

TERTIARY PYRIDYL AMINE MODULATORS OF CHOLESTEROL BIOSYNTHESIS AND THEIR USE FOR PROMOTING REMYLINATION

CROSS REFERENCE TO RELATED APPLICATIONS

[1] This application claims the benefit of priority to United States Provisional Patent Application No. 63/579,221, filed August 28, 2023, the contents of which is incorporated by reference in its entirety for all purposes.

FIELD

[2] The subject matter described herein is directed to myelin-promoting compounds of Formula I, methods of making the compounds, their pharmaceutical compositions, and their use in the treatment of myelin-related disorders.

BACKGROUND

[3] Myelin-related disorders are disorders that result in abnormalities of the myelin sheath (*e.g.*, dysmyelination, demyelination and hypomyelination) in a subject's neural cells, *e.g.*, CNS neurons including their axons. Loss or degradation of the myelin sheath in such disorders produces a slowing or cessation of nerve cell conduction. The resulting myelin related disorders are characterized by deficits in sensation, motor function, cognition, or other physiological functions. Myelin related disorders include, but are not limited to, multiple sclerosis (MS), neuromyelitis optica (NMO), optic neuritis, pediatric leukodystrophies, neonatal white matter injury, age-related dementia, schizophrenia, progressive multifocal leukoencephalopathy (PML), encephalomyelitis (EPL), central pontine myelolysis (CPM), adrenoleukodystrophy, Alexander's disease, Pelizaeus Merzbacher disease (PMD), Vanishing White Matter Disease, Wallerian Degeneration, transverse myelitis, amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, Parkinson's disease, spinal cord injury, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, stroke, acute ischemic optic neuropathy, vitamin E deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, trigeminal neuralgia, acute disseminated encephalitis, Guillian-Barre syndrome, Charcot-Marie-Tooth disease, Bell's palsy and radiation-induced demyelination.

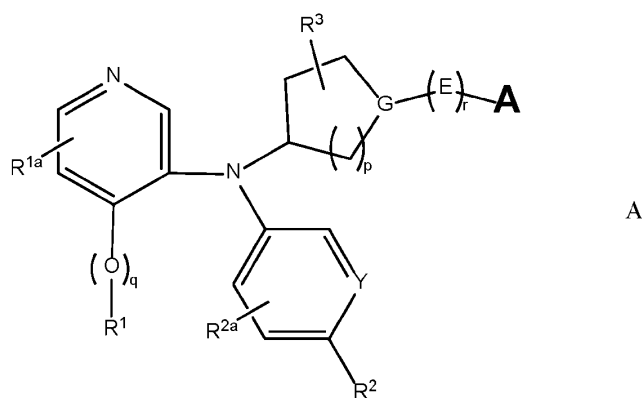
[4] MS is the most common myelin-related disorder affecting several million people globally and is estimated to result in about 18,000 deaths per year. MS is a complex neurological disease characterized by deterioration of central nervous system (CNS) myelin. Myelin, composed in its majority by lipids (70% lipids, 30% protein), protects axons and makes saltatory conduction possible, which speeds axonal electric impulse. Demyelination of axons in chronic MS can result in axon degeneration and neuronal cell death. Additionally, MS destroys oligodendrocytes, the highly specialized CNS cells that generate and maintain myelin. A repair process, called remyelination, takes place in early phases of the disease, but over time, the

oligodendrocytes are unable to completely rebuild and restore the myelin sheath. Repeated attacks lead to successively less effective remyelination, until a scar-like plaque is built up around the damaged axons.

[5] At present, there is no cure for myelin-related disorders, and no current therapy prevents progression in MS. Accordingly, there is a need for new therapeutic approaches to the treatment of myelin-related disorders, including the promotion of remyelination. The subject matter described herein addresses this unmet need.

BRIEF SUMMARY

[6] In certain embodiments, the subject matter described herein is directed to a compound of Formula A:



wherein,

A is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl and 5- to 6-membered heterocyclyl, each of which is optionally substituted with one or more of R^{A1}, R^{A2} and R^{A3},

wherein, R^{A1}, R^{A2} and R^{A3} are each independently selected from the group consisting of C₁-C₆ alkyl, halo-C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, cyano, oxo, -C(O)-R^{A4}, -S(O)-R^{A4} and -S(O)₂-R^{A4},

wherein, R^{A4} is C₁-C₆ alkyl or C₃-C₈ cycloalkyl, and

wherein the oxo, if present, is formed by two of R^{A1}, R^{A2} and R^{A3} together with a carbon to which each is attached;

G is -CH, C-OH, or N;

E, if present, is -C(O)- or -O-;

Y is -CH or N;

p is 1, 2 or 3;

q is 1 or 0;

r is 1 or 0;

wherein, when r is 0, A is other than C₁-C₆ alkyl;

R¹ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl and halo-C₁-C₆ alkyl; or

R¹ is halo and q is 0;

R^{1a} is selected from the group consisting of hydrogen, halo, C₁-C₆ alkyl;

R² is selected from the group consisting of halo, halo-C₁-C₆ alkyl, halo-C₁-C₆ alkoxy and -S(O)₂-(C₁-C₆ alkyl);

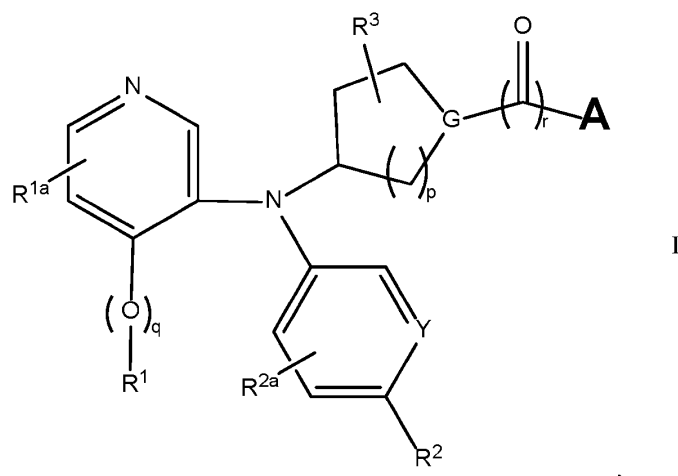
R^{2a} is selected from the group consisting of hydrogen and halo;

and,

R³ is hydrogen, halo, or C₁-C₆ alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

[7] In certain embodiments, the subject matter described herein is directed to a compound of Formula I:



wherein,

A is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl and 5- to 6-membered heterocyclyl, each of which is optionally substituted with one or more of R^{A1}, R^{A2} and R^{A3},

wherein, R^{A1}, R^{A2} and R^{A3} are each independently selected from the group consisting of C₁-C₆ alkyl, halo-C₁-C₆ alkyl, halo, cyano, oxo, -C(O)-R^{A4}, -S(O)-R^{A4} and -S(O)₂-R^{A4},

wherein, R^{A4} is C₁-C₆ alkyl or C₃-C₈ cycloalkyl, and

wherein the oxo, if present, is formed by two of R^{A1}, R^{A2} and R^{A3} together with a carbon to which each is attached;

G is -CH or N;

Y is -CH or N;

p is 1, 2 or 3;

q is 1 or 0;

r is 1 or 0;

wherein, when r is 0, A is other than C₁-C₆ alkyl;

R¹ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl and halo-C₁-C₆ alkyl;

R^{1a} is selected from the group consisting of hydrogen, halo, and C₁-C₆ alkyl;

R² is selected from the group consisting of halo, halo-C₁-C₆ alkyl, halo-C₁-C₆ alkoxy and -S(O)₂-(C₁-C₆ alkyl);

R^{2a} is selected from the group consisting of hydrogen and halo;

and,

R³ is hydrogen, halo, or C₁-C₆ alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

[8] In certain embodiments, the subject matter described herein is directed to a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[9] In certain embodiments, the subject matter described herein is directed to methods of promoting myelination in a subject in need thereof, comprising administering to the subject an effective amount of a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In certain embodiments, the subject has a myelin-related disorder.

[10] In certain embodiments, the subject matter described herein is directed to a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient, for use in treating a myelin-related disorder.

[11] In certain embodiments, the subject matter described herein is directed to the use of a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient, in the manufacture of a medicament for treating a myelin-related disorder.

[12] In certain embodiments, the subject matter described herein is directed to methods of preparing compounds of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof.

[13] In certain embodiments, the subject matter described herein is directed to methods of inhibiting CYP51 (lanosterol demethylase) comprising, contacting CYP51 with a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[14] Other embodiments are also described.

DETAILED DESCRIPTION

[15] Described herein are myelin-promoting compounds of Formula A and Formula I, methods of making the compounds, their pharmaceutical compositions, and their use in the treatment of myelin-related disorders.

[16] The enhancement and/or inducement of the accumulation of $\Delta 8,9$ -unsaturated sterol intermediates of the cholesterol biosynthesis pathway in oligodendrocyte progenitor cells (OPCs) can induce oligodendrocyte generation. Enhancement and/or inducement of the accumulation of $\Delta 8,9$ -unsaturated sterol intermediates can be provided by modulating and/or inhibiting enzymes within the cholesterol biosynthesis pathway in OPCs that enhance and/or induce $\Delta 8,9$ -unsaturated sterol intermediate accumulation and/or for which the $\Delta 8,9$ -unsaturated sterol intermediates are substrates as well as directly and/or indirectly administering $\Delta 8,9$ -unsaturated sterol intermediates to the OPCs. Enhancement and/or inducement of the accumulation of $\Delta 8,9$ -unsaturated sterol intermediates can promote OPC differentiation, survival, proliferation and/or maturation and treat disease and/or disorders in subjects where myelination is beneficial to the subject.

[17] As such, in some embodiments an agent, such as a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, that can enhance and/or induce accumulation of $\Delta 8,9$ -unsaturated sterol intermediates of the cholesterol biosynthesis pathway in the OPCs can be administered to a subject and/or the OPCs at an amount effective to promote and/or induce OPC differentiation, proliferation and/or maturation as well as oligodendrocyte generation. In certain embodiments, the agent, for example a compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, is a compound that inhibits enzyme mediated synthesis of one or more sterol intermediates in the cholesterol biosynthesis pathway of the OPCs and/or promotes accumulation of $\Delta 8,9$ -unsaturated sterol intermediates.

[18] In certain embodiments, the compound of Formula A or Formula I, or a pharmaceutically acceptable salt or solvate thereof, can modulate and/or inhibit one or more enzyme-mediated conversion steps of the cholesterol biosynthesis pathway, such as in the pathway from lanosterol to cholesterol, for example, between lanosterol and/or lathosterol; modulating and/or inhibiting one or more of these steps in

OPCs may promote and/or induce oligodendrocyte generation. For example, the compound of Formula A or Formula I can inhibit CYP51, sterol 14-reductase (TM7SF2 and/or LBR), SC4MOL, NSDHL, and/or EBP enzyme mediated synthesis of sterol intermediates in the cholesterol biosynthesis pathway. In certain embodiments, the compound of Formula A or Formula I can inhibit CYP51, sterol 14-reductase and/or EBP. In certain embodiments, the compound of Formula A or Formula I can inhibit CYP51.

[19] For example, in certain embodiments, the compound of Formula A or Formula I used in the methods described herein can inhibit CYP51 enzyme activity in the cholesterol biosynthetic pathway. Alternatively, in certain embodiments, the compound of Formula I used in the methods described herein can inhibit sterol C14 reductase enzyme activity in the cholesterol biosynthesis pathway or can inhibit enzyme mediated conversion of zymostenol to lathosterol through the inhibition of emopamil binding protein (EBP) isomerase enzyme activity.

[20] CYP51 belongs to the cytochrome P450 (CYP) monooxygenase superfamily and mediates an essential step in the sterol biosynthesis pathway. CYP51 proteins are the most conserved protein in the CYP superfamily. Unlike other CYP enzymes, CYP51 has a strong substrate specificity. It catalyzes the demethylation of a narrow range of substrates, including lanosterol, and 24,25-dihydrolanosterol. CYP51 proteins are also referred to as sterol 14 α -demethylases and are the only invariant P450 present in all sterol biosynthetic pathways.

[21] Without being bound by a particular theory, it is believed that compounds of Formula A and Formula I, or a pharmaceutically acceptable salt or solvate thereof, can inhibit CYP51 mediated conversion of lanosterol to 14-demethyl-14-dehydrolanosterol (FF-MAS) and 24,25-dihydrolanosterol to MAS-412 in the cholesterol biosynthesis pathway of OPCs resulting in enhancement and/or inducement of the accumulation of Δ 8,9-unsaturated sterol intermediates. In some embodiments, enhancement and/or inducement of the accumulation of Δ 8,9-unsaturated sterol intermediates can promote OPC differentiation, survival, proliferation and/or maturation and treat disease and/or disorders in subjects where myelination or myelinization is beneficial to the subject. This mechanism of promoting myelination is distinct from the primary action of immunomodulatory agents that are often used to treat myelin-related disorders.

[22] The presently disclosed subject matter will now be described more fully hereinafter. However, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. In other words, the subject matter described herein covers all alternatives, modifications, and equivalents. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as

commonly understood by one of ordinary skill in this field. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the event that one or more of the incorporated literature, patents, and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

I. Definitions

[23] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[24] A dash (“-”) that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -C(O)NH_2 is attached through the carbon atom. A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line or a dashed line drawn through or perpendicular across the end of a line in a structure indicates a specified point of attachment of a group. Unless chemically or structurally required, no directionality or stereochemistry is indicated or implied by the order in which a chemical group is written or named.

[25] The prefix “C_u-C_v” indicates that the following group has from u to v carbon atoms. For example, “C₁-C₆ alkyl” indicates that the alkyl group has from 1 to 6 carbon atoms.

[26] Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. In certain embodiments, the term “about” includes the indicated amount $\pm 50\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 20\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 10\%$. In other embodiments, the term “about” includes the indicated amount $\pm 5\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 1\%$. In certain other embodiments, the term “about” includes the indicated amount $\pm 0.5\%$ and in certain other embodiments, 0.1% . Such variations are appropriate to perform the disclosed methods or employ the disclosed compositions. Also, to the term “about x” includes description of “x”. Also, the singular forms “a” and “the” include plural references unless the context clearly dictates otherwise. Thus, *e.g.*, reference to “the compound” includes a plurality of such compounds and reference to “the assay” includes reference to one or more assays and equivalents thereof known to those skilled in the art.

[27] “Alkyl” refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkyl), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ alkyl), 1 to 8 carbon atoms (*i.e.*, C₁-C₈ alkyl), 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl), 1 to 4 carbon atoms (*i.e.*, C₁-C₄ alkyl), or 1 to 3

carbon atoms (*i.e.*, C₁-C₃ alkyl). Examples of alkyl groups include, *e.g.*, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, “butyl” includes n-butyl (*i.e.*, -(CH₂)₃CH₃), sec-butyl (*i.e.*, -CH(CH₃)CH₂CH₃), isobutyl (*i.e.*, -CH₂CH(CH₃)₂) and tert-butyl (*i.e.*, -C(CH₃)₃); and “propyl” includes n-propyl (*i.e.*, -(CH₂)₂CH₃) and isopropyl (*i.e.*, -CH(CH₃)₂).

[28] Certain commonly used alternative chemical names may be used. For example, a divalent group such as a divalent “alkyl” group, a divalent “aryl” group, etc., may also be referred to as an “alkylene” group or an “alkylenyl” group, an “arylene” group or an “arylenyl” group, respectively. Also, unless indicated explicitly otherwise, where combinations of groups are referred to herein as one moiety, *e.g.*, arylalkyl or aralkyl, the last-mentioned group contains the atom by which the moiety is attached to the rest of the molecule.

[29] “Alkenyl” refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (*i.e.*, C₂-C₂₀ alkenyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkenyl), 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkenyl) or 2 to 4 carbon atoms (*i.e.*, C₂-C₄ alkenyl). Examples of alkenyl groups include, *e.g.*, ethenyl, propenyl, butadienyl (including 1,2-butadienyl and 1,3-butadienyl).

[30] “Alkynyl” refers to an alkyl group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (*i.e.*, C₂-C₂₀ alkynyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkynyl), 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkynyl) or 2 to 4 carbon atoms (*i.e.*, C₂-C₄ alkynyl). The term “alkynyl” also includes those groups having one triple bond and one double bond.

[31] “Alkoxy” refers to the group “alkyl-O-” (*e.g.*, C₁-C₃ alkoxy or C₁-C₆ alkoxy). Examples of alkoxy groups include, *e.g.*, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy and 1,2-dimethylbutoxy.

[32] “Alkylthio” refers to the group “alkyl-S-”.

[33] “Acyl” refers to a group -C(O)R^y, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of acyl include, *e.g.*, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethyl-carbonyl and benzoyl.

[34] “Amido” refers to both a “C-amido” group which refers to the group -C(O)NR^yR^z and an “N-amido” group which refers to the group -NR^yC(O)R^z, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein, or R^y and R^z are taken together to form a heterocyclyl; which may be optionally substituted, as defined herein.

[35] “Amino” refers to the group $-NR^yR^z$ wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[36] “Amidino” refers to $-C(NR^y)(NR^z)$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[37] “Aryl” refers to an aromatic carbocyclic group having a single ring (*e.g.*, monocyclic) or multiple rings (*e.g.*, bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (*i.e.*, C_6 - C_{20} aryl), 6 to 12 carbon ring atoms (*i.e.*, C_6 - C_{12} aryl), or 6 to 10 carbon ring atoms (*i.e.*, C_6 - C_{10} aryl). Examples of aryl groups include, *e.g.*, phenyl, naphthyl, fluorenyl and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl regardless of the point of attachment. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl regardless of the point of attachment.

[38] “Arylalkyl” or “Aralkyl” refers to the group “aryl-alkyl-”, such as (C_6 - C_{10} aryl)- C_1 - C_3 alkyl. A non-limiting example of arylalkyl is benzyl.

[39] “Carbamoyl” refers to both an “O-carbamoyl” group which refers to the group $-O-C(O)NR^yR^z$ and an “N-carbamoyl” group which refers to the group $-NR^yC(O)OR^z$, wherein R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[40] “Carboxyl ester” or “ester” refer to both $-OC(O)R^x$ and $-C(O)OR^x$, wherein R^x is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[41] “Cycloalkyl” refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged and spiro ring systems. The term “cycloalkyl” includes cycloalkenyl groups (*i.e.*, the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (*i.e.*, at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (*i.e.*, C_3 - C_{20} cycloalkyl), 3 to 12 ring carbon atoms (*i.e.*, C_3 - C_{12} cycloalkyl), 3 to 10 ring carbon atoms (*i.e.*, C_3 - C_{10} cycloalkyl), 3 to 8 ring carbon atoms (*i.e.*, C_3 - C_8 cycloalkyl), 3 to 7 ring carbon atoms (*i.e.*, C_3 - C_7 cycloalkyl), or 3 to 6 ring carbon atoms (*i.e.*, C_3 - C_6 cycloalkyl). Monocyclic groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbornyl, decalanyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl and the like. Further, the term cycloalkyl is intended to encompass any moiety comprising a non-aromatic alkyl ring

which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also includes “spirocycloalkyl” when there are two positions for substitution on the same carbon atom, for example spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro[5.5]undecanyl. As used herein, “halocycloalkyl,” such as C₃-C₇ halocycloalkyl, refers to a C₃-C₇ cycloalkyl group that is substituted with one or more halogens.

[42] “Cycloalkylalkyl” refers to the group “cycloalkyl-alkyl-”, such as (C₃-C₆ cycloalkyl)-C₁-C₃ alkyl.

[43] “Guanidino” refers to -NR^yC(=NR^z)(NR^yR^z), wherein each R^y and R^z are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[44] “Hydrazino” refers to -NHNH₂.

[45] “Imino” refers to a group -C(NR^y)R^z, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[46] “Imido” refers to a group -C(O)NR^yC(O)R^z, wherein R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[47] “Halogen” or “halo” refers to atoms occupying group VIIA of the periodic table, such as fluoro (fluorine), chloro (chlorine), bromo (bromine) or iodo (iodine).

[48] “Haloalkyl” refers to an unbranched or branched alkyl group as defined above, wherein one or more (*e.g.*, 1 to 6, or 1 to 3) hydrogen atoms are replaced by a halogen. For example, halo-C₁-C₃ alkyl refers to an alkyl group of 1 to 3 carbons wherein at least one hydrogen atom is replaced by a halogen. Halo-C₁-C₆ alkyl refers to an alkyl group of 1 to 6 carbons wherein at least one hydrogen atom is replaced by a halogen. Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include, *e.g.*, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, 1,2-dibromoethyl and the like.

[49] “Haloalkoxy” refers to an alkoxy group as defined above, wherein one or more (*e.g.*, 1 to 6, or 1 to 3) hydrogen atoms are replaced by a halogen. For example, halo-C₁-C₃ alkoxy refers to an alkoxy group of 1 to 3 carbons wherein at least one hydrogen atom is replaced by a halogen. Halo-C₁-C₆ alkoxy refers to an alkoxy group of 1 to 6 carbons wherein at least one hydrogen atom is replaced by a halogen. Non-limiting examples of haloalkoxy are -OCH₂CF₃, -OCF₂H, and -OCF₃.

[50] “Hydroxyalkyl” refers to an alkyl group as defined above, wherein one or more (*e.g.*, 1 to 6, or 1 to 3) hydrogen atoms are replaced by a hydroxy group (*e.g.*, hydroxy-C₁-C₃-alkyl, hydroxy-C₁-C₆-alkyl). The term “hydroxy-C₁-C₃ alkyl” refers to a one to three carbon alkyl chain where one or more hydrogens on any carbon is replaced by a hydroxy group, in particular, one hydrogen on one carbon of the chain is replaced by a hydroxy group. The term “hydroxy-C₁-C₆ alkyl” refers to a one to six carbon alkyl chain where one or more hydrogens on any carbon is replaced by a hydroxy group, in particular, one hydrogen on one carbon of the chain is replaced by a hydroxy group. Non-limiting examples of hydroxyalkyl include -CH₂OH, -CH₂CH₂OH, and -C(CH₃)₂CH₂OH.

[51] “Heteroalkyl” refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group, provided the point of attachment to the remainder of the molecule is through a carbon atom. In certain embodiments, the heteroalkyl can have 1 to 3 carbon atoms (*e.g.*, C₁-C₃ heteroalkyl) or 1 to 6 carbon atoms (*e.g.*, C₁-C₆ heteroalkyl), and one or more (*e.g.*, 1, 2, or 3) heteroatoms or heteroatomic groups. The term “heteroalkyl” includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2, or 3 carbon atoms of the alkyl group in the “heteroalkyl” may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NR^y-, -O-, -S-, -S(O)-, -S(O)₂-, and the like, wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of heteroalkyl groups include, *e.g.*, ethers (*e.g.*, -CH₂OCH₃, -CH(CH₃)OCH₃, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OCH₃, etc.), thioethers (*e.g.*, -CH₂SCH₃, -CH(CH₃)SCH₃, -CH₂CH₂SCH₃, -CH₂CH₂SCH₂CH₂SCH₃, etc.), sulfoxides (*e.g.*, -CH₂S(O)CH₃, -CH(CH₃)S(O)CH₃, -CH₂CH₂S(O)CH₃, -CH₂CH₂S(O)CH₂CH₂OCH₃, etc.), sulfones (*e.g.*, -CH₂S(O)₂CH₃, -CH(CH₃)S(O)₂CH₃, -CH₂CH₂S(O)₂CH₃, -CH₂CH₂S(O)₂CH₂CH₂OCH₃, etc.), and amines (*e.g.*, -CH₂NR^yCH₃, -CH(CH₃)NR^yCH₃, -CH₂CH₂NR^yCH₃, -CH₂CH₂NR^yCH₂CH₂NR^yCH₃, etc., where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl, or heteroaryl; each of which may be optionally substituted, as defined herein). In certain embodiments, heteroalkyl can have 1 to 20 carbon atoms, 1 to 15 carbon atoms, 1 to 12 carbon atoms, 1 to 10 carbon atoms, 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatoms, 1 to 2 heteroatoms, or 1 heteroatom.

[52] “Heteroaryl” refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (*i.e.*, C₁-C₂₀ heteroaryl), 3 to 12 ring carbon atoms (*i.e.*, C₃-C₁₂ heteroaryl), or 3 to 8 carbon ring atoms (*i.e.*, C₃-C₈ heteroaryl), and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. In certain instances, heteroaryl includes 9-10 membered ring

systems (*i.e.*, 9-10 membered heteroaryl), 5-10 membered ring systems (*i.e.*, 5-10 membered heteroaryl), 5-7 membered ring systems (*i.e.*, 5-7 membered heteroaryl), 5-6 membered ring systems (*i.e.*, 5-6 membered heteroaryl), or 4-6 membered ring systems (*i.e.*, 4-6 membered heteroaryl), each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. Examples of heteroaryl groups include, *e.g.*, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazoliny, quinoxaliny, quinoliny, quinuclidinyl, isoquinoliny, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinoliny, isoquinoliny, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl and imidazo[1,5-a]pyridinyl, where the heteroaryl can be bound *via* either ring of the fused system. Any aromatic group, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (*i.e.*, through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[53] “Heteroarylalkyl” refers to the group “heteroaryl-alkyl-”, such as (5- to 10-membered monocyclic heteroaryl)-C₁-C₃ alkyl.

[54] “Heterocyclyl” refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term “heterocyclyl” includes heterocycloalkenyl groups (*i.e.*, the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the multiple rings may be fused, bridged or spiro. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (*i.e.*, can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass a moiety comprising any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. The term heterocyclyl is also intended to encompass a moiety comprising a cycloalkyl ring which is fused to a heteroaryl ring, regardless of the attachment to the remainder of the molecule. Additionally, the term heterocyclyl is intended to encompass a moiety comprising a cycloalkyl ring which is fused to a heterocyclyl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (*i.e.*, C₂-C₂₀ heterocyclyl), 2 to 12 ring carbon atoms (*i.e.*, C₂-

C₁₂ heterocyclyl), 2 to 10 ring carbon atoms (*i.e.*, C₂-C₁₀ heterocyclyl), 2 to 8 ring carbon atoms (*i.e.*, C₂-C₈ heterocyclyl), 3 to 12 ring carbon atoms (*i.e.*, C₃-C₁₂ heterocyclyl), 3 to 8 ring carbon atoms (*i.e.*, C₃-C₈ heterocyclyl), or 3 to 6 ring carbon atoms (*i.e.*, C₃-C₆ heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. When the heterocyclyl ring contains 4- to 6- ring atoms, it is also referred to herein as a 4- to 6-membered heterocyclyl. Also disclosed herein are 5- or 6-membered heterocyclyls, having 5 or 6 ring atoms, respectively, and 5- to 10-membered heterocyclyls, having 5 to 10 ring atoms. Examples of heterocyclyl groups include, *e.g.*, azetidiny, azepiny, benzodioxolyl, benzo[b][1,4]dioxepiny, 1,4-benzodioxany, benzopyrany, benzodioxiny, benzopyranony, benzofuranony, dioxolany, dihydropyrany, hydropyrany, thienyl[1,3]dithianyl, decahydroisoquinolyl, furanony, imidazoliny, imidazolidiny, indoliny, indoliziny, isoindoliny, isothiazolidiny, isoxazolidiny, morpholiny, octahydroindolyl, octahydroisoindolyl, 2-oxopiperaziny, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidiny, oxirany, oxetany, phenothiaziny, phenoxaziny, piperidinyl, piperaziny, 4-piperidonyl, pyrrolidinyl, pyrazolidiny, quinuclidiny, thiazolidiny, tetrahydrofuryl, tetrahydropyrany, trithianyl, tetrahydroquinoliny, thiophenyl (*i.e.*, thienyl), tetrahydropyrany, thiomorpholiny, thiamorpholiny, 1-oxo-thiomorpholiny and 1,1-dioxo-thiomorpholiny. In certain embodiments, the term “heterocyclyl” can include “spiroheterocyclyl” when there are two positions for substitution on the same carbon atom, wherein at least one ring of the spiro system comprises at least one heteroatom. Examples of the spiro-heterocyclyl rings include, *e.g.*, bicyclic and tricyclic ring systems, such as 2-oxa-7-azaspiro[3.5]nonany, 2-oxa-6-azaspiro[3.4]octany and 6-oxa-1-azaspiro[3.3]heptany. Examples of the fused-heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinoliny, 4,5,6,7-tetrahydrothieno[2,3-c]pyridiny, indoliny and isoindoliny, where the heterocyclyl can be bound *via* either ring of the fused system.

[55] “Heterocyclylalkyl” refers to the group “heterocyclyl-alkyl-.”

[56] “Oxime” refers to the group -CR^y(=NOH) wherein R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[57] “Oxo” refers to the group (=O).

[58] “Cyano” refers to the group (-CN).

[59] “N-oxide” refers to the group (-NO).

[60] “Thiol” refers to the group (-SH).

[61] “Sulfonyl” refers to the group -S(O)₂R^y, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. A non-limiting example of a sulfonyl group is -SO₂(C₁-C₆ alkyl), which is herein referred

to as alkylsulfonyl. Examples of sulfonyl are methylsulfonyl, ethylsulfonyl, phenylsulfonyl and toluenesulfonyl.

[62] “Sulfinyl” refers to the group $-S(O)R^y$, where R^y is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein. Examples of sulfinyl are methylsulfinyl, ethylsulfinyl, phenylsulfinyl and toluenesulfinyl.

[63] “Sulfonamido” refers to the groups $-SO_2NR^yR^z$ and $-NR^ySO_2R^z$, where R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroalkyl or heteroaryl; each of which may be optionally substituted, as defined herein.

[64] The terms “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances in which it does not. Also, the term “optionally substituted” refers to any one or more (*e.g.*, 1 to 5, 1 to 4, or 1 to 3) hydrogen atoms on the designated atom or group may or may not be replaced by a moiety other than hydrogen.

[65] The term “substituted” used herein means any of the above groups (*i.e.*, alkyl, alkenyl, alkynyl, alkylene, alkoxy, haloalkyl, haloalkoxy, cycloalkyl, aryl, heterocyclyl, heteroaryl, and/or heteroalkyl) wherein at least one (*e.g.*, 1 to 5, 1 to 4, or 1 to 3) hydrogen atom is replaced by a bond to a non-hydrogen atom such as, but not limited to alkyl, alkenyl, alkynyl, alkoxy, alkylthio, acyl, amido, amino, amidino, aryl, aralkyl, azido, carbamoyl, carboxyl, carboxyl ester, cyano, cycloalkyl, cycloalkylalkyl, guanidino, halo, haloalkyl, haloalkoxy, hydroxyalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, $-NHNH_2$, $=NNH_2$, imino, imido, hydroxy, oxo, oxime, nitro, sulfonyl, sulfinyl, alkylsulfonyl, alkylsulfinyl, thiocyanate, $-S(O)OH$, $-S(O)_2OH$, sulfonamido, thiol, thioxo, N-oxide or $-Si(R^y)_3$, wherein each R^y is independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl.

[66] In certain embodiments, “substituted” includes any of the above alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl groups in which one or more (*e.g.*, 1 to 5, 1 to 4, or 1 to 3) hydrogen atoms are independently replaced with deuterium, halo, cyano, nitro, azido, oxo, alkyl, alkenyl, alkynyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, $-NR^gR^h$, $-NR^gC(=O)R^h$, $-NR^gC(=O)NR^gR^h$, $-NR^gC(=O)OR^h$, $-NR^gS(=O)_{1-2}R^h$, $-C(=O)R^g$, $-C(=O)OR^g$, $-OC(=O)OR^g$, $-OC(=O)R^g$, $-C(=O)NR^gR^h$, $-OC(=O)NR^gR^h$, $-OR^g$, $-SR^g$, $-S(=O)R^g$, $-S(=O)_2R^g$, $-OS(=O)_{1-2}R^g$, $-S(=O)_{1-2}OR^g$, $-NR^gS(=O)_{1-2}NR^gR^h$, $=NSO_2R^g$, $=NOR^g$, $-S(=O)_{1-2}NR^gR^h$, $-SF_5$, $-SCF_3$ or $-OCF_3$. In certain embodiments, “substituted” also means any of the above groups in which one or more (*e.g.*, 1 to 5, 1 to 4, or 1 to 3) hydrogen atoms are replaced with $-C(=O)R^g$, $-C(=O)OR^g$, $-C(=O)NR^gR^h$, $-CH_2SO_2R^g$, or $-CH_2SO_2NR^gR^h$. In the foregoing, R^g and R^h are the same or different and independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and/or

heteroarylalkyl. In certain embodiments, “substituted” also means any of the above groups in which one or more (*e.g.*, 1 to 5, 1 to 4, or 1 to 3) hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, N-heterocyclyl, heterocyclalkyl, heteroaryl, and/or heteroarylalkyl, or two of R^g and R^h and Rⁱ are taken together with the atoms to which they are attached to form a heterocycl ring optionally substituted with oxo, halo or alkyl optionally substituted with oxo, halo, amino, hydroxyl, or alkoxy.

[67] Polymers or similar indefinite structures arrived at by defining substituents with further substituents appended ad infinitum (*e.g.*, a substituted aryl having a substituted alkyl which is itself substituted with a substituted aryl group, which is further substituted by a substituted heteroalkyl group, etc.) are not intended for inclusion herein. Unless otherwise noted, the maximum number of serial substitutions in compounds described herein is three. For example, serial substitutions of substituted aryl groups with two other substituted aryl groups are limited to ((substituted aryl)substituted aryl)substituted aryl. Similarly, the above definitions are not intended to include impermissible substitution patterns (*e.g.*, methyl substituted with 5 fluorines or heteroaryl groups having two adjacent oxygen ring atoms). Such impermissible substitution patterns are well known to the skilled artisan. When used to modify a chemical group, the term “substituted” may describe other chemical groups defined herein.

[68] In certain embodiments, as used herein, the phrase “one or more” refers to one to five. In certain embodiments, as used herein, the phrase “one or more” refers to one to four. In certain embodiments, as used herein, the phrase “one or more” refers to one to three.

[69] Any compound or structure given herein, is intended to represent unlabeled forms as well as isotopically labeled forms (isotopologues) of the compounds. These forms of compounds may also be referred to as and include “isotopically enriched analogs.” Isotopically labeled compounds have structures depicted herein, except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine and iodine, such as ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ³¹P, ³²P, ³⁵S, ¹⁸F, ³⁶Cl, ¹²³I, and ¹²⁵I, respectively. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ³H, ¹³C and ¹⁴C are incorporated. Such isotopically labelled compounds may be useful in metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or in radioactive treatment of patients.

[70] The term “isotopically enriched analogs” includes “deuterated analogs” of compounds described herein in which one or more hydrogens is/are replaced by deuterium, such as a hydrogen on a

carbon atom. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

[71] Deuterium labelled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to adsorption, distribution, metabolism, and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F , ^3H , ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein.

[72] The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium. Further, in some embodiments, the corresponding deuterated analog is provided.

[73] In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

[74] Provided also are a pharmaceutically acceptable salt, isotopically enriched analog, deuterated analog, isomer (such as a stereoisomer), and mixture of isomers (such as a mixture of stereoisomers), of the compounds described herein.

[75] "Pharmaceutically acceptable" or "physiologically acceptable" refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

[76] The term "pharmaceutically acceptable salt" of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" or "physiologically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. In addition, if the compounds described herein are

obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly 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 to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like. Salts derived from organic acids include, *e.g.*, acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines (*i.e.*, $\text{NH}_2(\text{alkyl})$), dialkyl amines (*i.e.*, $\text{HN}(\text{alkyl})_2$), trialkyl amines (*i.e.*, $\text{N}(\text{alkyl})_3$), substituted alkyl amines (*i.e.*, $\text{NH}_2(\text{substituted alkyl})$), di(substituted alkyl) amines (*i.e.*, $\text{HN}(\text{substituted alkyl})_2$), tri(substituted alkyl) amines (*i.e.*, $\text{N}(\text{substituted alkyl})_3$), alkenyl amines (*i.e.*, $\text{NH}_2(\text{alkenyl})$), dialkenyl amines (*i.e.*, $\text{HN}(\text{alkenyl})_2$), trialkenyl amines (*i.e.*, $\text{N}(\text{alkenyl})_3$), substituted alkenyl amines (*i.e.*, $\text{NH}_2(\text{substituted alkenyl})$), di(substituted alkenyl) amines (*i.e.*, $\text{HN}(\text{substituted alkenyl})_2$), tri(substituted alkenyl) amines (*i.e.*, $\text{N}(\text{substituted alkenyl})_3$), mono-, di- or tri- cycloalkyl amines (*i.e.*, $\text{NH}_2(\text{cycloalkyl})$, $\text{HN}(\text{cycloalkyl})_2$, $\text{N}(\text{cycloalkyl})_3$), mono-, di- or tri- arylamines (*i.e.*, $\text{NH}_2(\text{aryl})$, $\text{HN}(\text{aryl})_2$, $\text{N}(\text{aryl})_3$) or mixed amines, etc. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(isopropyl) amine, tri(n-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine and the like.

[77] The term “hydrate” refers to the complex formed by the combining of a compound described herein and water.

[78] A “solvate” refers to an association or complex of one or more solvent molecules and a compound of the disclosure. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, dimethylsulfoxide, ethylacetate, acetic acid and ethanolamine. Solvates include hydrates.

[79] Some of the compounds described herein may exist as tautomers. Tautomers are in equilibrium with one another. For example, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among

tautomers, the compounds are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, the amide containing compounds are understood to include their imidic acid tautomers. Likewise, the imidic acid containing compounds are understood to include their amide tautomers.

[80] The compounds described herein, or their pharmaceutically acceptable salts, may include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids. The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high performance liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

[81] A “stereoisomer” refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes “enantiomers,” which refers to two stereoisomers whose molecules are non-superimposable mirror images of one another.

[82] “Diastereomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other.

[83] Relative centers of the compounds as depicted herein are indicated graphically using the “thick bond” style (bold or parallel lines) and absolute stereochemistry is depicted using wedge bonds (bold or parallel lines).

[84] “Treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired clinical results may include one or more of the following: a) inhibiting the disease or condition (*e.g.*, decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); b) slowing or arresting the development of one or more clinical symptoms associated with the disease or condition (*e.g.*, stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition, and/or preventing or delaying the spread (*e.g.*, metastasis) of the disease or condition); and/or c) relieving the disease or condition, that is, causing the regression of clinical symptoms (*e.g.*, ameliorating the disease state, providing partial or total remission of the disease or condition, enhancing effect of another medication, delaying the

progression of the disease, increasing the quality of life, and/or prolonging survival).

[85] “Prevention” or “preventing” means any treatment of a disease or condition that causes the clinical symptoms of the disease or condition not to develop. Compounds may, in some embodiments, be administered to a subject (including a human) who is at risk or has a family history of the disease or condition.

[86] “Subject” refers to an animal, such as a mammal (including a human), that has been or will be the object of treatment, observation or experiment. The methods described herein may be useful in human therapy and/or veterinary applications. In some embodiments, the subject is a mammal. In one embodiment, the subject is a human.

[87] The term “therapeutically effective amount” or “effective amount” of a compound described herein or a pharmaceutically acceptable salt, tautomer, stereoisomer, mixture of stereoisomers, or deuterated analog thereof means an amount sufficient to effect treatment when administered to a subject, to provide a therapeutic benefit such as amelioration of symptoms or slowing of disease progression. The therapeutically effective amount may vary depending on the subject, and disease or condition being treated, the weight and age of the subject, the severity of the disease or condition, and the manner of administering, which can readily be determined by one of ordinary skill in the art. The effective amount of a compound of the disclosure in such a therapeutic method is, for example, from about 0.01 mg/kg/day to about 1000 mg/kg/day, or from about 0.1 mg/kg/day to about 100 mg/kg/day.

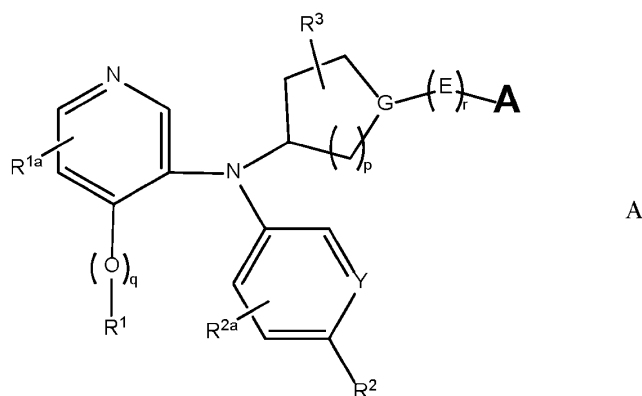
[88] The term “excipient” as used herein refers to an inert or inactive substance that may be used in the production of a drug or pharmaceutical composition, such as a tablet containing a compound as described herein (or pharmaceutically acceptable salt) as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a diluent, filler or extender, binder, disintegrant, humectant, coating, emulsifier or dispersing agent, compression/encapsulation aid, cream or lotion, lubricant, solution for parenteral administration, material for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders may include, e.g., carbomers, povidone, xanthan gum, etc.; coatings may include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include e.g. calcium carbonate, dextrose, fructose dc (dc – “directly compressible”), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, e.g., croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, e.g., maltodextrin, carrageenans, etc.; lubricants include, e.g., magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, e.g. dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.;

sweeteners include, e.g., aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc. In some cases, the term “excipient” encompasses pharmaceutically acceptable carriers.

[89] Additional definitions may also be provided below as appropriate.

II. Compounds

[90] In certain embodiments, the subject matter described herein is directed to a compound of Formula A:



wherein,

A is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl and 5- to 6-membered heterocyclyl, each of which is optionally substituted with one or more of R^{A1}, R^{A2} and R^{A3},

wherein, R^{A1}, R^{A2} and R^{A3} are each independently selected from the group consisting of C₁-C₆ alkyl, halo-C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, cyano, oxo, -C(O)-R^{A4}, -S(O)-R^{A4} and -S(O)₂-R^{A4},

wherein, R^{A4} is C₁-C₆ alkyl or C₃-C₈ cycloalkyl, and

wherein the oxo, if present, is formed by two of R^{A1}, R^{A2} and R^{A3} together with a carbon to which each is attached;

G is -CH, C-OH, or N;

E, if present, is -C(O)- or -O-;

Y is -CH or N;

p is 1, 2 or 3;

q is 1 or 0;

r is 1 or 0;

wherein, when r is 0, A is other than C_1-C_6 alkyl;

R^1 is selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl and halo- C_1-C_6 alkyl; or

R^1 is halo and q is 0;

R^{1a} is selected from the group consisting of hydrogen, halo, C_1-C_6 alkyl;

R^2 is selected from the group consisting of halo, halo- C_1-C_6 alkyl, halo- C_1-C_6 alkoxy and $-S(O)_2-(C_1-C_6$ alkyl);

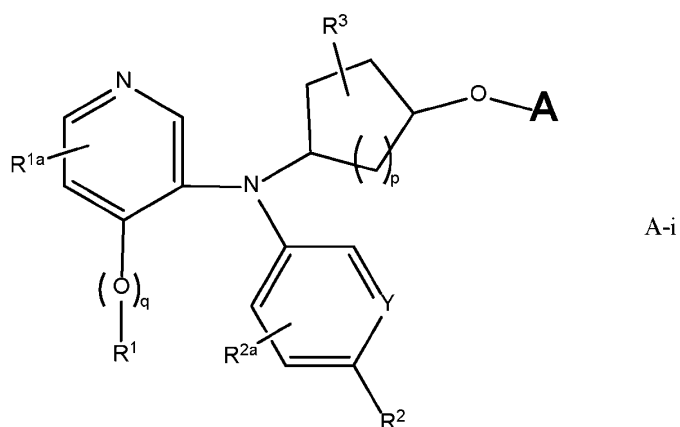
R^{2a} is selected from the group consisting of hydrogen and halo;

and,

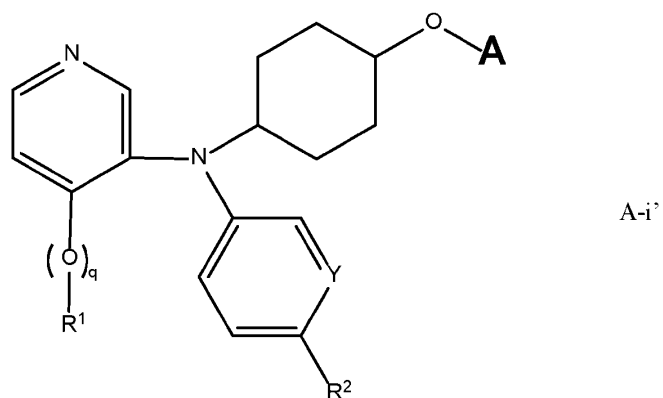
R^3 is hydrogen, halo, or C_1-C_6 alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

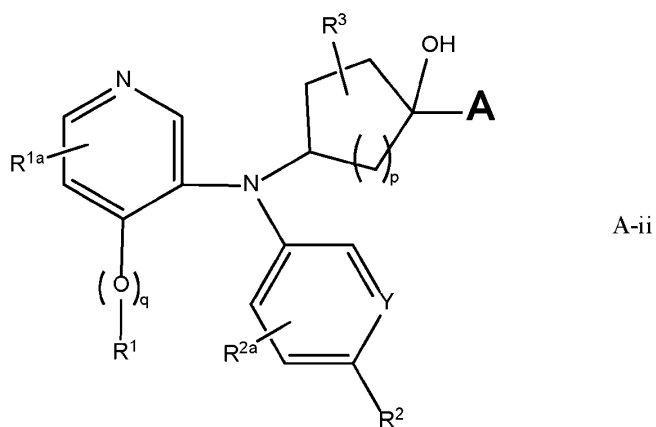
[91] In certain embodiments, compounds include those of Formula A, or pharmaceutically acceptable salts or solvates thereof, wherein G is CH , r is 1, and E is $-O-$, having a structure of Formula A-i:



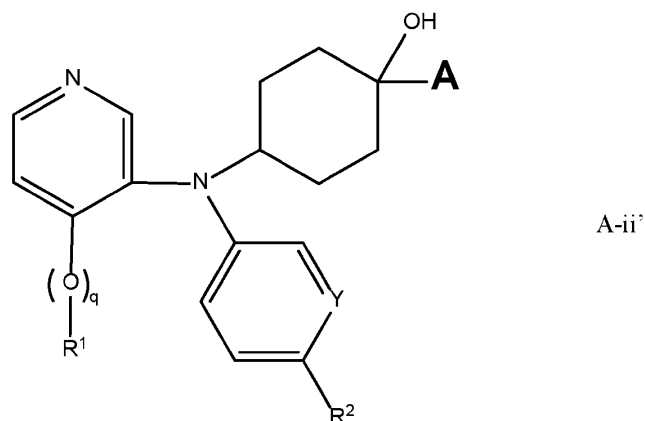
[92] In certain embodiments, compounds include those of Formula A-i, or pharmaceutically acceptable salts or solvates thereof, wherein p is 2; R^{1a} , R^{2a} , and R^3 are each hydrogen, and having a structure of Formula A-i':



[93] In certain embodiments, compounds include those of Formula A, or pharmaceutically acceptable salts or solvates thereof, wherein G is C-OH and r is 0, having a structure of Formula A-ii:



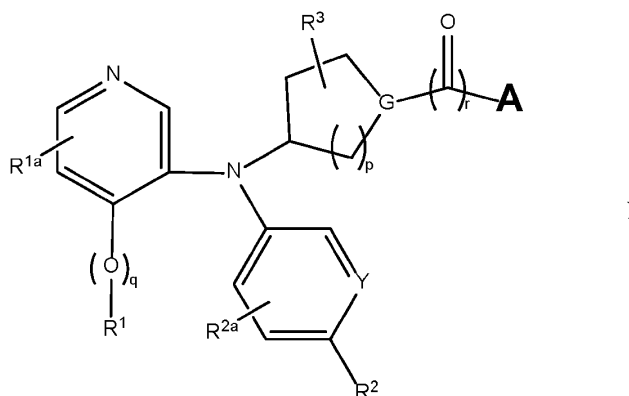
[94] In certain embodiments, compounds include those of Formula A, or pharmaceutically acceptable salts or solvates thereof, wherein p is 2 and R^{1a}, R^{2a}, and R³ are each hydrogen, having a structure of Formula A-ii:



[95] In certain embodiments, compounds include those of Formula A-i, Formula A-i', Formula A-ii, or Formula A-ii' or pharmaceutically acceptable salts or solvates thereof, wherein q is 1 and R^1 is CH_3 . In certain embodiments, compounds include those of Formula A-i, Formula A-i', Formula A-ii, or Formula A-ii', or pharmaceutically acceptable salts or solvates thereof, wherein R^2 is CF_3 or $OCHF_2$. In certain embodiments, compounds include those of Formula A-i, Formula A-i', Formula A-ii, or Formula A-ii', or pharmaceutically acceptable salts or solvates thereof, wherein Y is CH .

[96] In certain embodiments, compounds include those of Formula A, or pharmaceutically acceptable salts or solvates thereof, wherein E is $-C(O)-$, having a structure of Formula I.

[97] In certain embodiments, the subject matter described herein is directed to a compound of Formula I:



wherein,

A is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, phenyl, 5- to 6-membered heteroaryl and 5- to 6-membered heterocyclyl, each of which is optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} ,

wherein, R^{A1} , R^{A2} and R^{A3} are each independently selected from the group consisting of C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo, cyano, oxo, $-C(O)-R^{A4}$, $-S(O)-R^{A4}$ and $-S(O)_2-R^{A4}$,

wherein, R^{A4} is C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl, and

wherein the oxo, if present, is formed by two of R^{A1} , R^{A2} and R^{A3} together with a carbon to which each is attached;

G is -CH or N;

Y is -CH or N;

p is 1, 2 or 3;

q is 1 or 0;

r is 1 or 0;

wherein, when r is 0, A is other than C_1 - C_6 alkyl;

R^1 is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl and halo- C_1 - C_6 alkyl;

R^{1a} is selected from the group consisting of hydrogen, halo, and C_1 - C_6 alkyl;

R^2 is selected from the group consisting of halo, halo- C_1 - C_6 alkyl, halo- C_1 - C_6 alkoxy and $-S(O)_2-(C_1-C_6 \text{ alkyl})$;

R^{2a} is selected from the group consisting of hydrogen and halo;

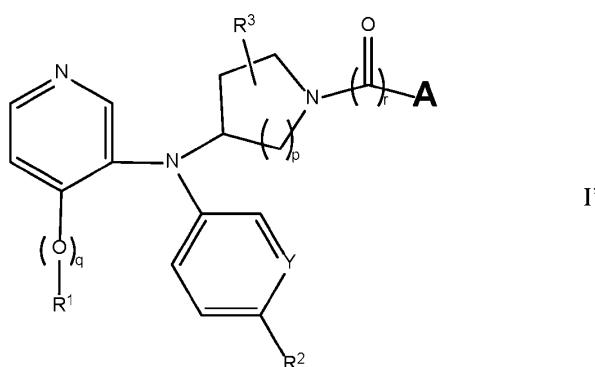
and,

R^3 is hydrogen, halo, or C_1 - C_6 alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

[98] In certain embodiments, compounds include those of Formulae A and I, or pharmaceutically acceptable salts or solvates thereof, wherein G is CH.

[99] In certain embodiments, compounds include those of Formula I, or pharmaceutically acceptable salts or solvates thereof, wherein G is N and include compounds having a structure of Formula I':

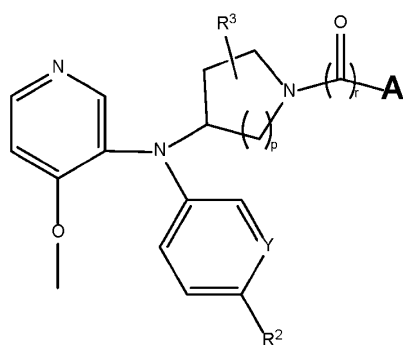


[100] In certain embodiments, compounds include those of Formula I or I', or pharmaceutically

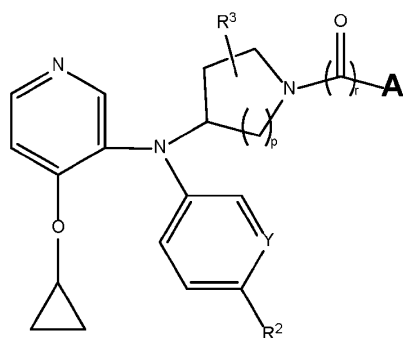
acceptable salts or solvates thereof, where q is 1. In certain embodiments, compounds include those of Formula I or I', or pharmaceutically acceptable salts or solvates thereof, where q is 0.

[101] In certain embodiments, compounds include those of Formula I or I', or pharmaceutically acceptable salts or solvates thereof, where R^1 is C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl. In certain embodiments, compounds include those of Formula I or I', or pharmaceutically acceptable salts or solvates thereof, where R^1 is methyl, ethyl or cyclopropyl.

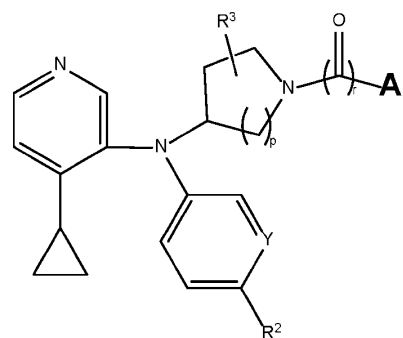
[102] In certain embodiments, compounds of Formula I or I', or pharmaceutically acceptable salts or solvates thereof, include compounds, or pharmaceutically acceptable salts or solvates thereof, having a structure of Formulae Ia, Ib, or Ic:



Ia

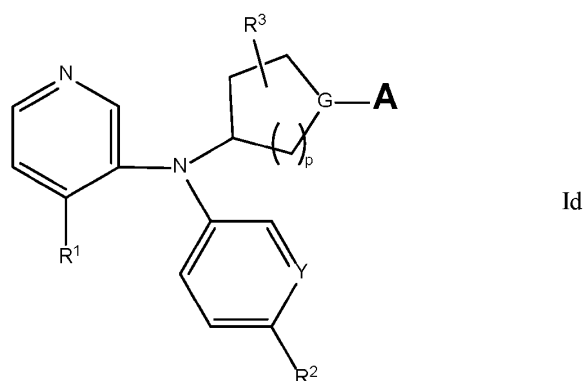


Ib



Ic

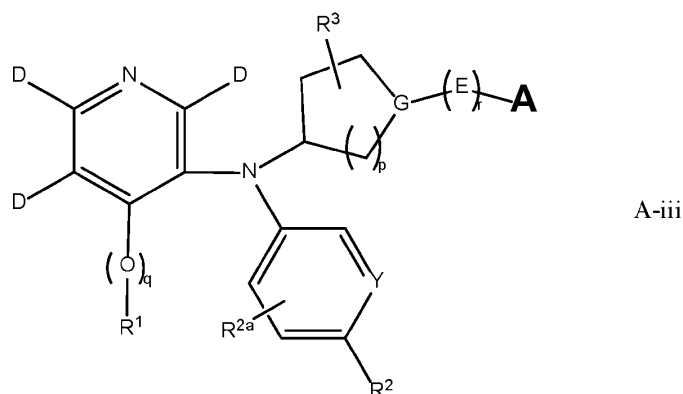
[103] In certain embodiments, compounds include those of Formula A, or pharmaceutically acceptable salts or solvates thereof, wherein q is 0 and R^1 is halogen. In certain embodiments, compounds include those of Formula A, or pharmaceutically acceptable salts or solvates thereof, wherein q is 0 and R^1 is -Cl. In certain embodiments, compounds include those of Formula A, or pharmaceutically acceptable salts or solvates thereof, wherein r and q are each 0, R^{1a} and R^{1b} are each hydrogen, and R^1 is halogen, having a structure of Formula Id:



[104] In certain embodiments, compounds include those of Formula Id, where R^1 is -Cl. In certain embodiments, compounds include those of Formula Id, where R^2 is CF_3 . In certain embodiments, compounds include those of Formula Id, where R^3 is hydrogen. In certain embodiments, compounds include those of Formula Id, where Y is N. In certain embodiments, compounds include those of Formula Id, where G is N and p is 2.

[105] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', I, I', Ia, Ib, Ic or Id, where one or more hydrogen atoms is replaced with deuterium.

[106] In certain embodiments, compounds include those of Formula A, having a structure of Formula A-iii:



[107] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic or Id, wherein R¹ is -CD₃.

[108] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, wherein Y is N. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id where Y is -CH.

[109] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id where R² is halo-C₁-C₆ alkyl or halo-C₁-C₆ alkoxy. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id where R² is halo-C₁-C₆ alkyl. In certain embodiments, compounds include those of Formulae I, I', Ia, Ib, or Ic, where R² is -CF₃. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R² is halo-C₁-C₆ alkyloxy. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R² is -O-CHF₂.

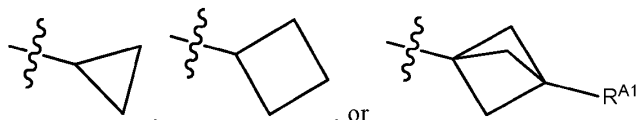
[110] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where p is 1 or 2. In certain embodiments, compounds include those of Formulae A, A-i, A-ii, A-iii, I, I', Ia, Ib, Ic, or Id, where p is 1. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where p is 2.

[111] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R³ is C₁-C₆ alkyl. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R³ is methyl. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R³ is hydrogen.

[112] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-iii, I, I', Ia, Ib, or Ic, where r is 1. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-iii, I, I', Ia, Ib, or Ic, where r is 1 and A is C₁-C₆ alkyl. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-iii, I, I', Ia, Ib, or Ic, where r is 1 and A is -CH₃ or -CH₂CH₃. In certain

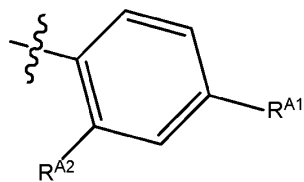
embodiments, compounds include those of Formulae A, A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where r is 0. In certain embodiments, compounds include those of Formulae A, A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where r is 0 and A is C₃-C₈ cycloalkyl, optionally substituted with one or more of R^{A1}, R^{A2}, and R^{A3}.

[113] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where r is 0 or 1 and A is C₃-C₅ cycloalkyl, optionally substituted with one or more of R^{A1}, R^{A2}, and R^{A3}. In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii',

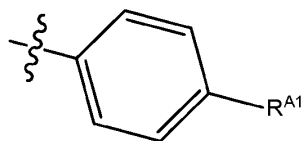


A-iii, I, I', Ia, Ib, Ic, or Id, where A is , , or . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R^{A1} is cyano or halo C₁-C₆ alkyl. In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, or Ic, where R^{A1} is -CF₃. In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-iii, I, I', Ia, Ib, or Ic, where r is 1.

[114] In certain embodiments, compounds include those of Formulae A, A-ii, A-ii', I, I', Ia, Ib, Ic, or Id, where r is 0 and A is phenyl, optionally substituted with one or more of R^{A1}, R^{A2}, and R^{A3}. In certain embodiments, compounds include those of Formulae A, A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where r is 0 and A is phenyl, optionally substituted with one or more of R^{A1} and R^{A2}. In certain embodiments, compounds include those of Formulae A, A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where r is 0 and A has the



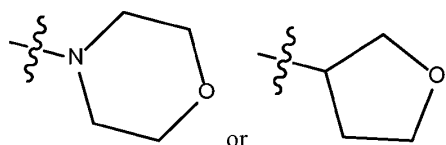
structure: . In instances of the above embodiments, compounds include those of Formulae A, A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R^{A1} is -S(O)₂-R^{A4} and R^{A2} is halo. In certain embodiments, compounds include those of Formulae A, A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where r is 0



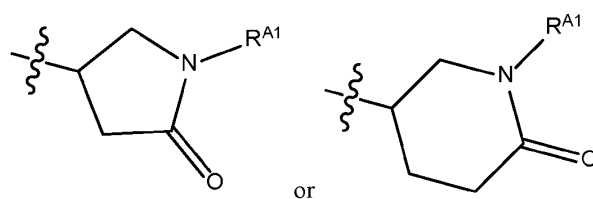
and A has the structure: . In instances of the above embodiment, compounds include those of Formulae A, A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R^{A1} is selected from the group consisting of halo, cyano, -S(O)₂-R^{A4} and -C(O)-R^{A4}.

[115] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where r is 0 or 1 and A is 5- to 6-membered heterocyclyl, optionally substituted with

one or more of R^{A1} , R^{A2} , and R^{A3} . In instances of the above embodiment, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is heterocyclyl comprising 1 or 2 heteroatoms selected from the group consisting of N, S, and O. In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is 5- to 6-membered heterocyclyl. In instances of the above embodiment, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is 5- to 6-membered heterocyclyl comprising 1 or 2 heteroatoms selected from the group consisting of N, S, and O. In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id,



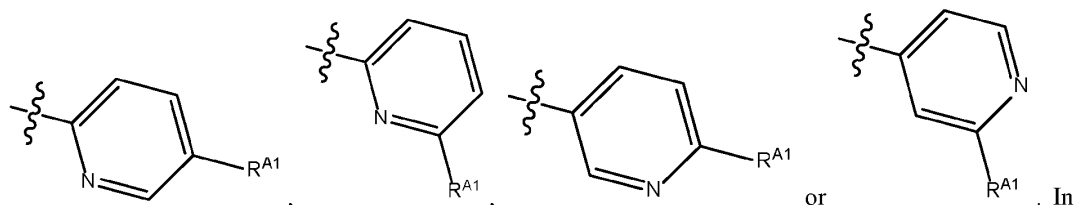
[116] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where r is 0 or 1 and A is 5- to 6-membered heterocyclyl, substituted with R^{A1} , R^{A2} , and R^{A3} . In instances of the above embodiment, compounds include those of Formulae A, A-i, A-i', A-ii, A-iii, A-ii', I, I', Ia, Ib, Ic or Id, where R^{A2} and R^{A3} together with a carbon to which each is attached form



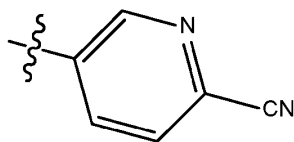
, and R^{A1} is C_1 - C_6 alkyl. In instances of the above embodiment, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where R^{A2} is ethyl.

[117] In certain embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, or Ic, where r is 0 or 1 and A is 5- to 6-membered heteroaryl, optionally substituted with one or more of R^{A1} , R^{A2} , and R^{A3} . In instances of the above embodiment, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, and thiazolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, oxadiazolyl, and pyrrolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is pyridinyl, optionally substituted with one or more of R^{A1} , R^{A2} , and R^{A3} . In instances of the above

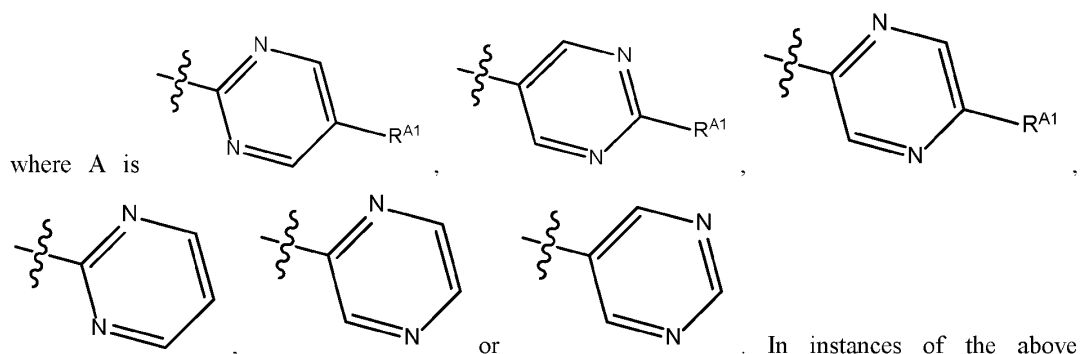
embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A pyridinyl, optionally substituted with R^{A1} . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is



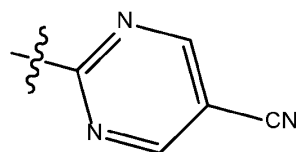
In instances of the above embodiments, compounds include those of Formulae I, I', Ia, Ib, or Ic, where R^{A1} is selected from the group consisting of C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo, cyano and $-S(O)_2-R^{A4}$. In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia,



Ib, Ic or Id, where A is . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is pyrimidinyl or pyrazinyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where A is pyrimidinyl or pyrazinyl, optionally substituted with R^{A1} . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id,

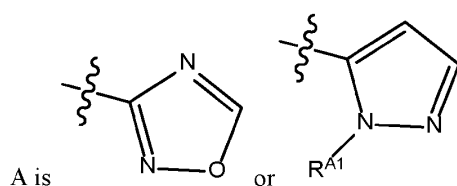


In instances of the above embodiments, compounds include those of Formulae I, I', Ia, Ib, Ic, or Id, where R^{A1} is selected from the group consisting of C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo, cyano and $-S(O)_2-R^{A4}$. In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic or Id, where R^{A1} is CH_2OCH_3 . In instances of the above embodiments, compounds include those of Formulae A,



A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic or Id, where A is

In instances of the above embodiments, compounds include those of Formulae I, I', Ia, Ib, or Ic, where A is oxadiazolyl and pyrrolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, or Id, where oxadiazolyl and pyrrolyl, optionally substituted with R^{A1} . In instances of the above embodiments, compounds include those of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, Id, where



[118] The subject matter described herein includes the following compounds in Table 1, or pharmaceutically acceptable salts thereof. Individual enantiomers and diastereomers are included in the table below by compound name, and their corresponding structures can be readily determined therefrom. In some instances, the enantiomers or diastereomers of the present disclosure may be identified by their respective properties, for example, retention times by chiral HPLC, NMR peaks, and/or biological activities (e.g., as described further in the Examples), whereas the absolute stereo configurations of one or more chiral centers has not been assigned.

[119] Table 1. Compounds

Cpd. No.	Structure	Compound Name
1		(S)-4-cyclopropyl-N-(4-(trifluoromethyl)phenyl)-N-(1-(5-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)pyridin-3-amine
2		2-(4-((4-cyclopropylpyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile

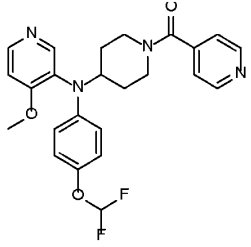
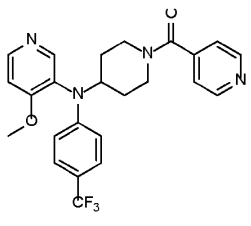
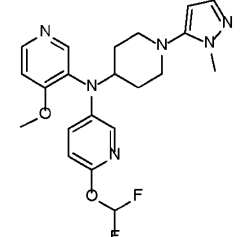
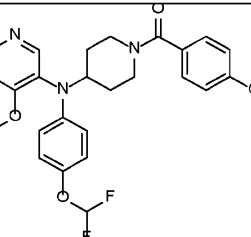
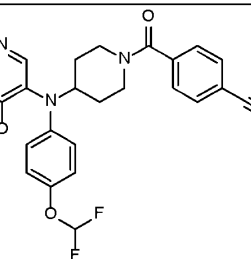
Cpd. No.	Structure	Compound Name
3		4-cyclopropyl-N-(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)-N-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine
4		2-(4-((4-ethylpyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
5		2-(4-((4-methoxypyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
6		1-(4-((4-cyclopropylpyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)ethan-1-one
7		1-(4-((4-cyclopropylpyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)propan-1-one

Cpd. No.	Structure	Compound Name
8		2-((4-(4-cyclopropoxy)pyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
9		4-(4-((4-methoxypyridin-3-yl)(4-(methylsulfonyl)phenyl)amino)piperidin-1-yl)benzonitrile
10		4-cyclopropyl-N-(1-(4-(cyclopropylsulfonyl)phenyl)piperidin-4-yl)-N-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine
11		6-(4-((4-methoxypyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)nicotinonitrile
12		4-methoxy-N-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine

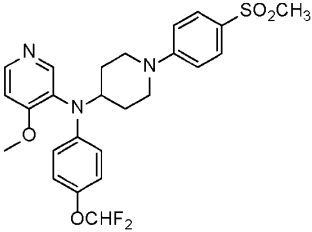
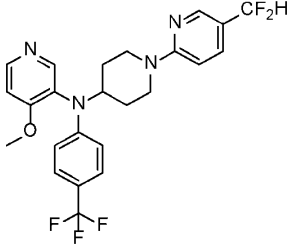
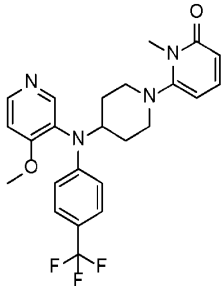
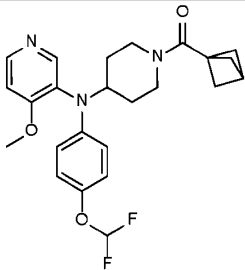
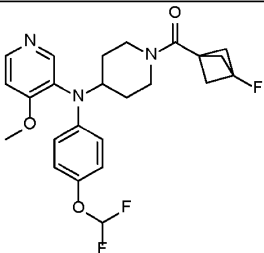
Cpd. No.	Structure	Compound Name
13		4-methoxy- <i>N</i> -(4-(trifluoromethyl)phenyl)- <i>N</i> -(1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)pyridin-3-amine
14		6-(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)nicotinonitrile
15		2-(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
16		4-methoxy- <i>N</i> -(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)- <i>N</i> -(4-(trifluoromethyl)phenyl)pyridin-3-amine
17		4-methoxy- <i>N</i> -(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)- <i>N</i> -(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine

Cpd. No.	Structure	Compound Name
18		2-(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
19		2-(4-((4-(difluoromethoxy)phenyl)(4-methylpyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
20		4-methoxy-N-(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine
21		(R)-4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl(tetrahydrofuran-3-yl)methanone
22		1-(4-((4-ethoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)-2-methylpiperidin-1-yl)propan-1-one

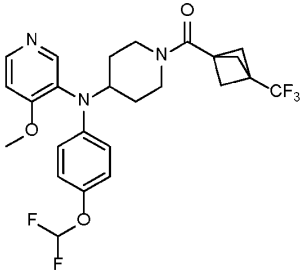
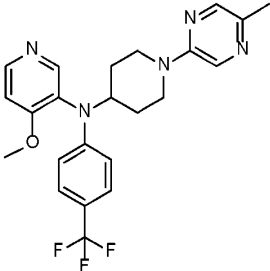
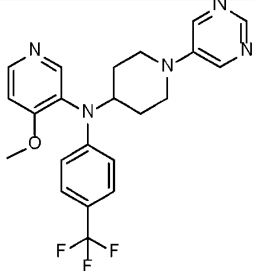
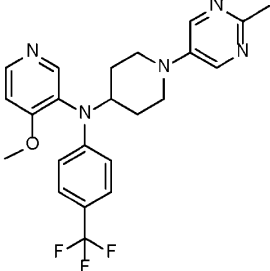
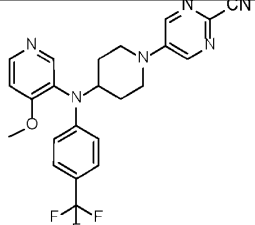
Cpd. No.	Structure	Compound Name
23		1-(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)propan-1-one
24		N-(4-(difluoromethoxy)phenyl)-4-methoxy-N-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)pyridin-3-amine
25		2-(4-((6-(difluoromethoxy)pyridin-3-yl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
26		6-(difluoromethoxy)-N-(4-methoxypyridin-3-yl)-N-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)pyridin-3-amine
27		N-(4-(difluoromethoxy)phenyl)-4-methoxy-N-(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)pyridin-3-amine

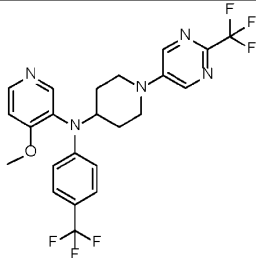
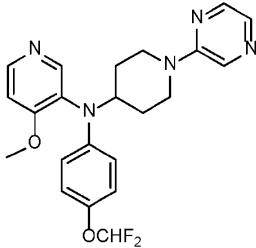
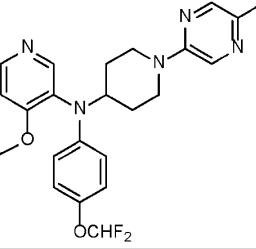
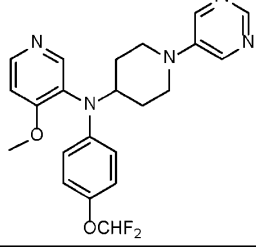
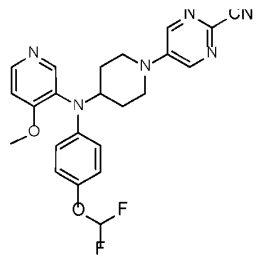
Cpd. No.	Structure	Compound Name
28		(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(pyridin-4-yl)methanone
29		(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(pyridin-4-yl)methanone
30		6-(difluoromethoxy)-N-(4-methoxypyridin-3-yl)-N-(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)pyridin-3-amine
31		(4-chlorophenyl)(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)methanone
32		4-(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carbonyl)benzonitrile

Cpd. No.	Structure	Compound Name
33		(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(4-(methylsulfonyl)phenyl)methanone
34		6-(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)nicotinonitrile
35		cyclobutyl(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)methanone
36		cyclobutyl(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone
37		(4-Fluoro-2-(methylsulfonyl)phenyl)(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone

Cpd. No.	Structure	Compound Name
38		<i>N</i> -(4-(Difluoromethoxy)phenyl)-4-methoxy- <i>N</i> -(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)pyridin-3-amine
39		<i>N</i> -(1-(5-(Difluoromethyl)pyridin-2-yl)piperidin-4-yl)-4-methoxy- <i>N</i> -(4-(trifluoromethyl)phenyl)pyridin-3-amine
40		6-(4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)-1-methylpyridin-2(1H)-one
41		bicyclo[1.1.1]pentan-1-yl(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)methanone
42		(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(3-fluorobicyclo[1.1.1]pentan-1-yl)methanone

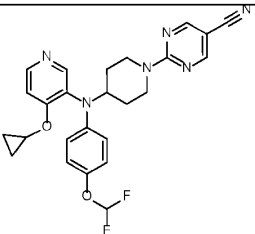
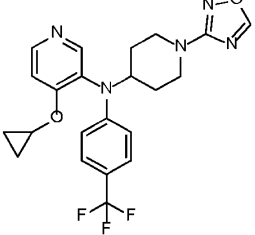
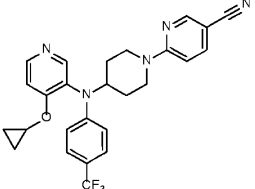
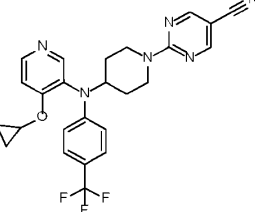
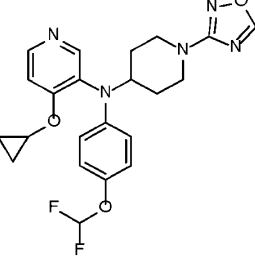
Cpd. No.	Structure	Compound Name
43		3-(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carbonyl)bicyclo[1.1.1]pentane-1-carbonitrile
44		4-methoxy-N-(1-(pyrazin-2-yl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine
45		bicyclo[1.1.1]pentan-1-yl(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone
46		(3-fluorobicyclo[1.1.1]pentan-1-yl)(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone
47		3-(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidine-1-carbonyl)bicyclo[1.1.1]pentane-1-carbonitrile
48		(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)methanone

Cpd. No.	Structure	Compound Name
49		(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)methanone
50		4-methoxy-N-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine
51		4-methoxy-N-(1-(pyrimidin-5-yl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine
52		4-methoxy-N-(1-(2-methylpyrimidin-5-yl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine
53		5-(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)pyrimidine-2-carbonitrile

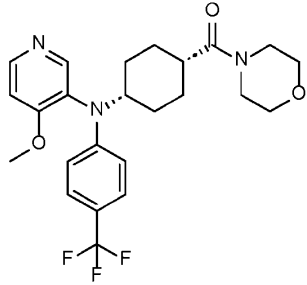
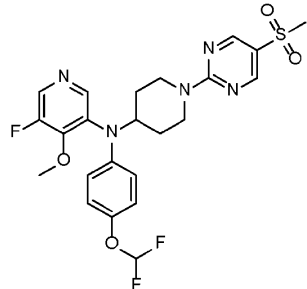
Cpd. No.	Structure	Compound Name
54		4-methoxy- <i>N</i> -(4-(trifluoromethyl)phenyl)- <i>N</i> -(1-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-4-yl)pyridin-3-amine
55		<i>N</i> -(4-(difluoromethoxy)phenyl)-4-methoxy- <i>N</i> -(1-(pyrazin-2-yl)piperidin-4-yl)pyridin-3-amine
56		<i>N</i> -(4-(difluoromethoxy)phenyl)-4-methoxy- <i>N</i> -(1-(5-methylpyrazin-2-yl)piperidin-4-yl)pyridin-3-amine
57		<i>N</i> -(4-(difluoromethoxy)phenyl)-4-methoxy- <i>N</i> -(1-(pyrimidin-5-yl)piperidin-4-yl)pyridin-3-amine
58		5-(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-2-carbonitrile

Cpd. No.	Structure	Compound Name
59		N-(4-(difluoromethoxy)phenyl)-4-methoxy-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-4-yl)pyridin-3-amine
60		((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl(2-methylpyridin-4-yl)methanone
61		4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl(2-(trifluoromethyl)pyridin-4-yl)methanone
62		4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl(2-methylpyridin-4-yl)methanone
63		4-Methoxy-N-(1-(4-(methylsulfinyl)phenyl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine

Cpd. No.	Structure	Compound Name
64		<i>N</i> -(1-(2-Fluoro-4-(methylsulfonyl)phenyl)piperidin-4-yl)-4-methoxy- <i>N</i> -(4-(trifluoromethyl)phenyl)pyridin-3-amine
65		2-(4-((4-Fluorophenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
66		4-cyclopropoxy- <i>N</i> -(4-(difluoromethoxy)phenyl)- <i>N</i> -(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)pyridin-3-amine
67		4-cyclopropoxy- <i>N</i> -(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)- <i>N</i> -(4-(trifluoromethyl)phenyl)pyridin-3-amine
68		6-(4-((4-cyclopropoxypyridin-3-yl)(4-(difluoromethoxy)phenyl)amino)piperidin-1-yl)nicotinonitrile

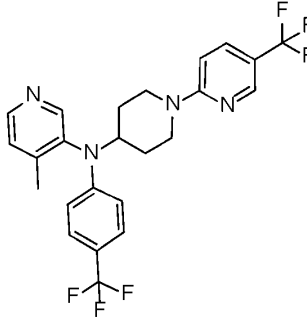
Cpd. No.	Structure	Compound Name
69		2-(4-((4-cyclopropoxypyridin-3-yl)(4-(difluoromethoxy)phenyl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
70		N-(1-(1,2,4-oxadiazol-3-yl)piperidin-4-yl)-4-cyclopropoxy-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine
71		6-(4-((4-cyclopropoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)nicotinonitrile
72		2-(4-((4-cyclopropoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
73		N-(1-(1,2,4-oxadiazol-3-yl)piperidin-4-yl)-4-cyclopropoxy-N-(4-(difluoromethoxy)phenyl)pyridin-3-amine

Cpd. No.	Structure	Compound Name
74		2-(4-((4-(difluoromethoxy)-3-fluorophenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile
75		N-(4-(difluoromethoxy)phenyl)-4-methoxy-N-(1-(5-(methylsulfonyl)pyridin-2-yl)piperidin-4-yl)pyridin-3-amine
76		4-methoxy-N-(1-(5-(methylsulfonyl)pyridin-2-yl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine
77		((trans)-4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)cyclohexyl)(morpholino) methanone

Cpd. No.	Structure	Compound Name
78		((cis)-4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)cyclohexyl)(morpholino)methanone
79		N-(4-(difluoromethoxy)phenyl)-5-fluoro-4-methoxy-N-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)pyridin-3-amine

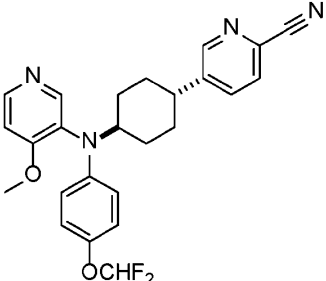
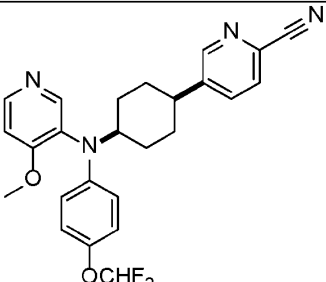
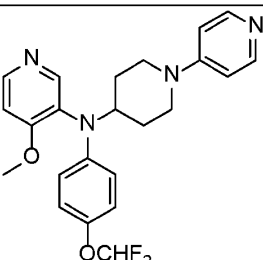
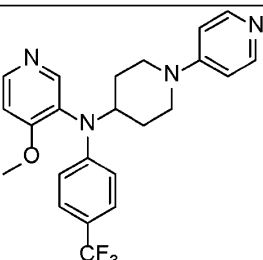
[120] The subject matter described herein includes the following compounds in Table A, or pharmaceutically acceptable salts thereof.

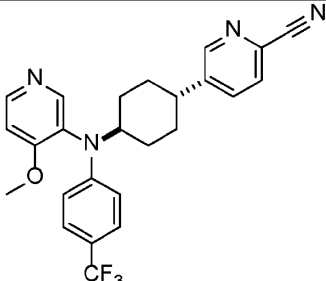
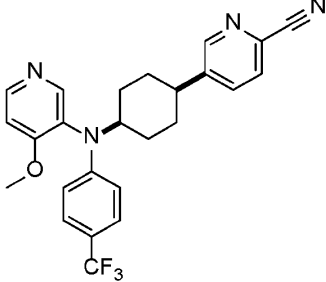
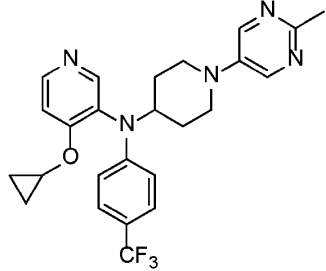
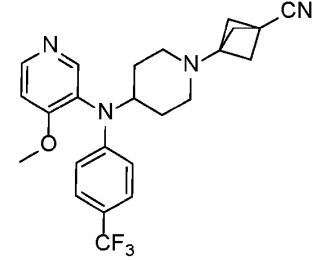
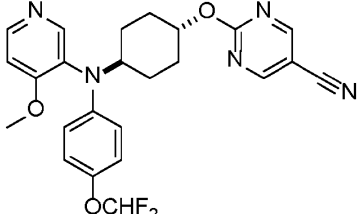
[121] Table A. Compounds

Cpd. No.	Structure	Compound Name
100		(4-methyl-3-pyridyl)[p-(trifluoromethyl)phenyl]{1-[5-(trifluoromethyl)-2-pyridyl]-4-piperidyl}amine

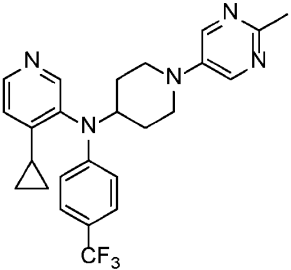
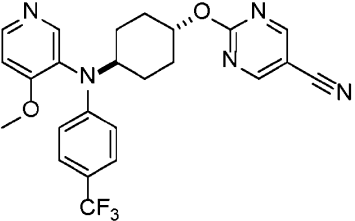
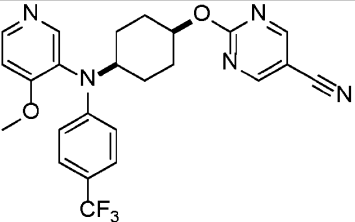
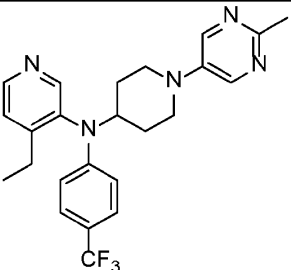
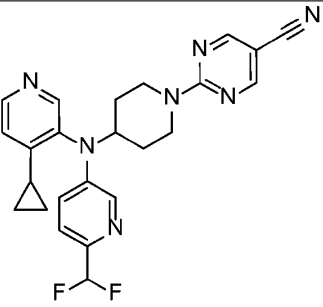
Cpd. No.	Structure	Compound Name
101		2-{4-[(4-methyl-3-pyridyl)[6-(trifluoromethyl)-3-pyridyl]amino]-1-piperidyl}-5-pyrimidinecarbonitrile
102		2-{4-[(4-chloro-3-pyridyl)[6-(trifluoromethyl)-3-pyridyl]amino]-1-piperidyl}-5-pyrimidinecarbonitrile
103		(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]amine
104-a		<i>trans</i> - 5-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyloxy}-2-pyridinecarbonitrile
104-b		<i>cis</i> - 5-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyloxy}-2-pyridinecarbonitrile

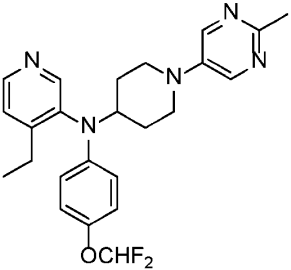
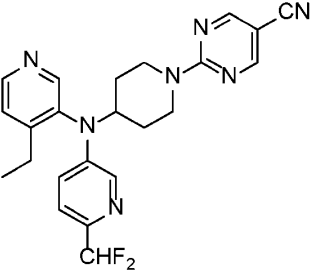
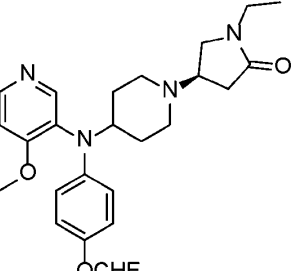
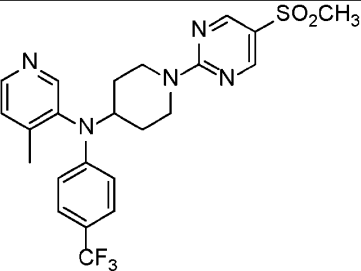
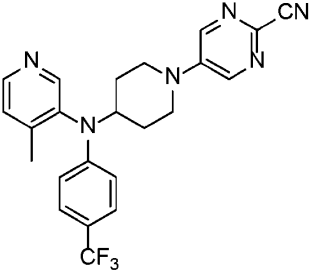
Cpd. No.	Structure	Compound Name
105-a		<i>trans</i> - 5-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyloxy}-2-pyridinecarbonitrile
105-b		<i>cis</i> - 5-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyloxy}-2-pyridinecarbonitrile
106		(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl){1-[p-(methylsulfinyl)phenyl]-4-piperidyl}amine
107		(p-difluoromethoxyphenyl)[1-(2-fluoro-4-mesylphenyl)-4-piperidyl](4-methoxy-3-pyridyl)amine
108-a		<i>trans</i> - 5-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyl}-2-pyridinecarbonitrile

Cpd. No.	Structure	Compound Name
		
108-b		<i>cis</i> - 5-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyl}-2-pyridinecarbonitrile
109		(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)[1-(4-pyridyl)-4-piperidyl]amine
110		(4-methoxy-3-pyridyl)[1-(4-pyridyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine

Cpd. No.	Structure	Compound Name
111-a		<i>trans</i> - 5-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyl}-2-pyridinecarbonitrile
111-b		<i>cis</i> - 5-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyl}-2-pyridinecarbonitrile
112		(4-cyclopropoxy-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine
113		3-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]-1-piperidyl}bicyclo[1.1.1]pentane-1-carbonitrile
114-a		<i>trans</i> - 2-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyloxy}-5-pyrimidinecarbonitrile

Cpd. No.	Structure	Compound Name
114-b		<i>cis</i> -2-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyloxy}-5-pyrimidinecarbonitrile
115		(4-methyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine
116		(p-difluoromethoxyphenyl)(4-methyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]amine
117		{1-[2-(methoxymethyl)-5-pyrimidinyl]-4-piperidyl}(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amine
118		(4-cyclopropyl-3-pyridyl)(p-difluoromethoxyphenyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]amine

Cpd. No.	Structure	Compound Name
119		(4-cyclopropyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine
120-a		<i>trans</i> -2-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyloxy}-5-pyrimidinecarbonitrile
120-b		<i>cis</i> -2-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyloxy}-5-pyrimidinecarbonitrile
121		(4-ethyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine
122		2-{4-[(4-cyclopropyl-3-pyridyl)[6-(difluoromethyl)-3-pyridyl]amino]-1-piperidyl}-5-pyrimidinecarbonitrile

Cpd. No.	Structure	Compound Name
123		(p-difluoromethoxyphenyl)(4-ethyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]amine
124		2-(4-{[6-(difluoromethyl)-3-pyridyl](4-ethyl-3-pyridyl)amino}-1-piperidyl)-5-pyrimidinecarbonitrile
126		(R)-4-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]-1-piperidyl}-1-ethyl-2-pyrrolidinone
127		[1-(5-mesyl-2-pyrimidinyl)-4-piperidyl](4-methyl-3-pyridyl)[p-(trifluoromethyl)phenyl]amine
128		5-{4-[(4-methyl-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]-1-piperidyl}-2-pyrimidinecarbonitrile

Cpd. No.	Structure	Compound Name
129		(S)-1'-ethyl-4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino][1,3'-bipiperidyl]-6'-one
130		[4-(² H ₃)methoxy(2,5,6- ² H ₃)-3-pyridyl][1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine
131		(p-difluoromethoxyphenyl)[1-(5-mesyl-2-pyrimidinyl)-4-piperidyl][4-(² H ₃)methoxy(2,5,6- ² H ₃)-3-pyridyl]amine
132		[4-(² H ₃)methoxy-3-pyridyl][1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine
133		(p-difluoromethoxyphenyl)[1-(5-mesyl-2-pyrimidinyl)-4-piperidyl][4-(² H ₃)methoxy-3-pyridyl]amine

Cpd. No.	Structure	Compound Name
134-a		2-((1S,4S)-1-hydroxy-4-((4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino)cyclohexyl)-5-pyrimidinecarbonitrile
134-b		2-((1R,4R)-1-hydroxy-4-((4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino)cyclohexyl)-5-pyrimidinecarbonitrile
135-a		2-((1S,4S)-4-((4-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino)-1-hydroxycyclohexyl)-5-pyrimidinecarbonitrile
135-b		2-((1R,4R)-4-((4-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino)-1-hydroxycyclohexyl)-5-pyrimidinecarbonitrile

[122] In certain embodiments, the subject matter described herein is directed to a compound selected from Table 1. In certain embodiments, the subject matter described herein is directed to a compound selected from Table A. In certain embodiments, the subject matter described herein is directed to a compound selected from Table 1 and Table A.

III. *Pharmaceutical Compositions and Modes of Administration*

[123] Compounds provided herein are usually administered in the form of pharmaceutical

compositions. Thus, provided herein are also pharmaceutical compositions that comprise one or more of the compounds described herein or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof and one or more pharmaceutically acceptable excipients. Suitable pharmaceutically acceptable excipients may include, for example, inert solid diluents and fillers, liquid diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art. See, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, Pa. 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.).

[124] In some embodiments, the pharmaceutical composition comprises a compound of Formula A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula A-i, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula A-i', or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula A-ii, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula A-ii', or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula A-iii, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula I', or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula Ia, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula Ib, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula Ic, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Formula Id, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Table A, or a pharmaceutically

acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises a compound of Table 1 and Table A, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[125] The pharmaceutical compositions may be administered in either single or multiple doses. The pharmaceutical composition may be administered by various methods including, for example, rectal, buccal, intranasal, and transdermal routes. In certain embodiments, the pharmaceutical composition may be administered by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

[126] One mode for administration is parenteral, for example, by injection. The forms in which the pharmaceutical compositions described herein may be incorporated for administration by injection include, for example, aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[127] Oral administration may be another route for administration of the compounds described herein. Administration may be via, for example, capsule or tablet, such as enteric coated tablets. In making the pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be in the form of a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable solutions, and sterile packaged powders.

[128] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[129] The compositions that include at least one compound described herein or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof can be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer

matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods disclosed herein employ transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds described herein in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

[130] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein or a pharmaceutically acceptable salt, a stereoisomer, or a mixture of stereoisomers thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[131] The tablets or pills of the compounds described herein may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. For example, the tablet or pill can include an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer that serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

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

[133] The specific dose level of a compound of the present application for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease in the subject undergoing therapy. For example, a

dosage may be expressed as a number of milligrams of a compound described herein per kilogram of the subject's body weight (mg/kg). Dosages of between about 0.1 and 150 mg/kg may be appropriate. In some embodiments, about 0.1 and 100 mg/kg may be appropriate. In other embodiments a dosage of between 0.5 and 60 mg/kg may be appropriate. Normalizing according to the subject's body weight is particularly useful when adjusting dosages between subjects of widely disparate size, such as occurs when using the drug in both children and adult humans or when converting an effective dosage in a non-human subject such as dog to a dosage suitable for a human subject. A dose may be administered once a day (QID), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. In addition, toxicity factors may influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less frequently for a specified period of time. The regimen may be repeated for a number of cycles of therapy.

IV. Methods of Treatment

[134] Described herein are methods for promoting myelination of central nervous system neurons in a subject suffering from a myelin-related disorder, the method comprising administering to the subject a therapeutically effective amount of a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutical composition comprising the same. In certain embodiments, the subject matter disclosed herein is directed to a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, for promoting myelination of central nervous system neurons in a subject suffering from a myelin-related disorder. In another embodiment, the subject matter described herein is directed to the use of a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for promoting myelination of central nervous system neurons in a subject suffering from a myelin-related disorder.

[135] In certain embodiments, in the methods for promoting myelination of central nervous system neurons in a subject suffering from a myelin-related disorder, the compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the same, inhibits enzyme mediated synthesis of one or more sterol intermediates in the cholesterol biosynthesis pathway.

[136] In certain embodiments, in the methods for promoting myelination of central nervous system neurons in a subject suffering from a myelin-related disorder, the compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the same, promotes accumulation of $\Delta 8,9$ -unsaturated sterol

intermediates in the cholesterol biosynthesis pathway.

[137] In certain embodiments, in the methods for promoting myelination of central nervous system neurons in a subject suffering from a myelin-related disorder, the compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the same, inhibits one or more of CYP51, sterol-14-reductase, or EBP enzyme mediated synthesis of sterol intermediates in the cholesterol biosynthesis pathway. In certain embodiments, the compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, and Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the same, inhibits CYP51.

[138] In certain embodiments, in the methods for promoting myelination of central nervous system neurons in a subject suffering from a myelin-related disorder, the compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the same, induces, promotes, and/or modulates oligodendrocyte precursor cell (OPC) differentiation, proliferation and/or maturation. In certain embodiments, the induction of OPC differentiation is characterized by an increase in myelin basic protein (MBP) expression.

[139] In certain embodiments, the subject matter described herein is directed to a method of treating a disorder in a subject in need thereof, the method comprising administering to the subject in need thereof a therapeutically effective amount of a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the subject has a myelin-related disorder. In some embodiments, the compound of Formula A is a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-iii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula Id, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula I', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula Ia, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ib, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ic, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments,

the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Table A, or a pharmaceutically acceptable salt or solvate thereof.

[140] In certain embodiments, the subject matter disclosed herein is directed to a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, for use in treating a disorder in a subject in need thereof. In certain embodiments, the subject has a myelin-related disorder. In some embodiments, the compound of Formula A is a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-iii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula Id, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula I', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula Ia, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ib, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ic, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Table A, or a pharmaceutically acceptable salt or solvate thereof.

[141] In certain embodiments, the subject matter disclosed herein is directed to the use of a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disorder in a subject in need thereof. In certain embodiments, the subject has a myelin-related disorder. In some embodiments, the compound of Formula A is a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii', or a pharmaceutically acceptable salt or solvate thereof.

acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-iii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula Id, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula I', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula Ia, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ib, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ic, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Table A, or a pharmaceutically acceptable salt or solvate thereof.

[142] In certain embodiments, the subject matter disclosed herein is directed to a method of promoting myelination in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the subject has a myelin-related disorder. In some embodiments, the compound of Formula A is a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-iii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula Id, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula I', or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the subject has a myelin-related disorder. In some embodiments, the compound of Formula I is a compound of Formula Ia, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ib, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ic, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Table A, or a pharmaceutically acceptable salt or solvate thereof.

[143] In certain embodiments, the subject matter disclosed herein is directed to a compound of

Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the compound, for use in promoting myelination in a subject in need thereof. In certain embodiments, the subject has a myelin-related disorder. In some embodiments, the compound of Formula A is a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-iii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula Id, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula I', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula Ia, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ib, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ic, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Table A, or a pharmaceutically acceptable salt or solvate thereof.

[144] In certain embodiments, the subject matter disclosed herein is directed to use of a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the compound, in the manufacture of a medicament for promoting myelination in a subject in need thereof. In certain embodiments, the subject has a myelin-related disorder. In some embodiments, the compound of Formula A is a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-iii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of

Formula Id, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula I', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula Ia, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ib, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ic, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Table A, or a pharmaceutically acceptable salt or solvate thereof.

[145] In certain embodiments, the subject matter disclosed herein is directed to a method of inducing endogenous oligodendrocyte precursor cell (OPC) differentiation in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising the same. In certain embodiments, the subject is suffering from a myelin-related disorder. In certain embodiments, the myelin-related disorder is multiple sclerosis.

[146] Such myelin-related disorders include, but are not limited to, multiple sclerosis (MS), neuromyelitis optica (NMO), optic neuritis, pediatric leukodystrophies, neonatal white matter injury, age-related dementia, schizophrenia, progressive multifocal leukoencephalopathy (PML), encephalomyelitis (EPL), central pontine myelolysis (CPM), adrenoleukodystrophy, Alexander's disease, Pelizaeus Merzbacher disease (PMD), Vanishing White Matter Disease, Wallerian Degeneration, transverse myelitis, amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, Parkinson's disease, spinal cord injury, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, stroke, acute ischemic optic neuropathy, vitamin E deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, trigeminal neuralgia, acute disseminated encephalitis, Guillian-Barre syndrome, Charcot-Marie-Tooth disease, Bell's palsy, and radiation-induced demyelination.

[147] The compound of Formulae A, A-i, A-i', A-ii, A-ii', A-iii, I, I', Ia, Ib, Ic, and Id, or a pharmaceutically acceptable salt or solvate thereof can be administered alone or in combination with another agent to a subject suffering from a myelin-related disorder to promote myelination of neurons (e.g., neuronal axons). A myelin-related disorder can include any disease, condition (e.g., those occurring from traumatic spinal cord injury and cerebral infarction), or disorder resulting in abnormalities of the myelin sheath. Abnormalities can be caused by loss of myelin referred to as demyelination, dysfunctional myelin referred to as dysmyelination, or failure to form enough myelin referred to as hypomyelination. A myelin related disorder as described herein can arise from a genetic disorder or from one or more of a variety of

neurotoxic insults. In some embodiments, the compound of Formula A is a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-i', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-ii', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula A-iii, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Formula Id, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula I', or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Formula Ia, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ib, or a pharmaceutically acceptable salt or solvate thereof. In other embodiments, the compound of Formula I is a compound of Formula Ic, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula A is a compound of Table A, or a pharmaceutically acceptable salt or solvate thereof.

[148] “Demyelination” as used herein, refers to the act of demyelinating, or the damage or loss of part or all of the myelin sheath insulating the nerves, and is the hallmark of myelin-related disorders. In certain embodiments, demyelination refers to the damage or loss of part or all of the myelin sheath insulating a subset of nerves in an individual, such as, for example, one or more nerves localized in a particular area of the body (e.g., neurons in the brain or spinal cord, or both brain and spinal cord; or the optic nerve).

[149] Myelination of neurons requires oligodendrocytes. The term “myelination”, as used herein, refers to the generation of the nerve’s myelin sheath by replacing myelin producing cells or restoring their function. The neurons that undergo remyelination may be in the brain, spinal cord, or both the brain and spinal cord. Restoring the function of a myelin producing cell may include, for example, increasing the rate of myelin production in a cell (or cells) with a less-than-average production level. Such increase may encompass raising the rate of myelin production up to or exceeding average production level; but also may encompass raising the rate of myelin production to a level that is still less than average, but higher than the previous level.

[150] “Promoting Myelination” as used herein refers to increasing the rate of myelin production rather than a mere net increase in the amount of myelin as compared to a baseline level of myelin production

rate in a subject. An increase in the rate of myelin production can be determined using imaging techniques or functional measurements. In some embodiments, myelination is promoted by increasing the differentiation of OPCs, increasing the accumulation of 8,9-unsaturated sterol intermediates in the biosynthetic pathway, increasing the formation of OPCs, or any combinations thereof. Such activities may be evaluated, for example, using one or more in vitro assays, such as those described herein or known to one of skill in the art.

[151] A “baseline level of myelin production rate” as used herein, refers to the rate of myelin production in subject being treated before the onset of treatment.

V. Methods of Preparing Compounds of Formula A and Formula I and Pharmaceutically Acceptable Salts Thereof

[152] Compounds can be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein, and those for other heterocycles described in: *Comprehensive Heterocyclic Chemistry II*, Editors Katritzky and Rees, Elsevier, 1997, e.g., Volume 3; *Liebigs Annalen der Chemie*, (9):1910-16, (1985); *Helvetica Chimica Acta*, 41:1052-60, (1958); *Arzneimittel-Forschung*, 40(12):1328-31, (1990), each of which are expressly incorporated by reference. Starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-23, Wiley, N.Y. (1967-2006 ed.), or *Beilsteins Handbuch der organischen Chemie*, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database).

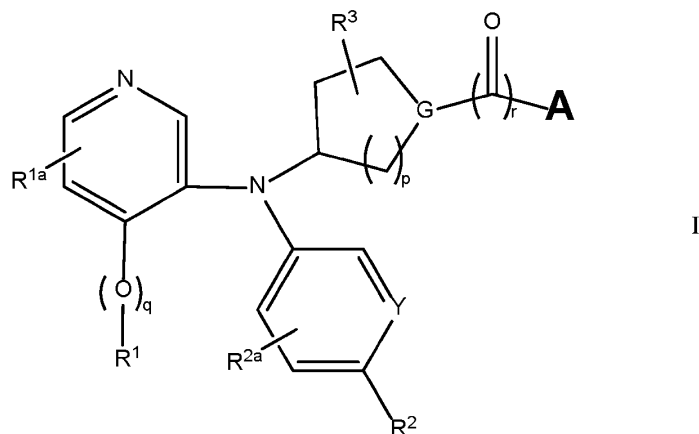
[153] Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing compounds and necessary reagents and intermediates are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

[154] Compounds may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds. Libraries of compounds of Formula A and Formula I, or pharmaceutically acceptable salts thereof, may be prepared by a combinatorial ‘split and mix’ approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus, according to a further aspect, there is provided a compound library comprising at least 2 compounds, or pharmaceutically acceptable salts thereof.

VI. Further Embodiments

[155] The subject matter described herein includes the following embodiments:

1. A compound of Formula I:



wherein,

A is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl and 5- to 6-membered heterocyclyl, each of which is optionally substituted with one or more of R^{A1}, R^{A2} and R^{A3},

wherein, R^{A1}, R^{A2} and R^{A3} are each independently selected from the group consisting of C₁-C₆ alkyl, halo-C₁-C₆ alkyl, halo, cyano, oxo, -C(O)-R^{A4}, -S(O)-R^{A4} and -S(O)₂-R^{A4},

wherein, R^{A4} is C₁-C₆ alkyl or C₃-C₈ cycloalkyl, and

wherein the oxo, if present, is formed by two of R^{A1}, R^{A2} and R^{A3} together with a carbon to which each is attached;

G is -CH or N;

Y is -CH or N;

p is 1, 2 or 3;

q is 1 or 0;

r is 1 or 0;

wherein, when r is 0, A is other than C₁-C₆ alkyl;

R¹ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl and halo-C₁-C₆ alkyl;

R^{1a} is selected from the group consisting of hydrogen, halo, and C₁-C₆ alkyl;

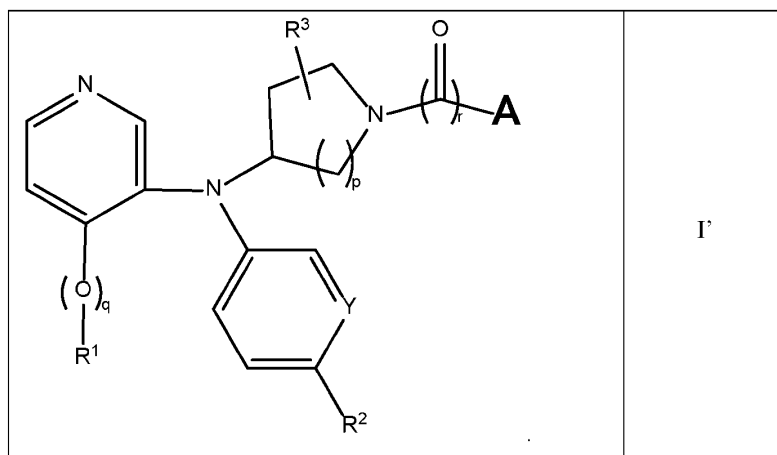
R² is selected from the group consisting of halo, halo-C₁-C₆ alkyl, halo-C₁-C₆ alkoxy and -S(O)₂-(C₁-C₆ alkyl);

R^{2a} is selected from the group consisting of hydrogen and halo;

and,

R^3 is hydrogen, halo, or C_1 - C_6 alkyl,
or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of embodiment 1, or a pharmaceutically acceptable salt or solvate thereof, wherein G is N and having a structure of Formula I':



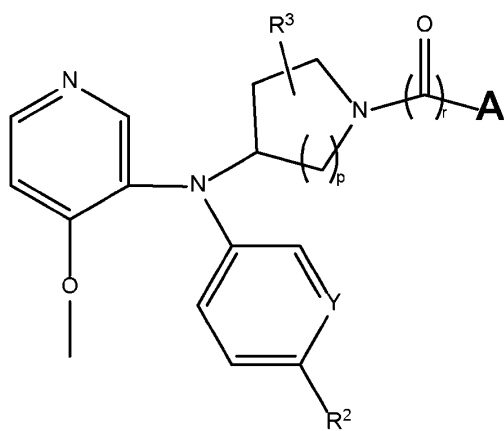
3. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1.

4. The compound of embodiment 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 0.

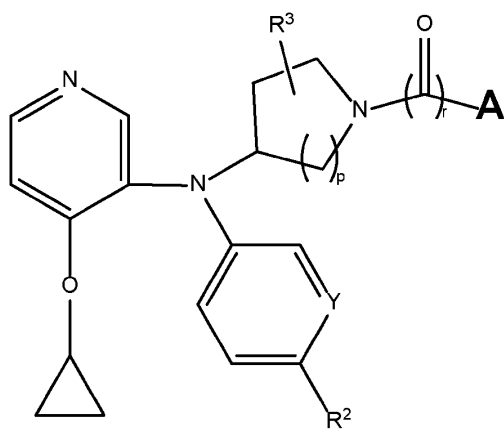
5. The compound of any one of embodiments 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is C_1 - C_6 alkyl or C_3 - C_8 cycloalkyl.

6. The compound of embodiment 5, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is methyl, ethyl or cyclopropyl.

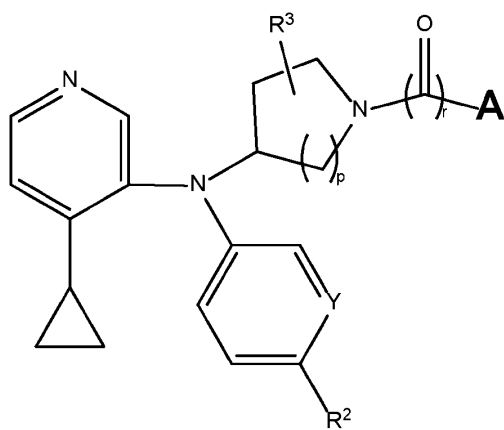
7. The compound of any one of embodiments 1-6, or a pharmaceutically acceptable salt or solvate thereof, having a structure of Formula Ia, Ib or Ic:



Ia



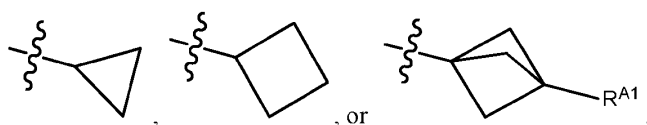
Ib



Ic

8. The compound of any one of embodiments 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is N.
9. The compound of any one of embodiments 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -CH.
10. The compound of any one of embodiments 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is halo-C₁-C₆ alkyl or halo-C₁-C₆ alkoxy.
11. The compound of embodiment 10, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is halo-C₁-C₆ alkyl.
12. The compound of embodiment 11, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is -CF₃.
13. The compound of embodiment 10, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is halo-C₁-C₆ alkoxy.
14. The compound of embodiment 11, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is -O-CHF₂.
15. The compound of any one of embodiments 1-14, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1 or 2.
16. The compound of any one of embodiments 1-15, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1.
17. The compound of any one of embodiments 1-15, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 2.
18. The compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is C₁-C₆ alkyl.

19. The compound of embodiment 18, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is methyl.
20. The compound of any one of embodiments 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen.
21. The compound of any one of embodiments 1-20, or a pharmaceutically acceptable salt or solvate thereof, wherein r is 1.
22. The compound of embodiment 21, or a pharmaceutically acceptable salt or solvate thereof, wherein A is C_1 - C_6 alkyl.
23. The compound of embodiment 22, or a pharmaceutically acceptable salt or solvate thereof, wherein A is $-CH_3$ or $-CH_2CH_3$.
24. The compound of any one of embodiments 1-20, or a pharmaceutically acceptable salt or solvate thereof, wherein r is 0.
25. The compound of embodiment 21 or 24, or a pharmaceutically acceptable salt or solvate thereof, wherein A is C_3 - C_8 cycloalkyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .
26. The compound of embodiment 25, or a pharmaceutically acceptable salt or solvate thereof, wherein A is C_3 - C_5 cycloalkyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .
27. The compound of embodiment 26, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



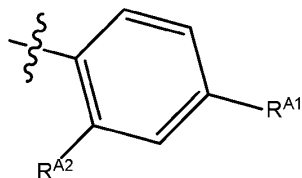
28. The compound of embodiment 27, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is cyano or halo- C_1 - C_6 alkyl.

29. The compound of embodiment 28, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is $-CF_3$.

30. The compound of embodiment 21 or 24, or a pharmaceutically acceptable salt or solvate thereof, wherein A is phenyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

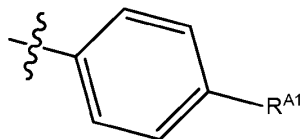
31. The compound of embodiment 30, or a pharmaceutically acceptable salt or solvate thereof, wherein A is phenyl, optionally substituted with one or more of R^{A1} and R^{A2} .

32. The compound of embodiment 31, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



33. The compound of embodiment 32, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is $-S(O)_2-R^{A4}$; and, R^{A2} is halo.

34. The compound of embodiment 31, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



35. The compound of embodiment 34, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is selected from the group consisting of halo, cyano, $-S(O)_2-R^{A4}$ and $-C(O)-R^{A4}$.

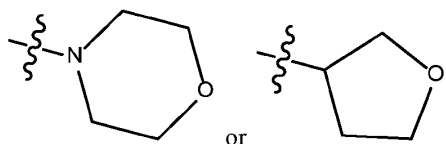
36. The compound of embodiment 21 or 24, or a pharmaceutically acceptable salt or solvate thereof, wherein A is 5- to 6-membered heterocyclyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

37. The compound of embodiment 36, or a pharmaceutically acceptable salt or solvate thereof, wherein the heterocyclyl comprises 1 or 2 heteroatoms selected from the group consisting of N, S, and O.

38. The compound of embodiment 36, or a pharmaceutically acceptable salt or solvate thereof, wherein A is 5- to 6-membered heterocyclyl.

39. The compound of embodiment 38, or a pharmaceutically acceptable salt or solvate thereof, wherein A is 5- to 6-membered heterocyclyl comprising 1 or 2 heteroatoms selected from the group consisting of N, S and O.

40. The compound of embodiment 39, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



41. The compound of embodiment 21 or 24, or a pharmaceutically acceptable salt or solvate thereof, wherein A is 5- to 6-membered heteroaryl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

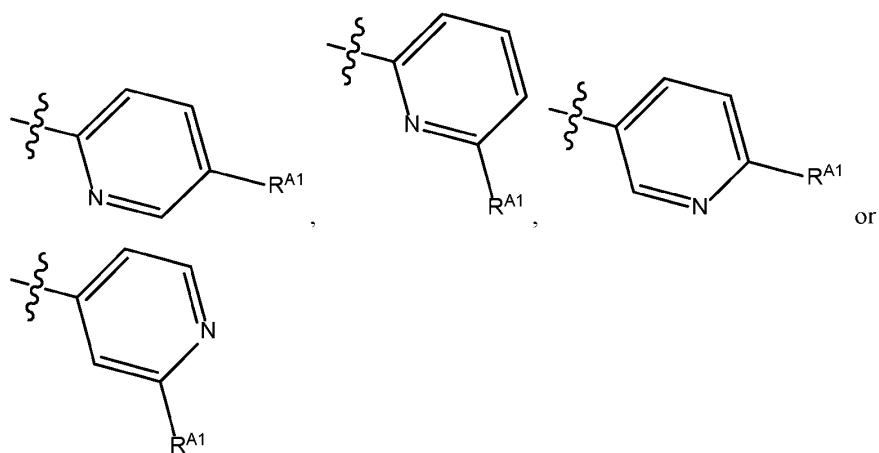
42. The compound of embodiment 41, or a pharmaceutically acceptable salt or solvate thereof, wherein A is selected from the group consisting of pyridinyl, pyrazinyl, pyrimidinyl, pyrazinyl, triazinyl, oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, and thiazolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

43. The compound of embodiment 42, or a pharmaceutically acceptable salt or solvate thereof, wherein A is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, oxadiazolyl and pyrrolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

44. The compound of embodiment 43, or a pharmaceutically acceptable salt or solvate thereof, wherein A is pyridinyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

45. The compound of embodiment 44, or a pharmaceutically acceptable salt or solvate thereof, wherein A is pyridinyl substituted with R^{A1} .

46. The compound of embodiment 45, or a pharmaceutically acceptable salt or solvate thereof, wherein A is

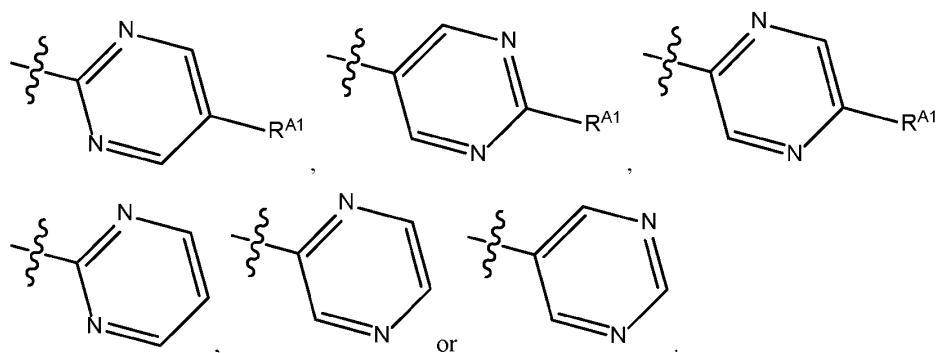


47. The compound of embodiment 46, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is selected from the group consisting of C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo, cyano and $-S(O)_2-R^{A4}$.

48. The compound of embodiment 43, or a pharmaceutically acceptable salt or solvate thereof, wherein A is pyrimidinyl or pyrazinyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

49. The compound of embodiment 48, or a pharmaceutically acceptable salt or solvate thereof, wherein A is pyrimidinyl or pyrazinyl, optionally substituted with R^{A1} .

50. The compound of embodiment 49, or a pharmaceutically acceptable salt or solvate thereof, wherein A is

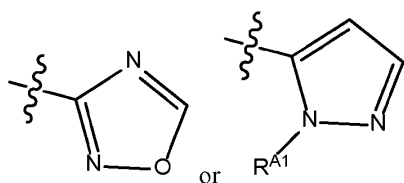


51. The compound of embodiment 50, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is selected from the group consisting of C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo, cyano and $-S(O)_2-R^{A4}$.

52. The compound of embodiment 43, or a pharmaceutically acceptable salt or solvate thereof, wherein A is oxadiazolyl and pyrrolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

53. The compound of embodiment 52, wherein or a pharmaceutically acceptable salt or solvate thereof, A is oxadiazolyl and pyrrolyl, optionally substituted with R^{A1} .

54. The compound of embodiment 53, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



55. The compound of embodiment 54, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} C_1 - C_6 alkyl.

56. The compound of embodiment 1, or a pharmaceutically acceptable salt or solvate thereof selected from Table 1.

57. A pharmaceutical composition comprising a compound of any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

58. A method of promoting myelination in a subject in need thereof, the method comprising administering to the subject in need thereof a therapeutically effective amount of a compound according

to any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of embodiment 57.

59. A compound of any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of embodiment 57, for use in treating a disorder in a subject in need thereof.

60. A compound of any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of embodiment 57, for use in promoting myelination in a subject in need thereof.

61. Use of a compound of any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of embodiment 57, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

62. Use of a compound of any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of embodiment 57, in the manufacture of a medicament for promoting myelination in a subject in need thereof.

63. The method of embodiment 58, wherein the subject has a myelin-related disorder.

64. The compound for use of embodiment 59 or 60, wherein the subject has a myelin-related disorder.

65. The use of embodiment 61 or 62, wherein the subject has a myelin-related disorder.

66. The method of embodiment 63, compound for use of embodiment 64, or use of embodiment 65, wherein the myelin-related disorder is multiple sclerosis (MS), neuromyelitis optica (NMO), optic neuritis, pediatric leukodystrophy, neonatal white matter injury, age-related dementia, schizophrenia, progressive multifocal leukoencephalopathy (PML), encephalomyelitis (EPL), central pontine myelolysis (CPM), adrenoleukodystrophy, Alexander's disease, Pelizaeus Merzbacher disease (PMD), Vanishing White Matter Disease, Wallerian Degeneration, transverse myelitis, amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, Parkinson's disease, spinal cord injury, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, stroke, acute ischemic optic neuropathy,

vitamin E deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, trigeminal neuralgia, acute disseminated encephalitis, Guillian-Barre syndrome, Charcot-Marie-Tooth disease, Bell's palsy, or radiation-induced demyelination.

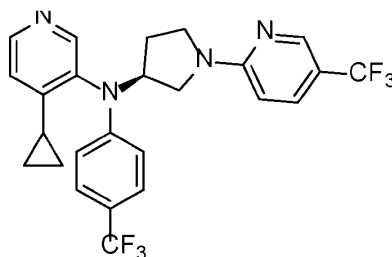
67. The method of embodiment 63, the compound of embodiment 64, or the use of embodiment 65, wherein the disorder is multiple sclerosis.

68. A method of inhibiting CYP51 (lanosterol demethylase) comprising, contacting CYP51 with a compound according to any one of embodiments 1-56, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of embodiment 57.

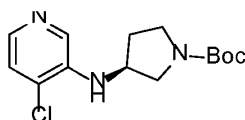
EXAMPLES

[156] The Examples provide exemplary methods for preparing compounds. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the compounds. Although specific starting materials and reagents are depicted and discussed in the Schemes, General Procedures, and Examples, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the exemplary compounds prepared by the described methods can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[157] **Example A: S)-4-Cyclopropyl-N-(4-(trifluoromethyl)phenyl)-N-(1-(5-(trifluoromethyl)pyridine-2-yl)pyrrolidin-3-yl)pyridin-3-amine (Compound 1):**



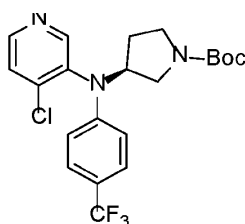
[158] Step 1: *Tert*-Butyl (S)-3-((4-chloropyridin-3-yl)amino)pyrrolidine-1-carboxylate



[159] To a mixture of *tert*-butyl (3S)-3-aminopyrrolidine-1-carboxylate (1.16 g, 6.24 mmol, 1.06

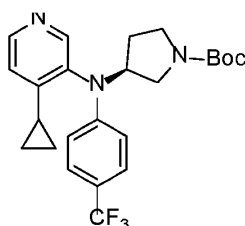
mL), 3-bromo-4-chloro-pyridine (1 g, 5.20 mmol), and *t*-BuONa (1.50 g, 15.59 mmol) in toluene (15 mL) was added Pd(OAc)₂ (233.33 mg, 1.04 mmol) and *t*-Bu₃P (2.08 mmol, 487.85 μ L, 10wt% in toluene), the mixture was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 12 hrs under N₂ atmosphere. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by silica flash chromatography (Eluent of 0~25% Ethyl acetate in Petroleum ether) to afford the title compound (633 mg, 2.13 mmol, 41% yield). LCMS [M+H]⁺ = 298.2.

[160] Step 2: *Tert*-butyl (S)-3-((4-chloropyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)pyrrolidine-1-carboxylate



[161] To a mixture of *tert*-butyl (3S)-3-[(4-chloro-3-pyridyl)amino]pyrrolidine-1-carboxylate (400 mg, 1.34 mmol), 1-bromo-4-(trifluoromethyl)benzene (604 mg, 2.69 mmol) and *t*BuONa (516 mg, 5.37 mmol) in toluene (5 mL) were added Pd(OAc)₂ (60.32 mg, 268.65 μ mol) and *t*-Bu₃P (537.31 μ mol, 1.26 mL, 10 wt% in toluene), the mixture was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 120 °C for 16 hrs under N₂ atmosphere. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by silica flash chromatography (Eluent of 0~25% Ethyl acetate in Petroleum ether) to provide title compound (409 mg, 925.60 μ mol, 69% yield). LCMS (ESI) [M+H]⁺ = 386.1

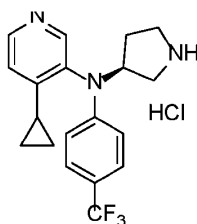
[162] Step 3: *Tert*-butyl (S)-3-((4-cyclopropylpyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)pyrrolidine-1-carboxylate



[163] A mixture of *tert*-butyl (3S)-3-[N-(4-chloro-3-pyridyl)-4-(trifluoromethyl)anilino]pyrrolidine-1-carboxylate (200 mg, 0.452 mmol), cyclopropylboronic acid (117 mg, 1.36 mmol), Pd(OAc)₂ (10.16 mg, 0.0452 mmol), Cs₂CO₃ (442.4 mg, 1.36 mmol) and bis(1-adamantyl)-butyl-phosphane (32 mg, 0.091 mmol) in toluene (1 mL) and H₂O (0.1 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 120 °C for 1 hr under N₂ atmosphere in microwave reactor. The reaction mixture was

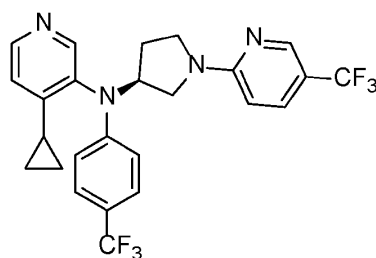
filtered and concentrated in vacuo. The residue was purified by prep-TLC (SiO₂, 50% Ethyl acetate in Petroleum ether) to provide title compound (100.4 mg, 224 μ mol, 50% yield). LCMS (ESI) [M+H]⁺ = 448.3.

[164] Step 4: (S)-4-Cyclopropyl-N-(pyrrolidin-3-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine hydrochloride



[165] To a mixture of *tert*-butyl (3S)-3-[N-(4-cyclopropyl-3-pyridyl)-4-(trifluoromethyl)anilino]pyrrolidine-1-carboxylate (180 mg, 402.24 μ mol) was added HCl/dioxane (4 M, 3.00 mL) in one portion at 25°C and stirred for 1 hours. The reaction mixture was concentrated under reduced pressure to give the title compound (130 mg, 374.23 μ mol, 93.04% yield), which was used into the next step without further purification. LCMS (ESI) [M+H]⁺ = 348.2

[166] Step 5: (S)-4-Cyclopropyl-N-(4-(trifluoromethyl)phenyl)-N-(1-(5-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)pyridin-3-amine (**Compound 1**)

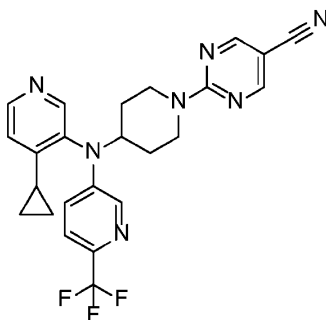


[167] To a mixture of 4-cyclopropyl-N-[(3S)-pyrrolidin-3-yl]-N-[4-(trifluoromethyl)phenyl]pyridin-3-amine (130 mg, 338.68 μ mol, HCl) and 2-fluoro-5-(trifluoromethyl)pyridine (83.87 mg, 508.03 μ mol) in DMF (1 mL) was added DIEA (131.31 mg, 1.02 mmol) in one portion at 25°C. The mixture was stirred at 80°C for 4 hours. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (50 mL x 3). The combined organics were washed with brine (10 mL x 3), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (10%-50% Ethyl acetate in Petroleum ether) to provide the title compound (140 mg, 284.29 μ mol, 83.94% yield) as yellow solid. (SFC: 30:70). The mixture of enantiomers (130 mg, 263.98 μ mol) was purified by SFC (SFC-12; DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 μ m), 0.1% NH₃H₂O ETOH; 30% ~ 30%, 60 mL/min) to afford the title compound-1 (the first peak on SFC, **Compound 1**, 50.7 mg, 101.92 μ mol, 38.61% yield).

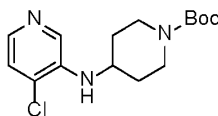
LCMS (ESI) $[M+H]^+ = 493.1$. Only the above enantiomer of **Compound 1** displayed activity.

[168] **Compound 1**: $^1\text{H NMR}$: (400 MHz, CDCl_3) δ 8.50 - 8.20 (m, 3H), 7.63 - 7.57 (m, 1H), 7.49 - 7.41 (m, 2H), 6.82 - 6.72 (m, 1H), 6.65 - 6.58 (m, 2H), 6.35 - 6.27 (m, 1H), 4.85-4.81 (m, 1H), 4.07 - 4.03 (m, 1H), 3.66 - 3.63 (m, 1H), 3.48 - 3.45 (m, 2H), 2.44 - 2.42 (m, 1H), 2.15 - 2.03 (m, 1H), 1.90 - 1.80 (m, 1H), 1.10 - 0.95 (m, 2H), 0.86 - 0.76 (m, 2H).

[169] **Example B: 2-((4-(Cyclopropylpyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 2):**



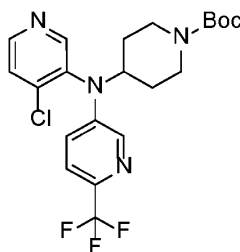
[170] Step 1: *Tert*-butyl 4-((4-chloropyridin-3-yl)amino)piperidine-1-carboxylate



[171] A mixture of *tert*-butyl 4-amino-1-piperidinecarboxylate (3747 mg, 18.71 mmol), *t*BuONa (4494 mg, 46.77 mmol), 3-bromo-4-chloro-pyridine (3000.0 mg, 15.59 mmol), *t*Bu₃P (7.33 mL, 3.12 mmol, 10wt% in toluene) and Pd(OAc)₂ (350 mg, 1.56 mmol) in toluene (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 19 hours under N₂.

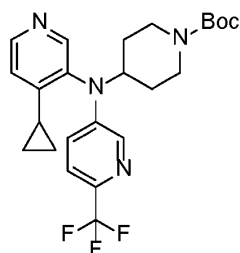
[172] The mixture was concentrated under reduced pressure to dryness and the residue was purified by silica flash chromatography (silica gel, 100 - 200 mesh, 50% ethyl acetate in petroleum ether) to give the title compound (2200 mg, 7.056 mmol, 45% yield). LCMS (ESI) $[M+H]^+ = 312.1$. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 8.07 (s, 1H), 7.89 (s, 1H), 7.23 (d, $J = 5.2$ Hz, 1H), 4.15 (d, $J = 6.8$ Hz, 1H), 4.00 - 4.12 (m, 2H), 3.51 - 3.65 (m, 1H), 2.98 (t, $J = 11.6$ Hz, 2H), 2.05 - 2.10 (m, 2H), 1.50 (d, $J = 1.6$ Hz, 2H), 1.48 (s, 9H).

[173] Step 2: *Tert*-butyl 4-((4-chloropyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate



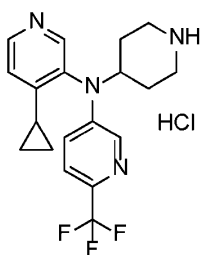
[174] A mixture of 5-bromo-2-(trifluoromethyl)pyridine (870 mg, 3.85 mmol), tBuONa (555 mg, 5.77 mmol), *tert*-butyl 4-[(4-chloro-3-pyridyl)amino]piperidine-1-carboxylate (600.0 mg, 1.92 mmol), tBu₃P (1.81 mL, 0.77 mmol, 10wt% in toluene) and Pd(OAc)₂ (86.4 mg, 0.38 mmol) in toluene (10 mL) was stirred at 120 °C for 12 hours under N₂. The mixture was concentrated under reduced pressure to dryness and the residue was purified by silica flash chromatography (0 to 50% ethyl acetate in petroleum ether) to give the title compound (600 mg, 1.31 mmol, 68% yield). LCMS (ESI) [M+H]⁺ = 401.2.

[175] Step 3: *Tert*-butyl 4-((4-cyclopropylpyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate



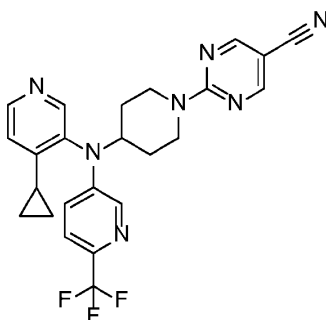
[176] A mixture of cyclopropylboronic acid (594 mg, 2.5 mmol), *tert*-butyl 4-((4-chloropyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate (1000.0 mg, 2.28 mmol), Cs₂CO₃ (2.224 g, 6.83 mmol), di(adamantan-1-yl)(butyl)phosphane (331 mg, 0.46 mmol) and Pd(OAc)₂ (51.1 mg, 0.23 mmol) in water (1 mL) and toluene (10 mL) was purged with N₂ for 3 min. The mixture was heated to 120 °C for 1 hr under N₂ in microwave reactor. The mixture was added water (20 mL) and extracted with ethyl acetate (50 mL x 3). The organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica flash chromatography (0-50% ethyl acetate in petroleum ether) to afford the title compound (600 mg, 1.30 mmol, 57% yield). LCMS (ESI) [M+H]⁺ = 463.2.

[177] Step 4: 4-Cyclopropyl-*N*-(piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine hydrochloride



[178] To a solution of *tert*-butyl 4-[(4-cyclopropyl-3-pyridyl)-[6-(trifluoromethyl)-3-pyridyl]amino]piperidine-1-carboxylate (600.0 mg, 1.3 mmol) in dioxane (5 mL) was added HCl/dioxane (5.0 mL, 20.0 mmol, 4M) and stirred at 25 °C for 2 hrs. The reaction mixture was concentrated under vacuum to give the title compound (517 mg, 1.3 mmol, 100% yield) as a white solid. LCMS (ESI) [M+H]⁺ = 363.2.

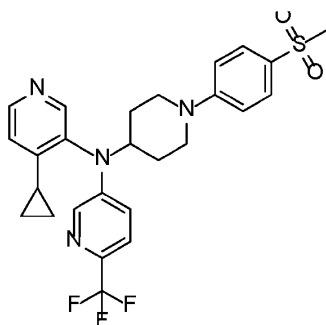
[179] Step 5: 2-(4-((4-Cyclopropylpyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 2**):



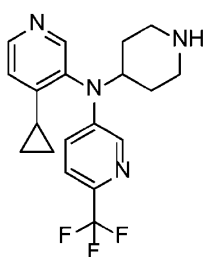
[180] To a solution of *N*-(4-cyclopropyl-3-pyridyl)-*N*-(4-piperidyl)-6-(trifluoromethyl)pyridin-3-amine (50.0 mg, 0.14 mmol) and 2-chloropyrimidine-5-carbonitrile (23.1 mg, 0.17 mmol) in *N,N*-dimethylformamide (1 mL) at 0 °C was added *N,N*-diisopropylethylamine (0.07 mL, 0.41 mmol) and stirred for 1 hr. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organics were washed with brine (10 mL x 3), dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (50% ethyl acetate in petroleum ether) to provide the title compound (10.5 mg, 0.0205 mmol, 15% yield). LCMS (ESI) [M+H]⁺ = 466.3.

[181] **Compound 2**: ¹H NMR (400 MHz, CDCl₃) δ ppm 8.49 (s, 3H), 8.28 (s, 1H), 8.11 (s, 1H), 7.50 (d, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 6.4 Hz, 2H), 5.06 (d, *J* = 14.0 Hz, 2H), 4.35 (s, 1H), 3.09 (t, *J* = 12.8 Hz, 2H), 2.23 (d, *J* = 12.0 Hz, 2H), 1.91 (s, 1H), 1.48 (d, *J* = 13.6 Hz, 2H), 1.15 (d, *J* = 6.4 Hz, 2H), 0.89 (d, *J* = 6.4 Hz, 2H).

[182] **Example C: 4-cyclopropyl-*N*-(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine (Compound 3):**

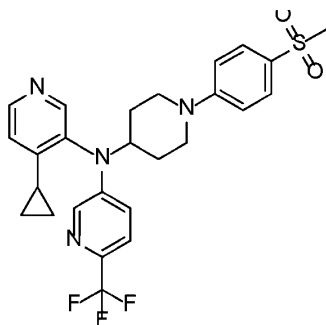


[183] Step 1: 4-Cyclopropyl-*N*-(piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine



[184] To a solution of *N*-(4-cyclopropyl-3-pyridyl)-*N*-(4-piperidyl)-6-(trifluoromethyl)pyridin-3-amine;hydrochloride (500.0 mg, 1.25 mmol) in methanol (10 mL) was added basic resin (1.0 g) and stirred at 25 °C for 2 hr. The reaction mixture was filtered and the methanol was concentrated under vacuum to give the title compound (420 mg, 1.16 mmol, 93% yield).

[185] Step 2: 4-Cyclopropyl-*N*-(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine (**Compound 3**):

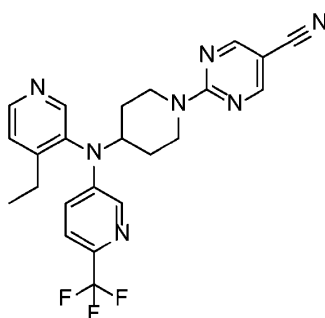


[186] To a solution of *N*-(4-cyclopropyl-3-pyridyl)-*N*-(4-piperidyl)-6-(trifluoromethyl)pyridin-3-amine (50.0 mg, 0.14 mmol), RuPhos Pd G3 (12 mg, 0.01 mmol), 1-bromo-4-(methylsulfonyl)benzene (39 mg, 0.17 mmol) and *t*BuONa (40 mg, 0.41 mmol) in 1,4-dioxane (3 mL) was purged with N₂ for 3 times. And the reaction mixture was stirred at 110 °C for 16 hrs. The resulting residue was concentrated under reduced pressure and the residue was purified by prep-TLC (50% ethyl acetate in petroleum ether) to afford

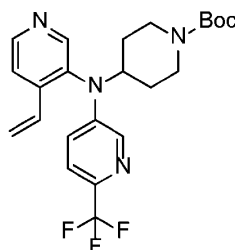
the title compound (53 mg, 0.0995 mmol, 72% yield). LCMS (ESI) $[M+H]^+ = 517.3$.

[187] **Compound 3:** ^1H NMR (400 MHz, CDCl_3) δ ppm 8.53 (d, $J = 5.6$ Hz, 1H), 8.30 (s, 1H), 8.10 (d, $J = 2.4$ Hz, 1H), 7.77 (d, $J = 8.8$ Hz, 2H), 7.49 (d, $J = 8.8$ Hz, 1H), 7.28 (s, 1H), 6.93 (d, $J = 9.2$ Hz, 2H), 6.78 - 6.86 (m, 1H), 4.24 (t, $J = 11.6$ Hz, 1H), 4.00 (d, $J = 12.8$ Hz, 2H), 3.04 - 3.13 (m, 2H), 3.03 (s, 3H), 2.25 - 2.21 (m, 2H), 1.86 - 1.92 (m, 1H), 1.66 - 1.63 (m, 2H), 1.12 (d, $J = 6.4$ Hz, 2H), 0.88 (d, $J = 6.0$ Hz, 2H).

[188] **Example D: 2-((4-Ethylpyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 4):**



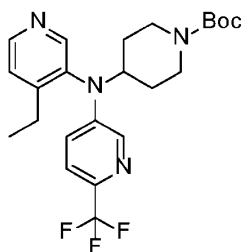
[189] Step 1: *Tert*-butyl 4-((6-(trifluoromethyl)pyridin-3-yl)(4-vinylpyridin-3-yl)amino)piperidine-1-carboxylate



[190] A mixture of *tert*-butyl 4-[(4-chloro-3-pyridyl)-[6-(trifluoromethyl)-3-pyridyl]amino]piperidine-1-carboxylate (300.0 mg, 0.66 mmol), Cs_2CO_3 (642 mg, 1.97 mmol), $\text{Pd}(\text{OAc})_2$ (7.4 mg, 0.033 mmol), bis(1-adamantyl)-butyl-phosphane (23.5 mg, 0.066 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (303.0 mg, 1.97 mmol) in water (1 mL) and toluene (9 mL) was purged with N_2 for 3 times. The mixture was heated to 120 $^\circ\text{C}$ for 1 hr under microwave reactor.

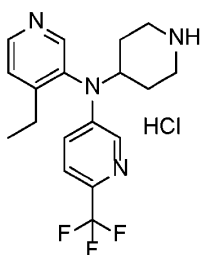
[191] The reaction was diluted with water (20 mL) and extracted with ethyl acetate (20 mL x 3). The organics were washed with brine (20 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure and the residue was purified by silica flash chromatography (0-50% ethyl acetate in petroleum ether) to provide the title compound (200 mg, 0.646 mmol, 68%). LCMS (ESI) $[M+H]^+ = 449.2$.

[192] Step 2: *Tert*-butyl 4-((4-ethylpyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate



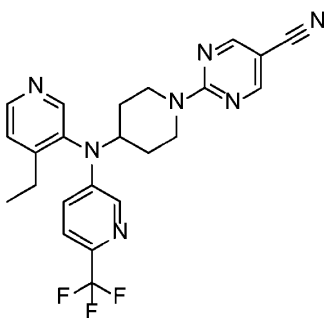
[193] A mixture of Pd/C (40 mg, 10wt% on carbon) and *tert*-butyl 4-[[6-(trifluoromethyl)-3-pyridyl]-(4-vinyl-3-pyridyl)amino]piperidine-1-carboxylate (200.0 mg, 0.45 mmol) in Ethanol (10 mL) was stirred at 25 °C for 1 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (180 mg, 0.40 mmol, 90% yield). LCMS (ESI) [M-56+H]⁺ = 395.1.

[194] Step 3: 4-Ethyl-*N*-(piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine hydrochloride



[195] *Tert*-butyl-4-[(4-ethyl-3-pyridyl)-(6-(trifluoromethyl)-3-pyridyl)amino]piperidine-1-carboxylate (180.0 mg, 0.40 mmol) was dissolved in HCl/dioxane (4 mL, 4 M) and stirred at 25 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to give the title compound (200 mg, 0.0034 mmol, 0.90% yield). LCMS (ESI) [M+H]⁺ = 350.2.

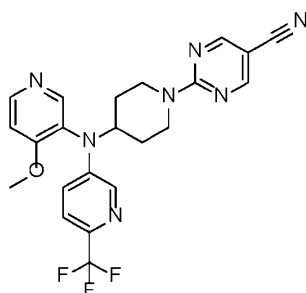
[196] Step 4: 2-(4-((4-Ethylpyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 4**):



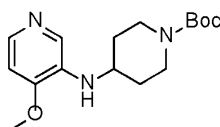
[197] To a solution of *N*-(4-ethyl-3-pyridyl)-*N*-(4-piperidyl)-6-(trifluoromethyl)pyridin-3-amine (80.0 mg, 0.23 mmol) in *N,N*-dimethylformamide (2 mL) was added *N,N*-diisopropylethylamine (0.12 mL, 0.68 mol) at 0 °C, and the mixture was stirred at 0 °C for 5 min, then 2-chloropyrimidine-5-carbonitrile (32 mg, 0.23 mmol) was added. Then the reaction mixture was stirred at 25 °C for 1 hr. The solvent was removed under reduced pressure and the residue was purified by silica flash chromatography (0-30% ethyl acetate in petroleum ether) to afford the title compound (11.6 mg, 0.0026 mmol, 12% yield). LCMS (ESI) [M+H]⁺ = 454.2.

[198] **Compound 4:** ¹H NMR (400 MHz, CD₃OD) δ 8.57 - 8.52 (m, 3H), 8.32 - 8.28 (m, 1H), 7.88 - 7.84 (m, 1H), 7.63 - 7.57 (m, 2H), 7.16 - 7.11 (m, 1H), 4.99 (d, *J* = 13.6 Hz, 2H), 4.64 - 4.48 (m, 1H), 3.22 - 3.11 (m, 2H), 2.65 (s, 2H), 2.22 - 2.02 (m, 2H), 1.39 - 1.28 (m, 2H), 1.18 (t, *J* = 7.6 Hz, 3H).

[199] **Example E: 2-((4-(4-Methoxypyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 5):**



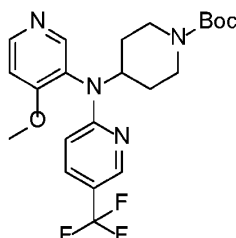
[200] Step 1: *Tert*-butyl 4-[(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate



[201] To a solution of 4-methoxypyridin-3-amine (10 g, 80.55 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (19.26 g, 96.66 mmol) in isopropyl acetate (100 mL) was added NaBH(OAc)₃ (20.49 g, 96.66 mmol) and stirred at 0 °C for 0.1 hr. Then 2,2,2-trifluoroacetic acid (27.56 g, 241.66 mmol, 17.89 mL) was added to the mixture and stirred at ice bath for 2 hr, and then stirred at 30 °C for 24 hr. The reaction mixture was adjusted with saturated NaHCO₃ aq. (200 mL) and stirred for 30 min. The resulting mixture was extracted with ethyl acetate (150 mLx3) and the combined organic layer was washed with brine (50 mLx3). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Petroleum ether/Ethyl acetate=5/1 to 1/1 then turn to use 3%-10% methanol in DCM) to give the title compound (21 g, 68.32 mmol, 85% yield, 100% purity). LCMS (ESI) [M+H]⁺ = 308.2. ¹H NMR (400 MHz, DMSO-*d*₆): 8.10 (d, *J* = 6.0

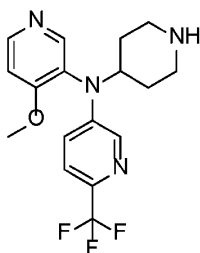
Hz, 1H), 8.05 (s, 1H), 7.32 (d, $J = 6.0$ Hz, 1H), 5.84 (d, $J = 8.4$ Hz, 1H), 4.04 (s, 3H), 3.96-3.93 (m, 2H), 3.57-3.54 (m, 2H), 2.84 (brs, 2H), 1.86-1.82 (m, 2H), 1.40 (s, 9H).

[202] Step 2: *Tert*-butyl 4-((4-methoxypyridin-3-yl)(5-(trifluoromethyl)pyridin-2-yl)amino)piperidine-1-carboxylate



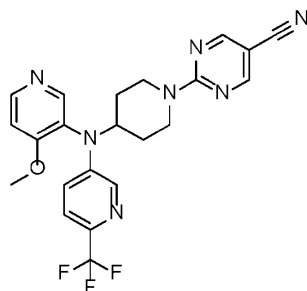
[203] A mixture of *tert*-butyl 4-[(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate (3 g, 9.76 mmol), 5-bromo-2-(trifluoromethyl)pyridine (4.41 g, 19.52 mmol), $t\text{Bu}_3\text{P}$ Pd G2 (1.00 g, 1.95 mmol), $t\text{BuONa}$ (2.81 g, 29.28 mmol) in toluene (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 120 °C for 12 hr under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by silica flash chromatography (0~60% Ethyl acetate in Petroleum ether) to provide the title compounds (2.78 g, 6.14 mmol, 63% yield). LCMS (ESI) $[\text{M}+\text{H}]^+ = 453.3$

[204] Step 3: 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine



[205] To a solution of *tert*-butyl 4-[(4-methoxy-3-pyridyl)-[6-(trifluoromethyl)-3-pyridyl]amino]piperidine-1-carboxylate (600 mg, 1.33 mmol) in dioxane (2 mL) was added HCl/dioxane (4 M, 3 mL). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to provide the title compound (510 mg, 1.31 mmol, 99% yield). LCMS (ESI) $[\text{M}+\text{H}]^+ = 353.2$.

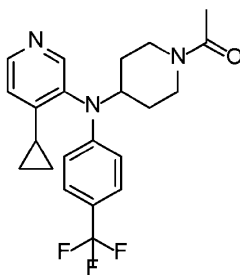
[206] Step 4: 2-(4-((4-Methoxypyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 5**):



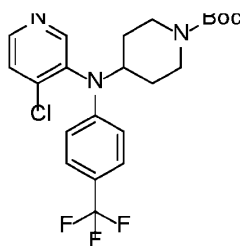
[207] To a solution of *N*-(4-methoxy-3-pyridyl)-*N*-(4-piperidyl)-6-(trifluoromethyl)pyridin-3-amine (50.0 mg, 0.13 mmol) and *N,N*-Diisopropylethylamine (0.07 mL, 0.39 mmol) in *N,N*-dimethylformamide (1 mL) at 0 °C was added 2-chloropyrimidine-5-carbonitrile (22 mg, 0.15 mmol) and stirred for 1 hr. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organics were washed with brine (10 mL x 3), dried over sodium sulfate, filtered and concentrated. The residue was purified by prep-TLC (50% ethyl acetate in petroleum ether) to provide the title compound (27.8 mg, 0.0574 mmol, 45% yield). LCMS (ESI) [M+H]⁺ = 456.2

[208] **Compound 5:** ¹H NMR (400 MHz, CDCl₃) δ ppm 8.58 (d, *J* = 5.2 Hz, 1H), 8.47 (s, 2H), 8.28 (s, 1H), 8.01 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 5.2 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 5.01 (d, *J* = 13.2 Hz, 2H), 4.23 (t, *J* = 11.6 Hz, 1H), 3.82 (s, 3H), 3.01 - 3.10 (m, 1H), 2.15 (d, *J* = 13.2 Hz, 2H), 1.40 (d, *J* = 9.2 Hz, 2H).

[209] **Example F: 1-(4-((4-Cyclopropylpyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)ethan-1-one (Compound 6):**

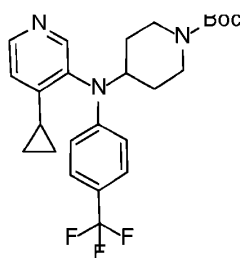


[210] Step 1: *Tert*-butyl 4-[*N*-(4-chloro-3-pyridyl)-4-(trifluoromethyl)anilino]piperidine-1-carboxylate



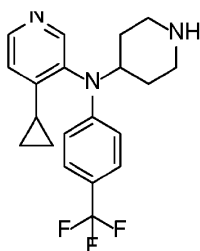
[211] A mixture of *tert*-butyl 4-[(4-chloro-3-pyridyl)amino]piperidine-1-carboxylate (600 mg, 1.92 mmol), 1-bromo-4-(trifluoromethyl)benzene (866 mg, 3.85 mmol), Pd(OAc)₂ (87 mg, 384.85 μmol), *t*-Bu₃P (1.56 g, 769.71 μmol, 1.81 mL, 10% purity) and *t*BuONa (740 mg, 7.70 mmol) in toluene (20 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 120 °C for 12 hr under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (0~40% Ethyl acetate in Petroleum ether) to provide the title compound (420 mg, 921.25 μmol, 47.88% yield). LCMS (ESI) [M-56+H]⁺ = 400.2

[212] Step 2: *Tert*-butyl 4-((4-cyclopropylpyridin-3-yl)(4-(trifluoromethyl)phenyl) amino) piperidine-1-carboxylate



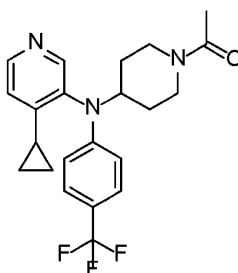
[213] A mixture of *tert*-butyl 4-[*N*-(4-chloro-3-pyridyl)-4-(trifluoromethyl)anilino]piperidine-1-carboxylate (250 mg, 548 μmol), cyclopropylboronic acid (94.21 mg, 1.10 mmol), Pd(OAc)₂ (12.31 mg, 55 μmol), bis(1-adamantyl)-butyl-phosphane (39 mg, 110 μmol) and Cs₂CO₃ (536.00 mg, 1.65 mmol) in H₂O (0.4 mL) and toluene (4 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 120 °C for 1 hr under microwave reactor. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of 0~45% Ethyl acetate in Petroleum ether) to provide the title compound (240 mg). LCMS (ESI) [M+H]⁺ = 462.3.

[214] Step 3: 4-Cyclopropyl-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine



[215] To a solution of *tert*-butyl 4-[*N*-(4-cyclopropyl-3-pyridyl)-4-(trifluoromethyl)anilino]piperidine-1-carboxylate (240 mg, 520.02 μmol) in dioxane (2 mL) was added HCl/dioxane (4 M, 1.30 mL) and the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to provide the title compound (200 mg, crude) as HCl salt. LCMS (ESI): $[M+H]^+ = 362.2$.

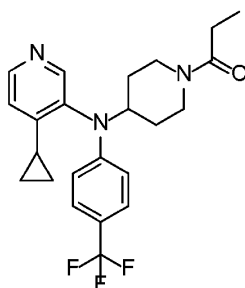
[216] Step 4: 1-(4-((4-Cyclopropylpyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)ethan-1-one (**Compound 6**):



[217] To a solution of 4-cyclopropyl-*N*-(4-piperidyl)-*N*-[4-(trifluoromethyl)phenyl]pyridin-3-amine (100 mg, 277 μmol) and acetyl chloride (43.44 mg, 553.40 μmol) in dichloromethane (2 mL) was added triethylamine (84 mg, 830 μmol) at 0 °C and the mixture was stirred for 1 hr. The reaction mixture was concentrated in vacuo and the residue was purified by reversed-phase HPLC (Welch Xtimate C18 150*30 mm*5 μm ; mobile phase: [water (FA)-ACN]; B%: 29%-59%, 7 min) to provide the title compound (33.3 mg, 82.54 μmol , 30% yield). LCMS (ESI) $[M+H]^+ = 403.9$.

[218] **Compound 6:** ^1H NMR (400 MHz, CDCl_3) δ 8.57 - 8.41 (m, 1H), 8.29 - 8.14 (m, 1H), 7.46 - 7.39 (m, 2H), 6.80 - 6.68 (m, 1H), 6.54 (d, $J = 8.8$ Hz, 2H), 4.79 - 4.75 (m, 1H), 4.26 - 4.16 (m, 1H), 3.96 - 3.88 (m, 1H), 3.28 - 3.17 (m, 1H), 2.71 - 2.61 (m, 1H), 2.19 - 2.09 (m, 2H), 2.08 (s, 3H), 1.92 - 1.84 (m, 1H), 1.48 - 1.35 (m, 2H), 1.08 - 1.01 (m, 2H), 0.82 - 0.81 (m, 2H).

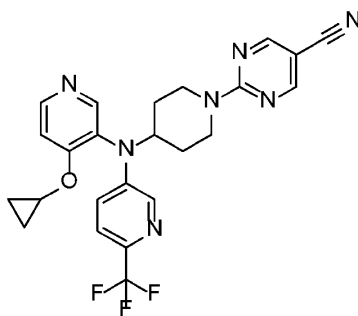
[219] **Example G:** 1-(4-((4-Cyclopropylpyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)propan-1-one (**Compound 7**)



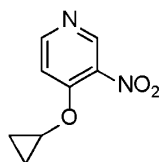
[220] To a solution of 4-cyclopropyl-*N*-(4-piperidyl)-*N*-[4-(trifluoromethyl)phenyl]pyridin-3-amine (50 mg, 125.67 μ mol) and propanoyl chloride (23.26 mg, 251.34 μ mol) in dichloromethane (2 mL) was added triethylamine (38 mg, 377.01 μ mol) and the mixture was stirred at 0 °C for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was purified by reversed-phase HPLC (Welch Xtimate C18 150 * 30 mm * 5 μ m; mobile phase: [water (FA)-ACN]; B%: 29% - 59%, 7 min) to provide title compound (**Compound 7**, 33.3 mg, 79.77 μ mol, 63% yield). LCMS (ESI) [M+H]⁺ = 418.0

[221] **Compound 7**: ¹H NMR (400 MHz, CDCl₃) δ 8.54 - 8.41 (m, 1H), 8.27 - 8.17 (m, 1H), 7.45 - 7.39 (m, 2H), 6.80 - 6.72 (m, 1H), 6.57 - 6.51 (m, 2H), 4.80 - 4.77 (m, 1H), 4.29 - 4.14 (m, 1H), 4.04 - 3.91 (m, 1H), 3.26 - 3.10 (m, 1H), 2.67 - 2.65 (m, 1H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.16 - 2.08 (m, 2H), 1.92 - 1.85 (m, 1H), 1.41 - 1.30 (m, 2H), 1.12 (t, *J* = 7.6 Hz, 3H), 1.08 - 1.03 (m, 2H), 0.82 - 0.81 (m, 2H).

[222] **Example H: 2-(4-((4-Cyclopropoxy)pyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino) piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 8):**



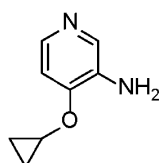
[223] Step 1: 4-Cyclopropoxy-3-nitropyridine



[224] To a solution of cyclopropanol (1.21 g, 20.81 mmol) and NaH (832.51 mg, 20.81 mmol, 60%

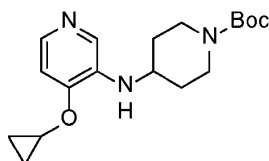
purity) in DMF (20 mL) was added 4-Chloro-3-nitro-pyridine (2.2 g, 13.88 mmol) at 0 °C and stirred at that temperature for 2 hr under N₂ atmosphere. The reaction mixture was quenched with NH₄Cl (70 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with brine (50 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of 0~30% Ethyl acetate in Petroleum ether) to provide the title compound (1.93 g, 10.50 mmol, 76% yield). LCMS (ESI) [M+H]⁺ = 181.0.

[225] Step 2: 4-Cyclopropoxypyridin-3-amine



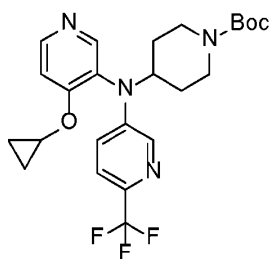
[226] A mixture of 4-(cyclopropoxy)-3-nitro-pyridine (2.13 g, 11.82 mmol) and Pd/C (0.5 g, 10% purity) in EtOH (20 mL) was degassed and purged with H₂ for 3 times, and then the mixture was stirred at 25 °C for 1 hr under H₂ (15 psi) atmosphere. The reaction mixture was filtered and concentrated in vacuo to provide the title compound (1.73 g, 11.52 mmol, 97% yield). LCMS (ESI) [M+H]⁺ = 151.2.

[227] Step 3: *Tert*-butyl 4-((4-cyclopropoxypyridin-3-yl)amino)piperidine-1-carboxylate



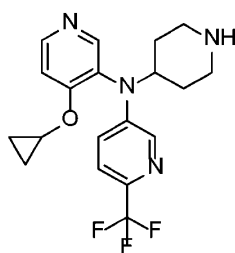
[228] To a solution of 4-(cyclopropoxy)pyridin-3-amine (1.73 g, 11.52 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (3.44 g, 17.28 mmol) in isopropyl acetate (30 mL) was added NaBH(OAc)₃ (2.93 g, 13.82 mmol) at 0 °C, and then TFA (3.94 g, 34.56 mmol, 2.56 mL) was added to above mixture in dropwise at 0 °C. The mixture was stirred at 25 °C for 12 hrs. The reaction mixture was adjusted with saturated NaOH aq. (50 mL) and stirred for 10 min. The resulting mixture was extracted with ethyl acetate (100 mL*3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of 0~3% Methanol in Dichloromethane) to provide the title compound (1.65 g, 4.95 mmol, 43% yield). LCMS (ESI) [M+H]⁺ = 334.3.

[229] Step 4: *Tert*-butyl 4-((4-cyclopropoxypyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate



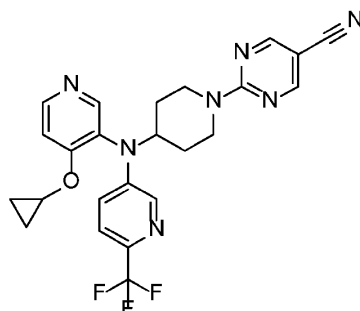
[230] A mixture of *tert*-butyl 4-[[4-(cyclopropoxy)-3-pyridyl]amino]piperidine-1-carboxylate (500 mg, 1.50 mmol), 5-bromo-2-(trifluoromethyl)pyridine (677.80 mg, 3.00 mmol), tBuONa (576.46 mg, 6.00 mmol), Pd(OAc)₂ (67.33 mg, 299.92 μmol) and t-Bu₃P (599.84 μmol, 1.41 mL, 10% purity) in toluene (15 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 120 °C for 24 hr under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by flash silica gel chromatography (Eluent of 0~60% Ethyl acetate in Petroleum ether) to provide the title compound (319 mg, 667 μmol, 44% yield). LCMS (ESI) [M+H]⁺ = 479.3.

[231] Step 5 : 4-Cyclopropoxy-*N*-(piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine.



[232] To a solution of *tert*-butyl 4-[[4-(cyclopropoxy)-3-pyridyl]-[6-(trifluoromethyl)-3-pyridyl]amino]piperidine-1-carboxylate (100 mg, 208.98 μmol) in dioxane (2 mL) was added HCl/dioxane (4 M, 5 mL) and the mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to provide the title compound (78 mg, 206.14 μmol crude) as yellow solid. LCMS (ESI) [M+H]⁺ = 379.2.

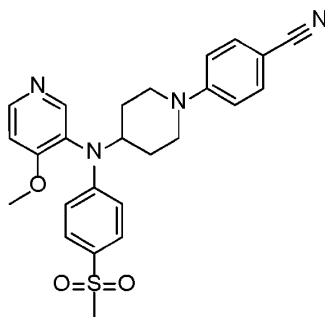
[233] Step 6: 2-(4-((4-Cyclopropoxypyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 8**):



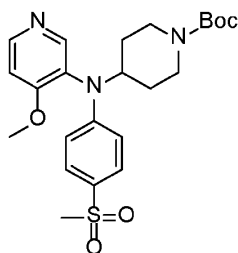
[234] To a solution of *N*-[4-(cyclopropoxy)-3-pyridyl]-*N*-(4-piperidyl)-6-(trifluoromethyl)pyridin-3-amine (78 mg, 206.14 μ mol) and DIEA (79.92 mg, 618.41 μ mol, 107.72 μ L) in DMF (2 mL) was added 2-chloropyrimidine-5-carbonitrile (28.76 mg, 206.14 μ mol) at 0 °C and the mixture was stirred at 0°C for 0.5 hr. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude residue. The residue was purified by reversed-phase HPLC (Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 39%-69%, 7 min) to provide the title compound (55.1 mg, 114.44 μ mol, 56% yield). LCMS (ESI) [M+H]⁺ = 482.4

[235] **Compound 8:** ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, *J* = 5.6 Hz, 1H), 8.47 (s, 2H), 8.24 (s, 1H), 7.98 (d, *J* = 2.8 Hz, 1H), 7.46 - 7.41 (m, 1H), 7.31 (d, *J* = 5.6 Hz, 1H), 6.80 (dd, *J* = 2.8, 8.8 Hz, 1H), 5.04 - 4.96 (m, 2H), 4.25 - 4.16 (m, 1H), 3.80 - 3.74 (m, 1H), 3.09 - 3.00 (m, 2H), 2.15 - 2.10 (m, 2H), 1.44 - 1.36 (m, 2H), 0.85 - 0.77 (m, 2H), 0.60 - 0.53 (m, 2H).

[236] **Example I: 4-((4-Methoxypyridin-3-yl)(4-(methylsulfonyl)phenyl)amino)piperidin-1-yl) benzonitrile: (Compound 9)**

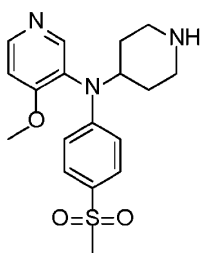


[237] Step 1: *Tert*-butyl 4-((4-methoxypyridin-3-yl)(4-(methylsulfonyl)phenyl)amino)piperidine-1-carboxylate:



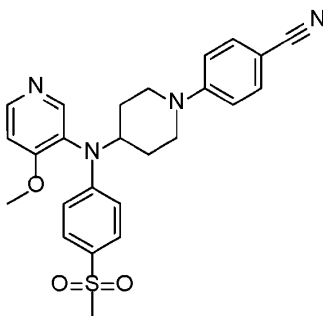
[238] A mixture of *tert*-butyl 4-[(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate (1 g, 3.25 mmol), 1-bromo-4-methylsulfonyl-benzene (1.53 g, 6.51 mmol), *t*Bu₃P Pd G2 (333.39 mg, 650.65 μ mol) and tBuONa (1.25 g, 13.01 mmol) in toluene (20 mL) and stirred at 125 °C for 12 hr under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash silica gel chromatography (0-5% MeOH in DCM) to provide the title compound (430 mg, 931.60 μ mol, 29% yield). LCMS (ESI), [M+H]⁺ = 462.3.

[239] Step 2: 4-Methoxy-*N*-(4-(methylsulfonyl)phenyl)-*N*-(piperidin-4-yl)pyridin-3-amine:



[240] *Tert*-butyl-4-(*N*-(4-methoxy-3-pyridyl)-4-methylsulfonyl-anilino)piperidine-1-carboxylate (430 mg, 931.60 μ mol) dissolved in HCl/dioxane (4 M, 4 mL) and the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to give the title compound (336 mg, 929.57 μ mol, 99.78% yield).

[241] Step 3: 4-(4-((4-Methoxypyridin-3-yl)(4-(methylsulfonyl)phenyl)amino)piperidin-1-yl) benzonitrile (**Compound 9**):

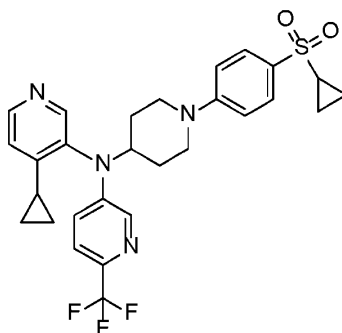


[242] A mixture of 4-methoxy-*N*-(4-methylsulfonylphenyl)-*N*-(4-piperidyl)pyridin-3-amine (50 mg,

138.33 μmol), 4-fluorobenzonitrile (25.13 mg, 207.49 μmol) and K_2CO_3 (95.59 mg, 691.64 μmol) in DMSO (3 mL) and then the mixture was stirred at 120 °C for 12 hr. The reaction mixture was purified by pre-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 22%-52%, 7 min) to provide the title compound (25 mg, 54.05 μmol , 39% yield). LCMS (ESI), $[\text{M}+\text{H}]^+ = 463.3$.

[243] **Compound 9:** ^1H NMR (400 MHz, CD_3OD) 8.51 (s, 1H), 8.19 (s, 1H), 7.68 (d, $J = 8.8$ Hz, 3H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.27 (d, $J = 5.6$ Hz, 1H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.70 (d, $J = 8.0$ Hz, 2H), 4.35 - 4.33 (m, 1H), 4.02 - 3.99 (m, 2H), 3.85 (s, 3H), 3.04 (s, 3H), 2.14 - 2.11 (m, 2H), 1.46 - 1.43 (m, 2H), 1.31 - 1.29 (m, 2H).

[244] **Example J: 4-Cyclopropyl-*N*-(1-(4-(cyclopropylsulfonyl)phenyl)piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine (Compound 10):**

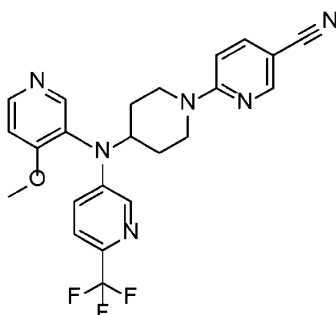


[245] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[246] The compound was purified by reversed-phase HPLC (Welch Xtimate C18 150 * 30 mm * 5 um; mobile phase: [water (FA)-ACN]; B%: 37%-67%, 7 min) to provide the title compound (1 mg, 1.84 μmol , 2.23% yield). LCMS (ESI), $[\text{M}+\text{H}]^+ = 543.0$.

[247] **Compound 10:** ^1H NMR (400 MHz, CDCl_3) δ 8.54 - 8.48 (m, 1H), 8.30 - 8.25 (m, 1H), 8.09 - 8.07 (m, 1H), 7.74 - 7.70 (m, 2H), 7.49 - 7.45 (m, 1H), 6.91 (d, $J = 9.2$ Hz, 2H), 6.82 - 6.76 (m, 2H), 4.27 - 4.17 (m, 1H), 4.02 - 3.95 (m, 2H), 3.09 - 2.99 (m, 2H), 2.46 (s, 1H), 2.26 - 2.18 (m, 2H), 1.90 - 1.84 (m, 1H), 1.26 (s, 2H), 1.10 - 1.06 (m, 2H), 1.01 - 0.97 (m, 2H), 0.89 - 0.80 (m, 4H).

[248] **Example K: 6-(4-((4-Methoxypyridin-3-yl)(6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)nicotinonitrile (Compound 11):**

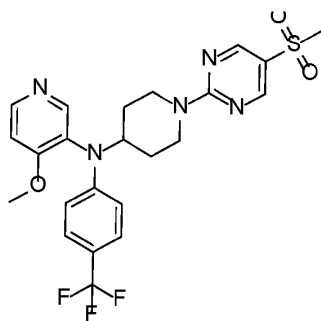


[249] The title compound was synthesized following a procedure similar to **Example E** (Compound 5).

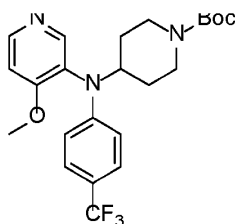
[250] The title compound was purified by flash silica gel chromatography (Eluent of 0~30% Ethyl acetate in Petroleum ether) to provide the title compound (30 mg, 66.01 μmol , 32% yield). LCMS (ESI), $[M+H]^+ = 455.3$.

[251] **Compound 11**: ^1H NMR (400 MHz, CDCl_3) δ 8.58 - 8.54 (m, 1H), 8.39 - 8.36 (m, 1H), 8.26 - 8.24 (m, 1H), 8.01 (d, $J = 2.8$ Hz, 1H), 7.62 - 7.57 (m, 1H), 7.47 - 7.43 (m, 1H), 6.98 - 6.95 (m, 1H), 6.85 - 6.80 (m, 1H), 6.61 - 6.58 (m, 1H), 4.60 - 4.53 (m, 2H), 4.25 - 4.16 (m, 1H), 3.81 (s, 3H), 3.09 - 3.01 (m, 2H), 2.18 - 2.11 (m, 2H), 1.47 - 1.37 (m, 2H).

[252] **Example L: 4-Methoxy-*N*-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 12):**

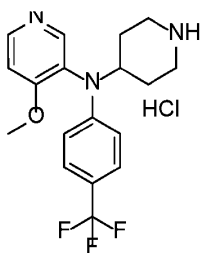


[253] Step 1: *Tert*-butyl 4-[*N*-(4-methoxy-3-pyridyl)-4-(trifluoromethyl)anilino]piperidine-1-carboxylate



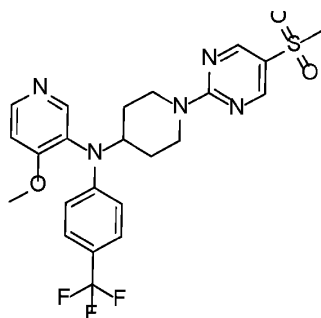
[254] To a mixture of *tert*-butyl 4-[(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate (2 g, 6.51 mmol) and 1-bromo-4-(trifluoromethyl)benzene (2.93 g, 13.01 mmol) in toluene (20 mL) was added tBu₃Pd G2 (333.39 mg, 650.65 μ mol) and tBuONa (1.88 g, 19.52 mmol) in one portion under N₂ and the reaction was stirred at 120 °C for 24 hr. The mixture was concentrated under reduced pressure and the residue was purified by silica flash chromatography (0~40% Ethyl acetate in Petroleum ether) to provide the title compound (2.9 g, 6.42 mmol, 99% yield). LCMS (ESI), [M+H]⁺ = 452.2.

[255] Step 2: 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine hydrochloride



[256] *Tert*-butyl-4-[*N*-(4-methoxy-3-pyridyl)-4-(trifluoromethyl)anilino]piperidine-1-carboxylate (2.9 g, 6.42 mmol) was dissolved in dioxane (3.0 mL), HCl/dioxane (4 M, 10 mL) was added and the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to provide the title compound (2.4 g, 6.19 mmol, 96% yield) as a yellow solid. LCMS (ESI), [M+H]⁺ = 352.1.

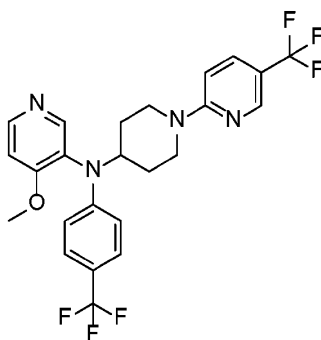
[257] Step 3: 4-Methoxy-*N*-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 12):



[258] To a solution of 4-methoxy-*N*-(4-piperidyl)-*N*-[4-(trifluoromethyl)phenyl]pyridin-3-amine (50 mg, 128.92 μ mol) and 2-chloro-5-methylsulfonyl-pyrimidine (24.83 mg, 128.92 μ mol) in DMF (1 mL) was added DIEA (49.99 mg, 386.77 μ mol) in one portion at 0 °C and the mixture was stirred at 0 °C for 0.5 hr. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (water (NH₃H₂O+NH₄HCO₃)-ACN]; B%: 45%-75%, 7 min) to provide the title compound (36.2 mg, 71.33 μ mol, 55.32% yield). LCMS (ESI), [M+H]⁺ = 508.1.

[259] **Compound 12:** ¹H NMR (400 MHz, CDCl₃) δ 8.66 (s, 2H), 8.53 (d, *J* = 5.6 Hz, 1H), 8.22 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.00 - 6.98 (m, 1H), 7.00 - 6.93 (m, 1H), 6.55 (d, *J* = 8.8 Hz, 2H), 5.04 (d, *J* = 13.6 Hz, 2H), 4.32 - 4.19 (m, 1H), 3.81 (s, 3H), 3.17 - 3.07 (m, 2H), 3.06 (s, 3H), 2.18 - 2.15 (m, 2H), 1.46 - 1.24 (m, 2H).

[260] **Example M: 4-Methoxy-*N*-(4-(trifluoromethyl)phenyl)-*N*-(1-(5-(trifluoromethyl)pyridin-2-yl)piperidin-4-yl)pyridin-3-amine (Compound 13):**

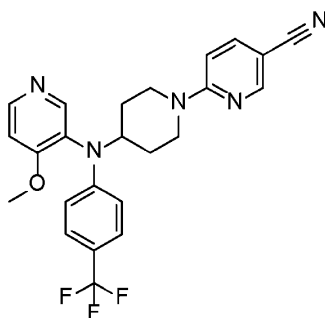


[261] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

[262] The title compound was purified by prep-HPLC (acetonitrile 50%/0.2% formic acid in water) to provide the title compound (120 mg, 241.72 μ mol, 42.58% yield). LCMS (ESI), [M+H]⁺ = 497.2.

[263] **Compound 13:** ¹H NMR (400 MHz, CD₃OD) 8.46 (d, *J* = 5.6 Hz, 1H), 8.28 (s, 1H), 8.16 (s, 1H), 7.69-7.60 (m, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 5.6 Hz, 1H), 6.85 (d, *J* = 9.2 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 4.55 - 4.52 (m, 2H), 4.39 - 4.28 (m, 1H), 3.83 (s, 3H), 3.11 - 3.08 (m, 2H), 2.14 - 2.11 (m, 2H), , 1.47 - 1.28 (m, 2H).

[264] **Example N: 6-(4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl) nicotinonitrile (Compound 14):**

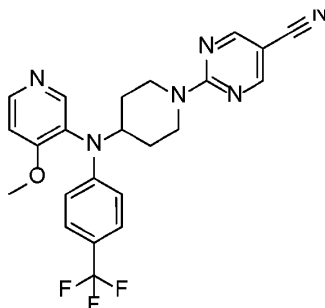


[265] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

[266] The title compound was purified by prep-HPLC (acetonitrile 50% / 0.2% formic acid in water) to provide the title compound (120 mg, 264.63 μ mol, 46.49% yield). LCMS (ESI), $[M+H]^+ = 454.2$.

[267] **Compound 14:** ^1H NMR (400 MHz, CD_3OD) 8.46 (d, $J = 5.6$ Hz, 1H), 8.34 (d, $J = 1.6$ Hz, 1H), 8.16 (s, 1H), 7.69 - 7.6 (m, 1H), 7.39 (d, $J = 8.8$ Hz, 2H), 7.22 (d, $J = 5.6$ Hz, 1H), 6.82 (d, $J = 8.8$ Hz, 1H), 6.65 (d, $J = 8.8$ Hz, 2H), 4.59 - 4.56 (m, 2H), 4.44 - 4.34 (m, 1H), 3.83 (s, 3H), 3.18 - 3.05 (m, 2H), 2.14 - 2.12 (m, 2H), 1.36 - 1.28 (m, 2H).

[268] **Example O: 2-(4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 15):**



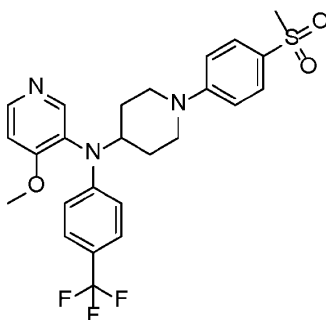
[269] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

[270] The title compound was purified by prep-HPLC (acetonitrile 35-50% / 0.2% formic acid in water) to provide the title compound (120 mg, 264.06 μ mol, 46.39% yield). LCMS (ESI), $[M+H]^+ = 455.2$.

[271] **Compound 15:** ^1H NMR (400 MHz, CD_3OD) 8.54 (s, 2H), 8.46 (d, $J = 6.4$ Hz, 1H), 8.16 (s, 1H), 7.39 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 2.0$ Hz, 1H), 6.65 (d, $J = 8.4$ Hz, 2H), 4.97 - 4.94 (m, 2H), 4.43 - 4.36 (m, 1H), 3.83 (s, 3H), 3.17 - 3.11 (m, 2H), 2.16 - 2.13 (m, 2H), 1.33 - 1.26 (m, 1H), 1.40 - 1.21 (m,

1H).

[272] **Example P: 4-Methoxy-*N*-(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 16):**

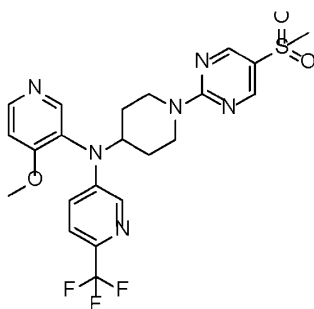


[273] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[274] The title compound was purified by prep-HPLC (Welch Xtimate C18 150*30mm*5um; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; B%: 50%-80%, 8min) to provide the title compound (82.5 mg, 163.19 μmol, 48.53% yield). LCMS (ESI), [M+H]⁺ = 506.1.

[275] **Compound 16:** ¹H NMR (400 MHz, CD₃OD) 8.47 (d, *J* = 6.0 Hz, 1H), 8.18 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 6.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 4.34 - 4.22 (m, 1H), 4.07 - 4.03 (m, 2H), 3.83 (s, 3H), 3.10 - 3.07 (m, 2H), 3.02 (s, 3H), 2.16 - 2.12 (m, 2H), 1.52 - 1.39 (m, 2H).

[276] **Example Q: 4-Methoxy-*N*-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)-*N*-(6-(trifluoromethyl)pyridin-3-yl)pyridin-3-amine (Compound 17):**



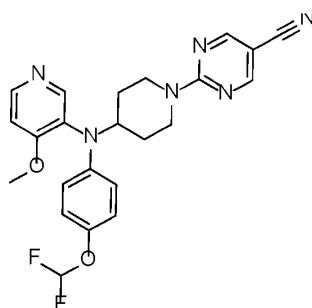
[277] The title compound was synthesized following a procedure similar to **Example E** (Compound 5).

[278] The title compound was purified by pre-HPLC (column: Welch Xtimate C18 150 * 30 mm * 5 μm; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; B%: 50%-80%, 8min) to provide the title compound (82.5 mg, 163.19 μmol, 48.53% yield). LCMS (ESI), [M+H]⁺ = 506.1.

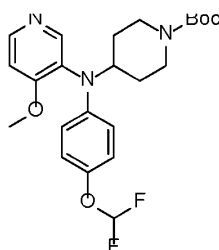
5um; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; B%: 37%-67%, 8 min) to provide the title compound (180 mg, 353.97 μ mol, 44.40% yield). LCMS (ESI), [M+H]⁺ = 509.1.

[279] **Compound 17:** ¹H NMR (400 MHz, CD₃OD) 8.65 (s, 2H), 8.51 (d, *J* = 5.6 Hz, 1H), 8.24 (s, 1H), 7.87 (d, *J* = 2.8 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 5.6 Hz, 1H), 7.18 (dd, *J* = 2.8, 8.8 Hz, 1H), 5.04 - 5.01 (m, 2H), 4.48 - 4.39 (m, 1H), 3.86 (s, 3H), 3.21 - 3.16 (m, 2H), 3.11 (s, 3H), 2.17 - 2.14 (m, 2H), 1.38 - 1.30 (m, 2H).

[280] **Example R: 2-(4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 18):**

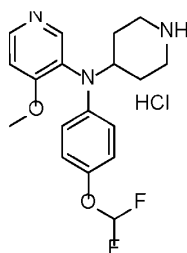


[281] Step 1: *Tert*-butyl 4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate



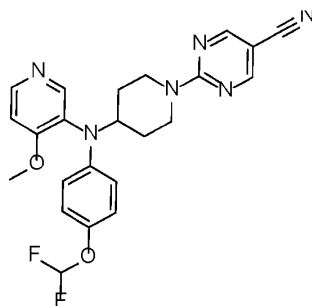
[282] A mixture of *tert*-butyl 4-[(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate (2.0 g, 6.51 mmol), 1-bromo-4-(difluoromethoxy)benzene (2.32 g, 10.41 mmol), tBu₃P Pd G2 (666.78 mg, 1.30 mmol), and tBuONa (1.88 g, 19.52 mmol) in dioxane (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 120 °C for 24 hr under N₂ atmosphere. The mixture was concentrated under reduced pressure and the residue was purified by silica flash chromatography (0~40% Ethyl acetate in Petroleum ether) to provide the title compound (1600 mg, 3.45 mmol, 52.98% yield). LCMS (ESI), [M+H]⁺ = 450.1.

[283] Step 2: *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride



[284] *Tert*-butyl-4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (1.6 g, 3.56 mmol) was dissolved in dioxane (3.0 mL), HCl/dioxane (4 M, 6 mL) was added and the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to provide the title compound (1.37 g, 3.56 mmol, 100% yield). LCMS (ESI), [M+H]⁺ = 350.1.

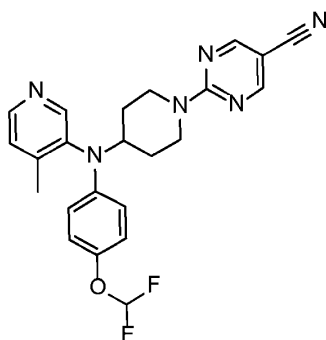
[285] Step 3: 2-(4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 18**):



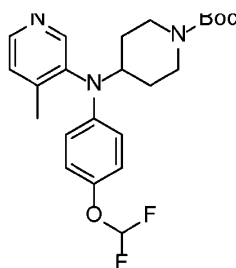
[286] To a mixture of *N*-[4-(difluoromethoxy)phenyl]-4-methoxy-*N*-(4-piperidyl)pyridin-3-amine (260 mg, 744.19 μmol) and triethylamine (301.22 mg, 2.98 mmol) in DMF (5 mL) was added 2-chloropyrimidine-5-carbonitrile (103.85 mg, 744.19 μmol) at 0°C under N₂. The mixture was stirred at 0 °C for 30 min. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic phase was washed with brine (20 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (water (NH₃H₂O+NH₄HCO₃)-ACN]; B%: 45%-75%, 7 min) to provide the title compound (153.4 mg, 339.04 μmol, 45.56% yield). LCMS (ESI), [M+H]⁺ = 453.2.

[287] **Compound 18**: ¹H NMR (400 MHz, CD₃OD) δ 8.53 (s, 2H), 8.41 (d, *J* = 5.6 Hz, 1H), 8.14 (s, 1H), 7.18 (d, *J* = 5.6 Hz, 1H), 6.94 (d, *J* = 9.2 Hz, 2H), 6.84 - 6.36 (m, 3H), 4.94 - 4.92 (m, 2H), 4.32 - 4.26 (m, 1H), 3.81 (s, 3H), 3.20 - 3.04 (m, 2H), 2.13 - 2.10 (m, 2H), 1.32 - 1.23 (m, 2H).

[288] **Example S**: 2-(4-((4-(Difluoromethoxy)phenyl)(4-methylpyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 19**):

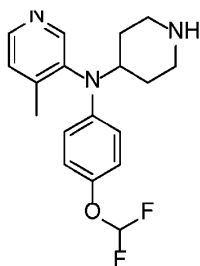


[289] Step 1: *Tert*-butyl-4-((4-(difluoromethoxy)phenyl)(4-methylpyridin-3-yl)amino)piperidine-1-carboxylate



[290] A mixture of *tert*-butyl 4-[(4-methyl-3-pyridyl)amino]piperidine-1-carboxylate (1 g, 3.43 mmol), 1-bromo-4-(difluoromethoxy)benzene (1.53 g, 6.86 mmol), $t\text{Bu}_3\text{PPdG}_2$ (351.70 mg, 686.37 μmol), $t\text{BuONa}$ (989.44 mg, 10.30 mmol) in toluene (20 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 120 $^\circ\text{C}$ for 12 hr under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by flash silica gel chromatography (Eluent of 0~35% Ethyl acetate in Petroleum ether) to provide the title compound (0.99 g, 2.28 mmol, 66.55% yield). LCMS (ESI), $[\text{M}+\text{H}]^+ = 434.2$.

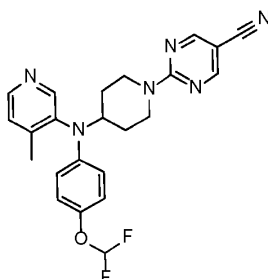
[291] Step 2: *N*-(4-(Difluoromethoxy)phenyl)-4-methyl-*N*-(piperidin-4-yl)pyridin-3-amine



[292] To a solution of *tert*-butyl-4-[4-(difluoromethoxy)-*N*-(4-methyl-3-pyridyl)anilino]piperidine-1-carboxylate (0.99 g, 2.28 mmol) in dioxane (5 mL) was added HCl/dioxane (4 M, 5 mL). The mixture was stirred at 25 $^\circ\text{C}$ for 1 hr. The reaction mixture was concentrated under reduced pressure to provide the

title compound (0.9 g, crude, HCl salt).

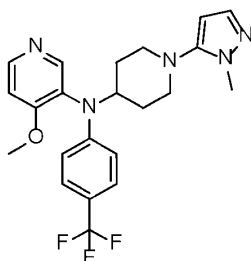
[293] Step 3: 2-((4-(4-(difluoromethoxy)phenyl)(4-methylpyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 19**):



[294] To a solution of *N*-[4-(difluoromethoxy)phenyl]-4-methyl-*N*-(4-piperidyl)pyridin-3-amine (300 mg, 811.17 μ mol) and 2-chloropyrimidine-5-carbonitrile (135.83 mg, 973.40 μ mol) in acetonitrile (5 mL) was added DIEA (524.19 mg, 4.06 mmol). The mixture was stirred at 0 °C for 0.5 hr. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by reversed-phase HPLC (Boston Prime C18 150*30 mm*5 μ m; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; B%: 60%-90%, 7min]) to provide the title compound (100.8 mg, 230.95 μ mol, 28.47% yield). LCMS (ESI), [M+H]⁺ = 437.1

[295] **Compound 19**: ¹H NMR (400 MHz, CD₃OD) δ 8.59 - 8.46 (m, 2H), 8.41 - 8.33 (m, 1H), 8.27 - 8.20 (m, 1H), 7.46 - 7.36 (m, 1H), 7.03 - 6.93 (m, 2H), 6.84 - 6.41 (m, 3H), 5.01 - 4.92 (m, 2H), 4.45 - 4.33 (m, 1H), 3.20 - 3.09 (m, 2H), 2.16 (s, 3H), 2.13 - 2.10 (m, 2H), 1.35 - 1.31 (m, 2H).

[296] **Example T: 4-Methoxy-*N*-(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 20)**:



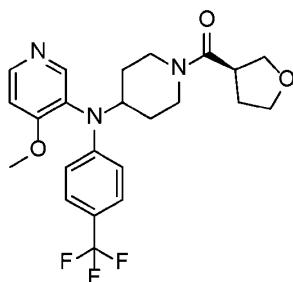
[297] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[298] The title compound was purified by prep-HPLC (Welch Xtimate C18 150*30mm*5 μ m; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; B%: 25%-40%, 8 min) to provide the title compound (75 mg,

173.83 μmol , 20.36% yield). LCMS (ESI), $[\text{M}+\text{H}]^+ = 432.2$.

[299] **Compound 20:** ^1H NMR (400 MHz, CD_3OD) 8.51 (d, $J = 6.0$ Hz, 1H), 8.23 (s, 1H), 7.39 (d, $J = 8.8$ Hz, 2H), 7.30 - 7.27 (m, 2H), 6.63 (d, $J = 8.8$ Hz, 2H), 5.90 (d, $J = 2.0$ Hz, 1H), 4.20 - 4.14 (m, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 3.22 - 3.19 (m, 2H), 2.91 - 2.85 (m, 2H), 2.14 - 2.10 (m, 2H), 1.67 - 1.57 (m, 2H).

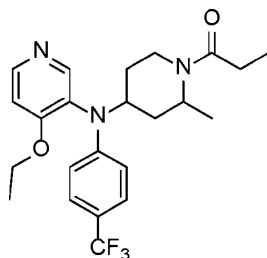
[300] **Example U:** (*R*)-(4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(tetrahydrofuran-3-yl)methanone (Compound 21):



[301] To a mixture of 4-methoxy-*N*-(4-piperidyl)-*N*-[4-(trifluoromethyl)phenyl]pyridin-3-amine (200 mg, 569.21 μmol) and (3*R*)-tetrahydrofuran-3-carboxylic acid (66.09 mg, 569.21 μmol) in DMF (3 mL) was added DIEA (220.70 mg, 1.71 mmol) and HATU (324.65 mg, 853.82 μmol) in one portion at 20°C. The mixture was stirred at 20 °C for 1 hr. The reaction mixture was purified by pre-HPLC (water ($\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3$)-ACN]; B%: 45%-75%, 7min) to provide the title compound (45.9 mg, 102.12 μmol , 17.94% yield, 100% purity). LCMS (ESI), $[\text{M}+\text{H}]^+ = 450.2$.

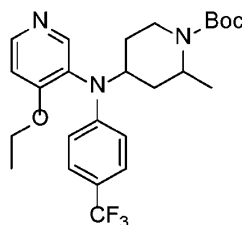
[302] **Compound 21:** ^1H NMR (400 MHz, CDCl_3) δ 8.55 (d, $J = 5.6$ Hz, 1H), 8.22 (s, 1H), 7.39 (d, $J = 8.8$ Hz, 2H), 6.99 (d, $J = 5.6$ Hz, 1H), 6.52 (d, $J = 8.8$ Hz, 2H), 4.77 - 4.73 (m, 1H), 4.15 - 4.08 (m, 1H), 4.04 - 3.97 (m, 2H), 3.87 - 3.83 (m, 3H), 3.81 (s, 3H), 3.26 - 3.15 (m, 2H), 2.69 - 2.64 (m, 1H), 2.18 - 2.04 (m, 4H), 1.78 - 1.73 (m, 1H), 1.35 - 1.18 (m, 2H).

[303] **Example V:** 1-(4-((4-Ethoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)-2-methylpiperidin-1-yl)propan-1-one (Compound 22):



[304] **Step 1:** *Tert*-butyl-4-[*N*-(4-ethoxy-3-pyridyl)-4-(trifluoromethyl)anilino]-2-methyl-piper-

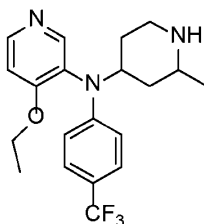
idine-1-carboxylate



[305] To a mixture of *tert*-butyl 4-[(4-ethoxy-3-pyridyl)amino]-2-methyl-piperidine-1-carboxylate (500 mg, 1.49 mmol) and 1-bromo-4-(trifluoromethyl)benzene (670.78 mg, 2.98 mmol) in toluene (20 mL) was added tBu3P Pd G2 (76.38 mg, 149.06 μ mol) and tBuONa (429.73 mg, 4.47 mmol) in one portion and the mixture was stirred at 120 °C for 19 hr under N₂. The mixture was concentrated in vacuum and the residue was purified by silica flash chromatography (0~30% Ethyl acetate in Petroleum ether) to provide the title compound (600 mg, 1.25 mmol, 83.94% yield). LCMS (ESI), [M+H]⁺ = 480.2.

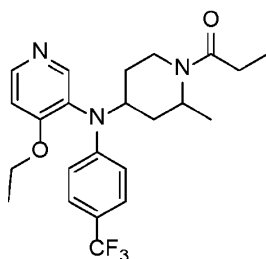
[306] ¹H NMR (400MHz, CD₃CN) δ 8.50 - 8.45 (m, 1H), 8.19 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.10 - 7.04 (m, 1H), 6.60 (d, *J* = 8.8 Hz, 2H), 4.11 - 4.05 (m, 2H), 3.83-3.84 (m, 1H), 3.57- 3.54 (m, 1H), 3.31 - 3.20 (m, 1H), 2.90 - 2.78 (m, 2H), 1.43 (s, 9H), 1.23 - 1.16 (m, 6H).

[307] Step 2: 4-Ethoxy-*N*-(2-methyl-4-piperidyl)-*N*-[4-(trifluoromethyl)phenyl]pyridin-3-amine



[308] To a solution of *tert*-butyl 4-[*N*-(4-ethoxy-3-pyridyl)-4-(trifluoromethyl)anilino]-2-methyl-piperidine-1-carboxylate (600 mg, 1.25 mmol) in dioxane (2.0 mL) was added HCl/dioxane (4 M, 1.61 mL) and the mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to provide the title compound (520 mg, 1.25 mmol, 99.93% yield, HCl salt) as a yellow solid. LCMS (ESI), [M+H]⁺ = 380.1.

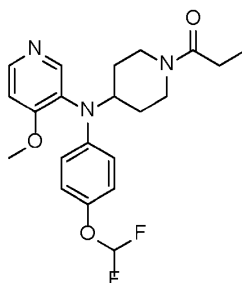
[309] Step 3: 1-(4-((4-Ethoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)-2-methylpiperidin-1-yl)propan-1-one (**Compound 22**):



[310] To a solution of 4-ethoxy-*N*-(2-methyl-4-piperidyl)-*N*-[4-(trifluoromethyl)phenyl]pyridin-3-amine (500 mg, 1.32 mmol) and Et₃N (400.05 mg, 3.95 mmol) in dichloromethane (3.0 mL) at 0 °C was added propanoyl chloride (182.89 mg, 1.98 mmol) in dropwise. The mixture was stirred at 0 °C for 1 hr. The mixture was concentrated in vacuum and the resulting residue was purified by pre-HPLC(water(0.05%FA)-ACN, 35%~65%) to provide the title compound (280 mg, 623.68 μmol, 47.33% yield). LCMS (ESI), [M+H]⁺ = 436.2.

[311] **Compound 22:** ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, *J* = 5.6 Hz, 1H), 8.29 (s, 1H), 8.15 (s, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 5.6 Hz, 1H), 6.53 (d, *J* = 8.8 Hz, 2H), 4.32 (s, 1H), 4.16 - 4.00 (m, 3H), 3.86 (s, 1H), 3.41 - 3.21 (m, 1H), 2.47 - 2.26 (m, 3H), 2.14 - 2.10 (m, 1H), 1.59 - 1.53 (m, 1H), 1.51 - 1.39 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.22 - 1.16 (m, 6H).

[312] **Example W: 1-(4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)propan-1-one (Compound 23):**



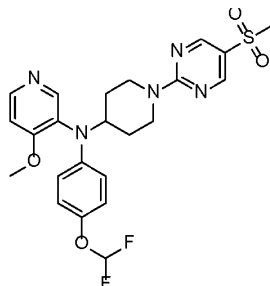
[313] The title compound was synthesized following a procedure similar to **Example V** (Compound 22).

[314] The title compound was purified by pre-HPLC (column: Welch Xtimate C18 150 * 30 mm * 5um; mobile phase: (water(0.05% FA)-ACN, 20%~50%, 8 min) to provide the title compound (87.1 mg, 214.83 μmol, 41.44% yield, 100% purity). LCMS (ESI), [M+H]⁺ = 406.1.

[315] **Compound 23:** ¹H NMR (400 MHz, CDCl₃) 8.50 (d, *J* = 5.6 Hz, 1H), 8.25 - 8.15 (m, 1H), 6.98 - 6.91 (m, 3H), 6.64 - 6.60 (m, 1H), 6.57 (s, 1H), 6.48 (d, *J* = 8.8 Hz, 2H), 6.38 (s, 1H), 4.74 - 4.70 (m, 1H), 4.08 - 4.02 (m, 1H), 3.98 - 3.86 (m, 1H), 3.79 (s, 3H), 3.16 - 3.09 (m, 1H), 2.64 - 2.61 (m, 1H),

2.38 - 2.25 (m, 2H), 2.07 - 2.02 (m, 2H), 1.38 - 1.19 (m, 2H), 1.10 (t, $J = 7.6$ Hz, 3H).

[316] **Example X: N-(4-(Difluoromethoxy)phenyl)-4-methoxy-N-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)pyridin-3-amine (Compound 24):**

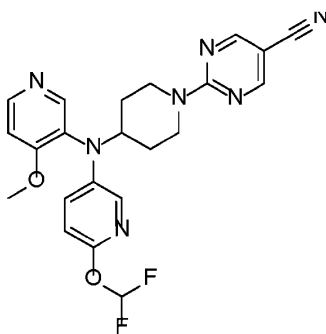


[317] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

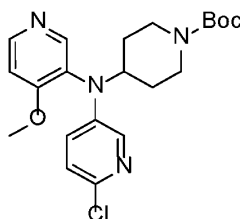
[318] The title compound was purified by prep-HPLC (acetonitrile 26 - 35% / 0.2% formic acid in water) to provide the title compound (172.4 mg, 334.20 μ mol, 42.98% yield, 98% purity). LCMS (ESI), $[M+H]^+ = 506.0$.

[319] **Compound 24:** ^1H NMR (400 MHz, CDCl_3) 8.66 (s, 2H), 8.49 (d, $J = 5.6$ Hz, 1H), 8.23 (s, 1H), 7.00 - 6.93 (m, 3H), 6.58 (s, 1H), 6.54 - 6.49 (m, 2H), 6.41 - 6.18 (m, 1H), 5.03 - 4.99 (m, 2H), 4.25 - 4.15 (m, 1H), 3.80 (s, 3H), 3.12 - 3.02 (m, 5H), 2.16 - 2.13 (m, 2H), 1.42 - 1.31 (m, 2H).

[320] **Example Y: 2-(4-((6-(Difluoromethoxy)pyridin-3-yl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 25):**

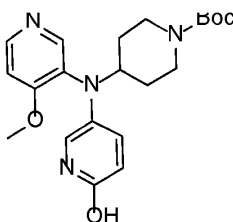


[321] Step 1: *Tert*-butyl 4-((6-chloropyridin-3-yl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate



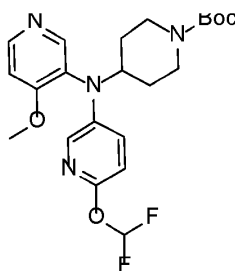
[322] A mixture of *tert*-butyl 4-[(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate (4.0 g, 13.01 mmol), 5-bromo-2-chloro-pyridine (5.01 g, 26.02 mmol), (tBu)₃P Pd G2 (666.78 mg, 1.30 mmol), and tBuONa (5.00 g, 52.04 mmol) in toluene (20 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 120 °C for 12 hrs under N₂ atmosphere. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by silica flash chromatography (20~70% Ethyl acetate in Petroleum ether) to provide the title compound (4.0 g, 9.55 mmol, 73.39% yield). LCMS (ESI) [M+H]⁺ = 419.2.

[323] Step 2: *Tert*-butyl 4-((6-hydroxypyridin-3-yl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate



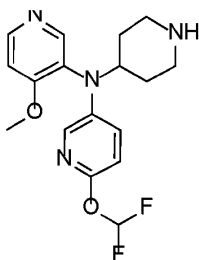
[324] To a solution of *tert*-butyl 4-[(6-chloro-3-pyridyl)-(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate (2000 mg, 4.77 mmol) in dioxane (20 mL) and H₂O (4 mL) was added di-*tert*-butyl-[2,3,4,5-tetramethyl-6-(2,4,6-triisopropylphenyl)phenyl]phosphane (183.45 mg, 381.60 μmol), Pd₂(dba)₃ (174.72 mg, 190.80 μmol) and KOH (1.07 g, 19.08 mmol). The reaction mixture was concentrated under reduced pressure to give the title compound (1.91 g, 3.86 mmol, 80.99% yield, 81% purity), crude used directly for next step. LCMS (ESI) [M+H]⁺ = 401.2.

[325] Step 3: *Tert*-butyl 4-((6-(difluoromethoxy)pyridin-3-yl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate



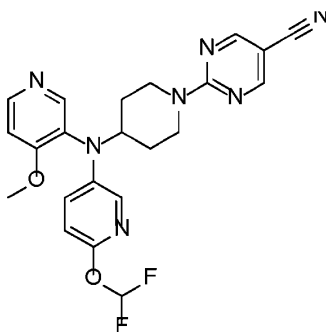
[326] A mixture of *tert*-butyl 4-[(6-hydroxy-3-pyridyl)-(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate (700 mg, 1.29 mmol, 74% purity) was dissolved in CH₃CN (6 mL), KOH (6 M, 2.58 mL), difluoromethyl trifluoromethanesulfonate (776 mg, 3.88 mmol), and then the mixture was stirred at 25 °C for 0.03 hr. The reaction mixture was diluted with brine (20 mL) and extracted with ethyl acetate (40 mL x 3). The combined organic layers was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Eluent of 0~60% Ethyl acetate/Petroleum ether) and then purified by prep-TLC (Petroleum ether/Ethyl acetate/ETOH=4/3/1) to provide title compound (240 mg, 41% yield). LCMS (ESI) [M+H]⁺ = 451.1.

[327] Step 4: 6-(Difluoromethoxy)-*N*-(4-methoxypyridin-3-yl)-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride



[328] To a solution of *tert*-butyl 4-[[6-(difluoromethoxy)-3-pyridyl]-(4-methoxy-3-pyridyl)amino]piperidine-1-carboxylate (215.07 mg, 477.42 μmol) in dioxane (2 mL) was added HCl/dioxane (4 M, 2 mL) at 25 °C and the mixture was stirred at 25 °C for 1 hr. The reaction was concentrated under reduced pressure to provide the title compound (184 mg, 475.67 μmol, 99.63% yield, HCl salt). LCMS (ESI) [M+H]⁺ = 351.1.

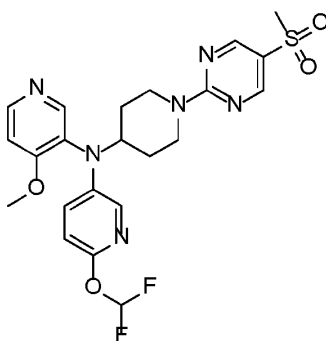
[329] Step 5: 2-(4-((6-(Difluoromethoxy)pyridin-3-yl)(4-methoxypyridin-3-yl)amino) piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 25**):



[330] A mixture of 6-(difluoromethoxy)-*N*-(4-methoxy-3-pyridyl)-*N*-(4-piperidyl)pyridin-3-amine (40 mg, 103.41 μmol , HCl salt), 2-chloropyrimidine-5-carbonitrile (17.32 mg, 124.09 μmol) and DIEA (40.09 mg, 310.22 μmol) in DMF (2.0 mL) and then the mixture was stirred at 0 °C for 1 hr. The reaction mixture was diluted with water (10 ml) and extracted with ethyl acetate (20 mL X 3). The combined organic layers was washed with brine (30 mL X 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified by flash silica gel chromatography (Eluent of 0~5% methanol in dichloromethane) to provide the title compound (34 mg, 72.73 μmol , 70.34% yield, 97% purity). LCMS (ESI) [M+H]⁺ = 454.1.

[331] **Compound 25:** ¹HNMR (400 MHz, DMSO-*d*₆): 8.71 (s, 2H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.20 (s, 1H), 7.54 (s, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 5.6 Hz, 1H), 7.02 (d, *J* = 3.2 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 4.78 - 4.75 (m, 2H), 4.34 - 4.28 (m, 1H), 3.76 (s, 3H), 3.19-3.14 (m, 2H), 2.05-2.02 (m, 2H), 1.17-1.14 (m, 2H).

[332] **Example Z: 6-(Difluoromethoxy)-*N*-(4-methoxypyridin-3-yl)-*N*-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)pyridin-3-amine (Compound 26):**



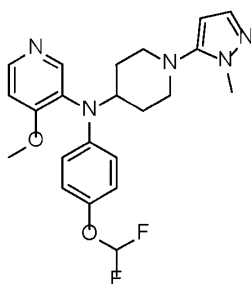
[333] The title compound was synthesized following a procedure similar to **Example Y** (Compound 25).

[334] The residue was purified by flash silica gel chromatography (Eluent of 0~5% methanol in

dichloromethane) to provide the title compound (40 mg, 77.39 μ mol, 74.84% yield). LCMS (ESI) [M+H]⁺ = 507.1.

[335] **Compound 26:** ¹H NMR (400 MHz, CDCl₃) 8.66 (s, 2H), 8.49 (d, *J* = 5.2 Hz, 1H), 8.25 (s, 1H), 7.58 (s, 1H), 7.27 (t, *J* = 75.2 Hz, 1H), 6.93 - 6.88 (m, 2H), 6.74 (d, *J* = 8.8 Hz, 1H), 5.03 - 4.99 (m, 2H), 4.15 - 4.09 (m, 1H), 3.79 (s, 3H), 3.09 - 3.03 (m, 5H), 2.15 - 2.12 (m, 2H), 1.42 - 1.34 (m, 2H).

[336] **Example AA:** *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(1-methyl-1H-pyrazol-5-yl) piperidin-4-yl)pyridin-3-amine (Compound 27):

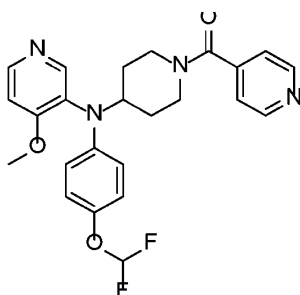


[337] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[338] The title compound was purified by prep-TLC (ethanol: ethyl acetate: Petroleum ether=1:3:4) to provide the title compound (41 mg, 92.60 μ mol, 16.18% yield). LCMS (ESI), [M+H]⁺ = 430.2.

[339] **Compound 27:** ¹H NMR (400 MHz, CDCl₃) 8.53 (d, *J* = 5.6 Hz, 1H), 8.30 (s, 1H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.05 - 6.93 (m, 3H), 6.59 (s, 1H), 6.53 (d, *J* = 9.2 Hz, 2H), 6.43 - 6.18 (m, 1H), 5.80 (d, *J* = 2.0 Hz, 1H), 4.01 - 3.92 (m, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 3.19 - 3.15 (m, 2H), 2.86 - 2.74 (m, 2H), 2.09 - 2.06 (m, 2H), 1.58 - 1.55 (m, 2H).

[340] **Example AB:** (4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(pyridin-4-yl)methanone (Compound 28):



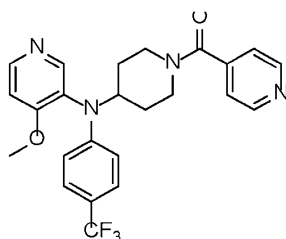
[341] The title compound was synthesized following a procedure similar to **Example U** (Compound

21).

[342] The title compound was purified by prep-TLC (10% methanol in dichloromethane) to provide the title compound (129.8 mg, 285.61 μ mol, 66.52% yield). LCMS (ESI), [M+H]⁺ = 455.2.

[343] **Compound 28:** ¹H NMR (400 MHz, CD₃OD) δ 8.69 - 8.59 (m, 2H), 8.46 (d, *J* = 5.6 Hz, 1H), 8.18 (s, 1H), 7.43 - 7.35 (m, 2H), 7.22 (d, *J* = 5.6 Hz, 1H), 7.00 - 6.89 (m, 2H), 6.80 - 6.39 (m, 3H), 4.68 (d, *J* = 13.6 Hz, 1H), 4.3 - 4.20 (m, 1H), 3.83 (s, 3H), 3.63 - 3.60 (m, 1H), 3.39 - 3.34 (m, 1H), 3.05 - 3.01 (m, 1H), 2.16 - 2.13 (m, 1H), 2.05 - 1.93 (m, 1H), 1.49 - 1.33 (m, 2H).

[344] **Example AC: (4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(pyridin-4-yl)methanone (Compound 29):**

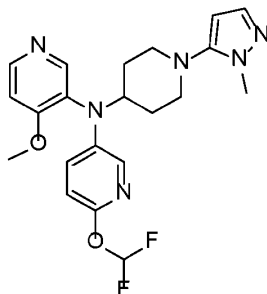


[345] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

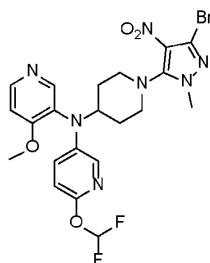
[346] The title compound was purified by prep-TLC (10% methanol in dichloromethane) to provide the title compound (135 mg, 295.75 μ mol, 69.28% yield). LCMS (ESI), [M+H]⁺ = 457.2.

[347] **Compound 29:** ¹H NMR (400 MHz, CD₃OD) δ 8.63 (d, *J* = 6.0 Hz, 2H), 8.51 (d, *J* = 5.6 Hz, 1H), 8.20 (s, 1H), 7.42 - 7.34 (m, 4H), 7.26 (d, *J* = 5.6 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 4.73 - 4.69 (m, 1H), 4.37 - 4.28 (m, 1H), 3.85 (s, 3H), 3.65 - 3.62 (m, 1H), 3.40 - 3.34 (m, 1H), 3.05 - 3.01 (m, 1H), 2.19 - 2.16 (m, 1H), 2.05 - 2.02 (m, 1H), 1.42 - 1.31 (m, 2H).

[348] **Example AD: 6-(Difluoromethoxy)-N-(4-methoxypyridin-3-yl)-N-(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)pyridin-3-amine (Compound 30):**

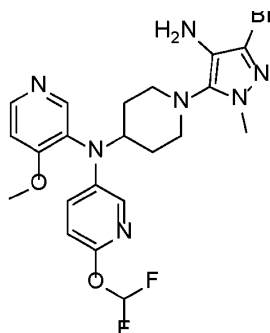


[349] Step 1: *N*-(1-(3-Bromo-1-methyl-4-nitro-1H-pyrazol-5-yl)piperidin-4-yl)-6-(difluoromethoxy)-*N*-(4-methoxypyridin-3-yl)pyridin-3-amine



[350] A mixture of 6-(difluoromethoxy)-*N*-(4-methoxy-3-pyridyl)-*N*-(4-piperidyl)pyridin-3-amine (60 mg, 155.11 μ mol, HCl salt), 3,5-dibromo-1-methyl-4-nitro-pyrazole (53.03 mg, 186.13 μ mol) and DIEA (60.14 mg, 465.33 μ mol) in CH₃CN (2.0 mL) and then the mixture was stirred at 80 °C for 4 hr. The reaction mixture was concentrated under reduced pressure to give the crude residue and the residue was purified by flash silica gel chromatography (10~45% ethyl acetate in petroleum ether) to provide the title compound (56 mg, 101.02 μ mol).

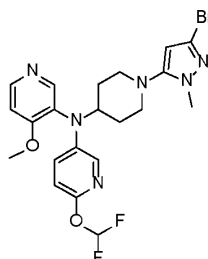
[351] Step 2: *N*-(1-(4-Amino-3-bromo-1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)-6-(difluoromethoxy)-*N*-(4-methoxypyridin-3-yl)pyridin-3-amine



[352] A solution of *N*-[1-(5-bromo-2-methyl-4-nitro-pyrazol-3-yl)-4-piperidyl]-6-(difluoromethoxy)-*N*-(4-methoxy-3-pyridyl)pyridin-3-amine (56 mg, 101.02 μ mol) in EtOH (5 mL) and H₂O (1 mL), NH₄Cl (27.02 mg, 505.10 μ mol) and Fe (28.21 mg, 505.10 μ mol) were added in one portion and then the mixture was stirred at 80 °C for 1 hr. The reaction mixture was cooled to room temperature and then filtered on a plug of kieselguhr and the filtrate was concentrated. The residue was diluted with ethyl acetate and the suspension was filtered. The filtrate was concentrated to provide the title compound (52 mg, 99.17 μ mol, 98.17% yield); it was used in next step without further purification. LCMS (ESI) [M+H]⁺ = 513.9.

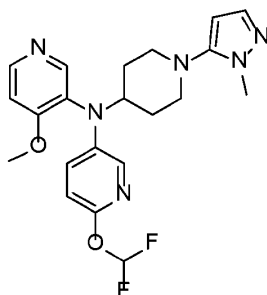
[353] Step 3: *N*-(1-(3-bromo-1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)-6-(difluoromethoxy)-*N*-(4-

methoxypyridin-3-yl)pyridin-3-amine



[354] To stirred solution of *N*-[1-(4-amino-5-bromo-2-methyl-pyrazol-3-yl)-4-piperidyl]-6-(difluoromethoxy)-*N*-(4-methoxy-3-pyridyl)pyridin-3-amine (52 mg, 99.17 μ mol) in EtOH (6 mL) at 0 °C was added concentrated H₂SO₄ (103.67 mg, 1.06 mmol) slowly. The reaction mixture was stirred at 0 °C for 5 min and then NaNO₂ (20.53 mg, 297.51 μ mol) in H₂O (0.4 mL) was added dropwise. The reaction mixture was stirred at ice bath for 15 min and then heated to 100 °C and stirred for 1 h. H₃PO₂ (128.90 mg, 991.68 μ mol, 50% purity) was added and the resulting reaction mixture was stirred at 0-100 °C for 3 hr. The reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (20 mLX3). The combined organic layers was washed with brine (30 mLX3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude residue. The residue was purified by flash silica gel chromatography (Eluent of 25~45% EE (Ethanol/ethyl acetate) in petroleum ether) to provide the title compound (38 mg, 74.61 μ mol, 75.23% yield) was obtained as a white solid. LCMS (ESI) [M+H]⁺ = 511.1.

[355] Step 4: 6-(Difluoromethoxy)-*N*-(4-methoxypyridin-3-yl)-*N*-(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)pyridin-3-amine (**Compound 30**):

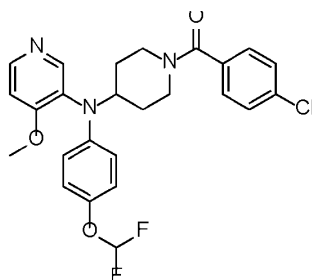


[356] A mixture of *N*-[1-(5-bromo-2-methyl-pyrazol-3-yl)-4-piperidyl]-6-(difluoromethoxy)-*N*-(4-methoxy-3-pyridyl)pyridin-3-amine (38 mg, 74.61 μ mol) and Pd/C (25 mg, 74.61 μ mol, 10% purity) in methanol (10 mL) was degassed and purged with H₂ for 3 times, and then the mixture was stirred at 28 °C for 4 hr under H₂ (15 psi). The reaction mixture was filtered and the filter was concentrated. The crude product was purified by silica gel chromatography (eluted with Petroleum ether/Ethyl acetate/ethanol=4:3:1, then purified by prep-TLC) to provide the title compound (22 mg, 48.04 μ mol, 64.40%

yield). LCMS (ESI) $[M+H]^+ = 431.2$.

[357] **Compound 30:** ^1H NMR (400 MHz, CDCl_3) 8.54 (d, $J = 5.6$ Hz, 1H), 8.32 (s, 1H), 7.55 (d, $J = 3.2$ Hz, 1H), 7.36 - 7.27 (m, 2H), 6.96 (d, $J = 5.6$ Hz, 1H), 6.88 (d, $J = 3.2$ Hz, 1H), 6.73 (d, $J = 8.8$ Hz, 1H), 5.79 (s, 1H), 3.97 - 3.91 (m, 1H), 3.81 (s, 3H), 3.62 (s, 3H), 3.19 - 3.16 (m, 2H), 2.81 - 2.75 (m, 12), 2.08 - 2.05 (m, 2H), 1.59 - 1.57 (m, 2H).

[358] **Example AE: (4-Chlorophenyl)(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)methanone (Compound 31):**

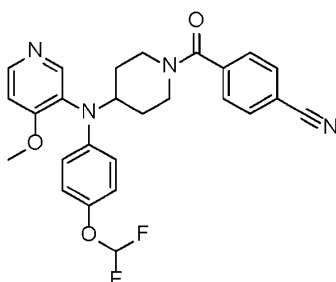


[359] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[360] The title compound was purified by prep-HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water ($\text{NH}_3\text{H}_2\text{O}+\text{NH}_4\text{HCO}_3$)-ACN]; B%: 50%-80%, 10 min) to provide the title compound (125 mg, 255.16 μmol , 44.57% yield). LCMS (ESI), $[M+H]^+ = 488.0$.

[361] **Compound 31:** ^1H NMR (400 MHz, CDCl_3) δ 8.53 (s, 1H), 8.24 (s, 1H), 7.43 - 7.34 (m, 2H), 7.33 - 7.28 (m, 2H), 6.95 (d, $J = 9.2$ Hz, 3H), 6.63 - 6.17 (m, 3H), 4.78 (s, 1H), 4.17 - 4.03 (m, 1H), 3.80 (s, 4H), 3.26 - 2.72 (m, 2H), 2.14 - 2.02 (m, 2H), 1.35 - 1.30 (m, 2H).

[362] **Example AF: 4-(4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carbonyl)benzonitrile (Compound 32):**



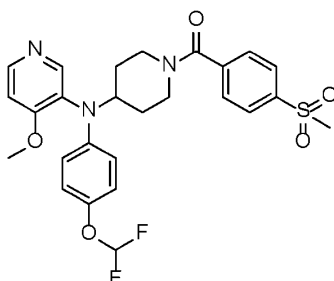
[363] The title compound was synthesized following a procedure similar to **Example U** (Compound

21).

[364] The title compound was purified by prep-HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (NH₃H₂O+NH₄HCO₃)-ACN];B%: 38%-50%,10 min) to provide the title compound (110 mg, 227.59 μ mol, 39.76% yield). LCMS (ESI), [M+H]⁺ = 479.0.

[365] **Compound 32:** ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, *J* = 4.8 Hz, 1H), 8.24 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 3H), 6.60 - 6.18 (m, 3H), 4.79 - 4.76 (m, 1H), 4.13 - 4.07 (m, 1H), 3.81 (s, 3H), 3.75 - 3.67 (m, 1H), 3.20 - 3.16 (m, 1H), 2.95 - 2.89 (m, 1H), 2.22 - 1.93 (m, 2H), 1.52 - 1.12 (m, 2H).

[366] **Example AG: (4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(4-(methylsulfonyl)phenyl)methanone (Compound 33):**

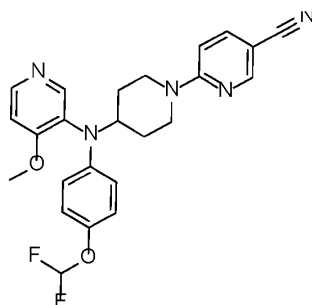


[367] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[368] The title compound was purified by prep-HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN];B%: 44%-74%,10 min) to provide the title compound (130 mg, 242.11 μ mol, 42.29% yield). LCMS (ESI), [M+H]⁺ = 532.0.

[369] **Compound 33:** ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, *J* = 5.2 Hz, 1H), 8.25 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 3H), 6.61 - 6.19 (m, 3H), 4.81 - 4.76 (m, 1H), 4.15 - 4.10 (m, 1H), 3.81 (s, 3H), 3.68 - 3.64 (m, 1H), 3.19-3.07 (m, 1H), 3.07 (s, 3H), 2.93 - 2.89 (m, 1H), 2.21 - 1.93 (m, 2H), 1.52 - 1.21 (m, 2H).

[370] **Example AH: 6-(4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)nicotinonitrile (Compound 34):**

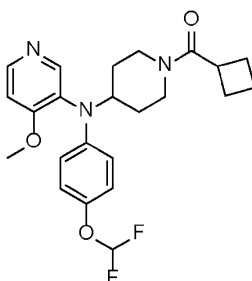


[371] The title compound was synthesized following a procedure similar to **Example R** (Compound 18).

[372] The title compound was purified by prep-HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN];B%: 55%-85%,10 min) to provide the title compound (104 mg, 223.45 μ mol, 39.03% yield). LCMS (ESI), [M+H]⁺ = 452.0.

[373] **Compound 34:** ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, *J* = 4.8 Hz, 1H), 8.24 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 3H), 6.60 - 6.18 (m, 3H), 4.81 - 4.76 (s, 1H), 4.14 - 4.09 (m, 1H), 3.81 (s, 3H), 3.69 - 3.66 (m, 1H), 3.21 - 3.18 (m, 1H), 2.94 - 2.88 (m, 1H), 2.22 - 1.93 (m, 2H), 1.52 - 1.12 (m, 2H).

[374] **Example AI: Cyclobutyl(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino) piperidin-1-yl)methanone (Compound 35):**



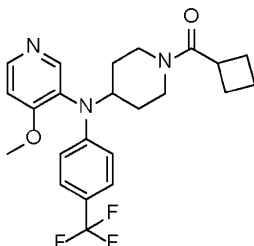
[375] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[376] The title compound was purified by prep-HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN];B%: 50%-80%,10 min) to provide the title compound (115.0 mg, 261.20 μ mol, 45.63% yield). LCMS (ESI), [M+H]⁺ = 432.2.

[377] **Compound 35:** ¹H NMR (400 MHz, CD₃OD) δ 8.43 (d, *J* = 5.6 Hz, 1H), 8.14 (s, 1H), 7.19 (d, *J* = 5.6 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.79 - 6.39 (m, 3H), 4.57 - 4.46 (m,

[378] 1H), 4.22-4.13 (m, 1H), 3.91 - 3.77 (m, 4H), 3.41 - 3.33 (m, 1H), 3.22 - 3.08 (m, 1H), 2.78-2.70 (m, 1H), 2.23 - 1.92 (m, 7H), 1.86 - 1.72 (m, 1H), 1.28 - 1.08 (m, 2H).

[379] **Example AJ: Cyclobutyl(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone (Compound 36):**

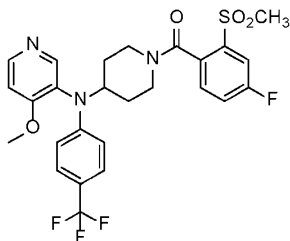


[380] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

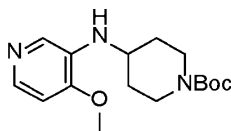
[381] The title compound was purified by prep-HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH3H2O+NH4HCO3)-ACN]; B%: 50%-80%, 10 min) to provide the title compound (131.8 mg, 304.06 μ mol, 53.42% yield). LCMS (ESI), [M+H]⁺ = 434.1.

[382] **Compound 36:** ¹H NMR (400 MHz, CD₃OD) δ 8.56 - 8.44 (m, 1H), 8.25 - 8.12 (m, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.30 - 7.21 (m, 1H), 6.70 - 6.57 (m, 2H), 4.63 - 4.54 (m, 1H), 4.36 - 4.26 (m, 1H), 3.92 - 3.89 (m, 1H), 3.86 (s, 3H), 3.44 - 3.36 (m, 1H), 3.25 - 3.12 (m, 1H), 2.83 - 2.72 (m, 1H), 2.29 - 2.05 (m, 6H), 2.03 - 1.91 (m, 1H), 1.87 - 1.74 (m, 1H), 1.32 - 1.14 (m, 2H).

[383] **Example AK: (4-Fluoro-2-(methylsulfonyl)phenyl)(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone (Compound 37):**



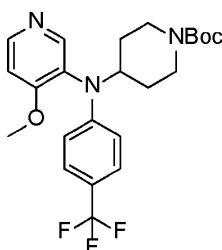
[384] Step 1: Preparation of *tert*-Butyl 4-((4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate:



[385] To a stirred solution of *tert*-Butyl 4-oxopiperidine-1-carboxylate (12.03 g, 60.41 mmol, 1.5 eq.) in anhydrous Dichloromethane (75 mL) was added 4-Methoxypyridin-3-amine (5.0 g, 40.27 mmol, 1.0 eq), Acetic acid (2.53 mL, 44.30 mmol, 1.1 eq) and Sodium triacetoxymethylborohydride (12.80 g, 60.41 mmol, 1.5 eq) sequentially at room temperature. The resulted reaction mixture was stirred at reflux for 20 h. The progress of the reaction was monitored by TLC and UPLC-MS which indicated product formation along with complete consumption of starting materials. Then, the reaction mixture was cooled to room temperature and adjusted the pH up to ~8 with 2M aqueous sodium hydroxide solution (100 mL) and extracted with Dichloromethane (2 × 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered the drying agent and concentrated the solution under reduced pressure to obtain crude residue. The crude material was purified by combi flash chromatography using silica gel by eluted with EtOAc and pure fractions are concentrated under reduced pressure to afford *tert*-Butyl 4-((4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (7.80 g, 63%). MS (ESI): mass calculated for C₁₆H₂₅N₃O₃, 307.39; m/z found, 308.2 [M+H]⁺.

[386] ¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H), 7.76 (d, *J* = 5.2 Hz, 1H), 6.83 (d, *J* = 5.2 Hz, 1H), 4.61 (d, *J* = 8.4 Hz, 1H), 3.90 (d, *J* = 12.4 Hz, 2H), 3.82 (s, 3H), 3.50 (br s, 1H), 2.86 (br s, 2H), 1.90 - 1.86 (m, 2H), 1.40 (s, 9H), 1.34 - 1.26 (m, 2H).

[387] Step 2: Preparation of *tert*-Butyl 4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate:

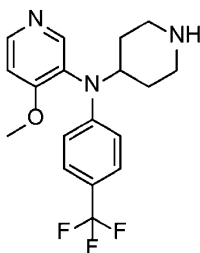


[388] The sealed tube was charged with *tert*-Butyl 4-((4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (7.80 g, 25.37 mmol, 1.0 eq), 1-Bromo-4-(trifluoromethyl)benzene (5.71 g, 25.37 mmol, 1.0 eq), Sodium *tert*-butoxide (4.80 g, 50.74 mmol, 2.0 eq) and toluene (150 mL) at room temperature under argon atmosphere. The resulting mixture was degassed using argon balloon for 10 min, then added Ruphos-Pd-G3 (1.06 g, 1.26 mmol, 0.05 eq) under argon. Then, sealed the tube and stirred for 16 h at 120 °C. The reaction was monitored by TLC and UPLC-MS which indicated product formation. The reaction mixture was cooled to room temperature, passed through a pad of celite. The filtrate was concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel by eluted with 80% EtOAc in hexanes and pure fractions were concentrated under reduced pressure to afford *tert*-Butyl 4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidine-1-

carboxylate (5, 4.40 g, 38%). MS (ESI): mass calculated for $C_{23}H_{28}F_3N_3O_3$, 451.49; m/z found, 452.2 $[M+H]^+$.

[389] 1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, $J = 5.6$ Hz, 1H), 8.21 (s, 1H), 7.36 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 6.0$ Hz, 1H), 6.47 (d, $J = 8.8$ Hz, 2H), 4.18 (br s, 2H), 4.06 – 3.97 (tt, $J = 11.6$ Hz, $J = 3.6$ Hz, 1H), 3.79 (s, 3H), 2.81 (m, 2H), 1.32 – 1.25 (td, $J = 12.4$ Hz, $J = 4.0$ Hz, 2H), 1.42 (s, 9H), 1.32 – 1.25 (td, $J = 12.4$ Hz, $J = 4.0$ Hz, 2H).

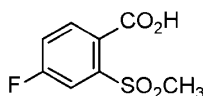
[390] Step 3: Preparation of 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine hydrochloride:



[391] To a solution of *tert*-Butyl 4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate (4.40 g, 9.74 mmol, 1.0 eq) in 2,2,2-Trifluoroethanol (25.0 mL) at 0 °C was added Chlorotrimethylsilane (6.80 mL) dropwise and stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC which showed complete consumption of starting material. The volatiles were removed under reduced pressure to obtain the crude material. Trituration of crude product using Acetonitrile (10.0 mL) to afford 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine hydrochloride (3.10 g (crude)). MS (ESI): mass calculated for $C_{18}H_{20}F_3N_3O$, 351.16; m/z found, 352.1 $[M+H]^+$.

[392] 1H NMR (400 MHz, $DMSO-d_6$) δ 9.11 (d, $J = 8.8$ Hz, 1H), 8.92 – 8.90 (m, 2H), 8.74 (s, 1H), 7.79 (d, $J = 6.4$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 2H), 4.43 (t, $J = 11.6$ Hz, 1H), 4.00 (s, 3H), 3.25 (d, $J = 12.0$ Hz, 2H), 3.11 – 3.02 (m, 2H), 2.03 (d, $J = 12.8$ Hz, 2H), 1.68 – 1.59 (m, 2H).

[393] Step 4: Preparation of 4-Fluoro-2-(methylsulfonyl)benzoic acid (7)

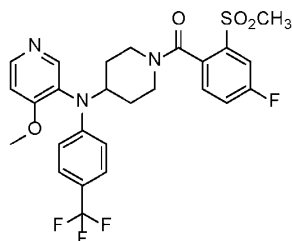


[394] To a solution of 2-Bromo-4-fluorobenzoic acid (0.25 g, 1.14 mmol, 1.0 eq) in Dimethyl sulfoxide (15.0 mL) was added Sodium methanesulfonate (0.47 g, 3.99 mmol, 3.5 eq), CuI (0.86 g, 4.56 mmol, 4.0 eq) and Sodium hydroxide (5N in H_2O , 0.22 mL, 1.14 mmol, 1.0 eq) at room temperature and stirred at 120 °C for 2 h. The progress of the reaction was monitored by TLC which showed complete consumption of starting material. The reaction mixture was cooled to room temperature, diluted with water

(20.0 mL) and washed with EtOAc (2×10 mL). The aqueous layer was acidified with 2N aq. HCl solution (2.0 mL) and extracted with EtOAc (2×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered the drying agent and concentrated the solution under reduced pressure to obtain 4-Fluoro-2-(methylsulfonyl)benzoic acid (0.15 g, Crude). MS (ESI): mass calculated for $\text{C}_8\text{H}_7\text{FO}_4\text{S}$, 218.00; m/z found, 216.98 $[\text{M}-\text{H}]^-$.

[395] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.93 - 7.88 (m, 2H), 7.40 - 7.37 (m, 1H), 3.44 (s, 3H).

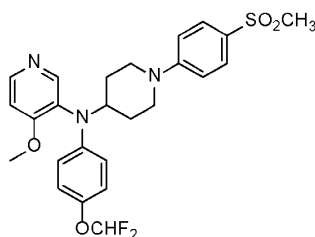
[396] Step 5: Preparation of (4-Fluoro-2-(methylsulfonyl)phenyl)(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone (**Compound 37**):



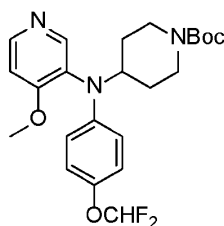
[397] To a stirred solution of 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl) pyridin-3-amine hydrochloride (0.10 g, 0.25 mmol, 1.0 eq.) and 4-Fluoro-2-(methylsulfonyl) benzoic acid (0.06 g, 0.30 mmol, 1.2 eq.) in *N,N*-Dimethylformamide (2.0 mL) was added Diisopropylethylamine (0.17 mL, 1.02 mmol, 4.0 eq.) and 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxidehexafluorophosphate (HATU, 0.11 g, 0.30 mmol, 1.2 eq.) at 0 °C. Then, the resulted reaction mixture was stirred at room temperature for 8 h. The progress of the reaction was monitored by TLC and UPLC-MS which indicated the product formation along with complete consumption of starting materials. The reaction mixture was poured into ice cold water (5.0 mL). The obtained solid was collected by filtration, the solid cake was washed with excess cold water (5.0 mL) and dried under vacuum to afford (4-Fluoro-2-(methylsulfonyl)phenyl)(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone (0.14 g, 66% yield). MS (ESI): mass calculated for $\text{C}_{26}\text{H}_{25}\text{F}_4\text{N}_3\text{O}_4\text{S}$, 551.15; m/z found, 552.3 $[\text{M}+\text{H}]^+$, HPLC purity: 95.77%

[398] **Compound 37:** ^1H NMR (400 MHz, CDCl_3) of rotamers δ 8.53 (dd, $J = 18.0$ Hz, $J = 5.6$ Hz, 1H), 8.17 (d, $J = 38.4$ Hz, 1H), 7.74 - 7.60 (m, 2H), 7.59 - 7.53 (m, 1H), 7.40 (d, $J = 8.8$ Hz, 2H), 7.25 (dd, $J = 16.8$ Hz, $J = 6.0$ Hz, 1H), 6.62 - 6.57 (m, 2H), 4.59 - 4.46 (m, 1H), 4.33 - 4.24 (dd, $J = 24.0$ Hz, $J = 11.6$ Hz, 1H), 3.76 (d, $J = 14.8$ Hz, 3H), 3.26 (d, $J = 7.6$ Hz, 3H), 3.25 - 3.09 (m, 2H), 2.99 - 2.86 (m, 1H), 2.06 - 1.94 (m, 2H), 1.85 - 1.68 (d, $J = 56.0$ Hz, $J = 12.0$ Hz, 1H), 1.48 - 1.23 (m, 2H).

[399] **Example AL:** *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)pyridin-3-amine (**Compound 38**):



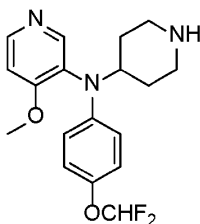
[400] Step 1: Preparation of *tert*-Butyl 4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate:



[401] The sealed tube charged with *tert*-Butyl 4-((4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (1.50 g, 4.88 mmol, 1.0 eq.), 1-Bromo-4-(difluoromethoxy)benzene (1.30 g, 5.86 mmol, 1.2 eq), Sodium *tert*-butoxide (0.93 g, 9.76 mmol, 2.0 eq) and toluene (30.0 mL) at room temperature under argon atmosphere. The resulting mixture was degassed by argon purging for 10 min, then added $P(t\text{-Bu})_3$ Pd-G2 (0.15 g, 0.29 mmol, 0.05 eq). Then sealed the cap and stirred at 120 °C for 16 h. The reaction was monitored by UPLC which showed product formation. The reaction mixture was cooled to room temperature, passed through a pad of celite. The filtrate was concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel by eluted with 60% EtOAc in hexanes, pure fractions were concentrated under reduced pressure to afford *tert*-Butyl 4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (0.40 g, 17% yield). MS (ESI): mass calculated for $C_{23}H_{29}F_2N_3O_4$, 449.21; m/z found, 450.2 $[M+H]^+$.

[402] 1H NMR (400 MHz, $DMSO-d_6$) δ 8.48 (d, $J = 5.6$ Hz, 1H), 8.15 (s, 1H), 7.21 (d, $J = 7.2$ Hz, 1H), 7.16 - 6.97 (t, $J = 7.5$ Hz, 1H), 6.96 - 6.93 (d, $J = 9.2$ Hz, 2H), 6.45 (d, $J = 9.2$ Hz, 2H), 4.09 - 4.05 (m, 1H), 3.93 (br s, 2H), 3.76 (s, 3H), 2.86 (br s, 2H), 1.88 (d, $J = 12.0$ Hz, 2H), 1.33 (s, 9H), 1.10 - 1.08 (m, 2H).

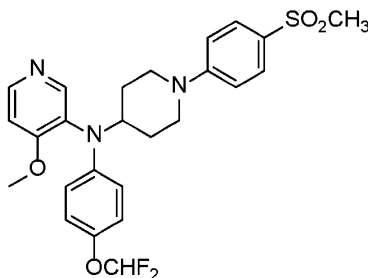
[403] Step 2: Preparation of *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride (11)



[404] To a solution of *tert*-Butyl 4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino) piperidine-1-carboxylate (0.40 g, 0.89 mmol, 1.0 eq.) in 2,2,2-Trifluoroethanol (3.0 mL) was added Chlorotrimethylsilane (0.70 mL) dropwise at 0 °C. Then, the reaction mixture was stirred for 1 h at room temperature. The volatiles were removed under reduced pressure to obtain the crude material. The obtained crude material was triturated with Acetonitrile (10.0 mL) to afford *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride (crude, 0.25 g). MS (ESI): mass calculated for $C_{18}H_{21}F_2N_3O_2$, 349.16; m/z found, 350.1 $[M+H]^+$

[405] 1H NMR (400 MHz, $DMSO-d_6$) δ 9.14 (d, $J = 9.2$ Hz, 1H), 8.84 - 8.82 (m, 2H), 8.69 (s, 1H), 7.73 (d, $J = 6.8$ Hz, 1H), 7.25 - 6.88 (t, $J = 75$ Hz, 1H), 7.01 (d, $J = 9.2$ Hz, 2H), 6.74 (d, $J = 12$ Hz, 2H), 4.31 - 4.25 (m, 1H), 3.97 (s, 3H), 3.25 (d, $J = 12$ Hz, 2H), 3.08 - 2.99 (m, 2H), 2.01 (d, $J = 12.4$ Hz, 2H), 1.67 - 1.58 (m, 2H).

[406] Step 3: Preparation of *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)pyridin-3-amine (**Compound 38**)

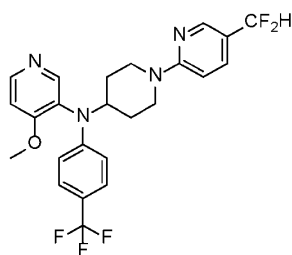


[407] The sealed tube was charged with *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride (0.21 g, 0.54 mmol, 1.0 eq.), 1-Bromo-4-(methylsulfonyl)benzene (0.19 g, 0.81 mmol, 1.5 eq), Sodium *tert*-butoxide (0.15 g, 1.62 mmol, 3.0 eq) and dry 1,4-dioxane (10.0 mL) at room temperature under argon atmosphere. The reaction mixture was degassed with argon for 10 min, then added Ruphos-Pd-G3 (0.02 g, 0.027 mmol, 0.05 eq) under argon. Sealed the tube with cap and stirred at 110 °C for 16 h. The reaction mixture was cooled to room temperature, passed through a pad of celite and the filtrate was concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel by eluted with 60% EtOAc in hexanes to afford *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(4-(methylsulfonyl)phenyl)piperidin-4-yl)pyri-

din-3-amine (0.08 g, 22% yield). MS (ESI): mass calculated for $C_{25}H_{27}F_2N_3O_4S$, 503.56; m/z found, 504.1 $[M+H]^+$, HPLC purity: 98.27%.

[408] **Compound 38:** 1H NMR (400 MHz, DMSO- d_6) δ 8.46 (d, $J = 5.6$ Hz, 1H), 8.16 (s, 1H), 7.61 (d, $J = 9.2$ Hz, 2H), 7.20 (d, $J = 5.6$ Hz, 1H), 7.17 (t, $J = 75$ Hz, 1H), 7.02 - 7.00 (d, $J = 9.2$ Hz, 2H), 6.97 - 6.94 (d, $J = 9.2$ Hz, 2H), 6.49 (d, $J = 9.2$ Hz, 2H), 4.20 - 4.14 (m, 1H), 3.97 (d, $J = 13.2$ Hz, 2H), 3.75 (s, 3H), 3.02 - 2.99 (m, 5H), 1.98 (d, $J = 11.6$ Hz, 2H), 1.29 - 1.21 (m, 2H).

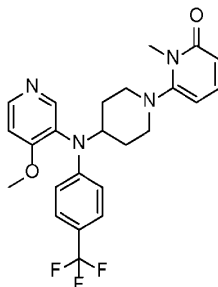
[409] **Example AM:** *N*-(1-(5-(Difluoromethyl)pyridin-2-yl)piperidin-4-yl)-4-methoxy-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 39):



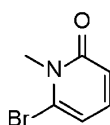
[410] The microwave tube was charged with 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine hydrogen chloride (0.60 g, 1.54 mmol, 1.0 eq), 2-Chloro-5-(difluoromethyl)pyridine (0.25 g, 1.54 mmol, 1.3 eq), Sodium *tert*-butoxide (0.297 g, 3.09 mmol, 2.0 eq) and Toluene (5.0 mL) at room temperature under argon atmosphere. Then, the resulting mixture was degassed with argon for 10 min, added Ruphos-Pd-G3 (0.06 g, 0.077 mmol, 0.05 eq) under argon. Sealed the microwave tube with cap and stirred at 130 °C under microwave for 2 h. The progress of the reaction was monitored by TLC and complete consumption of starting material was observed. The reaction mixture was cooled to room temperature, passed through a pad of celite and the filtrate was concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel by eluted with 100% EtOAc in hexanes to afford *N*-(1-(5-(Difluoromethyl)pyridin-2-yl)piperidin-4-yl)-4-methoxy-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (0.23 g, 31% yield). MS (ESI): mass calculated for $C_{24}H_{23}F_5N_4O$, 478.47; m/z found, 479.3 $[M+H]^+$, HPLC purity: 95.15%.

[411] **Compound 39:** 1H NMR (400 MHz, DMSO- d_6) δ 8.49 (d, $J = 5.6$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 8.18 (s, 1H), 7.61 (dd, $J = 9.2$ Hz, $J = 2.4$ Hz, 1H), 7.42 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 5.6$ Hz, 1H), 7.06 - 6.74 (t, $J = 50$ Hz, 1H), 6.89 - 6.87 (m, 1H), 6.61 (d, $J = 8.8$ Hz, 2H), 4.44 (d, $J = 13.6$ Hz, 2H), 4.36 - 4.31 (m, 1H), 3.76 (s, 3H), 3.07 - 3.01 (m, 2H), 2.10 (d, $J = 12.0$ Hz, 2H), 1.23 - 1.16 (m, 2H).

[412] **Example AN:** 6-(4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-

1-yl)-1-methylpyridin-2(1H)-one (Compound 40):

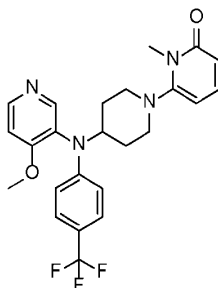
[413] Step 1: Preparation of 6-bromo-1-methylpyridin-2(1H)-one



[414] To a solution of 6-bromopyridin-2-ol (0.25 g, 1.43 mmol, 1.0 eq) in *N,N*-Dimethylformamide (5.0 mL) was added K_2CO_3 (0.99 g, 7.18 mmol, 5.0 eq), CH_3I (0.44 mL, 7.18 mmol, 5.0 eq) at room temperature. Then the reaction mixture was stirred at room temperature for 18 h. The progress of the reaction was monitored by TLC which showed complete consumption of starting material. The reaction mixture was quenched with water (5.0 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered the drying agent and concentrated the solution under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel by eluted with 30-35% EtOAc in hexanes, pure fractions were concentrated under reduced pressure to afford 6-bromo-1-methylpyridin-2(1H)-one (0.23 g, 31% yield).

[415] 1H NMR (400 MHz, $CDCl_3$) δ 7.16 - 7.12 (dd, $J = 9.2$ Hz, $J = 7.2$ Hz, 1H), 6.53 - 6.48 (m, 2H), 6.68 (d, $J = 8.0$ Hz, 1H), 3.74 (s, 3H).

[416] Step 2: Preparation of 6-(4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)-1-methylpyridin-2(1H)-one (Compound 40):

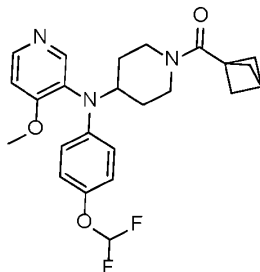


[417] The microwave tube was charged with 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-

(trifluoromethyl)phenyl)pyridin-3-amine hydrochloride (0.15 g, 0.38 mmol, 1.0 eq Curia lot # IN-NRM-G-39), 6-Bromo-1-methylpyridin-2(1H)-one (0.07 g, 0.42 mmol, 1.1 eq), Sodium *tert*-butoxide (0.11 g, 1.15 mmol, 3.0 eq) and dry Toluene (3.0 mL) at room temperature under argon atmosphere. The resulting mixture was degassed with argon for 10 min, added Ruphos-Pd-G3 (0.016 g, 0.01 mmol, 0.05 eq) under argon. The microwave tube was sealed with cap and stirred at 120 °C under microwave for 2 h. The progress of the reaction was monitored by TLC & UPLC-MS which showed product formation. The reaction mixture was cooled to room temperature, passed through a pad of celite and the filtrate was concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel by eluted with 4% MeOH in CH₂Cl₂, the pure fractions were concentrated under reduced pressure to afford 6-(4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)-1-methylpyridin-2(1H)-one (0.15 g, 51% yield). MS (ESI): mass calculated for C₂₄H₂₅F₃N₄O₂, 458.49; m/z found, 459.2 [M+H]⁺. HPLC purity: 99.73%.

[418] **Compound 40:** ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.55 (d, *J* = 5.6 Hz, 1H), 8.26 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.35 - 7.28 (m, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.08 (d, *J* = 8.4 Hz, 1H), 5.83 - 5.81 (m, 1H), 4.22 - 4.16 (m, 1H), 3.80 (s, 3H), 3.27 (s, 3H), 3.16 (d, *J* = 12.0 Hz, 2H), 2.83 (t, *J* = 11.6 Hz, 2H), 2.03 (d, *J* = 12.0 Hz, 2H), 1.47 - 1.39 (m, 2H).

[419] **Example AO: Bicyclo[1.1.1]pentan-1-yl(4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)methanone (Compound 41):**



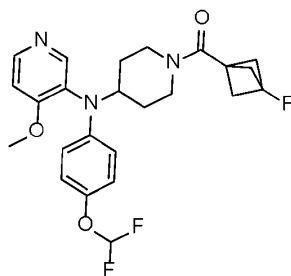
[420] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[421] The title compound was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 22%-52%, 7min) to provide the title compound (49.4 mg, 109.16 μmol, 84.24% yield). LCMS (ESI), [M+H]⁺ = 444.1.

[422] **Compound 41:** ¹H NMR (400 MHz, CD₃OD) δ 8.59 (d, *J* = 6.4 Hz, 1H), 8.49 (s, 1H), 7.58 (d, *J* = 6.8 Hz, 1H), 7.02 (d, *J* = 9.2 Hz, 2H), 6.88 - 6.45 (m, 3H), 4.52 - 4.48 (m, 1H), 4.35 - 4.31 (m, 1H), 4.27 - 4.16 (m, 1H), 3.99 (s, 3H), 3.26 - 3.23 (m, 1H), 2.84 - 2.71 (m, 1H), 2.45 (s, 1H), 2.16 - 2.11 (m,

6H), 2.10 - 1.96 (m, 2H), 1.36 - 1.21 (m, 2H).

[423] **Example AP: 4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(3-fluorobicyclo[1.1.1]pentan-1-yl)methanone (Compound 42):**

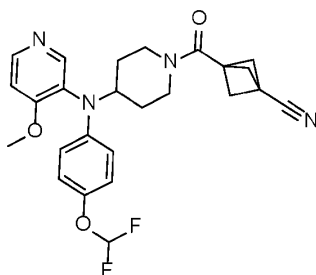


[424] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[425] The title compound was purified by prep-HPLC (column: Phenomenex C18 80*40mm*3um; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; B%: 50%-80%, 7min) to provide the title compound (26 mg, 55.05 μ mol, 70.79% yield). LCMS (ESI), [M+H]⁺ = 462.0.

[426] **Compound 42:** ¹H NMR (400 MHz, CD₃OD) δ 8.45 (s, 1H), 8.16 (s, 1H), 7.20 (d, *J* = 4.4 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.81 - 6.39 (m, 4H), 4.53 - 4.50 (m, 1H), 4.26 - 4.18 (m, 1H), 4.13 - 4.09 (m, 1H), 3.82 (s, 3H), 3.29 - 3.22 (m, 1H), 2.88 - 2.74 (m, 1H), 2.36 (s, 6 H), 2.13 - 2.09 (m, 1H), 2.08 - 2.06 (m, 1H), 1.33 - 1.09 (m, 3H).

[427] **Example AQ: 3-4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carbonyl)bicyclo[1.1.1]pentane-1-carbonitrile (Compound 43):**



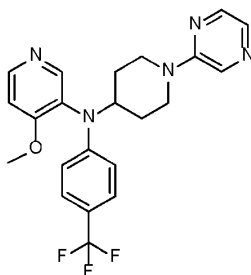
[428] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[429] The title compound was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 20%-50%, 7min) to provide the title compound

(56.6 mg, 118.40 μ mol, 91.36% yield). LCMS (ESI), $[M+H]^+ = 469.0$.

[430] **Compound 43:** ^1H NMR (400 MHz, CD_3OD) δ 8.60 (d, $J = 6.4$ Hz, 1H), 8.51 (s, 1H), 7.61 (d, $J = 6.8$ Hz, 1H), 7.03 (d, $J = 9.2$ Hz, 2H), 6.94 - 6.43 (m, 3H), 4.49 - 4.46 (m, 1H), 4.31 - 4.09 (m, 2H), 4.00 (s, 3H), 3.29 - 3.21 (m, 1H), 2.81 - 2.78 (m, 1H), 2.56 (s, 6H), 2.15 - 1.97 (m, 2H), 1.42 - 1.22 (m, 2H).

[431] **Example AR: 4-Methoxy-*N*-(1-(pyrazin-2-yl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 44):**

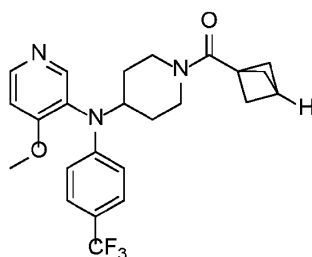


[432] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[433] The title compound was purified by prep-TLC (SiO_2 , Dichloromethane : Methanol = 10:1) to provide the title compound (129.2 mg, 288.82 μ mol, 50.74% yield). LCMS (ESI), $[M+H]^+ = 430.1$.

[434] **Compound 44:** ^1H NMR (400 MHz, CD_3OD) δ 8.47 (d, $J = 6.0$ Hz, 1H), 8.16 (d, $J = 4.4$ Hz, 2H), 8.04 - 8.03 (m, 1H), 7.71 (d, $J = 2.4$ Hz, 1H), 7.39 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 5.6$ Hz, 1H), 6.64 (d, $J = 8.8$ Hz, 2H), 4.47 - 4.44 (m, 2H), 4.37 - 4.29 (m, 1H), 3.83 (s, 3H), 3.11 - 3.00 (m, 2H), 2.15 - 2.11 (m, 2H), 1.43 - 1.33 (m, 2H).

[435] **Example AS: Bicyclo[1.1.1]pentan-1-yl(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone (Compound 45):**

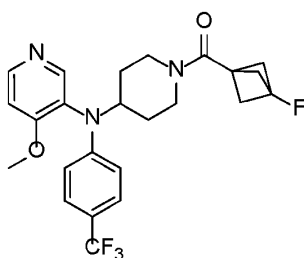


[436] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[437] The title compound was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 26%-56%, 7 min) to provide the title compound (56 mg, 125.71 μ mol, 97.51% yield). LCMS (ESI), [M+H]⁺ = 446.1.

[438] **Compound 45:** ¹H NMR (400 MHz, CD₃OD) δ 8.60 (d, *J* = 6.0 Hz, 1H), 8.35 (s, 1H), 7.45 - 7.39 (m, 3H), 6.70 (d, *J* = 8.8 Hz, 2H), 4.57 - 4.49 (m, 1H), 4.38 - 4.31 (m, 2H), 3.93 (s, 3H), 3.28 - 3.21 (m, 1H), 2.79 - 2.76 (m, 1H), 2.45 (s, 1H), 2.14 - 2.02 (m, 8H), 1.31 - 1.23 (m, 2H).

[439] **Example AT: (3-Fluorobicyclo[1.1.1]pentan-1-yl)(4-((4-methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone (Compound 46):**

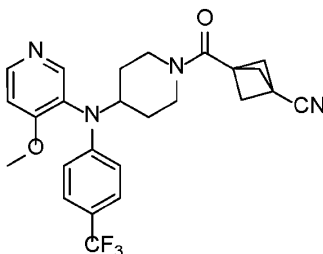


[440] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[441] The title compound was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 26%-56%, 7 min) to provide the title compound (69.9 mg, 150.82 μ mol, 97.49% yield). LCMS (ESI), [M+H]⁺ = 464.1.

[442] **Compound 46:** ¹H NMR (400 MHz, CD₃OD) δ 8.76 - 8.74 (m, 1H), 8.60 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.61 - 4.55 (m, 1H), 4.42 - 4.33 (m, 1H), 4.17 - 4.13 (m, 1H), 4.05 (s, 3H), 3.29 - 3.23 (m, 1H), 2.83 - 2.82 (m, 1H), 2.38 (s, 6H), 2.18 - 2.05 (m, 2H), 1.36 - 1.25 (m, 2H).

[443] **Example AU: 3-((4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidine-1-carbonyl)bicyclo[1.1.1]pentane-1-carbonitrile (Compound 47):**

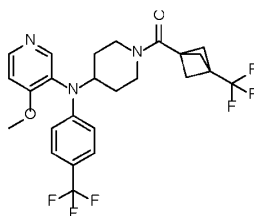


[444] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[445] The title compound was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 25%-55%, 7 min) to provide the title compound (65 mg, 125.72 μ mol, 97.52% yield). LCMS (ESI), [M+H]⁺ = 471.1.

[446] **Compound 47:** ¹H NMR (400 MHz, CD₃OD) δ 8.75 (dd, *J* = 0.8, 6.8 Hz, 1H), 8.60 (d, *J* = 0.8 Hz, 1H), 7.71 (d, *J* = 6.8 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 4.61 - 4.55 (m, 1H), 4.42 - 4.33 (m, 1H), 4.17 - 4.13 (m, 1H), 4.05 (s, 3H), 3.29 - 3.23 (m, 1H), 2.83 - 2.82 (m, 1H), 2.38 (s, 6H), 2.18 - 2.05 (m, 2H), 1.36 - 1.25 (m, 2H).

[447] **Example AV: (4-((4-(Trifluoromethyl)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)methanone (Compound 48):**

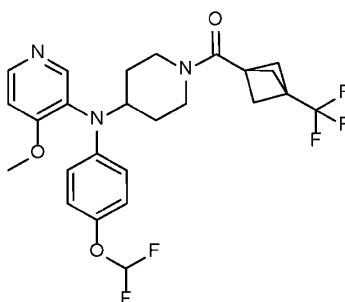


[448] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[449] The title compound was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 33% - 63%, 7 min) to provide the title compound (74.2 mg, 141.62 μ mol, 82.93% yield) as white solid. LCMS (ESI), [M+H]⁺ = 514.1.

[450] **Compound 48:** ¹H NMR (400 MHz, CD₃OD) δ 8.52 (d, *J* = 7.6 Hz, 1H), 8.19 (s, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 6.0 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.55 - 4.52 (m, 1H), 4.35 - 4.30 (m, 1H), 4.23 - 4.20 (m, 1H), 3.85 (s, 3H), 3.26 - 3.24 (m, 1H), 2.86 - 2.78 (m, 1H), 2.33 (s, 6H), 2.20 - 2.03 (m, 2H), 1.30 - 1.22 (m, 2H).

[451] **Example AW: (4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)methanone (Compound 49):**

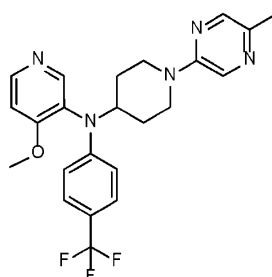


[452] The title compound was synthesized following a procedure similar to **Example U** (Compound 21).

[453] The title compound was purified by prep-HPLC (column: Welch Xtimate C18 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 29% - 59%, 7 min) to provide the title compound (56.45 mg, 110.37 μ mol, 77.12% yield). LCMS (ESI), [M+H]⁺ = 512.0.

[454] **Compound 49:** ¹H NMR (400 MHz, CD₃OD) δ 8.59 (d, *J* = 6.8, 1H), 8.511 (s, 1H), 7.61 (d, *J* = 6.8 Hz, 1H), 7.03 (d, *J* = 8.8, 2H), 6.87 - 6.50 (m, 3H), 4.57 - 4.47 (m, 1H), 4.23 - 4.19 (m, 2H), 3.99 (s, 3H), 3.31 - 3.26 (m, 1H), 2.88 - 2.72 (m, 1H), 2.31 (s, 6H), 2.16 - 2.07 (m, 1H), 2.06 - 1.97 (m, 1H), 1.43 - 1.29 (m, 2H).

[455] **Example AX: 4-Methoxy-*N*-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 50):**

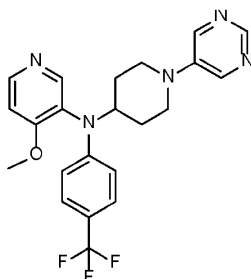


[456] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[457] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 32%-62%, 6min) to provide the title compound (136.4mg, 298.35 μ mol, 52.42% yield). LCMS (ESI), [M+H]⁺ = 444.1.

[458] **Compound 50:** ¹H NMR (400 MHz, CD₃OD) δ 8.47 (d, *J* = 4.4 Hz, 1H), 8.17 (s, 1H), 8.05 (s, 1H), 7.95 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 4.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 2H), 4.39 - 4.29 (m, 1H), 3.84 (s, 3H), 3.08 - 2.97 (m, 2H), 2.34 (s, 3H), 2.17 - 2.09 (m, 2H), 1.43 - 1.31 (m, 2H).

[459] **Example AY: 4-Methoxy-*N*-(1-(pyrimidin-5-yl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 51):**

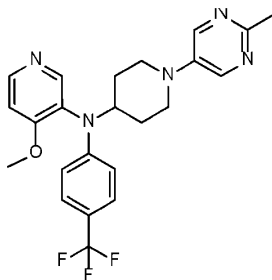


[460] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[461] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 32%-62%, 6min) to provide the title compound (156.6 mg, 364.66 μ mol, 64.07% yield). LCMS (ESI), [M+H]⁺ = 430.1.

[462] **Compound 51:** ¹H NMR (400 MHz, CD₃OD) δ 8.54 - 8.46 (m, 2H), 8.44 (s, 2H), 8.22 (s, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 6.0 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 4.29 - 4.21 (m, 1H), 3.93 - 3.89 (m, 2H), 3.85 (s, 3H), 3.07 - 2.98 (m, 2H), 2.18 - 2.15 (m, 2H), 1.54 - 1.48 (m, 2H).

[463] **Example AZ: 4-Methoxy-*N*-(1-(2-methylpyrimidin-5-yl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 52):**



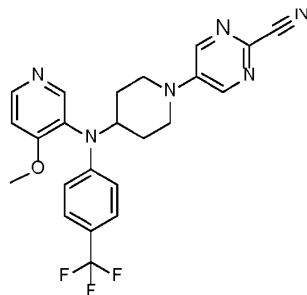
[464] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[465] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 30%-60%, 6min) to provide the title compound (126.6 mg, 279.77 μ mol, 49.15% yield). LCMS (ESI), [M+H]⁺ = 444.1.

[466] **Compound 52:** ¹H NMR (400 MHz, CD₃OD) δ 8.49 (d, *J* = 6.0 Hz, 1H), 8.35 (s, 2H), 8.22 -

8.20 (m, 1H), 7.41 - 7.38 (m, 2H), 7.26 - 7.25 (m, 1H), 6.65 - 6.63 (m, 2H), 4.25 - 4.22 (m, 1H), 3.86 (s, 3H), 3.84 - 3.81 (m, 2H), 3.01 - 2.94 (m, 2H), 2.56 - 2.55 (m, 3H), 2.17 - 2.14 (m, 2H), 1.58 - 1.50 (m, 2H).

[467] **Example BA: 5-((4-(4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)pyrimidine-2-carbonitrile (Compound 53):**

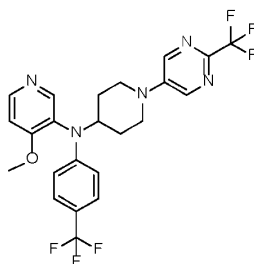


[468] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

[469] The title compound was purified by flash silica gel chromatography (SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether, 40 mL/min) to provide the title compound (164.2 mg, 328.80 μ mol, 63.76% yield). LCMS (ESI), [M+H]⁺ = 455.1.

[470] **Compound 53:** ¹H NMR (400 MHz, CD₃OD) δ 8.48 (d, *J* = 5.6 Hz, 1H), 8.44 (s, 2H), 8.19 (s, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 5.6 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 4.37 - 4.31 (m, 1H), 4.12 - 4.08 (m, 2H), 3.86 (s, 3H), 3.20 - 3.13 (m, 2H), 2.19 - 2.13 (m, 2H), 1.53 - 1.43 (m, 2H).

[471] **Example BB: 4-Methoxy-N-(4-(trifluoromethyl)phenyl)-N-(1-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-4-yl)pyridin-3-amine (Compound 54):**



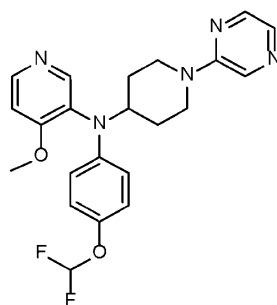
[472] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[473] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5 μ m; mobile phase: [water(FA)-ACN]; B%: 40%-70%, 6min) to provide the title compound

(160 mg, 308.78 μ mol, 54.25% yield). LCMS (ESI), [M+H]⁺ = 498.1.

[474] **Compound 54:** ¹H NMR (400 MHz, CD₃OD) δ 8.49 - 8.48 (m, 3H), 8.20 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 6.0 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 2H), 4.35 - 4.27 (m, 1H), 4.08 - 4.04 (m, 2H), 3.84 (s, 3H), 3.16 - 3.10 (m, 2H), 2.20 - 2.16 (m, 2H), 1.56 - 1.49 (m, 2H).

[475] **Example BC:** *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(pyrazin-2-yl)piperidin-4-yl)pyridin-3-amine (Compound 55):

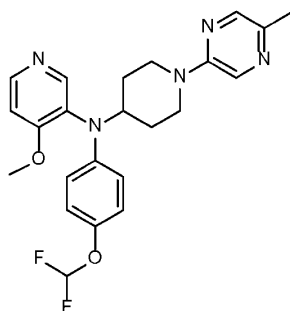


[476] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[477] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5 μ m; mobile phase: [water(FA)-ACN]; B%: 40% - 70%, 6min) to provide the title compound (0.20 g, 459.77 μ mol, 80.32% yield). LCMS (ESI), [M+H]⁺ = 428.0.

[478] **Compound 55:** ¹H NMR (400 MHz, CD₃OD) δ 8.41 (d, *J* = 5.6 Hz, 1H), 8.14 (d, *J* = 5.6 Hz, 2H), 8.02 (s, 1H), 7.69 (s, 1H), 7.17 (d, *J* = 5.6 Hz, 1H), 6.93 (d, *J* = 5.6 Hz, 2H), 6.78 (d, *J* = 5.6 Hz, 2H), 6.59 - 6.41 (m, 3H), 4.43 - 4.39 (m, 2H), 4.25 - 4.15 (m, 1H), 3.80 (s, 3H), 3.06 - 2.99 (m, 2H), 2.11 - 2.07 (m, 2H), 1.37 - 1.33 (m, 2H).

[479] **Example BD:** *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(5-methylpyrazin-2-yl)piperidin-4-yl)pyridin-3-amine (Compound 56):

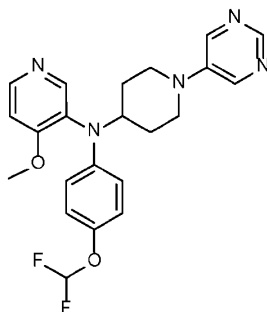


[480] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[481] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 23% - 53%, 7 min) to provide the title compound (113.62 mg, 257.37 μ mol, 44.96% yield). LCMS (ESI), [M+H]⁺ = 442.3.

[482] **Compound 56:** ¹H NMR (400 MHz, CD₃OD) δ 8.41 (d, *J* = 5.6 Hz, 1H), 8.26 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.24 (d, *J* = 5.6 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.65 - 6.35 (m, 3H), 4.44 - 4.32 (m, 2H), 4.19 - 4.09 (m, 1H), 3.81 (s, 3H), 3.12 - 2.99 (m, 2H), 2.33 (s, 3H), 2.18 - 2.10 (m, 2H), 1.43 - 1.32 (m, 2H).

[483] **Example BE: *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(pyrimidin-5-yl)piperidin-4-yl)pyridin-3-amine (Compound 57):**

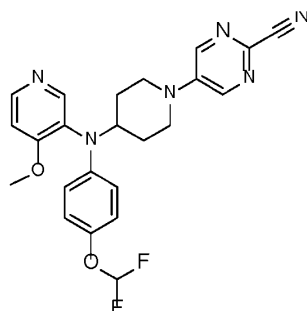


[484] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[485] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 15% - 45%, 7 min) to provide the title compound (238.4 mg, 557.73 μ mol, 97.43% yield). LCMS (ESI), [M+H]⁺ = 428.0.

[486] **Compound 57:** ¹H NMR (400 MHz, CD₃OD) δ 8.55 (s, 1H), 8.50 (s, 3H), 8.21 (s, 1H), 7.25 (d, *J* = 6.0 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.72 - 6.45 (m, 3H), 4.29 - 4.21 (m, 1H), 3.93 - 3.89 (m, 2H), 3.85 (s, 3H), 3.07 - 2.98 (m, 2H), 2.18 - 2.15 (m, 2H), 1.54 - 1.48 (m, 2H).

[487] **Example BF: 5-(4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-2-carbonitrile (Compound 58):**

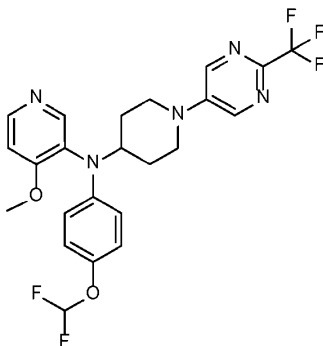


[488] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

[489] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 25% - 55%, 7 min) to provide the title compound (96.63 mg, 213.57 μ mol, 37.31% yield). LCMS (ESI), [M+H]⁺ = 455.1.

[490] **Compound 58:** ¹H NMR (400 MHz, CD₃OD) δ 8.45 - 8.41 (m, 3H), 8.17 (s, 1H), 7.19 (d, *J* = 5.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.79 - 6.42 (m, 3H), 4.26 - 4.20 (m, 1H), 4.10 - 4.07 (m, 2H), 3.82 (s, 3H), 3.17 - 3.11 (m, 2H), 2.17 - 2.13 (m, 2H), 1.50 - 1.43 (m, 2H).

[491] **Example BG:** *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(2-(trifluoromethyl)pyrimidin-5-yl)piperidin-4-yl)pyridin-3-amine (Compound 59):



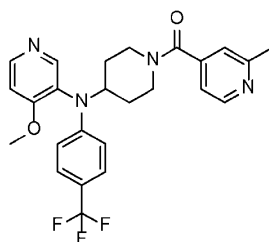
[492] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[493] The title compound was purified by column chromatography (10%-60% Ethyl acetate in petroleum ether) to provide the title compound (215 mg, 416.60 μ mol, 72.77% yield). LCMS (ESI), [M+H]⁺ = 496.0.

[494] **Compound 59:** ¹H NMR (400 MHz, CD₃OD) δ 8.48 (s, 2H), 8.43 (d, *J* = 5.6 Hz, 1H), 8.18 (s, 1H), 7.19 (d, *J* = 5.6 Hz, 1H), 6.96 (d, *J* = 8.8, 2H), 6.60 - 6.58 (m, 3H), 4.64 - 4.56 (m, 1H), 4.26 - 4.16

(m, 1H), 4.06 - 4.03 (m, 2H), 3.82 (s, 3H), 3.16 - 3.11 (m, 2H), 2.17 - 2.14 (m, 2H), 1.56 - 1.42 (m, 2H).

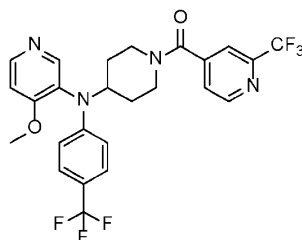
[495] **Example BH: ((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(2-methylpyridin-4-yl)methanone (Compound 60):**



[496] To a stirred solution of 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine hydrochloride (0.20 g, 0.51 mmol, 1.0 eq) and 2-Methylisonicotinic acid (0.07 g, 0.56 mmol, 1.1 eq) in *N,N*-Dimethylformamide (DMF, 2.0 mL) was added Diisopropylethylamine (0.26 g, 2.06 mmol, 4.0 eq) and 0-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 0.29 g, 0.77 mmol, 1.5 eq) at 0 °C. Then the reaction mixture was stirred at room temperature for 8 h. The progress of the reaction was monitored by TLC & UPLC-MS which showed product formation. The crude material was purified by combi flash chromatography using silica gel by eluted with 72% EtOAc in hexanes and pure fractions were concentrated under reduced pressure to afford (4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(2-methylpyridin-4-yl)methanone (0.16 g, 66% yield). MS (ESI): mass calculated for C₂₅H₂₅F₃N₄O₂, 470.50; *m/z* found, 471.5 [M+H]⁺, HPLC purity: 99.90%.

[497] **Compound 60:** ¹H NMR (400 MHz, CDCl₃) δ 8.55 (dd, *J* = 13.6, 5.6 Hz, 2H), 8.22 (s, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.09 (s, 1H), 7.00 - 6.97 (m, 2H), 6.50 (d, *J* = 8.8 Hz, 2H), 4.81 (d, *J* = 12.4 Hz, 1H), 4.19 - 4.14 (m, 1H), 3.80 (s, 3H), 3.70 (d, *J* = 12.4 Hz, 1H), 3.21 - 3.15 (m, 1H), 2.90 - 2.84 (m, 1H), 2.57 (s, 3H), 2.17 (d, *J* = 11.6 Hz, 1H), 1.99 (d, *J* = 10.4 Hz, 1H), 1.43 - 1.25 (m, 2H).

[498] **Example BI: 4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(2-(trifluoromethyl)pyridin-4-yl)methanone (Compound 61):**

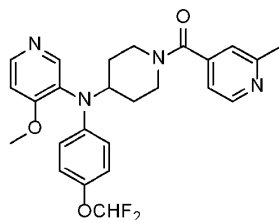


[499] To a stirred solution of 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-

3-amine hydrochloride (0.28 g, 0.51 mmol, 1.0 eq) and 2-(Trifluoromethyl)isonicotinic acid (0.11 g, 0.61 mmol, 1.2 eq) in *N,N*-Dimethylformamide (DMF, 2.0 mL) was added Diisopropylethylamine (0.33 mL, 2.06 mmol, 4.0 eq) and 0-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 0.29 g, 0.77 mmol, 1.5 eq) at 0 °C. Then, the reaction mixture was stirred at room temperature for 2 h. The progress of the reaction was monitored by TLC & UPLC-MS and complete consumption of starting materials was observed. The reaction mixture was poured into cold water (5.0 mL). The obtained solid was collected by filtration and solid cake was washed with excess cold water (5.0 mL). The solid was dried under vacuum to afford 4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(2-(trifluoromethyl)pyridin-4-yl)methanone (0.18 g, 67 % yield). MS (ESI): mass calculated for $C_{25}H_{22}F_6N_4O_2$, 524.47; m/z found, 525.1 $[M+H]^+$, HPLC purity: 99.76%.

[500] **Compound 61:** 1H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, J = 4.8 Hz, 1H), 8.58 (d, J = 5.6 Hz, 1H), 8.22 (s, 1H), 7.64 (s, 1H), 7.42 (d, J = 4.8 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 5.6 Hz, 1H), 6.50 (d, J = 8.8 Hz, 2H), 4.82 (d, J = 13.2 Hz, 1H), 4.22 - 4.14 (m, 1H), 3.80 (s, 3H), 3.63 (d, J = 8.4 Hz, 1H), 3.29 - 3.23 (m, 1H), 2.95 - 2.80 (m, 1H), 2.19 (d, J = 11.2 Hz, 1H), 2.04 - 2.02 (m, 1H), 1.50 - 1.25 (m, 2H).

[501] **Example BJ: 4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(2-methylpyridin-4-yl)methanone (Compound 62):**

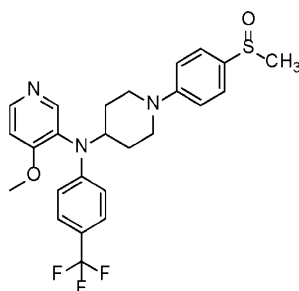


[502] To a stirred solution of *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride (0.15 g, 0.38 mmol, 1.0 eq.) in dry *N,N*-Dimethylformamide (DMF, 2.0 mL) was added Diisopropylethylamine (0.27 mL, 1.55 mmol, 4.0 eq), 2-Methylisonicotinic acid (0.05 g, 0.42 mmol, 1.1 eq) and 0-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 0.22 g, 0.58 mmol, 1.50 eq) at 0 °C. The resulted mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with ice cold water (10.0 mL) and extracted with Ethylacetate (2 × 10.0 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel, and eluted with 72% EtOAc in hexanes to afford 4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)(2-methylpyridin-4-yl)methanone (0.07 g, 39% yield). MS (ESI): mass

calculated for $C_{25}H_{26}F_2N_4O_3$, 468.50; m/z found, 469.4 $[M+H]^+$, HPLC purity: 98.95%.

[503] **Compound 62:** 1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 2H), 8.22 (s, 1H), 7.09 (s, 1H), 7.09 - 6.93 (m, 4H), 6.56 - 6.19 (t, $J = 75$ Hz, 1H), 6.47 (d, $J = 8.8$ Hz, 2H), 4.78 (d, $J = 11.6$ Hz, 1H), 4.11 - 4.06 (m, 1H), 3.79 (s, 3H), 3.70 - 3.67 (m, 1H), 3.26 - 3.16 (m, 1H), 2.90 - 2.87 (m, 1H), 2.57 (s, 3H), 2.16 (d, $J = 10.8$ Hz, 1H), 1.97 (d, $J = 12.8$ Hz, 1H), 1.68 - 1.25 (m, 2H).

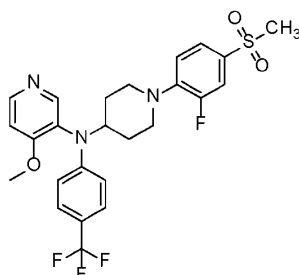
[504] **Example BK: 4-Methoxy-*N*-(1-(4-(methylsulfinyl)phenyl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 63):**



[505] The sealed tube was charged with 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine hydrochloride (0.25 g, 0.64 mmol, 1.0 eq), 1-Bromo-4-(methylsulfinyl)benzene (0.18 g, 0.83 mmol, 1.3 eq), Sodium *tert*-butoxide (0.18 g, 1.92 mmol, 3.0 eq) and dry 1,4-dioxane (10.0 mL) at room temperature under argon atmosphere. The reaction mixture was degassed with argon for 10 min, then added Ruphos-Pd-G3 (0.026 g, 0.032 mmol, 0.05 eq) under argon. Sealed the tube with cap and stirred at 110 °C for 16 h. The reaction mixture was cooled to room temperature, passed through a pad of celite and the filtrate was concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel, and eluted with 10% MeOH in EtOAc to afford 4-Methoxy-*N*-(1-(4-(methylsulfinyl)phenyl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (0.18 g, 48% yield). MS (ESI): mass calculated for $C_{25}H_{26}F_3N_3O_2S$, 489.56; m/z found, 490.5 $[M+H]^+$, HPLC purity: 98.39%.

[506] **Compound 63:** 1H NMR (400 MHz, $DMSO-d_6$) δ 8.52 (d, $J = 5.6$ Hz, 1H), 8.21 (s, 1H), 7.47 - 7.41 (m, 4H), 7.25 (d, $J = 5.6$ Hz, 1H), 7.04 (d, $J = 9.2$ Hz, 2H), 6.60 (d, $J = 8.8$ Hz, 2H), 4.26 - 4.21 (m, 1H), 3.87 (d, $J = 12.8$ Hz, 2H), 3.77 (s, 3H), 2.98 - 2.93 (m, 2H), 2.64 (s, 3H), 2.07 - 1.99 (m, 2H), 1.36 - 1.23 (m, 2H).

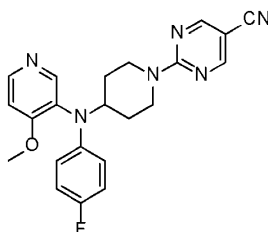
[507] **Example BL: *N*-(1-(2-Fluoro-4-(methylsulfonyl)phenyl)piperidin-4-yl)-4-methoxy-*N*-(4-(tri-fluoromethyl)phenyl)pyridin-3-amine (Compound 64):**



[508] The microwave tube was charged with 4-Methoxy-*N*-(piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine hydrochloride (0.25 g, 0.64 mmol, 1.0 eq), 1-Bromo-2-fluoro-4-(methylsulfonyl)benzene (0.21 g, 0.83 mmol, 1.3 eq), Sodium *tert*-butoxide (0.18 g, 1.92 mmol, 3.0 eq) and dry 1,4-dioxane (10.0 mL) at room temperature under argon atmosphere. The resulting mixture was degassed with argon for 10 min, added Ruphos-Pd-G3 (0.026 g, 0.032 mmol, 0.05 eq) under argon. The microwave tube was sealed with cap and stirred at 120 °C under microwave for 2 h. The progress of the reaction was monitored by TLC & UPLC-MS which showed product formation. The reaction mixture was cooled to room temperature, passed through a pad of celite and the filtrate was concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel and eluted with 80% EtOAc in hexanes to afford *N*-(1-(2-Fluoro-4-(methylsulfonyl)phenyl)piperidin-4-yl)-4-methoxy-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (0.18 g, 45% yield) as an off-white solid. MS (ESI): mass calculated for C₂₅H₂₅F₄N₃O₃S, 523.55; m/z found, 524.1 [M+H]⁺, HPLC purity: 99.52%.

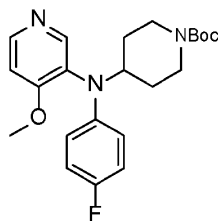
[509] **Compound 64:** ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.52 (d, *J* = 5.6 Hz, 1H), 8.21 (s, 1H), 7.62 (bs, 1H), 7.59 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 5.6 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 2H), 4.27 - 4.21 (m, 1H), 3.79 (s, 3H), 3.57 (d, *J* = 12.4 Hz, 2H), 3.17 (s, 3H), 3.03 (t, *J* = 11.6 Hz, 2H), 2.03 (d, *J* = 12.4 Hz, 2H), 1.45 - 1.36 (m, 2H).

[510] **Example BM: 2-((4-Fluorophenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 65):**



[511] Step 1: Preparation of *tert*-Butyl 4-((4-fluorophenyl)(4-methoxypyridin-3-yl)amino)

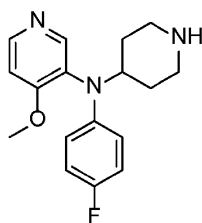
piperidine-1-carboxylate (22)



[512] The microwave tube was charged with *tert*-Butyl 4-((4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (0.45 g, 1.46 mmol, 1.0 eq), 1-Bromo-4-fluorobenzene (0.30 g, 1.75 mmol, 1.2 eq), Sodium *tert*-butoxide (0.28 g, 2.92 mmol, 2.0 eq) and Toluene (5.0 mL) at room temperature under argon atmosphere. The resulting mixture was degassed with argon for 10 min, added Ruphos-Pd-G3 (0.06 g, 0.07 mmol, 0.05 eq) under argon. Sealed the tube with cap and stirred under microwave at 130 °C for 2 h. TLC examination showed new non-polar spot along with some unreacted starting materials. The reaction mixture was cooled to room temperature, passed through a pad of celite and the filtrate was concentrated under reduced pressure to obtain crude material. The obtained crude material was purified by combi flash chromatography using silica gel, and eluted with 60- 65% EtOAc in hexanes to afford *tert*-Butyl 4-((4-fluorophenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (0.30 g, 35% yield). MS (ESI): mass calculated for C₂₂H₂₈FN₃O₃, 401.48; m/z found, 402.2 [M+H]⁺.

[513] ¹H NMR (400 MHz, CDCl₃) δ 8.47 (d, *J* = 5.6 Hz, 1H), 8.22 (s, 1H), 6.90 (d, *J* = 5.6 Hz, 1H), 6.87 - 6.83 (m, 2H), 6.47 - 6.44 (m, 2H), 4.16 - 4.11 (m, 2H), 3.92 (tt, *J* = 3.6 Hz, 1H), 3.77 (s, 3H), 2.83 - 2.77 (m, 2H), 1.96 (d, *J* = 12 Hz, 2H), 1.42 (s, 9H), 1.34 - 1.25 (m, 2H).

[514] Step 2: Preparation of *N*-(4-Fluorophenyl)-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride

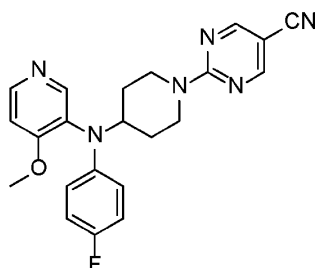


[515] To a solution of *tert*-Butyl 4-((4-fluorophenyl)(4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (0.30 g, 0.77 mmol, 1.0 eq) in 2,2,2-Trifluoroethanol (2.0 mL) at 0 °C was added Chlorotrimethylsilane (0.45 mL) dropwise at room temperature. Then the reaction mixture was stirred at room temperature for 1 h. TLC examination showed new polar spot along with complete conversion of starting material. The volatiles were removed under reduced pressure to obtain the crude material. The obtained crude material was triturated with ACN (10.0 mL) to afford *N*-(4-Fluorophenyl)-4-methoxy-*N*-

(piperidin-4-yl)pyridin-3-amine hydrochloride (0.21 g, 81% yield). MS (ESI): mass calculated for $C_{17}H_{20}FN_3O$, 301.37; m/z found, 302.1 $[M+H]^+$.

[516] 1H NMR (400 MHz, $DMSO-d_6$) δ 9.10 (d, $J = 10$ Hz, 1H), 8.81 - 8.79 (m, 2H), 8.64 (s, 1H), 7.70 (d, $J = 6.8$ Hz, 1H), 7.04 (t, $J = 8.8$ Hz, 2H), 6.79 - 6.75 (m, 2H), 4.28 - 4.22 (m, 1H), 3.94 (s, 3H), 3.25 (d, $J = 14.4$ Hz, 2H), 3.07 - 2.98 (m, 2H), 2.02 - 1.99 (m, 2H), 1.65 - 1.58 (m, 2H).

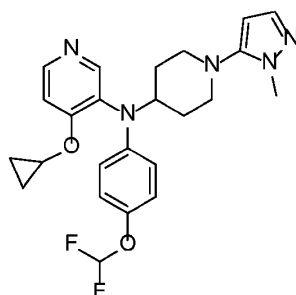
[517] Step 3: Preparation of 2-(4-((4-Fluorophenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (**Compound 65**):



[518] To a stirred solution of *N*-(4-Fluorophenyl)-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride (0.15 g, 0.44 mmol, 1.0 eq) in dry *N,N*-Dimethylformamide (DMF, 2.0 mL) was added Diisopropylethylamine (0.31 mL, 1.77 mmol, 2.0 eq), and 2-Chloropyrimidine-5-carbonitrile (0.07 g, 0.35 mmol, 1.0 eq) at room temperature and was stirred at 90 °C for 4 h. TLC examination showed new non polar spot along with complete conversion of starting materials. The reaction mixture was cooled to room temperature, diluted with ice cold water (10.0 mL) and extracted with Ethyl acetate (2 × 10.0 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered the drying agent and the filtrate was concentrated under reduced pressure to obtain crude material. The crude material was purified by combi flash chromatography using silica gel, and eluted with 65-70% EtOAc in hexanes to afford 2-(4-((4-Fluorophenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (0.12 g, 51% yield). MS (ESI): mass calculated for $C_{22}H_{21}FN_6O$, 404.45; m/z found, 405.1 $[M+H]^+$, HPLC purity: 98.93%.

[519] **Compound 65:** 1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, $J = 5.6$ Hz, 1H), 8.44 (s, 2H), 8.22 (s, 1H), 6.90 - 6.85 (m, 3H), 6.51-6.48 (m, 2H), 4.94 - 4.90 (m, 2H), 4.16 - 4.09 (m, 1H), 3.77 (s, 3H), 3.07 - 3.00 (m, 2H), 2.12 (d, $J = 13.2$ Hz, 2H), 1.42 - 1.29 (m, 2H).

[520] **Example BN: 4-Cyclopropoxy-*N*-(4-(difluoromethoxy)phenyl)-*N*-(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)pyridin-3-amine (Compound 66):**

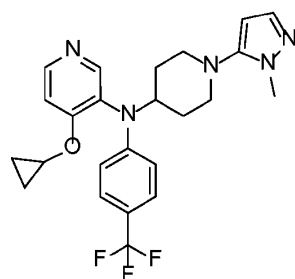


[521] The title compound was synthesized following a procedure similar to **Example AD** (Compound 30).

[522] The title compound was purified by column chromatography (10%-80% Ethyl acetate in petroleum ether) to provide the title compound (110.7 mg, 243.03 μ mol, 44.78% yield). LCMS (ESI), [M+H]⁺ = 456.2.

[523] **Compound 66:** ¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 5.6 Hz, 1H), 8.21 (s, 1H), 7.50 (d, J = 5.6 Hz, 1H), 7.29 (s, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.79 - 6.41 (m, 3H), 5.89 (s, 1H), 4.06 - 4.03 (m, 1H), 3.94 - 3.92 (m, 1H), 3.62 (s, 3H), 3.20 - 3.17 (m, 2H), 2.88 - 2.82 (m, 2H), 2.08 - 2.05 (m, 2H), 1.59 - 1.54 (m, 2H), 0.80 - 0.76 (m, 2H), 0.52 - 0.49 (m, 2H).

[524] **Example BO: 4-Cyclopropoxy-N-(1-(1-methyl-1H-pyrazol-5-yl)piperidin-4-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 67):**



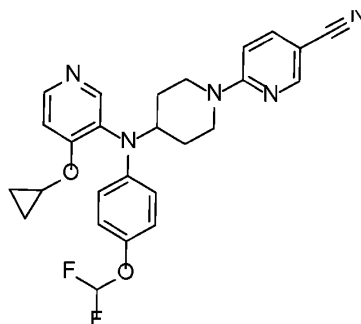
[525] The title compound was synthesized following a procedure similar to **Example AD** (Compound 30).

[526] The title compound was purified by column chromatography (10%-80% Ethyl acetate in petroleum ether) to provide the title compound (70.1 mg, 153.23 μ mol, 43.26% yield). LCMS (ESI), [M+H]⁺ = 458.2.

[527] **Compound 67:** ¹H NMR (400 MHz, CD₃OD) 8.51 (d, J = 5.6 Hz, 1H), 8.24 (s, 1H), 7.56 (d, J = 5.6 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 2.4 Hz, 1H), 6.61 (d, J = 8.8 Hz, 2H), 5.90 (s, 1H), 4.09 - 4.05 (m, 1H), 3.96 - 3.89 (m, 1H), 3.62 (s, 3H), 3.22 - 3.18 (m, 2H), 2.91 - 2.85 (m, 2H), 2.10 - 2.07

(m, 2H), 1.59 - 1.55 (m, 2H), 0.82 - 0.76 (m, 2H), 0.53 - 0.48 (m, 2H).

[528] **Example BP: 6-[4-[N-[4-(Cyclopropoxy)-3-pyridyl]-4-(difluoromethoxy)anilino]-1-piperidyl] pyridine-3-carbonitrile (Compound 68):**

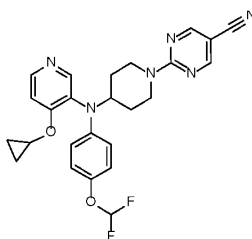


[529] The title compound was synthesized following a procedure similar to **Example R** (Compound 18).

[530] The title compound was purified by Silica Flash Column (10~50% Ethyl acetate in Petroleum ether) to provide the title compound (162.9 mg, 320.68 μ mol, 60.19% yield). LCMS (ESI), [M+H]⁺ = 478.1.

[531] **Compound 68:** ¹H NMR (400 MHz, CD₃OD) δ 8.40 (d, *J* = 5.6 Hz, 1H), 8.33 (s, 1H), 8.15 (s, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 5.6 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.83 - 6.79 (m, 1H), 6.61 - 6.41 (m, 3H), 4.55 - 4.52 (m, 2H), 4.26 - 4.22 (m, 1H), 3.89 - 3.87 (m, 1H), 3.12 - 3.06 (m, 2H), 2.08 - 2.05 (m, 2H), 1.31 - 1.27 (m, 2H), 0.79 - 0.73 (m, 2H), 0.46 - 0.42 (m, 2H).

[532] **Example BQ: (4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)(3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl)methanone (Compound 69):**



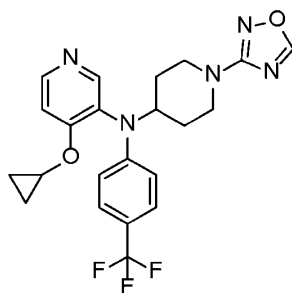
[533] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

[534] The title compound was purified by reversed-phase HPLC (Welch Xtimate C18 150*30mm*5 μ m; mobile phase: [water(FA)-ACN]; B%: 32%-62%, 7 min) to provide the title compound

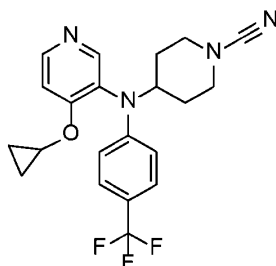
(73.5 mg, 150.54 μ mol, 28.26% yield). LCMS (ESI), $[M+H]^+ = 479.2$.

[535] **Compound 69:** ^1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 2H), 8.41 (d, $J = 5.6$ Hz, 1H), 8.16 (s, 1H), 7.46 (d, $J = 5.6$ Hz, 1H), 6.94 (d, $J = 8.8$ Hz, 2H), 6.60 - 6.42 (m, 3H), 4.60 - 4.59 (m, 2H), 4.29 - 4.22 (m, 1H), 3.92 - 3.88 (m, 1H), 3.15 - 3.06 (m, 2H), 2.11 - 2.07 (m, 2H), 1.29 - 1.24 (m, 2H), 0.79 - 0.74 (m, 2H), 0.47 - 0.43 (m, 2H).

[536] **Example BR:** *N*-(1-(1,2,4-Oxadiazol-3-yl)piperidin-4-yl)-4-cyclopropoxy-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 70):

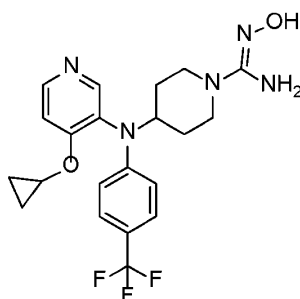


[537] Step 1: 4-((4-Cyclopropoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidine-1-carbonitrile



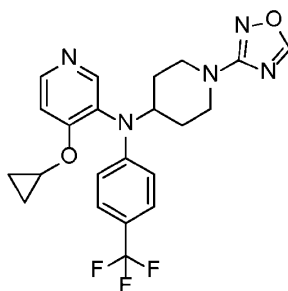
[538] To a solution of 4-(cyclopropoxy)-*N*-(4-piperidyl)-*N*-[4-(trifluoromethyl)phenyl]pyridin-3-amine (400 mg, 966.50 μ mol, HCl salt) in dichloromethane (4.0 mL) was added NaHCO_3 (405.96 mg, 4.83 mmol) in H_2O (1 mL) at $^\circ\text{C}$. Then carbononitridic bromide (1.1 g, 10.39 mmol) was added and stirred at 0°C for 1 hr. Sodium carbonate (2 g) was added in order to ensure the completion of neutralization. MgSO_4 (5 g) was added and the mixture was stirred vigorously for 15 minutes. The resulting suspension was filtered, rinsing with dichloromethane (50 mL x2). The organic layers were concentrated under reduced pressure and the residue was purified by flash silica gel chromatography (Eluent of 0~85% Ethyl acetate in Petroleum ether) to provide the title compound (200 mg, 497.00 μ mol, 51.42% yield). LCMS (ESI), $[M+H]^+ = 403.1$.

[539] Step 2: (*E*)-4-((4-Cyclopropoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)-*N'*-hydroxy piperidine-1-carboximidamide



[540] To a solution of 4-[N-[4-(cyclopropoxy)-3-pyridyl]-4-(trifluoromethyl)anilino]piperidine-1-carbonitrile (200 mg, 497.00 μmol) in THF (5 mL) was added NH_2OH (164.01 mg, 2.49 mmol, 50% purity in water) and the mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash silica gel chromatography (Eluent of 30~100% Ethyl acetate in Petroleum ether) to provide the title compound (190 mg, 436.34 μmol , 87.79% yield). LCMS (ESI), $[\text{M}+\text{H}]^+ = 436.2$

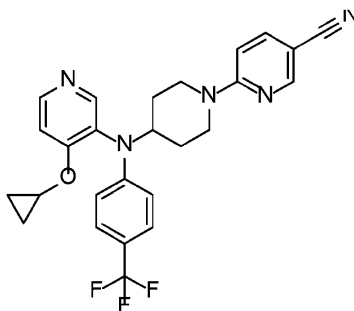
[541] Step 3: *N*-(1-(1,2,4-oxadiazol-3-yl)piperidin-4-yl)-4-cyclopropoxy-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (**Compound 70**):



[542] To a solution of 4-[N-[4-(cyclopropoxy)-3-pyridyl]-4-(trifluoromethyl)anilino]-*N*'-hydroxypiperidine-1-carboxamidinium (190 mg, 436.34 μmol) in triethoxymethane (5 mL) was added diethoxymethoxyethane (129.33 mg, 872.68 μmol), then HCl (12 M, 36.36 μL) was added. The resulting mixture was stirred at 110 °C for 0.5 hr. Sodium carbonate (2 g) was added in order to ensure the completion of neutralization. The reaction mixture was filtered and concentrated under reduced pressure and the residue was purified by flash silica gel chromatography (Eluent of 0~60% Ethyl acetate in Petroleum ether) to provide (80.5 mg, 180.72 μmol , 41.42% yield). LCMS (ESI), $[\text{M}+\text{H}]^+ = 446.1$

[543] **Compound 70:** ^1H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.48 (d, $J = 5.6$ Hz, 1H), 8.18 (s, 1H), 7.52 (d, $J = 5.6$ Hz, 1H), 7.38 (d, $J = 8.8$ Hz, 2H), 6.62 (d, $J = 8.8$ Hz, 2H), 4.27 - 4.19 (m, 1H), 4.07 - 4.03 (m, 2H), 3.94 - 3.92 (m, 1H), 3.17 - 3.11 (m, 2H), 2.07 - 2.03 (m, 2H), 1.41 - 1.37 (m, 2H), 0.81 - 0.77 (m, 2H), 0.53 - 0.49 (m, 2H).

[544] **Example BS: 6-((4-(4-Cyclopropoxyphenyl)-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)nicotinonitrile (Compound 71):**

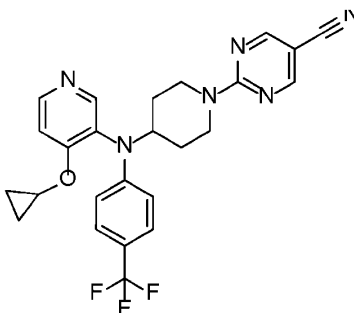


[545] The title compound was synthesized following a procedure similar to **Example R** (Compound 18).

[546] The title compound was purified by Silica Flash Column (10 ~ 40% Ethyl acetate in Petroleum ether, 40 mL/min) to provide the title compound (114.5 mg, 224.46 μ mol, 42.36% yield). LCMS (ESI), [M+H]⁺ = 480.1.

[547] **Compound 71:** ¹H NMR (400 MHz, CD₃OD) δ 8.46 (d, *J* = 5.6 Hz, 1H), 8.33 (d, *J* = 1.6 Hz, 1H), 8.15 (s, 1H), 7.68 - 7.65 (m, 1H), 7.50 (d, *J* = 5.6 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 6.83 - 6.81 (m, 1H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.59 - 4.55 (m, 2H), 4.38 - 4.35 (m, 1H), 3.93 - 3.89 (m, 1H), 3.14 - 3.08 (m, 2H), 2.11 - 2.07 (m, 2H), 1.32 - 1.28 (m, 2H), 0.81 - 0.76 (m, 2H), 0.49 - 0.45 (m, 2H).

[548] **Example BT: 2-((4-(4-Cyclopropoxyphenyl)-3-yl)(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 72):**



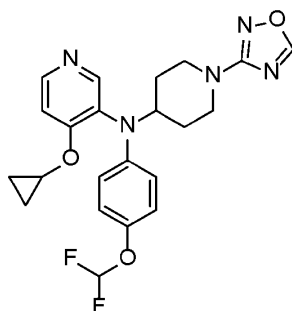
[549] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

[550] The title compound was purified by reversed-phase HPLC (Welch Xtimate C18 150*30mm*5 μ m; mobile phase: [water(FA)-ACN]; B%: 35% - 65%, 7 min) to provide the title compound

(130.3 mg, 271.18 μ mol, 56.12% yield). LCMS (ESI), [M+H]⁺ = 481.2.

[551] **Compound 72:** ¹H NMR (400 MHz, CD₃OD) δ 8.54 (s, 2H), 8.47 (d, *J* = 6.0 Hz, 1H), 8.17 (s, 1H), 7.50 (d, *J* = 6.0 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 4.61 - 4.59 (m, 2H), 4.40 - 4.37 (m, 1H), 3.95 - 3.92 (m, 1H), 3.18 - 3.09 (m, 2H), 2.15 - 2.08 (m, 2H), 1.32 - 1.23 (m, 2H), 0.81 - 0.76 (m, 2H), 0.51 - 0.45 (m, 2H).

[552] **Example BU:** *N*-(1-(1,2,4-Oxadiazol-3-yl)piperidin-4-yl)-4-cyclopropoxy-*N*-(4-(difluoromethoxy)phenyl)pyridin-3-amine (Compound 73):

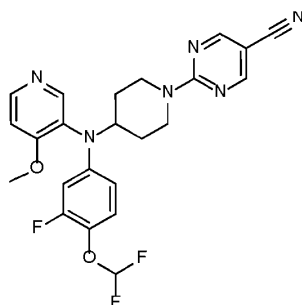


[553] The title compound was synthesized following a procedure similar to **Example BS** (Compound 70).

[554] The title compound was purified by Silica Flash Column (10 ~ 40% Ethyl acetate in Petroleum ether, 40 mL/min) to provide the title compound (67.5 mg, 152.22 μ mol, 21.28% yield). LCMS (ESI), [M+H]⁺ = 444.1.

[555] **Compound 73:** ¹H NMR (400 MHz, CD₃OD) δ 8.71 (s, 1H), 8.42 (d, *J* = 5.6 Hz, 1H), 8.17 (s, 1H), 7.47 (d, *J* = 5.6 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.79 - 6.41 (m, 3H), 4.18 - 4.14 (m, 1H), 4.05 - 4.02 (m, 2H), 3.91 - 3.89 (m, 1H), 3.15 - 3.07 (m, 2H), 2.04 - 2.01 (m, 2H), 1.39 - 1.32 (m, 2H), 0.79 - 0.75 (m, 2H), 0.49 - 0.47 (m, 2H).

[556] **Example BV:** 2-(4-((4-(Difluoromethoxy)-3-fluorophenyl)(4-methoxypyridin-3-yl)amino)piperidin-1-yl)pyrimidine-5-carbonitrile (Compound 74):

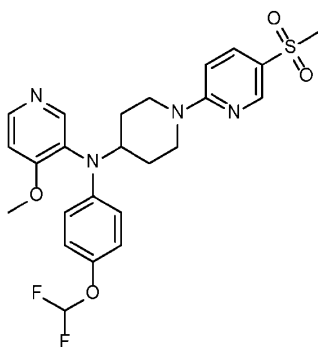


[557] The title compound was synthesized following a procedure similar to **Example L** (Compound 12).

[558] The title compound was purified by reversed-phase HPLC (Welch Xtimate C18 150*30 mm*5um; mobile phase: [water(FA)-ACN]; B%: 28% - 58%, 7 min) to provide the title compound (153.3 mg, 319.34 μ mol, 64.48% yield). LCMS (ESI), [M+H]⁺ = 471.2.

[559] **Compound 74:** ¹H NMR (400 MHz, CD₃OD) δ 8.55 (s, 2H), 8.47 (d, *J* = 5.6 Hz, 1H), 8.18 (s, 1H), 7.23 (d, *J* = 5.6 Hz, 1H), 7.05 - 7.03 (m, 1H), 6.64 (t, *J* = 74 Hz, 1H), 6.44 - 6.39 (m, 1H), 6.33 - 6.30 (m, 1H), 4.61 - 4.59 (m, 2H), 4.32 - 4.28 (m, 1H), 3.86 (s, 3H), 3.16 - 3.10 (m, 2H), 2.14 - 2.11 (d, *J* = 6 Hz, 2H), 1.32 - 1.22 (m, 2H).

[560] **Example BW:** *N*-(4-(Difluoromethoxy)phenyl)-4-methoxy-*N*-(1-(5-(methylsulfonyl)pyridin-2-yl)piperidin-4-yl)pyridin-3-amine (Compound 75):



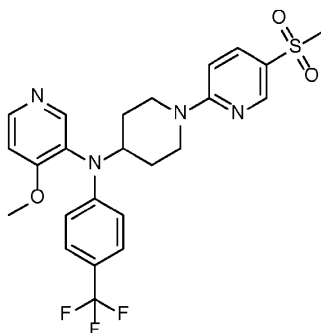
[561] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

[562] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 15% - 45%, 7 min) to provide the title compound (238.4 mg, 435.42 μ mol, 76.06% yield). LCMS (ESI), [M+H]⁺ = 505.2.

[563] **Compound 75:** ¹H NMR (400 MHz, CD₃OD) δ 8.59 (d, *J* = 2.4 Hz, 1H), 8.48 (d, *J* = 5.6 Hz,

1H), 8.24 (s, 1H), 7.82 (d, $J = 5.6$ Hz, 1H), 6.98 - 6.93 (m, 3H), 6.62 (d, $J = 9.2$ Hz, 1H), 6.53 (d, $J = 8.8$ Hz, 2H), 6.40 (t, $J = 74$ Hz, 1H), 4.59 - 4.51 (m, 2H), 4.18 - 4.14 (m, 1H), 3.80 (s, 3H), 3.18 - 3.6 (m, 2H), 3.03 (s, 3H), 2.15 - 2.10 (m, 2H), 1.42 - 1.38 (m, 2H).

[564] **Example BX: 4-Methoxy-*N*-(1-(5-(methylsulfonyl)pyridin-2-yl)piperidin-4-yl)-*N*-(4-(trifluoromethyl)phenyl)pyridin-3-amine (Compound 76):**

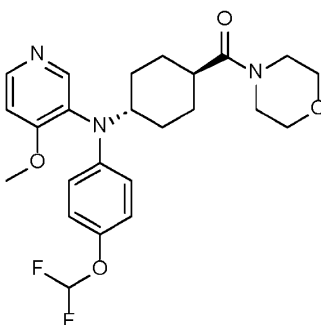


[565] The title compound was synthesized following a procedure similar to **Example C** (Compound 3).

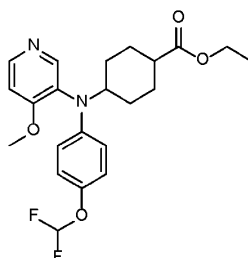
[566] The title compound was purified by reversed-phase HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(FA)-ACN]; B%: 7% - 37%, 7 min) to provide the title compound (153.9 mg, 300.79 μ mol, 48.04% yield). LCMS (ESI), $[M+H]^+ = 507.6$.

[567] **Compound 76:** $^1\text{H NMR}$ (400 MHz, CD_3OD) δ 8.48 (d, $J = 5.6$ Hz, 1H), 8.43 (s, 1H), 8.18 (s, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.42 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 5.6$ Hz, 1H), 6.92 (d, $J = 9.2$ Hz, 1H), 6.61 (d, $J = 8.8$ Hz, 2H), 4.55 - 4.52 (m, 2H), 4.41 - 4.35 (m, 1H), 3.76 (s, 3H), 3.15 - 3.09 (m, 5H), 2.04 - 2.01 (m, 2H), 1.23 - 1.13 (s, 2H).

[568] **Example BY: ((*Trans*)-4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)cyclohexyl)(morpholino)methanone (Compound 77):**

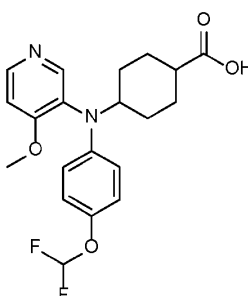


[569] Step 1: Ethyl 4-((4-(difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)cyclohexane-1-carboxylate



[570] A mixture of ethyl 4-[(4-methoxy-3-pyridyl)amino]cyclohexanecarboxylate (200 mg, 718.53 μmol), 1-bromo-4-(difluoromethoxy)benzene (320.49 mg, 1.44 mmol), *t*-Bu₃P (581.48 mg, 287.41 μmol , 674.58 μL , 10% purity), Pd(OAc)₂ (32.26 mg, 143.71 μmol) and *t*BuONa (207.16 mg, 2.16 mmol) in toluene (8 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 120 °C for 24 hr under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was purified by Silica Flash Column (0~30% Ethyl acetate in Petroleum ether) to provide the title compound (136 mg, 322.51 μmol , 45% yield). LCMS (ESI), [M+H]⁺ = 421.3.

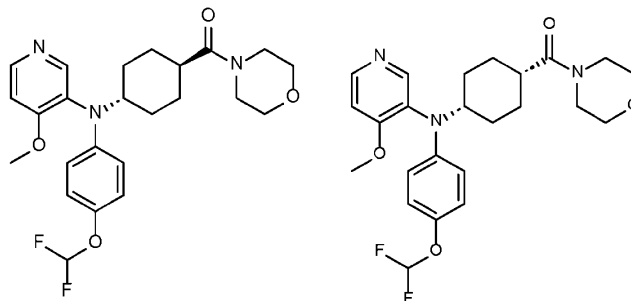
[571] Step 2: 4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)cyclohexane-1-carboxylic acid



[572] To a solution of ethyl 4-[4-(difluoromethoxy)-*N*-(4-methoxy-3-pyridyl)anilino]cyclohexanecarboxylate (403 mg, 958.50 μmol) in THF (5 mL) and methanol (5 mL) was added Lithium hydroxide monohydrate (201.11 mg, 4.79 mmol) in H₂O (5 mL) and the mixture was stirred at 25 °C for 2 hr. The reaction mixture was concentrated under reduced pressure and the residue was adjusted with HCl (4M) to pH 6. The resulting mixture was extracted with ethyl acetate (25 mL x3) and the combined organics was dried over Na₂SO₄, filtered. The filtrate was concentrated under reduced pressure to provide the title compound (376.11 mg, 958.50 μmol , 100.00% yield). LCMS (ESI), [M+H]⁺ = 393.1.

[573] Step 3: ((*Trans*)-4-((4-(Difluoromethoxy)phenyl)(4-methoxypyridin-3-yl)amino)cyclohexyl)(morpholino)methanone (**Compound 77**) & ((*Cis*)-4-((4-(difluoromethoxy)phenyl)(4-methoxy-

pyridin-3-yl)amino)cyclohexyl)(morpholino) methanone

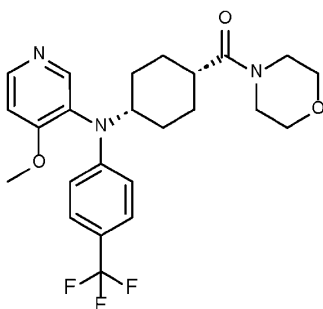


[574] To a solution of 4-[4-(difluoromethoxy)-*N*-(4-methoxy-3-pyridyl)anilino]cyclohexanecarboxylic acid (200 mg, 437.82 μmol) and morpholine (57.21 mg, 656.74 μmol) in dichloromethane (4 mL) was added DIEA (169.75 mg, 1.31 mmol) and HATU (332.95 mg, 875.65 μmol) at 0 °C and the mixture was stirred at 0 °C for 2 hr. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (column: Welch Xtimate C18 150 * 30 mm * 5 μm ; mobile phase: [water($\text{NH}_3\text{H}_2\text{O}$ + NH_4HCO_3)-ACN]; B%: 40%-70%, 7 min) to provide the title compound-1 (Peak 1 on HPLC, **Compound 77**, 31.9 mg, 68.63 μmol , 15.67% yield) and compound-2 (Peak 2 on HPLC, isomer of compound 77, 64.3 mg, 136.29 μmol , 31.13% yield). LCMS (ESI), $[\text{M}+\text{H}]^+ = 462.2$. Only the trans isomer, **Compound 77**, displayed activity.

[575] **Compound 77**: ^1H NMR (400 MHz, CD_3OD) δ 8.41 (d, $J = 5.6$ Hz, 1H), 8.15 (s, 1H), 7.18 (d, $J = 5.6$ Hz, 1H), 6.90 (d, $J = 9.2$, 2H), 6.76 - 6.38 (m, 3H), 3.98 - 3.86 (m, 1H), 3.81 (s, 3H), 3.62 - 3.53 (m, 8H), 2.60 - 2.44 (m, 1H), 2.11 - 2.09 (m, 2H), 1.87 - 1.74 (m, 2H), 1.74 - 1.60 (m, 2H), 1.26 - 1.22 (m, 2H).

[576] **Compound 77 cis-isomer**: ^1H NMR (400 MHz, CD_3OD) δ 8.38 (d, $J = 5.6$ Hz, 1H), 8.22 (s, 1H), 7.15 (d, $J = 5.6$ Hz, 1H), 6.91 (d, $J = 9.2$, 2H), 6.78 - 6.41 (m, 3H), 3.96 - 3.93 (m, 1H), 3.81 (s, 3H), 3.61 - 3.46 (m, 8H), 2.86 - 2.84 (m, 1H), 1.90 - 1.67 (m, 8H).

[577] **Example BZ: (*Cis*)-4-((4-Methoxypyridin-3-yl)(4-(trifluoromethyl)phenyl)amino)cyclohexyl)(morpholino)methanone (Compound 78):**



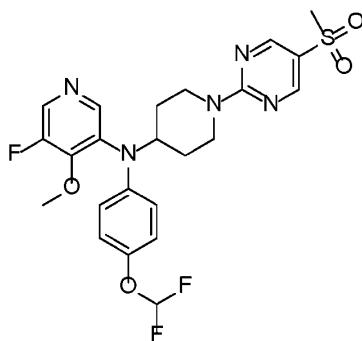
[578] The title compound was synthesized following a procedure similar to **Example BY** (Compound 77).

[579] The title compounds were purified by reversed-phase HPLC (column: Welch Xtimate C18 150 * 30 mm * 5um; mobile phase: [water(NH₃H₂O + NH₄HCO₃)-ACN]; B%: 40%-70%, 7 min) to provide the title compound-1 (Peak 1 on HPLC, 125 mg, 269.69 μ mol, 66.48% yield) and compound-2 (**Compound 78**, Peak 2 on HPLC, 60 mg, 129.45 μ mol, 31.91% yield). LCMS (ESI), [M+H]⁺ = 464.3. Only the cis isomer, **Compound 78**, displayed activity.

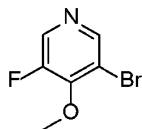
[580] **Compound 78**: ¹H NMR (400 MHz, CD₃OD) δ 8.45 (d, J = 5.6 Hz, 1H), 8.18 (s, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 5.6, 1H), 6.57 (d, J = 5.6, 2H), 4.01 - 3.98 (m, 1H), 3.83 (s, 3H), 3.65 - 3.60 (m, 4H), 3.52 - 3.46 (m, 4H), 2.91 - 2.88 (m, 1H), 1.90 - 1.86 (m, 4H), 1.76 - 1.71 (m, 4H).

[581] **Compound 78 isomer**: ¹H NMR (400 MHz, CD₃OD) δ 8.47 (d, J = 5.6 Hz, 1H), 8.18 (s, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 5.6, 1H), 6.57 (d, J = 8.8, 2H), 4.27 - 4.16 (m, 1H), 3.84 (s, 3H), 3.63 - 3.60 (m, 4H), 3.58 - 3.53 (m, 4H), 2.59 - 2.51 (m, 1H), 2.14 - 2.11 (m, 2H), 1.85 - 1.83 (m, 2H), 1.74 - 1.60 (m, 4H).

[582] **Example CA: N-(4-(difluoromethoxy)phenyl)-5-fluoro-4-methoxy-N-(1-(5-(methyl sulfonyl)pyrimidin-2-yl)piperidin-4-yl)pyridin-3-amine (Compound 79):**



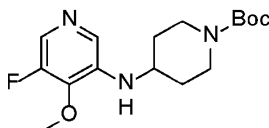
[583] Step 1: 3-bromo-5-fluoro-4-methoxypyridine



[584] To a solution of 3-bromo-4-chloro-5-fluoropyridine (3.0 g, 14.26 mmol, 1 eq) in THF (30 mL) was added NaOMe (5.4 M, 2.64 mL, 1 eq). The mixture was stirred at 50 °C for 1 h. LCMS (5-95AB/1.5min): RT = 0.656 min, $[M+H]^+ = 206.1$, showed 58% of desired product. The reaction was diluted with brine (50 mL). And the mixture was extracted with EtOAc (50 mL $\times$ 2). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (0 - 12.5% ethyl acetate in petroleum ether) to provide the title compound (760 mg, 26%).

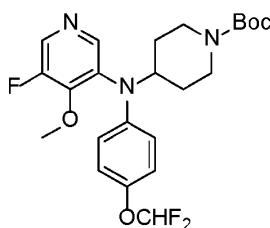
[585] 1H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.34 (d, $J = 2.8$ Hz, 1H), 4.21 (d, $J = 4.4$ Hz, 3H); LCMS (ESI): m/z 206.1 ($M+H$) $^+$.

[586] Step 2: *tert*-butyl 4-((5-fluoro-4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate



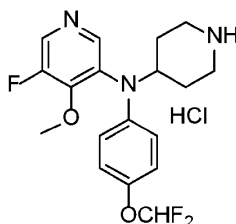
[587] The mixture of 3-bromo-5-fluoro-4-methoxypyridine (850 mg, 4.13 mmol, 1 eq), *tert*-butyl 4-aminopiperidine-1-carboxylate (992 mg, 4.95 mmol, 1.2 eq), $Pd(OAc)_2$ (93 mg, 412.60 μ mol, 0.1 eq), BINAP (514 mg, 825.19 μ mol, 0.2 eq) and *t*-BuONa (1.19 g, 12.38 mmol, 3 eq) in toluene (20 mL) was stirred at 100 °C for 12 h under N_2 atmosphere. LCMS (5-95AB/1.5min): RT = 0.655 min, $[M+H]^+ = 326.3$, showed 57% of desired product. The reaction was diluted with brine (50 mL), the mixture was extracted with EtOAc (50 mL $\times$ 2). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2 , Petroleum ether: Ethyl acetate = 2:1) to provide the title compound (830 mg, 62%). LCMS (ESI): m/z 326.3 ($M+H$) $^+$.

[588] Step 3: *tert*-butyl 4-((4-(difluoromethoxy)phenyl)(5-fluoro-4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate



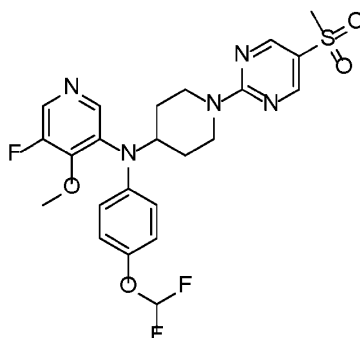
[589] The mixture of *tert*-butyl 4-((5-fluoro-4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (250 mg, 768.34 μ mol, 1 eq), 1-bromo-4-(difluoromethoxy)benzene (343 mg, 1.54 mmol, 210.12 μ L, 2 eq), *t*-Bu₃P-Pd-G2 (79 mg, 153.67 μ mol, 0.2 eq), *t*-BuONa (222 mg, 2.31 mmol, 3 eq) in toluene (5 mL) was stirred at 120 °C for 16 h under N₂ atmosphere. LCMS (5-95AB/1.5min): RT = 0.885 min, [M+H]⁺ = 468.3 showed 46% of desired product. The reaction was diluted with brine (50 mL), the mixture was extracted with EtOAc (50 mL $\times$ 2). The combined organic layers were washed with brine (50 mL $\times$ 2), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (0 - 5% EE (ethanol:EtOAc = 1:3) in Petroleum ether) to provide the title compound (350 mg, crude). LCMS (ESI): *m/z* 468.3 (M+H)⁺.

[590] Step 4: *N*-(4-(difluoromethoxy)phenyl)-5-fluoro-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride



[591] To a solution of *tert*-butyl 4-((4-(difluoromethoxy)phenyl)(5-fluoro-4-methoxypyridin-3-yl)amino)piperidine-1-carboxylate (350 mg, 748.69 μ mol, 1 eq) in dioxane (0.5 mL) was added HCl/dioxane (4 M, 5 mL, 26.71 eq). The mixture was stirred at 25 °C for 1 h. LCMS (5-95AB/1.5min): RT = 0.747 min, [M+H]⁺ = 368.2, showed 94% of desired product. The mixture was concentrated under reduced pressure to provide the title compound (275 mg, crude, HCl salt). The crude was used directly for next step. LCMS (ESI): *m/z* 368.2 (M+H)⁺.

[592] Step 5: *N*-(4-(difluoromethoxy)phenyl)-5-fluoro-4-methoxy-*N*-(1-(5-(methylsulfonyl)pyrimidin-2-yl)piperidin-4-yl)pyridin-3-amine (**Compound 79**)

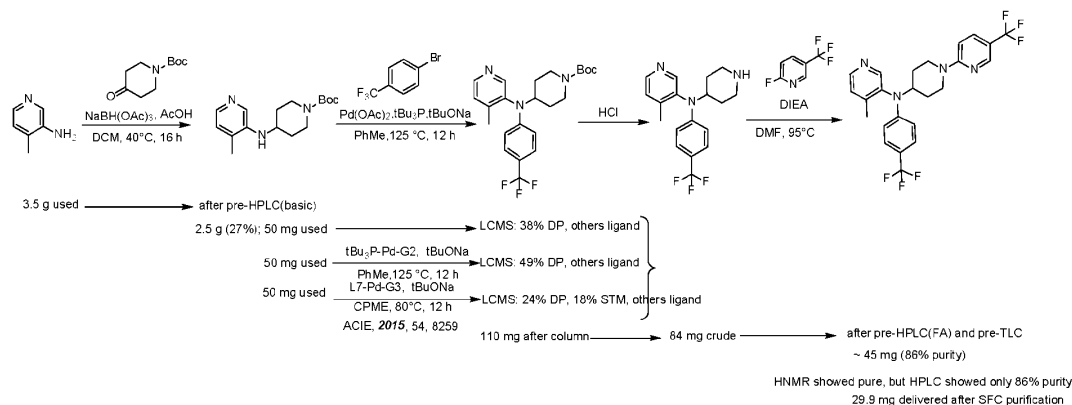


[593] To a solution of *N*-(4-(difluoromethoxy)phenyl)-5-fluoro-4-methoxy-*N*-(piperidin-4-yl)pyridin-3-amine hydrochloride (132 mg, 359.32 μmol , 1 eq) and 2-chloro-5-(methylsulfonyl)pyrimidine (70 mg, 359.32 μmol , 1 eq) in MeCN (5 mL) was added TEA (181.79 mg, 1.80 mmol, 250.06 μL , 5 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h. LCMS (5-95AB/1.5min): RT = 0.811 min, $[\text{M}+\text{H}]^+ = 524.2$, showed 70% of desired product. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (0 - 45% EtOAc in Petroleum ether) to provide the title compound (97.68 mg, 52%).

[594] **Compound 79:** ^1H NMR (400 MHz, CD_3OD): δ 8.65 (s, 2H), 8.38 (d, $J = 3.2$ Hz, 1H), 8.09 (s, 1H), 7.00 (d, $J = 9.2$ Hz, 2H), 6.84 - 6.39 (m, 3H), 5.01 - 4.97 (m, 2H), 4.33 - 4.30 (m, 1H), 3.93 (d, $J = 4.4$ Hz, 3H), 3.19 - 3.12 (m, 2H), 3.11 (s, 3H), 2.15 - 2.11 (m, 2H), 1.37 - 1.29 (m, 2H); LCMS (ESI): m/z 524.2 ($\text{M}+\text{H})^+$.

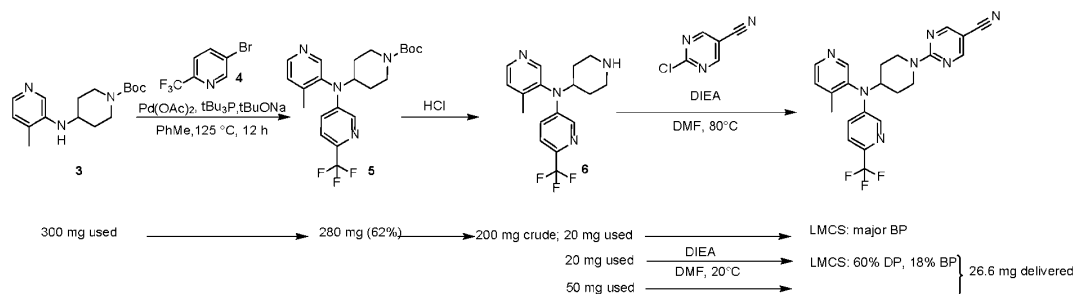
[595] The following compounds were preparing following similar protocols described above with appropriate reagents.

[596] **Example CB: (4-methyl-3-pyridyl)[p-(trifluoromethyl)phenyl]{1-[5-(trifluoromethyl)-2-pyridyl]-4-piperidyl}amine:**



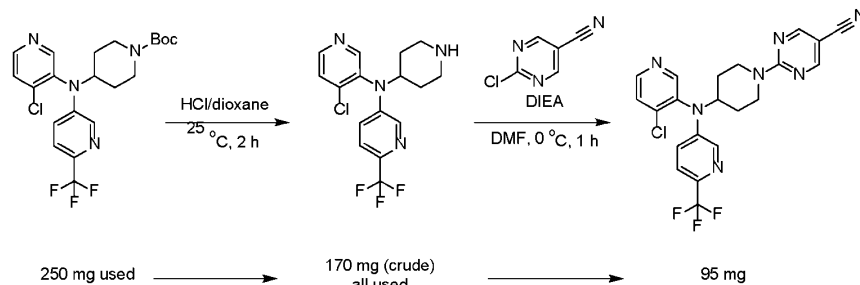
[597] **Compound 100:** 29.9 mg; ^1H NMR (400 MHz, CD_3OD) d 8.42 (d, 1H), 8.25 (m, 2H), 7.67 (d, 1H), 7.44 (m, 3H), 6.86 (d, 1H), 6.62 (m, 2H), 4.50 (m, 2H), 4.46 (m, 1H), 3.11 (m, 2H), 2.19 (s, 3H), 2.12 (m, 2H), 1.4 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 481$.

[598] **Example CD: 2-{4-[(4-methyl-3-pyridyl)[6-(trifluoromethyl)-3-pyridyl]amino]-1-piperidyl}-5-pyrimidinecarbonitrile:**



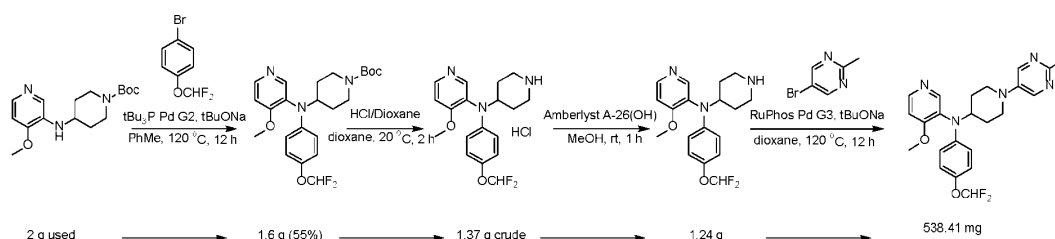
[599] **Compound 101:** 26.6 mg; ^1H NMR (400 MHz, CD_3OD) d 8.55 (s, 2H), 8.47 (d, 1H), 8.31 (s, 1H), 7.87 (s, 1H), 7.59 (d, 1H), 7.49 (d, 1H), 7.10 (d, 1H), 5.00 (m, 2H), 4.53 (m, 1H), 3.17 (m, 2H), 2.21 (s, 3H), 2.17 (m, 2H), 1.37 (m, 2H) LCMS (ESI) $[\text{M}+\text{H}]^+ = 440$.

[600] **Example CE: 2-{4-[(4-chloro-3-pyridyl)[6-(trifluoromethyl)-3-pyridyl]amino]-1-piperidyl}-5-pyrimidinecarbonitrile:**



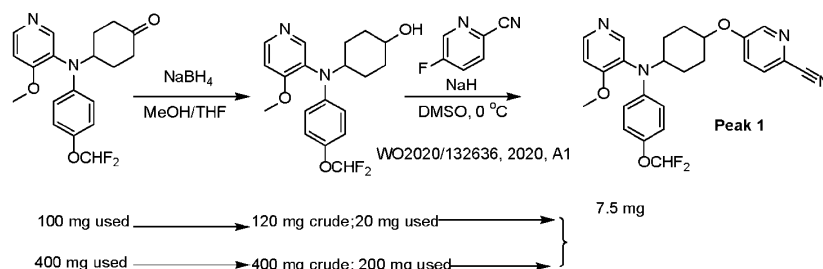
[601] **Compound 102:** 95 mg; ^1H NMR (400 MHz, CDCl_3) d 8.58 (m, 1H), 8.48 (m, 3H), 8.20 (s, 1H), 7.54 (dd, 2H), 6.84 (d, 1H), 5.03 (m, 2H), 4.30 (m, 1H), 3.08 (m, 2H), 2.22 (m, 2H), 1.41-1.50 (br. m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 460$.

[602] **Example CF: (p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]amine:**

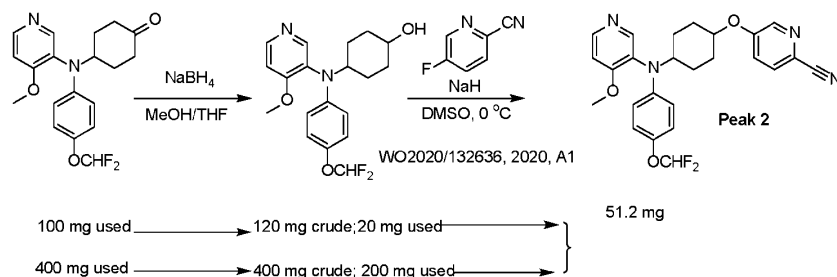


[603] **Compound 103:** 538 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.44 (d, 1H), 8.43 (s, 2H), 8.42 (s, 1H), 6.97 (m, 1H), 6.96 (m, 2H), 6.92 (m, 3H), 4.11 (m, 1H), 3.84 (s, 3H), 3.83 (m, 2H), 2.98 (m, 2H), 2.20 (s, 3H), 2.14 (m, 2H), 1.5 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 442$.

[604] **Example CG: 5-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyloxy}-2-pyridinecarbonitrile:**

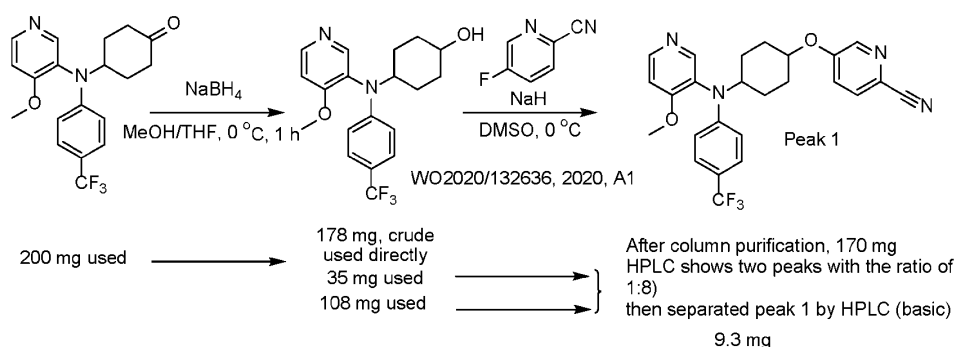


[605] **Compound 104-isomer 1:** 7.5 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.5 (d, 1H), 8.3 (d, 1H), 8.2 (d, 1H), 7.8 (d, 1H), 7.5 (d, 1H), 7.2 (d, 1H), 6.9 (d, 2H), 6.4-6.6 (m, 3H), 4.6 (m, 1H), 4.1 (m, 1H), 3.8 (s, 3H), 2.15 (m, 2H), 1.9 (br. m, 4H), 1.6 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 467$.

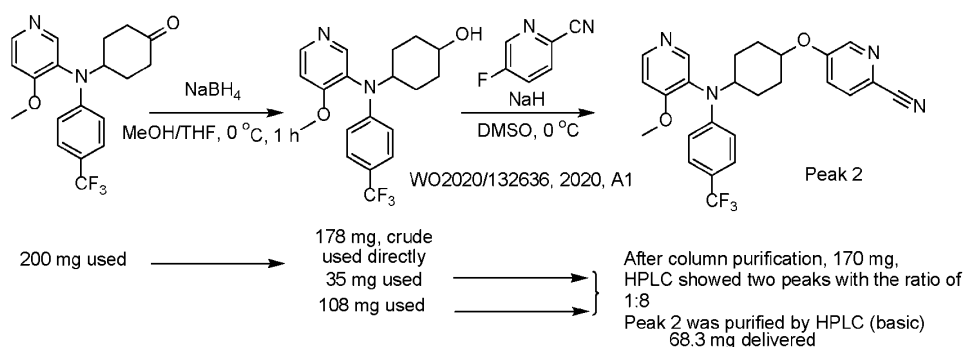


[606] **Compound 104-isomer 2:** 51 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.6 (d, 1H), 8.30 (d, 1H), 8.20 (s, 1H), 7.75 (d, 1H), 7.50 (d, 1H), 7.20 (s, 1H), 6.9 (d, 2H), 6.3-6.7 (m, 3H), 4.3 (m, 1H), 4.05 (m, 1H), 3.8 (s, 3H), 2.2 (m, 4H), 1.7 (m, 2H), 1.4 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 467$.

[607] **Example CH: 5-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyloxy}-2-pyridinecarbonitrile:**

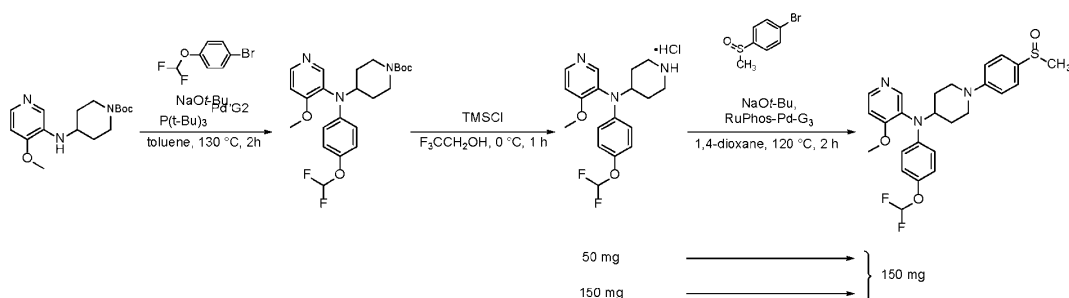


[608] **Compound 105-isomer 1:** 9.3 mg; ^1H NMR (400 MHz, CDCl_3) δ 8.28 (d, 1H), 7.59 (d, 1H), 7.38 (d, 2H), 7.2-7.3 (br. m, 4H), 4.67 (m, 1H), 4.0 (m, 1H), 3.81 (s, 3H), 2.17 (m, 2H), 1.93 (m, 2H), 1.77 (m, 2H), 1.6 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 469$.



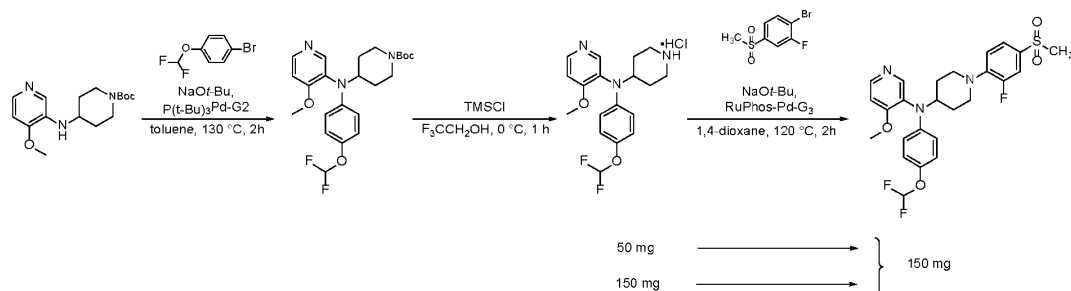
[609] **Compound 105-isomer 2:** 68 mg; ^1H NMR (400 MHz, CDCl_3) δ 8.6 (br. s, 1H), 8.35 (s, 1H), 8.30 (br. s, 1H), 7.6 (d, 1H), 7.4 (d, 2H), 7.15 (m, 1H), 7.0 (m, 1H), 6.5 (d, 2H), 4.2 (m, 1H), 4.0 (m, 1H), 3.80 (s, 3H), 2.2 (m, 4H), 1.7 (m, 2H), 1.3 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 469$.

[610] **Example CI: (p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl){1-[p-(methylsulfinyl)phenyl]-4-piperidyl}amine:**



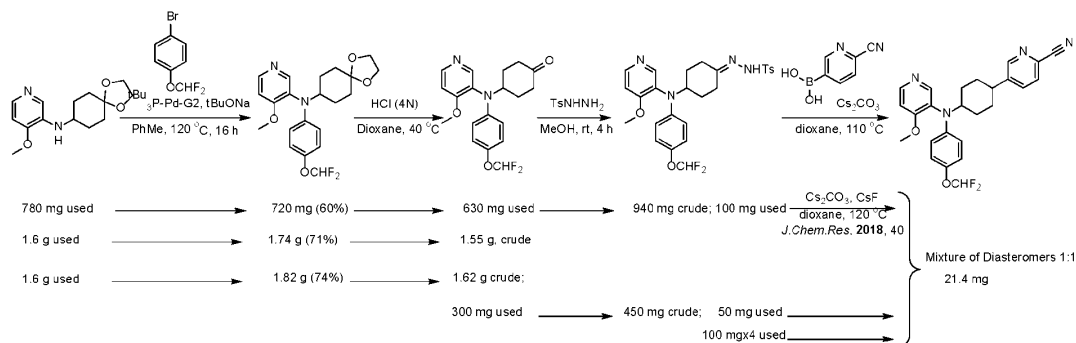
[611] **Compound 106:** 150 mg; ^1H NMR (400 MHz, DMSO- d_6) δ 8.48 (m, 1H), 8.20 (s, 1H), 7.45 (m, 2H), 7.2 (m, 1H), 6.8-7.1 (m, 5H), 6.5 (m, 2H), 4.15 (m, 1H), 3.85 (m, 2H), 3.75 (s, 3H), 2.95 (m, 2H), 2.68 (s, 3H), 2.0 (m, 2H), 1.3 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 488$.

[612] **Example CJ: p-difluoromethoxyphenyl)[1-(2-fluoro-4-mesyphenyl)-4-piperidyl](4-methoxy-3-pyridyl)amine:**



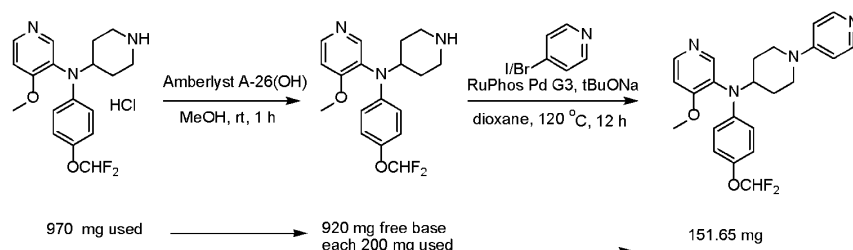
[613] **Compound 107:** 150 mg; ^1H NMR (400 MHz, DMSO- d_6) δ 8.50 (d, 1H), 8.20 (s, 1H), 7.60 (m, 2H), 6.8-7.3 (m, 5H), 6.5 (m, 2H), 4.15 (m, 1H), 3.80 (s, 3H), 3.55 (m, 2H), 3.20 (s, 3H), 3.00 (m, 2H), 2.0 (m, 2H), 1.4 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 522$.

[614] **Example CK: 5-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyl}-2-pyridinecarbonitrile:**



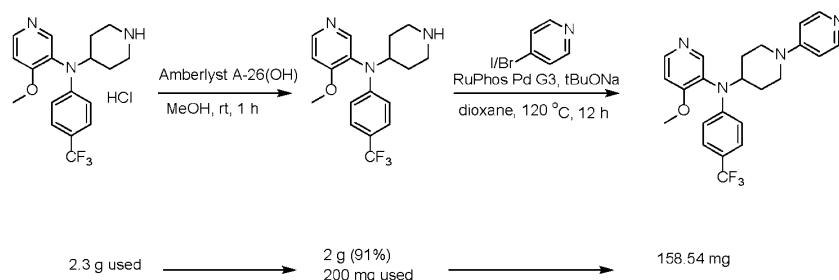
[615] **Compound 108:** 21.4 mg (1:1 mixture of diastereomers); ^1H NMR (400 MHz, CD_3OD) δ 8.65 (m, 1H), 8.25-8.5 (m, 2H), 7.8-7.9 (m, 2H), 7.1-7.2 (m, 1H), 6.9 (m, 2H), 6.4-6.7 (m, 3H), 4.0-4.25 (m, 1H), 3.80 (s, 3H), 2.6-2.95 (m, m, 1H), 2.2 (m, 1H), 2.0 (m, 2H), 1.7-1.9 (m, 5H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 451$

[616] **Example CL: (p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)[1-(4-pyridyl)-4-piperidyl]amine:**



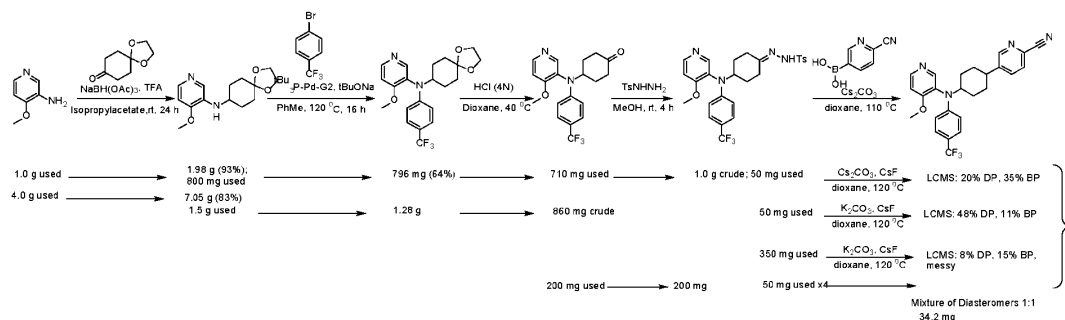
[617] **Compound 109:** 152 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1H), 8.2 (s, 1H), 8.10 (d, 2H), 7.2 (d, 1H), 6.9 (m, 4H), 6.6 (m, 3H), 4.25 (m, 1H) 4.1 (m, 2H), 3.80 (s, 3H), 3.1 (m, 2H), 2.1 (m, 2H), 1.4 (m, 2H) LCMS (ESI) $[\text{M}+\text{H}]^+ = 427$.

[618] **Example CM: (4-methoxy-3-pyridyl)[1-(4-pyridyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine:**



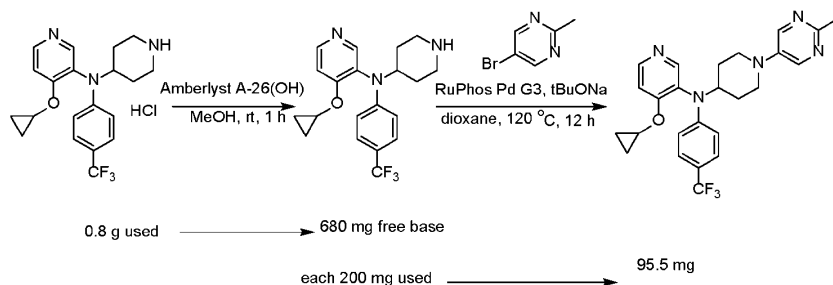
[619] **Compound 110:** 159 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.5 (m, 1H), 8.2 (s, 1H), 8.15 (d, 2H), 7.45 (d, 2H), 7.25 (s, 1H), 6.95 (d, 2H), 6.65 (d, 2H) 4.4 (m, 1H), 4.15 (m, 2H), 3.80 (s, 3H), 3.2 (m, 2H), 2.2 (m, 2H), 1.4 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 429$.

[620] **Example CN: 5-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyl}-2-pyridinecarbonitrile:**



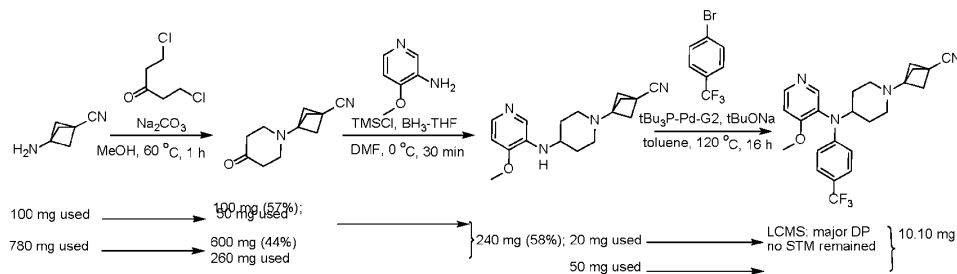
[621] **Compound 111:** 34.2 mg (41:59 mixture of diastereomers); ^1H NMR (400 MHz, CD_3OD) δ 8.65 (m, 1H), 8.4 (m, 1H), 7.9 (m, 1H), 7.8 (m, 1H), 7.35-7.55 (m, 4H), 6.65 (d, 2H), 4.2-4.3 (br. m, 1H), 3.85, 3.95 (s, s, 3H), 2.6-3.1 (m, m, 1H), 2.4 (br. s, 2H), 1.4-2.25 (m, 6H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 453$.

[622] **Example CO: (4-cyclopropoxy-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine:**



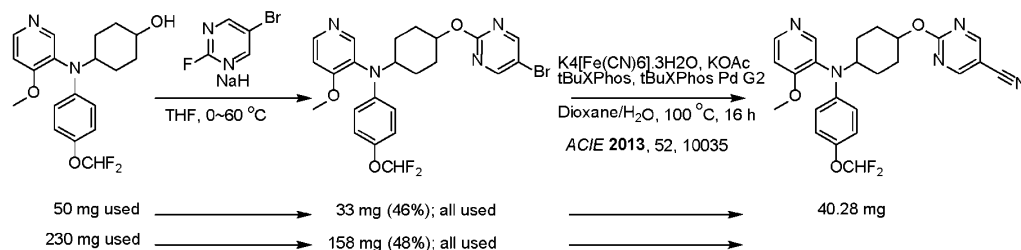
[623] **Compound 112:** 96 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.2-8.55 (m, 4H), 7.55 (d, 1H), 7.35 (d, 2H), 6.62 (d, 2H), 4.2 (m, 1H), 3.95 (m, 1H), 3.80 (m, 2H), 3.0 (m, 2H), 2.55 (s, 3H), 2.15 (m, 2H), 1.55 (m, 2H), 0.83 (m, 2H), 0.55 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 470$.

[624] **Example CP: 3-{4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]-1-piperidyl}bicyclo[1.1.1]pentane-1-carbonitrile:**



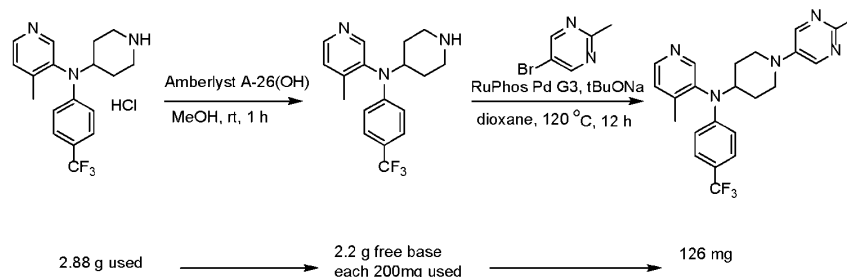
[625] **Compound 113:** 10 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.53 (d, 1H), 8.24 (s, 1H), 7.38 (d, 2H), 7.32 (d, 1H), 6.60 (d, 2H), 4.04 (m, 1H), 3.87 (s, 3H), 2.37 (m, 2H), 2.31 (m, 2H), 2.27 (s, 6H), 2.05 (m, 2H), 1.38 (m, 2H) LCMS (ESI) $[\text{M}+\text{H}]^+ = 443$.

[626] **Example CQ: 2-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]cyclohexyloxy}-5-pyrimidinecarbonitrile**



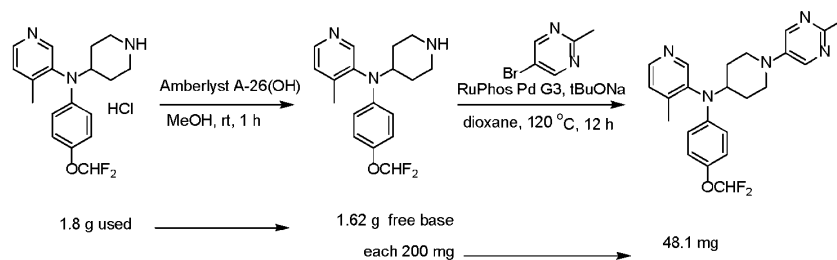
[627] **Compound 114:** 40 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.87 (d, 2H), 8.44 (d, 1H), 8.18 (s, 1H), 7.22 (d, 1H), 6.91 (d, 2H), 6.52 (m, 3H), 4.95 (m, 1H), 4.03 (m, 1H), 4.02 (s, 3H), 2.16 (m, 4H), 1.79 (m, 2H), 1.33 (m, 2H) LCMS (ESI) $[\text{M}+\text{H}]^+ = 468$.

[628] **Example CR: 4-methyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine:**



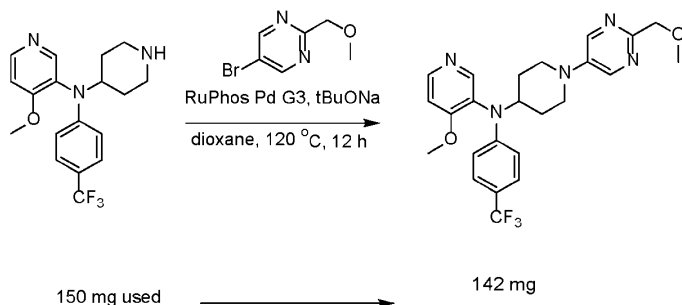
[629] **Compound 115:** 126 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.45 (d, 1H), 8.30 (m, 3H), 7.48 (d, 1H), 7.43 (d, 2H), 6.61 (d, 2H), 4.3 (m, 1H), 3.84 (m, 2H), 2.99 (m, 2H), 2.54 (s, 3H), 2.20 (s, 3H), 2.13 (m, 2H), 1.56 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 428$.

[630] **Example CS: (p-difluoromethoxyphenyl)(4-methyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]amine:**



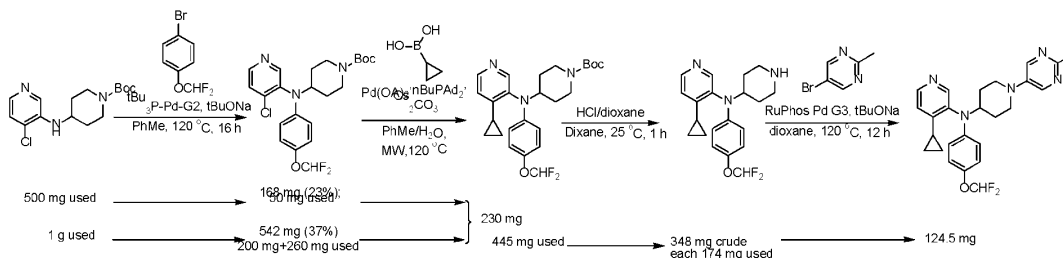
[631] **Compound 116:** 48 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.35 (br. m, 4H), 7.45 (s, 1H), 6.95 (s, 2H), 6.55 (m, 3H), 4.2 (m, 1H), 3.85 (m, 2H), 3.0 (m, 2H), 2.55 (s, 3H), 2.20 (s, 3H), 2.05 (m, 2H), 1.55 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 426$.

[632] **Example CT: {1-[2-(methoxymethyl)-5-pyrimidinyl]-4-piperidyl}(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amine:**



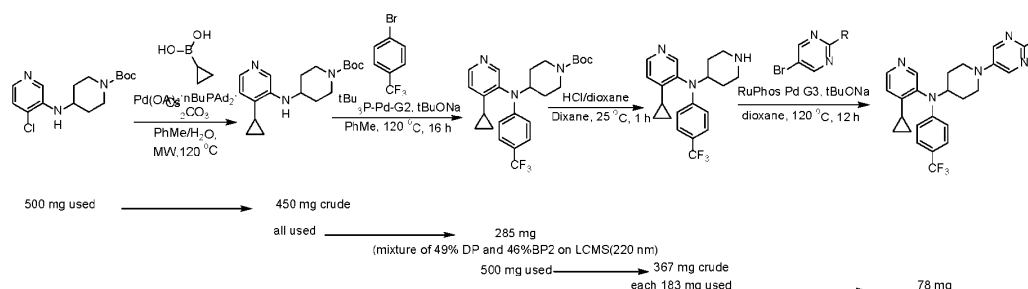
[633] **Compound 117:** 142 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.4-8.55 (m, 3H), 8.21 (s, 1H), 7.45 (m, 2H), 7.25 (d, 1H), 6.65 (m, 2H), 4.5 (m, 2H), 4.25 (m, 1H), 3.90 (m, 2H), 3.85 (s, 3H), 3.42 (s, 3H), 3.05 (m, 2H), 2.15 (m, 2H), 1.50 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 474$.

[634] **Example CU: (4-cyclopropyl-3-pyridyl)(p-difluoromethoxyphenyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]amine:**



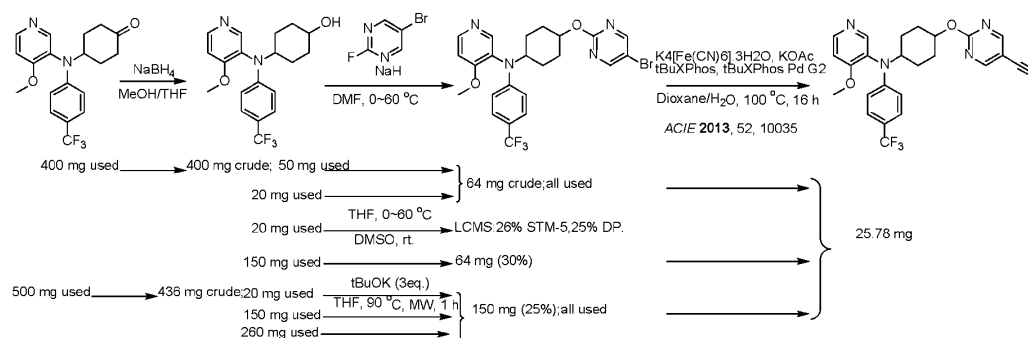
[635] **Compound 118:** 125 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.35 (m, 3H), 8.20 (s, 1H), 7.0 (m, 3H), 6.56 (m, 3H), 4.25 (m, 1H), 3.85 (m, 2H), 3.0 (m, 2H), 2.55 (s, 3H), 2.25 (m, 2H), 2.05 (m, 1H), 1.5 (m, 2H), 1.05 (m, 2H), 0.85 (m, 2H) LCMS (ESI) $[\text{M}+\text{H}]^+ = 452$.

[636] **Example CV: (4-cyclopropyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine:**



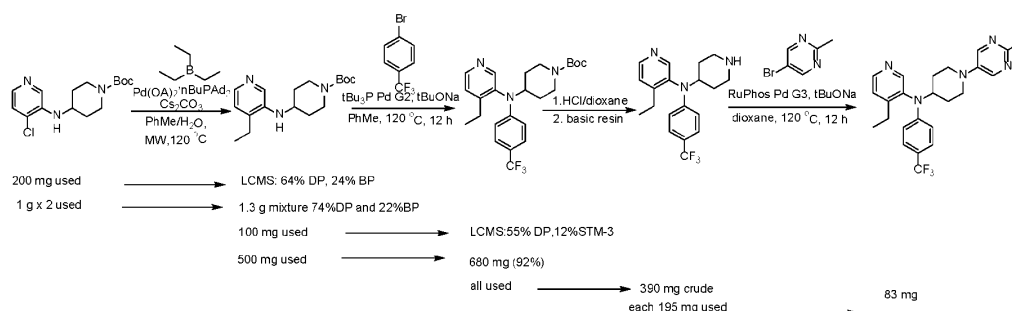
[637] **Compound 119:** 78 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.2-8.4 (m, 4H), 7.45 (d, 2H), 7.05 (d, 1H), 6.65 (d, 2H), 4.35 (m, 1H), 3.85 (m, 2H), 3.05 (m, 2H), 2.55 (s, 3H), 2.25 (m, 2H), 2.0 (m, 1H), 1.55 (m, 2H), 1.05 (m, 2H), 0.85 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 454$.

[638] **Example CW: 2-{4-[(4-methoxy-3-pyridyl)]p-(trifluoromethyl)phenyl}amino[cyclohexyloxy]-5-pyrimidinecarbonitrile:**



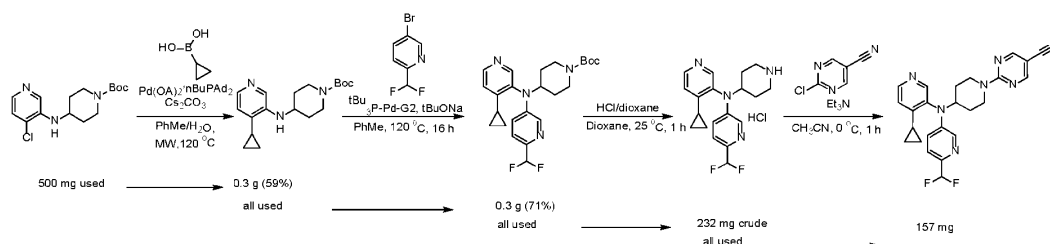
[639] **Compound 120:** 26 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.89 (s, 2H), 8.54 (br. s, 1H), 8.23 (br. s, 1H), 7.39 (d, 2H), 7.33 (m, 1H), 6.60 (d, 2H), 4.95 (s, 1H), 4.60 (m, 1H), 4.12 (s, 3H), 2.17 (m, 4H), 1.76 (m, 2H), 1.29 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 470$.

[640] **Example CX: (4-ethyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]p-(trifluoromethyl)phenyl]amine:**



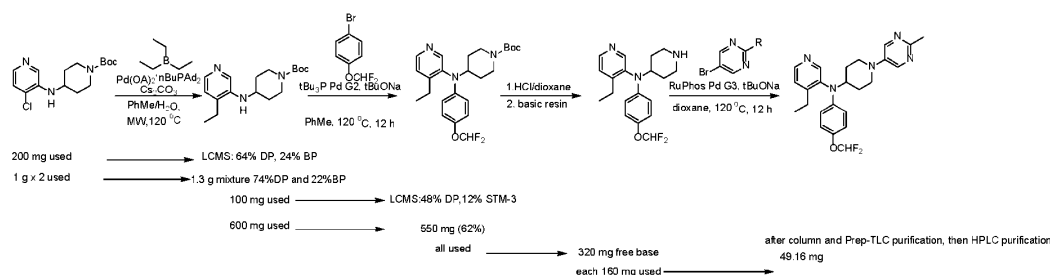
[641] **Compound 121:** 83 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.25-8.65 (m, 4H), 7.55 (m, 1H), 7.4 (m, 2H), 6.65 (m, 2H), 4.31 (m, 1H), 3.85 (m, 2H), 3.0 (m, 2H), 2.55 (m, 2H), 2.50 (s, 3H), 2.15 (m, 2H), 1.55 (q, 2H), 1.15 (t, 3H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 442$.

[642] **Example CY: 2-{4-[(4-cyclopropyl-3-pyridyl)[6-(difluoromethyl)-3-pyridyl]amino]-1-piperidyl}-5-pyrimidinecarbonitrile:**



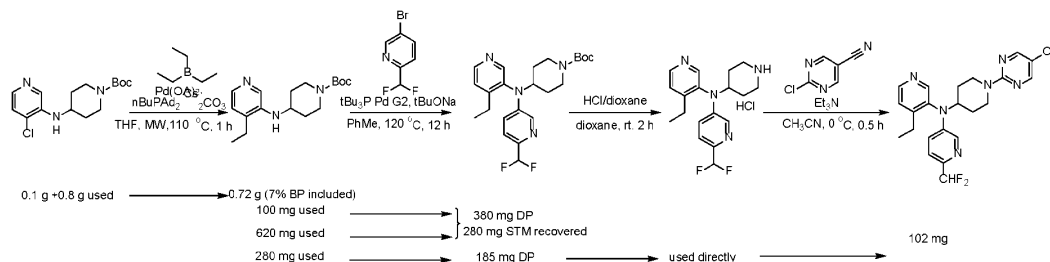
[643] **Compound 122:** 157 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.75 (s, 2H), 8.42 (m, 1H), 8.25 (s, 1H), 7.85 (m, 1H), 7.52 (m, 1H), 7.20 (m, 1H), 6.95 (m, 1H), 6.65 (m, 1H), 5.05 (m, 2H), 4.55 (m, 1H), 3.20 (m, 2H), 2.25 (m, 2H), 1.95 (m, 1H), 0.85-1.545 (br. m, 6H) LCMS (ESI) $[\text{M}+\text{H}]^+ = 448$.

[644] **Example CZ: (p-difluoromethoxyphenyl)(4-ethyl-3-pyridyl)[1-(2-methyl-5-pyrimidinyl)-4-piperidyl]amine:**



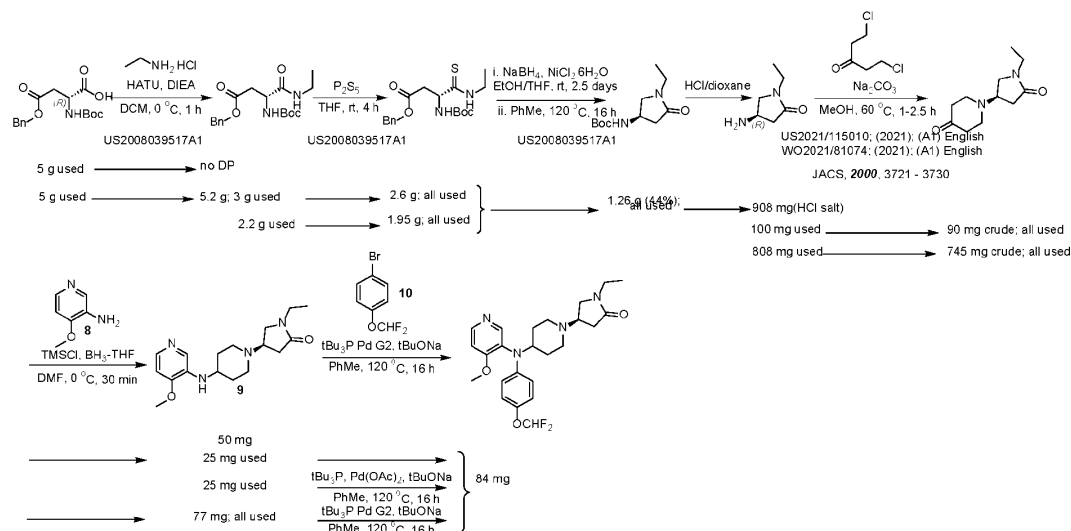
[645] **Compound 123:** 49 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.25-8.5 (m, 4H), 7.55 (s, 1H), 7.00 (m, 2H), 6.4-6.8 (m, 3H), 4.2 (m, 1H), 3.85 (m, 2H), 2.95 (m, 2H), 2.55 (s, 3H), 2.10 (q, 2H), 1.55 (m, 2H), 1.4 (m, 2H), 1.15 (t, 3H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 440$.

[646] **Example DA: 2-(4-{[6-(difluoromethyl)-3-pyridyl](4-ethyl-3-pyridyl)amino}-1-piperidyl)-5-pyrimidinecarbonitrile:**



[647] **Compound 124:** 102 mg; ^1H NMR (400 MHz, CD_3OD) δ 8.60 (s, 2H), 8.50 (m, 1H), 8.30 (s, 1H), 7.85 (d, 1H), 7.60 (d, 1H), 7.50 (d, 1H), 7.15 (d, 1H), 6.60 (m, 1H), 5.05 (m, 2H), 4.55 (m, 1H), 3.20 (m, 2H), 2.6 (m, 2H), 2.15 (m, 2H), 1.35 (m, 2H), 1.15 (t, 3H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 436$.

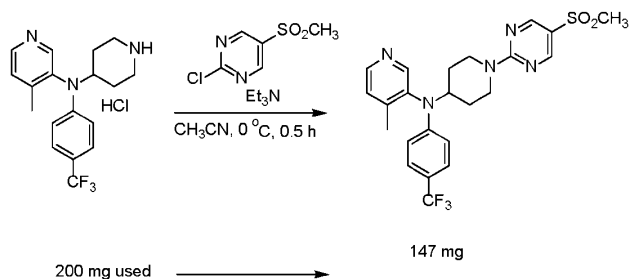
[648] **Example DB: (R)-4-[4-{(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino}-1-piperidyl]-1-ethyl-2-pyrrolidinone:**



[649] **Compound 126:** 84 mg; ^1H NMR (400 MHz, CDCl_3) δ 8.50 (d, 1H), 8.2 (s, 1H), 6.95 (m, 3H), 6.18-6.55 (br. m, 3H), 3.85 (m, 1H), 3.70 (s, 3H), 3.45 (m, 2H), 3.30 (m, 2H), 3.1 (m, 1H), 2.95 (m,

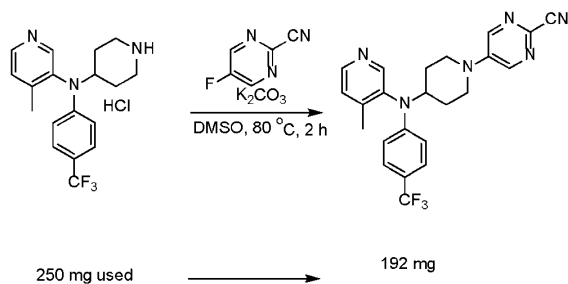
2H), 2.55 (m, 1H), 2.40 (m, 1H), 2.2 (m, 2H), 2.05 (m, 2H), 1.5 (m, 2H), 1.1 (t, 3H) LCMS (ESI) [M+H]⁺ = 461.

[650] **Example DC: [1-(5-mesyl-2-pyrimidinyl)-4-piperidyl](4-methyl-3-pyridyl)[p-(trifluoromethyl)phenyl]amine:**



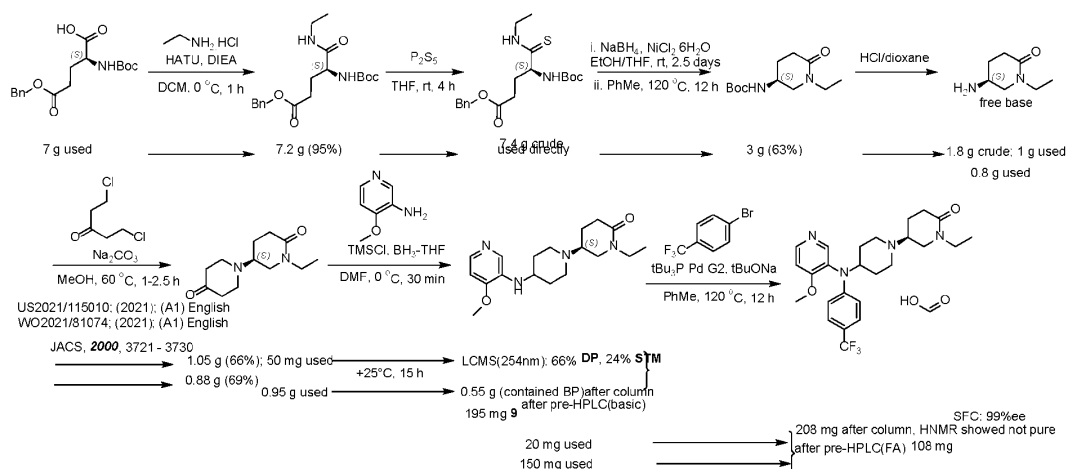
[651] **Compound 127:** 147 mg; ¹H NMR (400 MHz, DMSO-d₆) δ 8.7 (s, 2H), 8.49 (d, 1H), 8.3 (s, 1H), 7.45 (m, 3H), 6.60 (d, 2H), 4.85 (m, 2H), 4.50 (m, 1H), 3.25 (m, 2H), 3.1 (s, 3H), 2.1 (s, 3H), 2.05 (m, 2H), 1.25 (m, 2H) LCMS (ESI) [M+H]⁺ = 492.

[652] **Example DD: 5-{4-[(4-methyl-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]-1-piperidyl}-2-pyrimidinecarbonitrile:**



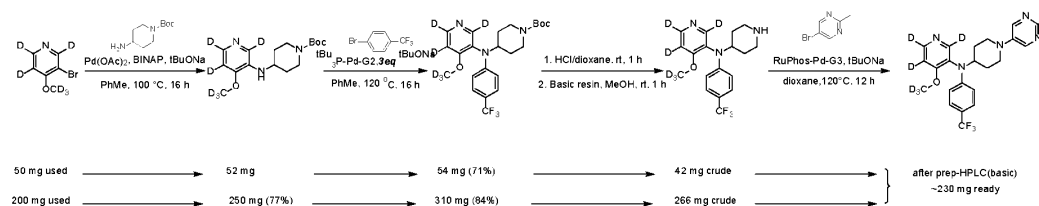
[653] **Compound 128:** 192 mg; ¹H NMR (400 MHz, DMSO-d₆) δ 8.55 (s, 2H), 8.3 (m, 2H), 7.45 (m, 3H), 6.60 (m, 2H), 4.45 (m, 1H), 4.15 (m, 2H), 3.15 (m, 2H), 2.15 (s, 3H), 2.0 (m, 2H), 1.35 (m, 2H); LCMS (ESI) [M+H]⁺ = 439.

[654] **Example DE: (S)-1'-ethyl-4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino][1,3'-bipiperidyl]-6'-one:**



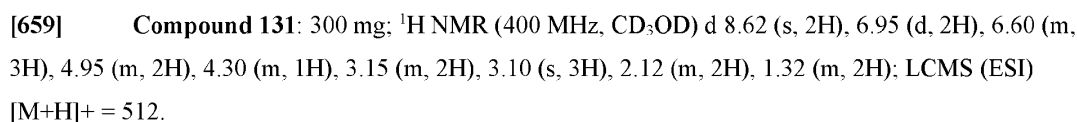
[655] **Compound 129:** 108 mg; ¹H NMR (400 MHz, CD₃OD) δ 8.55 (d, 1H), 8.25 (m, 2H), 7.45 (d, 2H), 7.30 (d, 1H), 6.65 (d, 2H), 4.2 (m, 1H), 3.92 (s, 3H), 3.05-3.55 (br. m, 6H), 2.80 (m, 2H), 2.5 (m, 1H), 2.4 (m, 1H), 2.05-2.2 (m, 3H), 1.85 (m, 1H), 1.55 (m, 1H), 1.15 (t, 3H) LCMS (ESI) [M+H]⁺ = 477.

[656] Example DF: [4-(²H₃)methoxy(2,5,6-²H₃)-3-pyridyl][1-(2-methyl-5-pyrimidinyl)-4-piperidyl][p-(trifluoromethyl)phenyl]amine:



[657] **Compound 130:** 230 mg; ¹H NMR (400 MHz, CD₃OD) δ 8.32 (s, 2H), 7.41 (d, 2H), 6.65 (d, 2H), 4.21 (m, 1H), 3.82 (m, 2H), 3.0 (m, 2H), 2.55 (s, 3H), 2.15 (m, 2H), 1.52 (m, 2H); LCMS (ESI) [M+H]⁺ = 450.

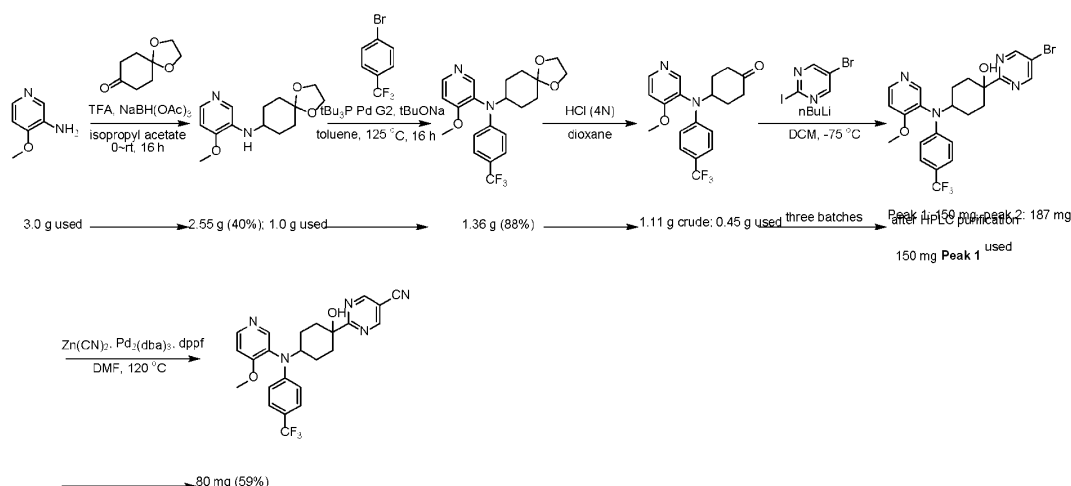
[658] Example DG: (p-difluoromethoxyphenyl)[1-(5-mesyl-2-pyrimidinyl)-4-piperidyl][4-(²H₃)methoxy(2,5,6-²H₃)-3-pyridyl]amine:



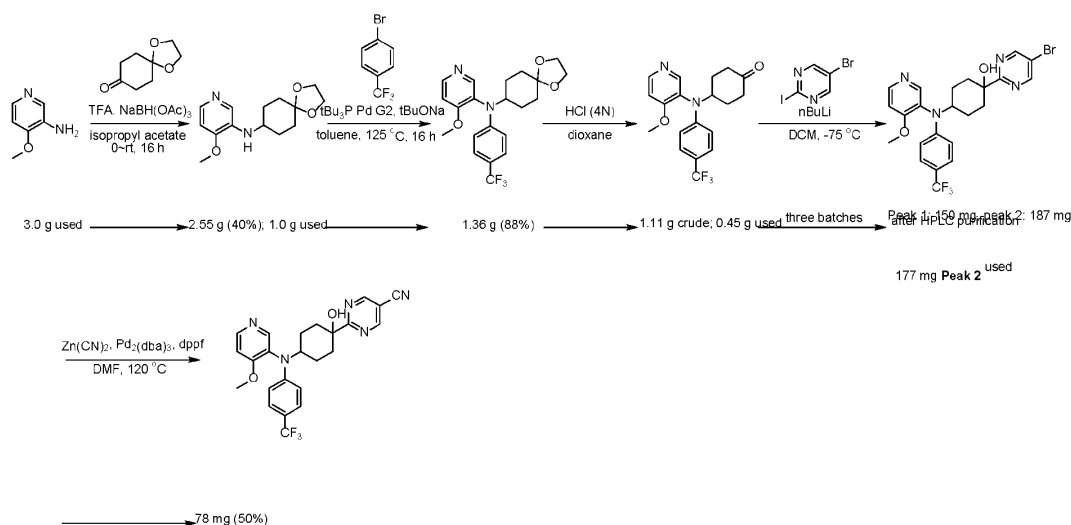
[661] **Compound 132:** 185 mg; ¹H NMR (400 MHz, CD₃OD) δ 8.5 (d, 1H), 8.40 (s, 2H), 8.25 (s, 1H), 7.45 (d, 2H), 7.25 (d, 1H), 6.65 (d, 2H), 4.25 (m, 1H), 3.82 (m, 2H), 2.95 (m, 2H), 2.55 (s, 3H), 2.15 (m, 2H), 1.55 (m, 2H); LCMS (ESI) [M+H]⁺ = 447.

[663] Compound 133: 300 mg; ¹H NMR (400 MHz, CD₃OD) δ 8.85 (s, 2H), 8.56 (d, 1H), 8.32 (s, 1H), 7.4 (d, 1H), 7.15 (d, 2H), 6.8 (m, 3H), 5.20 (m, 2H), 4.52 (m, 1H), 3.35 (m, 2H), 3.28 (s, 3H), 2.45 (m, 2H), 1.50 (m, 2H); LCMS (ESI) [M+H]⁺ = 509.

[664] Example DJ: 2-{1-hydroxy-4-[(4-methoxy-3-pyridyl)[p-(trifluoromethyl)phenyl]amino]cyclohexyl}-5-pyrimidinecarbonitrile:

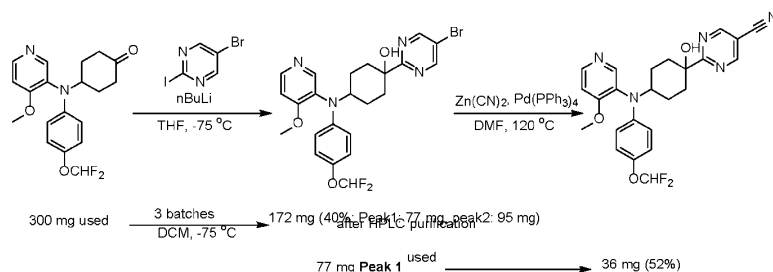


[665] Compound 134-isomer 1: 80 mg; ^1H NMR (400 MHz, CD_3CN) δ 9.1 (s, 2H), 8.52 (d, 1H), 8.28 (d, 1H), 7.40 (d, 2H), 7.15 (d, 1H), 6.61 (d, 2H), 4.15 (m, 1H), 3.85 (m, 1H), 3.70 (s, 3H), 2.5 (m, 2H), 2.0 (m, 2H), 1.85 (m, 2H), 1.32 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 470$.

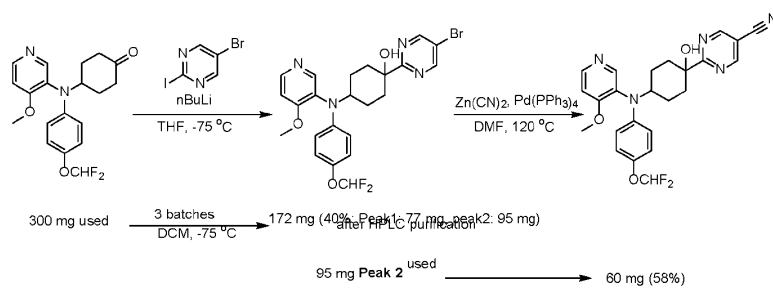


[666] Compound 134-isomer 2: 78 mg; ^1H NMR (400 MHz, CD_3CN) δ 9.1 (s, 2H), 8.52 (d, 1H), 8.28 (d, 1H), 7.40 (d, 2H), 7.15 (d, 1H), 6.61 (d, 2H), 4.15 (m, 1H), 4.05 (m, 1H), 3.80 (s, 3H), 2.22 (m, 2H), 2.02 (m, 2H), 1.6-1.8 (br. m, 4H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 470$.

[667] **Example DK: 2-{4-[(p-difluoromethoxyphenyl)(4-methoxy-3-pyridyl)amino]-1-hydroxycyclohexyl}-5-pyrimidinecarbonitrile:**



[668] **Compound 135-isomer 1:** 36 mg; $^1\text{H NMR}$ (400 MHz, CD_3OD) δ 9.1 (s, 2H), 8.35 (d, 1H), 8.06 (s, 1H), 7.10 (d, 1H), 6.9 (m, 2H), 6.56 (m, 3H), 4.12 (m, 1H), 3.75 (s, 3H), 2.66 (m, 2H), 1.97 (m, 2H), 1.85 (m, 2H), 1.29 (m, 2H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 468$.



[669] **Compound 135-isomer 2:** 60 mg; $^1\text{H NMR}$ (400 MHz, CD_3OD) δ 9.01 (s, 2H), 8.51 (br. s, 1H), 8.32 (br. s, 1H), 6.97 (m, 3H), 6.2-6.6 (br. m, 3H), 4.0 (m, 2H), 3.8 (s, 3H), 2.24 (m, 2H), 2.04 (m, 2H), 1.78 (m, 4H); LCMS (ESI) $[\text{M}+\text{H}]^+ = 468$.

BIOLOGICAL ASSAY EXAMPLES

Mouse OPC Preparation

[670] To assess effects of treatments on OPCs, all treatments were assayed in two or more independent platings of epiblast stem cell-derived OPCs (EpiSC). EpiSC-derived OPCs were obtained using in vitro differentiation protocols and culture conditions described previously (Najm et al, 2011, Nature Methods). OPCs were expanded and frozen down in aliquots. OPCs were thawed into growth conditions for at least one passage before use in further assays.

Determination of EC_{50} values of Compounds

A: In vitro phenotypic screening of OPCs

[671] Each compound's ability to induce maturation of murine OPCs into oligodendrocytes was assessed. EpiSC-derived OPCs were grown and expanded in poly-L-ornithine (PO) and laminin-coated

flasks in N2B27 media (DMEM/F12 (Gibco), N2-MAX (R&D Systems), B-27 (ThermoFisher), and GlutaMax (Gibco)) supplemented with FGF2 (10 µg/mL, R&D systems, 233-FB-025) and PDGF-AA (10 µg/mL, R&D systems, 233-AA-050) before harvesting for experiments. The cells were seeded onto poly-L-ornithine or poly-D-lysine coated CellCarrier Ultra plates (PerkinElmer) coated with laminin (Sigma, L2020) at a density of 150,000/cm² in N2B27 media without growth factors. For dose–response testing, a 1000x compound stock in dimethyl sulphoxide (DMSO) was added to assay plates, resulting in 8-point dose curves. Positive controls and DMSO vehicle controls were included in each assay plate. Cells were incubated under standard conditions (37 °C, 5% CO) for 3 days and fixed with 4% paraformaldehyde (PFA) in phosphate buffered saline (PBS) for 20 min. Fixed plates were washed with PBS, permeabilized with 0.1% Triton X-100, and blocked with 10% donkey serum (v/v) in PBS for 40 min. Then, cells were labelled with MBP antibodies (Abcam, ab7349; 1:200) overnight at 4°C, washed with PBS, and stained with Alexa Fluor conjugated secondary antibodies (1:500) for 45 min. Nuclei were visualized by DAPI staining (Sigma; 1 g/ml), followed by further PBS washes.

B: High-content imaging and analysis

[672] Cells and cell culture plates were imaged on the Operetta High Content Imaging and Analysis system (PerkinElmer). Analysis (PerkinElmer Harmony and Columbus software) began by identifying intact nuclei stained by DAPI. The peri-nuclear region of each cell was then cross-referenced with the mature myelin protein (MBP) stain to identify oligodendrocyte nuclei, and from this the percentage of oligodendrocytes was calculated. EC₅₀ values were calculated using The Levenberg–Marquardt algorithm to fit a Hill equation to the 8-point dose-response curve. The results are provided in Table 3 (OPC EC₅₀).

Determination of Potency and Enzyme Target

GC/MS-based sterol profiling

A: Murine Sterol Profiling Assay

[673] Each compound's ability to induce accumulation of key sterol intermediates within the cholesterol biosynthesis pathway was assessed. Sterols were monitored using a modified Folch wash protocol (Hubler et al, 2018, Nature). EpiSC-derived OPCs were plated at 100,000 cells per well in PO- and laminin-coated 96-well plates in N2B27 media without growth factors. After 24 hours, cells were rinsed with saline and plates were frozen. Cholesterol-d7 standard was then added to each well before drying under nitrogen stream and derivatization with 55 µl of bis(trimethylsilyl) trifluoroacetamide. After derivatization, 2 µl were analyzed by gas chromatography / mass spectrometry using an Agilent 5973 Network Mass Selective Detector equipped with a 6890 gas chromatograph system and a HP-5MS capillary column (30m x 0.25mm x 0.25mm). Samples were analyzed in full scan mode using electron impact ionization; ion fragment peaks were integrated to calculate sterol abundance, and quantitation was relative to cholesterol-

d7. The following ion fragments were used to quantitate each metabolite: cholesterol-d7 (465), FF-Mas (482), cholesterol (368), zymostenol (458), zymosterol (456), Desmosterol (456, 343), 7-dehydrocholesterol (456, 325), lanosterol (393), lathosterol (458), 14-dehydrozymostenol (456, 351), and dihydrolanosterol (395). For reference, Table 2 shows sterol GC-MS analytes and their relationship with inhibitors of cholesterol biosynthesis. All standards were obtained from Avanti Polar Lipids unless otherwise indicated. Calibration curves were generated by injecting varying concentrations of sterol standards and maintaining a fixed amount of cholesterol-D7. For normalized lanosterol accumulation results, the total amount of lanosterol measured after drug treatment was divided by the total amount of lanosterol accumulated after 24 hr treatment with 100 nM positive control reference. EC₅₀ values were calculated using The Levenberg–Marquardt algorithm to fit a Hill equation to an 8-point dose-response curve. EC₅₀ values for lanosterol (Murine GCMS EC₅₀) are provided in Table 3.

[674] Table 2. Sterol Analytes

Analyte increased	Cholesterol enzyme inhibited
Lanosterol	CYP51
Dihydrolanosterol	CYP51
FF-MAS	TM7SF2 (Sterol 14 Reductase)
14-dehydrozymostenol	TM7SF2 (Sterol 14 Reductase)
Zymosterol	EBP
Zymostenol	EBP
7-dehydrocholesterol	DHCR7

B: Human Sterol Profiling Assay

[675] Each compound's ability to induce accumulation of key sterol intermediates within the cholesterol biosynthesis pathway was assessed in human cells. Sterols were monitored using a modified Folch wash protocol (Hubler et al, 2018, Nature). Human Mesenchymal stem cells (hMSCs) were plated at 50,000 cells per well in Nunc MicroWell 96-well plates in hMSC High Performance Media Kit media (RoosterBio). After 24 hours, cells were rinsed with saline and plates were frozen. Cholesterol-d7 standard was then added to each well before drying under nitrogen stream and derivatization with 55 µl of bis(trimethylsilyl) trifluoroacetamide. After derivatization, 2 µl were analyzed by gas chromatography / mass spectrometry using an Agilent 5973 Network Mass Selective Detector equipped with a 6890 gas chromatograph system and a HP-5MS capillary column (30m x 0.25mm x 0.25mm). Samples were analyzed in full scan mode using electron impact ionization; ion fragment peaks were integrated to calculate sterol abundance, and quantitation was relative to cholesterol-d7. The following ion fragments were used to quantitate each metabolite: cholesterol-d7 (465), FF-Mas (482), cholesterol (368), zymostenol (458),

zymosterol (456), Desmosterol (456, 343), 7-dehydrocholesterol (456, 325), lanosterol (393), lathosterol (458), 14-dehydrozymosterol (456, 351), and dihydrolanosterol (395). For reference, Table 2 above shows sterol GC-MS analytes and their relationship with inhibitors of cholesterol biosynthesis. All standards were obtained from Avanti Polar Lipids unless otherwise indicated. Calibration curves were generated by injecting varying concentrations of sterol standards and maintaining a fixed amount of cholesterol-D7. For normalized lanosterol accumulation results, the total amount of lanosterol measured after drug treatment was divided by the total amount of lanosterol accumulated after 24 hr treatment with 100 nM positive control reference. EC_{50} values were calculated using The Levenberg–Marquardt algorithm to fit a Hill equation to an 8-point dose-response curve. EC_{50} values for lanosterol (Human GCMS EC_{50}) are provided in Table 3.

[676] Table 3. Assay Values

Compound No.	Human GC/MS EC_{50} (μ M)	Mouse GC/MS EC_{50} (μ M)	Mouse OPC Differentiation EC_{50} (μ M)
Fenarimol		53.2	>50
1	0.0025	0.00469	0.0326
2	0.0209	0.00341	0.0186
3	0.00149	0.00318	0.0182
4	0.00201	0.00258	0.0296
5	0.00244	0.00472	0.0404
6	0.00231	0.00844	0.0541
7	0.00273	0.00397	0.0269
8	0.00126	0.00256	0.015
9	0.00397	0.0113	0.0747
10	0.00241	0.0047	0.0164
11	0.00118	0.00539	0.0289
12	0.00124	0.00327	0.00743
13	0.00136	0.00529	0.0217
14	0.00103	0.00368	0.00885
15	0.00149	0.00402	0.00841
16	0.00107	0.00302	0.0126
17	0.00312	0.0107	0.0591
18	0.0016	0.00383	0.0107
19	0.00209	0.00508	0.057
20	0.00237	0.00452	0.0531
21	0.00383	0.00913	0.119
22	0.00642	0.0109	0.16
23	0.00328	0.0112	0.204

Compound No.	Human GC/MS EC ₅₀ (μ M)	Mouse GC/MS EC ₅₀ (μ M)	Mouse OPC Differentiation EC ₅₀ (μ M)
24	0.00129	0.00359	0.00803
25	0.00182	0.00376	0.0283
26	0.00292	0.00504	0.0442
27	0.00184	0.00526	0.0541
28	0.00294	0.0054	0.0682
29	0.00168	0.00574	0.0804
30	0.00161	0.0114	0.122
31	0.00102	0.00479	0.0307
32	0.00183	0.00734	0.0405
33	0.00218	0.0113	0.101
34	0.000809	0.0041	0.0128
35	0.00147	0.00542	0.0662
36	0.00157	0.0041	0.0507
37	0.00221	0.00795	0.0871
38	0.000846	0.00322	0.00675
39	0.00256	0.00929	0.0556
40	0.00207	0.00567	0.0808
41	0.0012	0.00463	0.0128
42	0.000768	0.00338	0.0135
43	0.00102	0.00471	0.0253
44	0.000754	0.00418	0.0248
45	0.00168	0.00461	0.0162
46	0.00153	0.00502	0.0163
47	0.00194	0.00561	0.0252
48	0.00148	0.00741	0.0499
49	0.00111	0.00561	0.0362
50	0.00126	0.00517	0.0257
51	0.00147	0.00746	0.0587
52	0.00218	0.0109	0.0515
53	0.00141	0.00717	0.0338
54	0.00134	0.00565	0.0192
55	0.0006	0.00759	0.0247
56	0.00128	0.00764	0.0393
57	0.000731	0.0119	0.0799
58	0.00095	0.00947	0.0429
59	0.000508	0.00971	0.0302
60	0.00121	0.00591	0.0291

Compound No.	Human GC/MS EC ₅₀ (μM)	Mouse GC/MS EC ₅₀ (μM)	Mouse OPC Differentiation EC ₅₀ (μM)
61	0.000632	0.0037	0.0292
62	0.00137	0.00529	0.0343
63		0.00287	0.00721
64	0.000532	0.00315	0.00849
65	0.00161	0.00719	0.052
66	0.000961	0.00299	0.00655
67	0.00118	0.00346	0.00897
68	0.000841	0.00296	0.00356
69	0.000851	0.00162	0.00419
70	0.00204	0.00442	0.0186
71	0.00079	0.0027	0.00477
72	0.000588	0.00321	0.005
73	0.00127	0.00378	0.0182
74	0.000365	0.00317	0.00468
75	0.000528	0.0034	0.00684
76	0.00131	0.00446	0.011
77	0.000672	0.0074	0.0238
78	0.00212	0.00734	0.0221
79	0.00153	0.00543	0.0200
100	0.00248	0.0157	0.0888
101	0.00399	0.0269	0.194
102	0.0145	0.0162	0.213
103	0.00131	0.0145	0.0956
104-isomer 1	0.0078	0.038	0.0564
104-isomer 2	0.00302	0.0343	0.202
105-isomer 1	0.00087	0.00438	0.0135
105-isomer 2	0.00637	0.0602	0.344
106	0.00124	0.00546	0.0165
107	0.000704	0.00402	0.01
108 (mixture of two isomers)	0.00156	0.00484	0.00708
109	0.00883	0.0155	0.0662
110	0.00605	0.00856	0.0462
111 (mixture of two isomers)	0.0023	0.00549	0.00931
112	0.00175	0.00369	0.00866
113	0.00459	0.036	0.271

Compound No.	Human GC/MS EC ₅₀ (μ M)	Mouse GC/MS EC ₅₀ (μ M)	Mouse OPC Differentiation EC ₅₀ (μ M)
114	0.00192	0.0152	0.0772
115	0.00578	0.0241	0.275
116	0.00711	0.0473	0.331
117	0.0039	0.0167	0.0957
118	0.00124	0.00539	0.0148
119	0.00162	0.00584	0.0104
120	0.00339	0.0326	0.367
121	0.00182	0.00713	0.0391
122	0.00679	0.0083	0.0917
123	0.0005	0.00935	0.0896
124	0.00529	0.0189	0.113
125	0.00442	0.0439	0.232
126	0.0217	0.0356	0.386
127	0.00162	0.00357	0.00975
128	0.0026	0.0205	0.104
129	0.0175	0.0612	0.493
130	0.00083	0.00391	0.0384
131	0.0005	0.00119	0.00575
132	0.00076	0.0034	0.0384
133	0.0005	0.00125	0.0048
134-isomer 1	0.0145	0.0271	0.354
134-isomer 2	0.922	> 1	
135-isomer 1	0.0313	0.0194	0.221
135-isomer 2	0.962	> 1	

[677] Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperature, etc.) but some experimental errors and deviations should be accounted for.

[678] One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practicing the subject matter described herein. The present disclosure is in no way limited to just the methods and materials described.

[679] Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this subject matter belongs, and are consistent with: Singleton et al (1994) Dictionary of Microbiology and Molecular Biology, 2nd Ed., J. Wiley & Sons, New York, NY; and Janeway, C., Travers, P., Walport, M., Shlomchik (2001) Immunobiology, 5th Ed., Garland Publishing, New York.

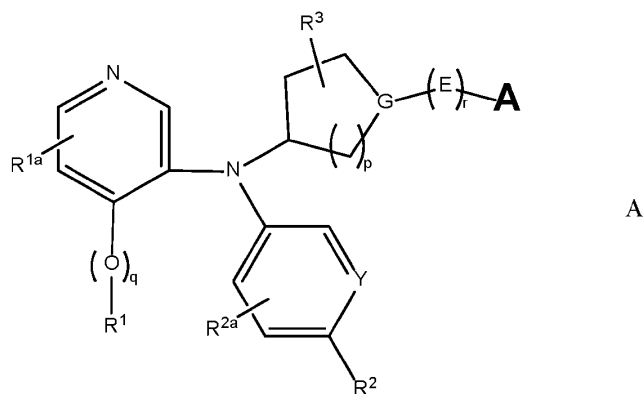
[680] Throughout this specification and the claims, the words “comprise,” “comprises,” and “comprising” are used in a non-exclusive sense, except where the context requires otherwise. It is understood that embodiments described herein include “consisting of” and/or “consisting essentially of” embodiments.

[681] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit, unless the context clearly dictates otherwise, between the upper and lower limit of the range and any other stated or intervening value in that stated range, is encompassed. The upper and lower limits of these small ranges which may independently be included in the smaller ranges is also encompassed, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included.

[682] Many modifications and other embodiments set forth herein will come to mind to one skilled in the art to which this subject matter pertains having the benefit of the teachings presented in the foregoing descriptions and the associated drawings. Therefore, it is to be understood that the subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims. Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation.

CLAIMS

1. A compound of Formula A:



wherein,

A is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, 5- to 6-membered heteroaryl and 5- to 6-membered heterocyclyl, each of which is optionally substituted with one or more of R^{A1}, R^{A2} and R^{A3},

wherein, R^{A1}, R^{A2} and R^{A3} are each independently selected from the group consisting of C₁-C₆ alkyl, halo-C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, cyano, oxo, -C(O)-R^{A4}, -S(O)-R^{A4} and -S(O)₂-R^{A4},

wherein, R^{A4} is C₁-C₆ alkyl or C₃-C₈ cycloalkyl, and

wherein the oxo, if present, is formed by two of R^{A1}, R^{A2} and R^{A3} together with a carbon to which each is attached;

G is -CH, C-OH, or N;

E, if present, is -C(O)- or -O-;

Y is -CH or N;

p is 1, 2 or 3;

q is 1 or 0;

r is 1 or 0;

wherein, when r is 0, A is other than C₁-C₆ alkyl;

R¹ is selected from the group consisting of C₁-C₆ alkyl, C₃-C₈ cycloalkyl and halo-C₁-C₆ alkyl; or R¹ is halo and q is 0;

R^{1a} is selected from the group consisting of hydrogen, halo, C₁-C₆ alkyl;

R² is selected from the group consisting of halo, halo-C₁-C₆ alkyl, halo-C₁-C₆ alkoxy and

-S(O)₂-(C₁-C₆ alkyl);

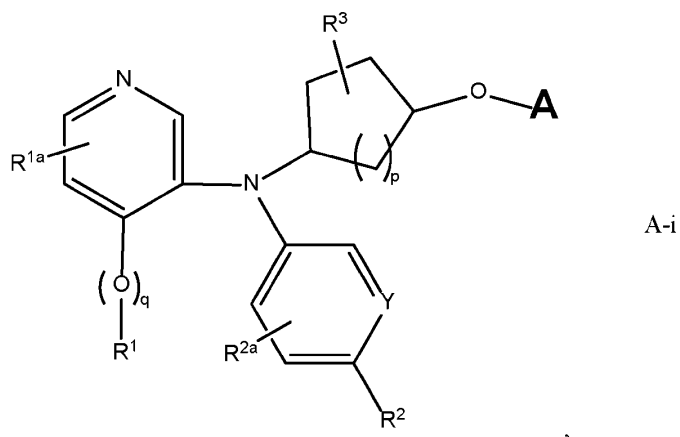
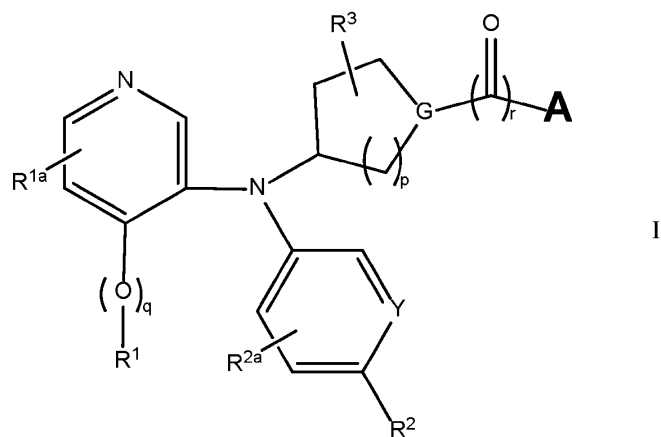
R^{2a} is selected from the group consisting of hydrogen and halo;

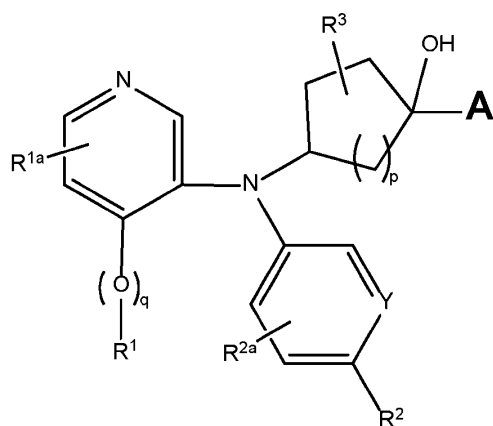
and,

R³ is hydrogen, halo, or C₁-C₆ alkyl,

or a pharmaceutically acceptable salt or solvate thereof.

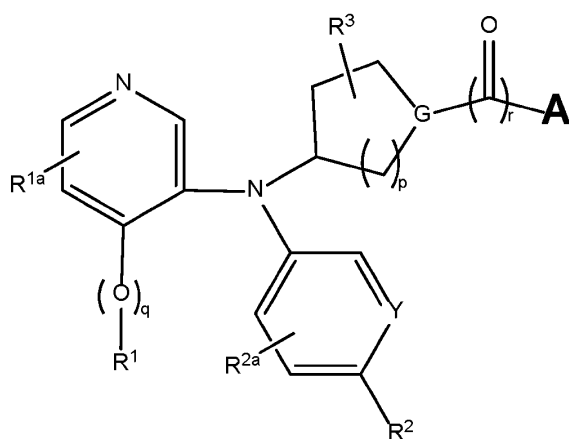
2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having a structure of Formula I, Formula A-i, or Formula A-ii:





A-ii

3. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, having a structure of Formula I:



I

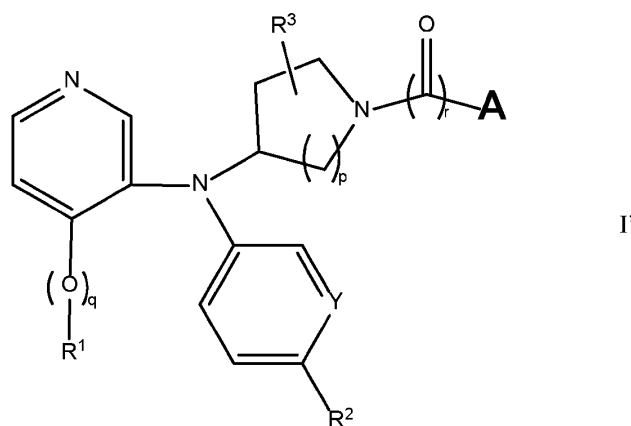
wherein,

R^{A1} , R^{A2} and R^{A3} are each independently selected from the group consisting of C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo, cyano, oxo, $-C(O)-R^{A4}$, $-S(O)-R^{A4}$ and $-S(O)_2-R^{A4}$;

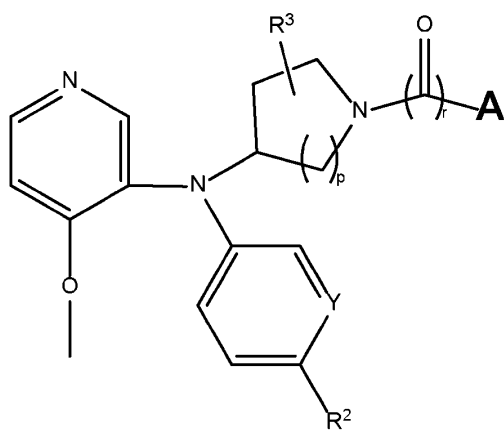
G is -CH or N; and

R^1 is selected from the group consisting of C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl and halo- C_1 - C_6 alkyl.

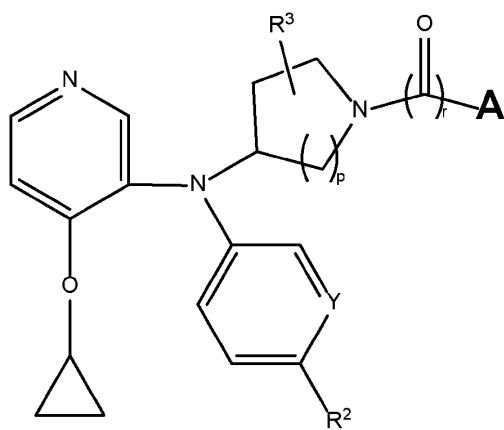
4. The compound of claim 3, or a pharmaceutically acceptable salt or solvate thereof, wherein G is N and having a structure of Formula I':



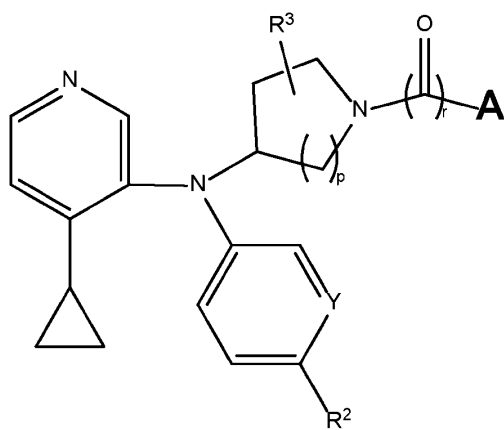
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1.
6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 0.
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is C₁-C₆ alkyl or C₃-C₈ cycloalkyl.
8. The compound of claim 7, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is methyl, ethyl or cyclopropyl.
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, having a structure of Formula Ia, Ib or Ic:



Ia



Ib



Ic

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is N.
11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is -CH.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is halo-C₁-C₆ alkyl or halo-C₁-C₆ alkoxy.
13. The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is halo-C₁-C₆ alkyl.
14. The compound of claim 13, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is -CF₃.
15. The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is halo-C₁-C₆ alkoxy.
16. The compound of claim 15, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is -O-CHF₂.
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1 or 2.
18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1.
19. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 2.
20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is C₁-C₆ alkyl.

21. The compound of claim 20, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is methyl.

22. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen.

23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, wherein r is 1.

24. The compound of claim 23, or a pharmaceutically acceptable salt or solvate thereof, wherein A is C_1 - C_6 alkyl.

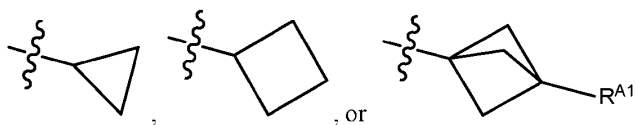
25. The compound of claim 24, or a pharmaceutically acceptable salt or solvate thereof, wherein A is $-CH_3$ or $-CH_2CH_3$.

26. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, wherein r is 0.

27. The compound of claim 23 or 26, or a pharmaceutically acceptable salt or solvate thereof, wherein G is $-CH$.

28. The compound of claim 27, or a pharmaceutically acceptable salt or solvate thereof, wherein A is C_3 - C_5 cycloalkyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

29. The compound of claim 28, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



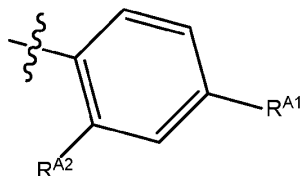
30. The compound of claim 29, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is cyano or halo- C_1 - C_6 alkyl.

31. The compound of claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is $-CF_3$.

32. The compound of claim 23 or 26, or a pharmaceutically acceptable salt or solvate thereof, wherein A is phenyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

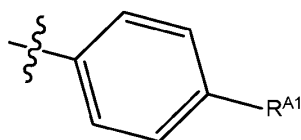
33. The compound of claim 32, or a pharmaceutically acceptable salt or solvate thereof, wherein A is phenyl, optionally substituted with one or more of R^{A1} and R^{A2} .

34. The compound of claim 33, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



35. The compound of claim 34, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is $-S(O)_2-R^{A4}$, and, R^{A2} is halo.

36. The compound of claim 33, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



37. The compound of claim 36, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is selected from the group consisting of halo, cyano, $-S(O)_2-R^{A4}$ and $-C(O)-R^{A4}$.

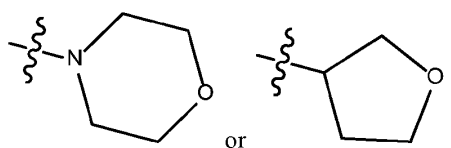
38. The compound of claim 23 or 26, or a pharmaceutically acceptable salt or solvate thereof, wherein A is 5- to 6-membered heterocyclyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

39. The compound of claim 38, or a pharmaceutically acceptable salt or solvate thereof, wherein the heterocyclyl comprises 1 or 2 heteroatoms selected from the group consisting of N, S, and O.

40. The compound of claim 38, or a pharmaceutically acceptable salt or solvate thereof, wherein A is 5- to 6-membered heterocyclyl.

41. The compound of claim 40, or a pharmaceutically acceptable salt or solvate thereof, wherein A is 5- to 6-membered heterocyclyl comprising 1 or 2 heteroatoms selected from the group consisting of N, S and O.

42. The compound of claim 41, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



43. The compound of claim 23 or 26, or a pharmaceutically acceptable salt or solvate thereof, wherein A is 5- to 6-membered heteroaryl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

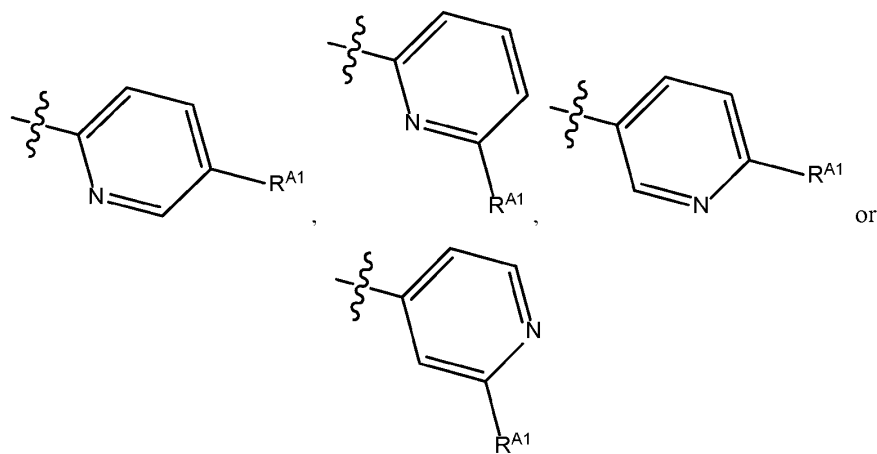
44. The compound of claim 43, or a pharmaceutically acceptable salt or solvate thereof, wherein A is selected from the group consisting of pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, oxadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, and thiazolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

45. The compound of claim 44, or a pharmaceutically acceptable salt or solvate thereof, wherein A is selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, oxadiazolyl and pyrrolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

46. The compound of claim 45, or a pharmaceutically acceptable salt or solvate thereof, wherein A is pyridinyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

47. The compound of claim 46, or a pharmaceutically acceptable salt or solvate thereof, wherein A is pyridinyl substituted with R^{A1} .

48. The compound of claim 47, or a pharmaceutically acceptable salt or solvate thereof, wherein A is

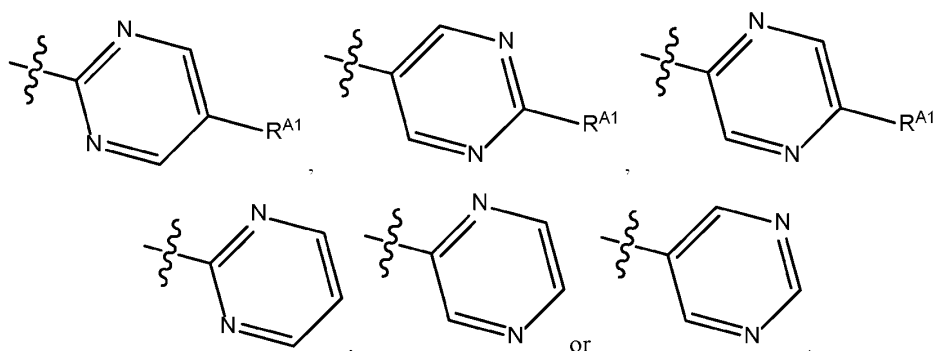


49. The compound of claim 48, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is selected from the group consisting of C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo, cyano and $-S(O)_2-R^{A4}$.

50. The compound of claim 45, or a pharmaceutically acceptable salt or solvate thereof, wherein A is pyrimidinyl or pyrazinyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

51. The compound of claim 50, or a pharmaceutically acceptable salt or solvate thereof, wherein A is pyrimidinyl or pyrazinyl, optionally substituted with R^{A1} .

52. The compound of claim 51, or a pharmaceutically acceptable salt or solvate thereof, wherein A is

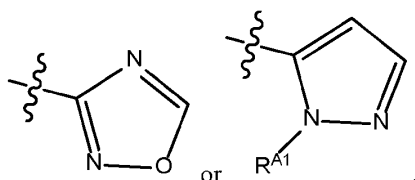


53. The compound of claim 52, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is selected from the group consisting of C_1 - C_6 alkyl, halo- C_1 - C_6 alkyl, halo, cyano and $-S(O)_2-R^{A4}$.

54. The compound of claim 45, or a pharmaceutically acceptable salt or solvate thereof, wherein A is oxadiazolyl and pyrrolyl, optionally substituted with one or more of R^{A1} , R^{A2} and R^{A3} .

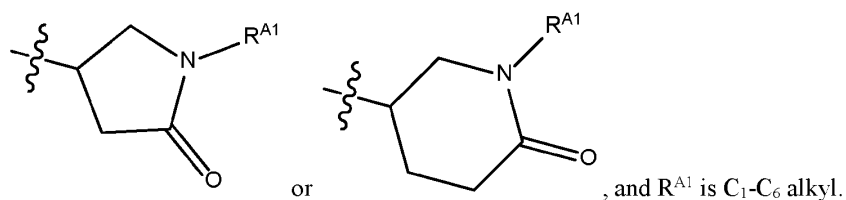
55. The compound of claim 54, wherein or a pharmaceutically acceptable salt or solvate thereof, A is oxadiazolyl and pyrrolyl, optionally substituted with R^{A1} .

56. The compound of claim 55, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



57. The compound of claim 56, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is C_1 - C_6 alkyl.

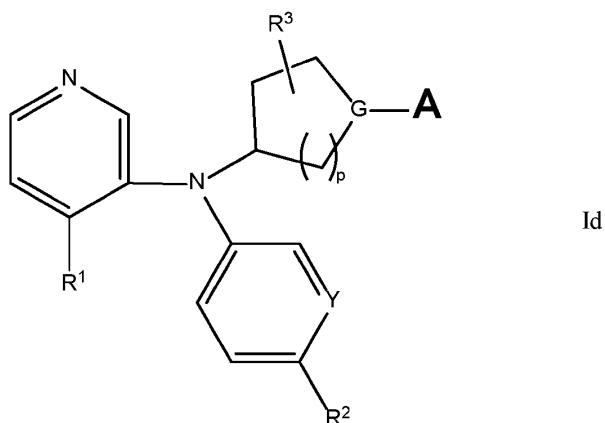
58. The compound of claim 38, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



59. The compound of claim 58, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is ethyl.

60. The compound of claim 43 or 52, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{A1} is CH_2OCH_3 .

61. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, having a structure of Formula Id:



wherein:

r and q are each 0;

R^{1a} and R^{1b} are each hydrogen; and,

R^1 is halogen.

62. The compound of claim 61, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -Cl.

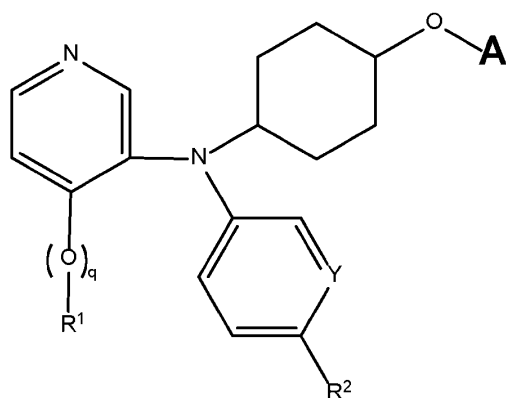
63. The compound of claim 61 or 62, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is CF_3 .

64. The compound of any one of claims 61-63, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen.

65. The compound of any one of claims 61-64, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is N.

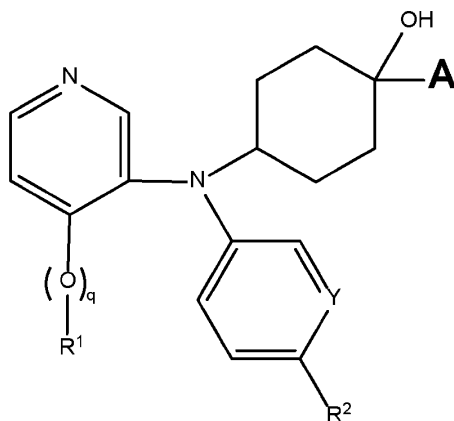
66. The compound of any one of claims 61-65, or a pharmaceutically acceptable salt or solvate thereof, wherein G is N and p is 2.

67. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein E is -O-; r is 1; p is 2; R^{1a} , R^{2a} , and R^3 are each hydrogen, and having a structure of Formula A-i':



A-i'

68. The compound of claim 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein r is 0; p is 2; R^{1a} , R^{2a} , and R^3 are each hydrogen, and having a structure of Formula A-ii':



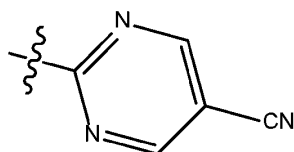
A-ii'

69. The compound of claim 67 or 68, or a pharmaceutically acceptable salt or solvate thereof, wherein q is 1 and R^1 is CH_3 .

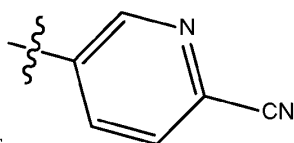
70. The compound of any one of claim 67-69, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is CF_3 or $OCHF_2$.

71. The compound of any one of claim 67-70, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is CH .

72. The compound of any one of claims 52 and 61-71, or a pharmaceutically acceptable salt or solvate thereof, wherein A is



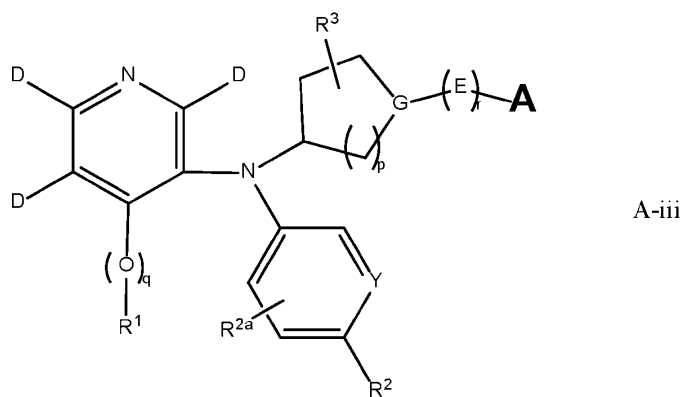
73. The compound of any one of claims 48 and 61-71, or a pharmaceutically acceptable salt or



solvate thereof, wherein A is

74. The compound of any one of claims 1-73, wherein one or more hydrogen atoms is replaced with deuterium.

75. The compound of claim 74, having a structure of Formula A-iii:

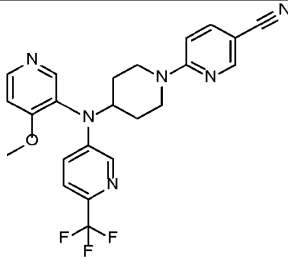
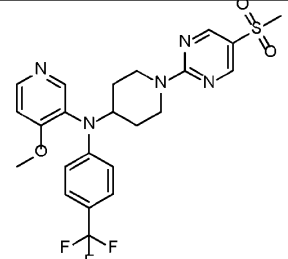
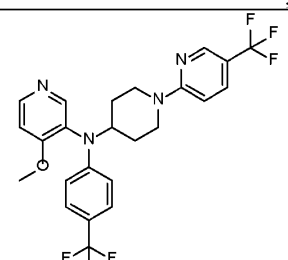
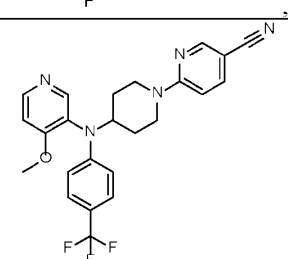
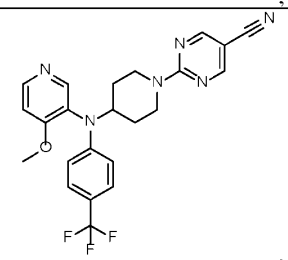


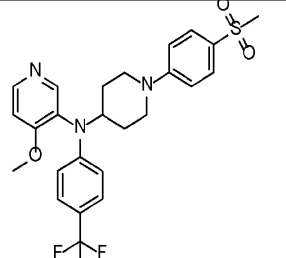
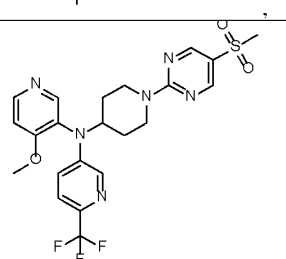
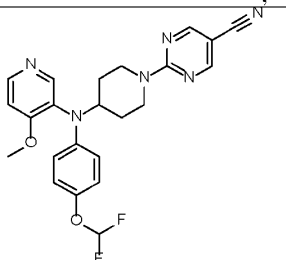
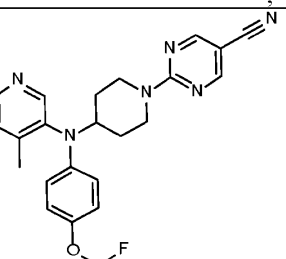
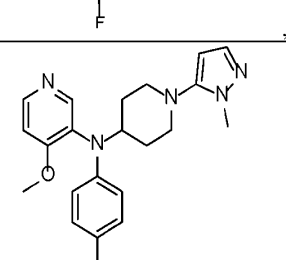
76. The compound of claim 74 or 75, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CD_3$.

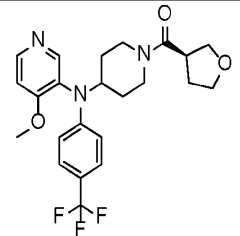
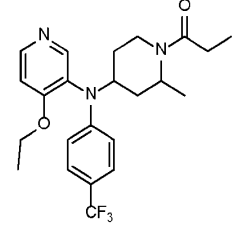
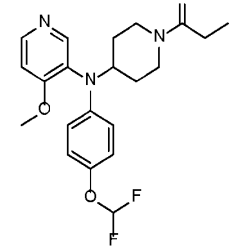
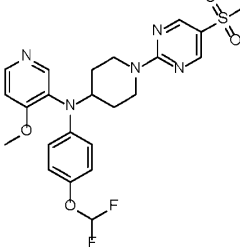
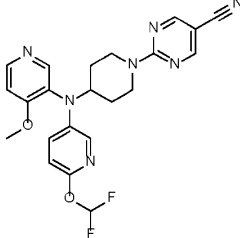
77. The compound of claim 1, 2 or 3, selected from the group consisting of:

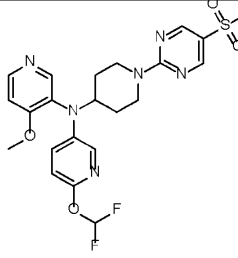
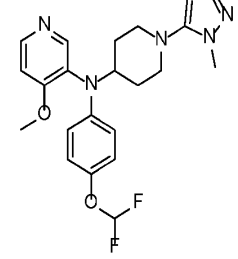
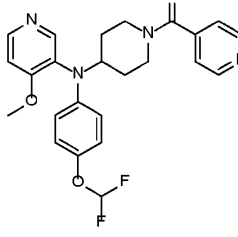
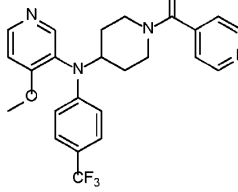
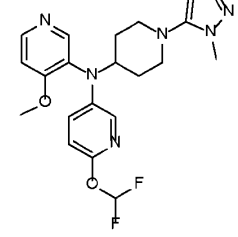
Cpd. No.	Structure
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Cpd. No.	Structure
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Cpd. No.	Structure
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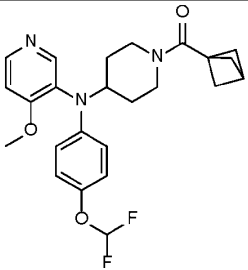
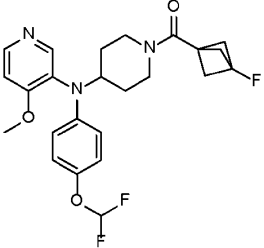
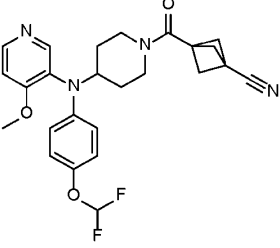
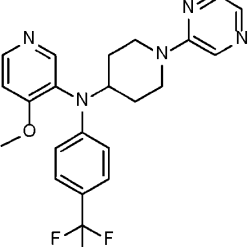
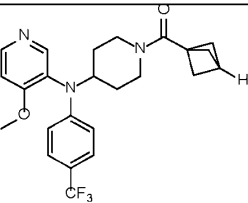
Cpd. No.	Structure
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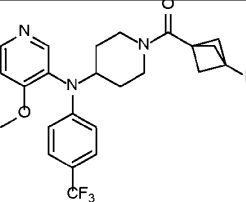
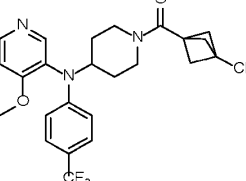
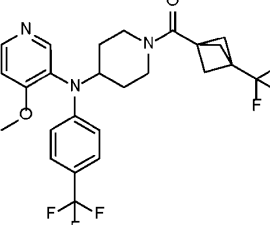
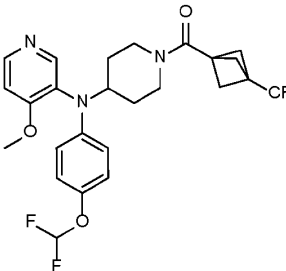
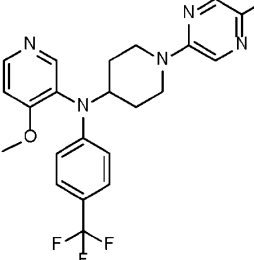
Cpd. No.	Structure
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Cpd. No.	Structure
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Cpd. No.	Structure
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Cpd. No.	Structure
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Cpd. No.	Structure
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Cpd. No.	Structure
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Cpd. No.	Structure
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Cpd. No.	Structure
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Cpd. No.	Structure
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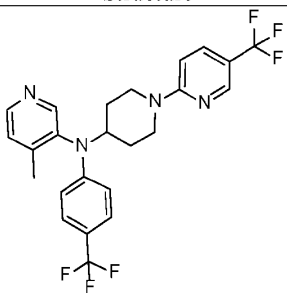
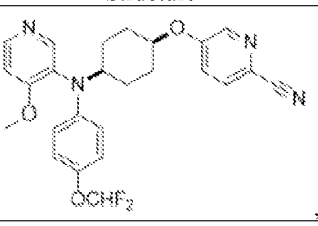
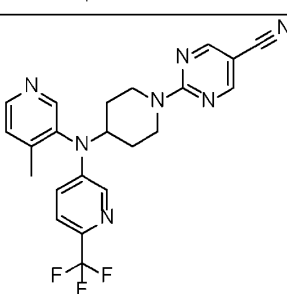
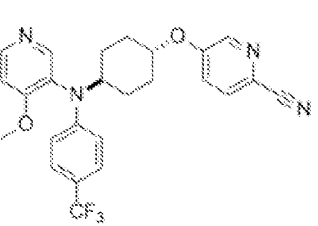
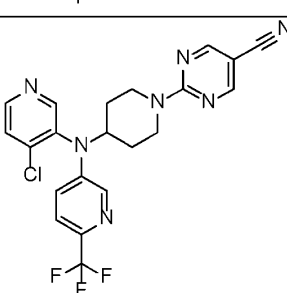
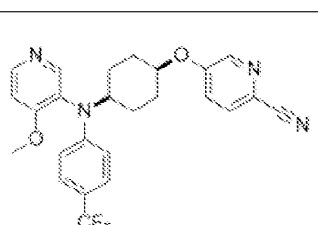
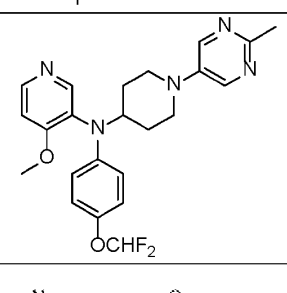
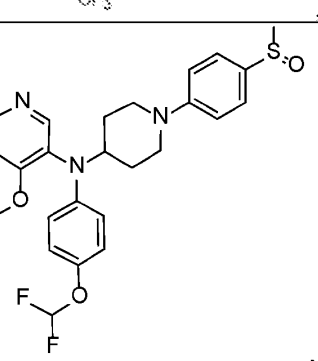
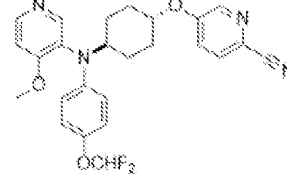
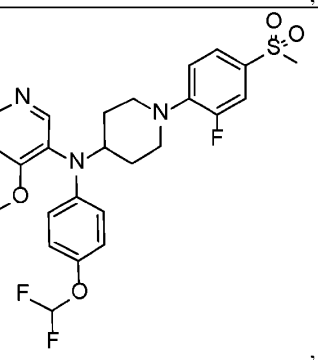
Cpd. No.	Structure
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Cpd. No.	Structure
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or a pharmaceutically acceptable salt or solvate thereof.

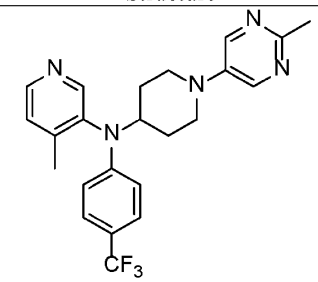
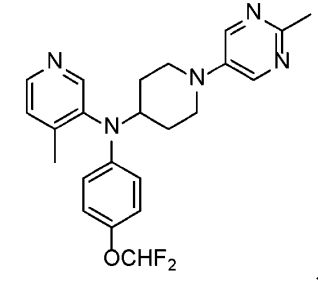
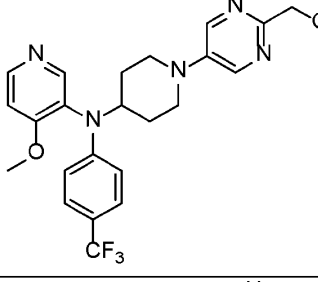
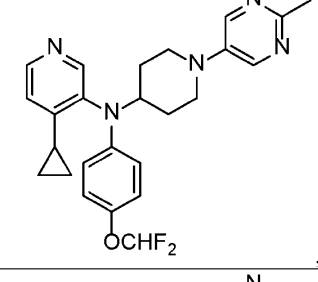
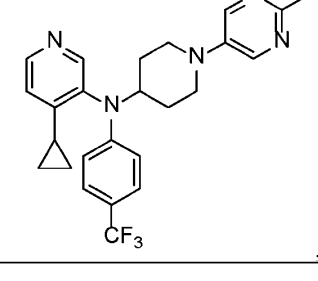
Cpd. No.	Structure
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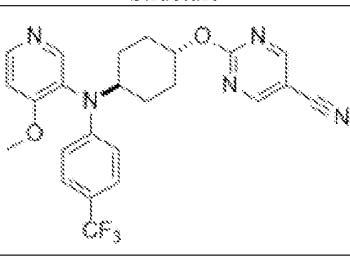
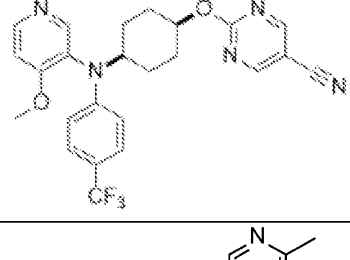
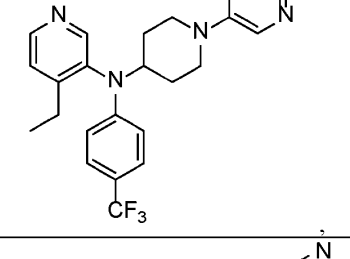
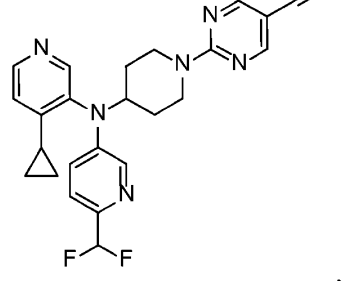
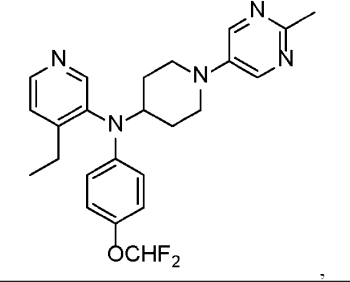
78. The compound of claim 1, selected from the group consisting of:

Cpd. No.	Structure	Cpd. No.	Structure
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101		105-a	
102		105-b	
103		106	
104-a		107	

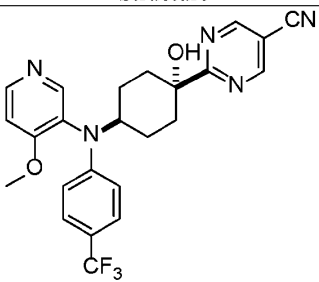
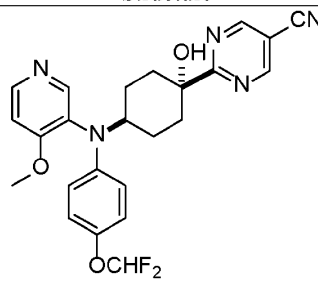
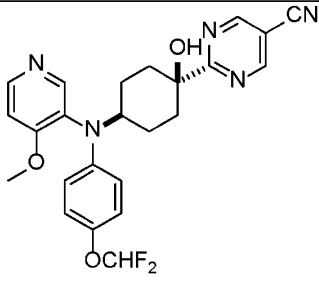
Cpd. No.	Structure
108-a	
108-b	
109	
110	
111-a	

Cpd. No.	Structure
111-b	
112	
113	
114-a	
114-b	

Cpd. No.	Structure
115	
116	
117	
118	
119	

Cpd. No.	Structure
120-a	
120-b	
121	
122	
123	

Cpd. No.	Structure	Cpd. No.	Structure
124		130	
126		131	
127		132	
128		133	
129		134-a	

Cpd. No.	Structure	Cpd. No.	Structure
134-b		135-b	
135-a			

, and
or a pharmaceutically acceptable salt or solvate thereof.

79. A pharmaceutical composition comprising a compound of any one of claims 1-78, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

80. A method of promoting myelination in a subject in need thereof, the method comprising administering to the subject in need thereof a therapeutically effective amount of a compound according to any one of claims 1-78, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 79.

81. A compound of any one of claims 1-78, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 79, for use in treating a disorder in a subject in need thereof.

82. A compound of any one of claims 1-78, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 79, for use in promoting myelination in a subject in need thereof.

83. Use of a compound of any one of claims 1-78, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 79, in the manufacture of a medicament for treating a disorder in a subject in need thereof.

84. Use of a compound of any one of claims 1-78, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 79, in the manufacture of a medicament for promoting myelination in a subject in need thereof.
85. The method of claim 80, wherein the subject has a myelin-related disorder.
86. The compound for use of claim 81 or 82, wherein the subject has a myelin-related disorder.
87. The use of claim 83 or 84, wherein the subject has a myelin-related disorder.
88. The method of claim 85, compound for use of claim 86, or use of claim 87, wherein the myelin-related disorder is multiple sclerosis (MS), neuromyelitis optica (NMO), optic neuritis, pediatric leukodystrophy, neonatal white matter injury, age-related dementia, schizophrenia, progressive multifocal leukoencephalopathy (PML), encephalomyelitis (EPL), central pontine myelolysis (CPM), adrenoleukodystrophy, Alexander's disease, Pelizaeus Merzbacher disease (PMD), Vanishing White Matter Disease, Wallerian Degeneration, transverse myelitis, amyotrophic lateral sclerosis (ALS), Huntington's disease, Alzheimer's disease, Parkinson's disease, spinal cord injury, traumatic brain injury, post radiation injury, neurologic complications of chemotherapy, stroke, acute ischemic optic neuropathy, vitamin E deficiency, isolated vitamin E deficiency syndrome, Bassen-Kornzweig syndrome, Marchiafava-Bignami syndrome, metachromatic leukodystrophy, trigeminal neuralgia, acute disseminated encephalitis, Guillian-Barre syndrome, Charcot-Marie-Tooth disease, Bell's palsy, or radiation-induced demyelination.
89. The method of claim 85, the compound of claim 86, or the use of claim 87, wherein the disorder is multiple sclerosis.
90. A method of inhibiting CYP51 (lanosterol demethylase) comprising, contacting CYP51 with a compound according to any one of claims 1-78, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 79.