J =

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8.7 Hz, 1H), 3.97 (t, J = 6.5 Hz, 1H), 3.88 – 3.79 (m, 2H), 3.62 (ddd, J = 10.3, 6.3, 2.4 Hz, 2H), 2.84 (s, 1H), 2.71 (d, J = 6.0 Hz, 2H), 2.15 (dd, J = 12.3, 10.3 Hz, 3H), 2.03 (d, J = 12.6 Hz, 2H), 1.83 (d, J = 10.4 Hz, 1H), 1.67 (s, 2H), 1.54 (dd, J = 24.3, 11.6 Hz, 6H), 1.32 – 1.23 (m, 3H), 1.14 (d, J = 6.2 Hz, 6H). Mass (m/z): 385.6 $[M+H]^+$. **516B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.93 (d, J = 8.8 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 3.97 (t, J = 6.5 Hz, 1H), 3.89 – 3.79 (m, 2H), 3.68 (ddd, J – 10.3, 6.3, 2.4 Hz, 2H), 2.86 (s, 1H), 2.71 (d, J – 6.0 Hz, 2H), 2.15 (dd, J = 12.3, 10.3 Hz, 3H), 2.03 (d, J = 12.7 Hz, 2H), 1.83 (d, J = 10.9 Hz, 1H), 1.67 (s, 2H), 1.52 (dd, J = 24.3, 11.6 Hz, 6H), 1.38 – 1.26 (m, 2H), 1.18 (d, J = 6.2 Hz, 6H). Mass (m/z): 385.6 $[M+H]^+$.

Compound 517

N4-(2-methyl-6-morpholinopyridin-3-yl)adamantane-1,4-diamine

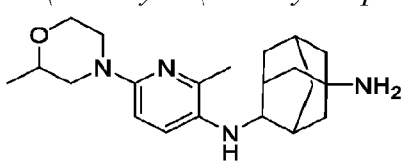


517

The title compound **517** (38.4 mg) was prepared in a yield of 30.5% as a white powder from 2-methyl-6-morpholinopyridin-3-amine (70 mg, 0.36 mmol) and tert-butyl (4-oxoadamantan-1-yl)carbamate (114mg, 0.44 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 2H), 8.18 (s, 1H), 6.99 (s, 1H), 6.59 (s, 1H), 4.00 (s, 1H), 3.69 (t, J = 4.7 Hz, 5H), 3.23 (s, 2H), 2.34 (dt, J = 4.0, 2.1 Hz, 2H), 2.22 – 2.00 (m, 5H), 1.99 – 1.86 (m, 4H), 1.86 – 1.73 (m, 3H), 1.62 (dd, J = 43.0, 12.0 Hz, 1H), 1.36 (d, J = 12.5 Hz, 2H). Mass(m/z): 343.4 $[M+H]^+$.

Compound 518

N4-(2-methyl-6-(2-methylmorpholino)pyridin-3-yl)adamantane-1,4-diamine



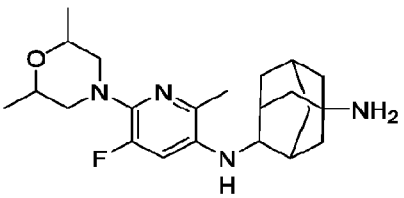
518

The title compound **518** (31.0 mg) was prepared in a yield of 27.7% as a white powder from 2-methyl-6-(2-methylmorpholino)pyridin-3-amine (70 mg, 0.34 mmol) and tert-butyl (4-oxoadamantan-1-yl)carbamate (108mg, 0.41 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 2H), 8.18 (s, 1H), 7.03 (s, 1H), 6.61 (s, 1H), 3.95 – 3.83 (m, 2H), 3.76 (d, J = 12.4 Hz, 1H), 3.54 (t, J = 11.3 Hz, 2H), 3.36 (s, 3H), 2.35 (s, 2H), 2.22 – 1.70 (m, 11H), 1.60 (dd, J = 41.7, 12.1 Hz, 1H), 1.34 (d, J = 12.4 Hz, 1H), 1.13 (d, J = 6.2 Hz, 3H). Mass (m/z): 357.4 $[M+H]^+$.

Compound 519

N1-(6-(2,6-dimethylmorpholino)-5-fluoro-2-methylpyridin-3-yl)adamantane-1,4-diamine

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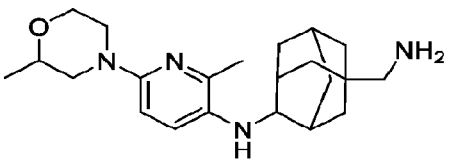


519

The title compound **519** (15.0 mg) was prepared in a yield of 18.5% as a white powder from 6-(2,6-dimethylmorpholino)-5-fluoro-2-methylpyridin-3-amine (50 mg, 0.21 mmol) and tert-butyl (4-oxoadamantan-1-yl)carbamate (67 mg, 0.25 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 3H), 6.87 (dd, J = 14.6, 8.5 Hz, 1H), 4.31 – 4.19 (m, 1H), 3.68 (ddd, J = 10.4, 6.2, 2.1 Hz, 2H), 3.38 (t, J = 13.2 Hz, 3H), 2.26 (d, J = 1.1 Hz, 2H), 2.19 – 2.05 (m, 3H), 2.04 – 1.92 (m, 3H), 1.87 (d, J = 11.6 Hz, 1H), 1.79 (d, J = 18.7 Hz, 3H), 1.65 (d, J = 12.6 Hz, 1H), 1.56 (d, J = 11.2 Hz, 1H), 1.35 (d, J = 12.8 Hz, 1H), 1.09 (d, J = 6.2 Hz, 6H). Mass (m/z): 389.5 $[M+H]^+$.

Compound 520

N-(5-(aminomethyl)adamantan-2-yl)-2-methyl-6-(2-methylmorpholino)pyridin-3-amine



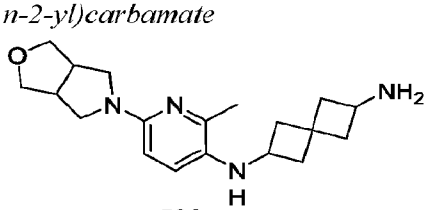
520

The title compound **520** (50.3 mg) was prepared in a two-step overall yield of 43.2% as a white powder from 2-methyl-6-(2-methylmorpholino)pyridin-3-amine (200 mg, 1.03 mmol) and 4-oxoadamantane-1-carboxylic acid (301 mg, 1.51 mmol) according to the procedure for **84**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 3H), 6.90 (s, 1H), 6.57 (s, 1H), 3.88 (d, J = 11.5 Hz, 3H), 3.76 (d, J = 12.3 Hz, 1H), 3.64 – 3.46 (m, 3H), 2.61 (d, J = 13.9 Hz, 2H), 2.33 (d, J = 10.8 Hz, 4H), 1.95 (d, J = 29.9 Hz, 5H), 1.80 – 1.67 (m, 2H), 1.64 (d, J = 2.9 Hz, 3H), 1.58 – 1.47 (m, 3H), 1.34 (dd, J = 26.2, 12.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H). Mass (m/z): 371.5 $[M+H]^+$.

Compound 521

tert-butyl

(6-((2-methyl-6-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyridin-3-yl)amino)spiro[3.3]hepta n-2-yl)carbamate



521

The title compound **521** (6.8 mg, 11.6% yield) as a light brown solid was prepared from tert-butyl

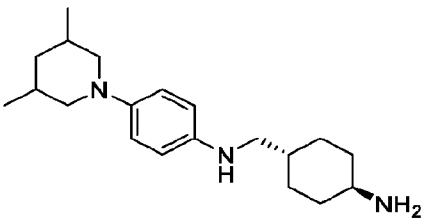
(6-((2-methyl-6-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)pyridin-3-yl)amino)spiro[3.3]hepta n-2-yl)carbamate (70 mg, 0.163 mmol), DCM (3 mL) and TFA (1 mL) and purified by prep-HPLC (CH_3CN/0.05% FA in water) according to the procedure for **24**. ^{1}H NMR (400

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MHz, DMSO-d_6) δ 6.87 (d, J = 8.7 Hz, 1H), 6.32 (d, J = 8.7 Hz, 1H), 3.96 – 3.91 (m, 2H), 3.74 – 3.63 (m, 1H), 3.60 (dd, J = 8.8, 3.9 Hz, 2H), 3.49 – 3.33 (m, 3H), 3.28 - 3.24 (m, 2H), 3.02 – 2.95 (m, 2H), 2.57 – 2.41 (m, 2H), 2.40 – 2.36 (m 1H), 2.31 – 2.23 (m, 4H), 2.02 – 1.86 (m, 4H). MS (m/z): 329.2 $[M+H]^+$.

Compound 522

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(3,5-dimethylpiperidin-1-yl)aniline

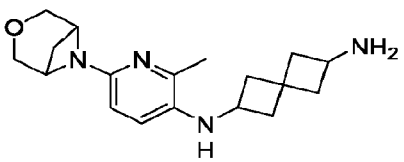


522

The title compound **522** (25.3 mg, 9.4%) as a white solid was prepared from tert-butyl ((1r,4r)-4-(((4-(3,5-dimethylpiperidin-1-yl)phenyl)amino)methyl)cyclohexyl)carbamate (350 mg, 0.8401 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.91 – 6.84 (m, 2H), 6.62 – 6.58 (m, 2H), 3.29 – 3.26 (m, 1H), 2.88 (d, J = 6.7 Hz, 2H), 2.55 (ddd, J = 14.4, 7.3, 3.5 Hz, 1H), 2.06 (t, J = 11.3 Hz, 2H), 1.90 – 1.76 (m, 7H), 1.52 (brs, 1H), 1.16 – 0.94 (m, 5H), 0.93 (d, J = 6.4 Hz, 6H), 0.67 – 0.57 (m, 1H). Mass (m/z): 316.3 $[M+H]^+$.

Compound 523

N^2-(6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

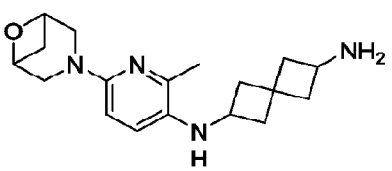


523

The title compound **523** (1.5 mg, 1.12% yield) as a white solid was prepared from tert-butyl (6-((6-(3-oxa-6-azabicyclo[3.1.1]heptan-6-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (170 mg, 0.4091 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.91 (d, J = 8.5 Hz, 1H), 6.34 (d, J = 8.5 Hz, 1H), 4.28 (m, 4H), 3.70 (m, 4H), 2.71 (d, J = 6.7 Hz, 1H), 2.52 – 2.34 (m, 3H), 2.26 (s, 3H), 2.03 -1.59 (m, 6H). Mass (m/z): 315.2 $[M+H]^+$.

Compound 524

N2-(6-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



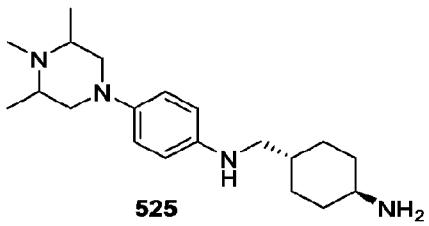
524

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The title compound **524** (6.9 mg, 9.1% yield) as yellow oil was prepared from tert-butyl (6-((6-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (0.1 g, 0.24 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.93 (d, J = 8.8 Hz, 1H), 6.39 (d, J = 8.8 Hz, 1H), 4.72 (d, J = 6 Hz, 2H), 3.75 – 3.63 (m, 3H), 3.50 (d, J = 12 Hz, 2H), 3.33 (t, J = 7.4 Hz, 1H), 3.18 – 3.20 (m, 1H), 2.55 – 2.15 (m, 7H), 2.01 – 1.81 (m, 5H). Mass (m/z): 314.9$[M+H]^+$.

Compound 525

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(3,4,5-trimethylpiperazin-1-yl)aniline

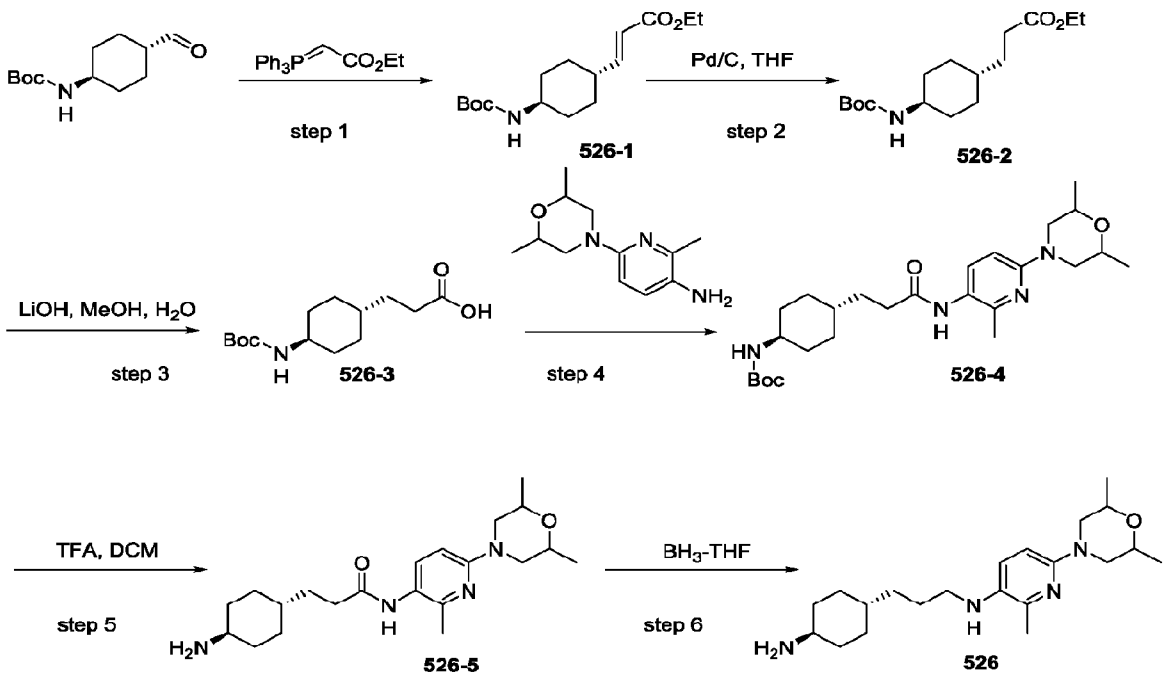


525

The title compound **525** (40.8 mg, 44.3% yield) as a yellow solid was prepared from tert-butyl ((1r,4r)-4-(((4-(3,4,5-trimethylpiperazin-1-yl)phenyl)amino)methyl)cyclohexyl)carbamate (0.12 g, 0.28 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.86 – 6.76 (m, 2H), 6.62 – 6.50 (m, 2H), 3.29 – 3.22 (m, 2H), 2.86 (d, J = 6.6 Hz, 2H), 2.58 – 2.56 (m, 1H), 2.45 – 2.37 (m, 4H), 2.31 (s, 3H), 1.94 – 1.82 (m, 4H), 1.51 (s, 1H), 1.20 – 0.97 (m, 10H). Mass (m/z): 330.9$[M+H]^+$.

Compound 526

N-(3-((1r,4s)-4-aminocyclohexyl)propyl)-6-(2,6-dimethylmorpholino)-2-methyl pyridin-3-amine



Step 1. Preparation of ethyl (E)-3-((1r,4r)-4-((tert-butoxycarbonyl)amino)cycloh exyl)acrylate (**526-1**)

A mixture of tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (3 g, 13.1 mmol), ethyl 2-(triphenyl-l5-phosphaneylidene)acetate (4.56 g, 13.1 mmol), NaH (0.38 g, 15.7 mmol) and THF (20 mL) was stirred at 25 °C for 2 hrs. The mixture was diluted with EA (20 mL) and washed with water (20 mL x 3). The organic phase was concentrated to give **526-1** as a yellow solid (4 g, 72%). Mass (m/z): 319.8 $[M+Na]^+$.

Step 2. Preparation of ethyl 3-((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohex yl)propanoate (**526-2**)

To a solution of **526-1** (4 g, 13.4 mmol) in THF (30 mL) was added wet Pd/C (1 g) under H_2 at 25 °C. The reaction was stirred at 25 °C for 3 hrs. The mixture was filtered and concentrated to give **526-2** as pale oil (2 g, 45%). Mass (m/z):199.9 $[M+H]^+$.

Step 3. Preparation of 3-((1r,4r)-4-((tert-butoxycarbonyl)amino)cyclohexyl) propanoic acid (**526-3**)

To a solution of **526-2** (2 g, 6.7 mmol) in MeOH (20 mL) was added LiOH (0.84 g, 20.1 mmol) at 25 °C. The reaction was stirred at 25 °C for 2 hrs. TLC showed SM was consumed. The mixture was poured into water and filtered to give **526-3** as a white solid (2 g, 100%).

Step 4. Preparation of tert-butyl ((1r,4r)-4-(3-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)-3-oxopropyl)cyclohe xyl)carbamate (**526-4**)

To a solution of **526-3** (0.2 g, 0.7 mmol), 6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine (0.15 g, 0.7 mmol) and HATU (0.27 g, 0.7 mmol) in DMF (5 mL) was added DIEA (0.27 g, 2.1 mmol). The reaction was stirred at 25 °C for 16 hrs. The mixture was poured into water and filtered to give **526-4** as a white solid (0.3 g, 86%). Mass (m/z): 474.8 $[M+H]^+$.

Step 5. Preparation of 3-((1r,4r)-4-aminocyclohexyl)-N-(6-(2,6-dimethylmorpholi no)-2-methylpyridin-3-yl)propanamide (**526-5**)

To a solution of **526-4** (0.3 g, 0.6 mmol) in DCM (5 mL) was added TFA (1 mL). The reaction was stirred at 25 °C for 2 hrs. The pH of the mixture was adjusted to 8 by aq. Na_2CO_3 and extracted with DCM. The organic phase was concentrated to give **526-5** as a brown solid (0.2 g, 89.3%). Mass (m/z): 374.8 $[M+H]^+$.

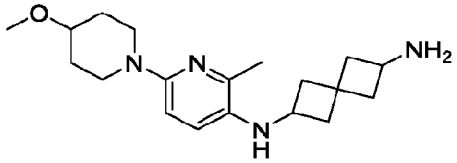
Step 6. N-(3-((1r,4s)-4-aminocyclohexyl)propyl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amin e (**526**)

To a solution of **526-5** (0.2 g, 0.5 mmol) in THF (1 mL) was added BH_3-THF (5 mL) at 25 °C. The reaction was stirred at 70 °C for 16 h. The mixture was diluted with EA (200 mL) and washed with water (200 mL x 3). The organic phase was concentrated and purification by Prep-TLC (DCM : MeOH = 10 : 1) to give **526** (12.5 mg, 6.5%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 6.96 (d, J = 8.6 Hz, 1H), 6.54 (d, J = 8.6 Hz, 1H), 3.78 – 3.67 (m, 4H), 3.02 (t, J = 7.2 Hz, 2H), 2.56 – 2.54 (m, 1H), 2.32 – 2.22 (m, 5H), 1.80 – 1.78 (m, 4H), 1.60 – 1.68 (m, 2H), 1.37 – 0.91 (m, 13H). Mass (m/z): 360.9 $[M+H]^+$.

Compound 527

6-(4-methoxypiperidin-1-yl)-2-methyl-3-nitropyridine

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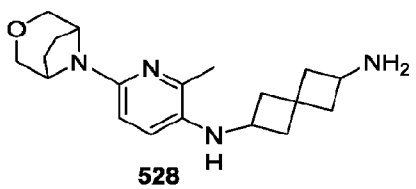


527

The title compound **527** (43 mg, 27.8) as a white solid was prepared from tert-butyl (6-((6-(4-methoxypiperidin-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (200 mg, 0.43 mmol), DCM (20 mL) and TFA (4 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.83 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 8.7 Hz, 1H), 3.68 (d, J = 7.8 Hz, 3H), 3.34 (m, 4H), 2.90 (t, 2H), 2.53 – 2.29 (m, 3H), 2.24 (m, 4H), 1.99 – 1.91 (m, 2H), 1.91 – 1.74 (m, 4H), 1.57 (s, 2H), 1.28 (t, J = 7.9 Hz, 1H). Mass (m/z): 330.8 $[M+H]^+$.

Compound 528

N2-(6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

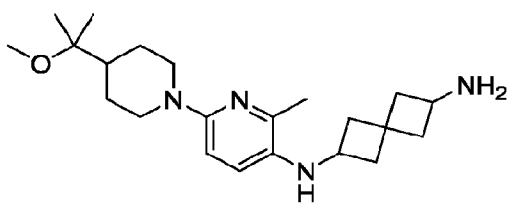


528

The desired product as a yellow solid (23.2 mg, 16.1% yield) was prepared from tert-butyl (6-((6-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (150 mg, 0.38 mmol), 1,4-dioxane (3 mL) and HCl/1,4-dioxane (1 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.71 (dd, *J* = 8.7, 4.0 Hz, 1H), 6.49 (d, *J* = 8.6 Hz, 1H), 4.45 (d, *J* = 7.3 Hz, 1H), 4.25 (s, 2H), 3.91 – 3.74 (m, 1H), 3.63 (m, 3H), 3.47 (d, *J* = 9.8 Hz, 2H), 3.23 – 3.13 (m, 1H), 2.42 – 2.22 (m, 3H), 2.18 (s, 3H), 2.15 – 2.09 (m, 1H), 1.84 (m, 4H), 1.74 – 1.63 (m, 3H). Mass(m/z): 328.8 $[M+H]^+$.

Compound 529

N2-(6-(4-(2-methoxypropan-2-yl)piperidin-1-yl)-2-methylpyridin-3-yl)spiro[3.3]-heptane-2,6-diamine

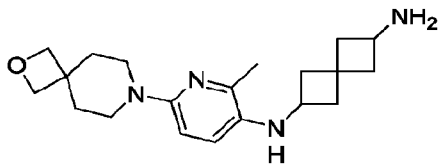


529

The title compound **529** (2.8 mg) as a yellow oil was prepared from tert-butyl (6-((6-(4-(2-methoxypropan-2-yl)piperidin-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (40 mg, 0.08 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (d, *J* = 9.4 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.20 (d, *J* = 9.6 Hz, 1H), 7.15 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 4.00 (d, *J* = 13.4 Hz, 2H), 3.52 – 3.40 (m, 2H), 3.37 – 3.27 (m, 3H), 1.93 (d, *J* = 13.2 Hz, 2H), 1.72 – 1.59 (m, 2H), 1.22 (s, 3H). Mass (m/z): 373.3 $[M+H]^+$.

Compound 530

2-N-(2-methyl-6-{2-oxa-7-azaspiro[3.5]nonan-7-yl}pyridin-3-yl)spiro[3.3]heptane-2,6-diamin e

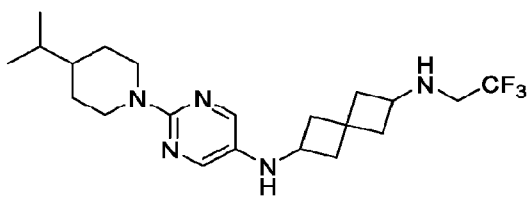


530

The title compound **530** (6.5 mg, 4.2%) as a light yellow solid was prepared from tert-butyl {6-[(2-methyl-6-{2-oxa-7-azaspiro[3.5]nonan-7-yl}pyridin-3-yl)amino]spiro[3.3]heptan-2-yl}a mino formate (70 mg, 0.16 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 5.83 (d, J = 6.0 Hz, 1H), 5.24 (d, J = 66.0 Hz, 1H), 4.12 (s, 2H), 3.87 – 3.72 (m, 4H), 3.67 (s, 1H), 3.50 (d, J = 7.6 Hz, 2H), 3.34 (s, 6H), 2.40 (d, J = 4.3 Hz, 1H), 2.33 (s, 2H), 2.19 (d, J = 3.9 Hz, 2H), 2.12 – 1.93 (m, 3H), 1.83 (s, 1H), 1.23 (s, 1H). Mass (m/z): 343.1 $[M+H]^+$.

Compound 531

N2-(2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl)-N6-(2,2,2-trifluoroethyl)spiro[3.3]heptane-2, 6-diamine

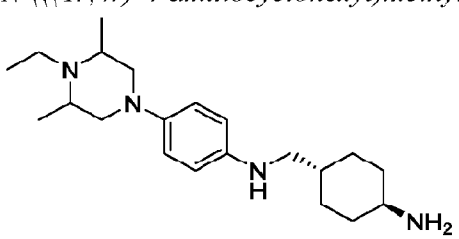


531

The desired product (3.3 mg, 2.9% yield) as a yellow solid was prepared from DIEA (106 mg, 0.82 mmol), 2,2,2-trifluoroethyl triflate (127 mg, 0.55 mmol), 2-N-[2-(4-isopropylpiperidin-1-yl)pyrimidin-5-yl]spiro[3.3]heptane-2,6-diamine hydrochloride (100 mg, 0.27 mmol) and dioxane (20 mL) according to the procedure for **414**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 0.7 Hz, 2H), 4.49 – 4.44 (m, 2H), 3.66 (t, J = 7.5 Hz, 1H), 3.21 (d, J = 7.5 Hz, 1H), 3.09 (d, J = 9.9 Hz, 2H), 2.74 – 2.67 (m, 2H), 2.48 (ddd, J = 11.3, 6.3, 2.8 Hz, 1H), 2.41 – 2.29 (m, 2H), 2.22 – 2.16 (m, 1H), 1.87 – 1.78 (m, 4H), 1.73 – 1.68 (m, 2H), 1.45 – 1.38 (m, 1H), 1.19 (m, 3H), 0.88 (d, J = 6.8 Hz, 6H). Mass (m/z): 412.3 $[M+H]^+$.

Compound 532

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(4-ethyl-3,5-dimethylpiperazin-1-yl)aniline



532

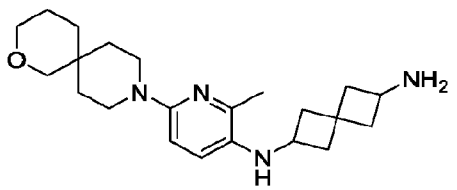
The title compound **532** (20 mg, 20%) as a yellow solid (21.1 mg, 18.5%) was prepared from

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tert-butyl ((1r,4r)-4-(((4-(4-ethyl-3,5-dimethylpiperazin-1-yl)phenyl)amino)methyl)cyclohexyl)carbamate (0.12 g, 0.3 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.83 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 8.8 Hz, 2H), 3.24 (d, J = 11.0 Hz, 2H), 2.98 (q, J = 7.2 Hz, 2H), 2.84 – 2.83 (m, 4H), 2.78 – 2.66 (m, 1H), 2.38 (t, J = 11.0 Hz, 2H), 1.8 9 – 1.91 (m, 4H), 1.51 – 1.49 (m, 1H), 1.25 – 0.91 (m, 13H). Mass (m/z): 345.1[M +H]$^+$.

Compound 533

N^2-(2-methyl-6-(2-oxa-9-azaspiro[5.5]undecan-9-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine

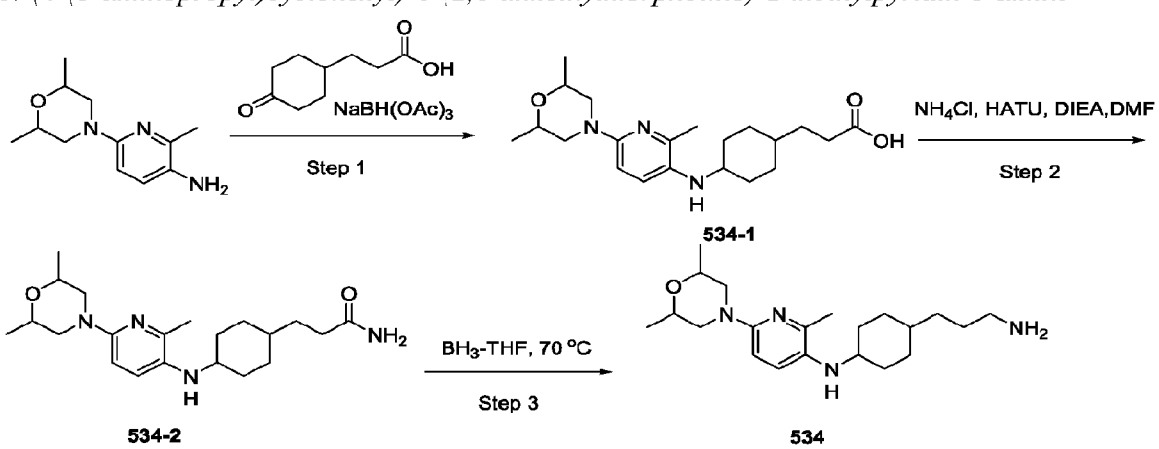


533

The title compound **533** (51.9 mg, 58.3% yield) as a yellow solid was prepared from tert-butyl (6-((2-methyl-6-(2-oxa-9-azaspiro[5.5]undecan-9-yl)pyridin-3-yl)amino)spiro[3.3]heptan-2-yl) carbamate (200 mg, 0.424 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.88 (d, J = 8.7 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.67 (dd, J = 10.5, 5.7 Hz, 2H), 3.49 (s, 2H), 3.30 (d, J = 1.1 Hz, 1H), 3.29 – 3.20 (m, 4H), 2.56 – 2.35 (m, 3H), 2.29 (s, 3H), 2.25 (m, 1H), 1.87 – 1.75 (m, 4H), 1.68 – 1.57 (m, 8H). Mass (m/z): 371.27 [M+H]$^+$.

Compound 534

N-(4-(3-aminopropyl)cyclohexyl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine



Step 1. Preparation of 3-(4-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)cyclohexyl)propanoic acid (**534-1**)

A mixture of 6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine (500 mg, 2.26 mmol), 3-(4-oxocyclohexyl)propanoic acid (384 mg, 2.26 mmol), and $NaBH(OAc)_3$ (479 mg, 2.26 mmol) in DCE (10 mL) was stirred overnight at 25 °C. After the reaction was completed,

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solvent was removed under vacuum and the crude was purified through silica gel chromatography to give of 3-(4-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)cyclohexyl)propanoic acid (300 mg, 35.3%) as a yellow solid. Mass(m/z): 376.1 $[M+H]^+$.

Step 2. Preparation of 3-(4-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl) amino) cyclohexyl) propanamide **(534-2)**

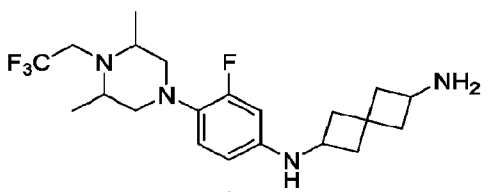
To a solution of 3-(4-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)cyclohexyl)propanoic acid (300 mg, 1.1 mmol), NH_4Cl (70 mg, 1.3 mmol), HATU (621 mg, 1.6 mmol) and DIEA (281 mg, 2.2 mmol) in DMF(10 ml). The reaction was stirred at R.T. for 18 hours. The solids were filtered and solvent was removed under vacuum. The residue was purified by silica gel column to provide 200 mg of 3-(4-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl) amino) cyclohexyl) propanamide as a yellow solid. Mass(m/z): 375.1 $[M+H]^+$.

Step 3. Preparation of N-(4-(3-aminopropyl)cyclohexyl)-6-(2,6-dimethylmorpholino)-2-methylpyridin-3-amine **(534)**

To a solution of 3-(4-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)cyclohexyl)propanamide (200 mg, 0.53 mmol), BH_3-THF (10 ml) in THF (5 mL). The reaction was stirred at 70 oC for 18 hours. The solids were filtered and solvent was removed under vacuum. The residue was purified by prep-HPLC (column-Xbridge-C18 150 x 19 mm, 5um; Mobile phase: ACN-H_2O (0.1% FA), 25%-40%) to afford **534** (8.0 mg) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 6.86 (d, J = 8.8 Hz, 1H), 6.50 – 6.46 (m, 1H), 3.83 – 3.78 (m, 3H), 3.61 – 3.54 (m, 2H), 2.85 (d, J = 5.8 Hz, 1H), 2.61 (dd, J = 3.8, 1.8 Hz, 1H), 2.51 – 2.48 (m, 1H), 2.20 (s, 3H), 2.17 – 2.13 (m, 1H), 2.12 (d, J = 1.6 Hz, 1H), 2.09 (d, J = 3.2 Hz, 0H), 1.56 – 1.28 (m, 10H), 1.25 – 1.18 (m, 3H), 1.10 (d, J = 6.2 Hz, 6H). Mass(m/z): 361.3 $[M+H]^+$.

Compound 535

N2-(4-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-3-fluorophenyl)spiro-[3.3]heptane-2,6-diamine



535A
535B

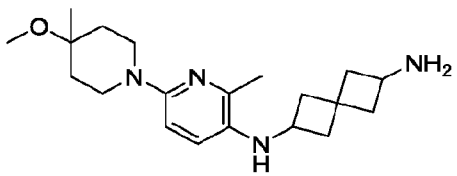
The title compound **535A** (5.4 mg) as a white solid and compound **535B** (5.8 mg) as a white solid were prepared from tert-butyl (6-((4-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-3-fluoro-phenyl)amino)spiro[3.3]heptan-2-yl)carbamate (150 mg, 0.29 mmol), DCM (10 mL) and TFA(1 mL) according to the procedure for **24**. **535A**: ^{1}HNMR (400 MHz, DMSO-d_6) δ 6.81 (t, J = 8.8 Hz, 1H), 6.31 – 6.26 (m, 2H), 3.76 – 3.59 (m, 2H), 3.34 (q, J = 9.8 Hz, 2H), 3.03 (dd, J = 8.6, 2.2 Hz, 2H), 2.93 (d, J = 6.2 Hz, 2H), 2.54 –2.30 (m, 6H), 2.20 – 2.09 (m, 2H), 1.94 – 1.86 (m, 2H), 1.11 (d, J = 6.2 Hz, 6H). Mass (m/z): 415.3 $[M+H]^+$. HPLC: Rt: 3.919 min (Column: XBRIDGE 2.1*50 mm,

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3.5 um; Mobile Phase: H_2O (0.05% TFA) ACN (0.05% TFA)/ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **535B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 (d, J = 8.6 Hz, 1H), 6.32 – 6.21 (m, 2H), 3.68 (d, J = 32.8 Hz, 2H), 3.34 (d, J = 10.0 Hz, 2H), 3.09 – 3.00 (m, 2H), 2.94 (dd, J = 14.2, 13.6 Hz, 2H), 2.61 – 2.48 (m, 2H), 2.40 (t, J = 10.8 Hz, 4H), 2.14 (s, 2H), 1.96 – 1.78 (m, 2H), 1.11 (d, J = 6.2 Hz, 6H). HPLC: Rt: 3.921 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 536

N2-(6-(4-methoxy-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

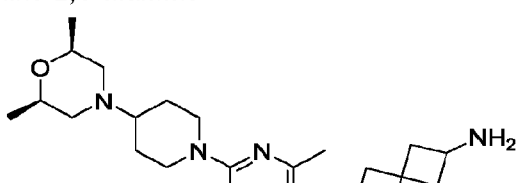


536

The title compound **536** (25.0 mg) was prepared in a total yield of 47.3% as a yellow solid from tert-butyl (6-((6-(4-methoxy-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl) carbamate (68 mg, 0.153 mmol), TFA (1 mL) and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 (s, 3H), 7.20 – 6.71 (m, 2H), 4.86 (s, 1H), 3.75 – 3.42 (m, 5H), 3.12 (s, 5H), 2.43 – 2.15 (m, 8H), 1.97 (s, 2H), 1.73 (d, J = 13.6 Hz, 2H), 1.53 (s, 2H), 1.12 (s, 3H). Mass (m/z): 345.3 $[M+H]^+$.

Compound 537

N2-(6-(4-((2S,6R)-2,6-dimethylmorpholino)piperidin-1-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



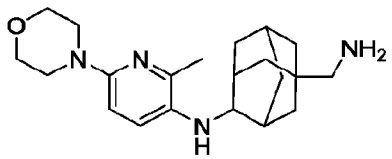
537

The title compound **537** (17.6 mg) was prepared in a total yield of 43.7% as a yellow solid from tert-butyl (6-((6-(4-((2S,6R)-2,6-dimethylmorpholino)piperidin-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (50 mg, 0.097 mmol), TFA (1 mL), and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 – 8.35 (m, 5H), 6.73 (d, J = 8.8 Hz, 1H), 6.56 (d, J = 8.8 Hz, 1H), 4.59 (s, 1H), 4.27 – 3.94 (m, 4H), 3.68 – 3.46 (m, 3H), 3.19 – 3.07 (m, 3H), 2.56 (d, J = 12.0 Hz, 2H), 2.45 (ddt, J = 9.2, 5.2, 1.6 Hz, 4H), 2.39 – 2.31 (m, 2H), 2.28 – 2.10 (m, 8H), 1.91 (td, J = 11.2, 10.4, 5.2 Hz, 2H), 1.70 (s, 2H), 1.12 (d, J = 6.4 Hz, 6H). Mass (m/z): 434.3 $[M+H]^+$.

Compound 538

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N-((2r,5s)-5-(aminomethyl)adamantan-2-yl)-2-methyl-6-morpholinopyridin-3-amine

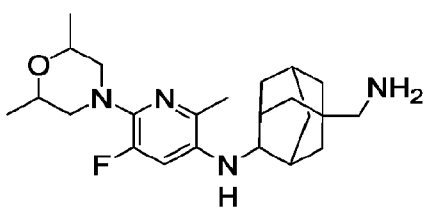


538 A
538 B

The title compound **538A** (Rt=9.41 min; 7.8 mg) was prepared in a two-step overall yield of 6.5% as a white powder and compound **538B** (Rt=10.48 min; 3.1 mg) was prepared in a two-step overall yield of 2.5% as a white powder from 2-methyl-6-morpholinopyridin-3-amine (200 mg, 1.03 mmol) and 4-oxoadamantane-1-carboxylic acid (301 mg, 1.55 mmol) according to the procedure for **84**, which were purified by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 0%-0%-30%-95%-95%-0%, 0 min-2 min-12 min-12.5 min-13.5 min-15.0 min). **538A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 (d, J = 8.8 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 3.86 (d, J = 6.3 Hz, 1H), 3.68 (t, J = 4.8 Hz, 4H), 3.18 (t, J = 4.8 Hz, 4H), 2.28 (s, 3H), 2.22 (s, 2H), 1.96 (d, J = 13.4 Hz, 4H), 1.87 (s, 1H), 1.51 (s, 4H), 1.42 (d, J = 3.1 Hz, 2H), 1.35 (d, J = 12.1 Hz, 2H). Mass (m/z): 357.3 $[M+H]^+$. **538B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.91 (dd, J = 8.8, 3.6 Hz, 1H), 6.53 (d, J = 8.7 Hz, 1H), 3.76 (d, J = 6.9 Hz, 1H), 3.72 – 3.63 (m, 4H), 3.19 (t, J = 4.8 Hz, 4H), 2.27 (d, J = 2.3 Hz, 3H), 2.20 (s, 2H), 1.95 (d, J = 21.2 Hz, 3H), 1.72 (q, J = 14.8, 13.7 Hz, 6H), 1.48 – 1.37 (m, 2H), 1.28 – 1.13 (m, 3H). Mass (m/z): 357.3 $[M+H]^+$.

Compound 539

N-((2r,5s)-5-(aminomethyl)adamantan-2-yl)-6-(2,6-dimethylmorpholino)-5-fluoro-2-methylpyridin-3-amine



539A
539B

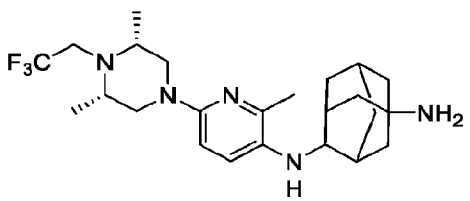
The title compound **539A** (Rt=6.04 min; 2.1 mg) was prepared in a two-step overall yield of 2.7% as a white powder and compound **539B** (Rt=6.82 min; 1.1 mg) was prepared in a two-step overall yield of 1.4% as a white powder from 6-(2,6-dimethylmorpholino)-5-fluoro-2-methylpyridin-3-amine (70 mg, 0.29 mmol) and 4-oxoadamantane-1-carboxylic acid (85 mg, 0.44 mmol) according to the procedure for **84**. The target products were purified by Prep-HPLC (Column: X Select-CSH-Prep 5 μm OBD, 19*150 mm; ACN/water (0.5% TFA) = 15%-45%-95%-95%-10%, 0 min-7 min-7.5 min-8.5 min-10.0 min). **539A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (d, J = 14.6 Hz, 1H), 4.21 (d, J = 6.0 Hz, 1H), 3.74 – 3.63 (m, 2H), 2.36 (d, J = 2.0 Hz, 2H), 2.29 – 2.24 (m, 5H), 2.02 – 1.85 (m, 5H), 1.55 (q, J = 12.2 Hz, 4H), 1.45 (d, J = 2.8 Hz, 2H), 1.38 (d, J = 12.2 Hz, 2H), 1.11 (d, J = 6.2 Hz, 6H). Mass (m/z): 403.5 $[M+H]^+$. **539B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 (dd, J =

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14.6, 6.4 Hz, 1H), 6.66 (s, 1H), 4.06 (d, J = 6.4 Hz, 1H), 3.73 – 3.61 (m, 2H), 3.37 (s, 3H), 2.38 – 2.33 (m, 2H), 2.25 (d, J = 1.1 Hz, 3H), 2.18 (s, 1H), 2.02 – 1.94 (m, 5H), 1.91 (s, 1H), 1.78 (d, J = 13.2 Hz, 2H), 1.71 – 1.61 (m, 4H), 1.44 (t, J = 6.8 Hz, 2H), 1.39 (s, 2H), 1.17 (s, 1H), 1.09 (d, J = 6.3 Hz, 6H), 0.86 – 0.80 (m, 2H). Mass (m/z): 403.5 $[M+H]^+$.

Compound 540

N4-(6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-yl)adamantane-1,4-diamine

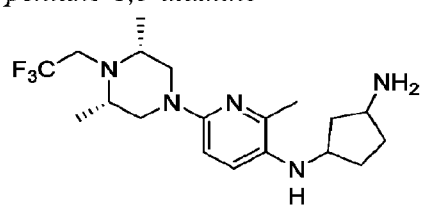


540

The title compound **540** (33.0 mg) was prepared in a yield of 52.6% as a white powder from 6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-amine (42 mg, 0.14 mmol) and tert-butyl (4-oxoadamantan-1-yl)carbamate (44 mg, 0.17 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, J = 34.9 Hz, 3H), 6.98 (s, 1H), 6.62 (s, 1H), 3.86 (d, J = 12.1 Hz, 2H), 3.39 (d, J = 10.8 Hz, 3H), 2.76 (s, 2H), 2.36 (s, 4H), 2.12 (d, J = 22.3 Hz, 3H), 2.01 (d, J = 22.0 Hz, 2H), 1.96 – 1.84 (m, 3H), 1.79 (d, J = 16.9 Hz, 3H), 1.68 (d, J = 12.7 Hz, 1H), 1.55 (d, J = 11.3 Hz, 1H), 1.36 (d, J = 12.5 Hz, 1H), 1.10 (d, J = 6.2 Hz, 6H). Mass (m/z): 451.7 $[M+H]^+$.

Compound 541

N1-(6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-yl)cyclopentane-1,3-diamine



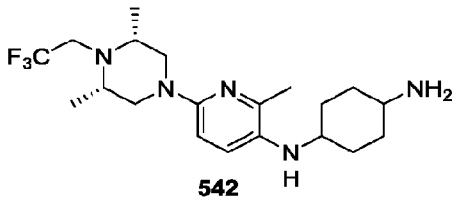
541

The title compound **541** (31.4 mg) was prepared in a yield of 57.89% as a white powder from 6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-amine (42 mg, 0.14 mmol) and tert-butyl (3-oxocyclopentyl)carbamate (42mg, 0.21 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, J = 29.6 Hz, 3H), 7.01 (s, 1H), 6.67 (s, 1H), 4.47 (s, 1H), 3.88 (s, 3H), 3.64 (t, J = 53.5 Hz, 4H), 2.76 (s, 2H), 2.43 – 2.23 (m, 4H), 2.10 (d, J = 15.5 Hz, 1H), 2.02 – 1.71 (m, 3H), 1.69 – 1.45 (m, 1H), 1.10 (d, J = 6.2 Hz, 6H). Mass (m/z): 386.3 $[M+H]^+$.

Compound 542

N1-(6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-yl)cyclohexane-1,4-diamine

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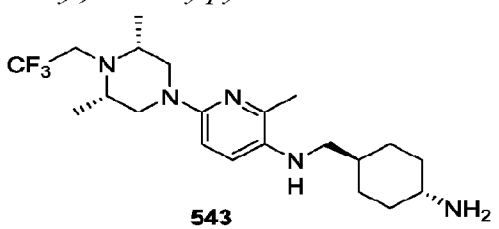


542

The title compound **542** (38.4 mg) was prepared in a yield of 69.19% as a white powder from 6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-amine (44 mg, 0.21 mmol) and tert-butyl (4-oxocyclohexyl)carbamate (42 mg, 0.21 mmol) according to the procedure for **20**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.21 (m, 3H), 7.04 (s, 1H), 6.65 (s, 1H), 3.88 (d, J = 12.9 Hz, 2H), 3.43 (d, J = 24.3 Hz, 1H), 3.11 (s, 1H), 2.92 (s, 1H), 2.75 (s, 2H), 2.35 (s, 5H), 1.99 (s, 2H), 1.75 (d, J = 26.4 Hz, 3H), 1.60 (s, 1H), 1.44 (d, J = 11.9 Hz, 1H), 1.09 (d, J = 6.2 Hz, 6H). Mass (m/z): 400.4 $[M+H]^+$.

Compound 543

N-(((1r,4R)-4-aminocyclohexyl)methyl)-6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-amine

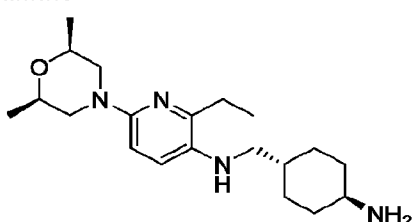


543

The title compound **543** (32.3 mg) was prepared in a yield of 56.2% as a white powder from 6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-amine (44 mg, 0.21 mmol) and tert-butyl ((1r,4r)-4-formylcyclohexyl)carbamate (47 mg, 0.21 mmol) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (s, 3H), 6.94 (s, 1H), 6.63 (s, 1H), 4.57 (s, 1H), 3.82 (s, 2H), 2.99 – 2.69 (m, 6H), 2.42 – 2.19 (m, 5H), 1.89 (dd, J = 27.9, 15.3 Hz, 4H), 1.49 (s, 1H), 1.35 – 1.21 (m, 2H), 1.08 (d, J = 6.0 Hz, 6H), 0.98 (d, J = 12.9 Hz, 2H). Mass (m/z): 414.7 $[M+H]^+$.

Compound 544

N-(((1r,4R)-4-aminocyclohexyl)methyl)-6-((2S,6R)-2,6-dimethylmorpholino)-2-ethylpyridin-3-amine



544

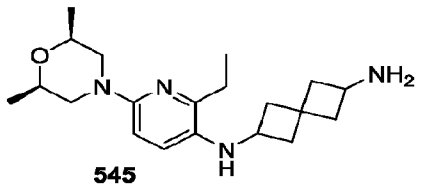
The title compound **544** (30.9 mg) was prepared in a total yield of 28.3% as a purple solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 3H), 6.88 (br, 1H), 6.53 (br, 1H), 4.66 – 4.29 (m, 1H), 3.98 – 3.72 (m, 2H), 3.71 – 3.55 (m, 2H), 2.96 – 2.82 (m, 2H), 2.26 – 2.10 (m, 2H), 2.03 – 1.91 (m, 2H), 1.89– 1.80 (m, 2H), 1.57 – 1.43 (m, 1H), 1.35 – 1.25 (m, 2H), 1.18 – 1.10 (m, 9H), 1.05 – 0.92 (m, 2H). Mass (m/z): 347.2

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$[M+H]^+$.

Compound 545

N^2-(6-((2S,6R)-2,6-dimethylmorpholino)-2-ethylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

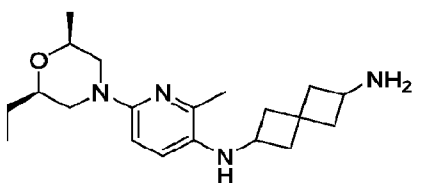


545

The title compound **545** (16.4 mg) was prepared in a total yield of 31.8% as a yellow solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J = 5.2 Hz, 3H), 6.76 (br, 1H), 6.51 (br, 1H), 4.72 – 4.43 (m, 1H), 3.94 – 3.78 (m, 2H), 3.70 – 3.48 (m, 5H), 2.62 – 2.53 (m, 2H), 2.43 – 2.33 (m, 2H), 2.22 – 2.13 (m, 4H), 1.97 – 1.85 (m, 2H), 1.17 – 1.12 (m, 9H). Mass (m/z): 345.2 $[M+H]^+$.

Compound 546

N^2-(6-((2R,6S)-2-ethyl-6-methylmorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

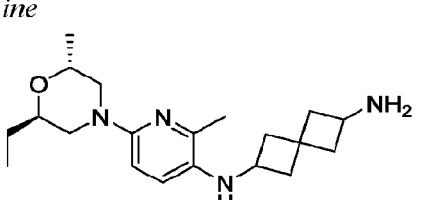


546

The title compound **546** (12.3 mg) was prepared in a total yield of 52.8% as a light yellow solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 3H), 6.80 – 6.66 (m, 1H), 6.56 – 6.46 (m, 1H), 4.61 – 4.49 (m, 1H), 4.41 – 4.31 (m, 1H), 3.88 – 3.78 (m, 2H), 3.67 – 3.52 (m, 4H), 2.29 – 2.07 (m, 8H), 2.01 – 1.83 (m, 2H), 1.53 – 1.43 (m, 2H), 1.14 (d, J = 6.1 Hz, 3H), 0.94 (d, J = 7.4 Hz, 3H). Mass (m/z): 345.3$[M+H]^+$.

Compound 547

N^2-(6-((2R,6R)-2-ethyl-6-methylmorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



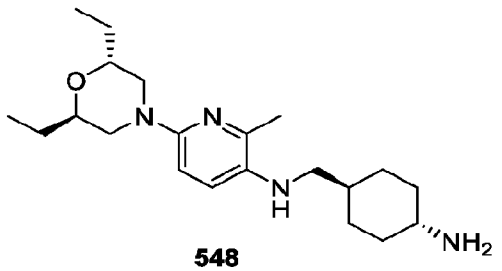
547

The title compound **547** (13.9 mg) was prepared in a total yield of 63.5% as a light yellow solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (s, 3H), 6.72 (d, J = 8.7 Hz, 1H), 6.48 (d, J = 8.7 Hz, 1H), 3.97 – 3.87 (m, 1H), 3.72 – 3.67 (m, 1H), 3.66 – 3.60 (m, 1H), 3.58 – 3.52 (m, 1H), 3.40 – 3.37 (m, 1H), 3.21 (dd, J = 12.2, 3.5 Hz, 1H), 3.05 (dd, J = 12.2, 5.5 Hz, 1H), 2.82 (dd, J = 12.1, 6.6 Hz, 1H), 2.45 – 2.34 (m, 2H), 2.26 – 2.04 (m, 7H), 1.94 – 1.85 (m, 2H), 1.69 – 1.59 (m, 2H), 1.53 – 1.43 (m, 1H), 1.16 (d, J = 6.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H). Mass (m/z): 345.3 $[M+H]^+$.

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Compound 548

N-(((1r,4R)-4-aminocyclohexyl)methyl)-6-((2R,6R)-2,6-diethylmorpholino)-2-methylpyridin-3-amine

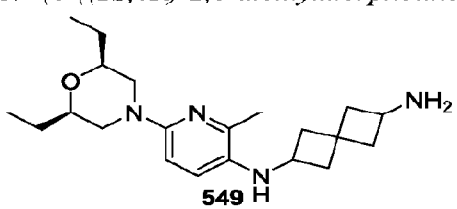


548

The title compound **548** (13.6 mg) was prepared in a total yield of 37.8% as a light yellow solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (s, 3H), 6.82 (d, J = 8.8 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.48 –4.37 (m, 1H), 3.67 – 3.61 (m, 1H), 3.28 (dd, J = 12.0, 3.3 Hz, 2H), 2.96 (dd, J = 12.2, 6.0 Hz, 2H), 2.87 – 2.79 (m, 2H), 2.21 (s, 3H), 1.98 – 1.92 (m, 2H), 1.89 – 1.81 (m, 2H), 1.68 – 1.60 (m, 2H), 1.51 – 1.44 (m, 2H), 1.28 – 1.22 (m, 2H), 1.04– 0.96 (m, 2H), 0.90 (t, J = 7.4 Hz, 6H). Mass (m/z): 361.3[M+H]$^+$.

Compound 549

N^2-(6-((2S,6R)-2,6-diethylmorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

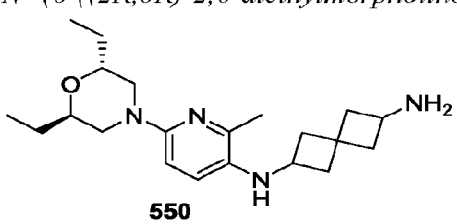


549

The title compound **549** (13.6 mg) was prepared in a total yield of 66.3% as a light yellow solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.90 (d, J = 8.8 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 3.81 – 3.75 (m, 2H), 3.51 – 3.43 (m, 2H), 2.65 – 2.45 (m, 4H), 2.43 – 2.25 (m, 7H), 2.21 – 2.14 (m, 2H), 2.05 – 1.97 (m, 2H), 1.62 – 1.52 (m, 4H), 1.02 (t, J = 7.4 Hz, 6H). Mass (m/z): 359.2[M+H]$^+$.

Compound 550

N^2-(6-((2R,6R)-2,6-diethylmorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



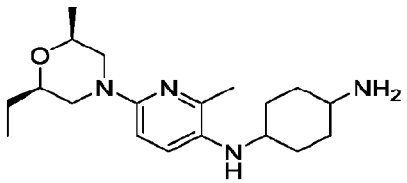
550

The title compound **550** (13.8 mg) was prepared in a total yield of 38.5% as a light yellow solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.92 (d, J = 6.8 Hz, 1H), 6.55 (d, J = 14.7 Hz, 1H), 3.83 – 3.72 (m, 2H), 3.41 – 3.33 (m, 2H), 3.07 – 2.96 (m, 2H), 2.68 – 2.52 (m, 2H), 2.50 – 2.13 (m, 9H), 2.05 – 1.95 (m, 2H), 1.83 – 1.69 (m, 2H), 1.58 – 1.48 (m, 2H), 0.98 (t, J = 7.5 Hz, 6H). Mass (m/z): 359.2[M+H]$^+$.

Compound 551

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N^1-(6-((2R,6S)-2-ethyl-6-methylmorpholino)-2-methylpyridin-3-yl)cyclohexane-1,4-diamine

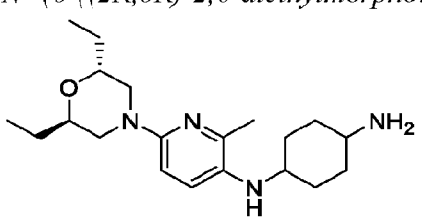


551A
551B

The title compound **551A** and **551B** were prepared according to the procedure for compound **24**. The crude residue was purified by preparative TLC (H_2O:MeOH:Dichloromethane=0.1:1:5) to afford compound **551A** in 26.1% yield as a light yellow solid and **551B** in 37.0% yield as a light yellow solid. **551A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.04 (d, J = 8.7 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 3.83 – 3.78 (m, 2H), 3.73 – 3.69 (m, 2H), 3.57 – 3.53 (m, 2H), 2.34 (s, 3H), 2.31 – 2.27 (m, 2H), 2.06 – 1.98 (m, 4H), 1.81 – 1.75 (m, 4H), 1.61 – 1.58 (m, 2H), 1.22 (d, J = 6.2 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H). Mass (m/z): 333.3 $[M+H]^+$. HPLC: Rt=2.846 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0 min-0.5 min-10 min-10.5 min-12.0 min) **551B**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.06 (d, J = 10.3 Hz, 1H), 6.59 (d, J = 9.3 Hz, 2H), 3.86 – 3.67 (m, 3H), 3.64 – 3.56 (m, 1H), 3.53 – 3.48 (m, 1H), 3.24 – 3.07 (m, 3H), 2.29 (s, 3H), 2.17 – 2.01 (m, 4H), 1.62 – 1.49 (m, 4H), 1.37 – 1.31 (m, 2H), 1.22 (d, J = 3.6 Hz, 3H), 1.07 – 0.95 (m, 3H). Mass (m/z): 333.3 $[M+H]^+$. HPLC: Rt=2.607 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0 min-0.5 min-10 min-10.5 min-12.0 min).

Compound 552

N^1-(6-((2R,6R)-2,6-diethylmorpholino)-2-methylpyridin-3-yl)cyclohexane-1,4-diamine



552A
552B

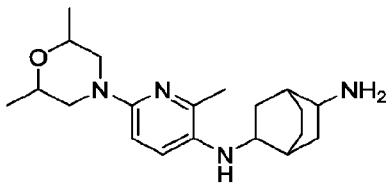
The title compound **552A**, **552B** was prepared according to the procedure for compound **24**. The crude residue was purified by preparative TLC (H_2O:MeOH:Dichloromethane=0.1:1:5) to afford compound **552A** in a 14.4% yield as a light yellow solid and **552B** in a 23.3% yield as a light yellow solid. **552A**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.04 (d, J = 8.7 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 4.22 – 4.11 (m, 1H), 3.84 – 3.77 (m, 2H), 3.57– 3.52 (m, 1H), 3.51 – 3.44 (m, 2H), 3.27 – 3.19 (m, 2H), 2.34 (s, 3H), 1.90 – 1.71 (m, 8H), 1.61 – 1.51 (m, 4H), 1.06 – 0.98 (m, 6H). Mass (m/z): 333.3 $[M+H]^+$. HPLC: Rt=3.329 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0 min-0.5 min-10 min-10.5 min-12.0 min). **552B**: ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.03 (br, 1H), 6.56 (br, 1H), 4.26 – 4.10 (m, 1H), 3.90 – 3.72 (m, 2H), 3.53 – 3.41 (m, 2H), 3.24 – 3.07 (m, 3H), 2.29

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(s, 3H), 2.18 – 2.02 (m, 4H), 1.64 – 1.47 (m, 6H), 1.41 – 1.30 (m, 2H), 1.09 – 0.94 (m, 6H). Mass(m/z): 333.3 $[M+H]^+$. HPLC: Rt=3.195 mins (Agilent, poroshell 120, SB-C18 2.7 μm, 4.6x50 mm, ACN/Water (0.1% FA)= 5%-5%-95%-95%-95%-5%, 0 min-0.5 min-10 min-10.5 min-12.0 min).

Compound 553

N2-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)bicyclo[2.2.2]octane-2,5-diamine

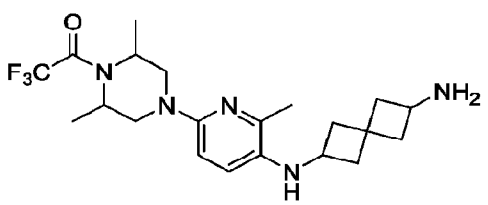


553

The title compound **553** (44.0 mg) was prepared in a total yield of 51.2% as a white solid according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.16 (m, 1H), 3.95 – 3.77 (m, 2H), 3.67 – 3.54 (m, 2H), 3.25 (m, 1H), 2.40 – 2.30 (m, 2H), 2.25 (s, 3H), 2.21 – 2.13 (m, 2H), 2.08 – 1.95 (m, 2H), 1.86 – 1.63 (m, 3H), 1.52 – 1.27 (m, 3H), 1.12 (d, J = 6.0 Hz, 6H). Mass (m/z): 345.3 $[M+H]^+$.

Compound 554

1-(4-(5-((6-aminospiro[3.3]heptan-2-yl)amino)-6-methylpyridin-2-yl)-2,6-dimethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one

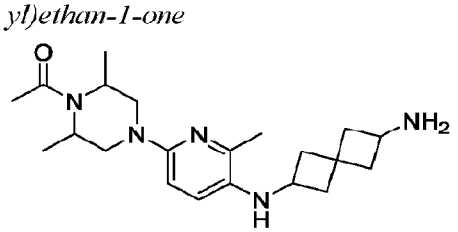


554

The title compound **554** as a yellow solid (23 mg, 28.5% yield) was prepared from tert-butyl (6-((6-(3,5-dimethyl-4-(2,2,2-trifluoroacetyl)piperazin-1-yl)-2-methylpyridin-3-yl)amino)spiro [3.3]heptan-2-yl)carbamate (0.1 g, 0.2 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.86 (d, J = 8.6 Hz, 1H), 6.60 (d, J = 8.6 Hz, 1H), 4.59 (s, 1H), 4.27 (s, 1H), 3.92 (d, J = 11.6 Hz, 2H), 3.71 – 3.73 (m, 1H), 3.47 – 3.49 (m, 1H), 2.82 – 2.84 (m, 2H), 2.59 – 2.35 (m, 3H), 2.33 – 2.25 (m, 4H), 1.97 – 1.99 (m, 4H), 1.43 (d, J = 22.2 Hz, 6H). Mass (m/z): 425.7$[M+H]^+$.

Compound 555

1-(4-(5-((6-aminospiro[3.3]heptan-2-yl)amino)-6-methylpyridin-2-yl)-2,6-dimethylpiperazin-1-yl)ethan-1-one



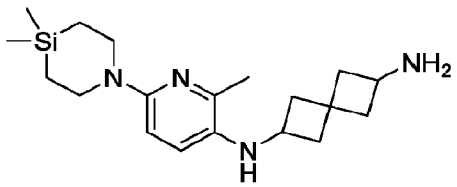
The title compound **555** (34.8 mg) was prepared in a total yield of 77.9 % as a yellow solid

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from tert-butyl (6-((6-(4-acetyl-3,5-dimethylpiperazin-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (56.6 mg, 0.12 mmol), TFA according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.78 - 4.26 (m, 2H), 3.95 - 3.81 (m, 2H), 3.65 (m, 1H), 3.54 (m, 1H), 2.75 - 2.60 (m, 2H), 2.44 - 2.28 (m, 2H), 2.22 (s, 3H), 2.20 – 2.13 (m, 4H), 2.04 (s, 3H), 1.97 – 1.85 (m, 2H), 1.22 (d, J – 6.4 Hz, 6H). Mass(m/z): 372.2 $[M+H]^+$

Compound 556

N2-(6-(4,4-dimethyl-1,4-azasilinan-1-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

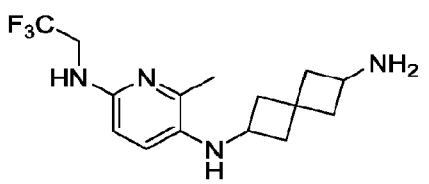


556

The title compound **556** (17.4 mg, 24%) as a yellow solid was prepared from tert-butyl (6-((6-(4,4-dimethyl-1,4-azasilinan-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-yl)ca rbamate (95 mg, 0.21 mmol), HCl in dioxane (5 mL) and DCM (5 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.88 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 8.7 Hz, 1H), 3.82 – 3.64 (m, 5H), 3.55-3.45 (m, 1H), 2.60 – 2.46 (m, 2H), 2.43 – 2.37 (m, 1H), 2.33-2.22 (m, 4H), 2.07 – 1.91 (m, 4H), 0.79 – 0.71 (m, 4H), 0.07 (s, 6H). Mass (m/z): 345.3$[M+H]^+$.

Compound 557

N^5-(6-aminospiro[3.3]heptan-2-yl)-6-methyl-N^2-(2,2,2-trifluoroethyl)pyridine-2,5-diamine



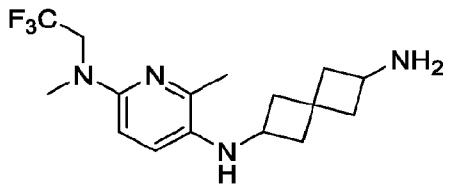
557

The title compound **557** (22.2 mg, 28.2%) as a white solid was prepared from tert-butyl (5-((6-((tert-butoxycarbonyl)amino)spiro[3.3]heptan-2-yl)amino)-6-methylpyridin-2-yl)(2,2,2-t rifluoroethyl)carbamate (129 mg, 0.2502 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.88 (d, J = 8.7 Hz, 1H), 6.41 (d, J = 8.5 Hz, 1H), 3.99 (q, J = 9.5 Hz, 2H), 3.70 (t, J = 7.6 Hz, 1H), 3.29 (d, J = 8.4 Hz, 1H), 2.56 – 2.42 (m, 2H), 2.36 (ddd, J = 11.6, 6.8, 5.1 Hz, 1H), 2.27 (s, 3H), 2.27 – 2.23 (m, 1H), 1.96 – 1.78 (m, 4H). Mass (m/z): 315.1 $[M+H]^+$.

Compound 558

N^5-(6-aminospiro[3.3]heptan-2-yl)-N^2,6-dimethyl-N^2-(2,2,2-trifluoroethyl)pyridine-2,5-diamin e

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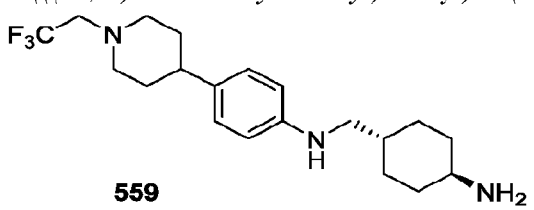


558

The title compound **558** (13.1 mg, 9.8%) as a yellow solid was prepared from tert-butyl (6-((2-methyl-6-(methyl(2,2,2-trifluoroethyl)amino)pyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (165 mg, 0.3851 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.92 (d, J = 8.7 Hz, 1H), 6.47 (d, J = 8.7 Hz, 1H), 4.29 (q, J = 9.5 Hz, 2H), 3.72 (p, J = 7.6 Hz, 1H), 3.32 – 3.28 (m, 1H), 3.03 (s, 3H), 2.58 – 2.42 (m, 2H), 2.37 (ddd, J = 11.7, 6.9, 5.0 Hz, 1H), 2.29 (s, 3H), 2.28 – 2.23 (m, 1H), 1.97 – 1.78 (m, 4H). Mass (m/z): 329.3 $[M+H]^+$.

Compound 559

N-(((1r,4r)-4-aminocyclohexyl)methyl)-4-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)aniline

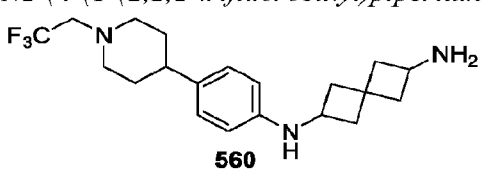


559

The title compound **559** (75.1 mg, 75%) as a white solid was prepared from tert-butyl ((1r,4r)-4-(((4-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)amino)methyl)cyclohexyl)carbamate (127 mg, 0.27 mmol) and HCl in dioxane (5 mL) and DCM (5 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.98 (d, J = 8.5 Hz, 2H), 6.57 (d, J = 8.6 Hz, 2H), 3.13-3.01 (m, 4H), 2.93 (d, J = 6.7 Hz, 2H), 2.90-2.81 (m, 1H), 2.50 – 2.40 (m, 2H), 2.40 – 2.31 (m, 1H), 2.06 – 1.87 (m, 4H), 1.78 – 1.68 (m, 4H), 1.63 – 1.53 (m, 1H), 1.32 – 1.22 (m, 2H), 1.15 – 1.02 (m, 2H). Mass (m/z): 370.2$[M+H]^+$.

Compound 560

N2-(4-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)spiro[3.3]heptane-2,6-diamine



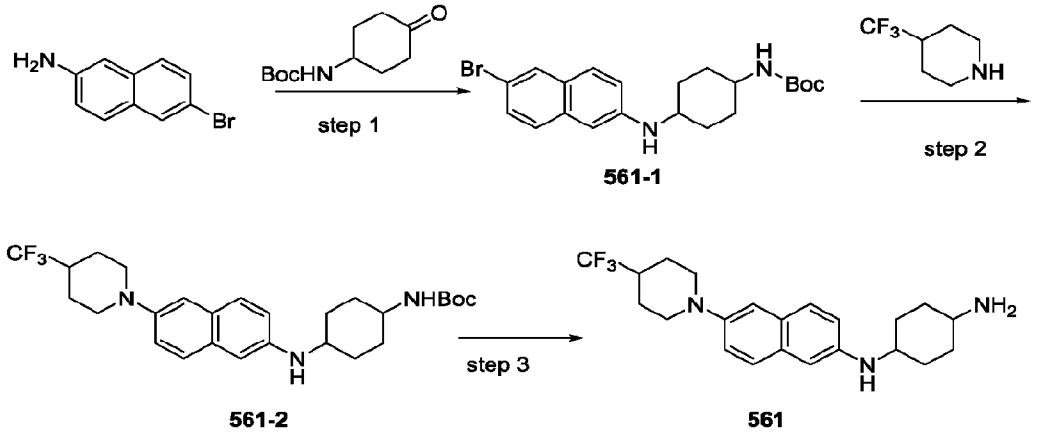
560

The title compound **560** (103.3 mg, 98%) as a yellow solid was prepared from tert-butyl (6-((4-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)amino)spiro[3.3]heptan-2-yl)carbamate (122 mg, 0.26 mmol), HCl in dioxane (5 mL) and DCM (5 mL) according to the procedure for **37**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.98 (d, J = 8.5 Hz, 2H), 6.53 (d, J = 8.5 Hz, 2H), 3.82 – 3.71 (m, 1H), 3.55 – 3.41 (m, 1H), 3.13 – 3.00 (m, 4H), 2.58 – 2.24 (m, 7H), 2.08 – 1.82 (m, 4H), 1.77 – 1.65 (m, 4H). Mass (m/z): 368.2$[M+H]^+$.

Compound 561

N1-(6-(4-(trifluoromethyl)piperidin-1-yl)naphthalen-2-yl)cyclohexane-1,4-diamine

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Step 1. Preparation of tert-butyl (4-((6-bromonaphthalen-2-yl)amino)cyclohexyl)carbamate **(561-1)**

A mixture of 6-bromonaphthalen-2-amine (300 mg, 1.35 mmol), tert-butyl (4-oxocyclohexyl)carbamate (345 mg, 1.62 mmol), $NaBH_3CN$ (169 mg, 2.7 mmol) in MeOH (20 mL), CH_3COOH (0.1 mL) was stirred at 50 °C for 2h. It was quenched with H_2O (30 mL) and extracted with EA (3x30 mL), and the organic layers were concentrated to afford product (0.4 g, yield: 70.4%) as a yellow solid. Mass (m/z): 419.2 $[M+H]^+$.

Step 2. Preparation of tert-butyl (4-((6-(4-(trifluoromethyl)piperidin-1-yl)naphthalen-2-yl)amino)cyclohexyl)carbamate **(561-2)**

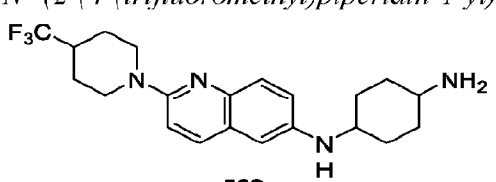
A mixture of tert-butyl (4-((6-bromonaphthalen-2-yl)amino)cyclohexyl)carbamate (200 mg, 0.47 mmol), 4-(trifluoromethyl)piperidine (88 mg, 0.57 mmol), RuPhos (44 mg, 0.09 mmol), $Pd_2(dba)_3$ (87 mg, 0.095 mmol), and Cs_2CO_3 (465 mg,1.42 mmol) in toluene (20 mL) was stirred at 110 °C for 3h. It was quenched with H_2O (30 mL) and extracted with EA (3x30 mL), the organic layers were concentrated to afford product (0.2 g, 85%) as a yellow solid. Mass (m/z): 491.7 $[M+H]^+$.

Step 3. Preparation of N1-(6-(4-(trifluoromethyl)piperidin-1-yl)naphthalen-2-yl)cyclohexane-1,4-diamine **(561)**

To a solution of 8 (200 mg, 0.21 mmol) in 1,4-dioxane (3 mL) was added HCl /1,4-dioxane (1 ml). Then the mixture was stirred overnight at 25 °C. Solvent was removed under vacuum and the residue was purified by prep-HPLC (column-Gemini -C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 5%-20%) to afford the desired product (33.5 mg, 21.0%) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ 7.87 – 7.67 (m, 3H), 7.46 (m,1H), 7.41 – 7.10 (m, 2H), 3.86 (t, J = 14.7 Hz, 10H), 3.86 (m, 2H), 3.70s (m, 1H), 3.1 (m, 1H), 2.37 – 1.75 (m, 12H), 2.04 (m, 2H). Mass (m/z): 491.7 $[M-H]^-$.

Compound 562

N^1-(2-(4-(trifluoromethyl)piperidin-1-yl)quinolin-6-yl)cyclohexane-1,4-diamine



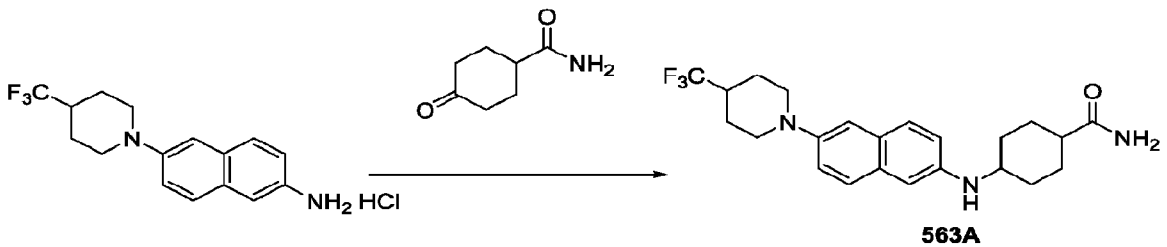
562

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The title compound **562A** (41.9 mg, 32.5%) as a yellow solid and **562B** as a yellow solid (36.4 mg, 28.2%) were prepared from tert-butyl (4-((2-(4-(trifluoromethyl)piperidin-1-yl)quinolin-6-yl)amino)cyclohexyl)carbamate (305 mg, 0.6179 mmol), 1.4-dioxane (10 mL) and HCl/1,4-dioxane (10 mL) according to the procedure for **24**. **562A**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, J = 9.1 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.10 (d, J – 9.2 Hz, 1H), 7.01 (dd, J – 9.0, 2.5 Hz, 1H), 6.66 (d, J – 2.4 Hz, 1H), 4.47 (d, J = 13.2 Hz, 2H), 3.19 (dd, J = 15.1, 6.5 Hz, 1H), 2.98 (t, J = 11.2 Hz, 1H), 2.84 (t, J = 11.9 Hz, 2H), 2.66 – 2.54 (m, 1H), 2.15 – 1.82 (m, 6H), 1.54 – 1.38 (m, 4H), 1.31 – 1.13 (m, 2H). Mass (m/z): 392.8 $[M+H]^+$. HPLC: Rt: 3.067 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **562B**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.25 – 6.96 (m, 2H), 6.64 (d, J = 2.2 Hz, 1H), 5.65 (s, 1H), 4.47 (d, J = 13.0 Hz, 2H), 3.51 (s, 1H), 3.05 (s, 1H), 2.84 (t, J = 11.9 Hz, 2H), 1.83 (dd, J = 34.8, 16.2 Hz, 6H), 1.75 – 1.54 (m, 4H), 1.45 (qd, J = 12.5, 3.9 Hz, 2H). Mass (m/z): 392.8 $[M+H]^+$. HPLC: Rt: 3.391 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA)/ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 563

4-((6-(4-(trifluoromethyl)piperidin-1-yl)naphthalen-2-yl)amino)cyclohexane-1-carboxamide



563A
563B

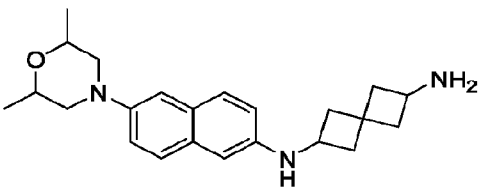
A mixture of 6-(4-(trifluoromethyl)piperidin-1-yl)naphthalen-2-amine hydrochloride (100 mg, 0.3014 mmol), 4-oxocyclohexane-1-carboxamide (42.55 mg, 0.3014 mmol) and sodium triacetoxyborohydride (191.64 mg, 0.9042 mmol) in DCE (20 mL) was stirred overnight at 25 °C. After cooling, the excess DCE was removed under vacuum and the residue was extracted three times with DCM (30 mL) and water (30 mL). Organic layer was combined, solvent was removed under vacuum and the crude was purified through prep-HPLC (column-Gemini -C18 150 x 21.2 mm, 5um; Mobile phase: ACN-H_2O (0.1%FA), 20%-50%) to afford the desired product **563A** as a gray solid (9.5 mg, 7.1%) and **563B** as a purple solid (9.9 mg, 7.4%). **563A**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (dd, J = 8.9, 2.5 Hz, 2H), 7.07 (dd, J = 9.0, 2.4 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 6.81 (dd, J = 8.8, 2.3 Hz, 1H), 6.70 (d, J = 2.1 Hz, 1H), 3.63 (d, J = 12.3 Hz, 2H), 3.28 – 3.22 (m, 1H), 2.59 (td, J = 12.2, 2.0 Hz, 2H), 2.26 – 2.07 (m, 4H), 1.94 – 1.79 (m, 4H), 1.66 (tt, J = 12.5, 6.4 Hz, 2H), 1.59 – 1.47 (m, 2H), 1.14 (dt, J = 13.1, 10.5 Hz, 2H). HPLC: Rt: 4.428 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA) ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min). **563B**: ^{1}H NMR (400 MHz, CD_3OD) δ 7.39 (dd, J = 8.8, 2.1 Hz, 2H), 7.08 (dd, J = 9.0, 2.4 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H),

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6.69 (d, *J* = 2.1 Hz, 1H), 3.64 (d, *J* = 11.7 Hz, 2H), 3.59 (s, 1H), 2.61 (dd, *J* = 12.3, 10.0 Hz, 2H), 2.32 – 2.17 (m, 2H), 1.91 (d, *J* = 11.7 Hz, 2H), 1.85 – 1.75 (m, 4H), 1.73 – 1.54 (m, 6H).Mass(m/z): 419.7 $[M+H]^+$. HPLC: Rt: 4.598 min (Column: XBRIDGE 2.1*50 mm, 3.5 um; Mobile Phase: H_2O (0.05% TFA) ACN (0.05% TFA), ACN from 0% to 60% over 7 minutes, 7-8 min, ACN from 60% to 100%; 0.8 mL/min).

Compound 564

N^2-(6-(2,6-dimethylmorpholino)naphthalen-2-yl)spiro[3.3]heptane-2,6-diamine

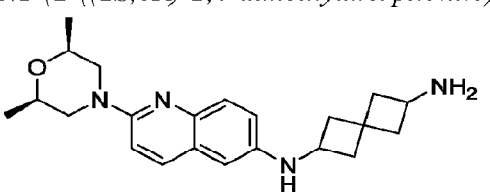


564

The title compound N^2-(6-(2,6-dimethylmorpholino)naphthalen-2-yl)spiro[3.3]heptane-2,6-diamine **564** (41.8 mg, 53%) as an off-white solid was prepared from tert-butyl (6-((6-(2,6-dimethylmorpholino)naphthalen-2-yl)amino)spiro[3.3]heptan-2-yl)carbamate (100 mg, 0.21 mmol), DCM (3 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.41 (t, *J* = 8.3 Hz, 2H), 7.14 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 5.76 (d, *J* = 6.6 Hz, 1H), 3.77 – 3.64 (m, 3H), 3.55 – 3.47 (m, 2H), 3.22 – 3.09 (m, 1H), 2.50 – 2.49 (m, 1H), 2.43 – 2.41 (m, 1H), 2.37 – 2.27 (m, 2H), 2.24 – 2.16 (m, 2H), 2.14 – 2.05 (m, 1H), 2.03 – 1.88 (m, 1H), 1.85 – 1.72 (m, 2H), 1.71 – 1.57 (m, 2H), 1.13 (d, *J* = 6.3 Hz, 6H). MS (m/z): 366.3$[M+H]^+$.

Compound 565

N2-(2-((2S,6R)-2,6-dimethylmorpholino)quinolin-6-yl)spiro[3.3]heptane-2,6-diamine

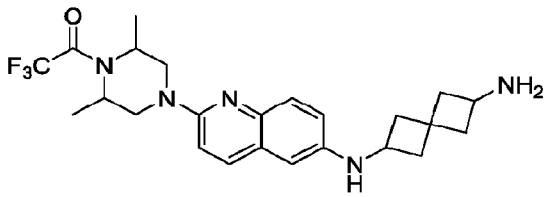


The title compound **565** (20.2 mg) was prepared in a total yield of 84.6 % as a light yellow solid from tert-butyl (6-((2-((2S,6R)-2,6-dimethylmorpholino)quinolin-6-yl)amino)spiro[3.3]heptan-2-yl)carbamate (30.0 mg, 0.065 mmol), TFA according to the procedure for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, *J* = 9.2 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 6.95 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 4.27 – 4.11 (m, 2H), 3.73 (m, 1H), 3.67 – 3.56 (m, 2H), 3.24 (m, 1H), 2.42 – 2.31 (m, 5H), 2.17 (m, 1H), 1.92 – 1.75 (m, 4H), 1.17 (d, *J* = 6.4 Hz, 6H). Mass (m/z): 367.2 $[M+H]^+$

Compound 566

1-(4-(5-((6-aminospiro[3.3]heptan-2-yl)amino)-6-methylpyridin-2-yl)-2,6-dimethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one

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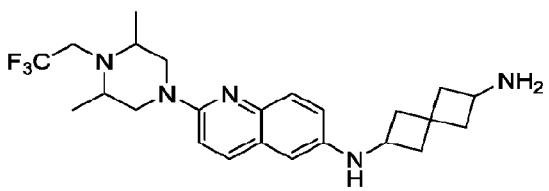


566

The title compound **566** (15 mg, 18.3%) as a yellow solid was prepared from tert-butyl (6-((2-(3,5-dimethyl-4-(2,2,2-trifluoroacetyl) piperazin-1-yl)quinolin-6-yl)amino)spiro[3.3]heptan-2-yl)carbamate (0.1 g, 0.2 mmol), DCM (5 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.82 (d, J = 9 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 7.00 (dd, J = 9.0, 2.5 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 4.63 (s, 1H), 4.32 – 4.31 (m, 3H), 3.83 – 3.81 (m, 1H), 3.46 – 3.45(m, 1H), 3.11 (d, J = 11.8 Hz, 2H), 2.64 – 2.41 (m, 3H), 2.36 – 2.24 (m, 1H), 2.07 – 1.87 (m, 4H), 1.42 (d, J = 19.8 Hz, 6H). Mass (m/z): 461.7[M +H]$^+$.

Compound 567

N2-(2-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)quinolin-6-yl)spiro-[3.3]heptane-2,6-diamine

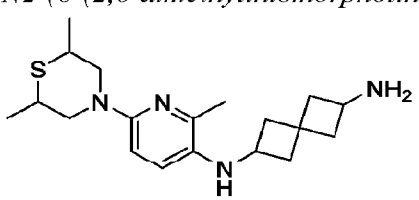


567

The title compound **567** (31.6 mg) as a white solid was prepared from tert-butyl (6-((2-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)quinolin-6-yl)amino)spiro[3.3]heptan-2-yl)carbamate (100 mg, 0.18 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 9.2 Hz, 1H), 7.31 (d, J = 9.0 Hz, 1H), 7.07 (d, J = 9.2 Hz, 1H), 6.91 (dd, J = 9.0, 2.6 Hz, 1H), 6.45 (d, J = 2.6 Hz, 1H), 5.79 (d, J = 6.4 Hz, 1H), 4.13 (d, J = 12.0 Hz, 2H), 3.69 (d, J = 7.0 Hz, 1H), 3.33 (t, J = 8.0 Hz, 3H), 3.27 – 3.22 (m, 1H), 2.76 – 2.69 (m, 2H), 2.56 – 2.48 (m, 3H), 2.37 – 2.29 (m, 2H), 2.16 – 2.07 (m, 1H), 1.76 (ddd, J = 14.2, 10.8, 2.6 Hz, 3H), 1.09 (d, J = 6.2 Hz, 6H). Mass (m/z): 448.2 [M+H]$^+$.

Compound 568

N2-(6-(2,6-dimethylthiomorpholino)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



568

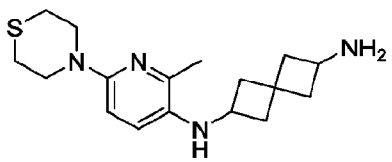
The title compound **568** (8.1 mg, 98.4%) as a white solid was prepared from tert-butyl (6-((6-(2,6-dimethylthiomorpholino)-2-methylpyridin-3-yl)amino)-spiro[3.3]heptan-2-yl)carba

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mate (100 mg, 0.22 mmol), DCM (10 mL) and TFA (1 mL) according to the procedure for **24**. ^{1}HNMR (400 MHz, CD_3OD) δ 6.89 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 4.24 (dd, J = 13.0, 2.6 Hz, 2H), 3.77 – 3.69 (m, 1H), 3.29 (dd, J = 8.6, 7.4 Hz, 1H), 3.06 (ddd, J = 10.6, 6.8, 2.8 Hz, 2H), 2.60 – 2.50 (m, 3H), 2.48 – 2.34 (m, 2H), 2.29 (s, 3H), 2.28 – 2.18 (m, 1H), 1.97 – 1.78 (m, 4H), 1.16 (d, J = 6.8 Hz, 6H). Mass (m/z): 347.2 $[M+H]^+$.

Compound 569

N^2-(2-methyl-6-thiomorpholinopyridin-3-yl)spiro[3.3]heptane-2,6-diamine

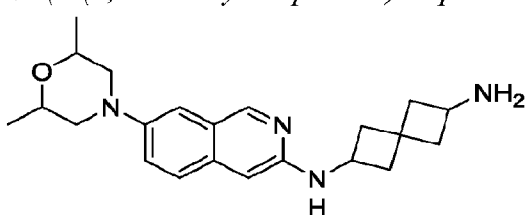


569

The desired product **569** (10.3 mg, 12.85%) as an oil was prepared from tert-butyl (6-((2-methyl-6-thiomorpholinopyridin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (100 mg, 0.2389 mmol), DCM (10 mL), and TFA (1 mL) according to the procedure for **568**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.77 (d, J = 8.7 Hz, 1H), 6.44 (d, J = 8.7 Hz, 1H), 3.61 (p, J = 7.6 Hz, 1H), 3.55 – 3.47 (m, 4H), 3.26 – 3.15 (m, 1H), 2.60 – 2.53 (m, 4H), 2.46 – 2.23 (m, 3H), 2.17 (s, 3H), 2.14 (dd, J = 6.7, 5.4 Hz, 1H), 1.86 – 1.67 (m, 4H). Mass (m/z): 318.9 $[M+H]^+$.

Compound 570

N2-(7-(2,6-dimethylmorpholino)isoquinolin-3-yl)spiro[3.3]heptane-2,6-diamine



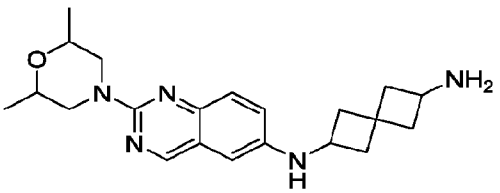
570

The title compound **570** (9.3 mg) as a white solid was prepared from tert-butyl (6-((7-(2,6-dimethylmorpholino)isoquinolin-3-yl)amino)spiro[3.3]heptan-2-yl)carbamate (150 mg, 0.21 mmol), TFA (2 mL) and DCM (10 mL) according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.48 (d, J = 9.2 Hz, 1H), 7.41 (dd, J = 9.2, 2.2 Hz, 1H), 7.06 (s, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 4.4 Hz, 1H), 6.27 (t, J = 8.4 Hz, 1H), 3.96 (dd, J = 14.8, 7.2 Hz, 1H), 3.83 (dd, J = 16.0, 8.0 Hz, 1H), 3.76 – 3.70 (m, 2H), 3.58 (d, J = 10.8 Hz, 2H), 3.24 – 3.13 (m, 1H), 2.38 – 2.30 (m, 2H), 2.28 – 2.22 (m, 2H), 2.14 (s, 1H), 1.97 – 1.92 (m, 1H), 1.90 – 1.85 (m, 2H), 1.74 – 1.61 (m, 1H), 1.17 (d, J = 6.2 Hz, 6H). Mass (m/z): 367.3 $[M+H]^+$.

Compound 571

N^2-(2-(2,6-dimethylmorpholino)quinazolin-6-yl)spiro[3.3]heptane-2,6-diamine

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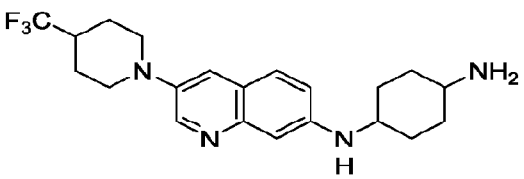


571

The title compound **571** (47.3 mg, 83.6%) was prepared from tert-butyl (6-((2-(2,6-dimethylmorpholino)quinazolin-6-yl)amino)spiro[3.3]heptan-2-yl)carbamate (72 mg, 0.15 mmol), 5 mL of a solution of HCl in 1,4-dioxane according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.10 (s, 2H), 7.41 – 7.31 (m, 2H), 7.26 – 7.15 (m, 1H), 6.57 (s, 1H), 6.17 (s, 1H), 4.53 (dd, J = 13.3, 2.4 Hz, 2H), 3.76 (t, J = 7.6 Hz, 1H), 3.63 – 3.52 (m, 3H), 2.62 – 2.56 (m, 1H), 2.53 – 2.52 (m, 2H), 2.48 – 2.40 (m, 2H), 2.29 – 2.10 (m, 3H), 1.94 – 1.83 (m, 2H), 1.17 (d, J = 6.2 Hz, 6H). Mass (m/z): 368.2 $[M+H]^+$.

Compound 572

N1-(3-(4-(trifluoromethyl)piperidin-1-yl)quinolin-7-yl)cyclohexane-1,4-diamine

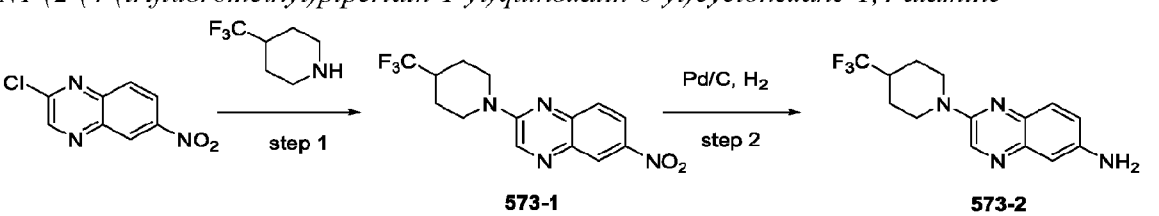


572

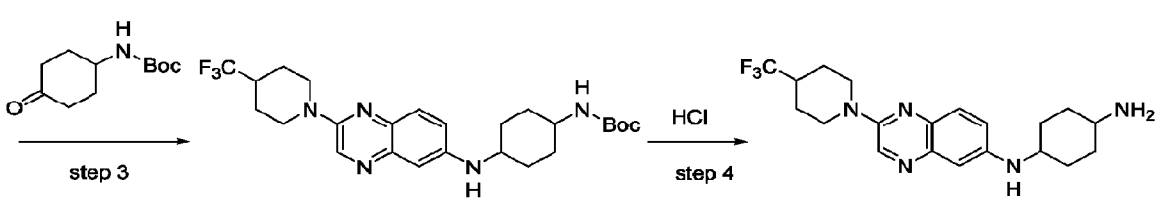
The title compound **572** (10.1 mg) as a white solid was prepared from tert-butyl (4-((3-(4-(trifluoromethyl)piperidin-1-yl) quinolin-7-yl)amino)cyclohexyl) carbamate (100 mg, 0.21 mmol) and HCl in 1,4-Dio. (10 mL, 4N) according to the procedure for **37**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, J = 2.8 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 6.76 (s, 1H), 5.96 (s, 1H), 3.76 (d, J = 12.2 Hz, 2H), 3.56 (s, 1H), 3.10 (s, 1H), 2.72 (t, J = 11.4 Hz, 2H), 2.54 (s, 1H), 1.99 – 1.55 (m, 13H). Mass (m/z): 393.2 $[M+H]^+$.

Compound 573

N1-(2-(4-(trifluoromethyl)piperidin-1-yl)quinoxalin-6-yl)cyclohexane-1,4-diamine



573-1 573-2



573-3 573

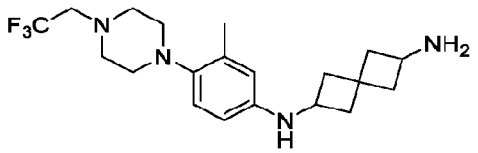
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Step 1. Preparation of 1-(3-nitrophenyl)-4-(trifluoromethyl)piperidine (**573-1**)
A mixture of 2-chloro-6-nitroquinoxaline (0.2 g, 0.95 mmol), 4-(trifluoromethyl)piperidine (0.15 g, 0.95 mmol), Cs_2CO_3 (617 mg, 1.9 mmol) and DMF (10 mL) was stirred at 100 °C for 3 h. The mixture was diluted with EA (400 mL) and washed with water (300 mL x 3). The organic phase was concentrated and purified by flash, eluted with PE : EA = 10 : 1 to 1 : 1 to give the desired product (0.33 g, 92.0%) as a yellow solid. Mass (m/z): 326.8 $[M+H]^+$.
Step 2. Preparation of 2-(4-(trifluoromethyl)piperidin-1-yl)quinoxalin-6-amine (**573-2**)
To a solution of 1-(3-nitrophenyl)-4-(trifluoromethyl)piperidine (0.33 g, 1 mmol) and Pd/C (80 mg) in THF (10 mL) was stirred under H_2 at 25 °C for 3 h. The organic phase was concentrated and purified by flash, eluted with DCM : MeOH = 10 : 1 to 5 : 1 to give the desired product as a yellow oil (0.3 g, 99%). Mass (m/z): 297.2 $[M+H]^+$.
Step 3. Preparation of tert-butyl (4-((3-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (**573-3**)
A mixture of 2-(4-(trifluoromethyl)piperidin-1-yl)quinoxalin-6-amine (0.3 g, 1 mmol), tert-butyl (4-oxocyclohexyl)carbamate (0.2 g, 1 mmol), $NaBH(OAc)_3$ (0.63 g, 3 mmol) and DCE (10 mL). The reaction was stirred for 3 h at R.T. Quenched with water (10 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, concentrated and purified by flash, eluted with PE/EA = 10:1 to 1:1 to give the desired product as a yellow oil (0.3 g, 60.8%). Mass(m/z): 493.7 $[M-tBu+H]^+$.
Step 4. Preparation of N1-(2-(4-(trifluoromethyl)piperidin-1-yl)quinoxalin-6-yl)cyclohexane-1,4-diamine (**573**):
To a solution of tert-butyl tert-butyl (4-((3-(4-(trifluoromethyl)piperidin-1-yl)phenyl)amino)cyclohexyl)carbamate (300 mg, 0.61 mmol) in DCM (5 ml) was added TFA (1 mL) and the mixture was stirred for 2 h. Quenched with $NaHCO_3$ (10 mL), the reaction was extracted by EA (10 mL) for 3 times. The combined organic layers were dried over sodium sulfate, removed under vacuum and the residue was purified by preparative (column-Gemini -C18 150 x 21.2 mm, 5 um; Mobile phase: ACN-H_2O (0.1% FA), 10%-30%) to afford **573A** (102.9 mg) as a yellow solid and **573B** (107.6 mg) as a yellow solid. **573A**: ^1H NMR (400 MHz, CD_3OD) δ 8.75 (s, 1H), 7.71 (d, J = 9.2 , 1H), 7.50 – 7.40 (m, 1H), 7.25 (d, J = 2.4, 1H), 4.66 (d, J = 13.6, 2H), 3.60 – 3.44 (m, 1H), 3.25 – 3.09 (m, 3H), 2.65 – 2.55 (m, 1H), 2.29 – 2.14 (m, 4H), 2.07 (d, J = 10.9, 2H), 1.77 – 1.41 (m, 6H). Mass (m/z): 394.2 $[M+H]^+$. HPLC: Rt = 3.886 min (Column: XBRIDGE 3.5 um, 2.1*50 mm; Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, Flow rate: 0.8 mL/min). **573B**: ^1H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 7.68 (d, J = 9.2, 1H), 7.44 (dd, J = 9.2, 2.4, 1H), 7.02 (d, J = 2.4, 1H), 4.62 (d, J = 13.6, 2H), 3.73 (s, 1H), 3.21 – 3.15 (m, 2H), 2.65 – 2.55 (m, 1H), 2.12 – 1.82 (m, 11H), 1.76 – 1.65 (m, 2H). Mass (m/z): 394.2 $[M+H]^+$. HPLC: Rt = 4.058 min (Column: XBRIDGE 3.5 um, 2.1*50 mm; Mobile phase: H_2O (0.05% TFA)-ACN (0.05% TFA), ACN from 0 to 60% over 7 minutes, Flow rate: 0.8 mL/min).

Compound 574

N^2-(3-methyl-4-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)phenyl)spiro[3.3]heptane-2,6-diamine

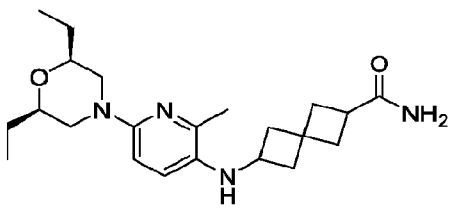
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The titled compound **574** (26.1 mg, 51.3%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 3H), 6.81 (d, J = 8.4 Hz, 1H), 6.33 (d, J = 2.8 Hz, 1H), 6.27 (d, J = 8.4 Hz, 1H), 5.68 - 5.26 (m, 1H), 3.64 (d, J = 7.2 Hz, 1H), 3.57 - 3.47 (m, 1H), 3.21 (q, J = 10.3 Hz, 2H), 2.71 (s, 7H), 2.39 - 2.30 (m, 2H), 2.23 - 2.15 (m, 3H), 2.13 (s, 3H), 1.86 - 1.76 (m, 2H). Mass(m/z): 383.2 $[M-H]^+$.

Compound 575

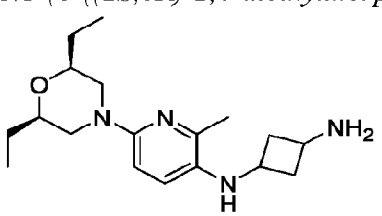
6-((6-((2S,6R)-2,6-diethylmorpholino)-2-methylpyridin-3-yl)amino)spiro[3.3]heptane-2-carboxamide



The titled compound **575** (9.3 mg, 23.5%) as a light-yellow solid was prepared according to the procedure outlined for compound **5**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (s, 2H), 6.73 (d, J = 8.7 Hz, 1H), 6.64 (s, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.58 – 4.41 (m, 1H), 3.84 (d, J = 11.9 Hz, 2H), 3.65 – 3.56 (m, 1H), 3.44 – 3.37 (m, 3H), 2.91 – 2.81 (m, 1H), 2.35 – 2.07 (m, 9H), 2.01 – 1.95 (m, 1H), 1.94 – 1.86 (m, 1H), 1.83 – 1.75 (m, 1H), 1.54 – 1.43 (m, 4H), 0.94 (t, J = 7.4 Hz, 6H). Mass(m/z): 387.3[M+H] $^+$.

Compound 576

N1-(6-((2S,6R)-2,6-diethylmorpholino)-2-methylpyridin-3-yl)cyclobutane-1,3-diamine

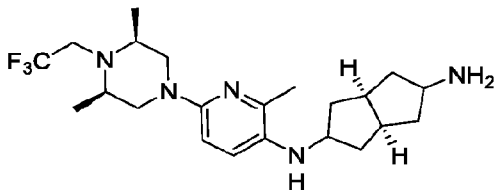


The titled compound **576** (4.2 mg, 15.5%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.79 (d, J = 8.7 Hz, 1H), 6.55 (d, J = 8.9 Hz, 1H), 4.16 – 4.03 (m, 1H), 3.98 – 3.90 (m, 1H), 3.85 – 3.75 (m, 2H), 3.54 – 3.44 (m, 2H), 2.61 – 2.49 (m, 2H), 2.33 (s, 3H), 1.67 – 1.50 (m, 4H), 1.39 – 1.26 (m, 4H), 1.02 (t, J = 7.5 Hz, 6H). Mass(m/z): 319.2[M+H] $^+$.

Compound 577

(3aR,6aS)-N2-(6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-yl)octahydropentalene-2,5-diamine

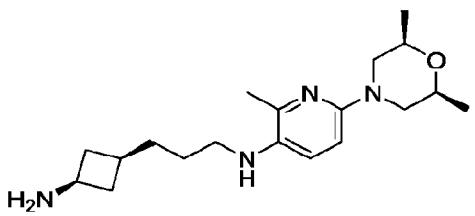
CA 03227251 2024-1-26



The title compound **577** (13.5 mg) was prepared in a two steps total yield of 17.5% as a white solid with 1:0.1 mixture by ^{1}H NMR from 6-((3R,5S)-3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-amine and (3as,6as)-tetrahydropentalene-2,5(1H,3H)-dione according to the procedure for **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 3H), 7.92 (s, 1H), 6.58 (s, 1H), 4.02 (s, 1H), 3.84 (s, 3H), 2.74 (s, 5H), 2.23 (s, 4H), 1.73 (d, J = 24.9 Hz, 4H), 1.39 (s, 3H), 1.10 (d, J = 6.3 Hz, 9H). Mass(m/z): 426.4 $[M+H]^+$.

Compound 578

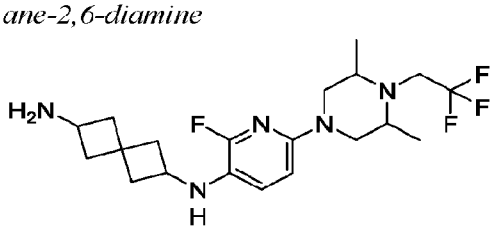
N-(3-((1s,3R)-3-aminocyclobutyl)propyl)-6-((2S,6R)-2,6-dimethylmorpholino)-2-methylpyridin-3-amine



The titled compound **578** (61.9 mg, 63.7%) as a white solid was prepared according to the procedure outlined for compound **23**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.32 (s, 1H), 3.83 (d, J = 11.2 Hz, 2H), 3.64 - 3.57 (m, 2H), 2.92 (s, 2H), 2.26 (d, J = 7.6 Hz, 1H), 2.20 (s, 3H), 2.18 - 2.11 (m, 2H), 1.82 - 1.66 (m, 1H), 1.46 - 1.37 (m, 4H), 1.23 (d, J = 6.4 Hz, 2H), 1.14 (d, J = 6.4 Hz, 6H). Mass(m/z): 332.9 $[M+H]^+$.

Compound 579

N^2-(6-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-fluoropyridin-3-yl)spiro[3.3]heptane-2,6-diamine



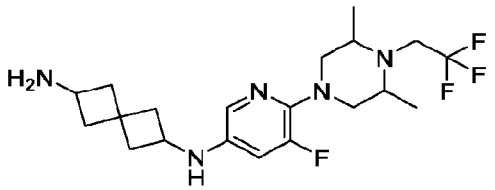
The titled compound **579** (37.6 mg, 50%) as brown oil was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.99 - 6.94 (m, 1H), 6.53 (d, J = 8.4, 1H), 4.96 (d, J = 6.0, 1H), 3.74 (d, J = 11.2, 2H), 3.66 - 3.61 (m, 1H), 3.38 - 3.30 (m, 2H), 3.20 - 3.13 (m, 1H), 2.74 - 2.72 (m, 2H), 2.39 - 2.28 (m, 5H), 2.26 - 2.17 (m, 2H), 2.16 - 2.04 (m, 1H), 1.87 - 1.80 (m, 2H), 1.69 - 1.57 (m, 2H), 1.09 (d, J = 6.4, 6H). Mass(m/z): 416.2 $[M+H]^+$.

Compound 580

N^2-(6-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-5-fluoropyridin-3-yl)spiro[3.3]hept

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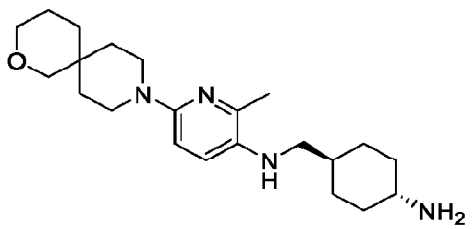
ane-2,6-diamine



The titled compound **580** (105.6 mg, 43.68%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (d, J = 2.0 Hz, 1H), 6.76 (dd, J = 14.0, 2.4 Hz, 1H), 3.73 (dt, J = 15.6, 7.6 Hz, 1H), 3.50 – 3.30 (m, 4H), 2.95 (br, 2H), 2.63 - 2.32 (m, 7H), 1.94 - 1.80 (m, 4H), 1.16 (d, J = 6.4 Hz, 6H). Mass(m/z): 415.8 $[M+H]^+$.

Compound 581

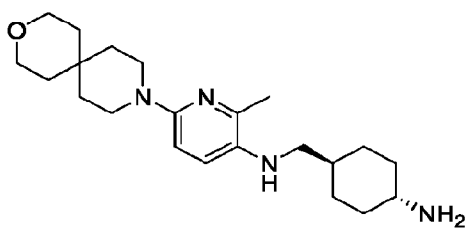
N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-methyl-6-(2-oxa-9-azaspiro[5.5]undecan-9-yl)pyridi n-3-amine



The titled compound **581** (39.1 mg, 12.7%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.79 (d, J = 8.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 4.30 (s, 1H), 3.53 (t, J = 4.8 Hz, 2H), 3.34 (s, 2H), 3.22 (t, J = 5.2 Hz, 4H), 2.81 (s, 2H), 2.46 (d, J = 3.2 Hz, 1H), 2.20 (s, 3H), 1.79 – 1.73 (m, 4H), 1.51 – 1.37 (m, 9H), 1.01 – 0.85 (m, 4H). Mass(m/z): 373.3 $[M+H]^+$.

Compound 582

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-methyl-6-(3-oxa-9-azaspiro[5.5]undecan-9-yl)pyridi n-3-amine

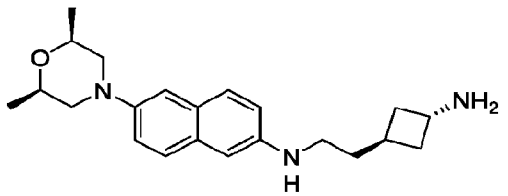


The titled compound **582** (33.60 mg, 28.42%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.84 (d, J = 8.8 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 3.61 – 3.57 (m, 4H), 3.18 – 3.11 (m, 4H), 2.83 (d, J = 6.8 Hz, 2H), 2.53 – 2.44 (m, 1H), 2.19 (s, 3H), 1.84 – 1.75 (m, 4H), 1.59 – 1.54 (m, 4H), 1.48 – 1.41 (m, 5H), 1.12 1.04 (m, 4H). Mass(m/z): 372.9 $[M+H]^+$.

Compound 583

N-(2-((1r,3S)-3-aminocyclobutyl)ethyl)-6-((2S,6R)-2,6-dimethylmorpholino)naphthalen-2-amin e

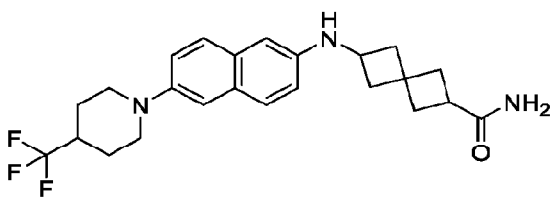
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The titled compound **583** as a yellow solid was prepared according to the procedure outlined for compound **78**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (dd, J = 8.8, 5.6 Hz, 2H), 7.18 (dd, J = 9.0, 2.4 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 6.91 (dd, J = 8.8, 2.3 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 3.89-2.79 (m, 2H), 3.60 – 3.55 (m, 2H), 3.51 (d, J = 10.8 Hz, 2H), 3.14 – 3.04 (m, 2H), 2.47 – 2.28 (m, 3H), 2.12 – 1.96 (m, 4H), 1.83 (dd, J = 14.6, 7.6 Hz, 2H), 1.62-1.57 (m, 1H), 1.24 (d, J = 6.3 Hz, 6H). Mass(m/z): 353.8 $[M+H]^-$.

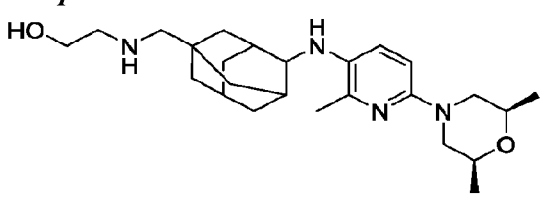
Compound 584

6-((6-(4-(trifluoromethyl)piperidin-1-yl)naphthalen-2-yl)amino)spiro[3.3]heptane-2-carboxamide



The title compound **584** as white solid (27.4 mg, 20%) was prepared according to the procedure outlined for compound **10**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (dd, J = 8.8, 4.7 Hz, 2H), 7.17 (dd, J = 9.0, 2.4 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H), 6.66 (d, J = 2.0 Hz, 1H), 3.90 – 3.79 (m, 1H), 3.72 (d, J = 12.3 Hz, 2H), 3.08 – 2.97 (m, 1H), 2.71-2.60 (m, 3H), 2.51 – 2.41 (m, 1H), 2.33 (d, J = 8.6 Hz, 2H), 2.31 – 2.19 (m, 2H), 2.17 – 2.09 (m, 1H), 2.03-1.94 (m, 3H), 1.86 (dd, J = 11.4, 8.0 Hz, 1H), 1.80 – 1.66 (m, 2H). Mass(m/z): 432.2$[M+H]^+$.

Compound 585

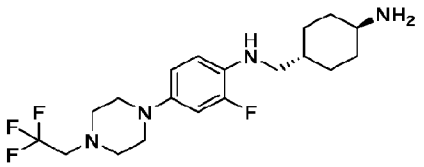


The titled compound **585** (51.2 mg, 55.6%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.51 (s, 2H), 7.01 – 6.74 (m, 1H), 6.67 – 6.34 (m, 1H), 5.35 – 5.20 (m, 1H), 4.42 – 4.28 (m, 1H), 3.91 – 3.82 (m, 3H), 3.76 – 3.68 (m, 2H), 3.64 – 3.55 (m, 2H), 3.47 – 3.37 (m, 2H), 3.15 (d, J = 12.5 Hz, 1H), 3.04 – 2.94 (m, 2H), 2.69 (d, J = 13.4 Hz, 2H), 2.37 – 2.28 (m, 3H), 2.24 – 2.14 (m, 2H), 2.06 – 1.90 (m, 4H), 1.77 – 1.66 (m, 3H), 1.62 – 1.53 (m, 2H), 1.44 – 1.34 (m, 3H), 1.16 – 1.06 (m, 9H). Mass(m/z): 429.3$[M+H]^+$.

Compound 586

N-(((1r,4r)-4-aminocyclohexyl)methyl)-2-fluoro-4-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)aniline

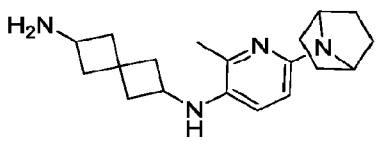
CA 03227251 2024-1-26



The titled compound **586** (5.2 mg, 19.8%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.71 (d, J = 14.4 Hz, 1H), 6.57 (d, J = 5.2 Hz, 2H), 4.77 (d, J = 6.4 Hz, 1H), 3.25 - 3.17 (m, 2H), 2.95 (t, J = 4.8 Hz, 4H), 2.83 (t, J = 6.8 Hz, 2H), 2.72 (t, J = 4.8 Hz, 4H), 1.74 (d, J = 9.2 Hz, 4H), 1.52 - 1.39 (m, 2H), 1.00 - 0.87 (m, 4H). Mass (m/z): 389.2 $[M+H]^-$.

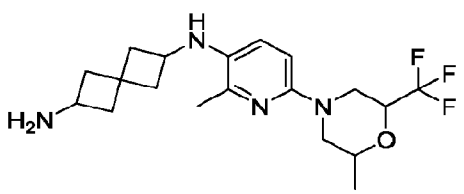
Compound 587

N^2-(6-(7-azabicyclo[2.2.1]heptan-7-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



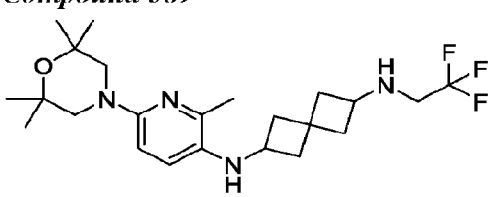
The titled compound **587** (28.5 mg, 54.4%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 3H), 6.80 (d, J = 8.4 Hz, 2H), 4.89 (s, 1H), 4.45 (s, 2H), 3.72 - 3.46 (m, 2H), 2.43 - 2.28 (m, 4H), 2.26 - 2.14 (m, 3H), 1.96 (d, J = 10.4 Hz, 2H), 1.68 - 1.60 (m, 3H), 1.40 (d, J = 7.6 Hz, 3H). Mass (m/z): 313.3 $[M+H]^+$.

Compound 588



The titled compound **588** (16.2 mg, 52.3%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (br s, 2H), 6.76 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 8.4 Hz, 1H), 4.61 (br s, 1H), 4.53 – 4.41 (m, 1H), 4.21 – 4.10 (m, 1H), 3.72 – 3.62 (m, 1H), 3.60 – 3.47 (m, 2H), 3.45 – 3.37 (m, 2H), 3.00 – 2.89 (m, 1H), 2.44 – 2.30 (m, 2H), 2.22 (s, 3H), 2.20 – 2.07 (m, 4H), 1.98 – 1.86 (m, 2H), 1.22 (d, J = 6.4 Hz, 3H). Mass(m/z): 385.2$[M+H]^+$.

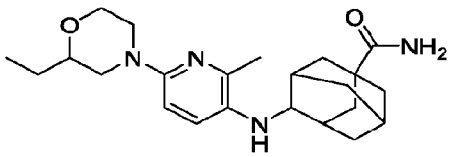
Compound 589



The titled compound **589** (17.6 mg, 34.1%) as a light-yellow solid was prepared according to the procedure outlined for compound **23**. ^{1}H NMR (400 MHz, Chloroform-d) δ 6.76 (d, J = 8.4 Hz, 1H), 6.42 (d, J = 8.4 Hz, 1H), 3.74 (p, J = 7.6 Hz, 1H), 3.29 (p, J = 7.6 Hz, 1H), 3.19 (s, 4H), 3.10 (q, J = 9.6 Hz, 2H), 2.59 – 2.49 (m, 1H), 2.47 – 2.38 (m, 2H), 2.29 (s, 3H), 2.28 –

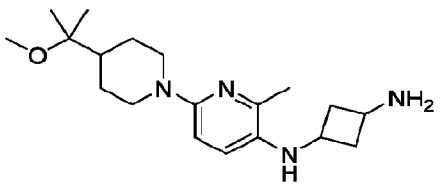
2.22 (m, 1H), 1.89 – 1.73 (m, 4H), 1.29 (s, 12H). Mass(m/z): 441.3[M+H] $^+$.

Compound 590



The titled compound **590** (10.0 mg, 31.2%) as a white solid was prepared according to the procedure outlined for compound **10**.^{1}H NMR (400 MHz, DMSO-d_6) δ 6.99 (s, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.73 (s, 1H), 6.54 (d, J = 8.7 Hz, 1H), 3.94 – 3.83 (m, 3H), 3.75 (d, J = 12.3 Hz, 1H), 3.54 (t, J = 11.4 Hz, 1H), 3.44 – 3.35 (m, 2H), 2.36 – 2.21 (m, 5H), 2.01 – 1.93 (m, 4H), 1.91 – 1.80 (m, 5H), 1.78 – 1.71 (m, 2H), 1.53 – 1.36 (m, 4H), 0.93 (t, J = 7.5 Hz, 3H). Mass(m/z): 399.3[M+H] $^+$.

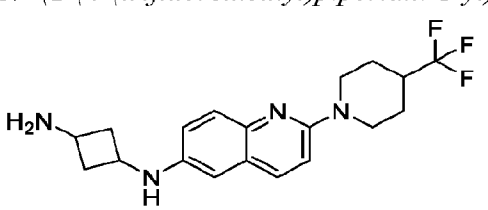
Compound 591



The titled compound 591 (20.8 mg, 46.2%) as a white solid was prepared according to the procedure outlined for compound 24. 1H NMR (400 MHz,) δ 6.83 – 6.74 (m, 1H), 6.64 – 6.56 (m, 1H), 4.18 – 3.84 (m, 4H), 3.21 (s, 3H), 2.67 – 2.48 (m, 4H), 2.47 – 2.26 (m, 5H), 1.82 – 1.71 (m, 2H), 1.68 – 1.56 (m, 1H), 1.51 – 1.37 (m, 2H), 1.15 (s, 6H). Mass(m/z): 333.4[M+H] $^+$.

Compound 592

N^1-(2-(4-(trifluoromethyl)piperidin-1-yl)quinolin-6-yl)cyclobutane-1,3-diamine

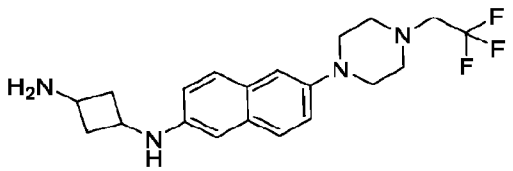


The titled compound **592** (15.9 mg, 36.1%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 9.2 Hz, 1H), 6.98 (d, J = 9.2 Hz, 1H), 6.41 (s, 1H), 5.98 - 5.74 (m, 1H), 4.47 (d, J = 13.2 Hz, 2H), 3.94 - 3.73 (m, 1H), 3.60 - 3.46 (m, 1H), 2.84 (t, J = 12.8 Hz, 2H), 2.73 - 2.52 (m, 3H), 2.06 (q, J = 8.4 Hz, 3H), 1.93 - 1.73 (m, 3H), 1.47 (t, J = 12.8 Hz, 2H). Mass (m/z): 365.2 [M+H] $^+$.

Compound 593

N^1-(6-(4-(2,2,2-trifluoroethyl)piperazin-1-yl)naphthalen-2-yl)cyclobutane-1,3-diamine

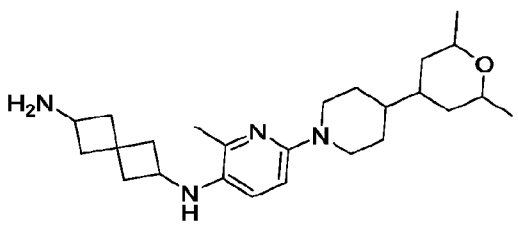
CA 03227251 2024-1-26



The titled compound **593** (6.5 mg, 15.9%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (s, 3H), 7.67 - 7.52 (m, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.00 (s, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.51 (s,1H), 6.18 - 6.02 (m, 1H), 4.17 (s, 1H), 3.77 (s, 1H), 3.24 (t, J = 10.4 Hz, 2H), 3.13 (s, 2H), 2.79 (s, 3H), 2.23 (s, 2H), 2.12 - 1.97 (m, 1H). Mass (m/z): 379.3 [M+H] $^+$.

Compound 594

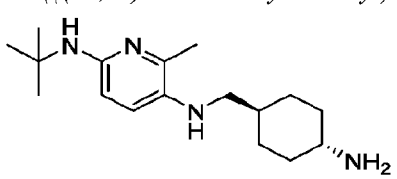
N^2-(6-(4-(2,6-dimethyltetrahydro-2H-pyran-4-yl)piperidin-1-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



The titled compound **594** (3.1 mg, 19.25%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.88 (d, J = 8.8 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 3.97 (d, J = 12.4 Hz, 2H), 3.80 - 3.67 (m, 2H), 3.50 (dd, J = 9.6, 6.4 Hz, 2H), 2.65 - 2.56 (m, 4H), 2.50 - 2.44 (m, 1H), 2.44 - 2.35 (m, 1H), 2.29 (s, 3H), 2.23 - 2.17 (m, 3H), 2.02 (d, J = 10.8 Hz, 2H), 1.83 (d, J = 12.6 Hz, 2H), 1.75 - 1.71 (m, 2H), 1.32 (s, 3H), 1.19 (d, J = 6.2 Hz, 6H), 0.90 - 0.86 (m, 3H). Mass(m/z): 413.4 [M+H] $^+$.

Compound 595

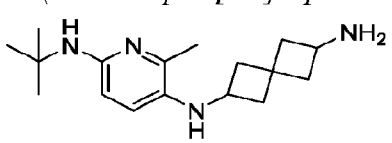
N^5-(((1r,4r)-4-aminocyclohexyl)methyl)-N^2-(tert-butyl)-6-methylpyridine-2,5-diamine



The titled compound **595** (65.2 mg, 33.3%) as a black solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.71 (d, J = 8.8, 1H), 6.27 (d, J = 8.8, 1H), 4.95 (s, 1H), 3.98 (s, 1H), 2.76 (d, J = 6.4, 2H), 2.49 - 2.40 (m, 1H), 2.17 (s, 3H), 1.79 - 1.75 (m, 4H), 1.43 - 1.31 (m, 1H), 1.31 (s, 9H), 1.04 - 0.83 (m, 4H). Mass(m/z): 290.9 [M+H] $^+$.

Compound 596

N^5-(6-aminospiro[3.3]heptan-2-yl)-N^2-(tert-butyl)-6-methylpyridine-2,5-diamine



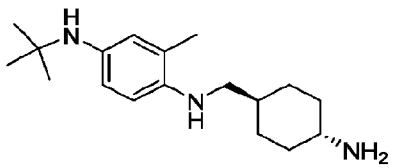
The titled compound **596** (101.7 mg, 58%) as a black solid was prepared according to the

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procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.60 (d, J = 8.8, 1H), 6.23 (d, J = 8.4, 1H), 5.00 (s, 1H), 4.12 (s, 1H), 3.56 - 3.52 (m, 1H), 3.19 - 3.12 (m, 1H), 2.39 - 2.35 (m, 1H), 2.33 - 2.27 (m, 1H), 2.26 - 2.19 (m, 1H), 2.15 (s, 3H), 2.12 - 2.08 (m, 1H), 1.83 - 1.77 (m, 2H), 1.67 - 1.59 (m, 2H), 1.30 (s, 9H). Mass(m/z): 288.9 $[M+H]^+$.

Compound 597

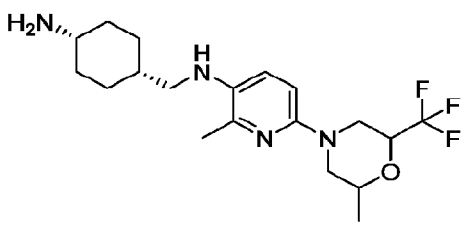
N^1-(((1r,4r)-4-aminocyclohexyl)methyl)-N^4-(tert-butyl)-2-methylbenzene-1,4-diamine



The titled compound **597** (92.3 mg, 82.82%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.55 (dd, J = 6.4, 2.4 Hz, 2H), 6.33 - 6.28 (m, 1H), 4.15 (s, 1H), 2.81 (d, J = 6.4 Hz, 2H), 2.46 (dd, J = 8.8, 5.2 Hz, 1H), 2.01 (s, 3H), 1.83 - 1.73 (m, 4H), 1.48 (dd, J = 6.8, 3.6 Hz, 1H), 1.10 (s, 9H), 0.95 (q, J = 10.4 Hz, 4H). Mass(m/z): 289.3 $[M+H]^+$.

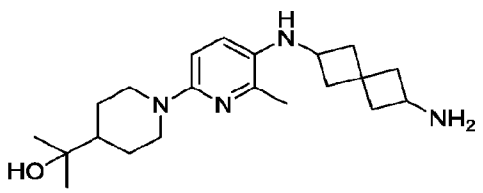
Compound 598

N-(((1s,4s)-4-aminocyclohexyl)methyl)-2-methyl-6-(2-methyl-6-(trifluoromethyl)morpholino)pyridin-3-amine



The titled compound **598** (15.3 mg, 42.5%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (br s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 4.62 – 4.42 (m, 2H), 4.23 – 4.10 (m, 1H), 3.56 – 3.46 (m, 1H), 3.46 – 3.37 (m, 2H), 3.17 (br s, 1H), 2.97 – 2.86 (m, 3H), 2.23 (d, J = 3.5 Hz, 3H), 1.78 – 1.58 (m, 5H), 1.57 – 1.46 (m, 4H), 1.23 (d, J = 6.4 Hz, 4H). Mass(m/z): 387.2$[M+H]^+$.

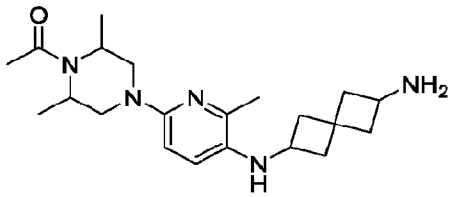
Compound 599



The titled compound **599** (13.1 mg, 22.5%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (br s, 3H), 6.85 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 8.4 Hz, 1H), 4.71 (br s, 1H), 4.26 – 3.88 (m, 3H), 3.74 – 3.48 (m, 2H), 2.44 – 2.31 (m, 3H), 2.25 (s, 3H), 2.21 – 2.09 (m, 3H), 2.03 – 1.86 (m, 2H), 1.83 – 1.66 (m, 2H), 1.40 – 1.15 (m, 4H), 1.04 (s, 6H). Mass(m/z): 359.3$[M+H]^+$.

Compound 600

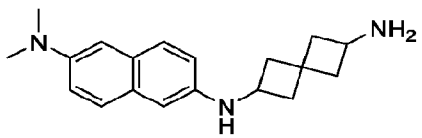
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The titled compound **600** (25.7 mg, 42.5%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (br s, 3H), 6.77 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 4.75 – 4.33 (m, 1H), 4.26 – 3.99 (m, 1H), 3.88 (d, J = 12.3 Hz, 2H), 3.72 – 3.59 (m, 1H), 3.57 – 3.46 (m, 1H), 2.78 – 2.54 (m, 2H), 2.40 – 2.28 (m, 2H), 2.28 – 2.10 (m, 6H), 2.04 (s, 3H), 2.00 – 1.74 (m, 3H), 1.22 (d, J = 6.4 Hz, 4H). Mass(m/z): 372.3[M+H] $^+$.

Compound 601

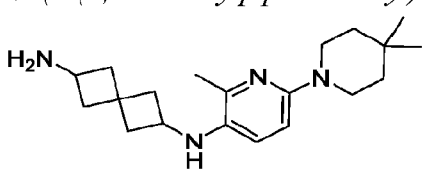
N^2-(6-aminospiro[3.3]heptan-2-yl)-N^6,N^6-dimethylnaphthalene-2,6-diamine



The titled compound **601** (38.7 mg, 43.5%) as yellow oil was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (dd, J = 14.8, 9.2 Hz, 2H), 7.07 (dd, J = 9.2, 2.4 Hz, 1H), 6.82 – 6.78 (m, 2H), 6.48 (d, J = 2.0 Hz, 1H), 5.68 (d, J = 6.8 Hz, 1H), 3.73 (dd, J = 14.4, 7.2 Hz, 1H), 3.19 (dd, J = 15.2, 7.6 Hz, 1H), 2.88 (s, 6H), 2.50 - 2.45 (m, 1H), 2.34 (dt, J = 11.6, 6.0 Hz, 2H), 2.15 - 2.11 (m, 1H), 1.83 – 1.77 (m, 2H), 1.69 – 1.63 (m, 2H). Mass(m/z): 296.2 [M+H] $^+$.

Compound 602

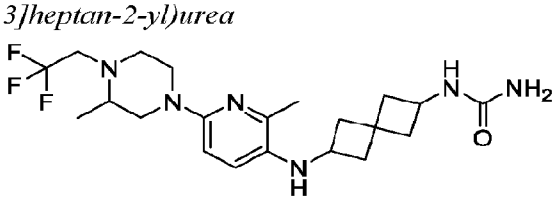
N^2-(6-(4,4-dimethylpiperidin-1-yl)-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



The titled compound **602** (33.1 mg, 58.3%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 3H), 6.99 (s, 1H), 6.75 (s, 1H), 4.96 (s, 1H), 3.70 (s, 1H), 3.52 (s, 1H), 3.38 - 3.23 (m, 5H), 2.43 - 2.13 (m, 8H), 2.00 (s, 2H), 1.41 (s, 4H), 0.95 (s, 6H). Mass (m/z): 329.3 [M+H] $^+$.

Compound 603

1-(6-((2-methyl-6-(3-methyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)pyridin-3-yl)amino)spiro[3.3]heptan-2-yl)urea



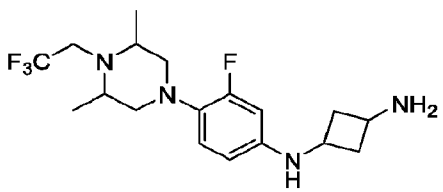
The titled compound 603 (15.1 mg, 33.6%) as a white solid was prepared according to the procedure outlined for compound 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.82 – 6.66 (m, 1H),

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6.57 – 6.43 (m, 1H), 6.15 (d, *J* = 8.2 Hz, 1H), 5.34 (s, 2H), 4.64 – 4.40 (m, 1H), 3.96 – 3.84 (m, 1H), 3.71 – 3.53 (m, 3H), 3.51 – 3.35 (m, 2H), 3.14 – 2.94 (m, 2H), 2.86 – 2.79 (m, 1H), 2.70 – 2.62 (m, 3H), 2.44 – 2.09 (m, 7H), 2.00 – 1.70 (m, 4H), 1.07 (d, *J* = 6.2 Hz, 3H). Mass(m/z): 441.2[M+H] $^+$.

Compound 604

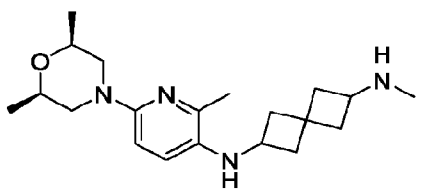
N^1-(4-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-3-fluorophenyl)cyclobutane-1,3-diamine



The titled compound **604** (214.9 mg, 83.3%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.81 - 6.77 (m, 1H), 6.25 - 6.18 (m, 2H), 5.85 - 5.76 (m, 1H), 3.79 (d, *J* = 5.6, 1H), 3.53 - 3.50 (m, 1H), 3.39 - 3.31 (m, 2H), 3.19 - 3.18 (m, 1H), 2.96 (d, *J* = 10.8, 2H), 2.84 (s, 2H), 2.62 - 2.58 (m, 1H), 2.35 (t, *J* = 10.8, 2H), 2.03 (t, *J* = 6.0, 3H), 1.52 - 1.44 (m, 1H), 1.05 (d, *J* = 6.0, 6H). Mass(m/z): 374.8 [M+H] $^+$.

Compound 605

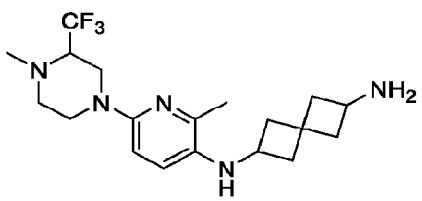
N^2-(6-((2R,6S)-2,6-dimethylmorpholino)-2-methylpyridin-3-yl)-N^6-methylspiro[3.3]heptane-2,6-diamine



The title compound **605** (20 mg, 29%) was prepared according to the procedure outlined for compound **23**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (d, *J* = 9.6 Hz, 1H), 7.10 (d, *J* = 9.6 Hz, 1H), 3.93 - 3.58 (m, 6H), 2.71 - 2.45 (m, 11H), 2.39 - 2.37 (m, 1H), 2.23 - 2.21 (m, 2H), 2.13 - 2.03 (m, 2H), 1.23 (d, *J* = 6.4 Hz, 6H). Mass(m/z): 344.9 [M+H] $^+$.

Compound 606

N^2-(2-methyl-6-(4-methyl-3-(trifluoromethyl)piperazin-1-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine

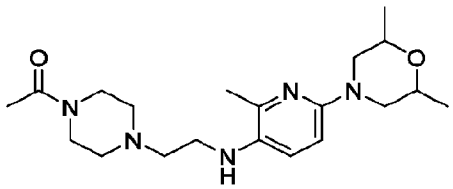


The titled compound **606** (20 mg, 26.1%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.77 (d, *J* = 8.8 Hz, 1H), 6.46 (d, *J* = 8.8 Hz, 1H), 3.89 (d, *J* = 10.0 Hz, 1H), 3.64 - 3.61 (m, 1H), 3.52 - 3.35 (m, 2H), 2.95 - 2.81 (m, 4H), 2.50 - 2.17 (m, 11H), 2.00 - 1.78 (m, 4H). Mass(m/z): 383.8 [M+H] $^+$.

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Compound 607

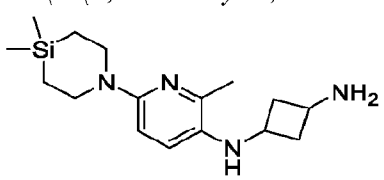
1-(4-(2-((6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)amino)ethyl)piperazin-1-yl)ethan-1-one



The title compound **607** (20.1 mg, 17.85% yield) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.05 (d, J = 8.8 Hz, 1H), 6.60 (d, J = 8.8 Hz, 1H), 3.82 -3.72 (m, 4H), 3.67 - 3.54 (m, 4H), 3.23 (t, J = 6.4 Hz, 2H), 2.68 (t, J = 6.4 Hz, 2H), 2.59 - 2.54 (m, 2H), 2.54 - 2.47 (m, 2H), 2.33 (s, 3H), 2.32 - 2.25 (m, 2H), 2.12 (s, 3H), 1.24 (d, J = 6.4 Hz, 6H). Mass(m/z): 375.8 $[M+H]^+$.

Compound 608

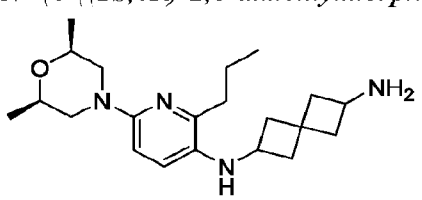
N1-(6-(4,4-dimethyl-1,4-azasilinan-1-yl)-2-methylpyridin-3-yl)cyclobutane-1,3-diamine



The title compound **608** (50.8 mg, 70%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.92 (d, J = 8.8 Hz, 0.16H), 6.81 (d, J = 8.8 Hz, 0.79H), 6.53 (d, J = 8.7 Hz, 1H), 4.01 – 3.89 (m, 0.78H), 3.79 – 3.61 (m, 5H), 3.25 – 3.15 (m, 0.28H), 2.84 – 2.73 (m, 0.32H), 2.30 (s, 3H), 2.26 – 2.16 (m, 3.27H), 1.69 – 1.60 (m, 0.38H), 0.78 – 0.72 (m, 4.24H), 0.07 (s, 6H). Mass(m/z): 304.9$[M+H]^+$.

Compound 609

N^2-(6-((2S,6R)-2,6-dimethylmorpholino)-2-propylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

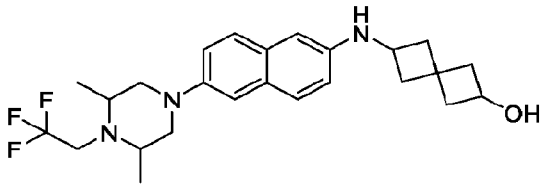


The titled compound **609** (106 mg, 59.1%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.83 (d, J = 8.8 Hz, 1H), 6.49 (t, J = 7.6 Hz, 1H), 3.79 (d, J = 11.6 Hz, 2H), 3.73 – 3.64 (m, 3H), 3.29 – 3.25 (m, 1H), 2.59 – 2.51 (m, 2H), 2.46 – 2.40 (m, 2H), 2.32 – 2.21 (m, 4H), 1.82 – 1.73 (m, 6H), 1.18 (t, J = 5.2 Hz, 6H), 0.96 (t, J = 7.6 Hz, 3H). Mass(m/z): 359.3 $[M+H]^+$.

Compound 610

6-((6-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)naphthalen-2-yl)amino)spiro[3.3]heptan-2-ol

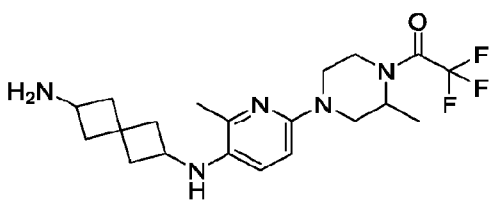
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The titled compound **610** (22.5 mg, 31.2%) as a light-yellow solid was prepared according to the procedure outlined for compound **5**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (dd, J = 8.8, 5.2 Hz, 2H), 7.17 (dd, J = 8.8, 2.4 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.82 (dd, J = 8.8, 2.4 Hz, 1H), 6.50 (d, J = 2.4 Hz, 1H), 5.79 (d, J = 6.4 Hz, 1H), 4.89 (d, J = 6.4 Hz, 1H), 4.06 – 3.92 (m, 1H), 3.81 – 3.67 (m, 1H), 3.52 (d, J = 11.5 Hz, 2H), 3.39 (q, J = 10.4 Hz, 2H), 2.96 – 2.78 (m, 2H), 2.48 2.29 (m, 5H), 2.26 2.12 (m, 1H), 1.92 1.75 (m, 4H), 1.12 (d, J = 6.2 Hz, 6H). Mass(m/z): 448.3 $[M+H]^+$.

Compound 611

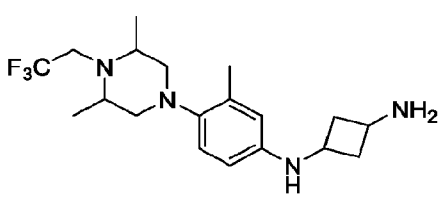
1-(4-(5-((6-aminospiro[3.3]heptan-2-yl)amino)-6-methylpyridin-2-yl)-2-methylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one



The titled compound **611** (25.1 mg, 34.1%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 3H), 6.74 (d, J = 8.7 Hz, 1H), 6.59 – 6.48 (m, 1H), 4.66 – 4.55 (m, 1H), 4.31 – 4.18 (m, 1H), 4.16 – 3.73 (m, 3H), 3.70 – 3.45 (m, 3H), 3.28 – 3.16 (m, 1H), 2.88 – 2.72 (m, 1H), 2.71 – 2.60 (m, 1H), 2.45 – 2.29 (m, 2H), 2.21 (s, 3H), 2.19 – 2.08 (m, 2H), 1.96 – 1.85 (m, 2H), 1.34 (d, J = 6.5 Hz, 1H), 1.24 (d, J = 6.5 Hz, 2H).Mass(m/z): 412.2 $[M+H]^+$.

Compound 612

N^1-(4-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-3-methylphenyl)cyclobutane-1,3-diamine

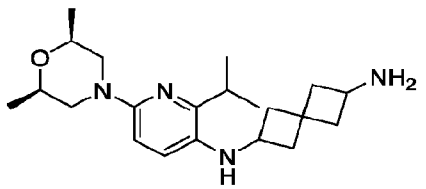


The titled compound **612** (23.1mg, 14.3%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.77 (d, J = 8.4, 1H), 6.29 (d, J = 2.0, 1H), 6.23 - 6.21 (m, 1H), 5.50 - 5.42 (m, 1H), 3.77 (d, J = 5.2, 1H), 3.48 - 3.45 (m, 1H), 3.40 - 3.33 (m, 3H), 2.82 (s, 2H), 2.74 (d, J = 11.2, 2H), 2.32 (t, J = 10.8, 2H), 2.14 (s, 4H), 2.02 - 1.94 (m, 4H), 1.04 (d, J = 6.0, 6H). Mass(m/z): 370.8 $[M+H]^+$.

Compound 613

N^2-(6-((2S,6R)-2,6-dimethylmorpholino)-2-isopropylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

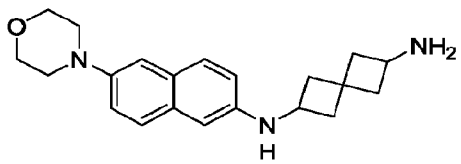
CA 03227251 2024-1-26



The titled compound **613** (1.5 mg, 2.36%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) 6.85 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 3.91 - 3.86 (m, 2H), 3.75 - 3.63 (m, 3H), 3.12 - 3.04 (m, 1H), 2.52 - 2.35 (m, 2H), 2.34 - 2.13 (m, 5H), 2.02 - 1.98 (m, 1H), 1.91 - 1.72 (m, 4H), 1.57 (dd, J = 6.8, 0.8 Hz, 1H), 1.18 (dd, J = 12.4, 6.4 Hz, 12H). Mass(m/z): 358.9 $[M+H]^-$.

Compound 614

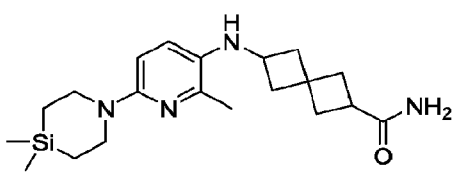
N^2-(6-morpholinonaphthalen-2-yl)spiro[3.3]heptane-2,6-diamine



The titled compound **614** (8.6 mg, 5.75%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}HNMR (400 MHz, CD_3OD) δ 7.47 (dd, J = 8.8, 6.4 Hz, 2H), 7.15 (dd, J = 9.2, 2.8 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.8, 2.4 Hz, 1H), 6.64 (d, J = 2.4 Hz, 1H), 3.86 - 3.82 (m, 5H), 3.32 (dd, J = 11.6, 4.4 Hz, 1H), 3.14 - 3.11 (m, 4H), 2.60 - 2.54 (m, 1H), 2.49 - 2.38 (m, 2H), 2.28 - 2.21 (m, 1H), 1.86 (m, 4H). Mass(m/z): 337.9 $[M+H]^+$.

Compound 615

6-((6-(4,4-dimethyl-1,4-azasilinan-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptane-2-carboxamide

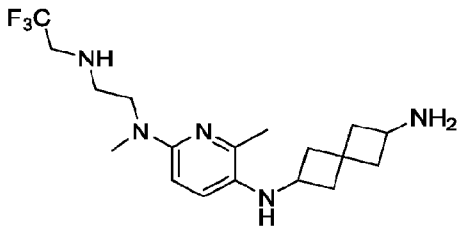


The title compound **615** (29.1 mg, 19%) a yellow solid was prepared according to the procedure outlined for compound **10**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.99 (s, 1H), 6.65 (s, 1H), 3.84 – 3.61 (m, 3H), 3.27 – 3.18 (m, 0.60H), 3.08 – 2.96 (m, 1H), 2.64 – 2.55 (m, 1H), 2.45 – 2.36 (m, 1.51H), 2.31 (d, J = 8.6 Hz, 2.51H), 2.28-2.21 (m, 1.54H), 2.17 – 2.08 (m, 1.40H), 2.01 – 1.93 (m, 1H), 1.91 – 1.82 (m, 1H), 1.37 (d, J = 6.6 Hz, 3.50H), 0.83 – 0.74 (m, 4H), 0.09 (s, 6H). Mass(m/z): 373.3$[M+H]^+$.

Compound 616

N^5-(6-aminospiro[3.3]heptan-2-yl)-N^2,6-dimethyl-N2-(2-((2,2,2-trifluoroethyl)amino)ethyl)pyridine-2,5-diamine

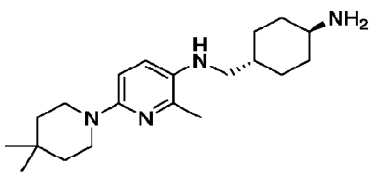
CA 03227251 2024-1-26



The titled compound **616** (12.7 mg, 15.9%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 8.8 Hz, 1H), 6.31 (d, *J* = 8.8 Hz, 1H), 3.75 - 3.68 (m, 1H), 3.59 (t, *J* = 6.0 Hz, 2H), 3.45 - 3.37 (m, 1H), 3.24 (q, *J* = 9.6 Hz, 2H), 2.95 - 2.90 (m, 5H), 2.56 - 2.37 (m, 4H), 2.27 (s, 3H), 1.88 - 1.77 (m, 4H). Mass(m/z): 371.9 $[M+H]^+$.

Compound 617

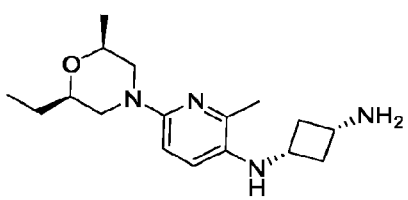
N-(((1r,4r)-4-aminocyclohexyl)methyl)-6-(4,4-dimethylpiperidin-1-yl)-2-methylpyridin-3-amine



The titled compound **617** (28.0 mg,29.4%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 3H), 7.08 (s, 1H), 6.77 (s, 1H), 4.89 (s, 1H), 3.35 - 3.26 (m, 2H), 2.89 (s, 3H), 2.34 (s, 3H), 2.00 (s, 2H), 1.86 (d, *J* = 12.8 Hz, 2H), 1.54 - 1.26 (m, 7H), 1.02 (d, *J* = 16.4 Hz, 2H), 0.95 (s, 6H). Mass (m/z): 331.3 $[M+H]^+$.

Compound 618

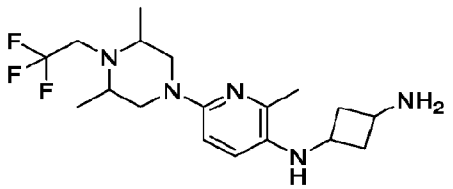
(1s,3S)-N^1-(6-((2R,6S)-2-ethyl-6-methylmorpholino)-2-methylpyridin-3-yl)cyclobutane-1,3-diamine



The titled compound **618** (1.7 mg,4.2%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.62 (d, *J* = 8.8 Hz, 1H), 6.50 (d, *J* = 8.8 Hz, 1H), 3.82 (t, *J* = 12.8 Hz, 3H), 3.59 (d, *J* = 10.0 Hz, 1H), 3.44 (d, *J* = 7.6 Hz, 2H), 2.26 - 2.20 (m, 3H), 2.16 (t, *J* = 11.2 Hz, 2H), 2.10 - 2.02 (m, 2H), 2.01 - 1.90 (m, 2H), 1.47 (q, *J* = 7.6 Hz, 2H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.98 - 0.90 (m, 3H). Mass (m/z): 305.3 $[M+H]^+$.

Compound 619

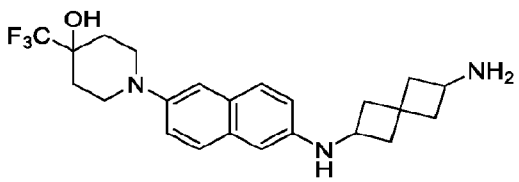
CA 03227251 2024-1-26



The titled compound 619 (35.6 mg, 56.2%) as a light-yellow solid was prepared according to the procedure outlined for compound 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 – 8.15 (m, 3H), 6.73 – 6.49 (m, 2H), 4.96 – 4.65 (m, 1H), 4.12 – 3.99 (m, 1H), 3.89 – 3.67 (m, 3H), 2.82 – 2.70 (m, 2H), 2.46 – 2.40 (m, 2H), 2.37 – 2.17 (m, 7H), 1.09 (d, J = 6.2 Hz, 6H). Mass(m/z): 372.2[M+H] $^+$.

Compound 620

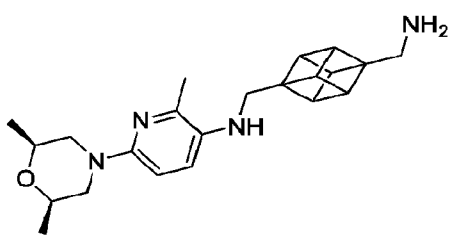
1-(6-((6-aminospiro[3.3]heptan-2-yl)amino)naphthalen-2-yl)-4-(trifluoromethyl)piperidin-4-ol



The titled compound **620** (3 mg, 4.03%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dd, J = 8.8, 5.6 Hz, 2H), 7.17 (dd, J = 9.2, 2.4 Hz, 1H), 7.11 (d, J = 1.6 Hz, 1H), 6.85 (dd, J = 8.8, 2.4 Hz, 1H), 6.64 (d, J = 1.6 Hz, 1H), 3.84 (p, J = 7.6 Hz, 1H), 3.53 (d, J = 12.0 Hz, 2H), 2.99 (dd, J = 12.0, 10.4 Hz, 2H), 2.59 - 2.52 (m, 1H), 2.48 - 2.37 (m, 2H), 2.26 - 2.19 (m, 1H), 2.03 - 1.75 (m, 9H). Mass(m/z): 420.2 [M+H] $^+$.

Compound 621

N-((4-(aminomethyl)cuban-1-yl)methyl)-6-((2S,6R)-2,6-dimethylmorpholino)-2-methylpyridin-3-amine

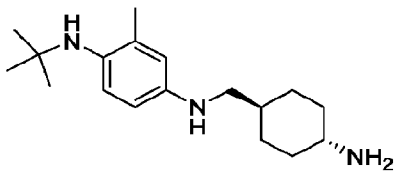


The titled compound **621** (11 mg, 12.5%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H), 6.97 (d, J = 8.8, 1H), 6.51 (d, J = 8.8, 1H), 3.85 (d, J = 10.8, 2H), 3.63 - 3.59 (m, 8H), 3.20 (s, 2H), 3.12 (s, 2H), 2.22 (s, 2H), 2.20 - 2.11 (m, 2H), 1.64 (s, 1H), 1.13 (d, J = 6.4, 6H). Mass(m/z): 367.3 [M+H] $^+$.

Compound 622

N^4-(((1r,4r)-4-aminocyclohexyl)methyl)-N^1-(tert-butyl)-2-methylbenzene-1,4-diamine

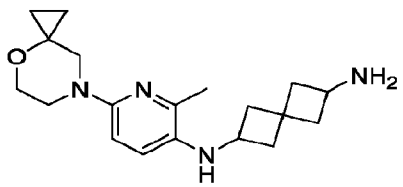
CA 03227251 2024-1-26



The titled compound **622** (43 mg, 32.15%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.86 (d, J = 8.4 Hz, 1H), 6.52 - 6.44 (m, 2H), 2.90 (d, J = 6.8 Hz, 2H), 2.59 (m, J = 10.8, 3.6 Hz, 1H), 2.21 (s, 3H), 1.91 (d, J = 9.6 Hz, 4H), 1.59 - 1.51 (m, 1H), 1.21 (s, 9H), 1.17 – 1.01 (m, 4H). Mass(m/z): 290.0 $[M+H]^+$.

Compound 623

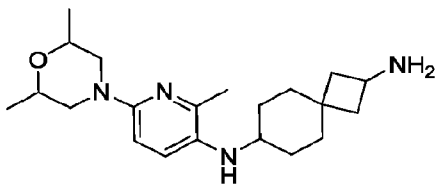
N^2-(2-methyl-6-(4-oxa-7-azaspiro[2.5]octan-7-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine



The titled compound **623** (15.3 mg, 12.10%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.89 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 8.8 Hz, 1H), 3.90 - 3.85 (m, 2H), 3.73 (t, J = 7.6 Hz, 1H), 3.37 (s, 1H), 3.31 (dd, J = 3.2, 1.6 Hz, 2H), 3.23 (s, 2H), 2.56 - 2.35 (m, 3H), 2.29 (s, 3H), 2.28 - 2.23 (m, 1H), 1.96 - 1.77 (m, 4H), 0.79 (d, J = 5.2 Hz, 2H), 0.72 - 0.64 (m, 2H). Mass(m/z): 328.9 $[M+H]^+$.

Compound 624

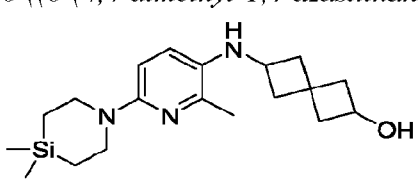
N^7-(6-(2,6-dimethylmorpholino)-2-methylpyridin-3-yl)spiro[3.5]nonane-2,7-diamine



The titled compound **624** (57.4 mg,50.8%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 3H), 7.02 (s, 1H), 6.56 (s, 1H), 4.03 - 3.81 (m, 2H), 3.60 (t, J = 8.4 Hz, 3H), 3.06 (s, 1H), 2.39 - 2.08 (m, 6H), 1.98 (d, J = 8.0 Hz, 2H), 1.89 (t, J = 10.0 Hz, 1H), 1.74 (t, J = 14.4 Hz, 4H), 1.46 - 1.26 (m, 3H), 1.14 (d, J = 6.4 Hz, 6H). Mass (m/z): 359.2 $[M+H]^+$.

Compound 625

6-((6-(4,4-dimethyl-1,4-azasilinan-1-yl)-2-methylpyridin-3-yl)amino)spiro[3.3]heptan-2-ol



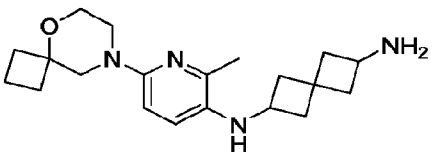
The title compound **625** (24.7 mg, 27%) as a yellow oil was prepared according to the procedure outlined for compound **5**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.88 (d, J = 8.8 Hz, 1H),

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6.52 (d, J = 8.8 Hz, 1H), 4.16 – 4.05 (m, 1H), 3.78 – 3.65 (m, 5H), 2.51 – 2.42 (m, 2H), 2.40-2.33 (m, 1H), 2.31 – 2.24 (m, 4H), 2.00 – 1.88 (m, 4H), 0.78 – 0.73 (m, 4H), 0.07 (s, 6H). Mass(m/z): 346.2$[M+H]^+$.

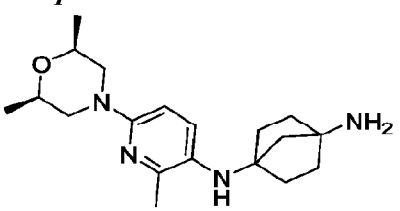
Compound 626

N^2-(2-methyl-6-(5-oxa-8-azaspiro[3.5]nonan-8-yl)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine



The titled compound **626** (4.0 mg, 6.2%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}HNMR (400 MHz, CD_3OD) δ 6.78 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 3.64 - 3.60 (m, 3H), 3.22 - 3.19 (m, 1H), 3.07 - 3.04 (m, 2H), 2.44 - 2.39 (m, 1H), 2.35 (dd, J = 11.2, 5.2 Hz, 1H), 2.29 - 2.24 (m, 1H), 2.19 (s, 3H), 2.15 (dd, J = 8.8, 3.6 Hz, 1H), 2.04 - 1.88 (m, 5H), 1.85 - 1.61 (m, 7H). Mass(m/z): 343.3 $[M+H]^+$

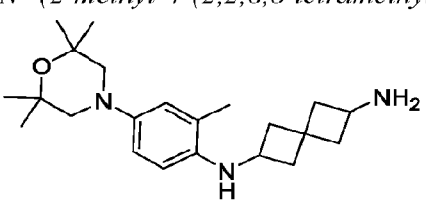
Compound 627



The titled compound **627** (21.1 mg, 32.2%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (br s, 3H), 6.74 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 4.75 – 4.42 (m, 1H), 3.83 (d, J = 12.0 Hz, 2H), 3.72 – 3.41 (m, 5H), 2.49 – 2.43 (m, 1H), 2.42 – 2.28 (m, 2H), 2.23 (s, 3H), 2.20 – 2.06 (m, 5H), 1.98 – 1.84 (m, 2H), 1.12 (d, J = 6.2 Hz, 6H). Mass(m/z): 331.3 $[M+H]^+$.

Compound 628

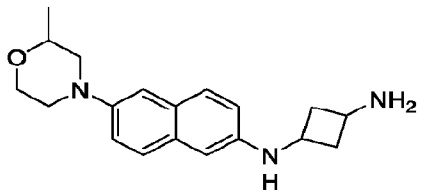
N^2-(2-methyl-4-(2,2,6,6-tetramethylmorpholino)phenyl)spiro[3.3]heptane-2,6-diamine



The titled compound **628** (24.6 mg, 36.5%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 3H), 6.73 - 6.52 (m, 2H), 6.34 (s, 1H), 4.59 (s, 1H), 3.68 (s, 1H), 3.58 - 3.47 (m, 1H), 2.75 - 2.62 (m, 3H), 2.42 - 2.31 (m, 2H), 2.28 - 2.15 (m, 3H), 2.13 - 2.01 (m, 3H), 1.99 - 1.86 (m, 2H), 1.20 (s, 12H). Mass (m/z): 358.3 $[M+H]^+$.

Compound 629

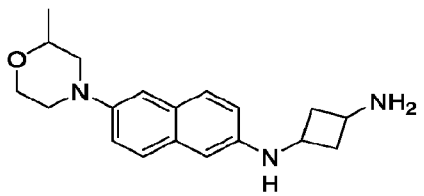
N^1-(6-(2-methylmorpholino)naphthalen-2-yl)cyclobutane-1,3-diamine



The titled compound **629** (1.2 mg, 1.09%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 8.8 Hz, 2H), 7.17 (dd, J = 9.2, 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 6.43 (d, J = 2.0 Hz, 1H), 5.87 (d, J = 5.6 Hz, 1H), 3.91 (dd, J = 11.2, 1.6 Hz, 2H), 3.71 - 3.63 (m, 2H), 3.57 - 3.44 (m, 3H), 2.65 – 2.60 (m, 1H), 2.31 (dd, J = 11.6, 10.4 Hz, 1H), 2.11 - 2.01 (m, 4H), 1.16 (d, J = 6.4 Hz, 3H). Mass(m/z): 311.9 $[M+H]^+$.

Compound 630

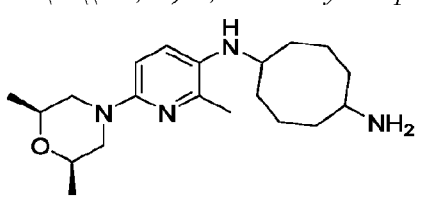
N^1-(6-(2-methylmorpholino)naphthalen-2-yl)cyclobutane-1,3-diamine



The titled compound **630** (20.3 mg, 18.37%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (dd, J = 8.8, 4.4 Hz, 2H), 7.17 (dd, J = 8.8, 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.8, 2.2 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 5.77 (d, J = 6.4 Hz, 1H), 3.91 (dd, J = 11.2, 2.0 Hz, 1H), 3.71 - 3.63 (m, 2H), 3.55 (d, J = 11.6 Hz, 1H), 3.46 (d, J = 11.6 Hz, 1H), 3.39 (d, J = 6.8 Hz, 1H), 3.11 - 3.03 (m, 1H), 2.74 - 2.66 (m, 2H), 2.62 (td, J = 11.6, 3.2 Hz, 1H), 2.31 (dd, J = 11.6, 10.0 Hz, 1H), 1.49 (J = 8.8, 2.8 Hz, 2H), 1.16 (d, J = 6.2 Hz, 3H). Mass(m/z): 311.9 $[M+H]^+$.

Compound 631

N1-(6-((2R,6S)-2,6-dimethylmorpholino)-2-methylpyridin-3-yl)cyclooctane-1,5-diamine

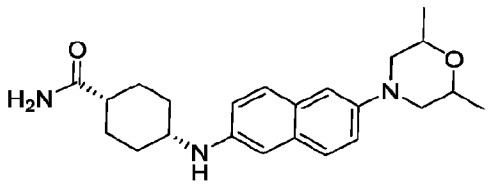


The title compound **631** (8.1 mg, 13 %) as a yellow oil was prepared according to the procedure outlined for compound **24.** ^{1}HNMR (400 MHz, CD_3OD) δ 7.57 (d, J = 9.4 Hz, 1H), 7.07 (d, J = 9.5 Hz, 1H), 3.75 (d, J = 10.8 Hz, 4H), 3.59 (d, J = 2.8 Hz, 1H), 3.38 (t, J = 9.2 Hz, 1H), 2.64 (dd, J = 16.2, 7.2 Hz, 2H), 2.47 (s, 3H), 1.81 (m, 12H), 1.21 (d, J = 6.2 Hz, 6H). Mass(m/z): 346.9 $[M+H]^+$.

Compound 632

(1s,4s)-4-((6-(2,6-dimethylmorpholino)naphthalen-2-yl)amino)cyclohexane-1-carboxamide

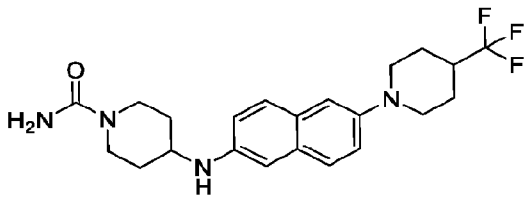
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The titled compound **632** (12.7 mg,19.0%) as a purple solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (d, J = 8.8 Hz, 2H), 7.20 - 7.14 (m, 2H), 7.00 - 6.94 (m, 2H), 6.71 (s, 1H), 6.63 (d, J = 2.0 Hz, 1H), 5.49 (d, J = 7.2 Hz, 1H), 3.78 - 3.68 (m, 2H), 3.58 - 3.49 (m, 3H), 2.27 - 2.15 (m, 3H), 1.89 - 1.69 (m, 4H), 1.67 - 1.48 (m, 4H), 1.16 (d, J = 6.0 Hz, 6H). Mass (m/z): 382.3 $[M+H]^+$.

Compound 633

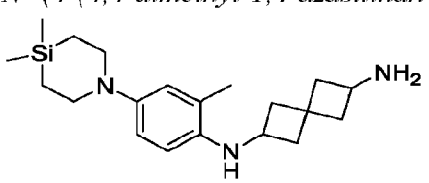
4-((6-(4-(trifluoromethyl)piperidin-1-yl)naphthalen-2-yl)amino)piperidine-1-carboxamide



The titled compound **633** (2.8 mg, 4.9%) as a orang solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 (d, J = 8.8 Hz, 2H), 7.17 (dd, J = 8.8, 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 5.92 (s, 2H), 5.51 (d, J = 8.0 Hz, 1H), 3.88 (d, J = 13.6 Hz, 2H), 3.74 (d, J = 12.0 Hz, 2H), 3.54 - 3.42 (m, 1H), 2.96 - 2.83 (m, 2H), 2.75 - 2.62 (m, 3H), 1.97 - 1.84 (m, 4H), 1.67 - 1.53 (m, 2H), 1.32 - 1.24 (m, 2H). Mass (m/z): 421.2 $[M+H]^+$.

Compound 634

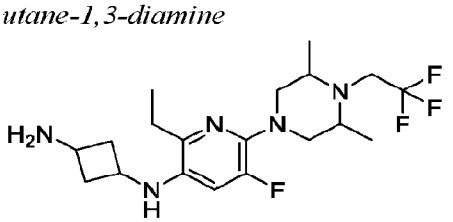
N^2-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-2-methylphenyl)spiro[3.3]heptane-2,6-diamine



The titled compound **634** (32.4 mg, 38.9%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, J = 8.8 Hz, 2H), 6.36 (d, J = 8.1 Hz, 1H), 3.74 - 3.68 (m, 1H), 3.41 (d, J = 5.6 Hz,4H), 2.49 - 2.22 (m, 7H), 2.04 (s, 3H), 1.74 (ddd, J = 22.2, 10.8, 5.3 Hz, 5H), 0.77 - 0.68 (m, 6H). Mass(m/z): 344.2 $[M+H]^+$.

Compound 635

N1-(6-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-ethyl-5-fluoropyridin-3-yl)cyclobutane-1,3-diamine

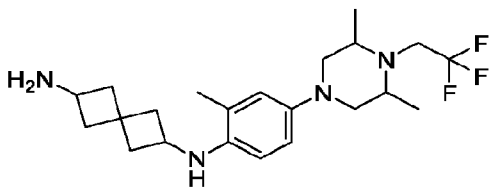


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The titled compound **635** (26.2, 50%) as an oil was **prepared according to the procedure outlined for compound 24.** ^{1}H NMR (400 MHz, CD_3OD) δ 6.60 (dd, J = 47.5, 14.1 Hz, 1H), 3.97 – 3.87 (m, 0.5H), 3.65 (dd, J = 13.8, 6.3 Hz, 0.5H), 3.50 (d, J = 12.2 Hz, 2H), 3.37 (s, 2H), 3.19 (dd, J = 15.3, 7.9 Hz, 1H), 2.95 (s, 2H), 2.84 – 2.72 (m, 1H), 2.59 (s, 4H), 2.30 – 2.14 (m, 2H), 1.65 (ddd, J = 17.4, 8.7, 2.8 Hz, 1H), 1.23 (td, J = 7.5, 2.0 Hz, 3H), 1.14 (d, J = 6.3 Hz, 6H).Mass(m/z): 404.3 $[M+H]^+$.

Compound 636

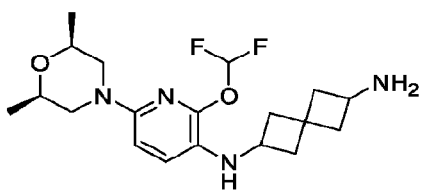
N2-(4-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylphenyl)spiro[3.3]heptane-2,6-diamine



The titled compound **636** (8 mg, 10%) as an oil was **prepared according to the procedure outlined for compound 24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.73 (m, 2H), 6.64 (m, 3H), 6.47 (m, 1H), 3.77 (m, 1H), 3.37 (m, 3H), 3.25 (d, J = 11.4 Hz, 2H), 2.93 (m, 2H), 2.55 (td, J = 11.4, 5.8 Hz, 1H), 2.47 (m, 1H), 2.37 (dt, J = 11.4, 9.2 Hz, 3H), 2.27 (m, 1H), 2.12 (s, 3H), 1.89 (m, 4H), 1.16 (d, J = 6.3 Hz, 7H). Mass(m/z): 411.3 $[M+H]^+$.

Compound 637

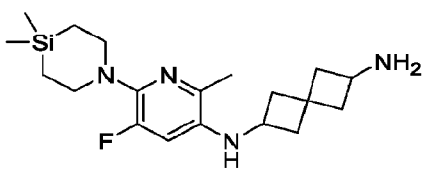
N2-(2-(difluoromethoxy)-6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine



The titled compound 637 (18.6 mg, 48.9%) as a purple solid was prepared according to the procedure outlined for compound 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 2H), 7.70 (t, J = 73.5 Hz, 2H), 7.00 – 6.88 (m, 1H), 6.47 (d, J = 8.4 Hz, 1H), 4.68 (s, 1H), 3.89 – 3.77 (m, 2H), 3.73 – 3.52 (m, 4H), 2.49 – 2.43 (m, 2H), 2.40 – 2.28 (m, 2H), 2.24 – 2.13 (m, 4H), 2.00 – 1.86 (m, 2H). Mass(m/z): 383.2$[M+H]^+$.

Compound 638

N^2-(6-(4,4-dimethyl-1,4-azasilinan-1-yl)-5-fluoro-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine



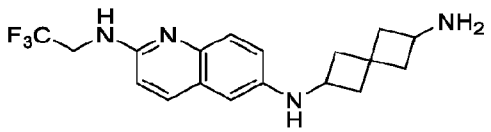
The titled compound **638** (59.1 mg, 75.42%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}HNMR (400 MHz, CD_3OD) δ 6.61 (d, J = 14.0 Hz, 1H), 3.74 - 3.66 (m, 1H), 3.51 - 3.44 (m, 4H), 3.28 (dd, J = 8.8, 7.2 Hz, 1H), 2.57 - 2.36 (m, 3H),

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2.31 - 2.24 (m, 1H), 2.24 (d, *J* = 1.2 Hz, 3H), 1.97 - 1.77 (m, 4H), 0.90 - 0.84 (m, 4H), 0.13 - 0.08 (m, 6H). Mass(m/z): 363.3 $[M+H]^+$.

Compound 639

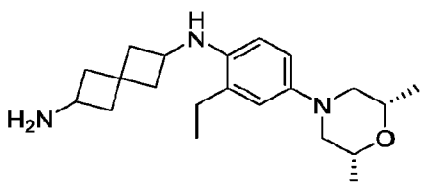
N^6-(6-aminospiro[3.3]heptan-2-yl)-N^2-(2,2,2-trifluoroethyl)quinoline-2,6-diamine



The titled compound **639** (10.3 mg, 13.24%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}HNMR (400 MHz, CD_3OD) δ 7.75 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 7.01 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 4.23 (q, *J* = 9.6 Hz, 2H), 3.90 - 3.82 (m, 1H), 3.36 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.63 - 2.56 (m, 1H), 2.53 - 2. 41 (m, 2H), 2.32 - 2.24 (m, 1H), 1.99 - 1.79 (m, 4H). Mass(m/z): 351.2 $[M+H]^+$.

Compound 640

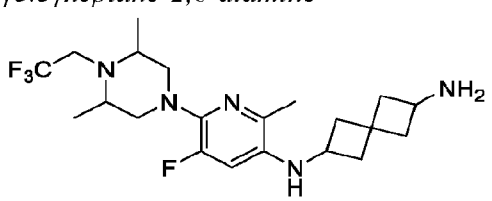
N2-(4-((2S,6R)-2,6-dimethylmorpholino)-2-ethylphenyl)spiro[3.3]heptane-2,6-diamine



The title compound **640** (41.6 mg, 73%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD_SPE) δ 6.76 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 6.50 (d, J = 8.6 Hz, 1H), 3.85 – 3.73 (m, 3H), 3.42 – 3.33 (m, 1H), 3.27 (d, *J* = 10.9 Hz, 2H), 2.59 – 2.43 (m, 4H), 2.42 - 2.36 (m, 1H), 2.31 - 2.22 (m, 3H), 1.99 – 1.82 (m, 4H), 1.22 – 1.16 (m, 9H). Mass(m/z): 344.2 $[M+H]^+$.

Compound 641

N^2-(6-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-5-fluoro-2-methylpyridin-3-yl)spiro[3.3]heptane-2,6-diamine

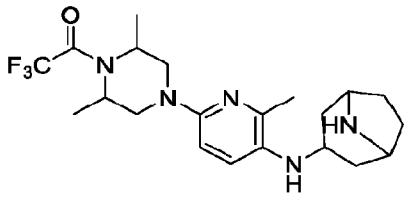


The titled compound **641** (5 mg, 31.2%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.59 (d, *J* = 13.6 Hz, 1H), 3.74 - 3.63 (m, 1H), 3.47 - 3.30 (m, 5H), 2.90 (d, *J* = 6.4 Hz, 2H), 2.60 - 2.35 (m, 5H), 2.32 - 2.18 (m, 4H), 1.93 - 1.90 (m, 4H), 1.11 (d, *J* = 6.4 Hz, 6H). Mass (m/z): 430.1 $[M+H]^+$.

Compound 642

1-(4-(5-((8-azabicyclo[3.2.1]octan-3-yl)amino)-6-methylpyridin-2-yl)-2,6-dimethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one

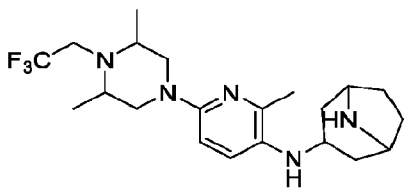
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The titled compound **642** (27.9 mg, 28.76%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.67 (s, 1H), 4.26 (s, 1H), 3.97 (s, 2H), 3.68 (d, J = 4.4 Hz, 3H), 3.28 (s, 1H), 2.90 (s, 2H), 2.33 (s, 3H), 2.29 - 2.23 (m, 2H), 2.11 (s, 1H), 2.01 - 1.95 (m, 2H), 1.81 (d, J = 14.4 Hz, 2H), 1.46 (d, J = 17.2 Hz, 6H). Mass (m/z): 426.2 $[M+H]^+$.

Compound 643

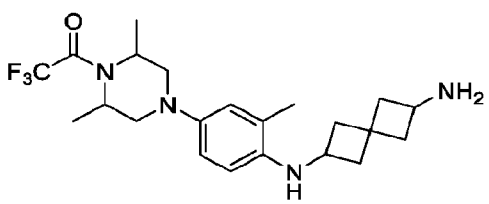
N-(6-(3,5-dimethyl-4-(2,2,2-trifluoroethyl)piperazin-1-yl)-2-methylpyridin-3-yl)-8-azabicyclo[3.2.1]octan-3-amine



The titled compound **643** (4.5 mg, 4.65%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CDCl3) δ 6.75 (d, J = 8.8 Hz, 1H), 6.44 (d, J = 8.8 Hz, 1H), 3.85 (d, J = 11.2 Hz, 2H), 3.65 (s, 3H), 3.33 - 3.26 (m, 2H), 2.97 (s, 2H), 2.48 - 2.42 (m, 2H), 2.32 (s, 3H), 2.21 (d, J = 11.2 Hz, 2H), 2.09 (d, J = 7.6 Hz, 2H), 1.95 (s, 2H), 1.79 (d, J = 14.4 Hz, 2H), 1.19 (d, J = 6.4 Hz, 6H). Mass (m/z): 412.1 $[M+H]^+$.

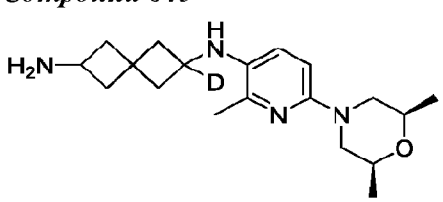
Compound 644

1-(4-(4-((6-aminospiro[3.3]heptan-2-yl)amino)-3-methylphenyl)-2,6-dimethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one



The titled compound **644** (12.5 mg, 10.30%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 - 6.70 (m, 2H), 6.43 (d, J = 8.4 Hz, 1H), 4.63 (s, 1H), 4.21 (s, 1H), 3.84 - 3.76 (m, 1H), 3.42 (s, 1H), 3.21 (d, J = 11.2 Hz, 2H), 2.84 (d, J = 12.0 Hz, 2H), 2.58 - 2.43 (m, 3H), 2.30 (dd, J = 11.2, 5.6 Hz, 1H), 2.12 (s, 3H), 1.89 - 1.81 (m, 4H), 1.51 (d, J = 24.4 Hz, 6H). Mass (m/z): 425.1 $[M+H]^+$.

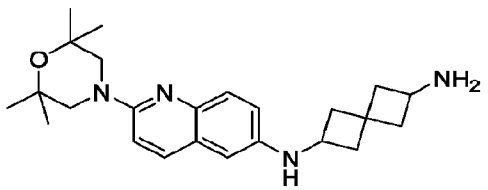
Compound 645



The titled compound **645** (15.2 mg, 21.1%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (br s, 2H), 6.81 – 6.67 (m, 1H), 6.50 (d, J = 8.4 Hz, 1H), 4.54 (br s, 1H), 3.83 (d, J = 12.0 Hz, 2H), 3.68 – 3.52 (m, 3H), 2.48 – 2.27 (m, 4H), 2.21 (s, 3H), 2.19 – 2.07 (m, 4H), 1.96 – 1.82 (m, 2H), 1.13 (d, J = 6.2 Hz, 6H). Mass(m/z): 332.3 $[M+H]^+$.

Compound 646

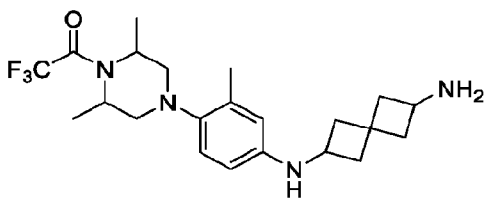
N^2-(2-(2,2,6,6-tetramethylmorpholino)quinolin-6-yl)spiro[3.3]heptane-2,6-diamine



The titled compound **646** (10 mg, 41.6%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.79 (d, J = 9.2 Hz, 1H), 7.44 (d, J = 9.2 Hz, 1H), 6.99 (dd, J = 9.2, 2.4 Hz, 2H), 6.59 (d, J = 2.4 Hz, 1H), 3.89 - 3.75 (m, 1H), 3.47 (s, 4H), 2.61 - 2.35 (m, 3H), 2.25 - 2.23 (m, 1H), 1.95 - 1.74 (m, 4H), 1.26 (s, 12H). Mass (m/z): 395.1 $[M+H]^+$.

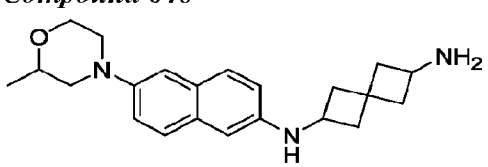
Compound 647

1-(4-(4-((6-aminospiro[3.3]heptan-2-yl)amino)-2-methylphenyl)-2,6-dimethylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one



The titled compound **647** (15.4 mg, 23.79%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, J = 8.4 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.35 (dd, J = 8.4, 2.8 Hz, 1H), 4.62 (s, 1H), 4.20 (s, 1H), 3.80 - 3.73 (m, 1H), 3.46 - 3.39 (m, 1H), 2.87 (s, 4H), 2.55 - 2.41 (m, 3H), 2.32 (d, J = 12.0 Hz, 4H), 1.85 (m, J = 11.6, 8.8 Hz, 4H), 1.60 – 1.51 (m, 6H). Mass (m/z): 429.2 $[M+H]^+$.

Compound 648

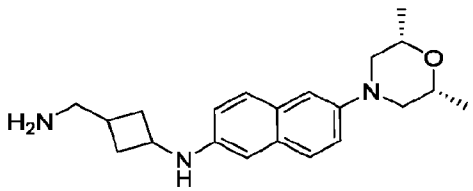


The titled compound 648 (48.8 mg, 83.1%) as a white solid was prepared according to the procedure outlined for compound 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.97 (s, 2H), 7.46 (dd, J = 9.0, 2.2 Hz, 2H), 7.18 (dd, J = 9.0, 2.5 Hz, 1H), 6.98 (d, J = 2.5 Hz, 1H), 6.83 (dd, J = 8.8, 2.3 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 5.85 (d, J = 6.4 Hz, 1H), 3.95 – 3.89 (m, 1H), 3.82 – 3.74 (m, 1H), 3.71 – 3.63 (m, 2H), 3.61 – 3.52 (m, 2H), 3.50 – 3.43 (m, 1H), 2.70 – 2.55 (m, 2H), 2.47 – 2.40 (m, 2H), 2.37 – 2.28 (m, 1H), 2.26 – 2.10 (m, 3H), 1.95 – 1.82 (m, 2H), 1.16 (d, J = 6.2 Hz, 3H). Mass(m/z): 352.4[M+H] $^+$.

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Compound 649

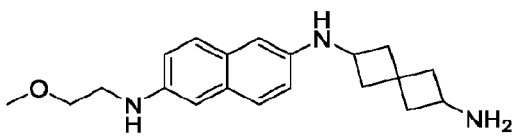
N-(3-(aminomethyl)cyclobutyl)-6-((2S,6R)-2,6-dimethylmorpholino)naphthalen-2-amine



The titled compound **649** (7.6 mg, 10.2%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (d, J = 8.8 Hz, 2H), 7.18 (dd, J = 9.2, 2.4 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.88 - 6.82(m, 1H), 6.56 - 6.44 (m, 1H), 5.82 (d, J = 6.4 Hz, 1H), 3.91 (h, J = 6.8 Hz, 1H), 3.78 - 3.66 (m, 2H), 3.59 - 3.51 (m, 2H), 3.30 (s, 1H), 2.24 (t, J = 10.4 Hz, 2H), 2.11 - 2.19 (m, 2H), 1.96 - 1.85 (m, 1H), 1.29 (s, 1H), 1.16 (d, J = 6.0 Hz, 6H). Mass (m/z): 340.2 $[M+H]^+$.

Compound 650

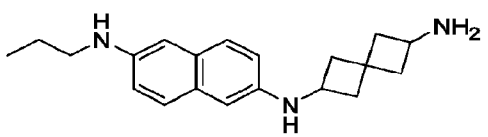
N2-(6-aminospiro[3.3]heptan-2-yl)-N6-(2-methoxyethyl)naphthalene-2,6-diamine



The titled compound **650** (18.4 mg, 24.6%) as a light-yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (br s, 2H), 7.49 – 7.12 (m, 3H), 6.88 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 8.8 Hz, 1H), 6.63 (s, 1H), 6.51 (s, 1H), 5.69 (br s, 1H), 3.76 (s, 1H), 3.66 – 3.48 (m, 3H), 3.29 (s, 3H), 3.26 – 3.16 (m, 2H), 2.63 – 2.53 (m, 1H), 2.46 – 2.34 (m, 2H), 2.27 – 2.10 (m, 3H), 1.98 – 1.79 (m, 2H). Mass(m/z): 326.3 $[M+H]^+$.

Compound 651

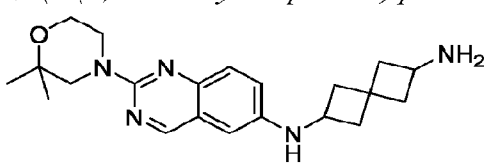
N^2-(6-aminospiro[3.3]heptan-2-yl)-N^6-propylnaphthalene-2,6-diamine



The titled compound **651** (13.5 mg, 8.81%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, J = 7.6 Hz, 2H), 6.90 (dd, J = 8.8, 2.4 Hz, 1H), 6.85 (dd, J = 8.8, 2.4 Hz, 1H), 6.77 (d, J = 1.6 Hz, 1H), 6.69 (d, J = 1.6 Hz, 1H), 3.90 - 3.82 (m, 1H), 3.34 (d, J = 4.4 Hz, 1H), 3.11 (t, J = 7.2 Hz, 2H), 2.62 - 2.55 (m, 1H), 2.52 - 2.40 (m, 2H), 2.31 - 2.24 (m, 1H), 1.96 - 1.81 (m, 4H), 1.70 (dd, J = 14.4, 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H). Mass (m/z): 310.1 $[M+H]^+$.

Compound 652

N^2-(2-(2,2-dimethylmorpholino)quinazolin-6-yl)spiro[3.3]heptane-2,6-diamine

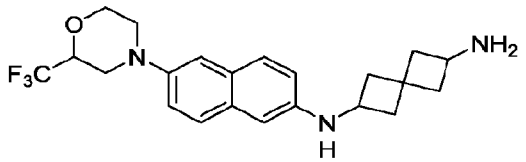


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The titled compound **652** (4.9 mg, 4.10%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (s, 1H), 7.31 (d, J = 9.2 Hz, 1H), 7.17 (dd, J = 9.2, 2.4 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.05 (d, J = 6.4 Hz, 1H), 3.72 (dd, J = 14.4, 7.2 Hz, 1H), 3.63 (s, 4H), 3.20 (d, J = 7.6 Hz, 2H), 2.39 - 2.33 (m, 2H), 2.13 (dd, J = 10.4, 5.6 Hz, 1H), 2.04 - 1.87 (m, 1H), 1.81 (d, J = 8.0 Hz, 3H), 1.70 (s, 2H), 1.18 (s, 12H). Mass (m/z): 396.1 $[M+H]^+$.

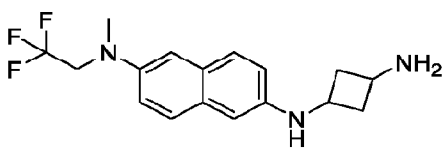
Compound 653

N^2-(6-(2-(trifluoromethyl)morpholino)naphthalen-2-yl)spiro[3.3]heptane-2,6-diamine



The titled compound **653** (10.6 mg, 14.58%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (dd, J = 8.8, 5.2 Hz, 2H), 7.22 (dd, J = 9.2, 2.4 Hz, 1H), 7.09 (s, 1H), 6.85 (dd, J = 8.8, 2.4 Hz, 1H), 6.52 (s, 1H), 5.87 (d, J = 6.4 Hz, 1H), 4.37 (s, 1H), 4.09 (d, J = 9.2 Hz, 1H), 3.86 - 3.64 (m, 4H), 3.55 (d, J = 12.0 Hz, 1H), 3.24 - 3.18 (m, 1H), 2.79 - 2.66 (m, 3H), 2.49 - 2.46 (m, 2H), 2.40 - 2.32 (m, 2H), 2.13 (dd, J = 11.2, 5.2 Hz, 1H), 1.88 - 1.63 (m, 4H). Mass (m/z): 406.2 $[M+H]^+$.

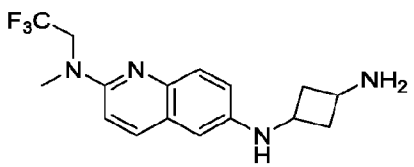
Compound 654



The titled compound 654 (49.6 mg, 78.3%) as a white solid was prepared according to the procedure outlined for compound 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (s, 2H), 7.48 (d, J – 8.8 Hz, 2H), 7.17 (dd, J – 9.0, 2.6 Hz, 1H), 6.95 (d, J – 2.7 Hz, 1H), 6.90 – 6.81 (m, 1H), 6.58 – 6.43 (m, 1H), 6.06 – 5.89 (m, 1H), 4.34 – 4.19 (m, 2H), 4.15 – 4.05 (m, 1H), 3.88 – 3.75 (m, 1H), 3.03 (s, 3H), 2.57 – 2.51 (m, 1H), 2.31 – 2.17 (m, 2H). Mass(m/z): 324.2$[M+H]^+$.

Compound 655

N^6-(3-aminocyclobutyl)-N^2-methyl-N^2-(2,2,2-trifluoroethyl)quinoline-2,6-diamine

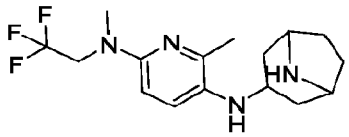


The titled compound **655** (6.6 mg, 5.96%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 9.2 Hz, 1H), 7.39 (d, J = 9.2 Hz, 1H), 6.95 - 6.88 (m, 2H), 6.56 (d, J = 2.8 Hz, 1H), 4.34 (q, J = 9.2 Hz, 2H), 3.47 (dd, J = 11.2, 4.0 Hz, 1H), 3.14 - 3.08 (m, 4H), 2.76 - 2.70 (m, 2H), 1.58 - 1.45 (m, 2H). Mass (m/z): 325.0 $[M+H]^+$.

Compound 656

N^5-(8-azabicyclo[3.2.1]octan-3-yl)-N^2,6-dimethyl-N^2-(2,2,2-trifluoroethyl)pyridine-2,5-diamin e

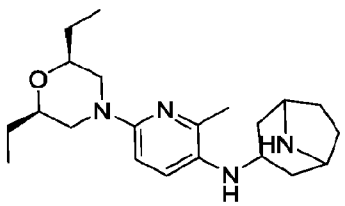
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The titled compound **656** (37.2 mg, 50.6%) as a white solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (s, 2H), 6.88 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 4.45 - 4.27 (m, 3H), 3.87 (q, J = 3.2 Hz, 2H), 3.58 (t, J = 5.6 Hz, 1H), 2.98 (s, 3H), 2.27 (d, J = 12.0 Hz, 7H), 2.01 - 1.89 (m, 4H). Mass (m/z): 329.2 $[M+H]^+$.

Compound 657

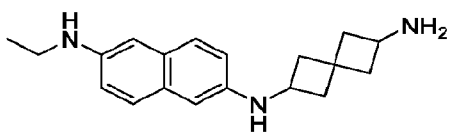
N-(6-((2S,6R)-2,6-diethylmorpholino)-2-methylpyridin-3-yl)-8-azabicyclo[3.2.1]octan-3-amine



The titled compound **657** (25.9 mg, 35.7%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 9.31 (s, 1H), 6.86 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 4.43 (s, 1H), 3.96 - 3.83 (m, 4H), 3.59 (t, J = 5.6 Hz, 1H), 3.96 - 3.83 (m, 1H), 2.33 - 2.16 (m, 9H), 2.00 - 1.88 (m, 4H), 1.56 - 1.40 (m, 4H), 0.95 (t, J = 7.6 Hz, 6H). Mass (m/z): 359.3 $[M+H]^+$.

Compound 658

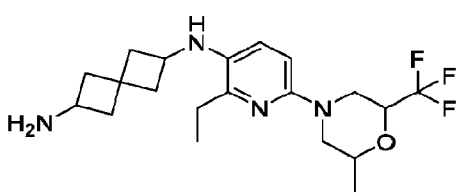
N^2-(6-aminospiro[3.3]heptan-2-yl)-N^6-ethylnaphthalene-2,6-diamine



The titled compound **658** (17.1 mg, 18.66%) as a purple solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (d, J = 8.8 Hz, 2H), 6.82 -6.73 (, 2H), 6.66 (d, J = 2.0 Hz, 1H), 6.56 (d, J = 2.0 Hz, 1H), 3.73 (p, J = 7.6 Hz, 1H), 3.16 (dd, J = 8.4, 7.6 Hz, 1H), 3.05 (q, J = 7.2 Hz, 2H), 2.48 - 2.40 (m, 1H), 2.38 - 2.25 (m, 2H), 2.16 - 2.09 (m, 1H), 1.82 - 1.64 (m, 4H), 1.16 (t, J = 7.2 Hz, 3H). Mass (m/z): 296.1 $[M+H]^+$.

Compound 659

N2-(2-ethyl-6-(2-methyl-6-(trifluoromethyl)morpholino)pyridin-3-yl)spiro[3.3]heptane-2,6-diamine



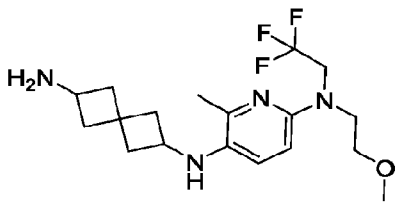
The titled compound **659** (4 mg, 15.5%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, CD_3OD) δ 6.86 (d, J = 8.6 Hz, 1H),

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6.54 (d, J = 8.6 Hz, 1H), 4.16 – 4.08 (m, 2H), 3.88 – 3.66 (m, 3H), 3.49 – 3.36 (m, 1H), 2.66 – 2.21 (m, 8H), 1.95 – 1.83 (m, 4H), 1.24 – 1.09 (m, 6H). MS (ESI) m/z 399.1 $[M+H]^+$

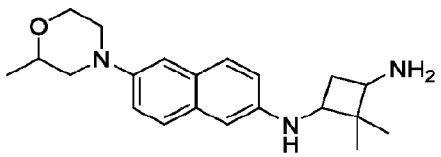
Compound 660

N^5-(6-aminospiro[3.3]heptan-2-yl)-N^2-(2-methoxyethyl)-6-methyl-N^2-(2,2,2-trifluoroethyl)pyridine-2,5-diamine



The titled compound **660** (21.2 mg, 26.0%) as a yellow solid was prepared according to the procedure outlined for compound **24**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.73 (d, J = 8.8, 1H), 6.50 (d, J = 8.8 Hz, 1H), 4.33 (q, J = 9.6 Hz, 2H), 3.64 - 3.54 (m, 3H), 3.46 (t, J = 6.0 Hz, 2H), 3.23 (s, 3H), 3.14 (q, J = 7.6 Hz, 1H), 2.43 - 2.35 (m, 1H), 2.35 - 2.29 (m, 1H), 2.27 - 2.21 (m, 1H), 2.19 (s, 3H), 2.15 - 2.07 (m, 1H), 1.88 - 1.78 (m, 2H), 1.70 - 1.58 (m, 2H). Mass (m/z): 346.3 $[M+H]^+$.

Compound 661



The titled compound 661 (51.7 mg, 77.8%) as a white solid was prepared according to the procedure outlined for compound 24. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 – 7.28 (m, 4H), 7.22 – 7.13 (m, 1H), 7.02 – 6.88 (m, 2H), 6.64 – 6.49 (m, 1H), 5.98 – 5.79 (m, 1H), 3.96 – 3.80 (m, 2H), 3.74 – 3.62 (m, 2H), 3.59 – 3.43 (m, 3H), 3.26 – 3.17 (m, 1H), 2.68 – 2.54 (m, 1H), 2.39 – 2.27 (m, 2H), 2.26 – 2.16 (m, 1H), 1.28 (d, J = 7.7 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H), 0.97 (d, J = 10.2 Hz, 3H). Mass(m/z): 340.2$[M+H]^+$.

Example 2. Determination of EC50 values in HT-1080 cell viability assay

HT-1080 (ATCC, CCL-121) cells (6000 in 100 μl) were seeded in 96-well plates (Corning) and cultured in a 37°C incubator with a humidified atmosphere of 5% CO_2 for overnight. Cells were then treated with ferroptosis inducer RSL3 (TargetMol) and a 3-fold, 10-point serial dilution series of compounds with 1.1 μM as the highest concentration, for 20 hours. Cell viability was assessed using the Cell Titer-Glo Kit (Promega). The luminescence intensity was measured with a microplate reader (Envision, PerkinElmer), and cell viability was calculated by normalizing the data to untreated controls. The EC50 values of the compounds (e.g., Compounds 1-573 and 574-661) were calculated in GraphPad Prism (GraphPad Software, Inc., San Diego, CA, USA). The curves were fitted using a non-linear regression model with a sigmoidal dose response.

Ferroptosis inhibitory activity of compounds 1-573 is summarized in Table 2. In Table 2, activity is provided as follows: +++ = 0.1 nM ≤ EC50 < 100 nM; ++ = 100 nM ≤ EC50 < 1000 nM; + = 1000 nM ≤ EC50 < 10000 nM.

Table 2. EC50 Values of Compounds 1 to 573

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Cmpd No.	EC_{50} (nM)	Cmpd No.	EC_{50} (nM)	Cmpd No.	EC_{50} (nM)
1	+++	192	++	383	+++
2	+++	193A/B	++/++	384	++
3	+++	194	++	385	++
4A/B	+++/+++	195	++	386	+++
5	+++	196	+++	387	+++
6A/B	+++/+++	197	+++	388	+++
7	+++	198	++	389	+++
8	+++	199	+	390	+++
9	+	200A/B	+++/+++	391	+++
10	+++	201	++	392	+++
11	++	202	+	393	+++
12	+++	203	++	394	+++
13	+++	204	++	395	+++
14	+++	205A/B	+++/+++	396	+++
15	+++	206	+	397	+++
16	+++	207	+	398	+++
17	+++	208	+	399	+++
18	+++	209	+++	400	+
19	+++	210	+	401	+++
20	+++	211	+	402	+++
21	+++	212	+	403	+++
22	++	213A/B	++/++	404	+++
23A/B	+++/+++	214	+++	405	+++
24A/B	+++/+++	215	+++	406	+++
25	+++	216A/B	++/++	407	+++
26	+++	217	+++	408	+++
27	++	218	++	409	+++
28	+++	219	+	410	+++
29	+++	220	+++	411	+++
30	+++	221	+++	412	+++
31	+++	222	+	413	+++
32A/B	+++/+++	223	+	414	+++
33A/B	+/+	224	++	415	+++
34A/B	+++/+++	225	+++	416	+++
35	+++	226	+++	417A/B	+++/++
36	+++	227	+	418	+++
37A/B	+/+	228A/B	+++/+++	419	+++
38	+++	229	+	420	+++
39	+++	230	+++	421A/B	+++/+++
40	+++	231A/B	+++/+++	422	+++

41A/B	++/++	**232A/B**	+++/+++	**423**	+++
42	+++	**233A/B**	++/++	**424**	+++
43	+++	**234**	+	**425**	+++
44	+++	**235**	+++	**426**	+++
45	+++	**236**	+++	**427**	+++
46	++	**237**	+	**428**	+++
47	++	**238**	+++	**429**	+++
48	+++	**239**	+++	**430**	+++
49	+++	**240**	++	**431**	+++
50	+++	**241**	+++	**432**	+++
51	+++	**242A/B**	+++/+++	**433**	+++
52	+++	**243**	+++	**434**	+
53A/B	+++/+++	**244A/B**	+++/+++	**435**	+++
54A/B	+++/+++	**245**	+	**436**	+++
55	+++	**246**	++	**437**	+++
56	+++	**247**	+++	**438**	+++
57	+++	**248**	++	**439**	++
58	+++	**249**	+++	**440**	++
59	+++	**250A/B**	+++/+++	**441**	++
60	+++	**251A/B**	+++/+++	**442**	++
61	+++	**252A/B/C/D**	++/+++/+++/+++	**443**	++
62	+++	**253A/B**	+++/+++	**444**	+++
63	+++	**254**	+++	**445**	+++
64A/B	+/+	**255**	+	**446A/B**	+++/+++
65A/B	+++/+++	**256**	+	**447**	+++
66	+++	**257**	+++	**448**	+++
67	+++	**258**	+	**449**	+
68	+++	**259A/B**	++/++	**450**	++
69	+++	**260**	+++	**451**	+++
70	+++	**261**	++	**452**	+++
71	+++	**262**	++	**453**	+++
72	+++	**263**	++	**454**	+++
73	+++	**264**	+++	**455A/B**	++/++
74	+++	**265**	+++	**456**	++
75	++	**266A/B**	++/++	**457**	++
76A/B	+++/+++	**267**	+	**458**	++
77	+++	**268**	+++	**459**	+++
78	+++	**269**	++	**460**	+++
79	++	**270**	++	**461**	+++
80	++	**271**	+++	**462**	+
81A/B	++/++	**272**	+++	**463**	+++

82A/B	+++/+++	**273**	+++	**464**	+++
83	+++	**274**	+++	**465**	+++
84	+++	**275A/B**	+++/+++	**466**	++
85	+++	**276**	+++	**467**	+++
86	+++	**277**	+++	**468**	+++
87	+++	**278**	+++	**469**	++
88	+	**279**	+++	**470**	+++
89	+++	**280**	+++	**471**	+++
90	+++	**281**	+++	**472**	+++
91A/B	+++/+++	**282**	++	**473**	+++
92A/B	+/++	**283**	+++	**474A/B**	+++/+++
93	+++	**284**	+++	**475A/B**	+++/+++
94	+++	**285**	+++	**476**	+++
95	+++	**286**	+++	**477**	++
96	+++	**287**	+++	**478**	+++
97A/B	+++/+++	**288**	+++	**479**	+++
98	+++	**289A/B**	+++/+++	**480**	++
99	+++	**290**	+++	**481**	++
100	++	**291**	+++	**482**	+++
101	+++	**292**	+++	**483**	+++
102	+++	**293**	++	**484**	+
103	++	**294A/B**	+++/+++	**485**	+++
104	++	**295A/B**	++/+++	**486**	+++
105	+++	**296A/B**	+++/+++	**487**	++
106A/B	+++/+++	**297**	+++	**488A/B**	+++/+++
107A/B	+++/+++	**298**	++	**489**	+++
108	++	**299A/B**	+++/+++	**490**	+++
109	++	**300A/B**	+++/+++	**491**	+++
110	++	**301A/B**	+++/+++	**492**	+++
111	++	**302**	+++	**493**	+++
112	++	**303**	+++	**494**	++
113	++	**304**	++	**495**	++
114A/B	++/++	**305A/B**	+++/+++	**496**	++
115A/B	++/++	**306A/B**	++/++	**497**	+++
116	+++	**307**	+++	**498**	+++
117A/B	+++/+++	**308**	+++	**499**	++
118	+++	**309**	+++	**500**	+++
119	+++	**310**	+++	**501**	+
120A/B	+++/+++	**311**	+	**502**	+++
121A/B	+++/+++	**312**	+++	**503**	+++
122	+++	**313A/B**	+++/+++	**504**	+++

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123	++	**314**	+++	**505**	+++
124	++	**315**	+++	**506**	+++
125	++	**316**	+++	**507**	++
126	+	**317**	+++	**508**	+++
127	++	**318A/B**	+++/+++	**509**	+++
128	++	**319A/B**	++/++	**510**	+++
129	++	**320A/B**	++/++	**511**	+++
130	++	**321**	++	**512**	+++
131	+++	**322**	+++	**513**	+++
132	+++	**323**	+++	**514**	+++
133	+++	**324**	+++	**515**	+++
134	+	**325A/B**	+++/+++	**516A/B**	+++/+++
135A/B	++/++	**326**	+++	**517**	++
136	+++	**327**	++	**518**	+++
137	+++	**328**	+++	**519**	+++
138	++	**329**	+++	**520**	+++
139A/B	+++/+++	**330A/B**	+++/+++	**521**	+++
140	+++	**331**	++	**522**	+++
141	++	**332**	+++	**523**	+
142A/B	+++/+++	**333**	+++	**524**	++
143A/B	++/++	**334**	++	**525**	++
144A/B	++/++	**335A/B**	++/+++	**526**	+++
145	+++	**336A/B**	+++/+++	**527**	+++
146A/B	+++/+++	**337A/B**	+++/+++	**528**	++
147	+++	**338**	+++	**529**	+++
148A/B	+++/+++	**339**	+++	**530**	+
149A/B	++/++	**340**	+++	**531**	+++
150	++	**341**	+++	**532**	++
151	+++	**342**	+++	**533**	+++
152	++	**343**	+++	**534**	+++
153A/B	++/++	**344**	+++	**535**	+++
154	++	**345**	++	**536**	+++
155	+++	**346**	+++	**537**	++
156A/B/C	+++	**347**	+++	**538A/B**	+++/+++
157A/B	+++/+++	**348**	+++	**539A/B**	+++/++
158	++	**349A/B**	+++/+++	**540**	+++
159A/B	+++/++	**350**	+++	**541**	+++
160	+	**351**	+++	**542**	+++
161	+	**352**	+	**543**	+++
162	++	**353**	+++	**544**	+++
163	+	**354**	+++	**545**	+++

164	+	**355**	+++	**546**	+++
165	+	**356**	+++	**547**	+++
166	+	**357**	+++	**548**	+++
167	++	**358**	+++	**549**	+++
168A/B	+/+	**359**	+++	**550**	+++
169	++	**360**	+++	**551**	++
170	+	**361**	+++	**552**	+++
171	+++	**362**	+++	**553**	++
172	+++	**363**	+++	**554**	+++
173	++	**364**	+++	**555**	+++
174	+++	**365**	+++	**556**	+++
175	+	**366**	+++	**557**	+++
176	++	**367**	+++	**558**	+++
177	+	**368**	+++	**559**	+++
178	+	**369**	+++	**560**	+++
179	+	**370**	+++	**561**	+++
180	++	**371**	+++	**562**	+++
181	++	**372**	+++	**563**	+++
182A/B	++/++	**373**	+++	**564**	+++
183A/B	+/+	**374**	+++	**565**	+++
184	++	**375**	+++	**566**	+++
185	+	**376**	+++	**567**	+++
186	++	**377**	+++	**568**	+++
187	+	**378**	+++	**569**	+++
188	++	**379**	+++	**570**	+++
189	+	**380**	+++	**571**	+++
190	++	**381**	+++	**572**	+++
191A/B	+/+	**382**	+++	**573**	+++

Ferroptosis inhibitory activity of compounds 574-661 is summarized in Table 3. In Table 3, activity is provided as follows: +++ = 0.1 nM ≤ EC50 < 100 nM; ++ = 100 nM ≤ EC50 < 1000 nM; + = 1000 nM ≤ EC50 < 10000 nM.

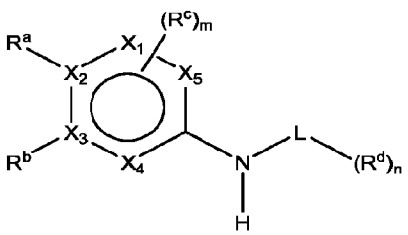
Table 3. EC_{50} Values of Compounds 574 to 661

Cmpd No.	EC_{50} (nM)	Cmpd No.	EC_{50} (nM)	Cmpd No.	EC_{50} (nM)
574	+++	**604**	+++	**634**	+++
575	+++	**605**	+++	**635**	+++
576	+++	**606**	+++	**636**	+++
577	+++	**607**	++	**637**	+++
578	+++	**608**	+++	**638**	+++
579	+++	**609**	+++	**639**	+++
580	+++	**610**	+++	**640**	+++

581	+++	**611**	+++	**641**	+++
582	+++	**612**	+++	**642**	+++
583	+++	**613**	+++	**643**	+++
584	+++	**614**	+++	**644**	+++
585	+++	**615**	+++	**645**	+++
586	+++	**616**	+++	**646**	+++
587	++	**617**	+++	**647**	+++
588	+++	**618**	++	**648**	+++
589	+++	**619**	+++	**649**	+++
590	++	**620**	+++	**650**	+++
591	++	**621**	+++	**651**	+++
592	+++	**622**	+++	**652**	+++
593	+++	**623**	+++	**653**	+++
594	+++	**624**	+++	**654**	+++
595	+++	**625**	+++	**655**	+++
596	+++	**626**	+++	**656**	+++
597	+++	**627**	++	**657**	+++
598	+++	**628**	+++	**658**	+++
599	++	**629**	+++	**659**	+++
600	++	**630**	+++	**660**	+++
601	+++	**631**	+++	**661**	+++
602	+++	**632**	+++		
603	+++	**633**	+++		

The present disclosure involves the following technical solutions:

1. A compound of the following structural Formula I:



Formula I

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

L is cycloalkyl, heterocyclyl, or C;

X_1, X_2, X_3, X_4, and X_5 are each independently C or N;

R^a is absent or selected from H, halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is absent or selected from H, halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl;

R^a and R^b may join together to form an optionally substituted 3- to 10-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring;

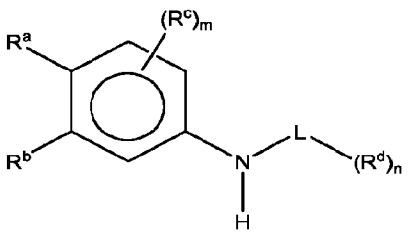
R^c, for each occurrence, is independently selected from halogen, optionally substituted heteroatom, and optionally substituted alkyl;

R^b and one of R^c may join together to form an optionally substituted 3- to 10-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring;

R^d, for each occurrence, is independently selected from halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and

m and n are each an integer independently selected from 0, 1, 2, and 3.

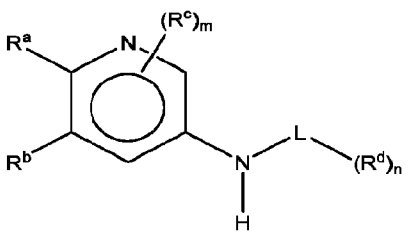
2. The compound of technical solution 1, wherein the compound has the following structural Formula IIa:



Formula IIa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

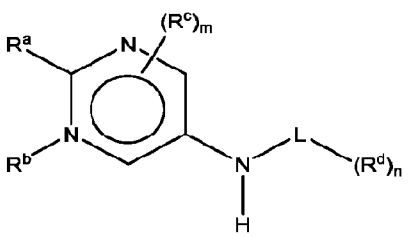
3. The compound of technical solution 1, wherein the compound has the following structural Formula IIb:



Formula IIb

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

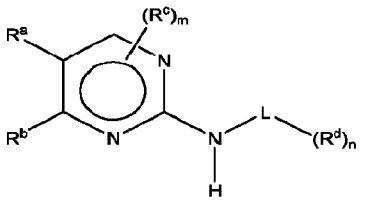
4. The compound of technical solution 1, wherein the compound has the following structural Formula IIc:



Formula IIc

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

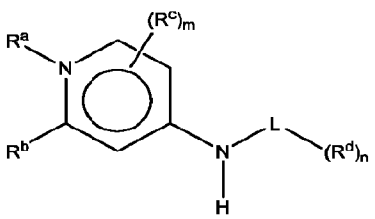
5. The compound of technical solution 1, wherein the compound has one of the following structural Formulae IId:



Formula IId

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

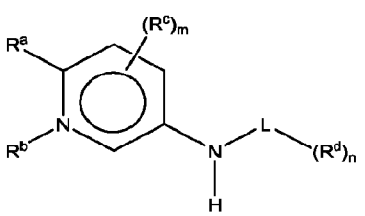
6. The compound of technical solution 1, wherein the compound has one of the following structural Formulae IIe:



Formula IIe

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

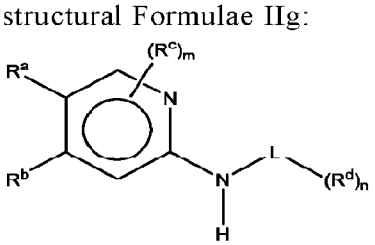
7. The compound of technical solution 1, wherein the compound has one of the following structural Formulae IIf:



Formula IIf

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

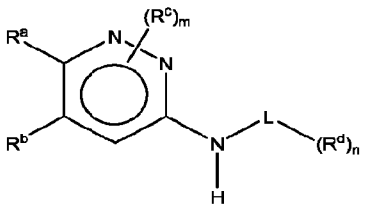
8. The compound of technical solution 1, wherein the compound has one of the following structural Formulae IIg:



Formula IIg

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

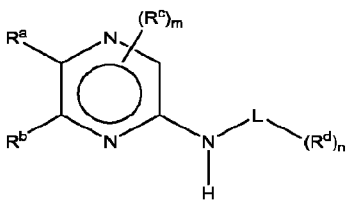
9. The compound of technical solution 1, wherein the compound has one of the following structural Formulae IIh:



Formula IIh

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

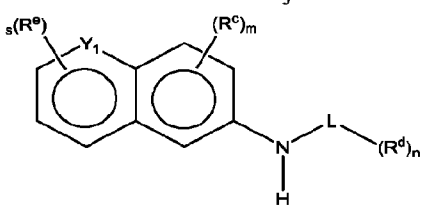
10. The compound of technical solution 1, wherein the compound has one of the following structural Formulae IIi:



Formula IIi

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

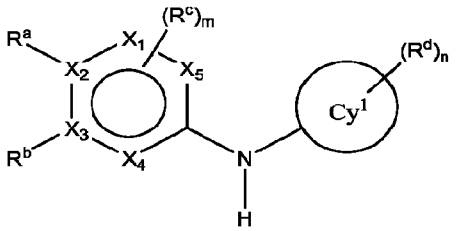
11. The compound of technical solution 1, wherein the compound has one of the following structural Formulae IIj:



Formula IIj

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Y1 is N or C; R^e, for each occurrence, is independently selected from optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and s is an integer selected from 0, 1, 2, and 3.

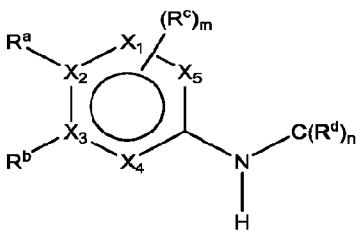
12. The compound of technical solution 1, wherein the compound has the following structural Formula IIIa:



Formula IIIa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Cy^1 is 3- to 10-membered cycloalkyl or 3- to 10-membered heterocyclyl.

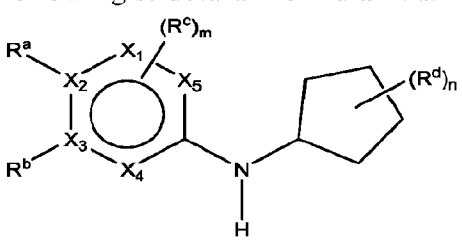
13. The compound of technical solution 1, wherein the compound has the following structural Formula IIIb:



Formula IIIb

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

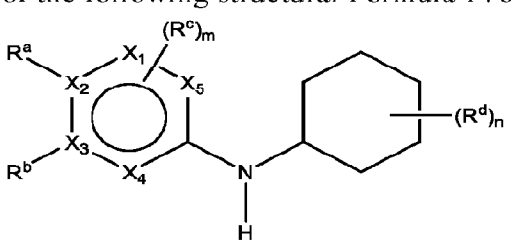
14. The compound of any one of technical solutions 1 and 12, wherein the compound has the following structural Formula IVa:



Formula IVa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

15. The compound of any one of technical solutions 1 and 12, wherein the compound has one of the following structural Formula IVb:



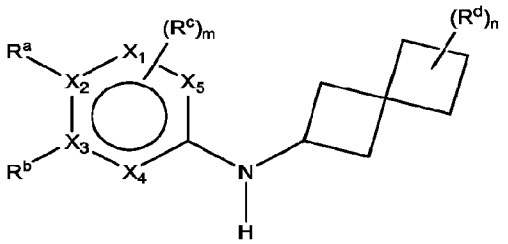
Formula IVb

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a

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pharmaceutically acceptable salt of the foregoing.

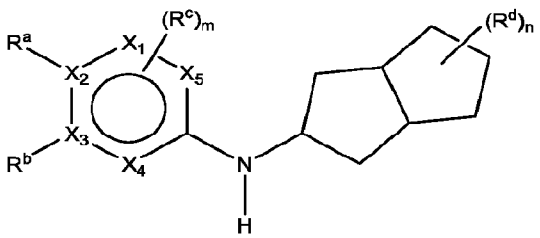
16. The compound of any one of technical solutions 1 and 12, wherein the compound has one of the following structural Formula IVc:



Formula IVc

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

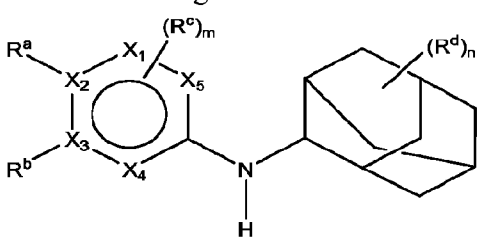
17. The compound of any one of technical solutions 1 and 12, wherein the compound has one of the following structural Formula IVd:



Formula IVd

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

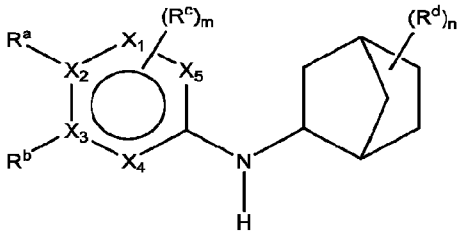
18. The compound of any one of technical solutions 1 and 12, wherein the compound has one of the following structural Formula IVe:



Formula IVe

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

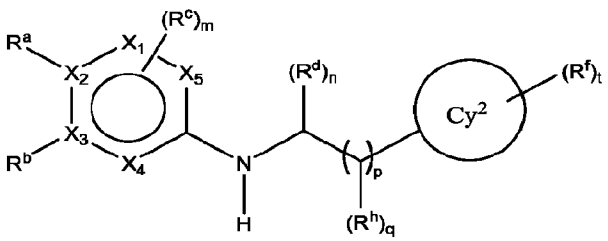
19. The compound of any one of technical solutions 1 and 12, wherein the compound has one of the following structural Formula IVf:



Formula IVf

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

20. The compound of any one of technical solutions 1 and 13, wherein the compound has one of the following structural Formula Va:

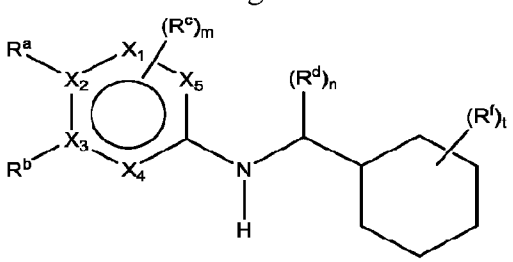


Formula Va

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Cy^2 is 3- to 10-membered cycloalkyl or 3- to 10-membered heterocyclyl; R^f, for each occurrence, is independently selected from halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; R^h, for each occurrence, is independently selected from halogen, CN, and optionally substituted C_1 to C_6 alkyl; n is an integer selected from 0, 1, and 2; p is an integer selected from 0, 1, 2, 3, 4, and 5; q is an integer selected from 0, 1, and 2; and t is an integer independently selected from 0, 1, 2, and 3.

21. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of technical solution 20, wherein n is 0, q is 0, and p is 0, 1, 2, and 3.

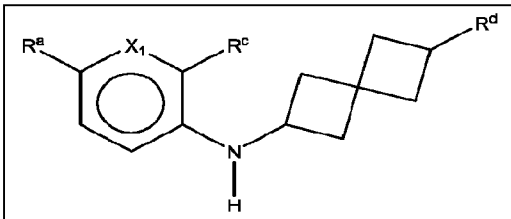
22. The compound of any one of technical solutions 1, 13, and 20, wherein the compound has one of the following structural Formula VIa:



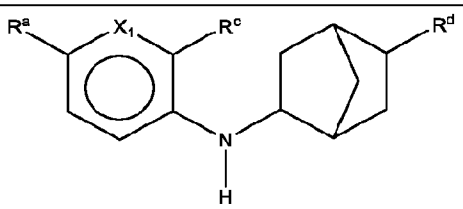
Formula VIa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

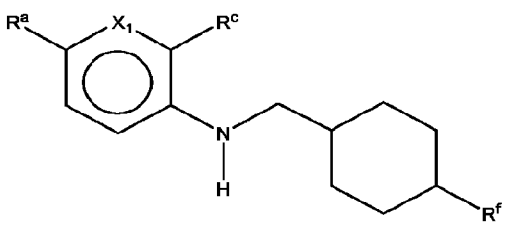
23. The compound of technical solution 1, wherein the compound has one of the following structural Formulae VIIa-VIIe:



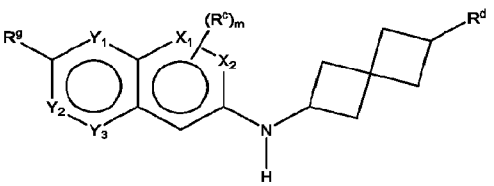
VIIa



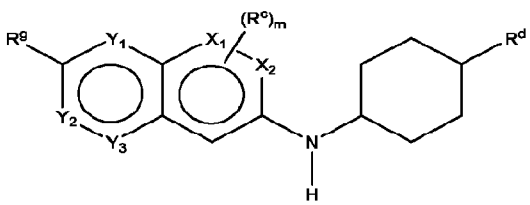
VIIb



VIIc



VIId

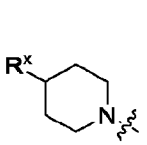
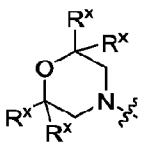
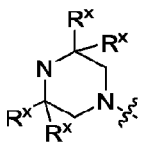


VIIe

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

X_1 and X_2 are independently C or N;

Y_1, Y_2, and Y_3 are independently C or N;

R^a is selected from  ,  , and  , wherein R^x, for each occurrence, is independently selected from H, CF_3, $-CH_3$, and $-CH_2CH_3$;

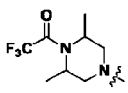
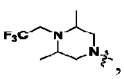
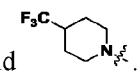
R^c is selected from halogen, C_1 to C_2 alkyl, and C_1 to C_2 alkoxy;

R^d is selected from NH_2 and $-C(=O)NH_2$;

R^f is selected from NH_2 and $-C(=O)NH_2$; and

m is 0 or 1.

24. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of technical solution 11, wherein R^e, for each occurrent, is independently selected from 5- to 6-membered cycloalkyl and 5- to 6-membered heterocyclyl, each independently substituted with 0, 1, 2, or 3 groups selected from C_1-C_6 alkyl optionally substituted with 1 to 4 groups selected from =O, and halogen.

25. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 11 and 24, wherein R^c, for each occurrence, is independently selected from  ,  ,  , and  .

26. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 20-22, wherein R^f, for each occurrence, is independently selected from H, halogen, cyano, C_1-C_{10} alkyl, phenyl, 5- to 7-membered heteroaryl, phenyl, 3- to 10-membered heterocyclyl, C_3-C_{10} cycloalkyl, -C(=O)R^s, C_2-C_{10} alkenyl, =O, =NR^p; -C(=O)OR^s, -C(=O)NR^pR^q, -NR^pR^q, and -NR^pC(=O)R^s, wherein

the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^f are each optionally substituted with 1 to 3 groups selected from 5- to 7-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, -OR^s, -C(=O)NR^pR^q, -NR^pC(=O)NR^qR^r, and -NR^pR^q;

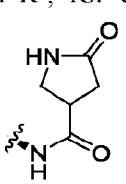
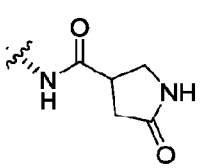
the 3- to 10-membered heterocyclyl and C_3-C_{10} cycloalkyl of R^f and the 3- to 10-membered heterocyclyl and C_3-C_6 cycloalkyl of the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^f, are each optionally substituted with 1 to 3 groups selected from =O and C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halogen and -OR^s;

the phenyl and 5- to 7-membered heteroaryl of R^f and the 5- to 7-membered heteroaryl of the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^f are each optionally substituted with 1 to 3 groups selected from C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halogen and -OR^s;

R^p, R^q, and R^r, for each occurrence, are independently selected from hydrogen, C_3-C_{10} cycloalkyl, and C_1-C_{10} alkyl, wherein the C_3-C_{10} cycloalkyl and C_1-C_{10} alkyl of R^p, R^q, and R^r are each optionally substituted with 1 to 3 groups selected from halogen, -OR^s and -C(=O)OR^s;

R^s, for each occurrence, is independently selected from H, NH_2, C_3-C_{10} cycloalkyl, 3- to 10- membered heterocyclyl, and C_1-C_{10} alkyl optionally substituted with 1 to 3 groups selected from halogen, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, and C_1-C_6 alkoxy, wherein

the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of R^s and the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of the C_1-C_{10} alkyl of R^s are each optionally substituted with 1 to 3 groups of C_1-C_6 alkyl optionally substituted by =O, and halogen, and the C_1-C_6 alkoxy of the C_1-C_{10} alkyl of R^s is optionally substituted with 1 to 3 groups of halogen.

27. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of 20-22 and 26, wherein R^f, for each occurrence, is selected from H, methyl, NH_2,-$NH(CH_2)_2OH$, -CH_2NH_2,  ,  , -NHC(=O)NH_2, -$NHCH_3$, -C(=O)NH_2, and -NHBoc.

28. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of

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any one of technical solutions 1-10, 12-22, and 26-27, wherein R^a is absent or selected from hydrogen, halogen, cyano, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_{10} cycloalkyl, 3- to 10- membered heterocyclyl, phenyl, 5- to 7- membered heteroaryl, $-C(=O)R^s$, $-C(=O)OR^s$, $-NR^pR^q$, $-OR^s$, wherein

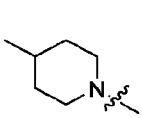
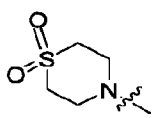
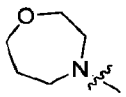
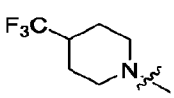
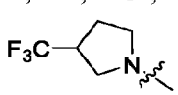
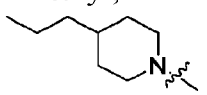
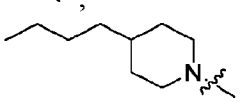
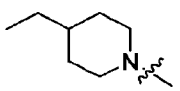
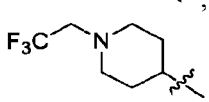
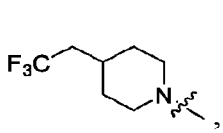
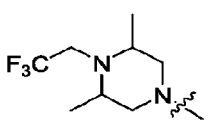
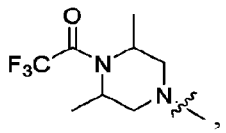
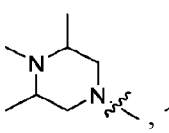
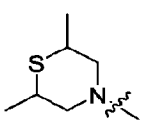
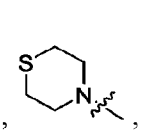
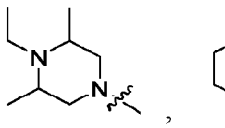
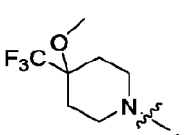
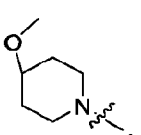
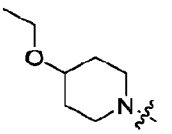
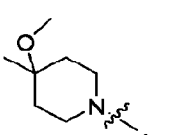
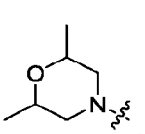
the C_3-C_{10} cycloalkyl, 3- to 10- membered heterocyclyl, phenyl, and 5- to 7- membered heteroaryl of R^a are each optionally substituted with 1-3 groups selected from halogen, =O, OR^s, and C_1-C_{10} alkyl optionally substituted with 1 to 3 groups selected from =O, OH, $-OR^s$, and halogen;

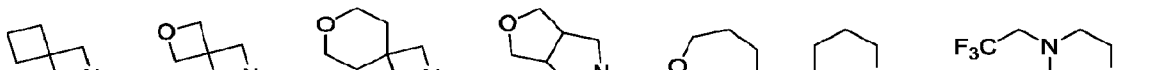
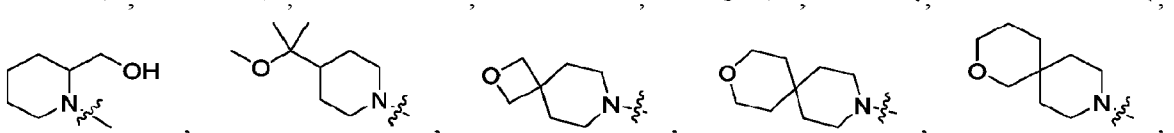
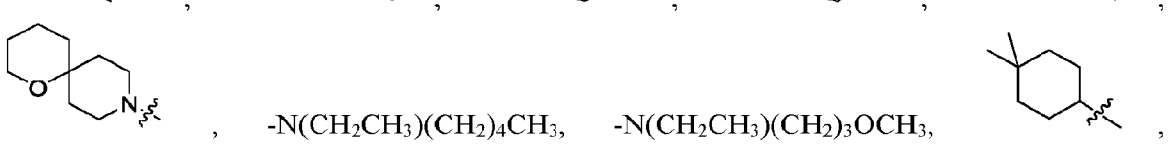
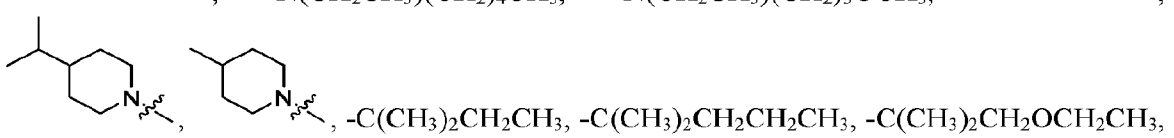
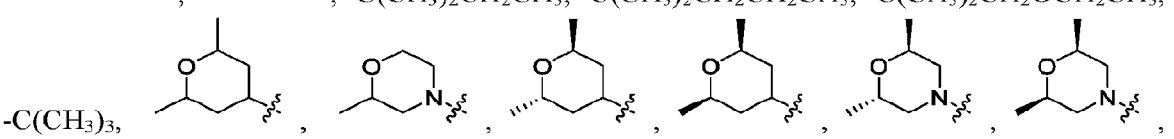
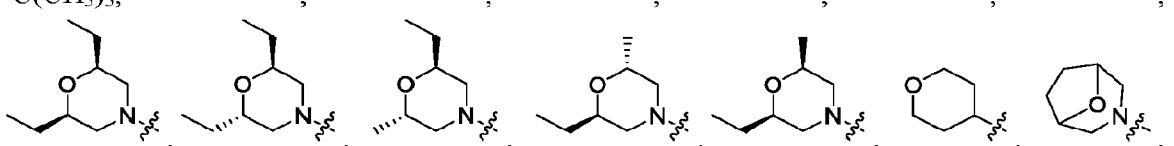
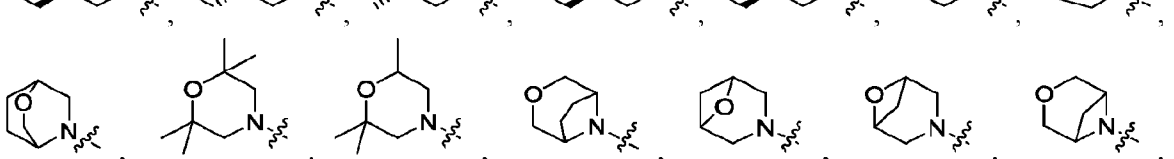
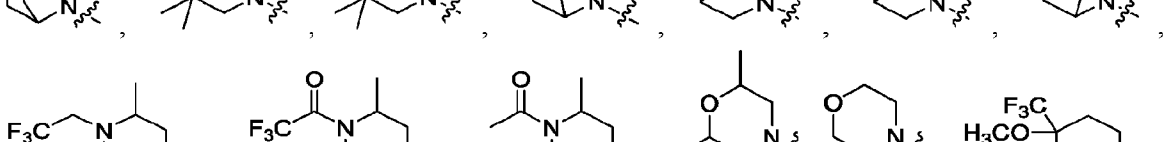
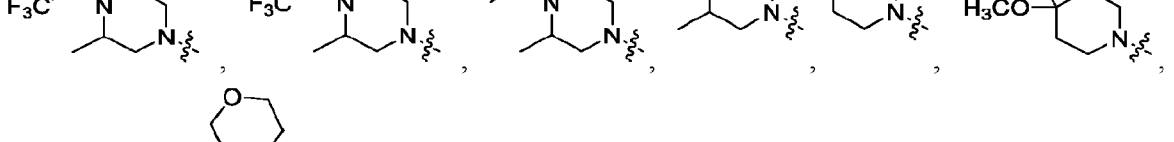
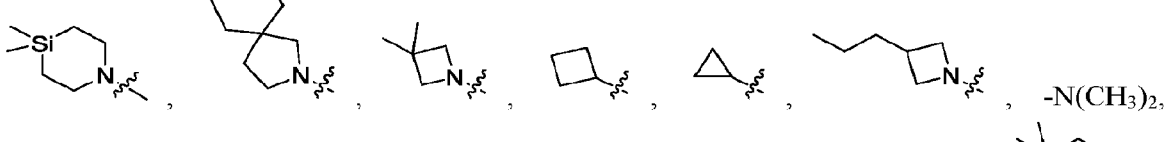
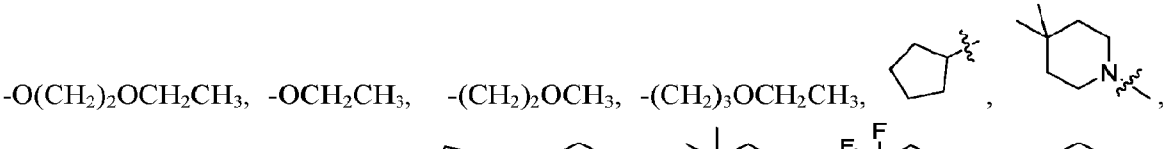
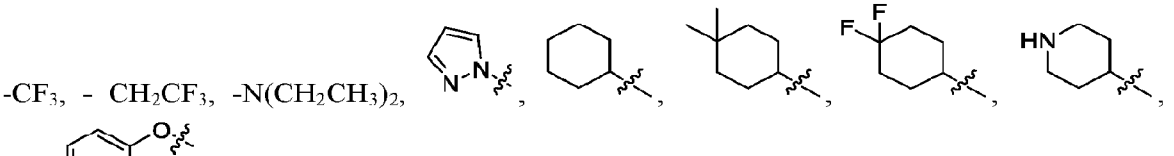
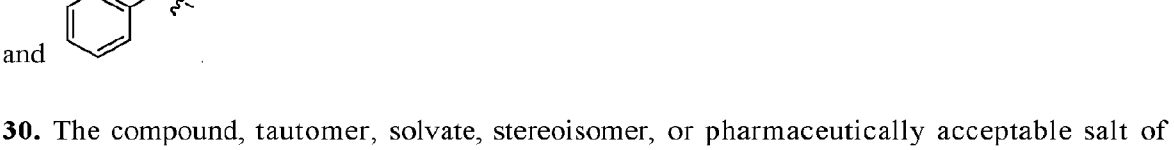
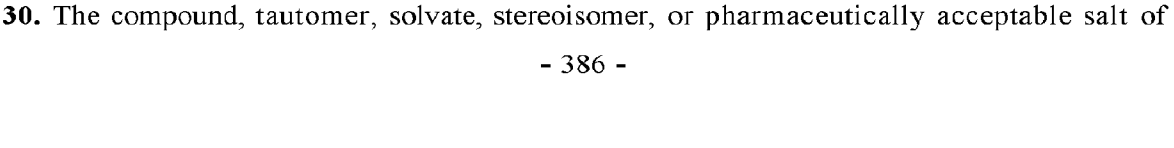
the C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl of R^a are each optionally substituted with 1 to 3 groups selected from halogen, 3- to 10- membered heterocyclyl, and $-OR^s$;

R^p and R^q, for each occurrence, are independently selected from hydrogen, C_3-C_{10} cycloalkyl, and C_1-C_{10} alkyl, wherein the C_3-C_{10} cycloalkyl and C_1-C_{10} alkyl of R^p and R^q are each optionally substituted with 1 to 3 groups selected from halogen, $-OR^s$ and $-C(=O)OR^s$;

R^s, for each occurrence, is selected from H, NH_2, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, 5- to 6-membered aryl, and C_1-C_{10} alkyl optionally substituted with 1 to 3 groups selected from halogen, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, and C_1-C_6 alkoxy, wherein the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of R^s and the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of the C_1-C_{10} alkyl of R^s are each optionally substituted with 1 to 3 groups of C_1-C_6 alkyl optionally substituted with =O, and halogen, and the C_1-C_6 alkoxy of the C_1-C_{10} alkyl of R^s is optionally substituted with 1 to 3 groups of halogen.

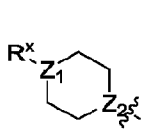
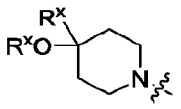
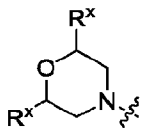
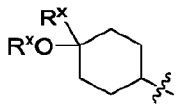
29. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-10, 12-22, and 26-28, wherein R^a is absent or selected from

H, F, Cl, Br, methyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , , , , , , -$CH(CH_2CH_3)_2$, -$CH(CH_3)_2$, -$OCH(CH_3)_2$, -CH_2CH_3, -$CH_2CH_2CH_3$, -$NHCH_2CF_3$, -$N(CH_3)CH_2CF_3$, -$O(CH_2)_3CH_3$, -$O(CH_2)_2CH_3$, -$(CH_2)_2CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_3CH_3$,  ,  ,  ,  ,  ,

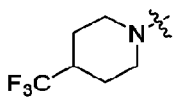















30. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of

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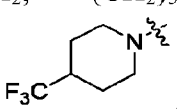
any one of technical solutions 1-10, 12-22, and 26-28, wherein R^a is selected from  ,  ,  ,  ,  , $-OR^x$, and $-CH_2R^x$, wherein Z_1 and Z_2 are independently selected from C and N, R^x, for each occurrence, is independently selected from C_1 to C_4 alkyl optionally substituted with 1 to 3 groups of halogen.

31. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-10, 12-22, and 26-30, wherein R^b is absent or selected from is H, halogen, C_1 to C_6 alkyl, $-NR^pR^q$, CN, C_1-C_6 alkoxy, and 5- to 6- membered heterocyclyl optionally substituted with C_1-C_3 alkyl optionally substituted with 1 to 3 groups selected from halogen, wherein R^p and R^q are each selected from C_1 to C_6 alkyl, and wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy of R^b and the C_1-C_6 alkyl of R^p and R^q are each optionally substituted with 1 to 3 groups selected from halogen , $-OR^s$, and $-NH_2$.

32. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-10, 12-22, and 26-31, wherein R^b absent or is H, methyl, ethyl , $-O(CH_2)_4OCH_3$, $-O(CH_2)_3OCH_3$, $-O(CH_2)_2OCH_3$, $-O(CH_2)_2NH_2$, $-(CH_2)_5CH_3$, $-O(CH_2)_5CH_3$, $-(CH_2)_2OCH_3$, $-O(CH_2)_2OH$, F, $-OCH_3$, $-CF_3$, Cl, CN, $-C(CH_3)_3$, and  .

33. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-10, 12-22, and 26-31, wherein R^b is absent or selected from halogen, C_1-C_2 alkyl, and C_1-C_2 alkoxy.

34. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-22 and 24-33, wherein R^c, for each occurrence, is independently selected from halogen, C_1-C_6 alkyl, $-NR^pR^q$, CN, and C_1-C_6 alkoxy, wherein R^p and R^q are each selected from C_1 to C_6 alkyl, and wherein the C_1-C_6 alkyl and C_1-C_6 alkoxy of R^b and the C_1-C_6 alkyl of R^p and R^q are each optionally substituted with 1 to 3 groups selected from halogen, $-OR^s$, and $-NH_2$.

35. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-22 and 24-34, wherein R^c is selected from methyl, ethyl, $-O(CH_2)_4OCH_3$, $-O(CH_2)_3OCH_3$, $-O(CH_2)_2OCH_3$, $-O(CH_2)_2NH_2$, $-(CH_2)_5CH_3$, $-O(CH_2)_5CH_3$, $-(CH_2)_2OCH_3$, $-O(CH_2)_2OH$, F, $-OCH_3$, $-CF_3$, Cl, CN,  , and $-C(CH_3)_3$.

36. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-22 and 24-34, wherein R^c is selected from halogen, C_1-C_2 alkyl, and C_1-C_2 alkoxy.

37. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-22 and 24-36, wherein R^d, for each occurrence, is absent or

independently selected from halogen, -OH, cyano, C_1-C_{10} alkyl, phenyl, 5- to 7-membered heteroaryl, phenyl, 3- to 10-membered heterocyclyl, C_3-C_{10} cycloalkyl, $-C(=O)R^s$, $-SO_2R^s$, C_2-C_{10} alkenyl, =O, $=NR^p$; $-C(=O)OR^s$, $-C(=O)NR^pR^q$, $-NR^pR^q$, $-NR^pC(=O)R^s$, and $-NR^pSO_2R^s$, wherein

the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^d are each optionally substituted with 1 to 3 groups selected from 5- to 7-membered heteroaryl, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, $-OR^s$, $-C(=O)NR^pR^q$, $NR^pC(=O)R^s$, $-NR^pC(=NH)R^s$, $-NR^pC(=O)NR^qR^r$, and $-NR^pR^q$;

the 3- to 10-membered heterocyclyl and C_3-C_{10} cycloalkyl of R^d and the 3- to 10-membered heterocyclyl and C_3-C_6 cycloalkyl of the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^d, are each optionally substituted with 1 to 3 groups selected from =O, $-NR^pR^q$, $NR^pC(=O)R^s$, and C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halogen and $-OR^s$;

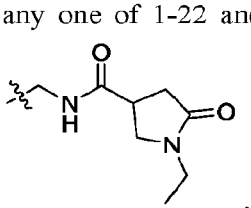
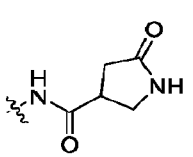
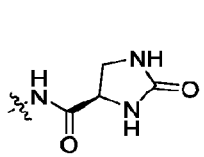
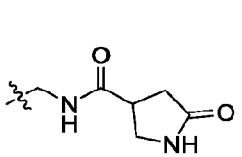
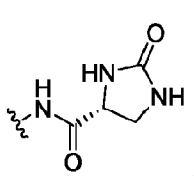
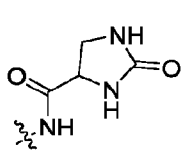
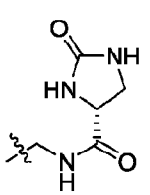
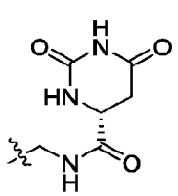
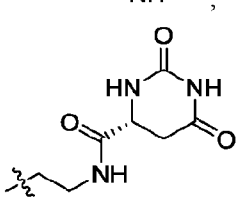
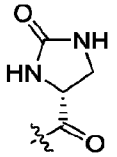
the phenyl and 5- to 7-membered heteroaryl of R^d and the 5- to 7-membered heteroaryl of the C_1-C_{10} alkyl and C_2-C_{10} alkenyl of R^d are each optionally substituted with 1 to 3 groups selected from C_1-C_6 alkyl optionally substituted with 1 to 3 groups selected from halogen and $-OR^s$;

R^p, R^q, and R^r, for each occurrence, are independently selected from hydrogen, -OH, C_3-C_{10} cycloalkyl, 5- to 7-membered heteroaryl, 5- to 6-membered aryl, and C_1-C_{10} alkyl, wherein the C_3-C_{10} cycloalkyl, 5- to 7-membered heteroaryl, 5- to 6-membered aryl, and C_1-C_{10} alkyl of R^p, R^q, and R^r are each optionally substituted with 1 to 3 groups selected from halogen, C_1-C_6 alkyl, $-OR^s$ and $-C(=O)OR^s$;

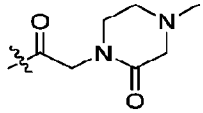
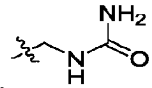
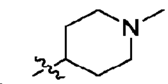
R^s, for each occurrence, is independently selected from H, $-NH_2$, C_3-C_{10} cycloalkyl, 3- to 10- membered heterocyclyl, and C_1-C_{10} alkyl optionally substituted with 1 to 3 groups selected from halogen, =O, NH_2, C_3-C_{10} cycloalkyl, 3- to 10-membered heterocyclyl, and C_1-C_6 alkoxy, wherein

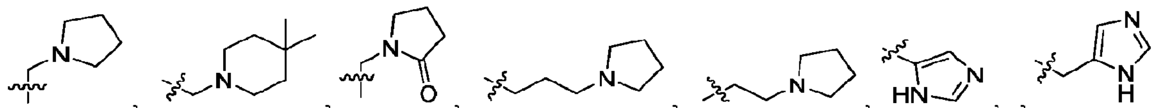
the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of R^s and the C_3-C_{10} cycloalkyl and 3- to 10-membered heterocyclyl of the C_1-C_{10} alkyl of R^s are each optionally substituted with 1 to 3 groups selected from =O and C_1-C_6 alkyl optionally substituted by halogen, and the C_1-C_6 alkoxy of the C_1-C_{10} alkyl of R^s is optionally substituted with 1 to 3 groups of halogen.

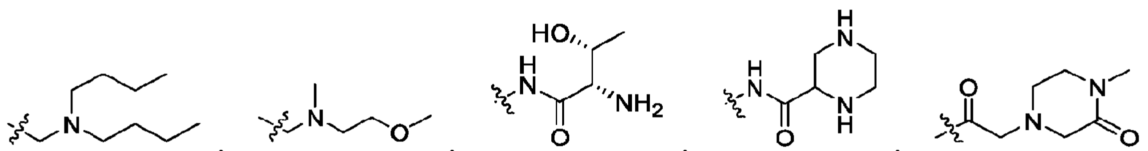
38. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of 1-22 and 24-37, wherein R^d, for each occurrence, is absent or selected from

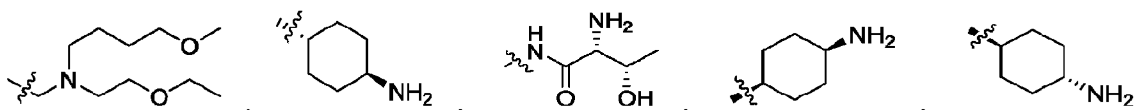

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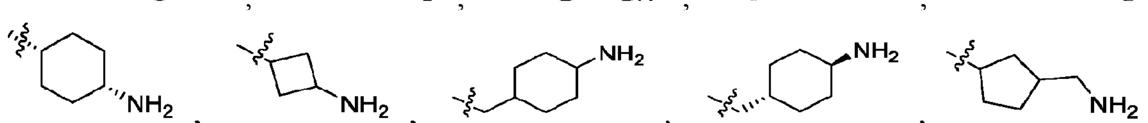
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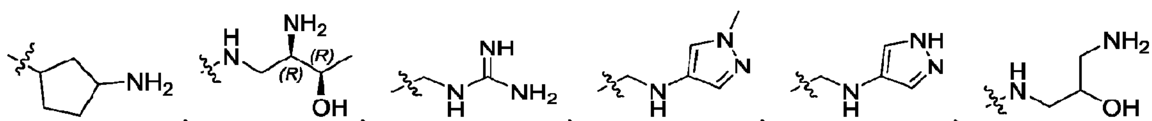
 ,  , F, methyl, ethyl, propyl, butyl, $-(CH_2)_3NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2N^{-}(CH_3)_3$, $-(CH_2)_3N(CH_3)_2$, $-(CH_2)_3NH_2$, $-(CH_2)_5NH_2$, $-(CH_2)_4NH_2$, $-CH_2CH_2NH_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CHCH_3NH_2$, $-C(CH_3)_2NH_2$, $-CH_2NH(CH_2)_2OH$, $-(CH_2)_2NHC(=O)NH_2$, $-CH_2OCH_2CH_2NH_2$, $-CH_2CH_2OH$, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2CH_2CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2OCH_2CH_2OH$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_3$, $-C(=O)NHNH_2$, $-C(=O)NHOH$, $-CH_2OH$, OH, $-O(CH_2)_2N(CH_3)_2$, =O, $-C(=O)OCH_3$, $-C(=O)OH$, $-C(=O)NH_2$, $-NH_2$, $-NHC(=O)CH_3$, $-NHC(=O)NH_2$, $-NH(CH_2)_2OH$, $-NH(CH_2)_3OH$, $-NH(CH_2)_4OH$, $-NH(CH_2)_3NH_2$, $-NH(CH_2)_2NH_2$, $-NHCH_2CH_2N(CH_3)_2$, $-NHCH_2CF_3$, $-NHCH_2CH_2F$, $-NHCH_2CHF_2$, $-NHCH_2CH_3$, $-NHCH_2CH_2OCH_3$, $-N(CH_3)_2$, $-NHCH_3$, -NHOH, $-NHSO_2NH_2$, $-SO_2NH_2$,  ,

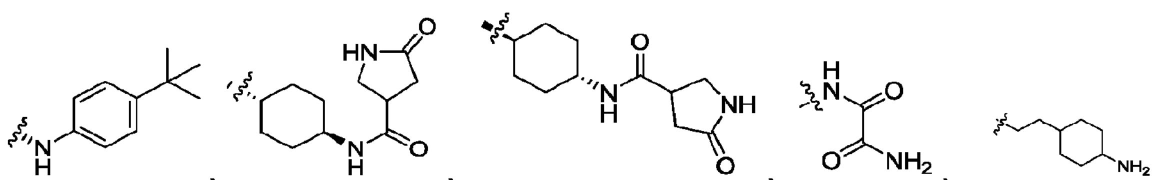


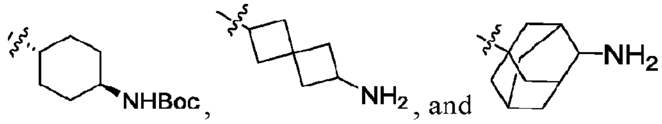










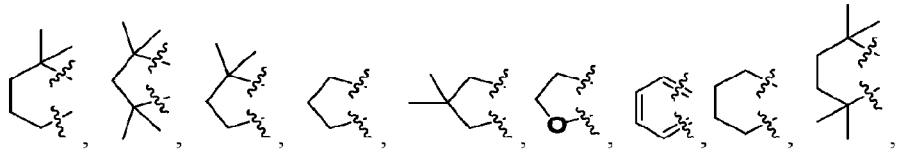


39. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of 1-22 and 24-37, wherein R^d is selected from $-C(=O)NR^pR^q$, and C_1-C_6 alkyl, wherein the C_1-C_6 alkyl is optionally substituted with 1 to 3 groups selected from C_1-C_3 alkoxy, $-C(=O)NR^pR^q$, and $-NR^pR^q$, wherein R^p and R^q are each selected from H and

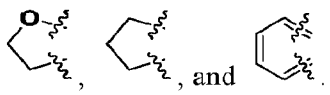
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C_1-C_3 alkyl.

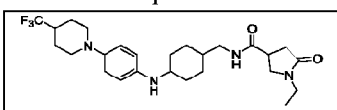
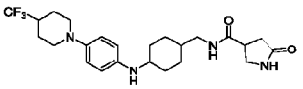
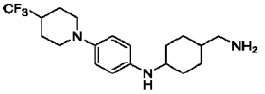
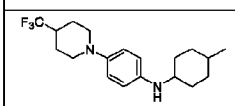
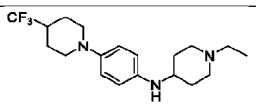
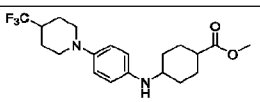
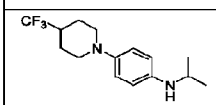
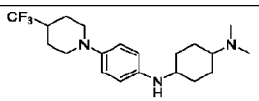
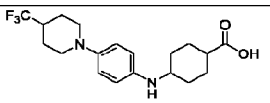
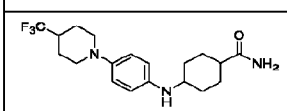
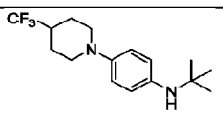
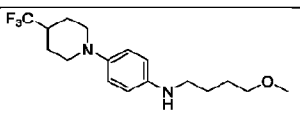
40. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-10 and 12-22, wherein R^a and R^b join to form a 5- to 6-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring optionally substituted with 1 to 4 groups selected from optionally substituted C_1-C_6 alkyl.

41. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of technical solutions 1-10, 12-22, and 40, wherein R^a and R^b join to form a structure selected from:  , and  .

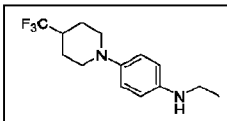
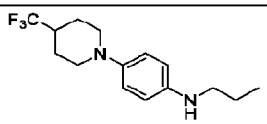
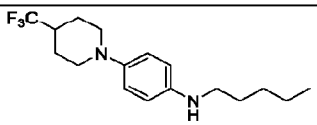
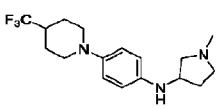
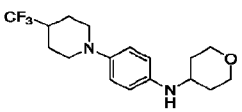
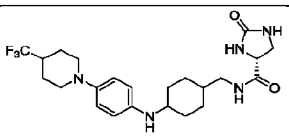
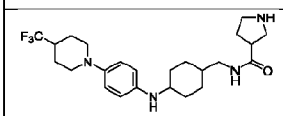
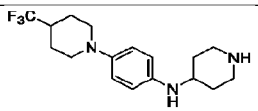
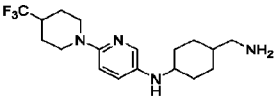
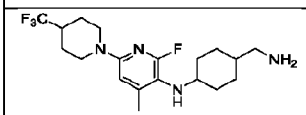
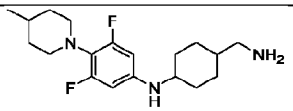
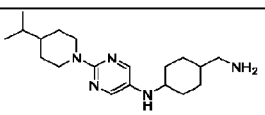
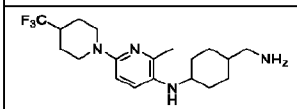
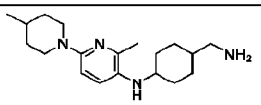
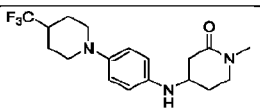
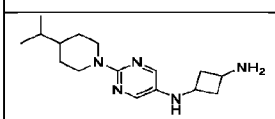
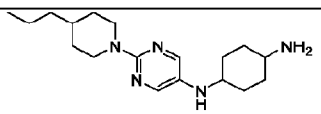
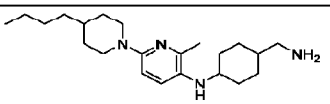
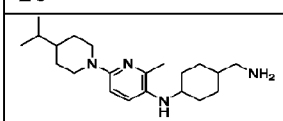
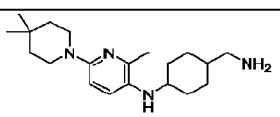
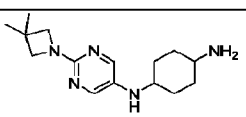
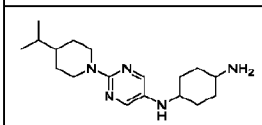
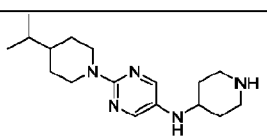
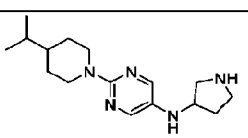
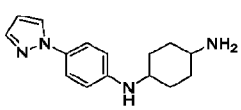
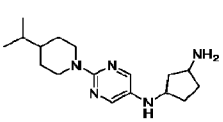
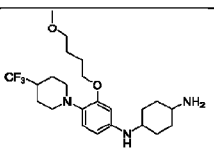
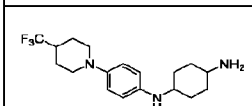
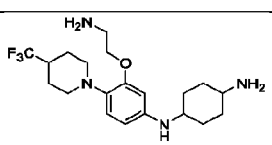
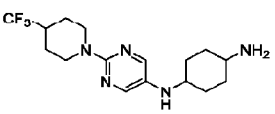
42. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of 1-10 and 12-22, wherein R^b and R^c join to form a 5- to 6-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring optionally substituted with 1 to 4 groups selected from optionally substituted C_1-C_6 alkyl.

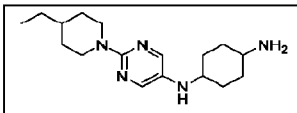
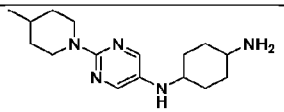
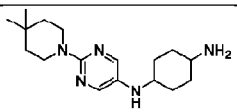
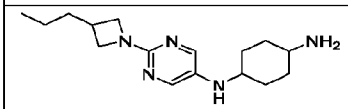
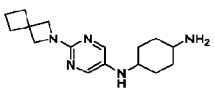
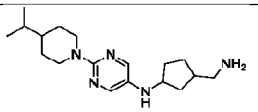
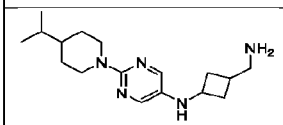
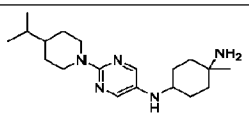
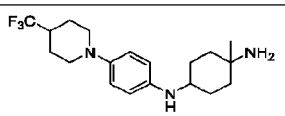
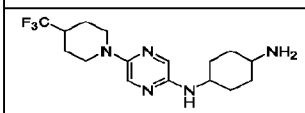
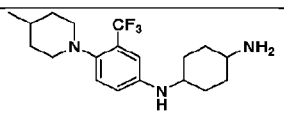
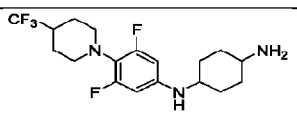
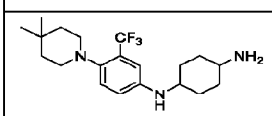
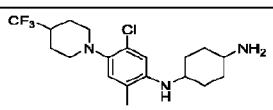
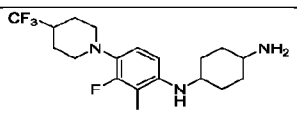
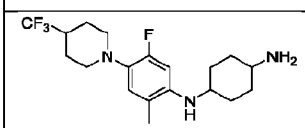
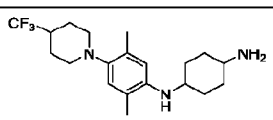
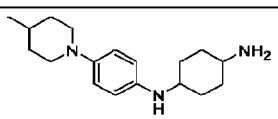
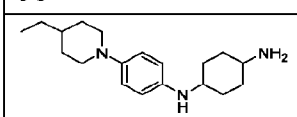
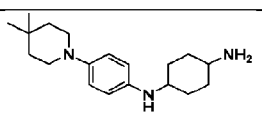
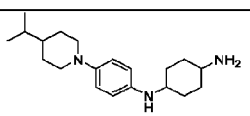
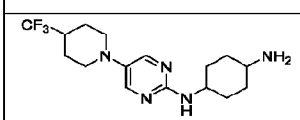
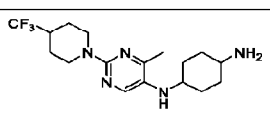
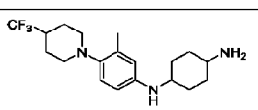
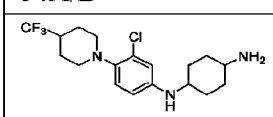
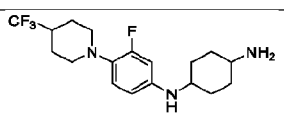
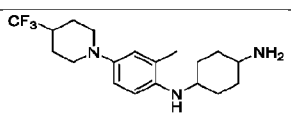
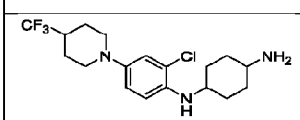
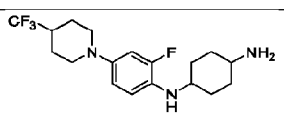
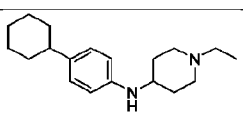
43. The compound, tautomer, solvate, stereoisomer, or pharmaceutically acceptable salt of any one of 1-10, 12-22, and 42, wherein R^b and R^c join to form a structure selected from:  .

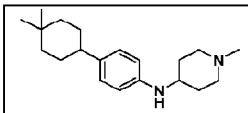
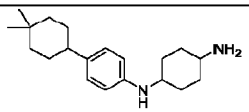
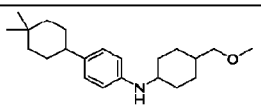
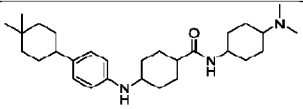
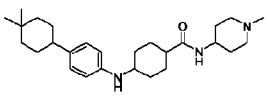
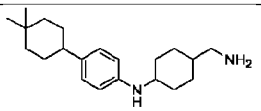
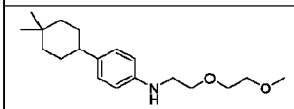
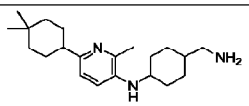
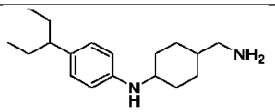
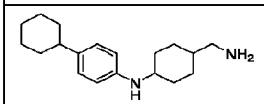
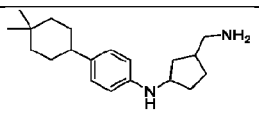
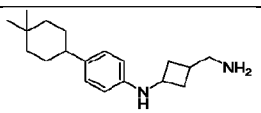
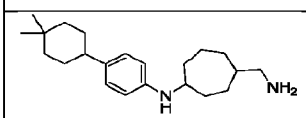
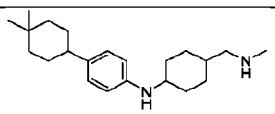
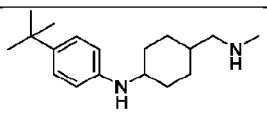
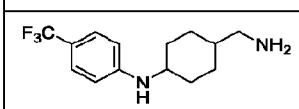
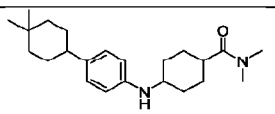
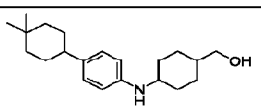
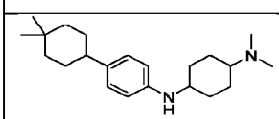
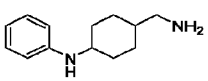
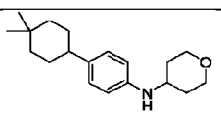
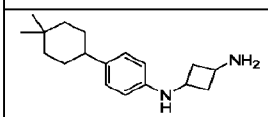
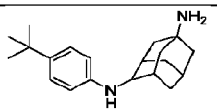
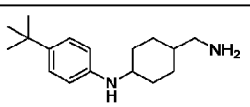
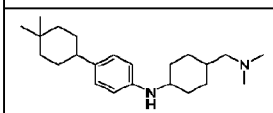
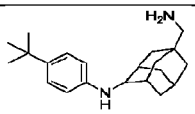
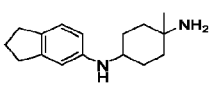
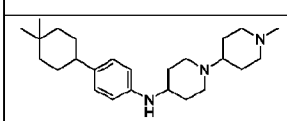
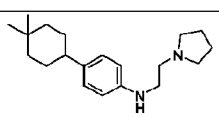
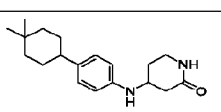
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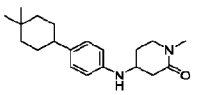
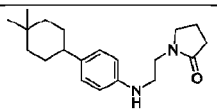
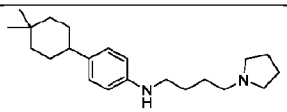
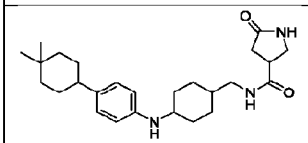
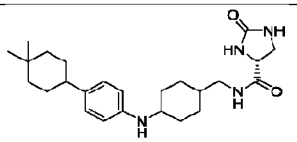
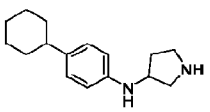
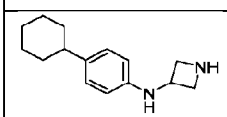
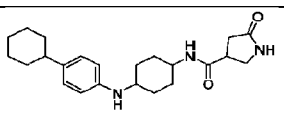
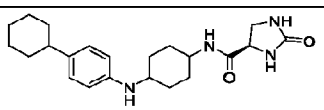
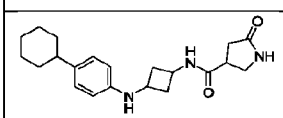
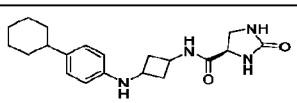
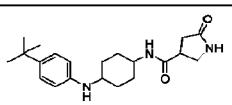
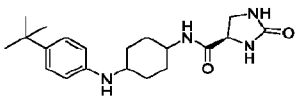
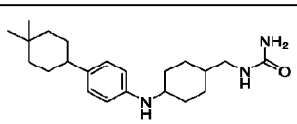
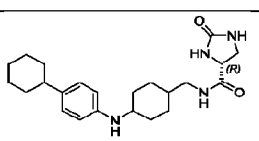
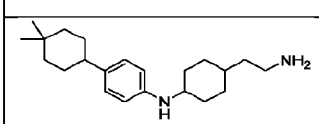
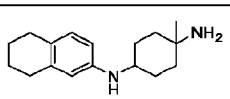
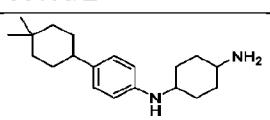
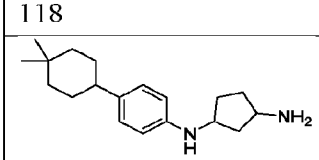
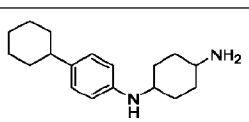
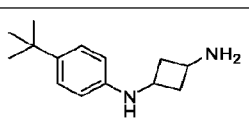
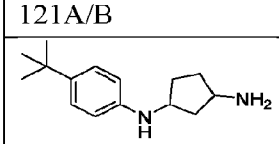
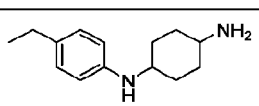
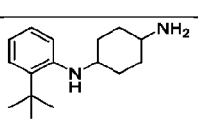
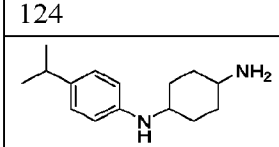
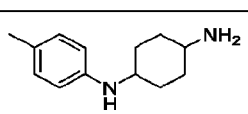
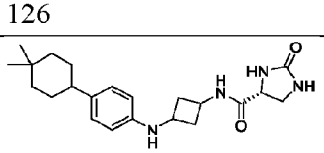
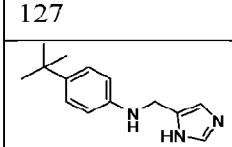
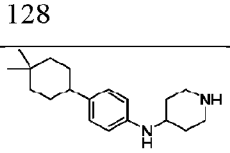
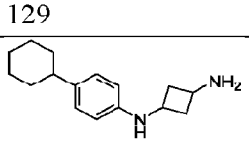
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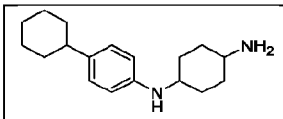
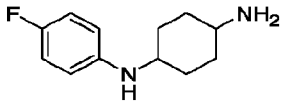
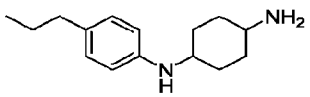
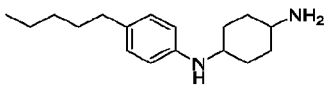
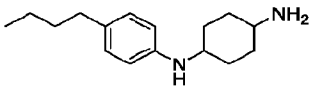
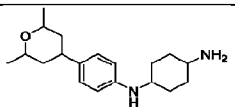
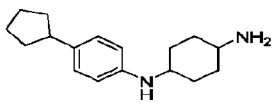
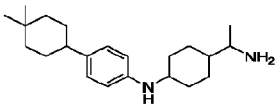
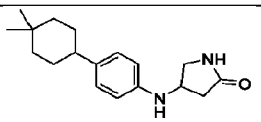
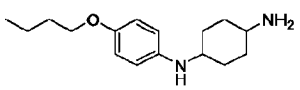
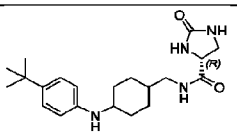
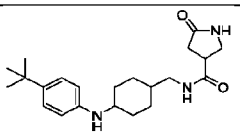
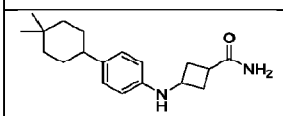
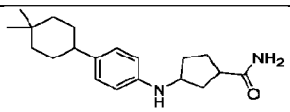
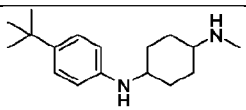
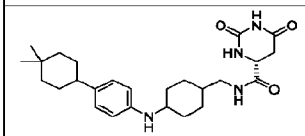
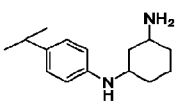
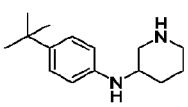
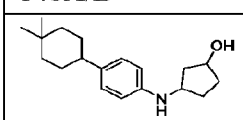
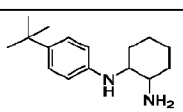
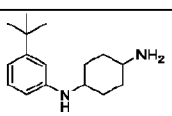
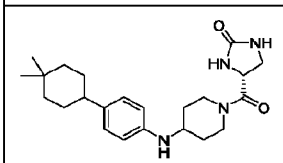
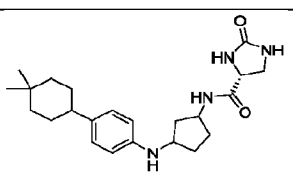
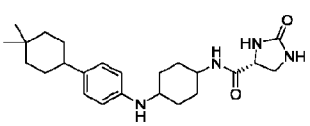
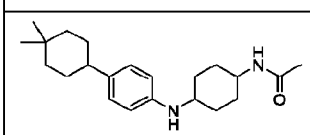
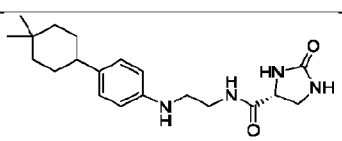
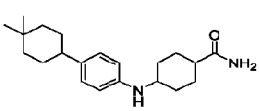
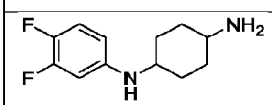
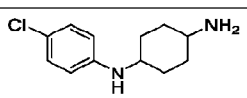
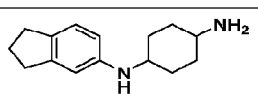
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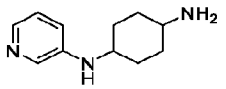
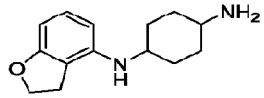
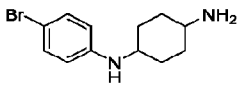
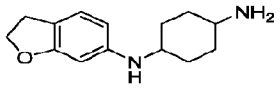
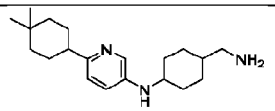
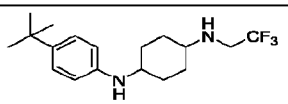
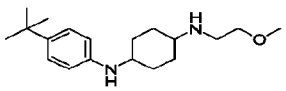
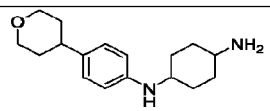
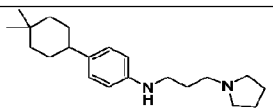
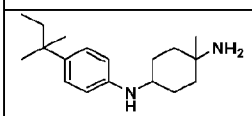
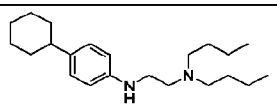
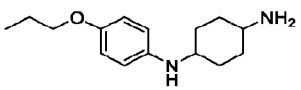
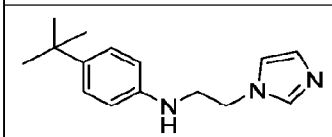
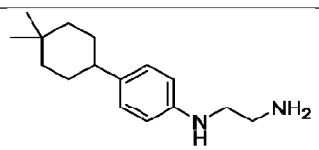
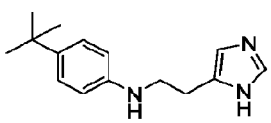
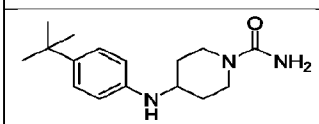
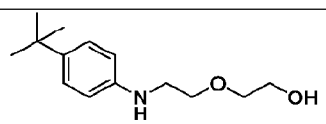
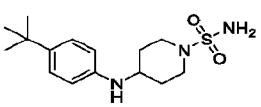
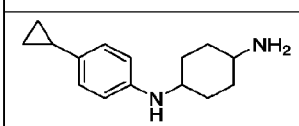
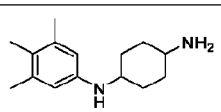
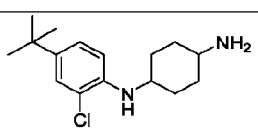
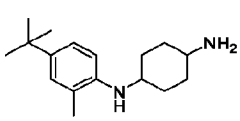
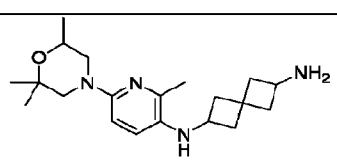
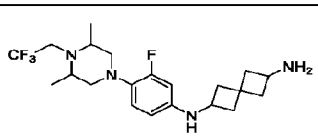
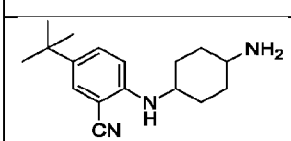
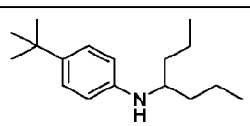
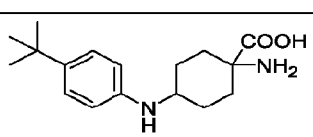
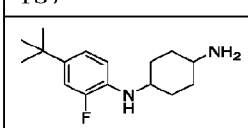
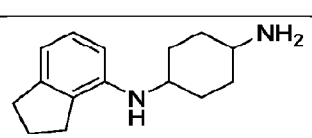
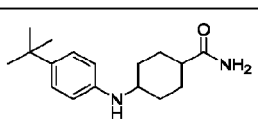
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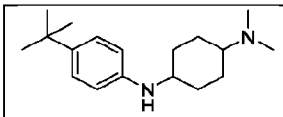
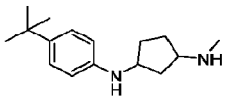
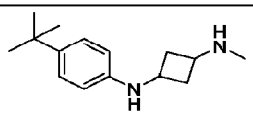
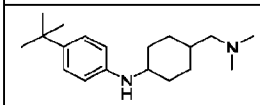
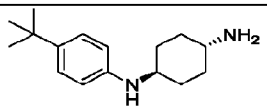
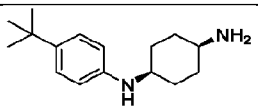
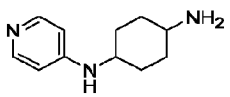
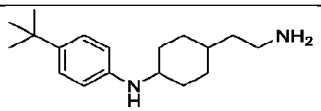
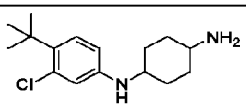
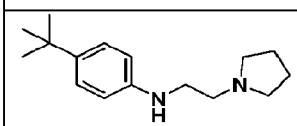
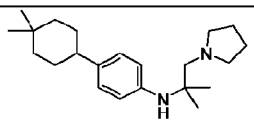
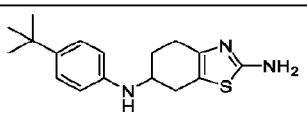
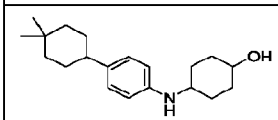
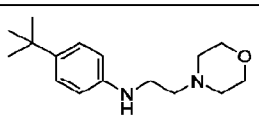
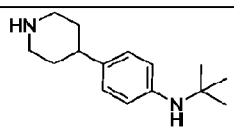
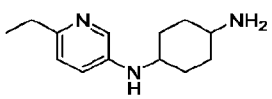
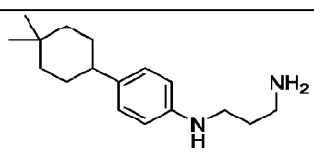
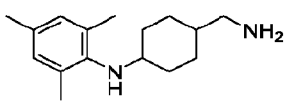
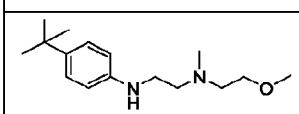
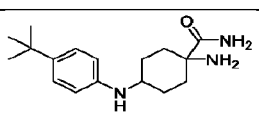
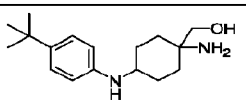
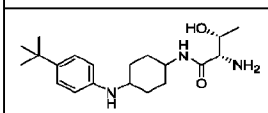
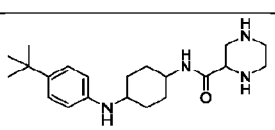
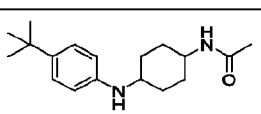
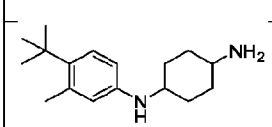
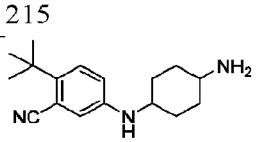
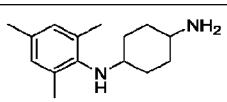
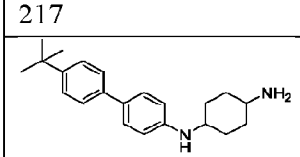
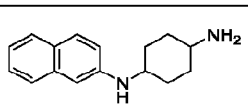
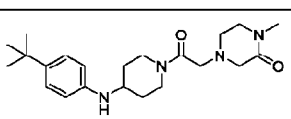
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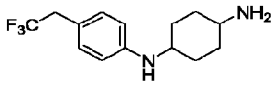
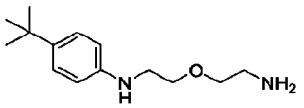
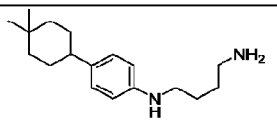
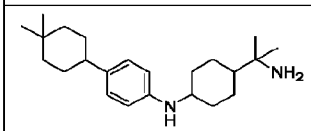
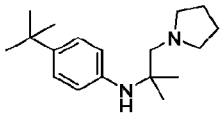
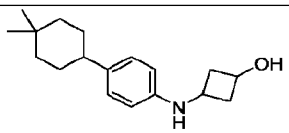
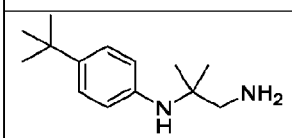
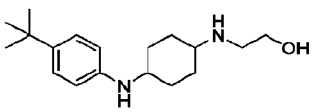
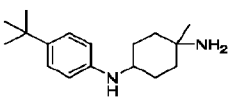
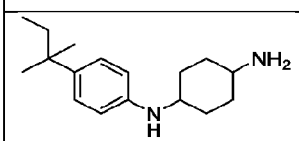
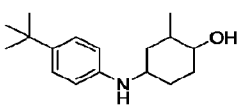
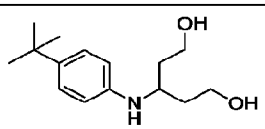
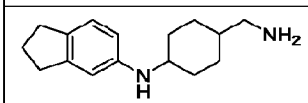
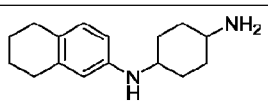
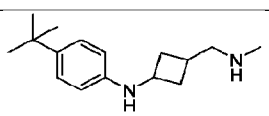
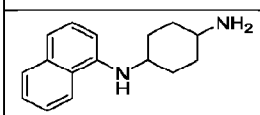
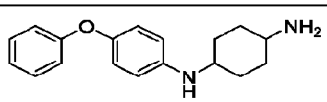
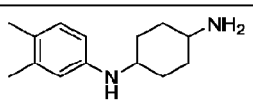
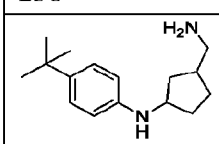
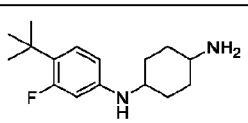
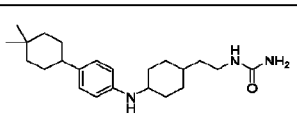
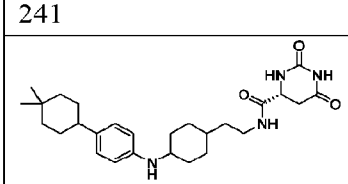
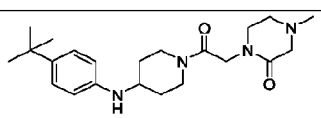
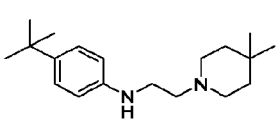
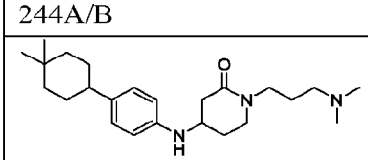
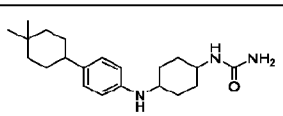
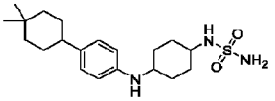
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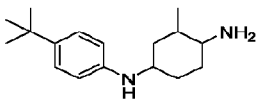
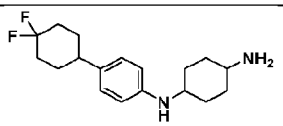
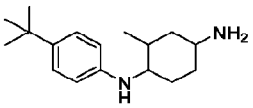
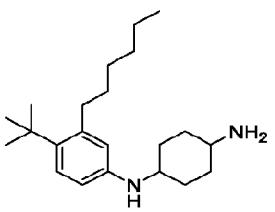
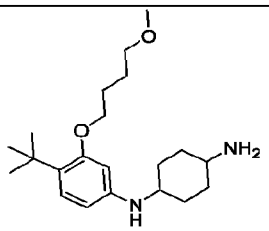
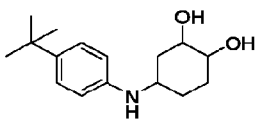
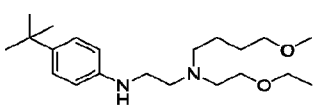
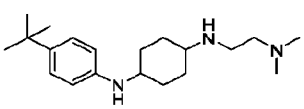
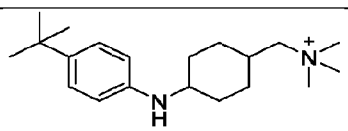
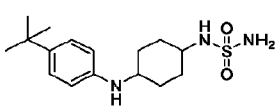
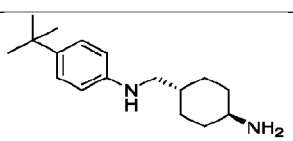
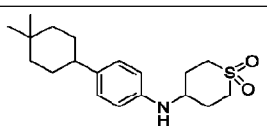
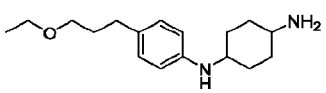
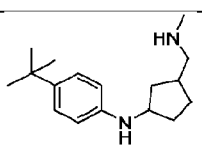
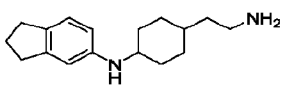
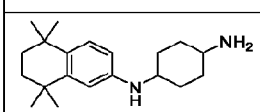
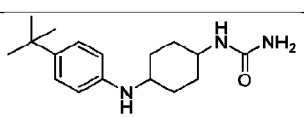
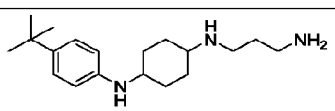
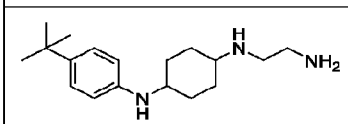
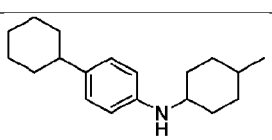
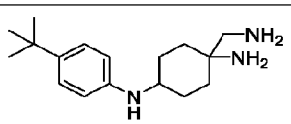
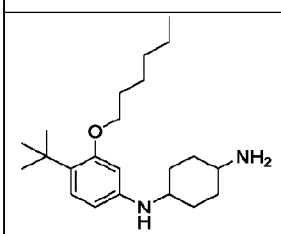
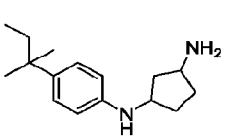
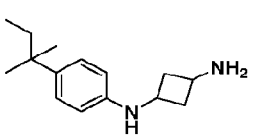
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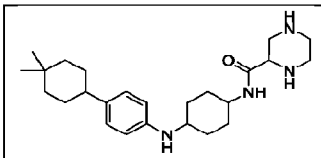
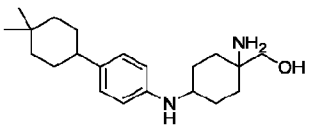
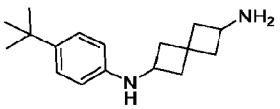
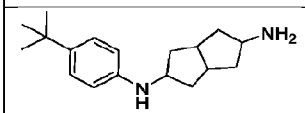
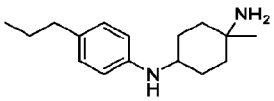
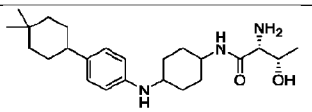
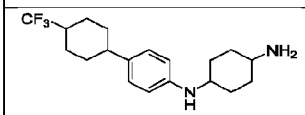
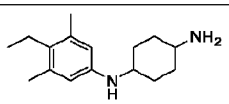
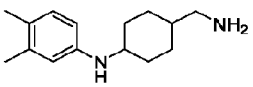
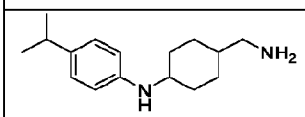
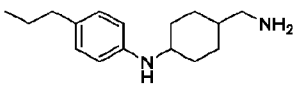
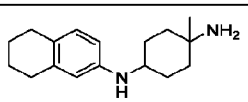
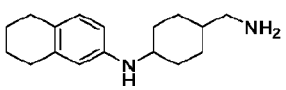
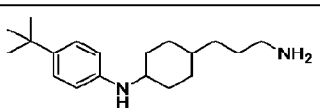
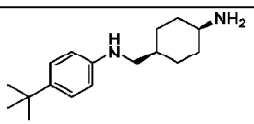
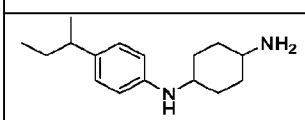
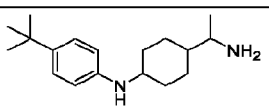
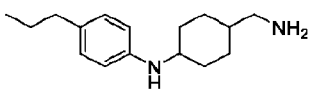
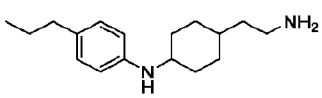
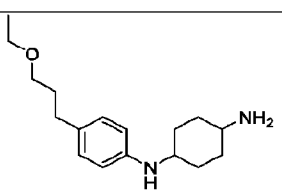
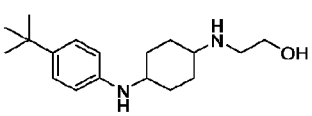
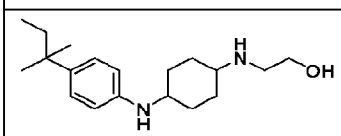
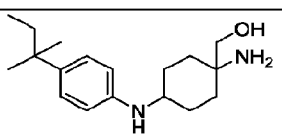
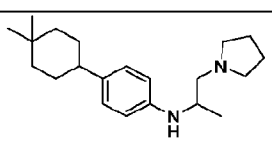
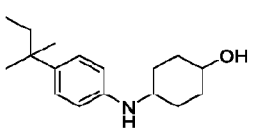
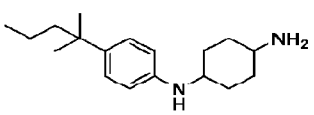
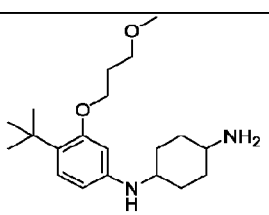
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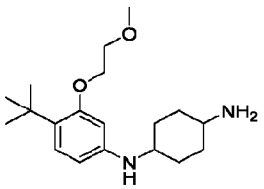
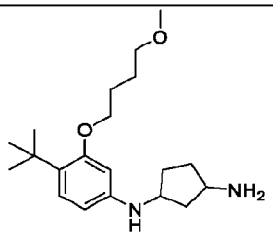
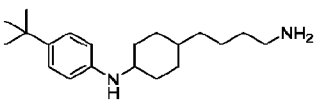
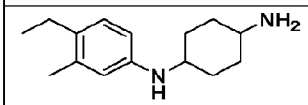
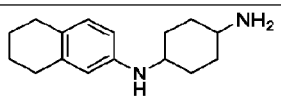
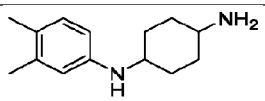
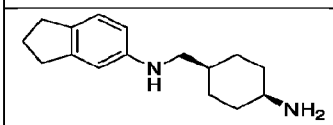
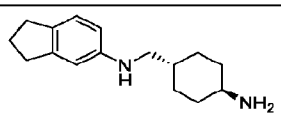
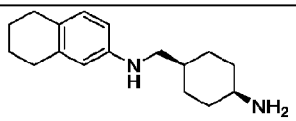
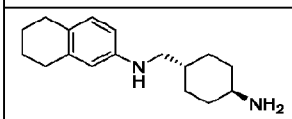
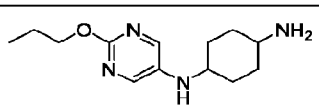
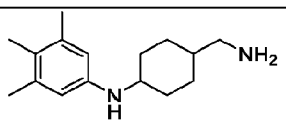
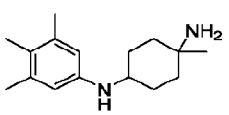
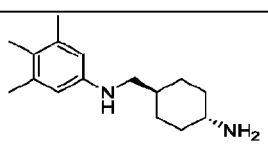
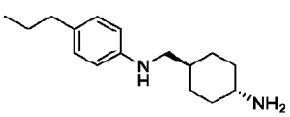
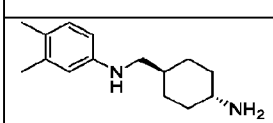
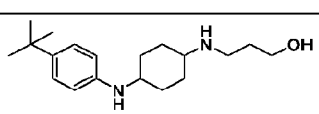
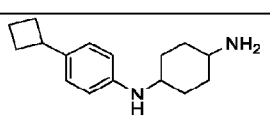
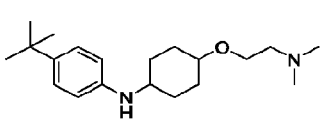
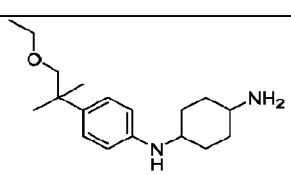
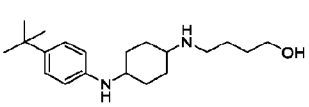
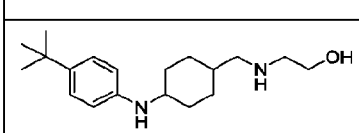
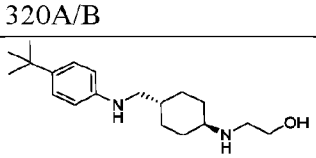
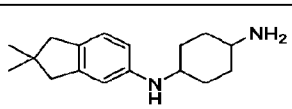
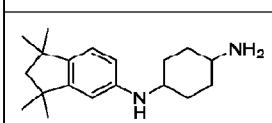
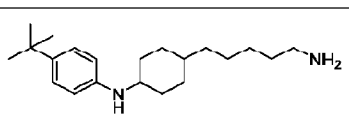
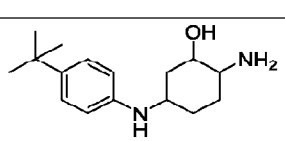
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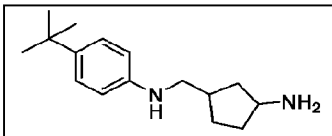
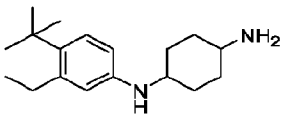
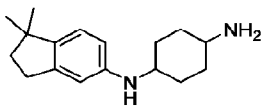
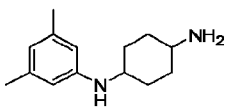
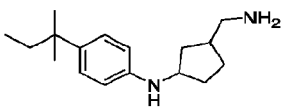
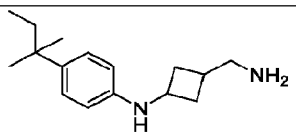
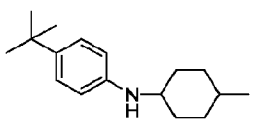
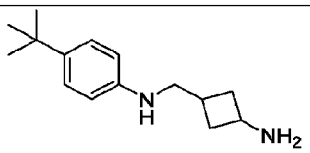
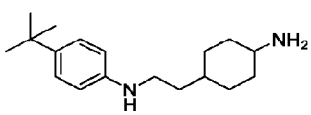
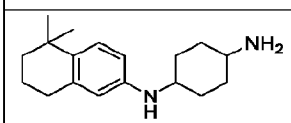
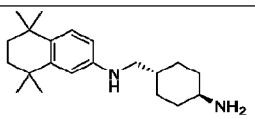
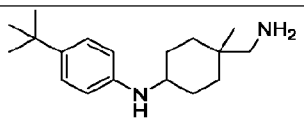
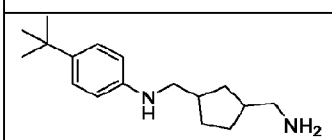
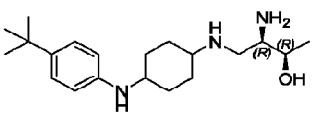
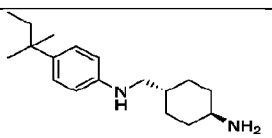
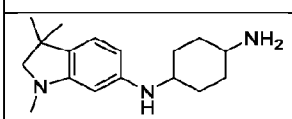
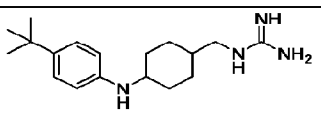
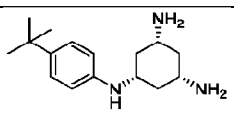
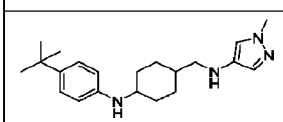
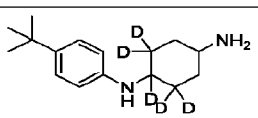
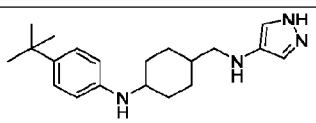
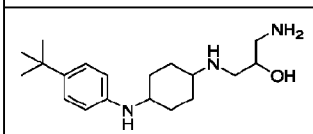
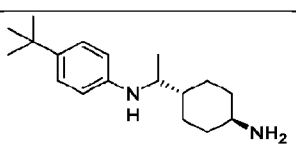
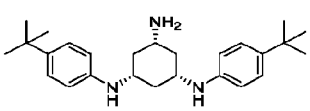
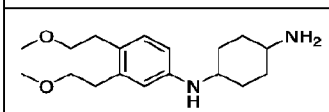
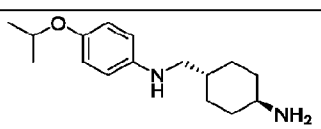
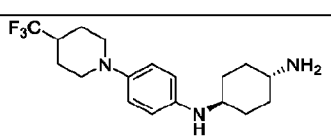
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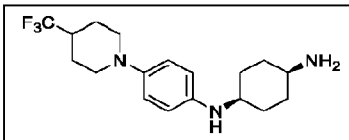
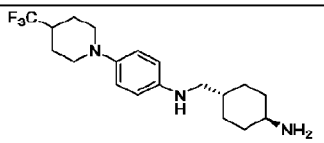
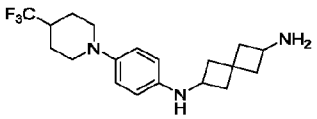
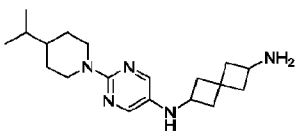
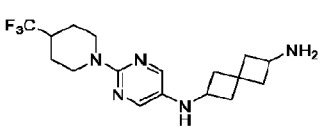
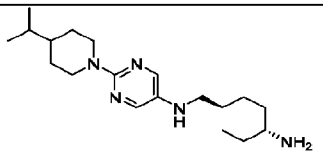
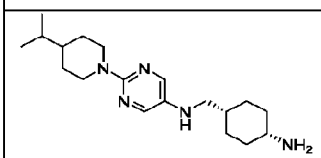
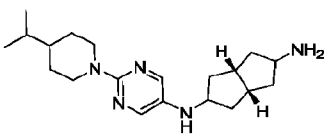
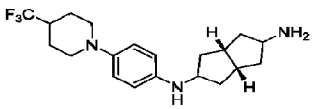
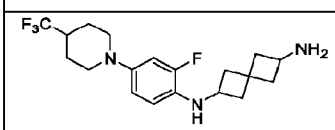
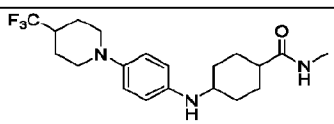
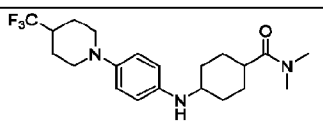
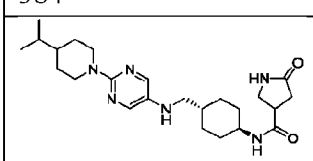
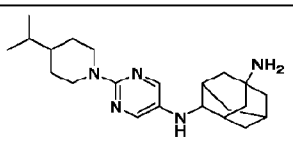
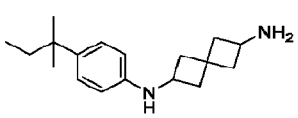
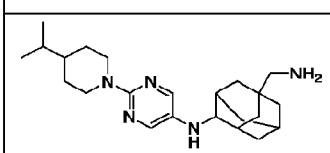
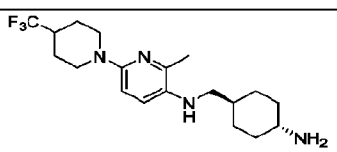
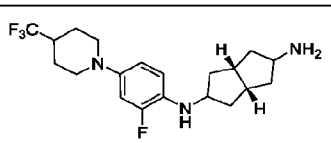
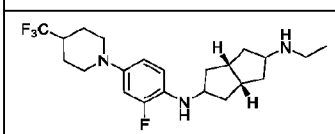
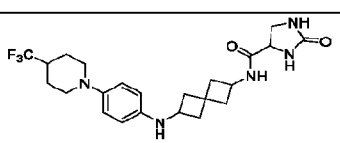
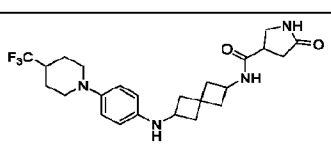
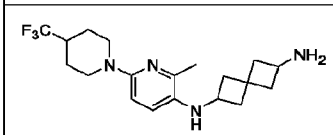
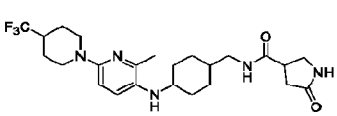
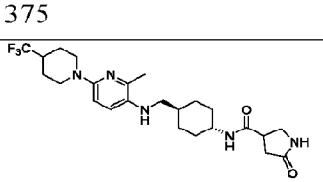
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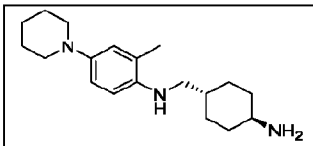
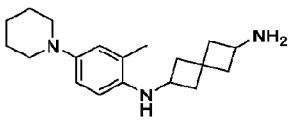
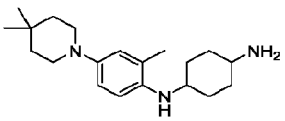
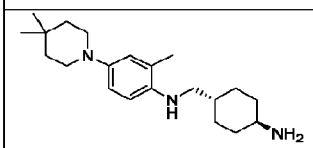
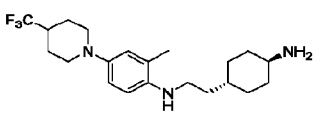
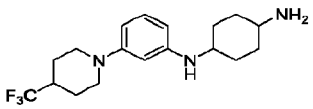
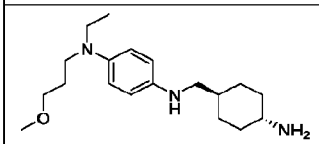
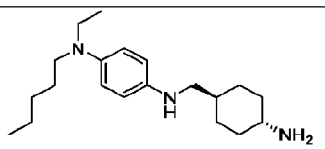
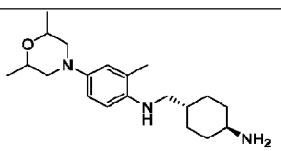
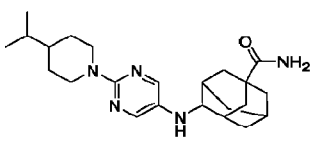
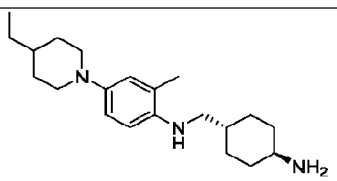
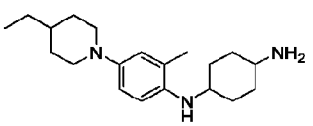
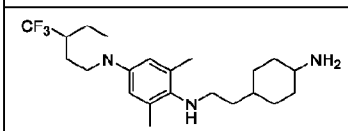
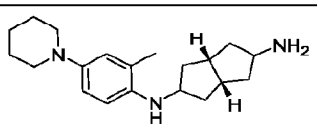
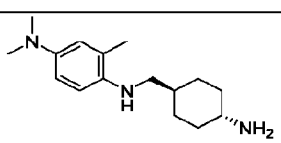
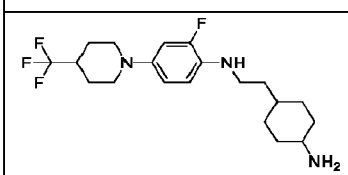
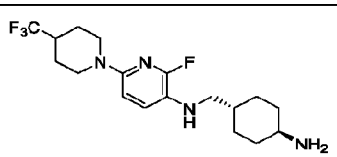
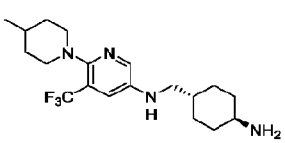
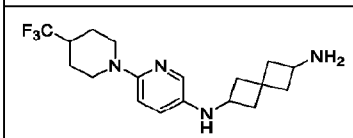
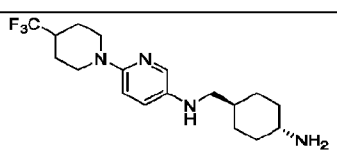
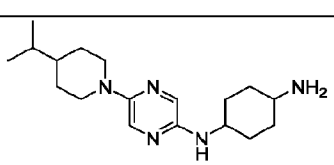
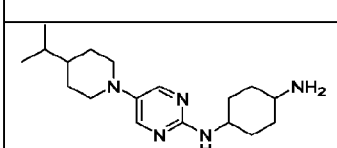
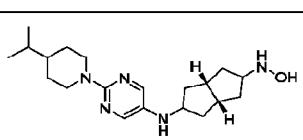
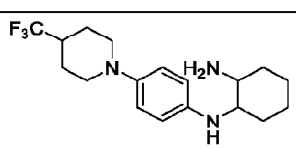
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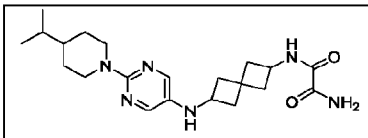
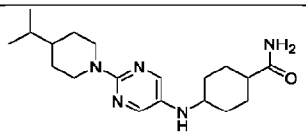
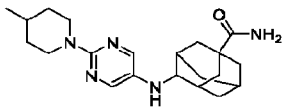
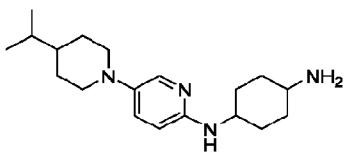
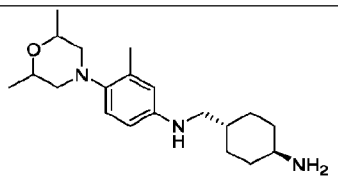
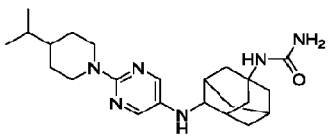
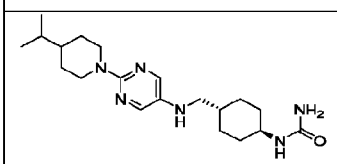
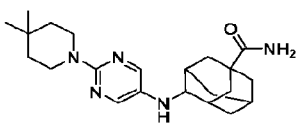
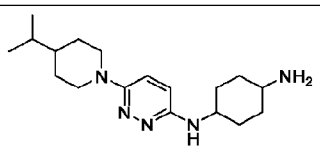
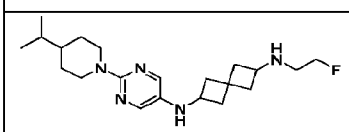
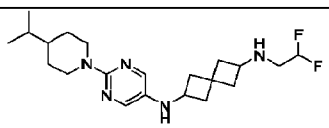
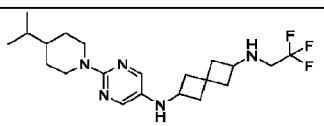
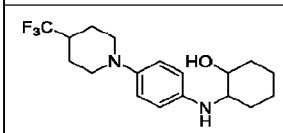
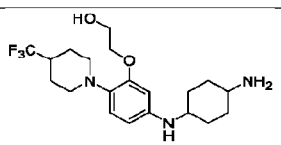
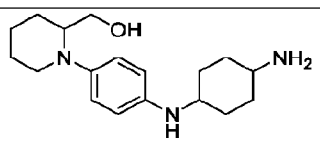
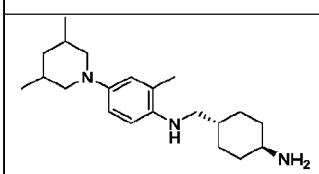
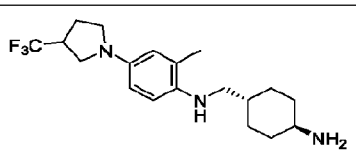
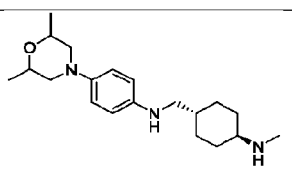
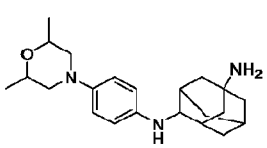
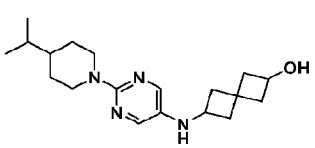
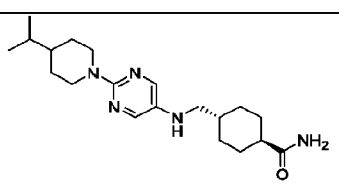
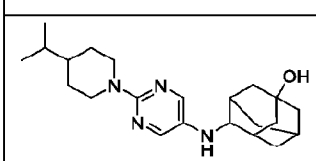
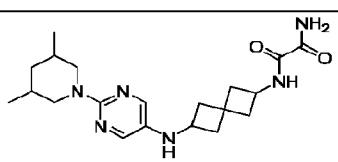
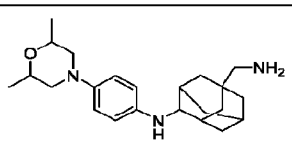
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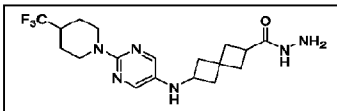
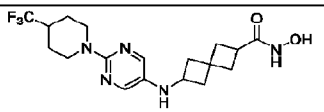
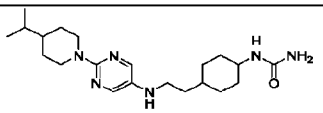
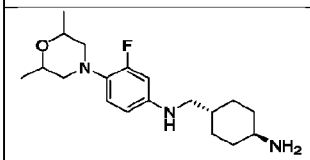
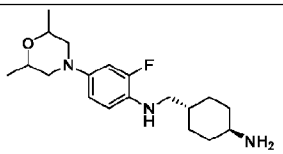
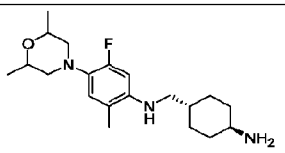
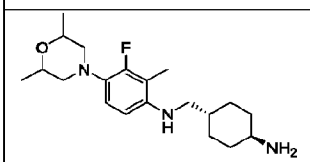
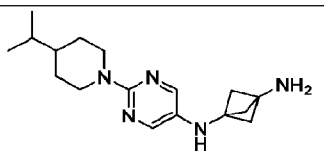
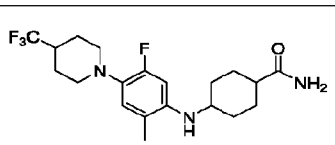
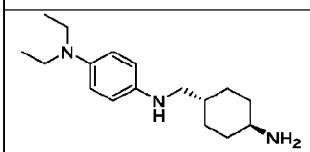
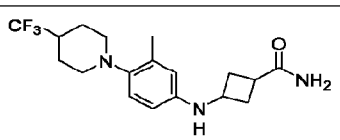
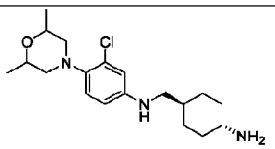
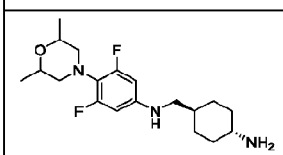
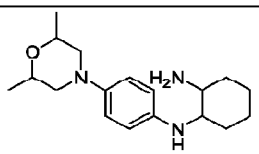
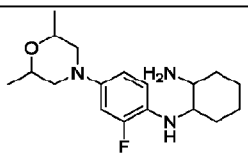
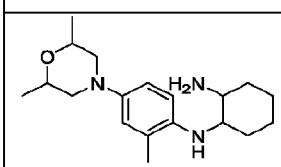
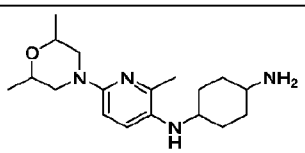
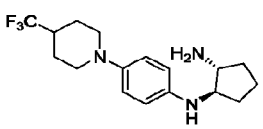
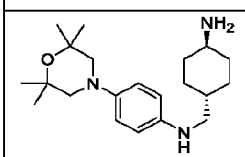
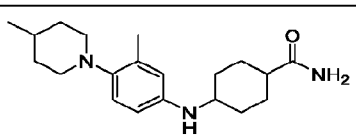
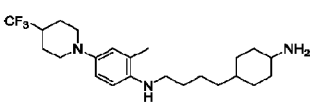
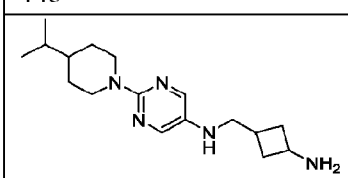
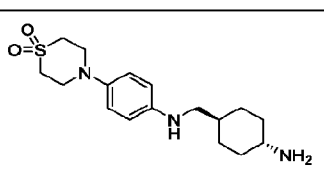
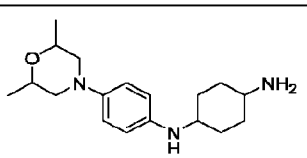
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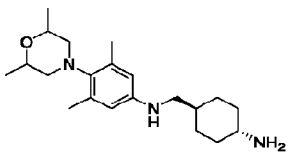
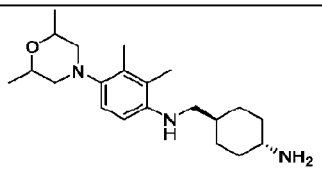
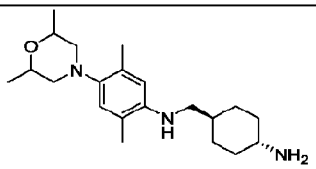
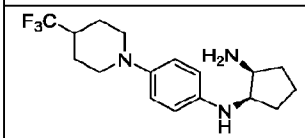
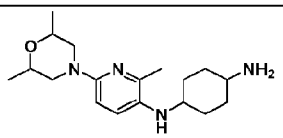
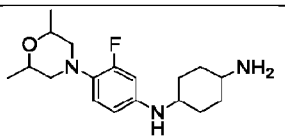
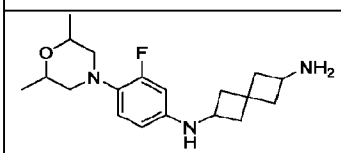
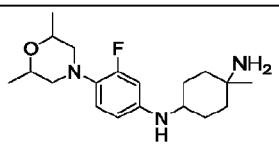
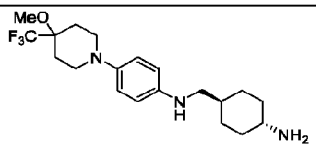
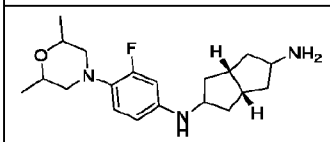
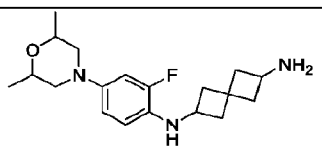
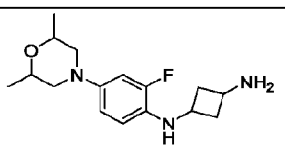
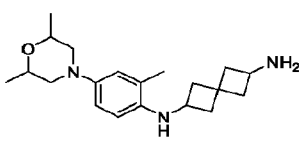
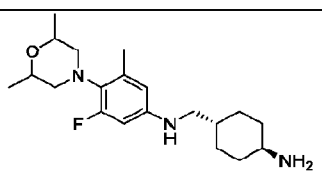
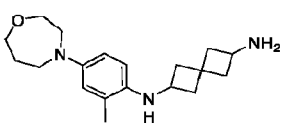
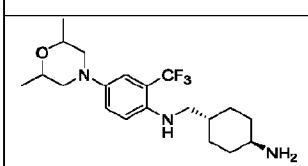
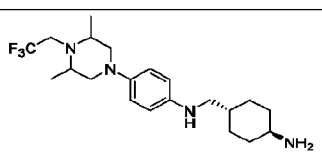
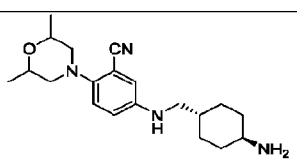
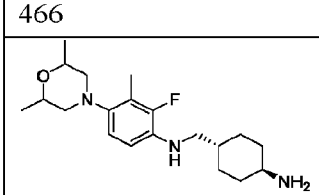
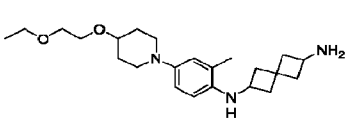
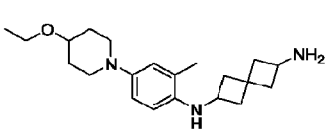
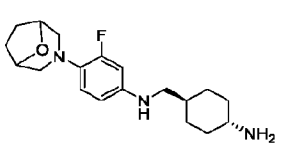
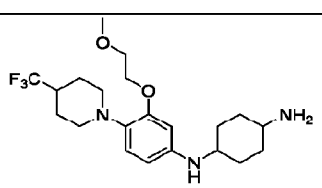
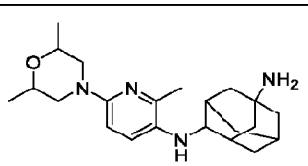
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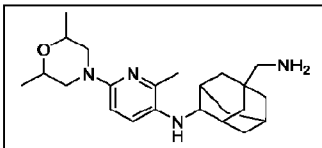
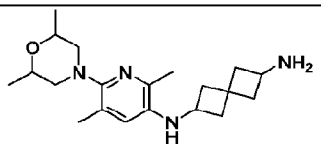
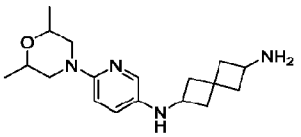
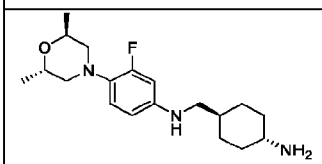
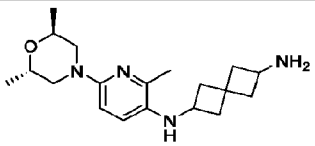
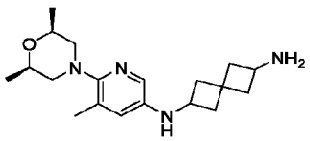
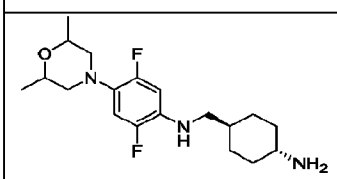
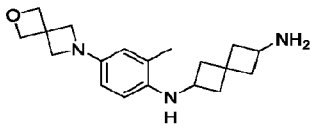
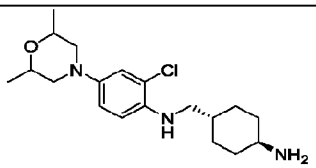
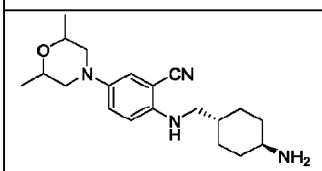
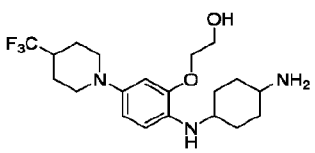
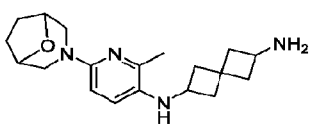
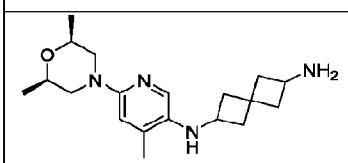
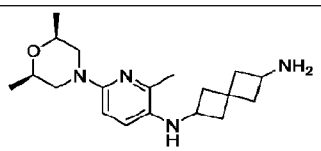
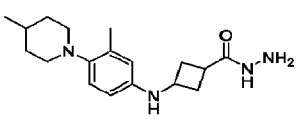
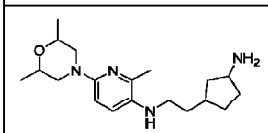
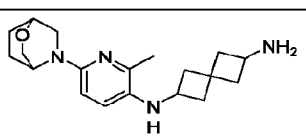
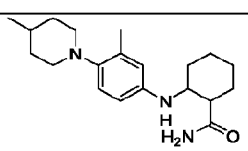
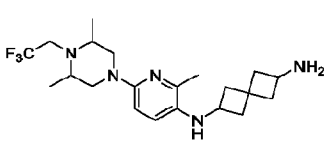
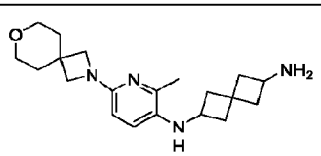
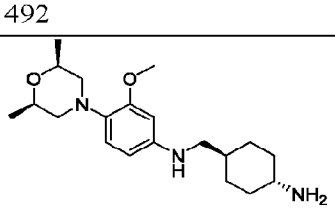
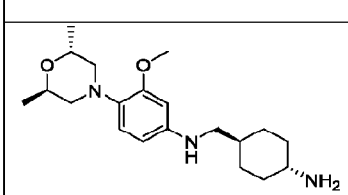
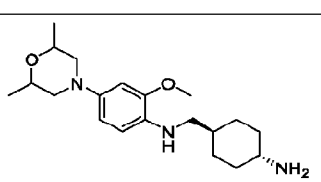
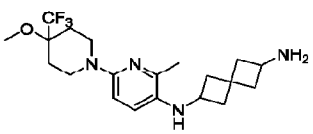
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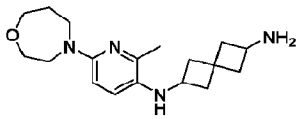
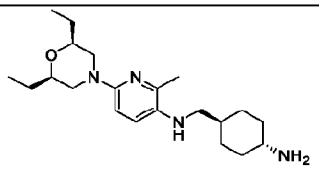
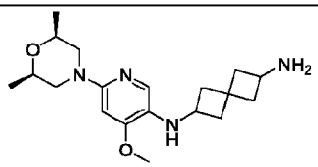
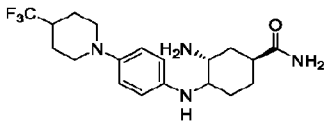
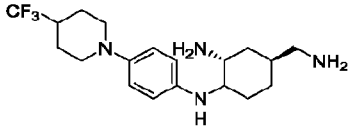
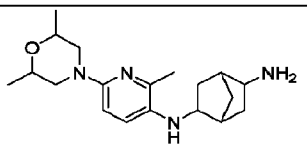
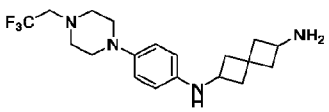
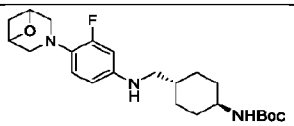
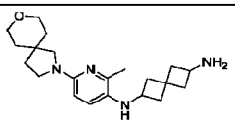
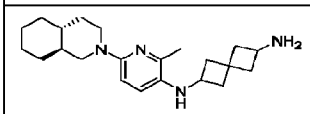
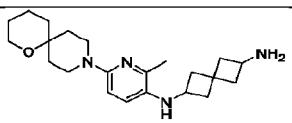
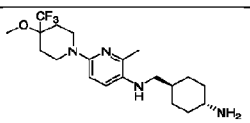
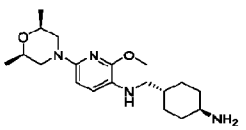
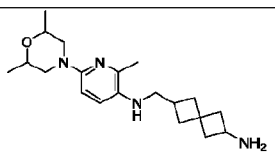
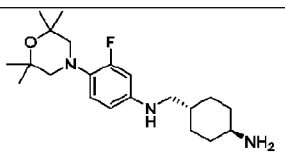
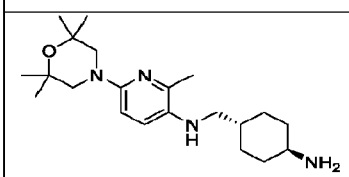
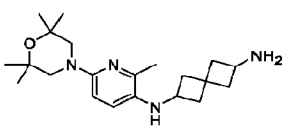
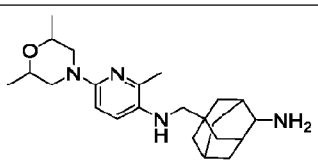
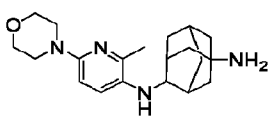
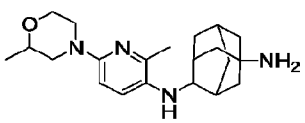
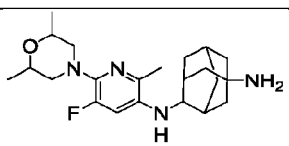
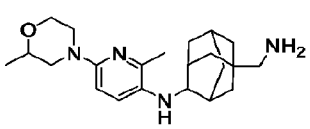
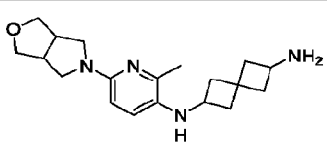
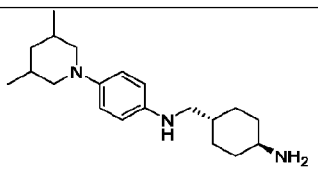
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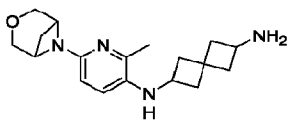
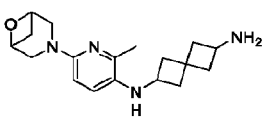
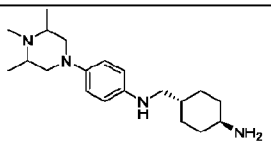
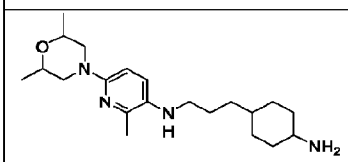
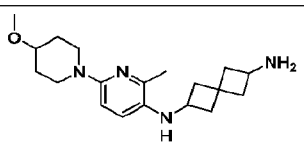
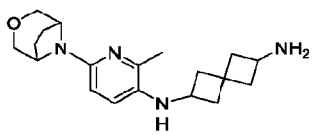
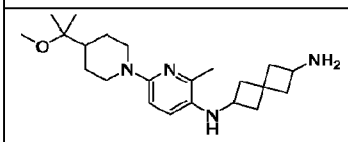
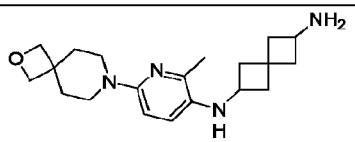
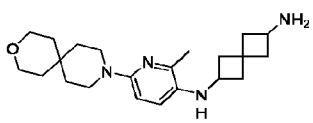
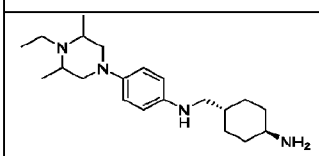
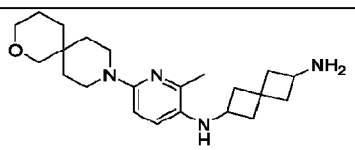
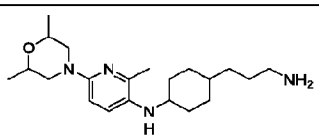
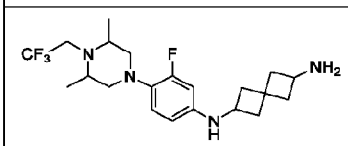
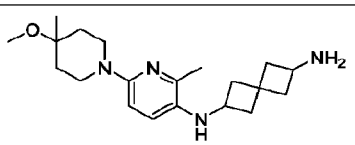
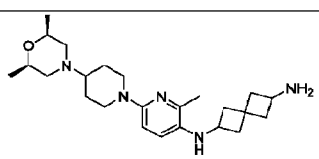
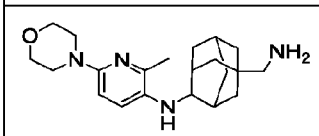
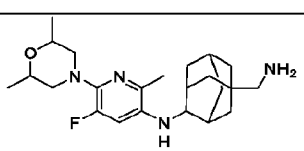
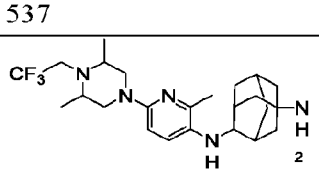
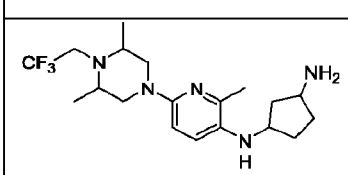
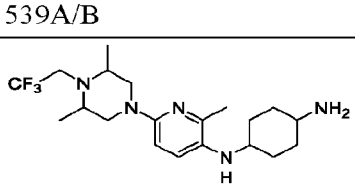
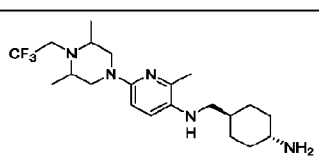
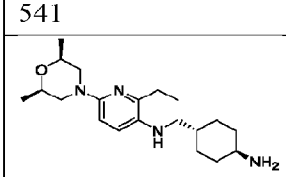
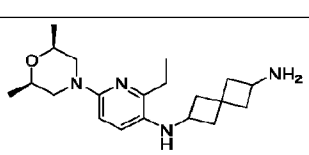
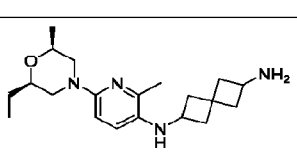
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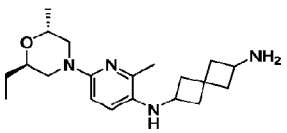
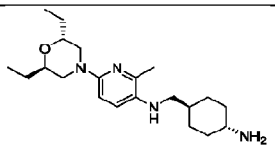
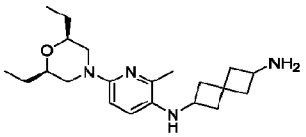
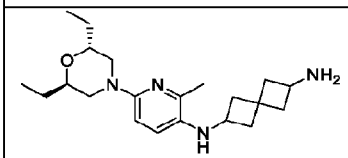
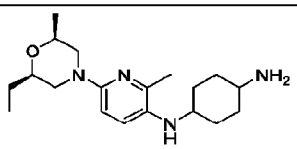
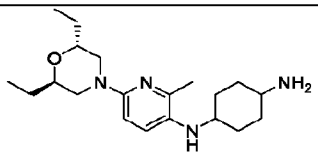
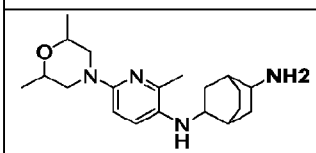
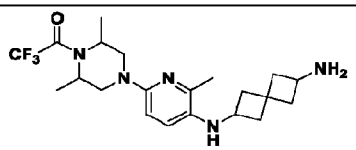
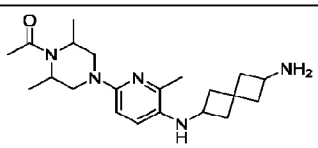
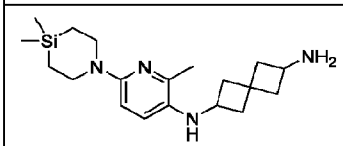
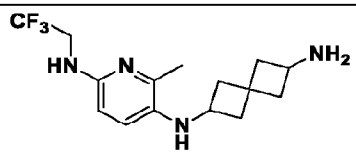
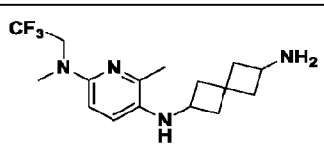
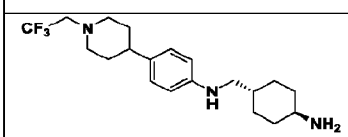
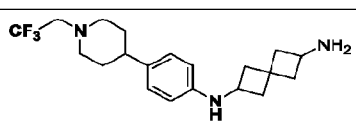
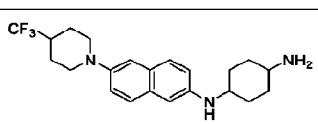
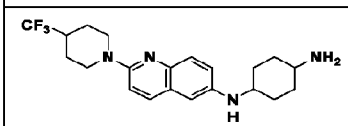
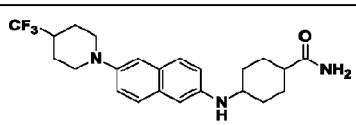
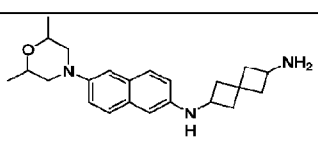
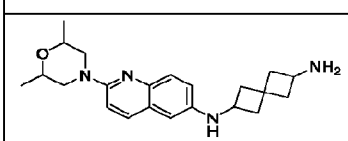
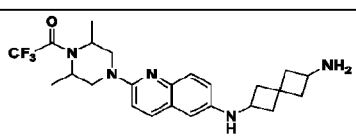
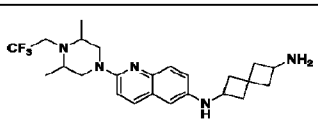
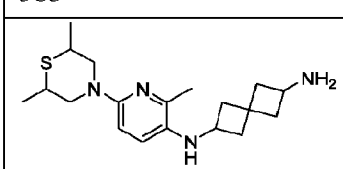
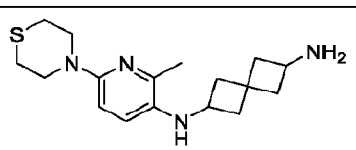
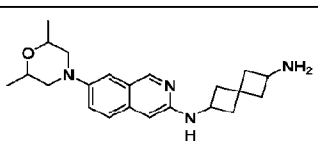
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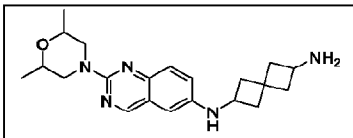
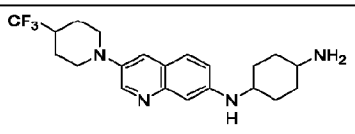
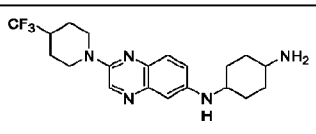
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 487	 488A/B	 489
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 514	 515	 516A/B
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 529	 530	 531
 532	 533	 534
 535	 536	 537
 538A/B	 539A/B	 540
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a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

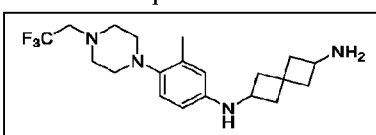
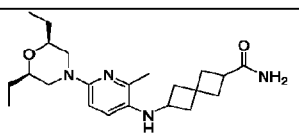
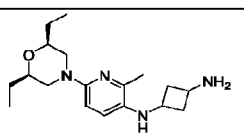
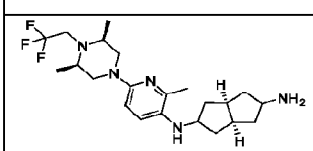
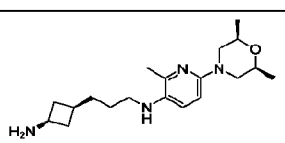
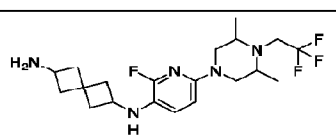
45. A pharmaceutical composition comprising a compound according to any one of technical solutions 1 to 44, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing and at least one pharmaceutically acceptable carrier.

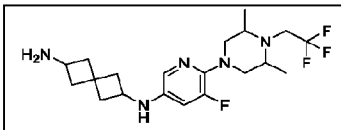
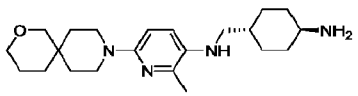
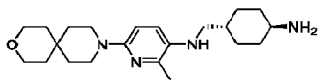
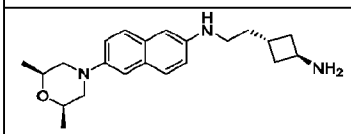
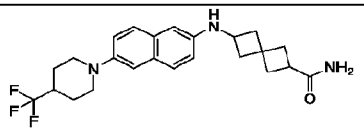
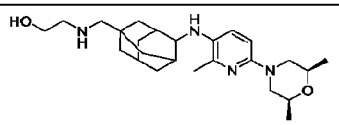
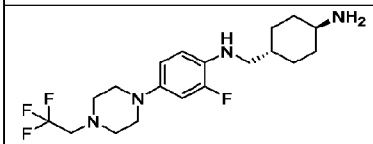
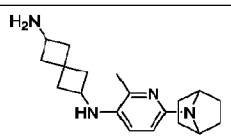
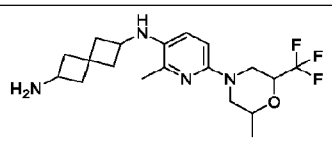
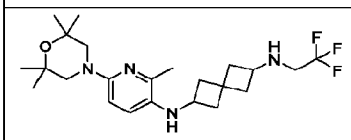
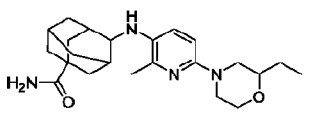
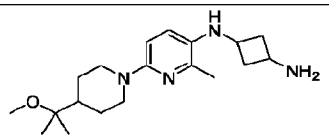
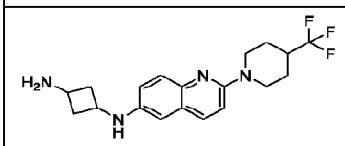
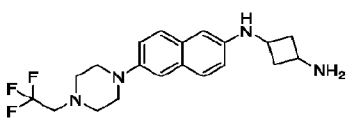
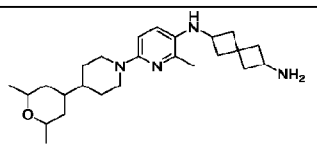
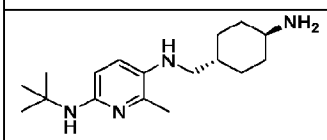
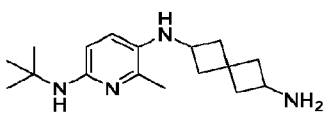
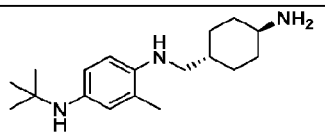
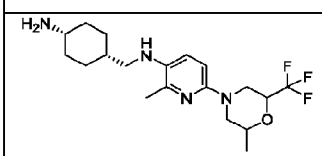
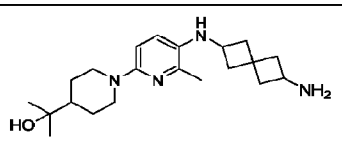
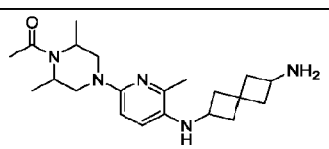
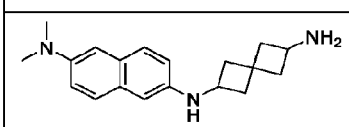
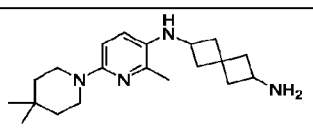
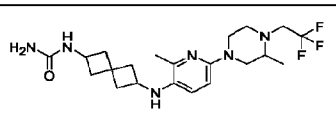
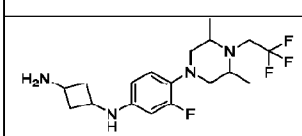
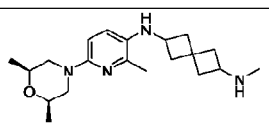
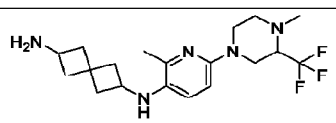
46. A method of treating a disease or condition, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of technical solutions 1 to 44, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing or the pharmaceutical composition according to technical solution 45; wherein the disease or condition is selected from neuropathy, stroke, neurodegenerative disease, Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction.

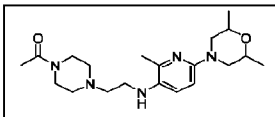
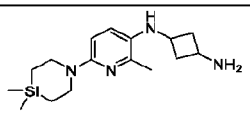
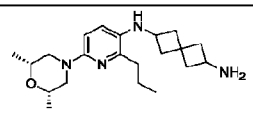
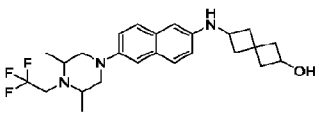
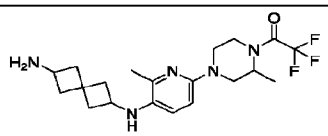
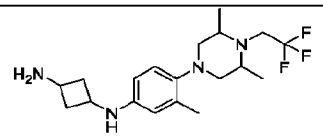
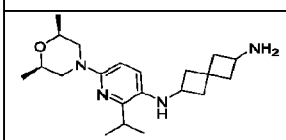
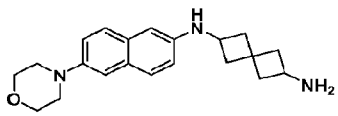
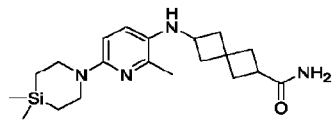
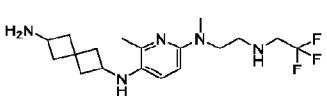
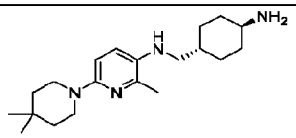
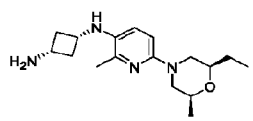
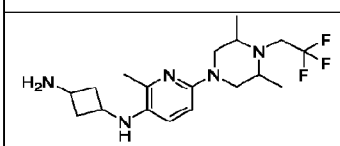
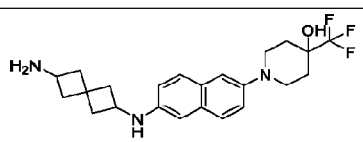
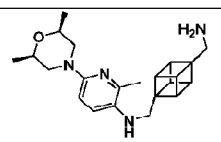
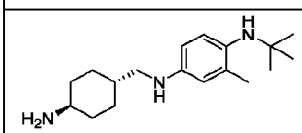
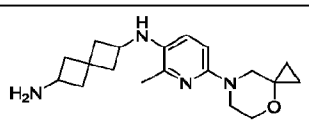
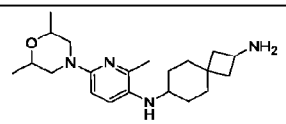
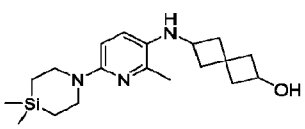
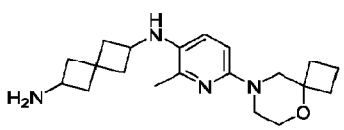
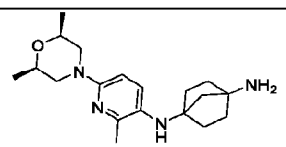
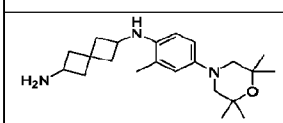
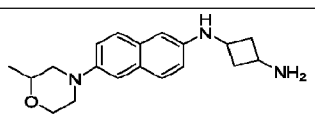
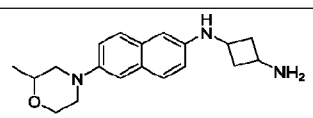
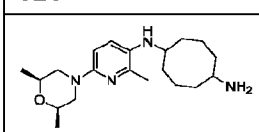
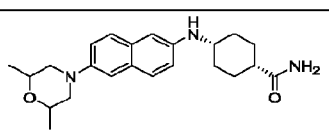
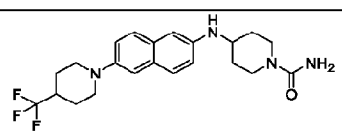
47. A method of treating a disease or condition involving ferroptosis, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any one of technical solutions 1 to 44, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing or the pharmaceutical composition according to technical solution 45.

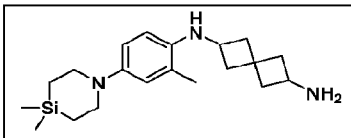
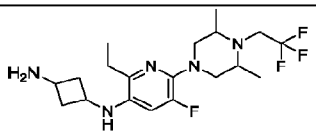
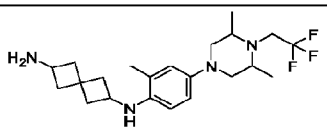
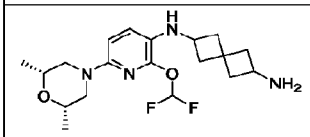
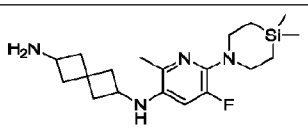
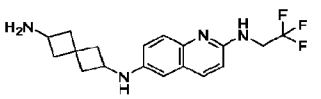
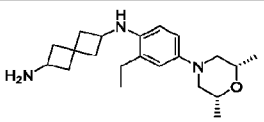
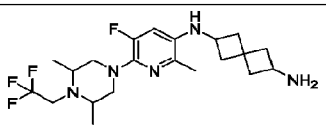
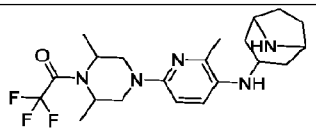
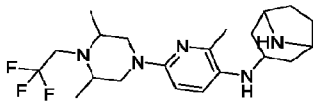
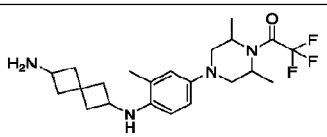
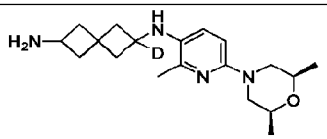
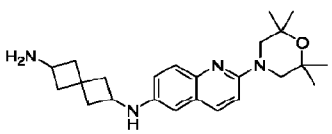
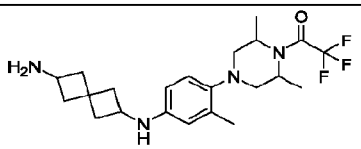
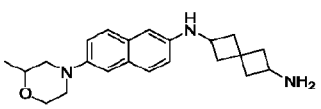
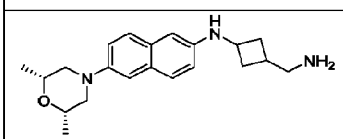
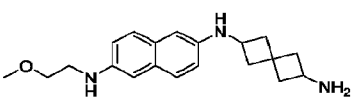
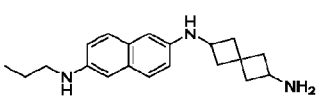
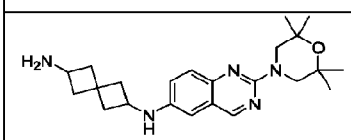
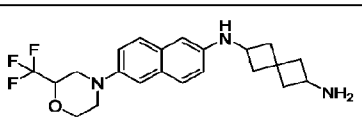
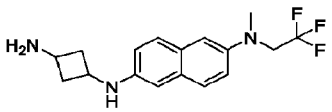
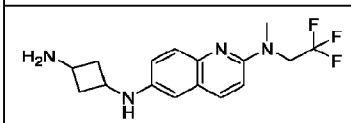
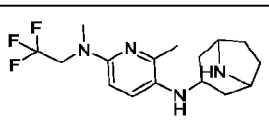
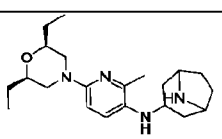
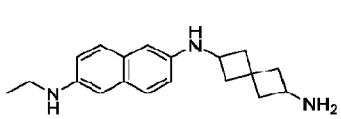
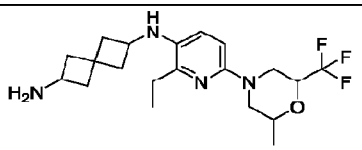
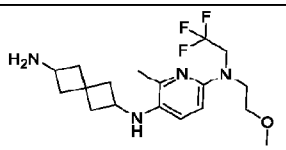
48. A method of modulating ferroptosis, comprising contacting a subject in need thereof with a compound according to any one of technical solutions 1 to 44, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing or the pharmaceutical composition according to technical solution 45.

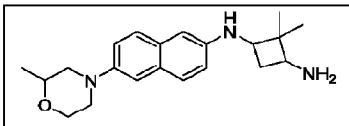
49. A compound selected from:

 574	 575	 576
 577	 578	 579

 580	 581	 582
 583	 584	 585
 586	 587	 588
 589	 590	 591
 592	 593	 594
 595	 596	 597
 598	 599	 600
 601	 602	 603
 604	 605	 606

 607	 608	 609
 610	 611	 612
 613	 614	 615
 616	 617	 618
 619	 620	 621
 622	 623	 624
 625	 626	 627
 628	 629	 630
 631	 632	 633

 634	 635	 636
 637	 638	 639
 640	 641	 642
 643	 644	 645
 646	 647	 648
 649	 650	 651
 652	 653	 654
 655	 656	 657
 658	 659	 660

 661		

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

50. A pharmaceutical composition comprising a compound according to technical solution 49, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing and at least one pharmaceutically acceptable carrier.

51. A method of treating a disease or condition, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to technical solution 49, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing or the pharmaceutical composition according to technical solution 50; wherein the disease or condition is selected from neuropathy, stroke, neurodegenerative disease, Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction.

52. A method of treating a disease or condition involving ferroptosis, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to technical solution 49, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing or the pharmaceutical composition according to technical solution 50.

53. A method of modulating ferroptosis, comprising contacting a subject in need thereof with a compound according to technical solution 49, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing or the pharmaceutical composition according to technical solution 50.

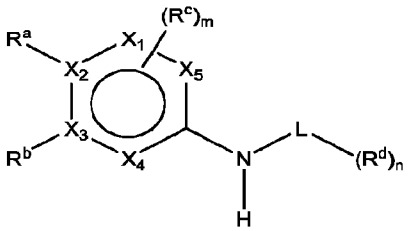
All publications, including but not limited to disclosures and disclosure applications, cited in this specification are herein incorporated by reference as though fully set forth. If certain content of a publication cited herein contradicts or is inconsistent with the present disclosure, the present disclosure controls.

One skilled in the art will readily recognize from the disclosure and claims that various changes, modifications, and variations can be made therein without departing from the spirit and scope of the disclosure as defined in the following claims.

CA 03227251 2024-1-26

CLAIMS

1. A compound of the following structural Formula I:



Formula I

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

L is cycloalkyl, heterocyclyl, or C;

X_1, X_2, X_3, X_4, and X_5 are each independently C or N;

R^a is absent or selected from H, halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

R^b is absent or selected from H, halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl;

R^a and R^b may join together to form an optionally substituted 3- to 10-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring;

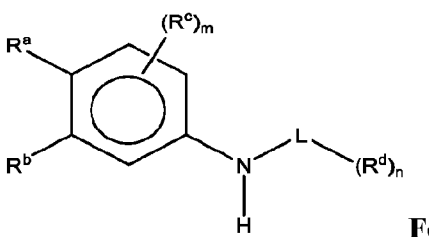
R^c, for each occurrence, is independently selected from halogen, optionally substituted heteroatom, and optionally substituted alkyl;

R^b and one of R^c may join together to form an optionally substituted 3- to 10-membered carbocyclic, heterocyclic, aromatic, or heteroaromatic ring;

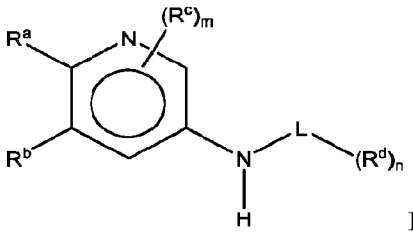
R^d, for each occurrence, is independently selected from halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and

m and n are each an integer independently selected from 0, 1, 2, and 3.

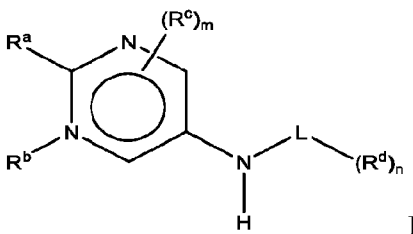
2. The compound of claim 1, wherein the compound has one of the following structural Formulae IIa to IIh:



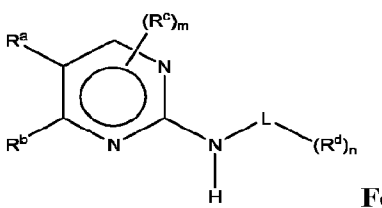
Formula IIa



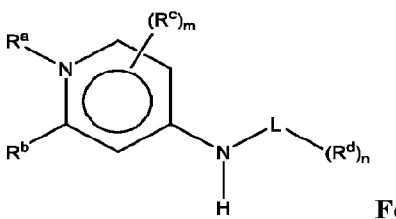
Formula IIb



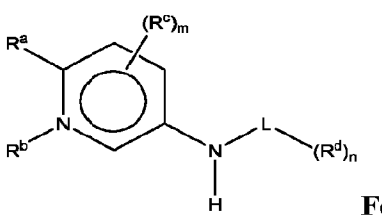
Formula IIc



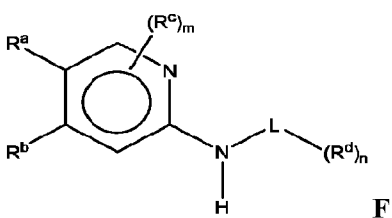
Formula IId



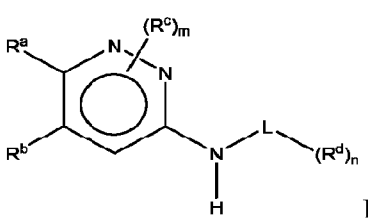
Formula IIe



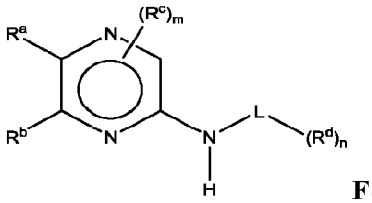
Formula IIf



Formula IIg



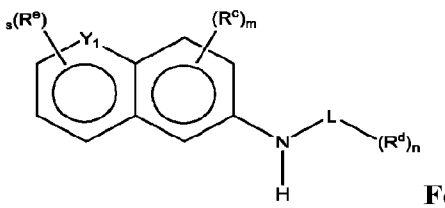
Formula IIh



Formula IIi

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

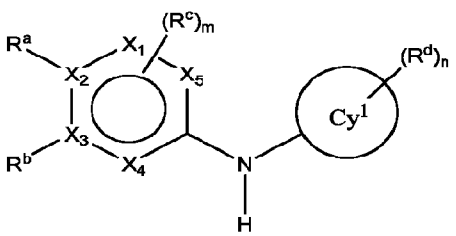
3. The compound of claim 1, wherein the compound has one of the following structural Formulae IIj:



Formula IIj

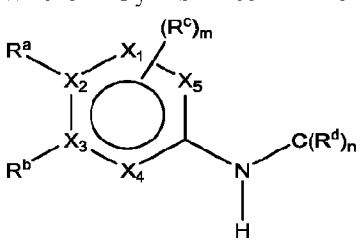
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Y_1 is N or C; R^c, for each occurrence, is independently selected from optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; and s is an integer selected from 0, 1, 2, and 3.

4. The compound of claim 1, wherein the compound has one of the following structural Formulae IIIa and IIIb:



Formula IIIa

wherein Cy^1 is 3- to 10-membered cycloalkyl or 3- to 10-membered heterocyclyl;

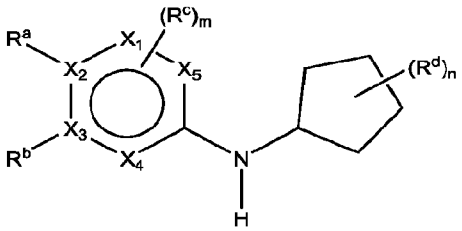


Formula IIIb

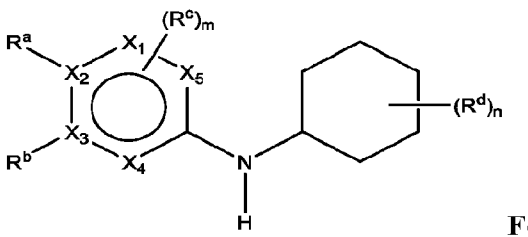
a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

5. The compound of any one of claims 1 and 4, wherein the compound has one of the following structural Formulae IVa to IVf:

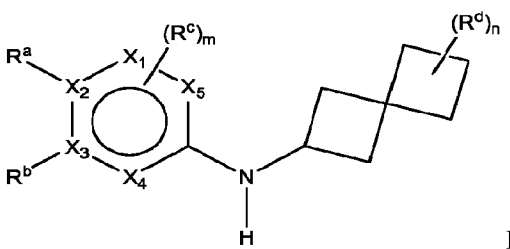
CA 03227251 2024-1-26



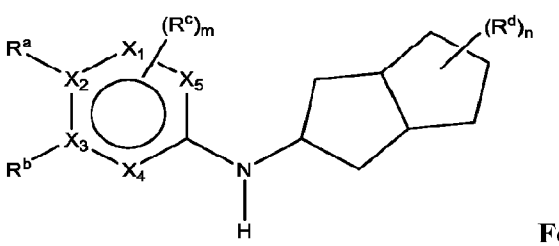
Formula IVa



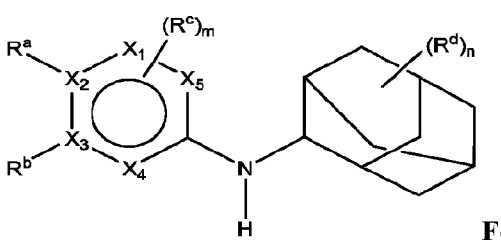
Formula IVb



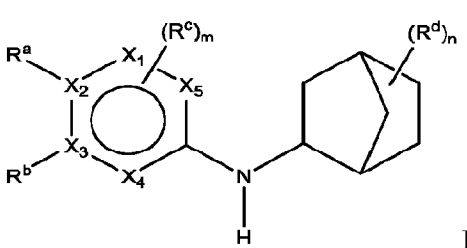
Formula IVc



Formula IVd



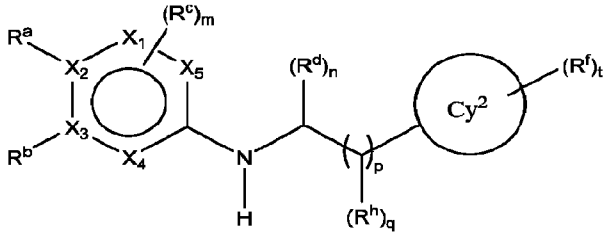
Formula IVe



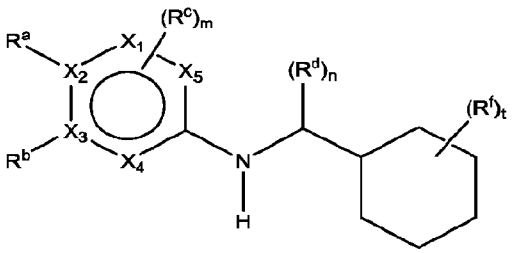
Formula IVf

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

6. The compound of any one of claims 1 and 4, wherein the compound has one of the following structural Formula Va and Formula VIa:



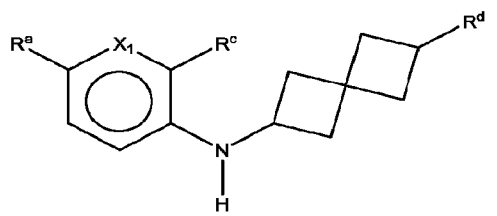
Formula Va



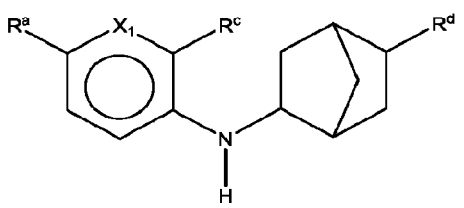
Formula VIa

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein Cy^2 is 3- to 10-membered cycloalkyl or 3- to 10-membered heterocyclyl; R^f, for each occurrence, is independently selected from halogen, CN, optionally substituted heteroatom, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted acyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl; R^h, for each occurrence, is independently selected from halogen, CN, and optionally substituted C_1 to C_6 alkyl; n is an integer selected from 0, 1, and 2; p is an integer selected from 0, 1, 2, 3, 4, and 5; q is an integer selected from 0, 1, and 2; and t is an integer independently selected from 0, 1, 2, and 3; preferably n is 0, q is 0, and p is 0, 1, 2, and 3.

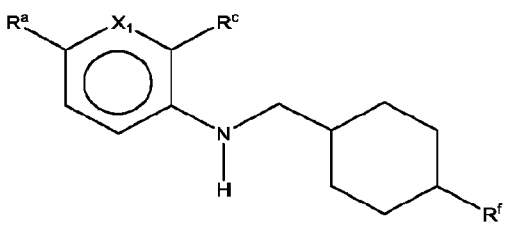
7. The compound of claim 1, wherein the compound has one of the following structural Formulae VIIa-VIIe:



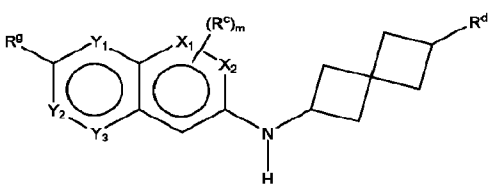
VIIa



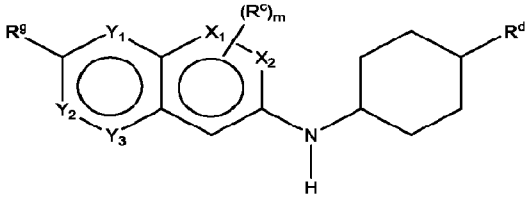
VIIb



VIIc



VIId

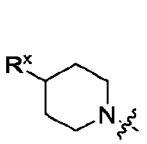
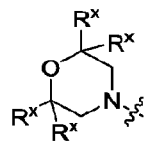
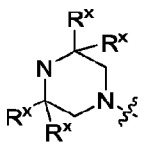


VIIe

a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing, wherein:

X_1 and X_2 are independently C or N;

Y_1, Y_2, and Y_3 are independently C or N;

R^a is selected from  ,  , and  , wherein R^x, for each occurrence, is independently selected from H, CF_3, $-CH_3$, and $-CH_2CH_3$;

R^c is selected from halogen, C_1 to C_2 alkyl, and C_1 to C_2 alkoxy;

R^d is selected from NH_2 and $-C(=O)NH_2$;

R^f is selected from NH_2 and $-C(=O)NH_2$; and

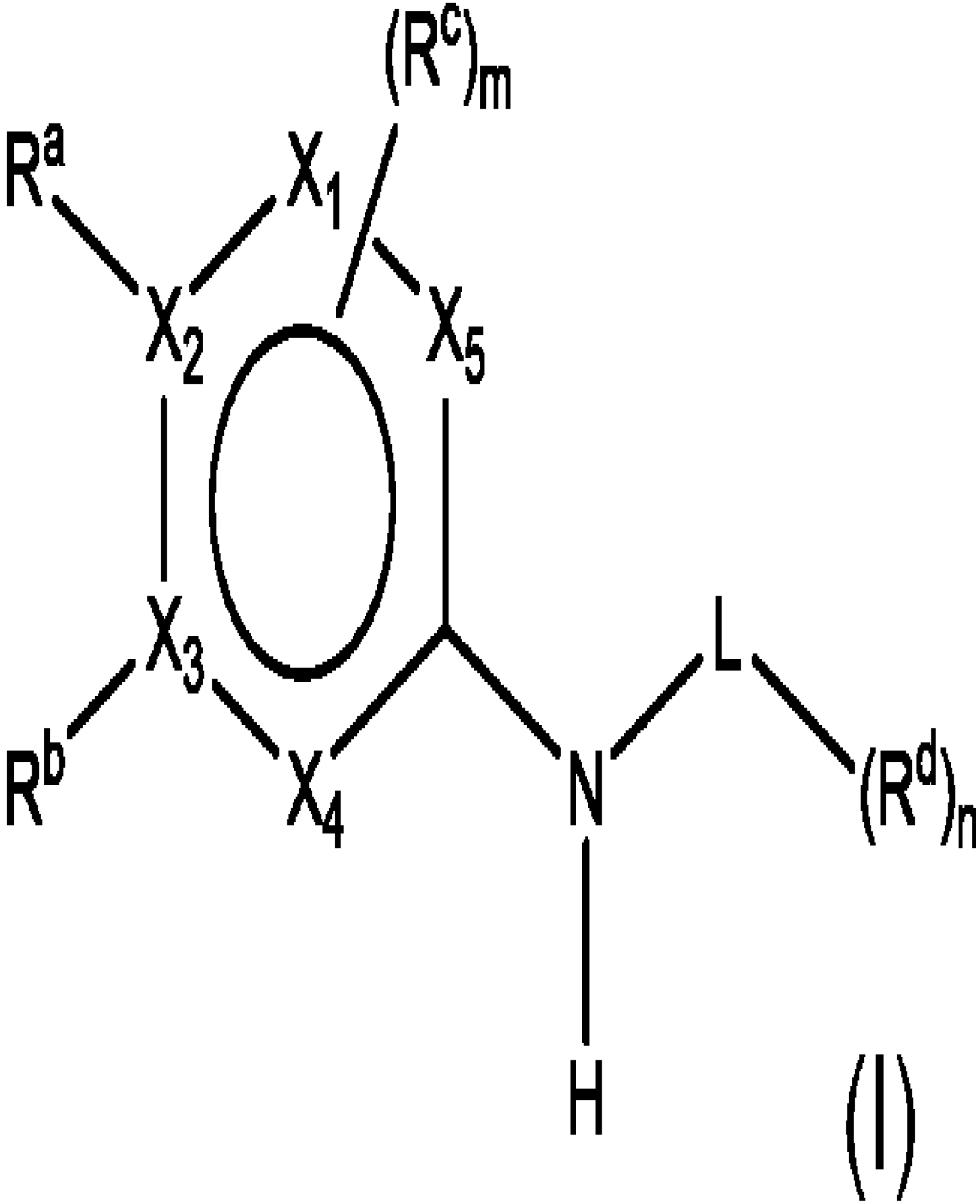
m is 0 or 1.

8. A compound selected from Compounds 1-661 as disclosed in the description, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing.

9. A pharmaceutical composition comprising a compound according to any of claims 1-8, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing and at least one pharmaceutically acceptable carrier.

10. A method of treating a disease or condition (preferably selected from neuropathy, stroke, neurodegenerative disease, Parkinson's Disease, amyotrophic lateral sclerosis (AML), multiple sclerosis, Huntington's Disease, dementia with Lewy bodies, Friedreich's ataxia, hair follicle morphogenesis, diabetes, sepsis, transplant rejection, periventricular leukomalacia, ischemia reperfusion injury, blood coagulation, myocardial infarction, and kidney dysfunction), treating a disease or condition involving ferroptosis, or modulating ferroptosis,

comprising administering to a subject in need thereof, a therapeutically effective amount of a compound according to any of claims 1-8, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing or the pharmaceutical composition according to claim 9; or contacting a subject in need thereof with a compound according to any of claims 1-8, a tautomer thereof, a solvate or stereoisomer of the compound or the tautomer, or a pharmaceutically acceptable salt of the foregoing or the pharmaceutical composition according to claim 9.



(I)