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(54) **THERAPEUTICALLY ACTIVE COMPOSITIONS AND THEIR METHODS OF USE**

(75) Inventors: **Sheldon Cao**, San Diego, CA (US); **Janeta Popovici-Muller**, Windham, NH (US); **Francesco G. Salituro**, Marlborough, MA (US); **Jeffrey O. Saunders**, Lincoln, MA (US); **Xuefei Tan**, Shanghai (CN); **Jeremy Travins**, Southborough, MA (US); **Shunqi Yan**, Irvine, CA (US); **Zhixiong Ye**, West Windsor, NJ (US)

(73) Assignee: **AGIOS PHARMACEUTICALS, INC**, Cambridge, MA (US)

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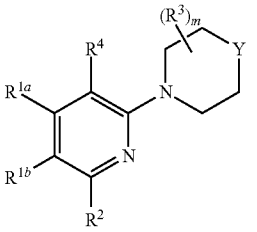
(57) **ABSTRACT**

Provided are compounds with the following structure, formula (I) pharmaceutically acceptable salts thereof, use of those compounds for treating cancer and pharmaceutical compositions comprising those compounds.

(I)



THERAPEUTICALLY ACTIVE COMPOSITIONS AND THEIR METHODS OF USE

CLAIM OF PRIORITY

[0001] This application claims priority from Chinese Patent Application No. CN 201110172169.1, filed Jun. 17, 2011, U.S. Ser. No. 61/509,071, filed Jul. 18, 2011 and U.S. Ser. No. 61/584,210, filed Jan. 6, 2012, each of which is incorporated by reference in its entirety.

BACKGROUND OF INVENTION

[0002] Isocitrate dehydrogenases (IDHs) catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate (i.e., α-ketoglutarate). These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron acceptor and the other NADP(+). Five isocitrate dehydrogenases have been reported: three NAD(+)-dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two NADP(+)-dependent isocitrate dehydrogenases, one of which is mitochondrial and the other predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer.

[0003] IDH1 (isocitrate dehydrogenase 1 (NADP+), cytosolic) is also known as IDH; IDP; IDCD; IDPC or PICD. The protein encoded by this gene is the NADP(+)-dependent isocitrate dehydrogenase found in the cytoplasm and peroxisomes. It contains the PTS-1 peroxisomal targeting signal sequence. The presence of this enzyme in peroxisomes suggests roles in the regeneration of NADPH for intraperoxisomal reductions, such as the conversion of 2,4-dienoyl-CoAs to 3-enoyl-CoAs, as well as in peroxisomal reactions that consume 2-oxoglutarate, namely the alpha-hydroxylation of phytanic acid. The cytoplasmic enzyme serves a significant role in cytoplasmic NADPH production.

[0004] The human IDH1 gene encodes a protein of 414 amino acids. The nucleotide and amino acid sequences for human IDH1 can be found as GenBank entries NM_005896.2 and NP_005887.2 respectively. The nucleotide and amino acid sequences for IDH1 are also described in, e.g., Nekrutenko et al., Mol. Biol. Evol. 15:1674-1684 (1998); Geisbrecht et al., J. Biol. Chem. 274:30527-30533 (1999); Wiemann et al., Genome Res. 11:422-435 (2001); The MGC Project Team, Genome Res. 14:2121-2127(2004); Lubec et al., Submitted (December 2008) to UniProtKB; Kullmann et al., Submitted (June 1996) to the EMBL/GenBank/DDBJ databases; and Sjoeblom et al., Science 314:268-274 (2006).

[0005] Non-mutant, e.g., wild type, IDH1 catalyzes the oxidative decarboxylation of isocitrate to a-ketoglutarate thereby reducing NAD^+ ($NADP^+$) to NADP (NADPH), e.g., in the forward reaction:

$$\text{Isocitrate}+NAD^+(NADP^+)\rightarrow\alpha\text{-KG}+CO_2+NADH\ (NADPH)+H^+.$$

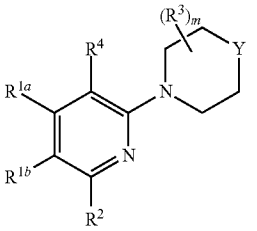
[0006] It has been discovered that mutations of IDH1 present in certain cancer cells result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to R(−)-2-hydroxyglutarate (2HG). 2HG is not formed by wild-type IDH1. The production of 2HG is believed to contribute to the formation and progression of cancer (Dang, L et al, Nature 2009, 462:739-44).

[0007] The inhibition of mutant IDH1 and its neoactivity is therefore a potential therapeutic treatment for cancer. Accordingly, there is an ongoing need for inhibitors of IDH1 mutants having alpha hydroxyl neoactivity.

SUMMARY OF INVENTION

[0008] Described herein are compounds of Structural Formula I:

(I)



or a pharmaceutically acceptable salt thereof, wherein:

[0009] Y is —$N(R^5)$—, —$N(R_5)$—CH_2—, —CH_2—$N(R^5)$—, or —$CH(R^5)$—;

[0010] each R^{1a} and R^{1b} is independently hydrogen, —C_1-C_4 alkyl, —$N(R^7)$(C_1-C_4 alkylene)-$N(R^7)$(C_1-C_4 alkyl), aryl, heteroaryl, heterocyclyl, —$C(O)N(R^7)$-aryl, —$N(R^7)C(O)$-aryl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, —O—(C_0-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-heterocyclyl, —O—(C_0-C_4 alkylene)-carbocyclyl, —$N(R^7)$-aryl, —$N(R^7)$-heteroaryl, —$N(R^9)$-aryl, —$N(R^9)$-heteroaryl, —O—(C_1-C_4 alkeylene)-$N(R^7)C(O)O$—(C_1-C_4 alkylene)-aryl, or —$N(R^9)$—$C(O)$—(C_2-C_4 alkenyl) wherein:

[0011] at least one of R^{1a} and R^{1b} is not hydrogen or methyl; any alkylene moiety present in R^{1a} or R^1 is optionally substituted with OH or F;

[0012] each R^7 is independently selected from hydrogen and C_1-C_4 alkyl; and

[0013] any aryl, carbocyclyl, heteroaryl, or heterocyclyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from -G-L-M, halo, —NO_2, C_1-C_6 alkyl, —C≡N, =O, —CF_3 and —OCF_3;

[0014] G is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by —NR^8—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —$C(=NR^8)$—, —N=N—, or —$C(=N_2)$—;

[0015] L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR^8—, —$N(R^8)C(O)$—, —$C(O)N(R^8)$—, —$N(R^8)SO_2$—, $SO_2N(R^8)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —$C(=NR^8)$—, —N=N—, or —$C(=N_2)$—;

[0016] M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -D-E, oxo, NO_2, halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

[0017] D is a covalent bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched, hydrocarbon chain,

wherein one or two methylene units of D are optionally and independently replaced by —NR^8—, —S—, —O—, —C(O)—, —SO—, or —SO_2—;

[0018] E is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

[0019] each R^8 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, —$S(O)_2$—C_2-C_4 alkenyl, —C_1-C_6 alkoxy, or an optionally substituted group selected from phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

[0020] R^2 is selected from phenyl, a 3-7 membered cycloalkyl, C_2-C_4 alkyl, or CF_3, wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

[0021] each R^3 is independently selected from halo, —(C_1-C_4 alkylene)-O—(C_1-C_4 alkyl), —C_1-C_4 fluoroalkyl, —C(O)—O—(C_1-C_4 alkyl), -phenyl, -heteroaryl, C_3-C_7 cycloalkyl, —CH_2—N(C_1-C_4 alkyl)$_2$, C(O)—N—(C_1-C_4 alkyl)$_2$, —C(O)—NH—(C_1-C_4 alkyl), —C_1-C_4 alkyl optionally substituted with one or more halo or —OH, or two R^3s are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl;

[0022] R^4 is selected from hydrogen, —CN, halo, C_1-C_4 alkoxy, —CH_2NH(C_1-C_4 alkyl), C_2-C_4 alkenyl, C_2-C_4 alkynyl, —(C_1-C_4 alkyl)-O—(C_1-C_4 alkyl), C_1-C_4 fluoroalkyl, C(O)—N—(C_1-C_4 alkyl)$_2$, —C(O)—NH—(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkyl), —C(O)—OH, —$S(O)_2$—(C_1-C_4 alkyl), and a 5-membered heteroaryl;

[0023] R^5 is selected from: —C(O)—(C_1-C_5 alkyl), —C(O)—(C_2-C_6 alkenyl), —C(O)—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_4 alkenylene)-Q, —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_0-C_2 alkylene)-Q, —C(O)—O—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_2 alkylene)-O—(C_0-C_2 alkylene)-Q, —C(O)—C(O)-Q, —$S(O)_2$-Q, —C(O)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_1-C_6 alkyl), —C(O)—(C_0-C_2 alkylene)N(R^6)—(C_2-C_6 alkynyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_2-C_6 alkenyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_0-C_2 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-C(O)C(O)N(R)(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkylene)-O—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-S$(O)_{0\text{-}2}$-(C_1-C_4 alkyl), —$S(O)_2$—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)C(O)N(R^6)(C_1-C_6 alkyl), —C(O)—(C_1-C_4 alkylene)-N(R^6)$S(O)_2$—(C_1-C_6 alkyl), or —C(O)—(C_1-C_4 alkylene)-N(R^6)$S(O)_2$Q, wherein:

[0024] any alkylene moiety present in R^5 is optionally substituted with OCH_3, OH or F;

[0025] any terminal methyl moiety present in R^5 is optionally replaced with —CH_2OH, CF_3, —CH_2F, —CH_2Cl, C(O)CH_3, C(O)CF_3, CN, —OCH_3, —C(O)H, —OP(O)$(OH)_2$, —OP(O)(C_1-C_4 alkoxy)$_2$ or CO_2H;

[0026] each R^6 is independently selected from hydrogen and methyl;

[0027] Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3 substituents independently selected from C_1-C_4 alkyl optionally substituted with —OH, C_1-C_4 alkoxy, —C(O)O—(C_1-C_4 alkyl), —(C_1-C_4 alkylene)-(C_1-C_4 alkoxy), —CN, —OH, fluoro, chloro, and bromo;

[0028] R^9 is selected from aryl and heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one or more substituents selected from -G-L-M, halo, C_1-C_6 alkyl, —C≡N, =O, —CF_3 and —OCF_3; and

[0029] m is 0, 1, 2 or 3.

[0030] The compound of formula I inhibits mutant IDH1, particularly mutant IDH1 having alpha hydroxyl neoactivity. Also described herein are pharmaceutical compositions comprising a compound of formula I or a salt thereof and methods of using such compositions to treat cancers characterized by the presence of a mutant IDH1.

DETAILED DESCRIPTION OF THE INVENTION

[0031] This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

DEFINITIONS

[0032] The term "halo" or "halogen" refers to any radical of fluorine, chlorine, bromine or iodine.

[0033] The term "alkyl" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C_1-C_{12} alkyl indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it. The term "haloalkyl" refers to an alkyl in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkyl). The terms "arylalkyl" or "aralkyl" refer to an alkyl moiety in which an alkyl hydrogen atom is replaced by an aryl group. Aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of "arylalkyl" or "aralkyl" include benzyl, 2-phenylethyl, 3-phenylpropyl, 9-fluorenyl, benzhydryl, and trityl groups.

[0034] The term "alkylene" refers to a divalent alkyl, e.g., —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$— and —$CH_2CH(CH_3)CH_2$—.

[0035] The term "alkenyl" refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and having one or more double bonds. Examples of alkenyl groups include, but are not limited to, allyl, propenyl, 2-butenyl, 3-hexenyl and 3-octenyl groups. One of the double bond carbons may optionally be the point of attachment of the alkenyl substituent.

[0036] The term "alkynyl" refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and characterized in having one or more triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, prop-

argyl, and 3-hexynyl. One of the triple bond carbons may optionally be the point of attachment of the alkynyl substituent.

[0037] The term "alkoxy" refers to an —O-alkyl radical. The term "haloalkoxy" refers to an alkoxy in which one or more hydrogen atoms are replaced by halo, and includes alkoxy moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkoxy).

[0038] The term "aryl" refers to a fully aromatic monocyclic, bicyclic, or tricyclic hydrocarbon ring system. Examples of aryl moieties are phenyl, naphthyl, and anthracenyl. Unless otherwise specified, any ring atom in an aryl can be substituted by one or more substituents.

[0039] The term "carbocyclyl" refers to a non-aromatic, monocyclic, bicyclic, or tricyclic hydrocarbon ring system. Carbocyclyl groups include fully saturated ring systems (e.g., cycloalkyls), and partially saturated ring systems.

[0040] The term "cycloalkyl" as employed herein includes saturated cyclic, bicyclic, tricyclic, or polycyclic hydrocarbon groups having 3 to 12 carbons. Any ring atom can be substituted (e.g., by one or more substituents). Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclohexyl, methylcyclohexyl, adamantyl, and norbornyl.

[0041] The term "heteroaryl" refers to a fully aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (or the oxidized forms such as N^+—O^-, S(O) and $S(O)_2$).

[0042] The term "heterocyclyl" refers to a nonaromatic, 3-10 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (or the oxidized forms such as N^+—O^-, S(O) and $S(O)_2$). The heteroatom may optionally be the point of attachment of the heterocyclyl substituent. Examples of heterocyclyl include, but are not limited to, tetrahydropyranyl, tetrahydropyranyl, piperidinyl, morpholino, pyrrolinyl, pyrimidinyl, and pyrrolidinyl. Heterocyclyl groups include fully saturated ring systems, and partially saturated ring systems.

[0043] Bicyclic and tricyclic ring systems containing one or more heteroatoms and both aromatic and non-aromatic rings where the point of attachment from the ring system to the rest of the molecule is through a non-aromatic ring are considered to be heterocyclyl groups. Bicyclic or tricyclic ring systems where an aryl or a heteroaryl is fused to a carbocyclyl or heterocyclyl and the point of attachment from the ring system to the rest of the molecule is through an aromatic ring are considered to be aryl or heteroaryl groups.

[0044] Aryl, heteroaryl, carbocyclyl (including cycloalkyl), and heterocyclyl groups, either alone or a part of a group (e.g., the aryl portion of an aralkyl group), are optionally substituted at one or more substitutable atoms with, unless specified otherwise, substituents independently selected from: halo, —CN, C_1-C_4 alkyl, =O, —OR^b, —$OR^{b'}$, —SR^b, —$SR^{b'}$, —(C_1-C_4 alkyl)-$N(R^b)(R^b)$, —(C_1-C_4 alkyl)-$N(R^b)(R^{b'})$, —$N(R^b)(R^b)$, —$N(R)(R^{b'})$, —O—(C_1-C_4 alkyl)-$N(R^b)(R^b)$, —O—(C_1-C_4 alkyl)-$N(R^b)(R^{b'})$, —(C_1-C_4 alkyl)-O—(C_1-C_4 alkyl)-$N(R^b)(R^b)$, —(C_1-C_4 alkyl)-O—(C_1-C_4 alkyl)-$N(R^b)(R^{b'})$, —C(O)—$N(R^b)(R^b)$, —(C_1-C_4 alkyl)-C(O)—$N(R^b)(R^b)$, —(C_1-C_4 alkyl)-C(O)—$N(R^b)(R^{b'})$, —$OR^{b'}$, $R^{b'}$, —C(O)(C_1-C_4 alkyl), —C(O)$R^{b'}$, —C(O)$N(R^{b'})(R^b)$, —$N(R^b)C(O)(R^b)$, —$N(R^b)C(O)(R^{b'})$, —$N(R^b)SO_2(R^b)$, —$SO_2N(R^b)(R^b)$, —$N(R^b)SO_2(R^{b'})$, and —$SO_2N(R^b)(R^{b'})$, wherein any alkyl substituent is optionally further substituted with one or more of —OH, —O—(C_1-C_4 alkyl), halo, —NH_2, —NH(C_1-C_4 alkyl), or —N(C_1-C_4 alkyl)$_2$;

[0045] each R^b is independently selected from hydrogen, and —C_1-C_4 alkyl; or

[0046] two R^bs are taken together with the nitrogen atom to which they are bound to form a 4- to 8-membered heterocyclyl optionally comprising one additional heteroatom selected from N, S, and O; and

[0047] each $R^{b'}$ is independently selected from C_3-C_7 carbocylyl, phenyl, heteroaryl, and heterocyclyl, wherein one or more substitutable positions on said phenyl, cycloalkyl, heteroaryl or heterocycle substituent is optionally further substituted with one or more of —(C_1-C_4 alkyl), —(C_1-C_4 fluoroalkyl), —OH, —O—(C_1-C_4 alkyl), —O—(C_1-C_4 fluoroalkyl), halo, —NH_2, —NH(C_1-C_4 alkyl), or —N(C_1-C_4 alkyl)$_2$.

[0048] Heterocyclyl groups, either alone or as part of a group, are optionally substituted on one or more any substitutable nitrogen atom with oxo, —C_1-C_4 alkyl, or fluoro-substituted C_1-C_4 alkyl.

[0049] The term "substituted" refers to the replacement of a hydrogen atom by another group.

[0050] As used herein, the term "elevated levels of 2HG" means 10%, 20% 30%, 50%, 75%, 100%, 200%, 500% or more 2HG then is present in a subject that does not carry a mutant IDH1 allele. The term "elevated levels of 2HG" may refer to the amount of 2HG within a cell, within a tumor, within an organ comprising a tumor, or within a bodily fluid.

[0051] The term "bodily fluid" includes one or more of amniotic fluid surrounding a fetus, aqueous humour, blood (e.g., blood plasma), serum, Cerebrospinal fluid, cerumen, chyme, Cowper's fluid, female ejaculate, interstitial fluid, lymph, breast milk, mucus (e.g., nasal drainage or phlegm), pleural fluid, pus, saliva, sebum, semen, serum, sweat, tears, urine, vaginal secretion, or vomit.

[0052] As used herein, the terms "inhibit" or "prevent" include both complete and partial inhibition and prevention. An inhibitor may completely or partially inhibit the intended target.

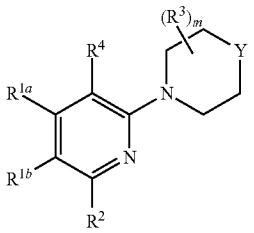
[0053] The term "treat" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease/disorder (e.g., a cancer), lessen the severity of the disease/disorder (e.g., a cancer) or improve the symptoms associated with the disease/disorder (e.g., a cancer).

[0054] As used herein, an amount of a compound effective to treat a disorder, or a "therapeutically effective amount" refers to an amount of the compound which is effective, upon single or multiple dose administration to a subject, in treating a cell, or in curing, alleviating, relieving or improving a subject with a disorder beyond that expected in the absence of such treatment.

[0055] As used herein, the term "subject" is intended to include human and non-human animals. Exemplary human subjects include a human patient (referred to as a patient) having a disorder, e.g., a disorder described herein or a normal subject. The term "non-human animals" of the invention includes all vertebrates, e.g., non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, e.g., sheep, dog, cat, cow, pig, etc.

Compounds

[0056] Provided is a compound of Structural Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

[0057] Y is —N(R^5)—, —N(R_5)—CH_2—, —CH_2—N(R^5)—, or —CH(R^5)—;

[0058] each R^{1a} and R^{1b} is independently hydrogen, —C_1-C_4 alkyl, —N(R^7)(C_1-C_4 alkylene)-N(R^7)(C_1-C_4 alkyl), aryl, heteroaryl, heterocyclyl, —C(O)N(R^7)-aryl, —N(R^7)C(O)-aryl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, —O—(C_0-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-heterocyclyl, —O—(C_0-C_4 alkylene)-carbocyclyl, —N(R^7)-aryl, —N(R^7)-heteroaryl, —N(R^9)-aryl, —N(R^9)-heteroaryl, —O—(C_1-C_4 alkeylene)-N(R^7)C(O)O—(C_1-C_4 alkylene)-aryl, or —N(R^9)—C(O)—(C_2-C_4 alkenyl) wherein:

[0059] at least one of R^{1a} and R^{1b} is not hydrogen or methyl;

[0060] any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;

[0061] each R^7 is independently selected from hydrogen and C_1-C_4 alkyl; and

[0062] any aryl, carbocyclyl, heteroaryl, or heterocyclyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from -G-L-M, halo, —NO_2, C_1-C_6 alkyl, —C≡N, =O, —CF_3 and —OCF_3;

[0063] G is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by —NR^8—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR^8)—, —N=N—, or —C(=N_2)—;

[0064] L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR^8—, —N(R^8)C(O)—, —C(O)N(R^8)—, —N(R^8)SO_2—, SO_2N(R^8)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR^8)—, —N=N—, or —C(=N_2)—;

[0065] M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -D-E, oxo, NO_2, halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

[0066] D is a covalent bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by —NR^8—, —S—, —O—, —C(O)—, —SO—, or —SO_2—;

[0067] E is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

[0068] each R^8 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, —C_1-C_6 alkoxy, —$S(O)_2$—C_2-C_4 alkenyl, or an optionally substituted group selected from phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

[0069] R^2 is selected from phenyl, a 3-7 membered cycloalkyl, C_2-C_4 alkyl, or CF_3, wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

[0070] each R^3 is independently selected from halo, —(C_1-C_4 alkylene)-O—(C_1-C_4 alkyl), —C_1-C_4 fluoroalkyl, —C(O)—O—(C_1-C_4 alkyl), -phenyl, -heteroaryl, C_3-C_7 cycloalkyl, —CH_2—N(C_1-C_4 alkyl)$_2$, C(O)—N—(C_1-C_4 alkyl)$_2$, —C(O)—NH—(C_1-C_4 alkyl), —C_1-C_4 alkyl optionally substituted with one or more halo or —OH, or two R^5 are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl;

[0071] R^4 is selected from hydrogen, —CN, halo, C_1-C_4 alkoxy, —CH_2NH(C_1-C_4 alkyl), C_2-C_4 alkenyl, C_2-C_4 alkynyl, —(C_1-C_4 alkyl)-O—(C_1-C_4 alkyl), C_1-C_4 fluoroalkyl, C(O)—N—(C_1-C_4 alkyl)$_2$, —C(O)—NH—(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkyl), —C(O)—OH, —$S(O)_2$—(C_1-C_4 alkyl), and a 5-membered heteroaryl;

[0072] R^5 is selected from: —C(O)—(C_1-C_5 alkyl), —C(O)—(C_2-C_6 alkenyl), —C(O)—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_4 alkenylene)-Q, —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_0-C_2 alkylene)-Q, —C(O)—O—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_2 alkylene)-O—(C_0-C_2 alkylene)-Q, —C(O)—C(O)-Q, —$S(O)_2$-Q, —C(O)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_1-C_6 alkyl), —C(O)—(C_0-C_2 alkylene)N(R^6)—(C_2-C_0 alkynyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_2-C_6 alkenyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_0-C_2 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-C(O)C(O)N(R)(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkylene)-O—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-$S(O)_{0-2}$-(C_1-C_4 alkyl), —$S(O)_2$—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)C(O)N(R^6)(C_1-C_6 alkyl), —C(O)—(C_1-C_4 alkylene)-N(R^6)$S(O)_2$—(C_1-C_6 alkyl), or —C(O)—(C_1-C_4 alkylene)-N(R^6)$S(O)_2$Q, wherein:

[0073] any alkylene moiety present in R^5 is optionally substituted with OCH_3, OH or F;

[0074] any terminal methyl moiety present in R^5 is optionally replaced with —CH_2OH,

[0075] CF_3, —CH_2F, —CH_2Cl, C(O)CH_3, C(O)CF_3, CN, —OCH_3, —C(O)H, —OP(O)$(O)_2$, —OP(O)(C_1-C_4 alkoxy)$_2$ or CO_2H;

[0076] each R^6 is independently selected from hydrogen and methyl;

[0077] Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3

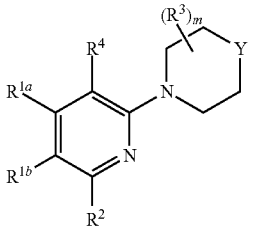
substituents independently selected from C_1-C_4 alkyl optionally substituted with —OH, C_1-C_4 alkoxy, —C(O)O—(C_1-C_4 alkyl), —(C_1-C_4 alkylene)-(C_1-C_4 alkoxy), —CN, —OH, fluoro, chloro, and bromo;

[0078] R^9 is selected from aryl, and heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one or more substituents selected from -G-L-M, halo, C_1-C_6 alkyl, —C≡N, =O, —CF_3 and —OCF_3; and

[0079] m is 0, 1, 2 or 3.

[0080] In some embodiments, provided is a compound of Structural Formula I:

(I)



or a pharmaceutically acceptable salt thereof, wherein:

[0081] Y is —N(R^5)— or —CH(R^5)—;

[0082] each R^{1a} and R^{1b} is independently hydrogen, —C_1-C_4 alkyl, —N(R^7)(C_1-C_4 alkylene)-N(R^7)(C_1-C_4 alkyl), aryl, heteroaryl, heterocyclyl, —C(O)N(R^7)-aryl, —N(R^7)C(O)-aryl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_1-C_4 alkylene)-aryl, —O—(C_1-C_4 alkylene)-heteroaryl, —O—(C_1-C_4 alkylene)-heterocyclyl, —N(R^7)-aryl, or —N(R^7)-heteroaryl, wherein:

[0083] at least one of R^{1a} and R^{1b} is not hydrogen or methyl;

[0084] any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;

[0085] each R^7 is independently selected from hydrogen and C_1-C_4 alkyl; and

[0086] any aryl, heteroaryl, or hetercylyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from -G-L-M, halo, C_1-C_6 alkyl, —C≡N, =O, —CF_3 and —OCF_3;

[0087] G is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by —NR^8—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR^8)—, —N=N—, or —C(=N_2)—;

[0088] L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —NR^8—, —N(R^8)C(O)—, —C(O)N(R^8)—, —N(R^8)SO_2—, SO_2N(R^8)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR^8)—, —N=N—, or —C(=N_2)—; M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -D-E, oxo, NO_2, halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

[0089] D is a covalent bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by —NR^8—, —S—, —O—, —C(O)—, —SO—, or —SO_2—;

[0090] E is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

[0091] each R^8 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or an optionally substituted group selected from phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

[0092] R^2 is selected from phenyl, a 3-7 membered cycloalkyl, and C_2-C_4 alkyl, wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

[0093] each R^3 is independently selected from —C_1-C_4 alkyl, —(C_1-C_4 alkyl)-O—(C_1-C_4 alkyl), —C_1-C_4 fluoroalkyl, —C(O)—O—(C_1-C_4 alkyl), -phenyl, -heteroaryl, C_3-C_7 cycloalkyl, —CH_2—N(C_1-C_4 alkyl)$_2$, C(O)—N—(C_1-C_4 alkyl)$_2$, and —C(O)—NH—(C_1-C_4 alkyl), or

[0094] or two R^3s are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl groups;

[0095] R^4 is selected from hydrogen, —CN, halo, C_1-C_4 alkoxy, —CH_2NH(C_1-C_4 alkyl), C_2-C_4 alkenyl, C_2-C_4 alkynyl, —(C_1-C_4 alkyl)-O—(C_1-C_4 alkyl), C_1-C_4 fluoroalkyl, C(O)—N—(C_1-C_4 alkyl)$_2$, —C(O)—NH—(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkyl), —C(O)—OH, —S(O)$_2$—(C_1-C_4 alkyl), and a 5-membered heteroaryl;

[0096] R^5 is selected from: —C(O)—(C_1-C_4alkyl), —C(O)—(CH_2)$_{0-2}$-Q, —C(O)—(CH_2)$_{0-2}$—N(R^6)—(CH_2)$_{0-2}$-Q, —C(O)—O—(CH_2)$_{1-2}$-Q, —C(O)—(CH_2)$_{1-2}$—O—(CH_2)$_{0-2}$-Q, —C(O)—C(O)-Q, —S(O)$_2$-Q, —C(O)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—(CH_2)$_{0-2}$—N(R^6)—(C_1-C_6 alkyl), —C(O)—(CH_2)$_{0-2}$—N(R^6)—(C_2-C_6 alkynyl), —C(O)—(CH_2)$_{0-2}$—N(R^6)—(C_2-C_6 alkenyl), —C(O)—(CH_2)$_{0-2}$—N(R^6)—(CH_2)$_{0-2}$—O—(C_1-C_4 alkyl), —C(O)—(CH_2)$_{1-2}$—O—(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkylene)-O—(C_1-C_4 alkyl), —(CH_2)$_{04}$—O—C(O)—(C_1-C_4 alkyl), —(CH_2)$_{0-4}$—C(O)—O—(C_1-C_4 alkyl), —(CH_2)$_{0-4}$—O—(C_1-C_4 alkyl), —C(O)—(CH_2)$_{1-2}$—S—(C_1-C_4 alkyl), —S(O)$_2$—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)C(O)N(R^6)(C_1-C_6 alkyl), —C(O)—(C_1-C_4 alkylene)-N(R^6)S(O)$_2$—(C_1-C_6 alkyl), and —C(O)—(C_1-C_4 alkylene)-N(R^6)S(O)$_2$Q, wherein:

[0097] any alkylene moiety present in R^5 is optionally substituted with OH or F;

[0098] any terminal methyl moiety present in R^5 is optionally replaced with —CH_2OH, CF_3, —CH_2F, —CH_2Cl, C(O)CH_3, or C(O)CF_3;

[0099] each R^6 is independently selected from hydrogen and methyl;

[0100] Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3

substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, —CN, fluoro, chloro, and bromo; and

[0101] m is 0, 1, 2 or 3.

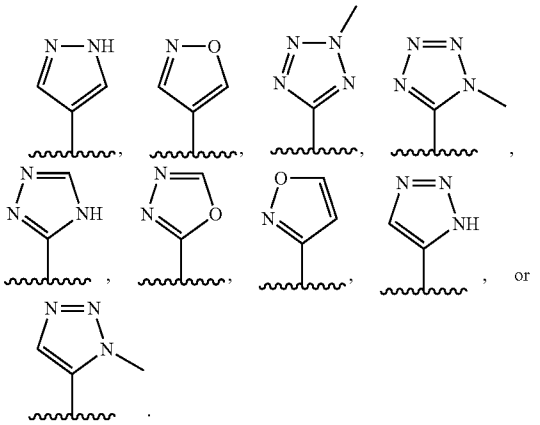
[0102] In some embodiments, m is 0, 1 or 2; and each R^3, if present, is independently selected from methyl, ethyl, CF_3, isopropyl, cyclopropyl and phenyl. In some embodiments, R^3 is methyl or cyclopropyl. In some embodiments, R^3 is methyl. In some embodiments, R^3 is cyclopropyl.

[0103] In some embodiments, m is 1. In some embodiments, m is 2.

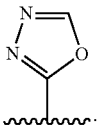
[0104] In some embodiments, m is 1 and R^3 is C_{3-7} cycloalkyl (e.g., cyclopropyl). In some embodiments, m is 1 and R^3 is C_1-C_4 (alkyl) (e.g., methyl or isopropyl). In some embodiments, m is 1 and R^3 is haloalkyl (e.g., C_1-C_4 fluoroalkyl, e.g., CF_3). In some embodiments, m is 2, one R^3 is C_{1-4} alkyl (e.g., methyl) and the other R^3 is halo (e.g., fluoro).

[0105] In some embodiments, R^4 is —CN or —C(O)—O—(C_1-C_4 alkyl). In some embodiments, R^4 is CN.

[0106] In some embodiments, R^4 is:



In some embodiments, R^4 is



[0107] In some embodiments, Y is —$N(R_5)$—CH_2— or —CH_2—$N(R^5)$—; R^5 is —C(O)-Q and Q is cyclopropyl.

[0108] In some embodiments, Y is —$N(R^5)$—; R^5 is —$C(O)R^{10}$; and R^{10} is selected from heteroaryl, aryl, —CH_2-aryl, —CH_2-heteroaryl, and —$(CH_2)_2$—O—CH_3, wherein any aryl or heteroaryl portion of R^8 is optionally substituted with methyl.

[0109] In some embodiments, Y is —$N(R^5)$—; R^5 is selected from selected from: —C(O)—(C_1-C_5 alkyl), —C(O)—(C_2-C_6 alkenyl), —C(O)—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_4 alkenylene)-Q, —C(O)-(C_0-C_2 alkylene)-$N(R^6)$—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_2 alkylene)-O—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—(C_0-C_2 alkylene)-$N(R^6)$—(C_1-C_6 alkyl), —C(O)—(C_0-C_2 alkylene)$N(R^6)$—(C_2-C_6 alkynyl), —C(O)—(C_0-C_2 alkylene)-$N(R^6)$—(C_2-C_6 alkenyl), —C(O)—(C_0-C_2 alkylene)-$N(R^6)$—(C_0-C_2 alkylene)-O—(C_1-C_4 alkyl), —(C_0 alkylene)-C(O)O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-C(O)C(O)N(R)(C_1-C_4 alkyl), or —C(O)—(C_1-C_4 alkylene)-C(O)C(O)$N(R^6)$(C_1-C_6 alkyl), wherein:

[0110] any alkylene moiety present in R^5 is optionally substituted with OCH_3, OH or F;

[0111] any terminal methyl moiety present in R^5 is optionally replaced with —CH_2OH, CF_3, —CH_2F, —CH_2Cl, $C(O)CH_3$, $C(O)CF_3$, CN, —OCH_3, —C(O)H, —$OP(O)(OH)_2$, —$OP(O)(C_1$-C_4 alkoxy$)_2$ or CO_2H;

[0112] each R^6 is independently selected from hydrogen and methyl;

[0113] Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with up to 3 substituents independently selected from C_1-C_4 alkyl optionally substituted with OH, C_1-C_4 alkoxy, —C(O)O—(C_1-C_4 alkyl), —(C_1-C_4 alkylene)-(C_1-C_4 alkoxy), —CN, —OH, fluoro, chloro, and bromo.

[0114] In some embodiments, Y is —$N(R^5)$—; and R^5 is —C(O)—(C_1-C_3 alkyl)-O—(C_1-C_2 alkyl), —C(O)-Q, —C(O)—(C_1-C_5 alkyl), —C(O)—(C_1-C_2 alkylene)-Q, —C(O)—(C_2-C_4 alkenyl), —C(O)O—(C_1-C_4 alkyl), or —C(O)—(C_1-C_4 alkenylene)-Q; wherein: any alkylene moiety present in R^5 is optionally substituted with OH; any terminal methyl moiety present in R^5 is optionally replaced with —OH, CF_3, OCH_3, —C(O)H, $OP(O)(C_1$-C_4 alkoxy$)_2$, or —$OP(O)(OH)_2$ (or a salt thereof, such as a sodium salt); Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with one substituent independently selected from C_1-C_4 alkyl optionally substituted with OH, C_1-C_4 alkoxy, —(C_1-C_4 alkylene)-(C_1-C_4 alkoxy), and —OH.

[0115] In some embodiments, Y is —$N(R^5)$—; and R^5 is —C(O)—(C_1-C_3 alkyl)-O—(C_1-C_2 alkyl). In some embodiments, Y is —$N(R^5)$—; and R^5 is —C(O)—$(CH_2)_2$—OCH_3. In some embodiments, Y is —$N(R^5)$— and R^5 is —C(O)—(C_1-C_3 alkyl)-CF_3. In some embodiments, Y is —$N(R^5)$— and R^5 is —C(O)—CH_2—CF_3. In some embodiments, Y is —$N(R^5)$—; R^5 is —C(O)-Q and Q is cyclopropyl, oxetanyl or furanyl. In some embodiments, Y is —$N(R^5)$— and R^5 is —C(O)—CH_2—CH_2OH. In some embodiments, Y is —$N(R^5)$—; R^5 is —C(O)-Q where Q is substituted with C_{1-4} alkoxy. In some embodiments, Y is —$N(R^5)$— and R^5 is —C(O)-cyclopropyl substituted with C_{1-4} alkoxy (e.g., ethoxy). In some embodiments, Y is —$N(R^5)$— and R^5 is —C(O)—OCH_3. In some embodiments, Y is —$N(R^5)$— and R^5—C(O)-Q where Q is substituted with (C_{1-4} alkylene)-OCH_3. In some embodiments, Y is —$N(R^5)$— and R^5—C(O)-cyclopropyl substituted with CH_2OCH_3. In some embodiments, Y is —$N(R^5)$— and R^5—C(O)-Q where Q is substituted with C_{1-4} alkyl wherein alkyl is optionally substituted with —OH. In some embodiments, Y is —$N(R^5)$— and R^5—C(O)-cyclopropyl substituted with CH_2OH. In some embodiments, Y is —$N(R^5)$—; R^5 is —C(O)-Q where Q is substituted with OH. In some embodiments, Y is —$N(R^5)$—; R^5 is —C(O)-cyclopropyl substituted with OH. In some embodiments, Y is —$N(R^5)$—; R^5 is —C(O)—(C_{1-4} alkyl)-OH. In some embodiments, Y is —$N(R^5)$—; R^5 is —C(O)—$CH_2C(OH)(CH_3)_2$. In some embodiments, Y is —$N(R^5)$—; R^5 is —C(O)—$CH_2CH(OH)CH_3$. In some embodiments, Y is

—N(R^5)—; R^5 is —C(O)—$CH_2CH_2CH_2OH$. In some embodiments, Y is —N(R^5)—; R^5 is —C(O)—CH_2CH_2OH. In some embodiments, Y is —N(R^5)—; and R^5 is —C(O)—(C_1-C_4 alkyl). In some embodiments, Y is —N(R^5)—; and R^5 is —C(O)—CH_3. In some embodiments, Y is —N(R^5)—; R^5 is —C(O)—(C_{1-4} alkyl)-$(OCH_3)_2$. In some embodiments, Y is —N(R^5)—; R^5 is —C(O)—$CH_2CH_2C(H)(OCH_3)_2$. In some embodiments, Y is —N(R^5)—; R^5 is —C(O)—(C_{1-4} alkyl)-C(O)H. In some embodiments, Y is —N(R^5)—; R^5 is —C(O)—$CH_2CH_2C(O)H$. In some embodiments, Y is —N(R^5)—; R^5 is —C(O)—C(cyclopropyl)(OH). In some embodiments, Y is —N(R^5)—; R^5 is —C(O)—(C_{1-4} alkyl)-$C(O)OCH_3$. In some embodiments, Y is —N(R^5)—; R^5 is —C(O)—$CH_2CH_2C(O)OCH_3$. In some embodiments, Y is —N(R^5)— and R^5 is —C(O)—(C_0-C_2 alkylene)-Q. In some embodiments, Y is —N(R^5)— and R^5 is —C(O)—(C_0-C_2 alkylene)-Q, where Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl. In some embodiments, Y is —N(R^5)— and R^5 is —C(O)—CH_2-oxetanyl, —C(O)—CH_2-azetidinonyl, —C(O)—CH_2-pyrrolidinonyl, —C(O)—CH_2-cyclobutyl, —C(O)—CH_2-cyclopropyl, —C(O)—CH_2CH_2-cyclopropyl, —C(O)—CH_2-tetrahydrofuranyl, —C(O)—CH_2-dihydrofuranone, —C(O)—CH_2CH_2-oxetanyl, —C(O)—CH_2CH_2-furanyl, —C(O)—CH_2-ietrahydrofuranyl, —C(O)—CH_2CH_2-tetrahydrofuranyl or —C(O)—CH_2-cyclopentyl. In some embodiments, Y is —N(R^5)— and R^5 is —C(O)—(C_2-C_4 alkenyl)-OH. In some embodiments, Y is —N(R^5)— and R^5 is —C(O)—CH=CH—CH_2CH_2OH. In some embodiments, Y is —N(R^5)— and R^5—(C_0-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl). In some embodiments, Y is —N(R^5)— and R^5—C(O)—O-(t-butyl). In some embodiments, Y is —N(R^5)— and R^5—C(O)—(C_1-C_4 alkyl)-OP(O)(C_1-C_4 alkoxy)$_2$. In some embodiments, Y is —N(R^5)— and R^5—C(O)—$CH_2CH_2CH_2$—OP(O)(t-butoxy)$_2$. In some embodiments, Y is —N(R^5)— and R^5—C(O)—(C_1-C_4 alkyl)-$OP(O)(OH)_2$ or a salt thereof, such as a sodium salt. In some embodiments, Y is —N(R^5)— and R^5—C(O)—CH_2CH_2—OP(O)(t-butoxy)$_2$. In some embodiments, Y is —N(R^5)—; and R^5 is —C(O)—(C_1-C_5 alkyl). In some embodiments, Y is —N(R^5)—; and R^5 is —C(O)-pentyl. In some embodiments, Y is —N(R^5)—; and R^5—C(O)—(C_1-C_4 alkenylene)-Q. In some embodiments, Y is —N(R^5)—; and R^5—C(O)—CH=cyclobutyl.

[0116] In some embodiments, one of R^{1a} or R^{1b} is selected from hydrogen and methyl; and the other of R^{1a} or R^{1b} is selected from isopropyl, —N(CH_3)—$(CH_2)_2$—NH—CH_3, aryl, heteroaryl, —CH_2-aryl, —CH_2-heteroaryl, —O—CH_2-aryl, and —O—CH_2-heteroaryl; wherein any aryl or heteroaryl of R^{1a} or R^{1b} is optionally substituted with one or more substituents independently selected from alkoxy, OH, halo, C_1-C_6 alkyl, —CF_3, CN, —OC(O)CH_3, and —OCF_3.

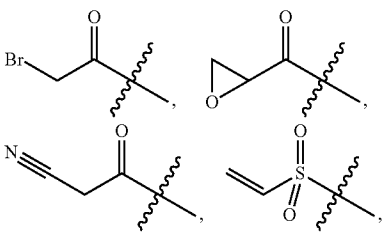
[0117] In some embodiments, one of R^{1a} or R^{1b} is selected from hydrogen and methyl; and the other of R^{1a} or R^{1b} is selected from aryl, heteroaryl, heterocyclyl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, —O—(C_0-C_4 alkylene)-heteroaryl, —N(R^7)-aryl, —N(R^7)heteroaryl, —N(R^9)-aryl, or —N(R^9)-heteroaryl, wherein said aryl, heterocyclyl, or heteroaryl is substituted with -G-L-M, CH_3, CN, alkoxy, OH, halo, C_1-C_6 alkyl, —CF_3, —OC(O)CH_3, or —OCF_3.

[0118] In some embodiments, one of R^{1a} or R^{1b} is selected from hydrogen and methyl; and the other of R^{1a} or R^{1b} is selected from aryl, heteroaryl, heterocyclyl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, —O—(C_0-C_4 alkylene)-heteroaryl, —N(R^7)-aryl, —N(R^7)heteroaryl, —N(R^9)-aryl, —N(R^9)-heteroaryl, wherein said aryl or heteroaryl is substituted with -G-L-M, CH_3, or CN.

[0119] In some embodiments, R^{1a} is H and R^{1b} is aryl, heteroaryl, heterocyclyl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, or —O—(C_0-C_4 alkylene)-heteroaryl, —N(R^7)-aryl, —N(R^7)heteroaryl, —N(R^9)-aryl, —N(R^9)-heteroaryl, wherein said aryl or heteroaryl is substituted with -G-L-M, CH_3, or CN. In some aspects of the preceding embodiments, R^{1a} is H and R^{1b} is aryl, heteroaryl, heterocyclyl, —CH_2-aryl, —CH_2-heteroaryl, -D-aryl, —O-heteroaryl, —O—(CH_2)-aryl, —O—$CH(CH_3)$-aryl, —O$(CH)(C(CH_3)_2)$-aryl, —O—$CH(CH_2CH_3)$-aryl, —NH-aryl, —NH-heteroaryl, —N(CH_3)-aryl, —N(CH_3)-heteroaryl, —N(aryl)-aryl, —N(heteroaryl)-heteroaryl, —O—(CH_2)-heteroaryl or —O—$CH(CH_3)$-heteroaryl, wherein aryl is phenyl, heteroaryl is pyridyl, pyrimidinyl, naphthyridinyl, quinolyl, isoquinolyl, isoxazolyl, benzoxazolyl, imidazopyrazinyl, benzothiazolyl, benzimidazolyl, pyrollopyridinyl, pyrazolopyridinyl, indolyl, indazolyl, imidazopyridinyl, quinoxalinyl, quinazolinyl, pyridazinyl or pyrazolyl, and heterocyclyl is benzodioxole, pyridazinone, benzoxazolone, indolinone, N-methylindolinone, piperazinyl, N-methylisoquinolinone, tetrahydropyridinyl, dihydropyrrolyl and said phenyl, pyridyl, pyrimidinyl, naphthyridinyl, quinolyl, isoquinolyl, isoxazolyl, benzoxazolyl, imidazopyrazinyl, benzothiazolyl, benzimidazolyl, pyrollopyridinyl, pyrazolopyridinyl, indolyl, indazolyl, imidazopyridinyl, quinoxalinyl, quinazolinyl, pyridazinyl, pyrazolyl, benzodioxole, pyridazinone, benzoxazolone, indolinone, N-methylindolinone, piperazinyl, N-methylisoquinolinone, tetrahydropyridinyl, or dihydropyrrolyl is substituted with -G-L-M, —CF_3, —OCF_3, halo (e.g., fluoro, chloro or bromo), CH_3, or CN.

[0120] In some embodiments, R^{1a} is methyl and R^{1b} is aryl, heteroaryl, heterocyclyl, —O—(C_0-C_4 alkylene)-aryl, or —O—(C_0-C_4 alkylene)-heteroaryl, wherein said aryl or heteroaryl is substituted with -G-L-M, CH_3, or CN. In some aspects of the preceding embodiments, R^{1a} is methyl or H and R^{1b} is aryl, heteroaryl, heterocyclyl, —O—(CH_2)-aryl, —O—$CH(CH_3)$-aryl, —O—(CH_2)-heteroaryl or —O—$CH(CH_3)$-heteroaryl, wherein aryl is phenyl or naphthyl and heteroaryl is quinolinyl, pyrazolyl, isoquinolinyl, pyridyl, pyrimidinyl, indolyl, or pyrazolyl, and heterocyclyl is tetrahydropyridinyl and said phenyl, pyridyl, pyrimidinyl, indolyl, or pyrazolyl is substituted with -G-L-M, halo (e.g., chloro or fluoro), CH_3, or CN.

[0121] In some embodiments, -G-L-M is:



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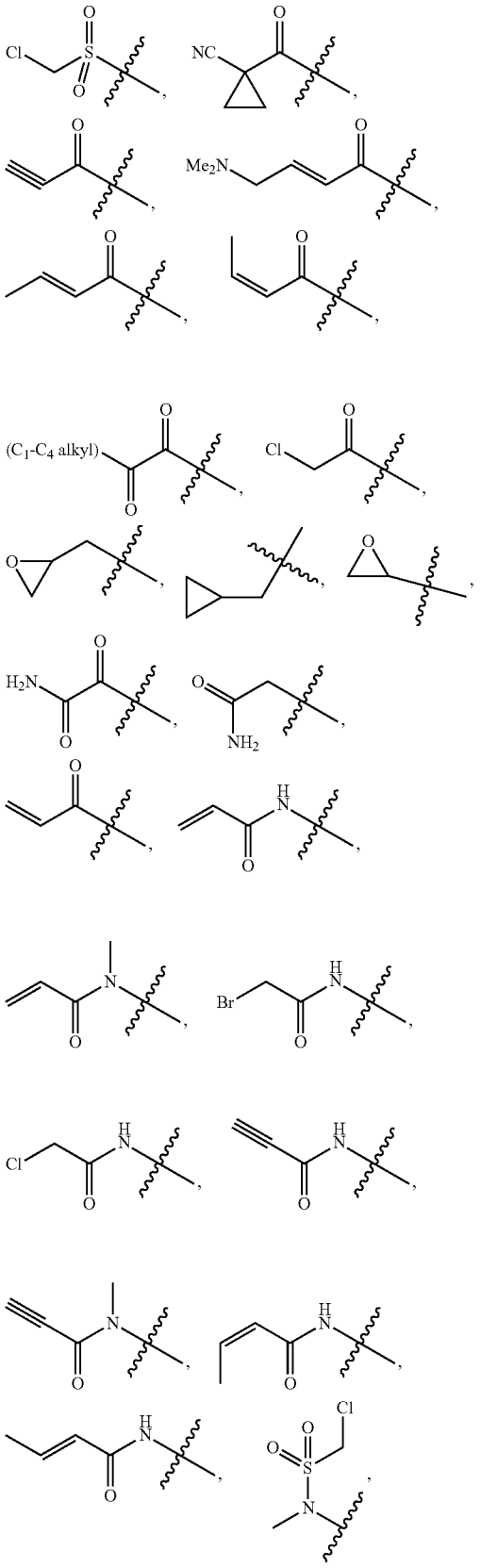

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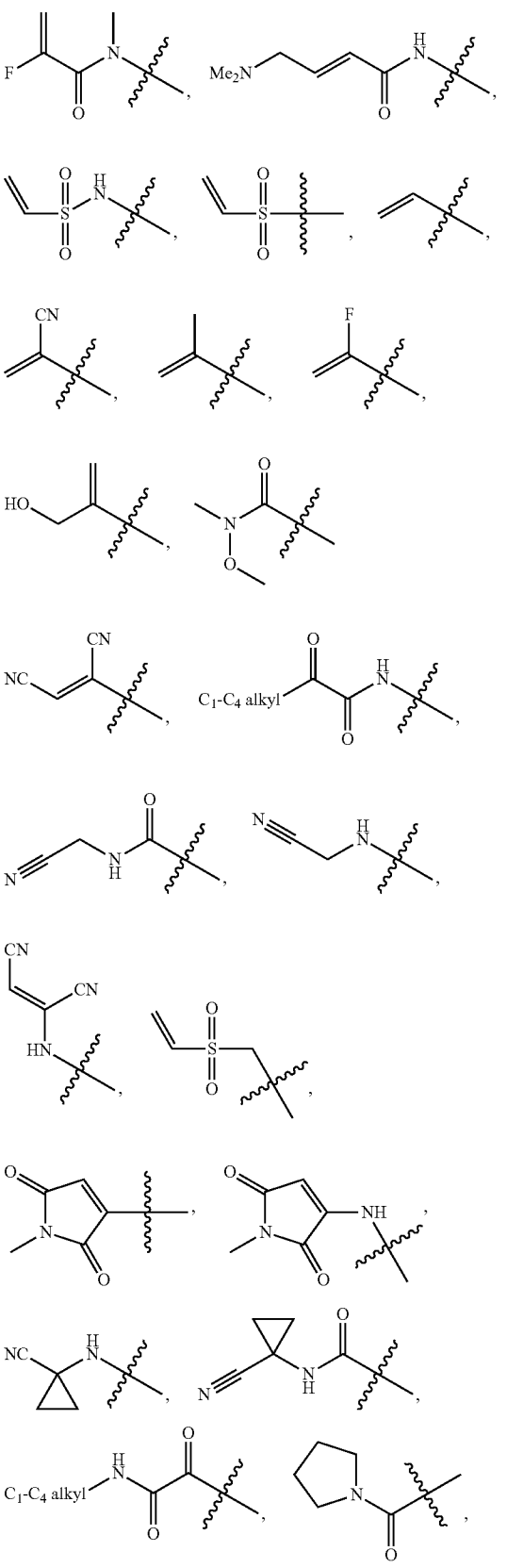

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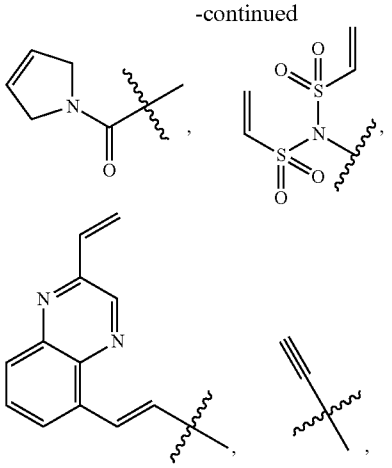
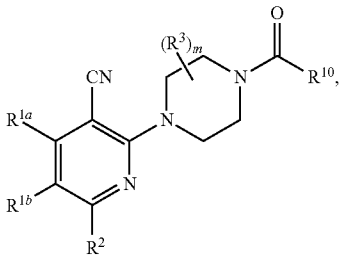


C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoxy, hydrogen, tetrazolyl, morpholino, piperazinyl, pyrrolidinone, pyrazolyl, benzyl, —$(CH_2)_{1-4}$—SH, —$(CH_2)_{1-4}$—NH_2, —NH_2, —$(CH_2)_{1-4}$—OH, —N(H)C(O)OCH$(CH_3)_3$, —$(CH_2)_{1-4}$—OCH_3, —NH—$(CH_2)_{1-4}$—OH, —C(O)—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkenyl), —O—$(CH_2)_{1-4}$—C(O)—O—(C_1-C_4 alkyl), —$C(O)NH_2$, —$(CH_2)_{1-4}C(O)CH_3$, —N(CH_3) (CH_3), —NHC(O)(C_2-C_4 alkenyl), —NHC(O)(C_2-C_4 alkyl), —$SO_2(CH_2)_{1-4}$, —$(CH_2)_{1-4}$—$NHSO_2Me$, —$NHSO_2(CH_2)$ $_{1-4}$, —O—SO_2CF_3, —SO_2NH—(C_1-C_4 alkyl), —SO_2NH—(C_2-C_4 alkenyl), SO_2—NH_2 or —$NHSO_2Me$.

[0122] In some embodiments, R^2 is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl. In some embodiments, R^2 is cyclopropyl. In some embodiments, R_2 is isopropyl.

[0123] In some embodiments, R^4 is CN; Y is —N(R^5)—; R^5 is —C(O)R^{10}; and the compound has Structural Formula II:

(II)



or a pharmaceutically acceptable salt thereof, wherein:

[0124] one of R^{1a} or R^{1b} is selected from hydrogen and methyl;

[0125] the other of R^{1a} or R^{1b} is selected from aryl, heteroaryl, heterocyclyl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, —O—(C_0-C_4 alkylene)-heteroaryl, —N(R^7)-aryl, —N(R^7)heteroaryl, —N(R^9)-aryl, or —N(R^9)-heteroaryl, wherein said aryl, heterocyclyl, or heteroaryl is substituted with -G-L-M, CH_3, CN, alkoxy, OH, halo, C_1-C_6 alkyl, —CF_3, —OC(O)CH_3, or —OCF_3;

[0126] R^2 is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl;

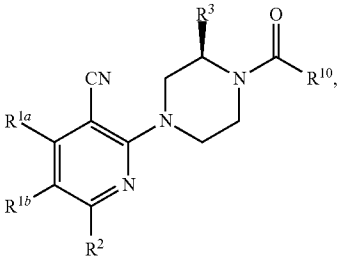
[0127] each R^3, if present, is selected from methyl, ethyl, isopropyl, CF_3, cyclopropyl and phenyl;

[0128] R^{10} is selected from —(C_1-C_3 alkyl)-O—(C_1-C_2 alkyl), Q, (C_1-C_5 alkyl), C_1-C_2 alkylene)-Q, (C_2-C_4 alkenyl), —O—(C_1-C_4 alkyl), or —(C_1-C_4 alkenylene)-Q; wherein: any alkylene moiety present in R^{10} is optionally substituted with OH; any terminal methyl moiety present in R^{10} is optionally replaced with —OH, CF_3, OCH_3, —C(O)H, —OP(O)(C_1-C_4 alkoxy)$_2$, or —OP(O)(OH)$_2$ (or a salt thereof, such as a sodium salt); Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with one substituent independently selected from C_1-C_4 alkyl optionally substituted with OH, C_1-C_4 alkoxy, —(C_1-C_4 alkylene)-(C_1-C_4 alkoxy), and —OH; and

[0129] m is 0, 1, or 2.

[0130] In certain embodiments, m is 1; and the compound has Structural Formula IIa:

(IIa)



or a pharmaceutically acceptable salt thereof, wherein:

[0131] R^{1a} is hydrogen or methyl;

[0132] R^{1b} is selected from aryl, heteroaryl, heterocyclyl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, —O—(C_0-C_4 alkylene)-heteroaryl, —N(R^7)-aryl, —N(R^7)heteroaryl, —N(R^9)-aryl, or —N(R^9)-heteroaryl, wherein said aryl, heterocyclyl, or heteroaryl is substituted with -G-L-M, CH_3, CN, alkoxy, OH, halo, C_1-C_6 alkyl, —CF_3, —OC(O)CH_3, or —OCF_3;

[0133] R^2 is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl;

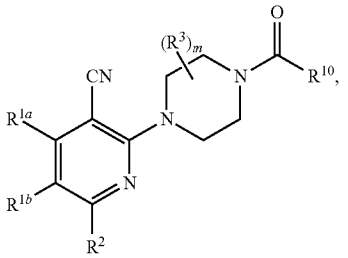
[0134] each R^3, if present, is selected from methyl, isopropyl, and cyclopropyl;

[0135] R^{10} is selected from —(C_1-C_3 alkyl)-O—(C_1-C_2 alkyl), Q, (C_1-C_5 alkyl), C_1-C_2 alkylene)-Q, (C_2-C_4 alkenyl), —O—(C_1-C_4 alkyl), or —(C_1-C_4 alkenylene)-Q; wherein: any alkylene moiety present in R^{10} is optionally substituted with OH; any terminal methyl moiety present in R^{10} is optionally replaced with —OH, CF_3, OCH_3, —C(O)H, —OP(O)(C_1-C_4 alkoxy)$_2$, or —OP(O)(OH)$_2$ (or a salt thereof, such as a sodium salt); Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with one substituent independently selected from C_1-C_4 alkyl optionally substituted with OH, C_1-C_4 alkoxy, —(C_1-C_4 alkylene)-(C_1-C_4 alkoxy), and —OH; and

[0136] m is 0, 1, or 2.

[0137] In some embodiments, R^4 is CN; Y is —N(R^5)—; R^5 is —C(O)R^{10}; and the compound has Structural Formula II:

(II)



or a pharmaceutically acceptable salt thereof, wherein:

[0138] one of R^{1a} or R^{1b} is selected from hydrogen and methyl;

[0139] the other of R^{1a} or R^{1b} is selected from isopropyl, —N(CH_3)—(CH_2)$_2$—NH—CH_3, aryl, heteroaryl, —CH_2-aryl, —CH_2-heteroaryl, —O—CH_2-aryl, and —O—CH_2-heteroaryl; wherein any aryl or heteroaryl portion of R^{1a} or R^{1b} is optionally substituted with one or more substituents independently selected from alkoxy, hydroxy, halo, C_1-C_6 alkyl, —CF_3, —OC(O)CH_3, and —OCF_3;

[0140] R^2 is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl;

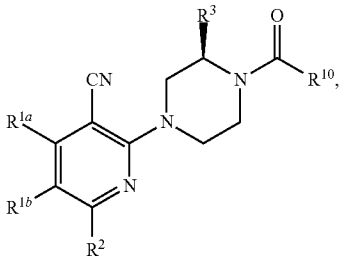
[0141] each R^3, if present, is selected from methyl, ethyl, isopropyl, cyclopropyl and phenyl;

[0142] R^{10} is selected from heteroaryl, aryl, —CH_2-aryl, —CH_2-heteroaryl, and —(CH_2)$_2$—O—CH_3, wherein any aryl or heteroaryl portion of R^{10} is optionally substituted with methyl; and

[0143] m is 0, 1, or 2.

[0144] In certain embodiments, m is 1; and the compound has Structural Formula IIa:

(IIa)



or a pharmaceutically acceptable salt thereof, wherein:

[0145] R^{1a} is selected from hydrogen and methyl;

[0146] R^{1b} is selected from aryl, and heteroaryl; wherein the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from methoxy, fluoro, chloro, methyl, —CF_3, —OCF_3;

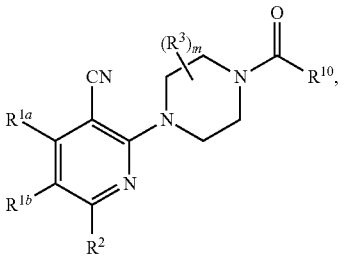
[0147] R^2 is selected from isopropyl and cyclopropyl;

[0148] R^3 is selected from methyl, ethyl, isopropyl and cyclopropyl; and

[0149] R^{10} is selected from —(CH_2)$_2$—O—CH_3, furan-3-yl, 2-methylfuran-3-yl and thien-2-yl.

[0150] In some embodiments, R^4 is CN; Y is —N(R^5)—; R^5 is —C(O)R^{10}; and the compound has Structural Formula II:

(II)



or a pharmaceutically acceptable salt thereof, wherein:

[0151] R^{1a} is H;

[0152] R^{1b} is aryl, heteroaryl, —O—(C_1-C_4 alkylene)-aryl, or —O—(C_1-C_4 alkylene)-heteroaryl, wherein said aryl or heteroaryl is substituted with -G-L-M, CH_3, or CN;

[0153] R^2 is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl;

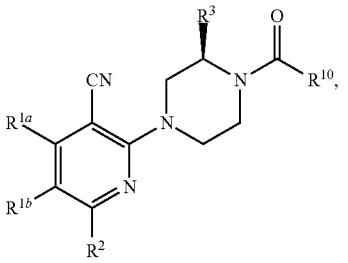
[0154] each R^3, if present, is selected from methyl, ethyl, isopropyl, cyclopropyl and phenyl;

[0155] R^{10} is selected from heteroaryl, aryl, —CH_2-aryl, —CH_2-heteroaryl, and —(CH_2)$_2$—O—CH_3, wherein any aryl or heteroaryl portion of R^{10} is optionally substituted with methyl; and

[0156] m is 0, 1, or 2.

[0157] In certain embodiments, m is 1; and the compound has Structural Formula IIa:

(IIa)



or a pharmaceutically acceptable salt thereof, wherein:

[0158] R^{1a} is H;

[0159] R^{1b} is aryl, heteroaryl, —O—(CH_2)-aryl, —O—CH(CH_3)-aryl, —O—(CH_2)-heteroaryl or —O—CH(CH_3)-heteroaryl, wherein aryl is phenyl and heteroaryl is pyridyl, pyrimidinyl, indolyl, or pyrazolyl, and said phenyl, pyridyl, pyrimidinyl, indolyl or pyrazolyl is substituted with -G-L-M, CH_3, or CN;

[0160] R^2 is selected from isopropyl and cyclopropyl;

[0161] R^3 is selected from methyl, ethyl, isopropyl and cyclopropyl; and

[0162] R^{10} is selected from —(CH_2)$_2$—O—CH_3, furan-3-yl, 2-methylfuran-3-yl and thien-2-yl.

[0163] In another embodiment, the compound is selected from any one of the compounds set forth in Table 1, below.

TABLE 1

Exemplary Compounds of Formula I.

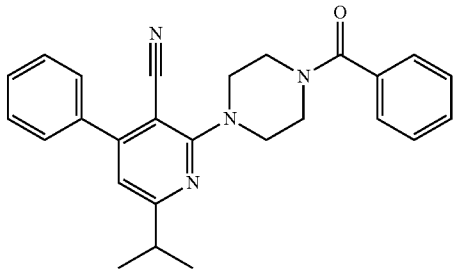
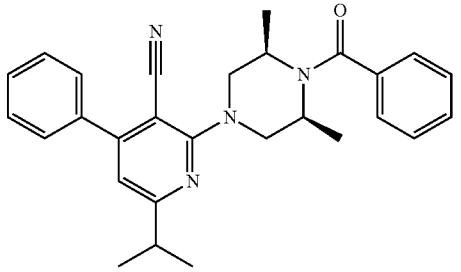
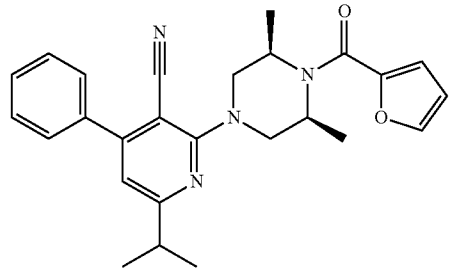
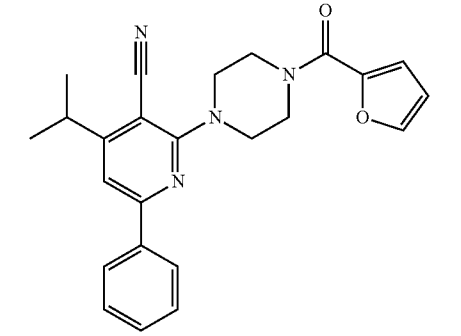
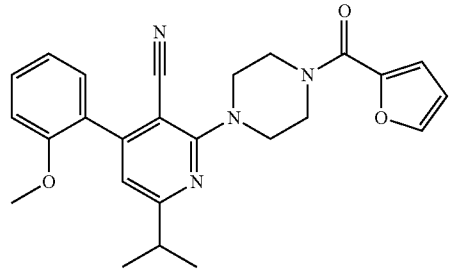
Cmpd No.	Structure
100	
101	
102	
103	
104	

TABLE 1-continued

Exemplary Compounds of Formula I.

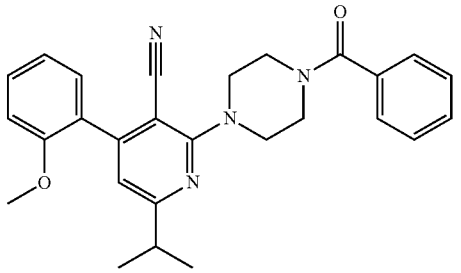
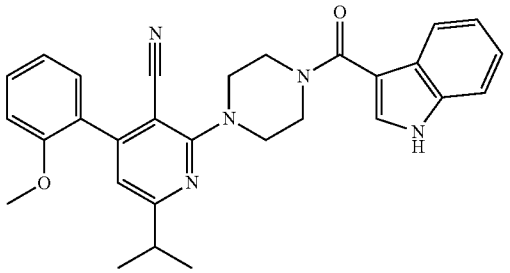
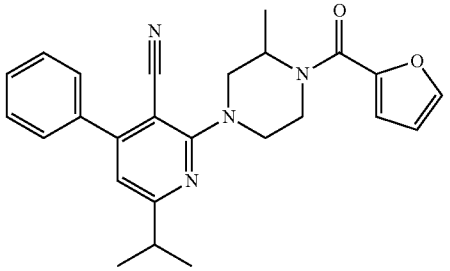
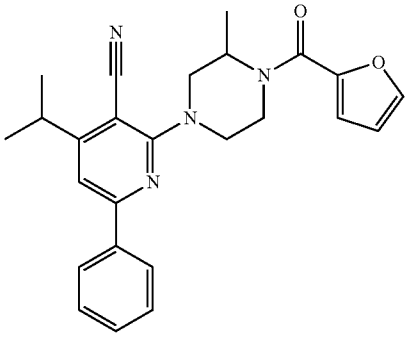
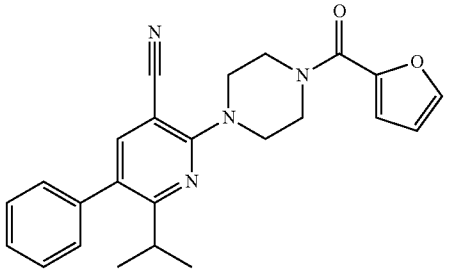
Cmpd No.	Structure
105	
106	
107	
108	
109	

TABLE 1-continued

Exemplary Compounds of Formula I.

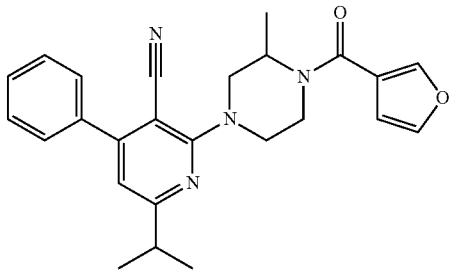
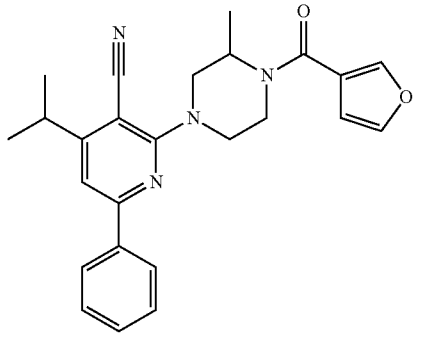
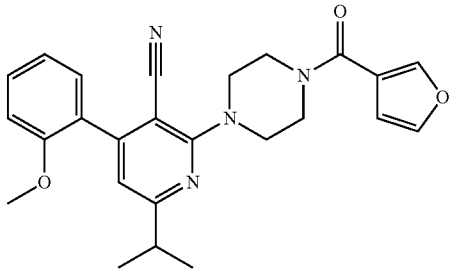
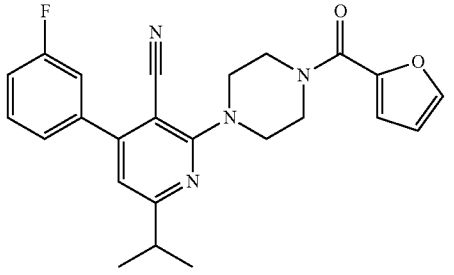
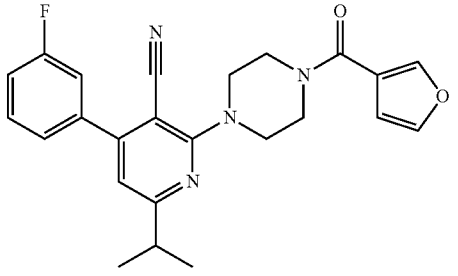
Cmpd No.	Structure
110	
111	
113	
114	
115	

TABLE 1-continued

Exemplary Compounds of Formula I.

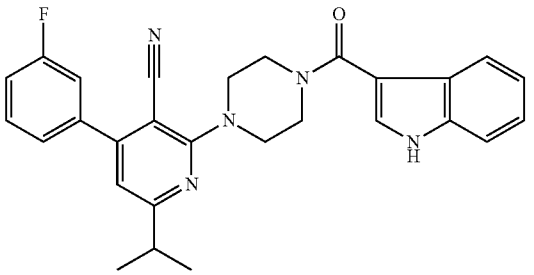
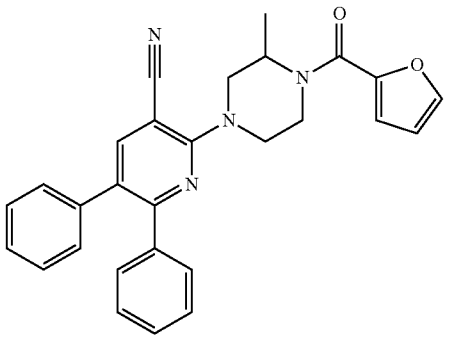
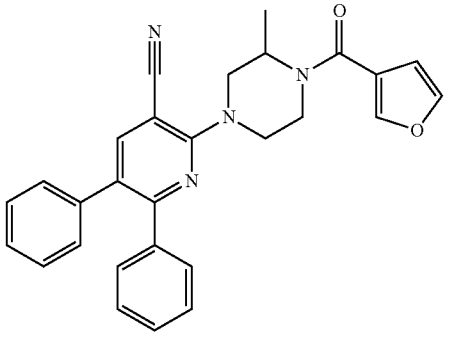
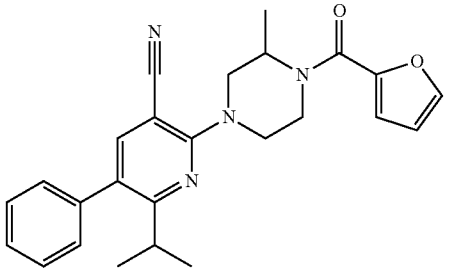
Cmpd No.	Structure
116	
117	
118	
119	

TABLE 1-continued

Exemplary Compounds of Formula I.

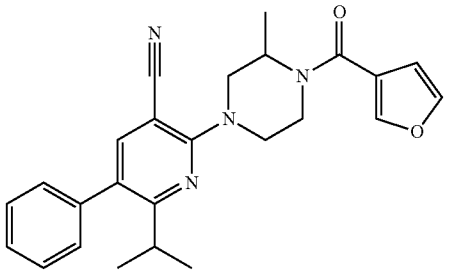
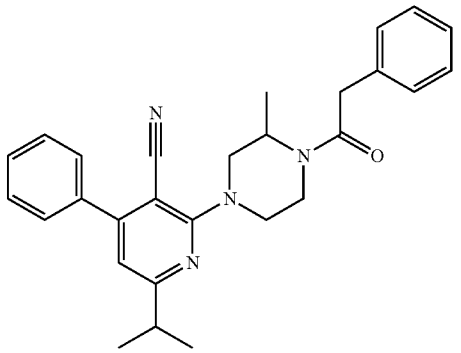
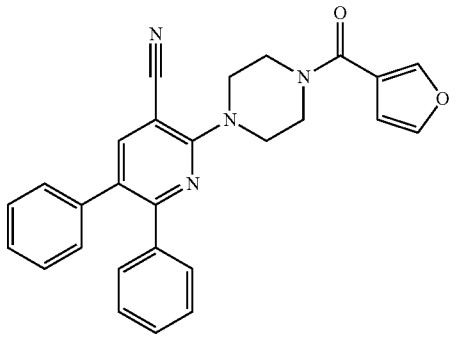
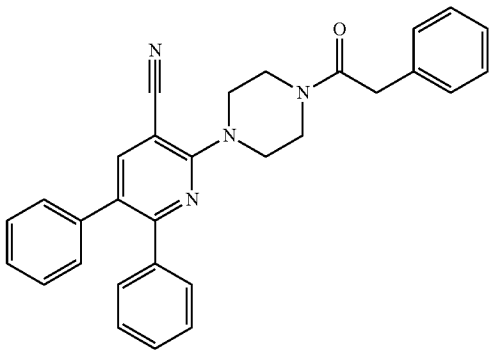
Cmpd No.	Structure
120	
121	
122	
123	

TABLE 1-continued

Exemplary Compounds of Formula I.

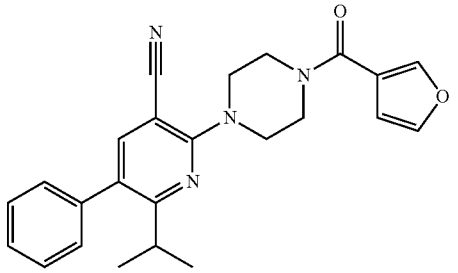
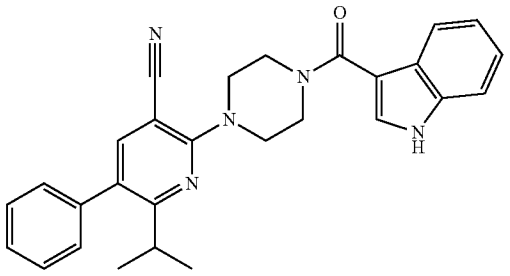
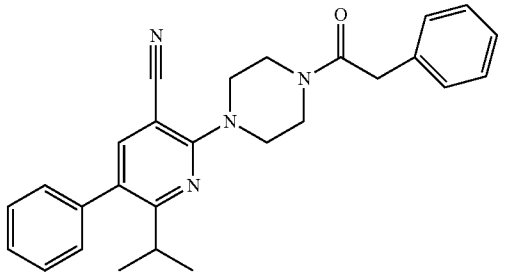
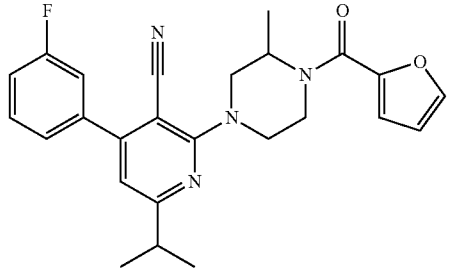
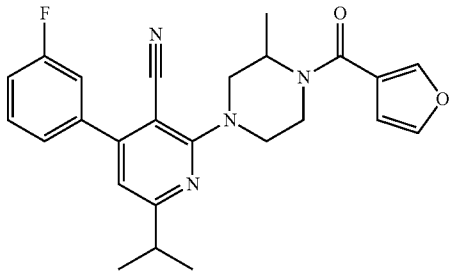
Cmpd No.	Structure
124	
125	
126	
127	
128	

TABLE 1-continued

Exemplary Compounds of Formula I.

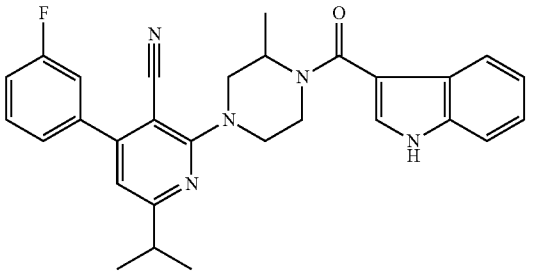
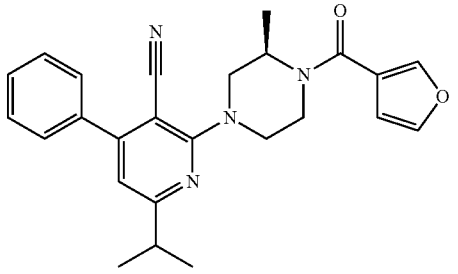
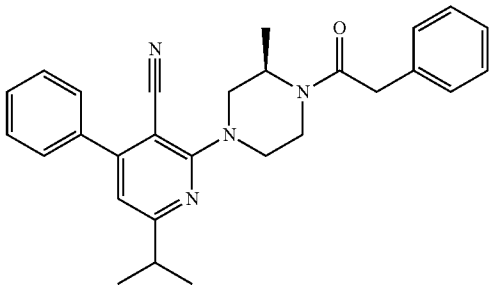
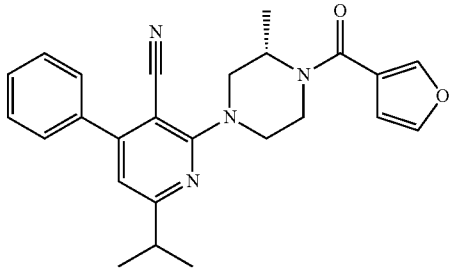
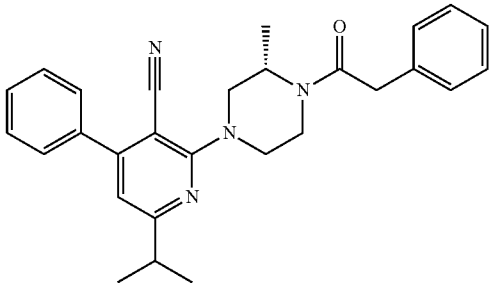
Cmpd No.	Structure
129	
130	
131	
132	
133	

TABLE 1-continued

Exemplary Compounds of Formula I.

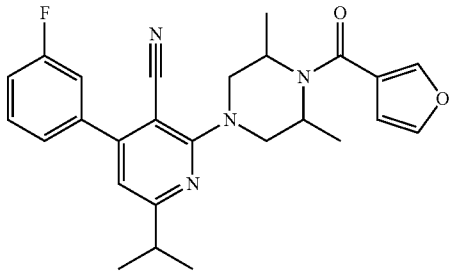
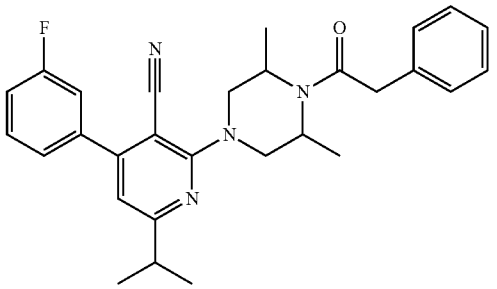
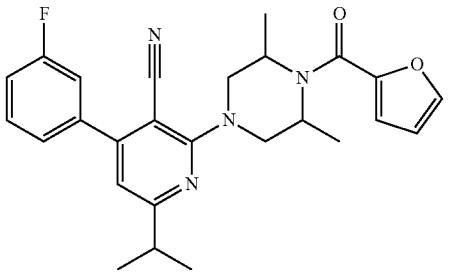
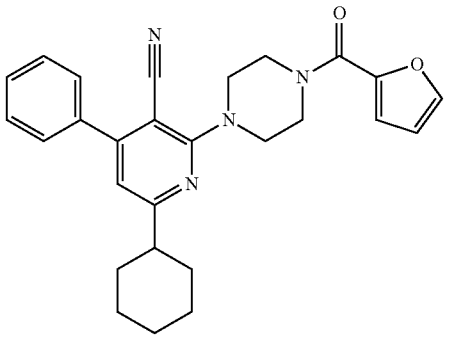
Cmpd No.	Structure
134	
135	
136	
137	

TABLE 1-continued

Exemplary Compounds of Formula I.

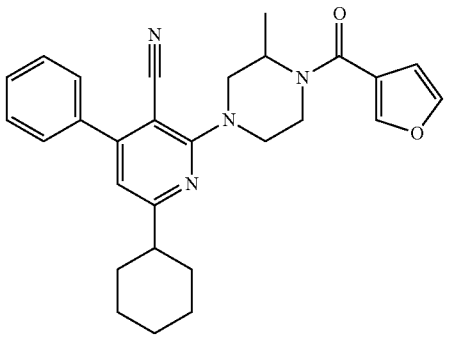
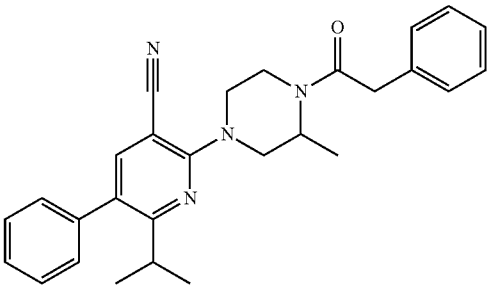
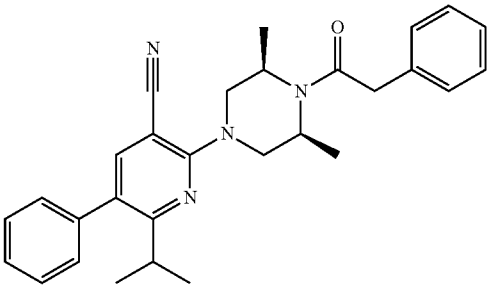
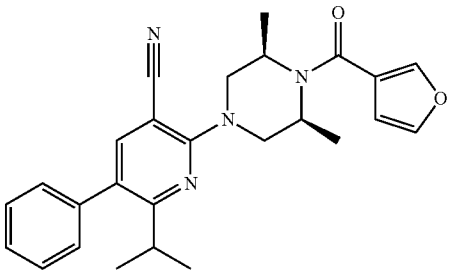
Cmpd No.	Structure
138	
139	
140	
141	

TABLE 1-continued

Exemplary Compounds of Formula I.

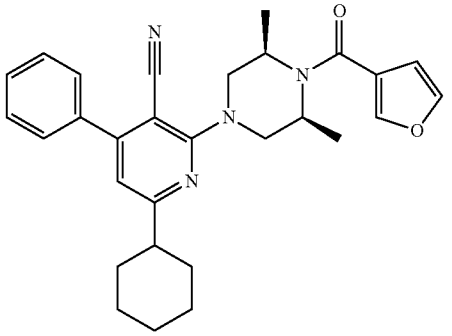
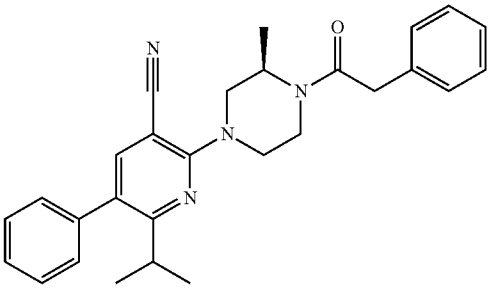
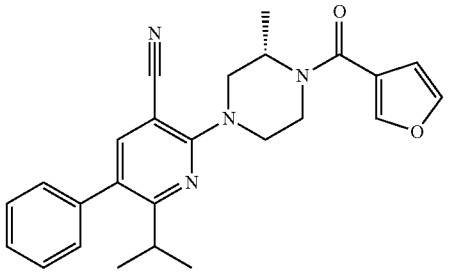
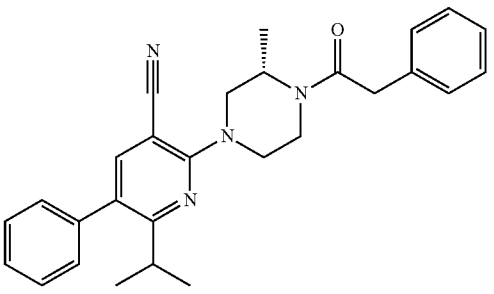
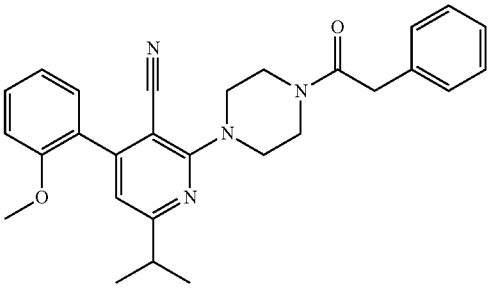
Cmpd No.	Structure
142	
143	
144	
145	
146	

TABLE 1-continued

Exemplary Compounds of Formula I.

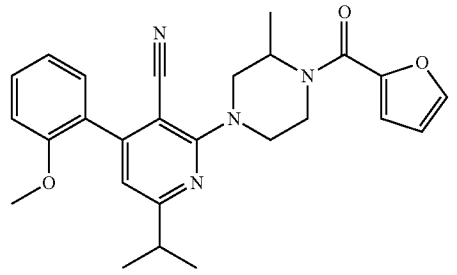
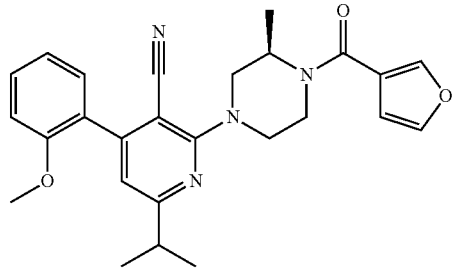
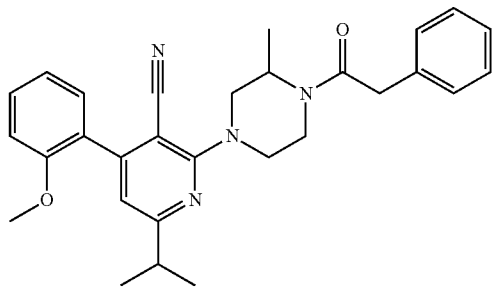
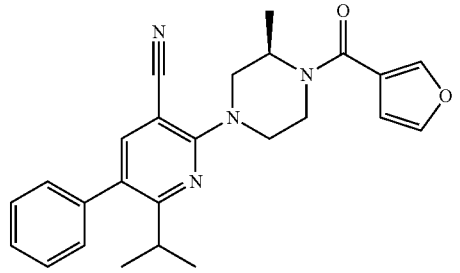
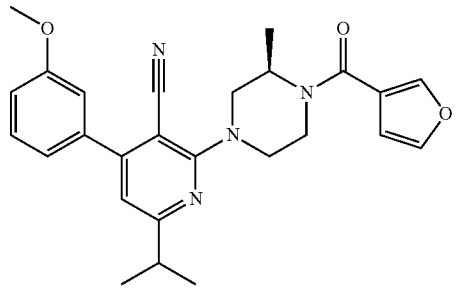
Cmpd No.	Structure
147	
148	
149	
150	
151	

TABLE 1-continued

Exemplary Compounds of Formula I.

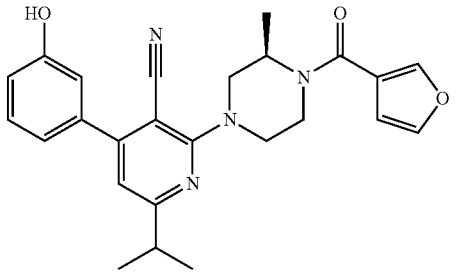
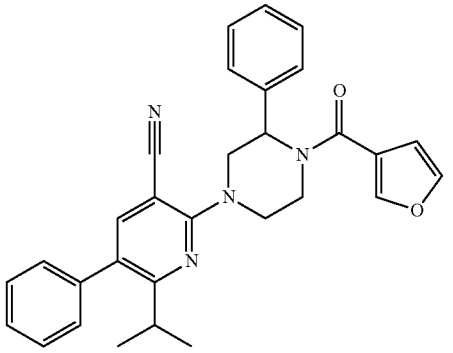
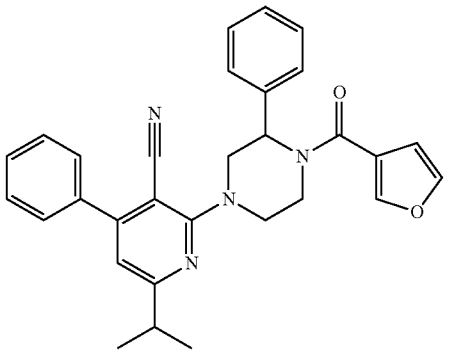
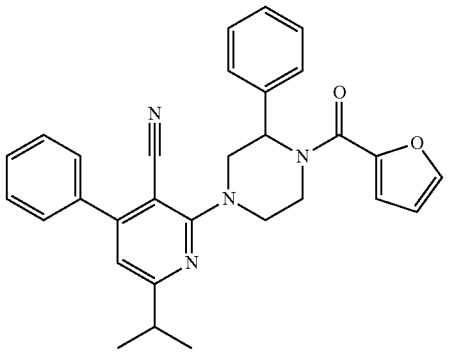
Cmpd No.	Structure
152	
153	
154	
155	

TABLE 1-continued

Exemplary Compounds of Formula I.

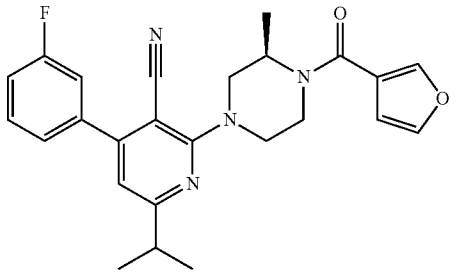
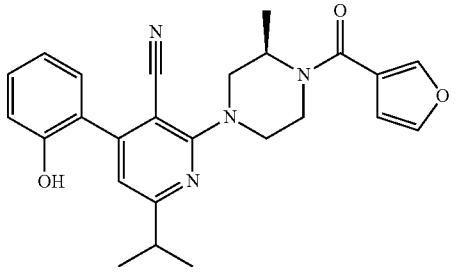
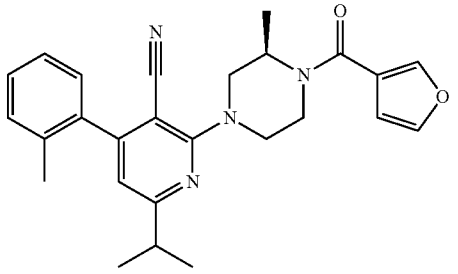
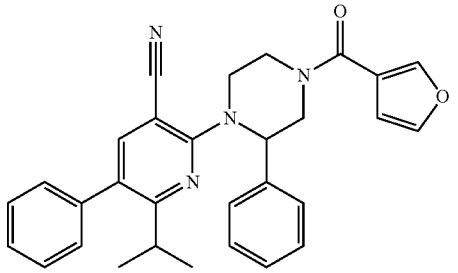
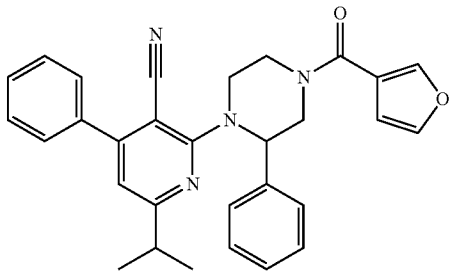
Cmpd No.	Structure
156	
157	
158	
159	
160	

TABLE 1-continued

Exemplary Compounds of Formula I.

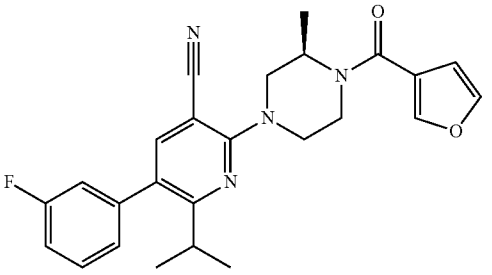
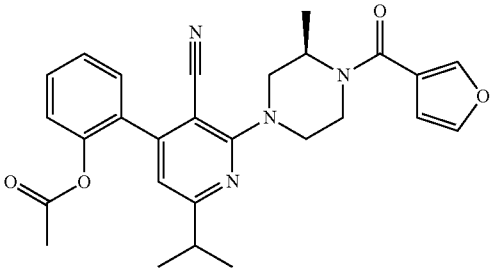
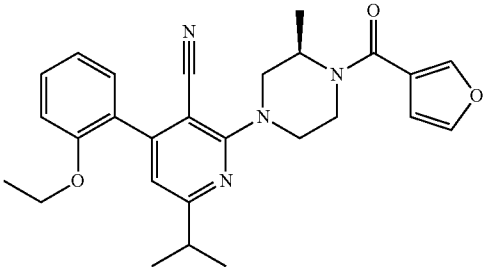
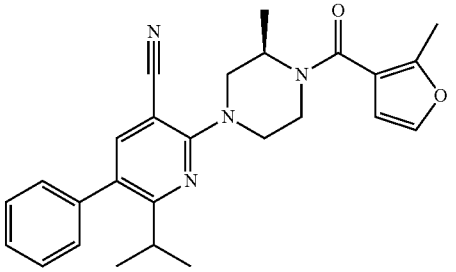
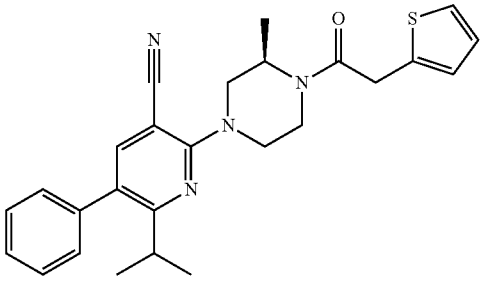
Cmpd No.	Structure
161	
162	
163	
164	
165	

TABLE 1-continued

Exemplary Compounds of Formula I.

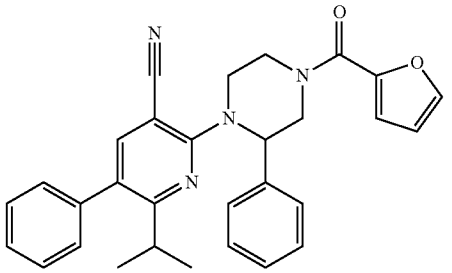
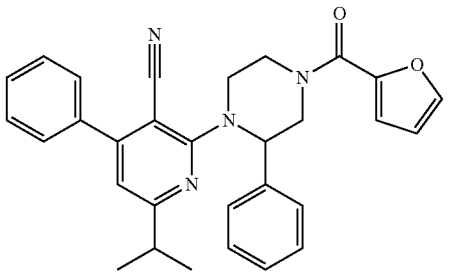
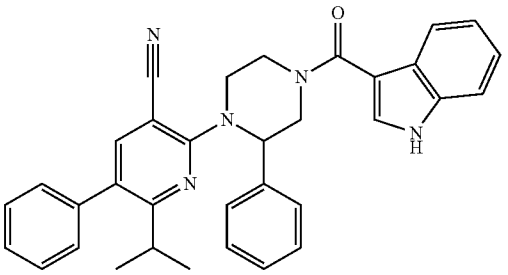
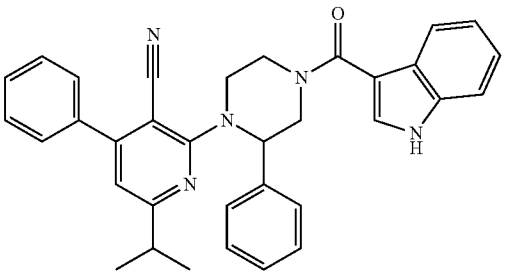
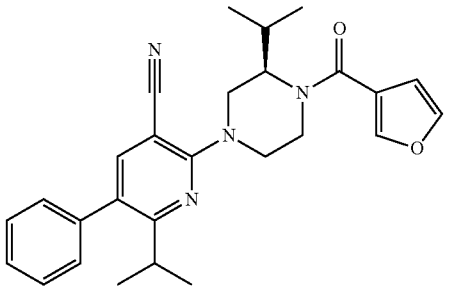
Cmpd No.	Structure
166	
167	
168	
169	
170	

TABLE 1-continued

Exemplary Compounds of Formula I.

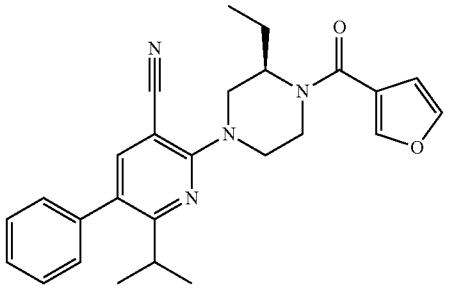
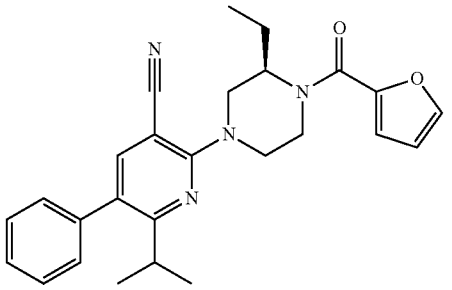
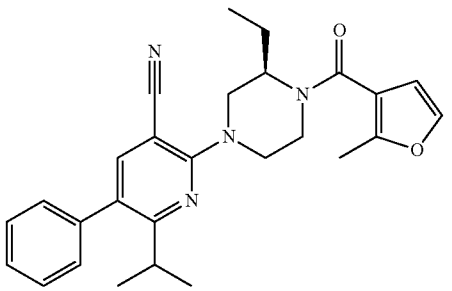
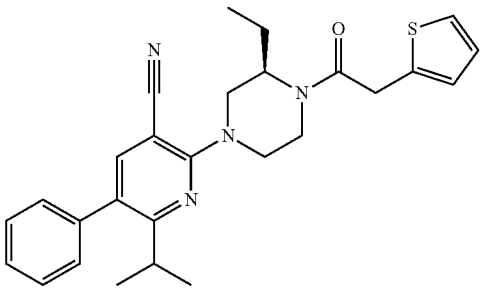
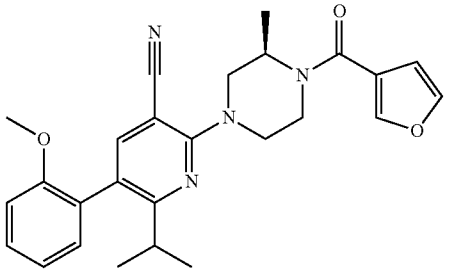
Cmpd No.	Structure
171	
172	
173	
174	
175	

TABLE 1-continued

Exemplary Compounds of Formula I.

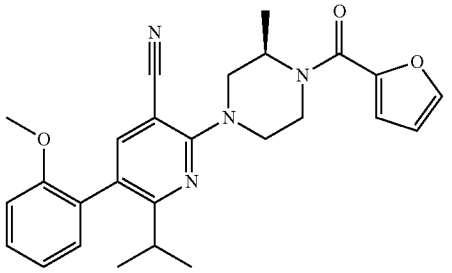
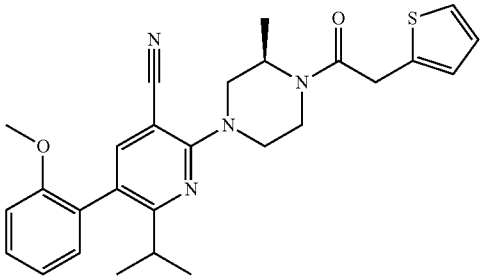
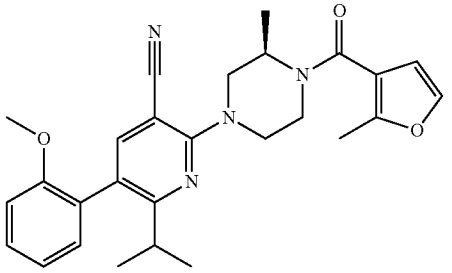
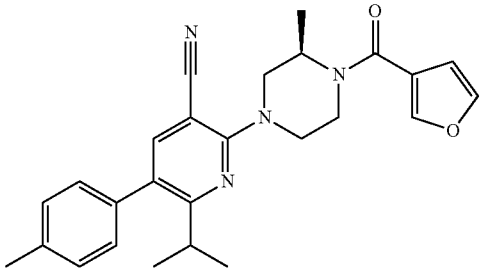
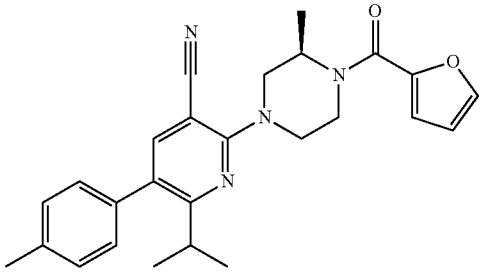
Cmpd No.	Structure
176	
177	
178	
179	
180	

TABLE 1-continued

Exemplary Compounds of Formula I.

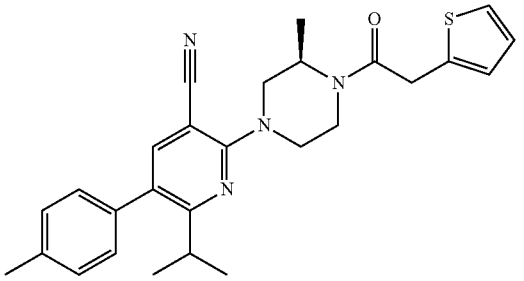
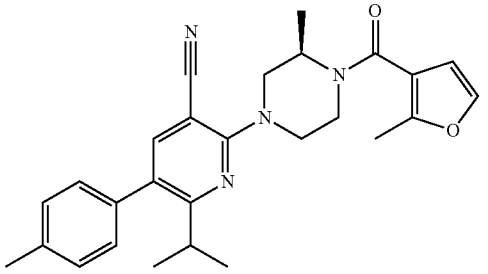
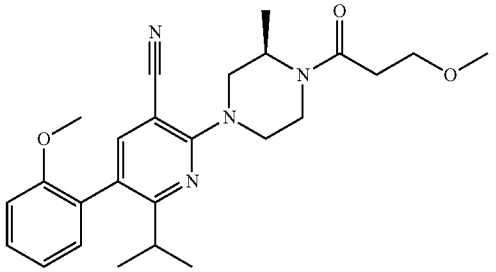
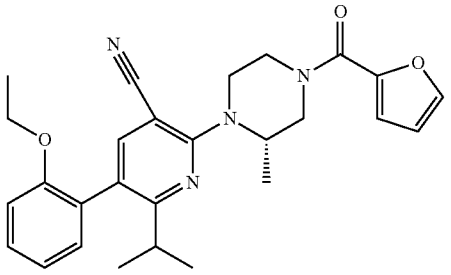
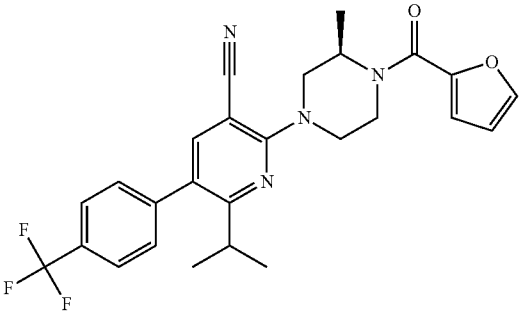
Cmpd No.	Structure
181	
182	
183	
184	
185	

TABLE 1-continued

Exemplary Compounds of Formula I.

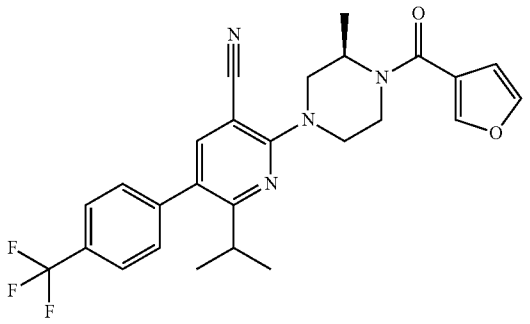
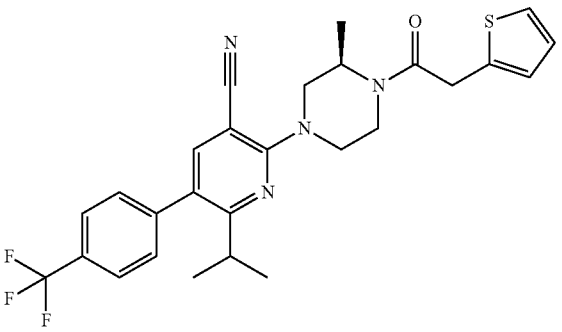
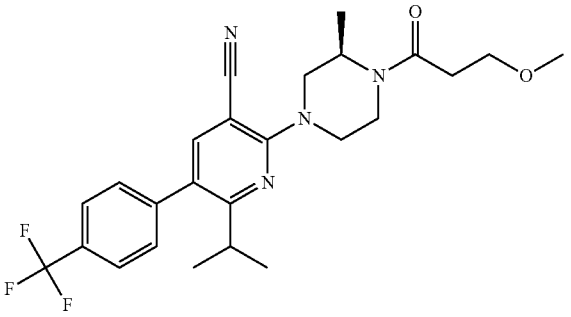
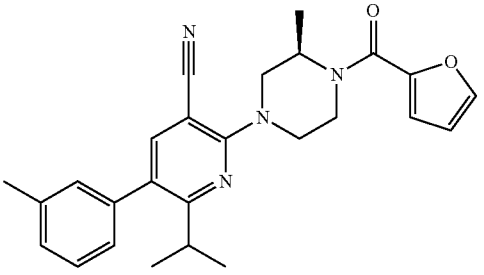
Cmpd No.	Structure
187	
188	
189	
190	

TABLE 1-continued

Exemplary Compounds of Formula I.

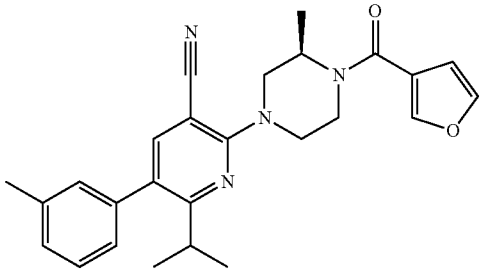
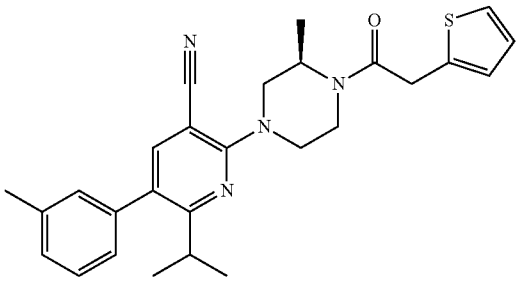
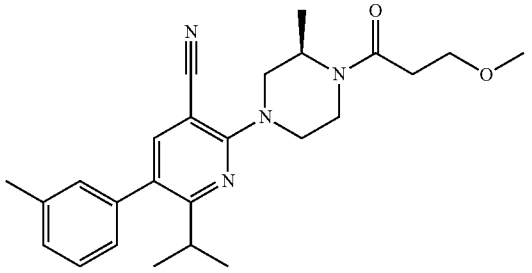
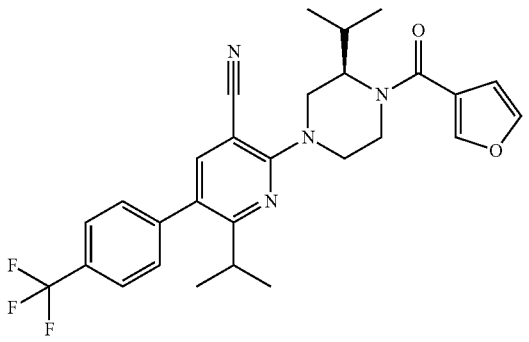
Cmpd No.	Structure
191	
192	
193	
195	

TABLE 1-continued

Exemplary Compounds of Formula I.

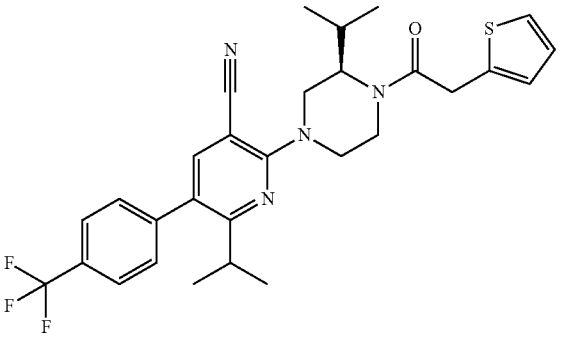
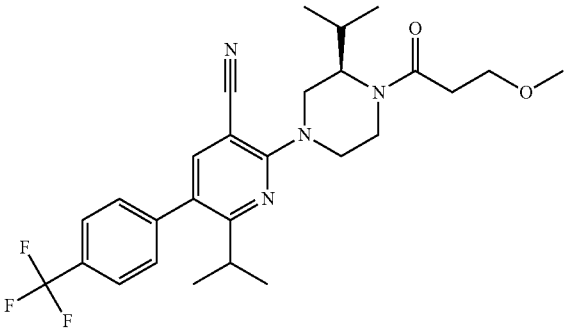
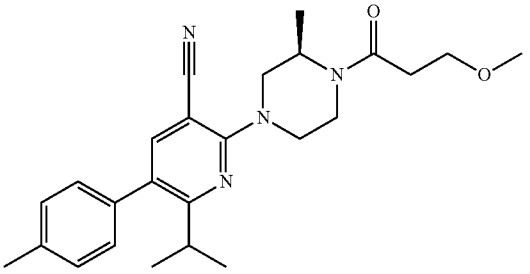
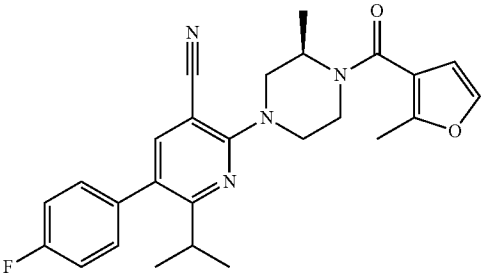
Cmpd No.	Structure
196	
197	
198	
199	

TABLE 1-continued

Exemplary Compounds of Formula I.

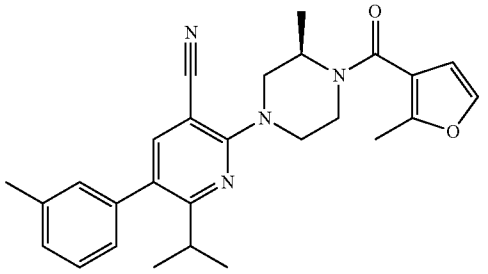
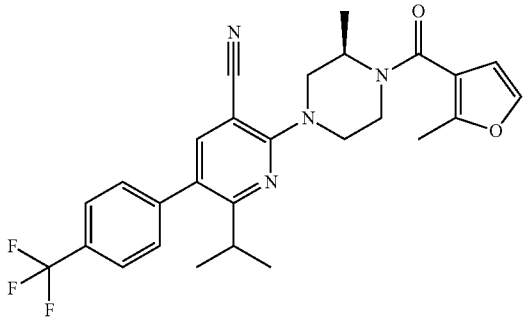
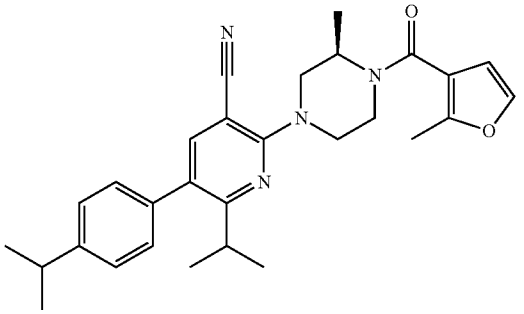
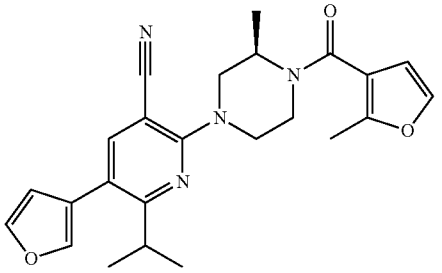
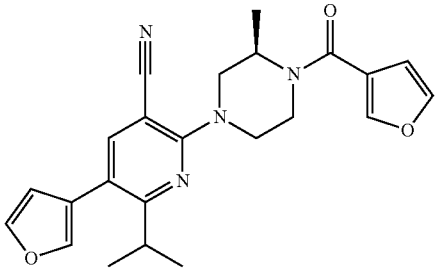
Cmpd No.	Structure
200	
201	
202	
203	
204	

TABLE 1-continued

Exemplary Compounds of Formula I.

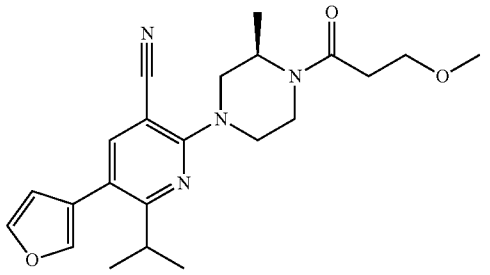
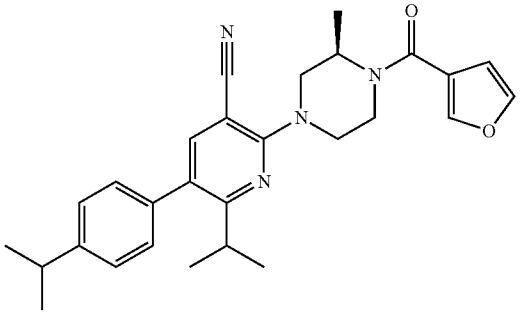
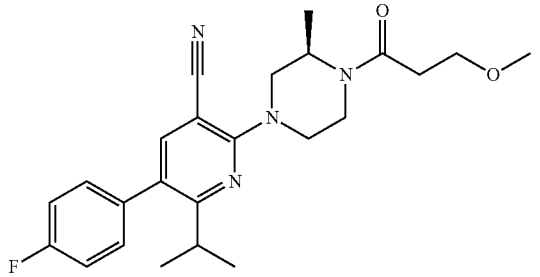
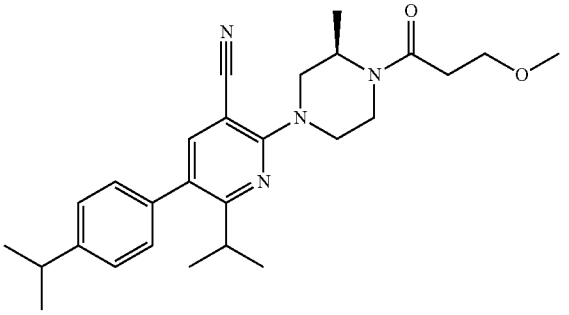
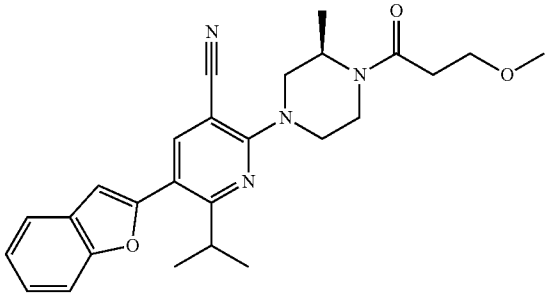
Cmpd No.	Structure
205	
206	
207	
208	
209	

TABLE 1-continued

Exemplary Compounds of Formula I.

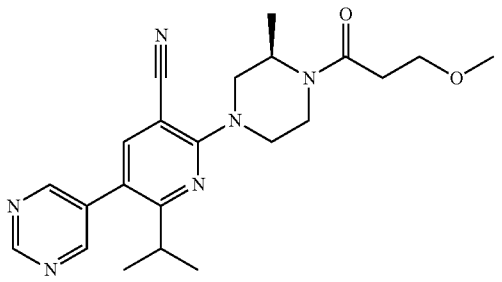
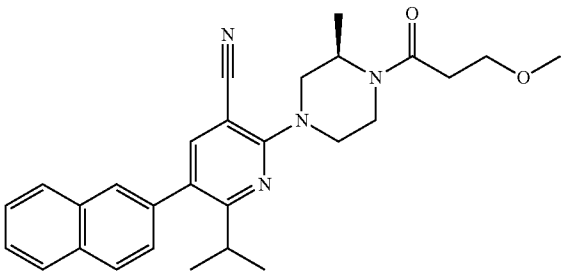
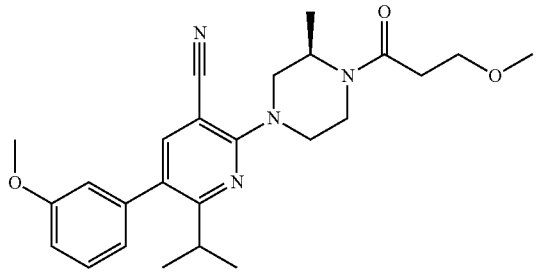
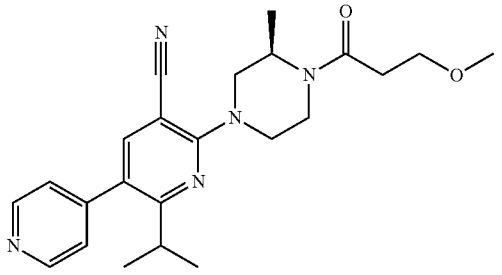
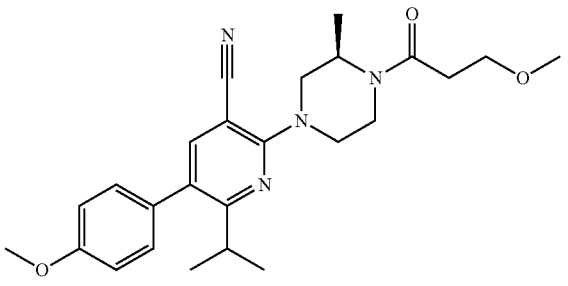
Cmpd No.	Structure
210	
211	
212	
213	
214	

TABLE 1-continued

Exemplary Compounds of Formula I.

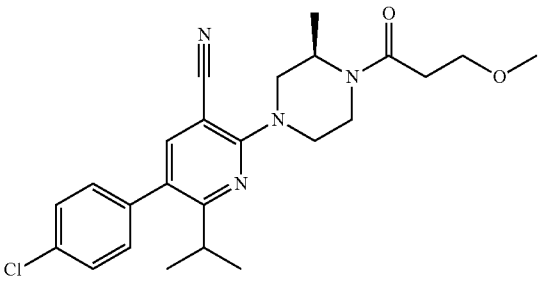
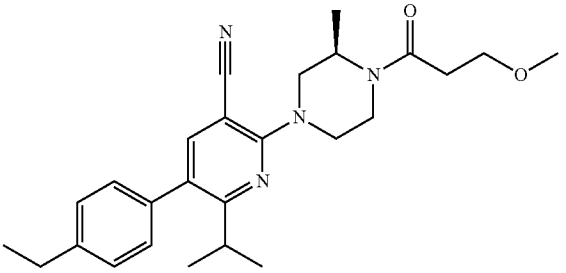
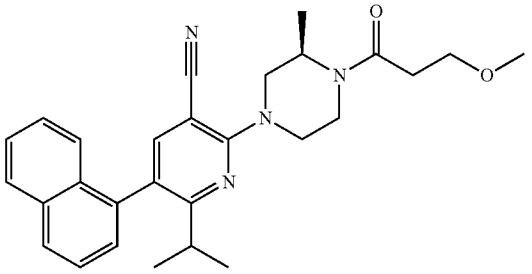
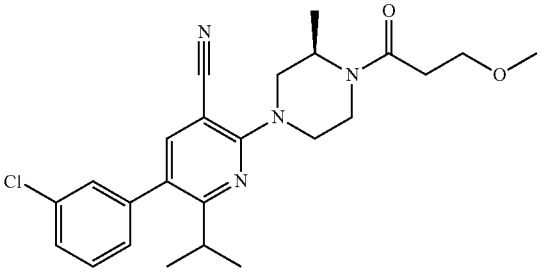
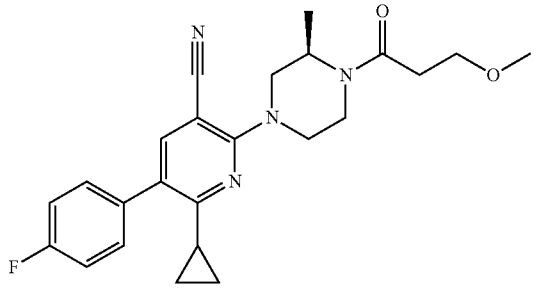
Cmpd No.	Structure
215	
216	
217	
218	
219	

TABLE 1-continued

Exemplary Compounds of Formula I.

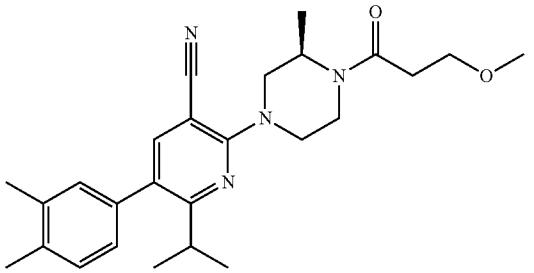
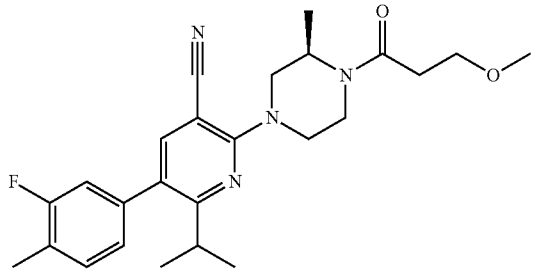
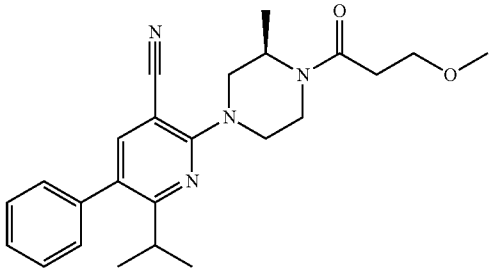
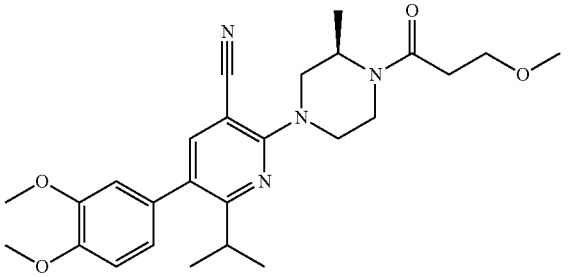
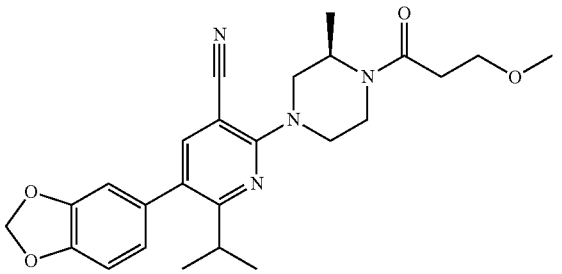
Cmpd No.	Structure
220	
221	
222	
223	
224	

TABLE 1-continued

Exemplary Compounds of Formula I.

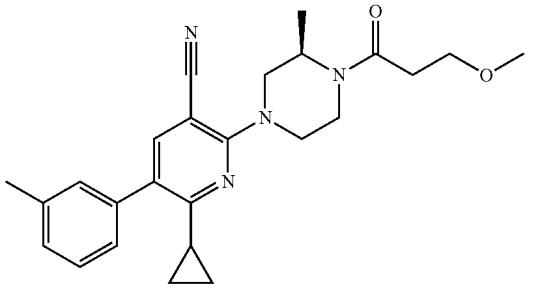
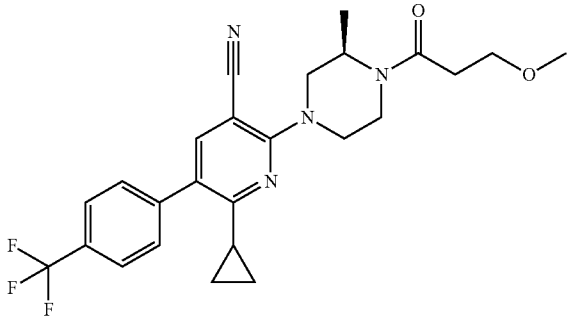
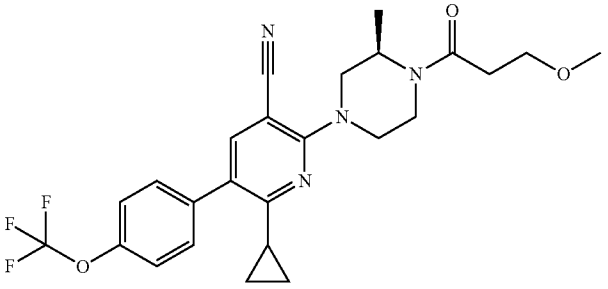
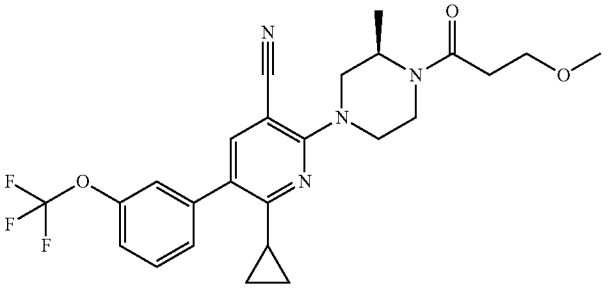
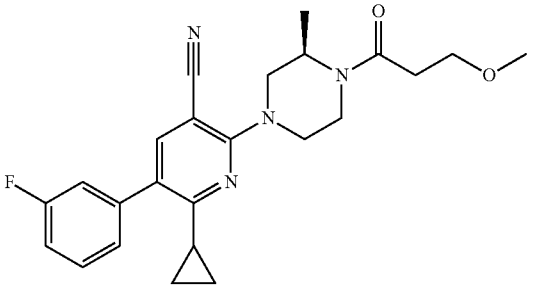
Cmpd No.	Structure
225	
226	
227	
228	
229	

TABLE 1-continued

Exemplary Compounds of Formula I.

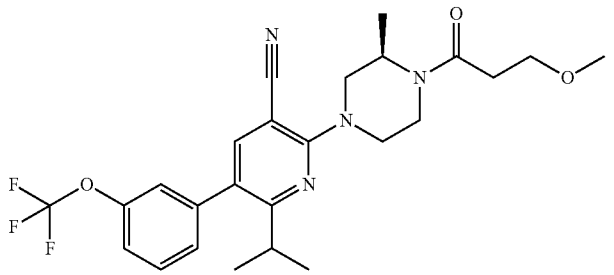
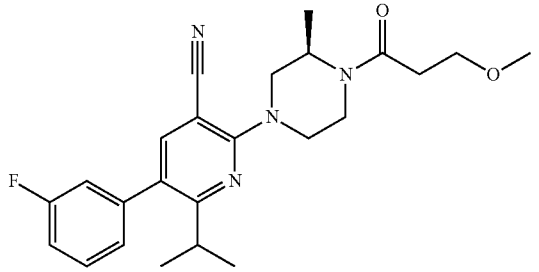
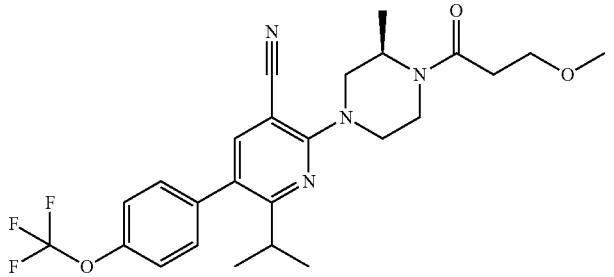
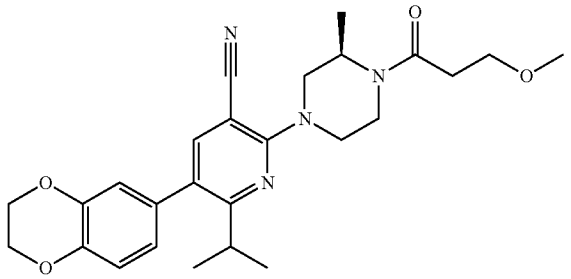
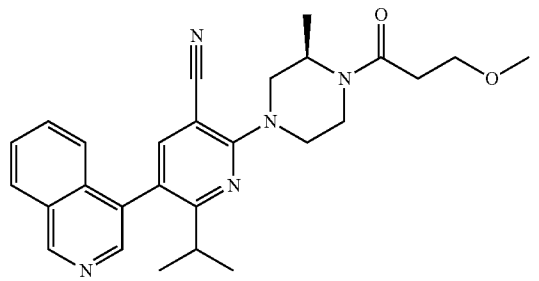
Cmpd No.	Structure
230	
231	
232	
233	
234	

TABLE 1-continued

Exemplary Compounds of Formula I.

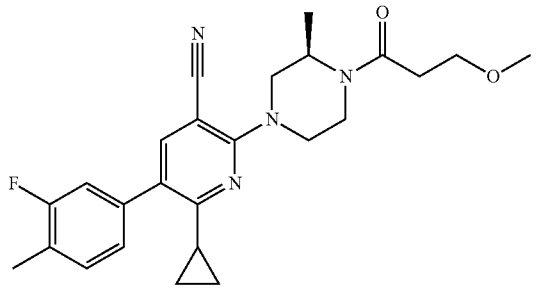
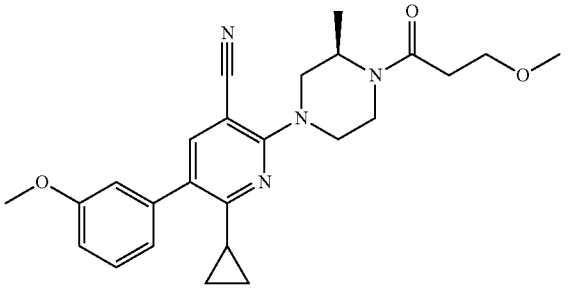
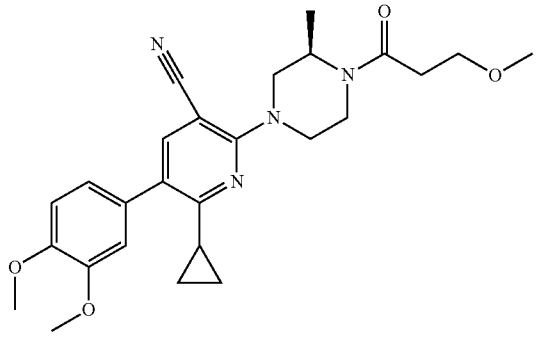
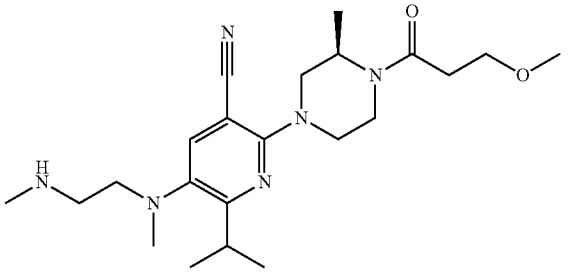
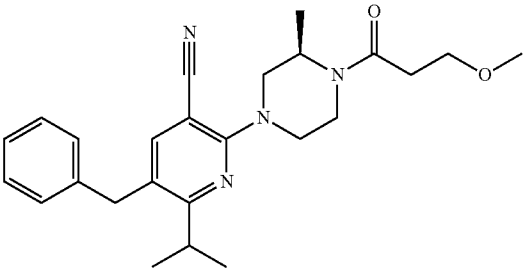
Cmpd No.	Structure
235	
236	
237	
238	
239	

TABLE 1-continued

Exemplary Compounds of Formula I.

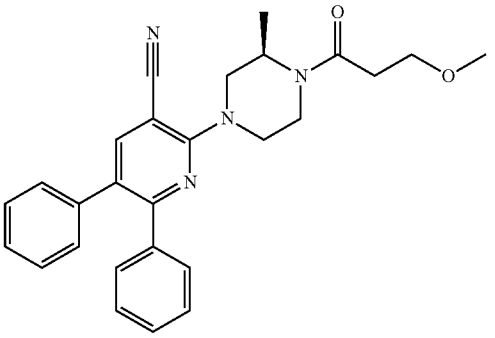
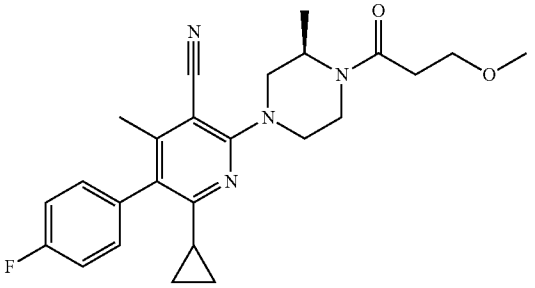
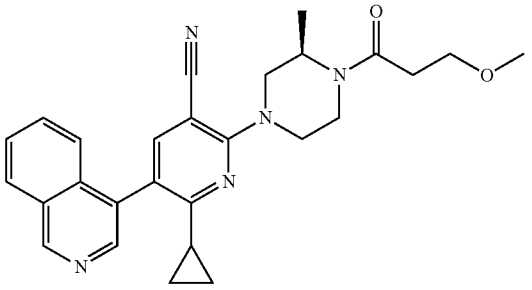
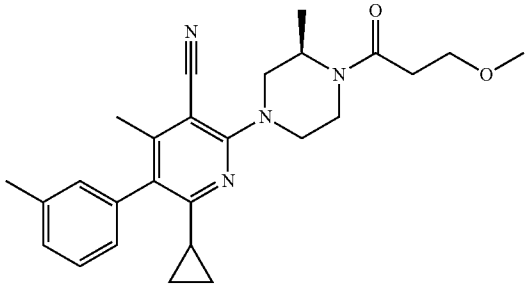
Cmpd No.	Structure
240	
241	
242	
243	

TABLE 1-continued

Exemplary Compounds of Formula I.

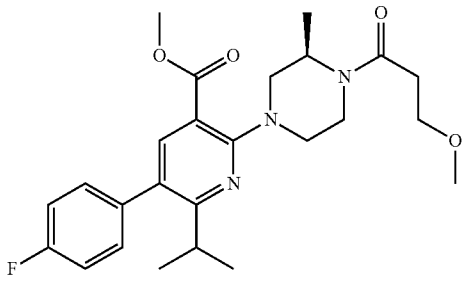
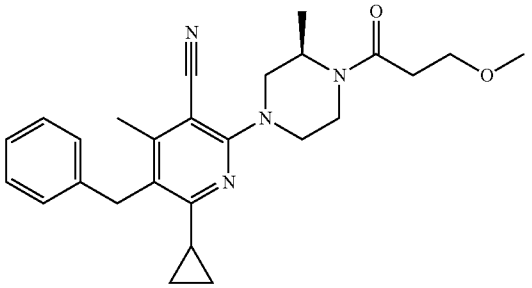
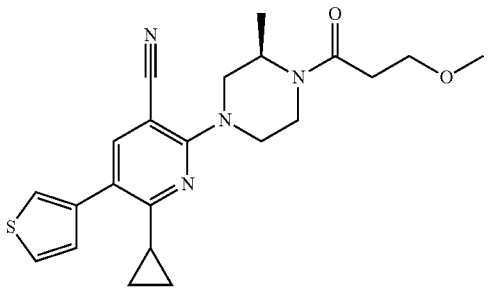
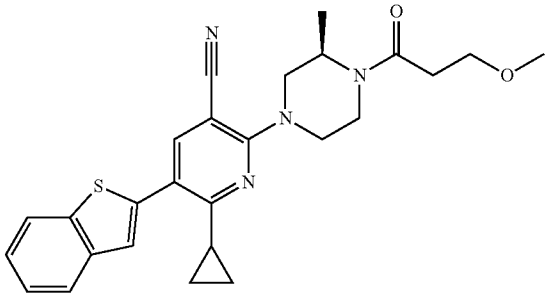
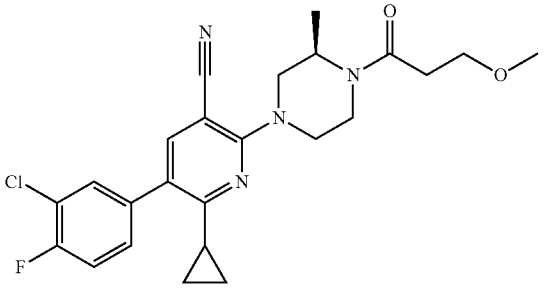
Cmpd No.	Structure
244	
245	
246	
247	
248	

TABLE 1-continued

Exemplary Compounds of Formula I.

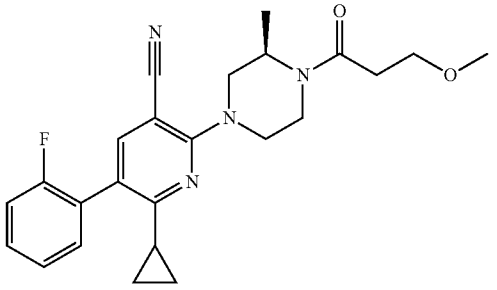
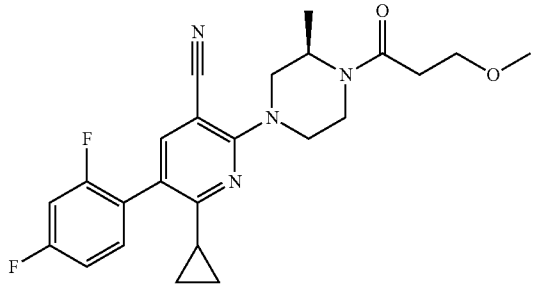
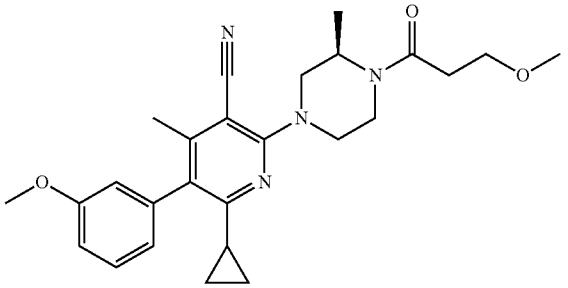
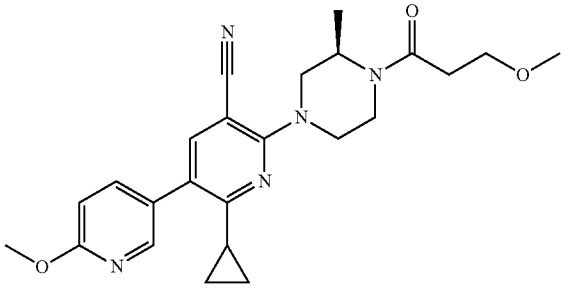
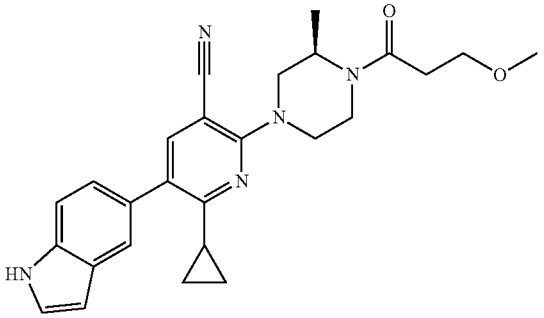
Cmpd No.	Structure
249	
250	
251	
252	
253	

TABLE 1-continued

Exemplary Compounds of Formula I.

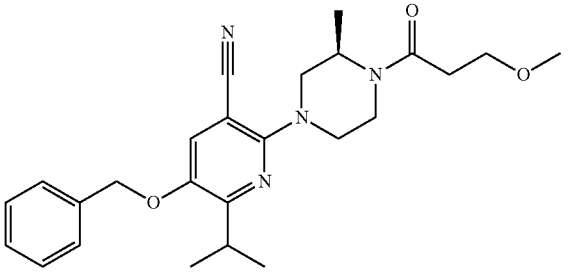
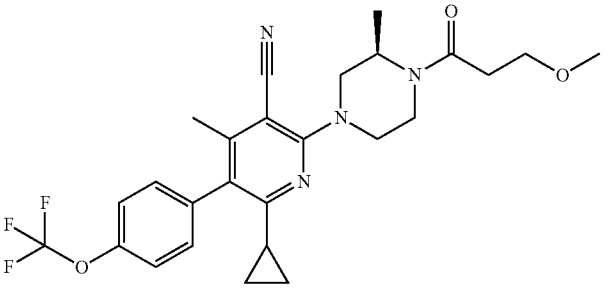
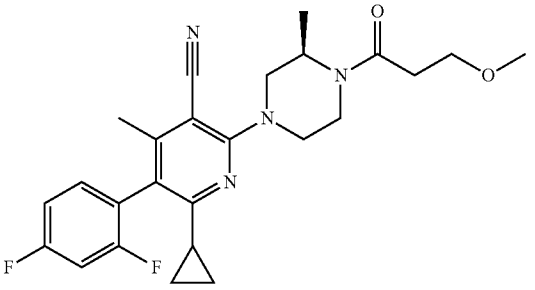
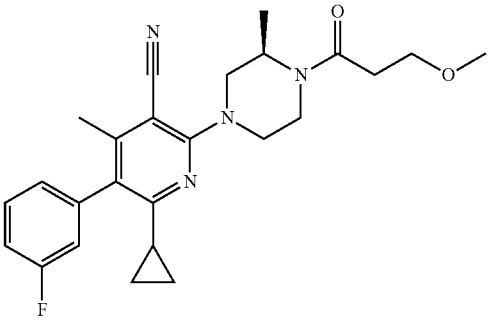
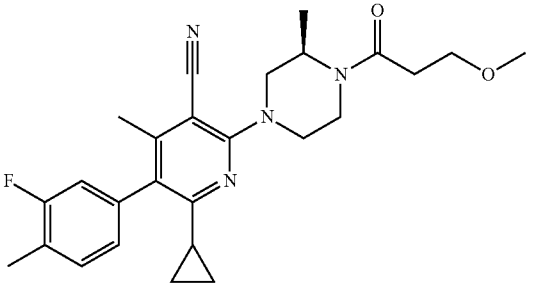
Cmpd No.	Structure
254	
255	
256	
257	
258	

TABLE 1-continued

Exemplary Compounds of Formula I.

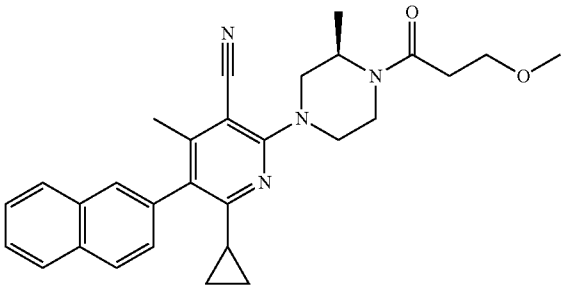
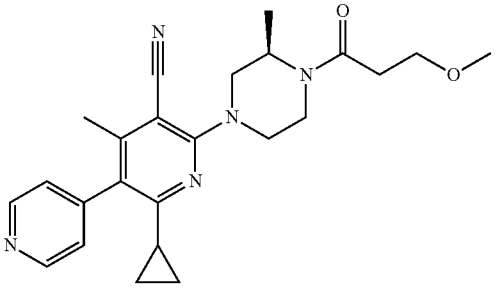
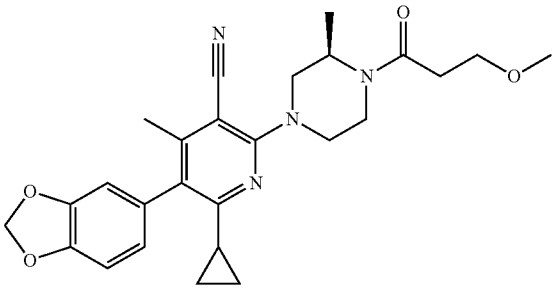
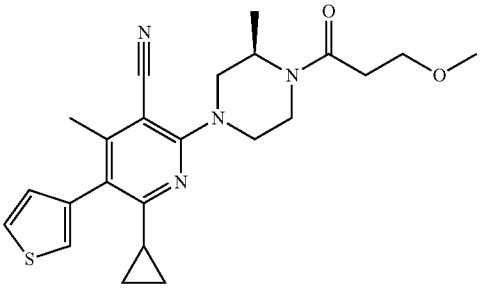
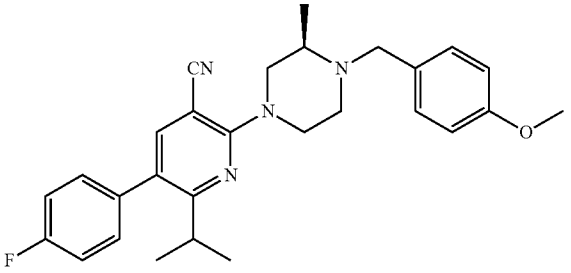
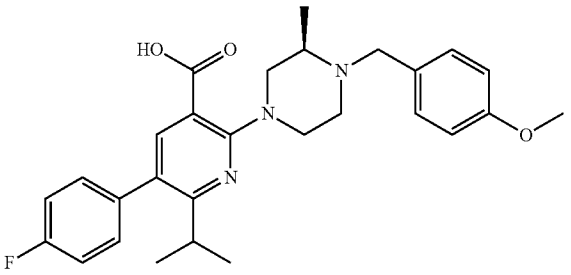
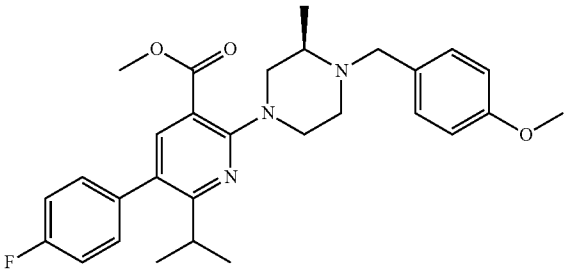
Cmpd No.	Structure
259	
260	
261	
262	
59	

TABLE 1-continued

Exemplary Compounds of Formula I.

Cmpd No.	Structure
60	
61	

[0164] In another embodiment, the compound is selected from any one of the compounds set forth in Table 5, below.

TABLE 5

Exemplary Compounds of Formula I.

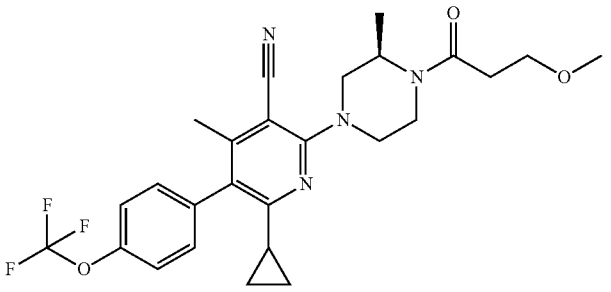
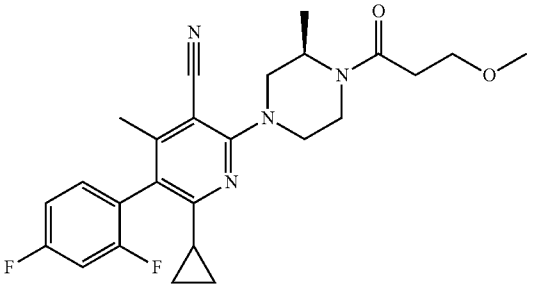
Cpd #	Structure
263	
264	

TABLE 5-continued

Exemplary Compounds of Formula I.

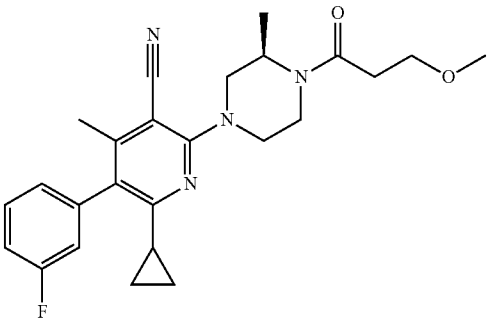
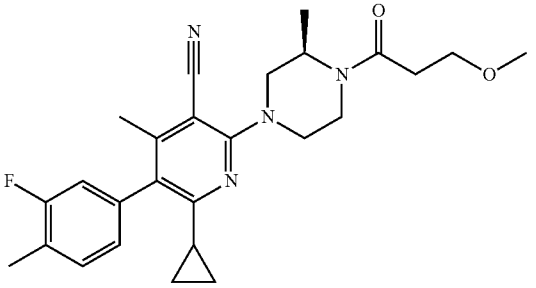
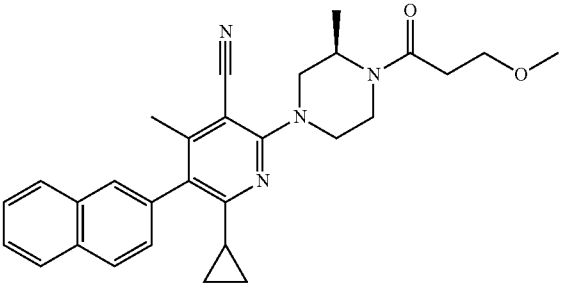
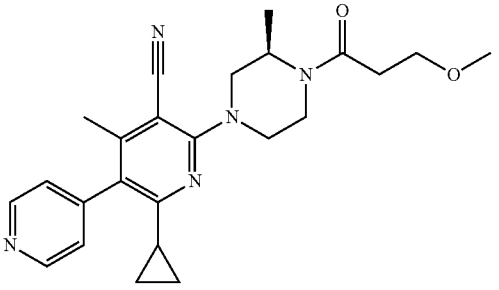
Cpd #	Structure
265	
266	
267	
268	

TABLE 5-continued

Exemplary Compounds of Formula I.

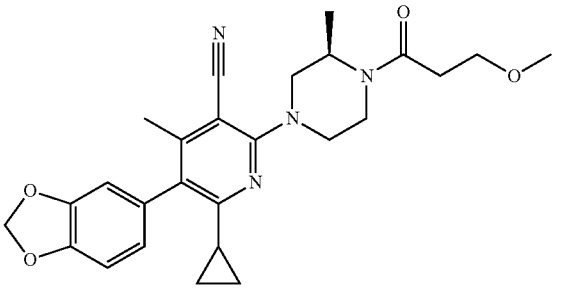
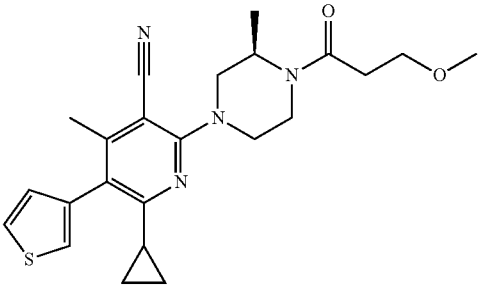
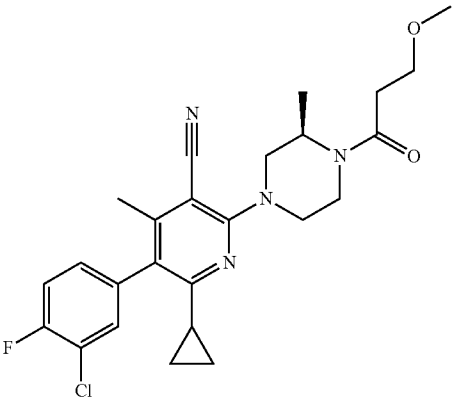
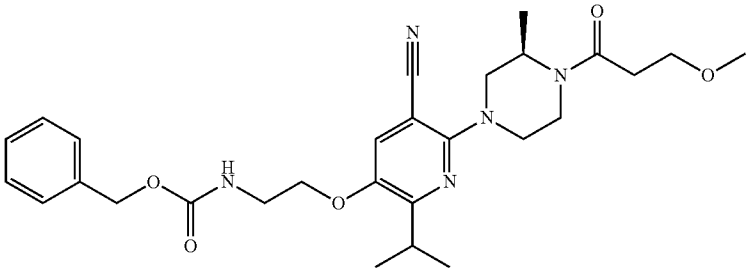
Cpd #	Structure
269	
270	
271	
272	

TABLE 5-continued

Exemplary Compounds of Formula I.

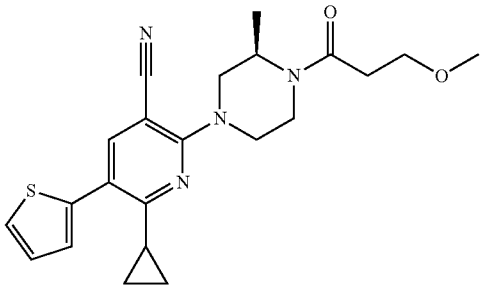
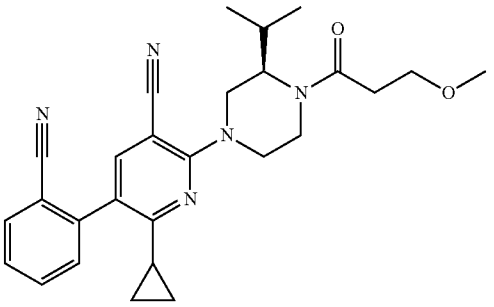
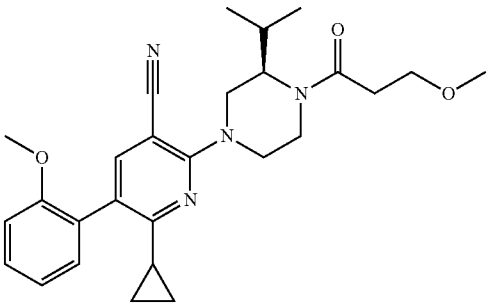
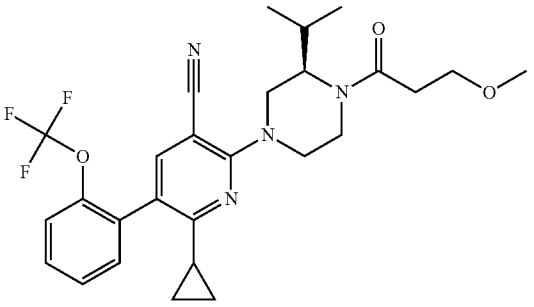
Cpd #	Structure
273	
274	
275	
276	

TABLE 5-continued

Exemplary Compounds of Formula I.

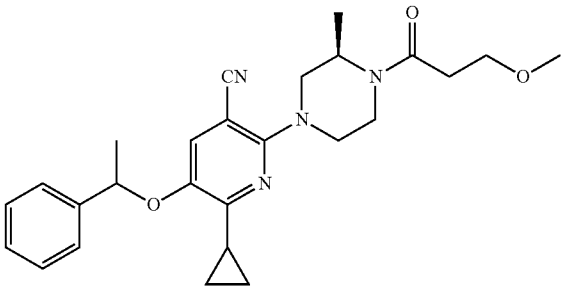
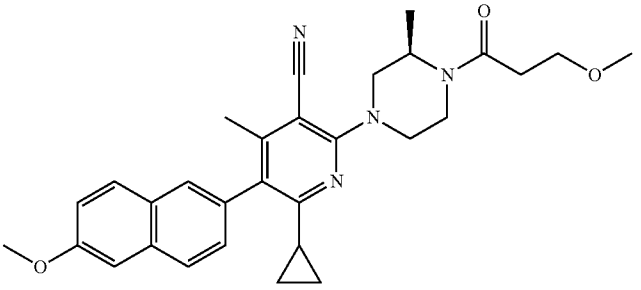
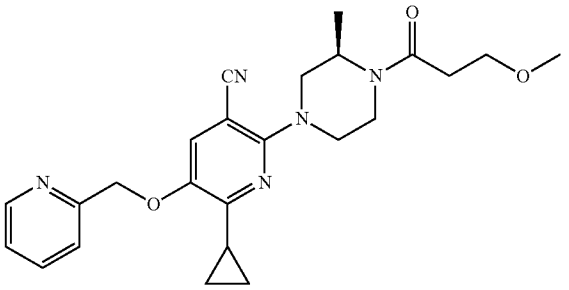
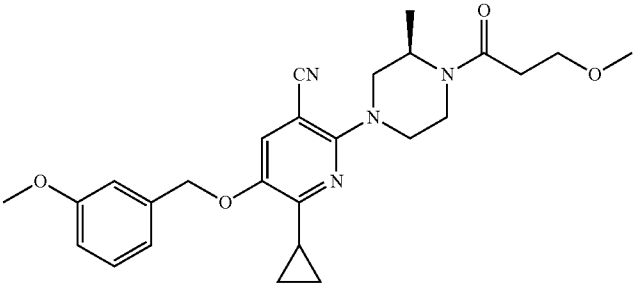
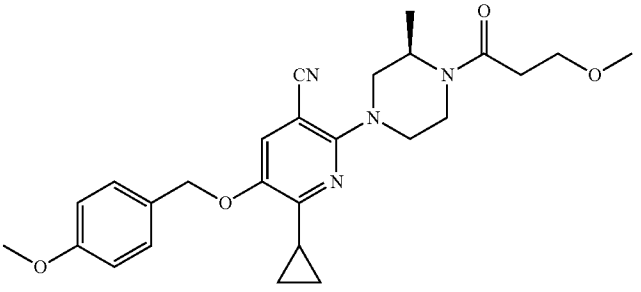
Cpd #	Structure
277	
278	
279	
280	
281	

TABLE 5-continued

Exemplary Compounds of Formula I.

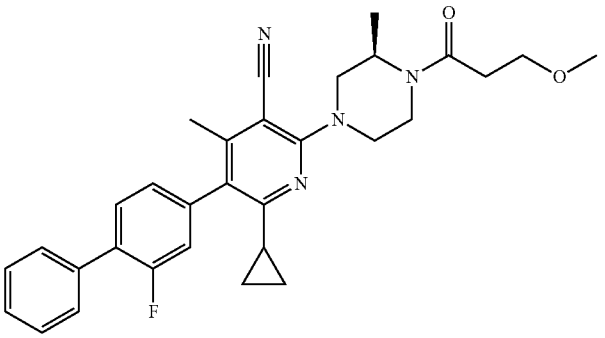
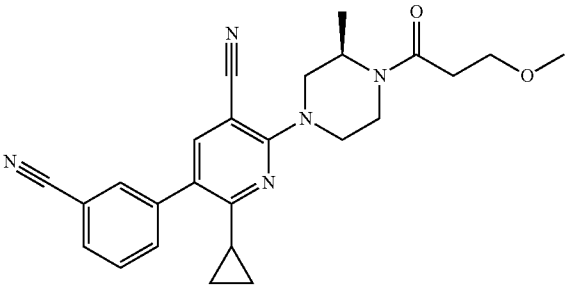
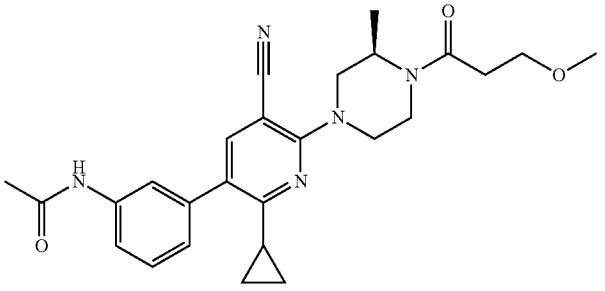
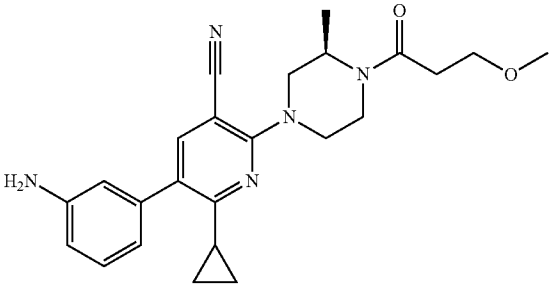
Cpd #	Structure
282	
283	
284	
285	

TABLE 5-continued

Exemplary Compounds of Formula I.

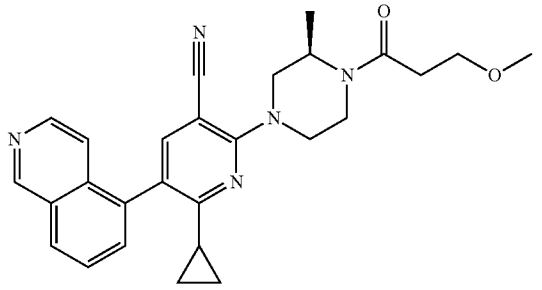
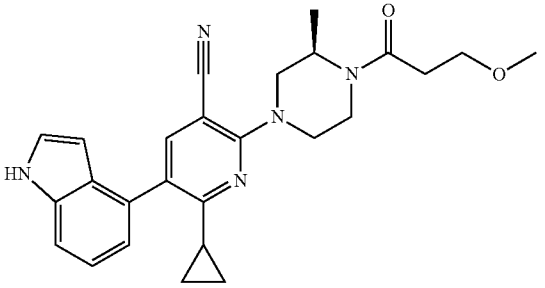
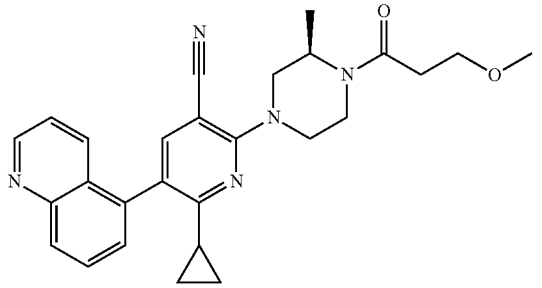
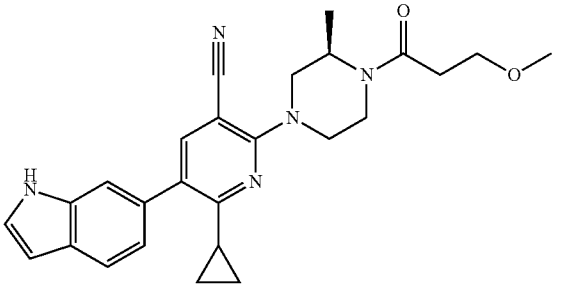
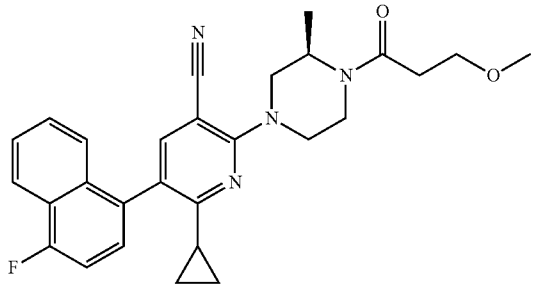
Cpd #	Structure
286	
287	
288	
289	
290	

TABLE 5-continued

Exemplary Compounds of Formula I.

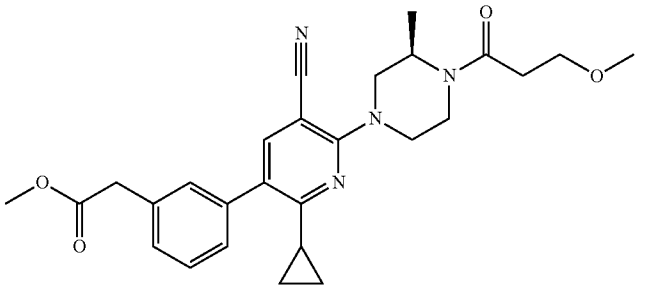
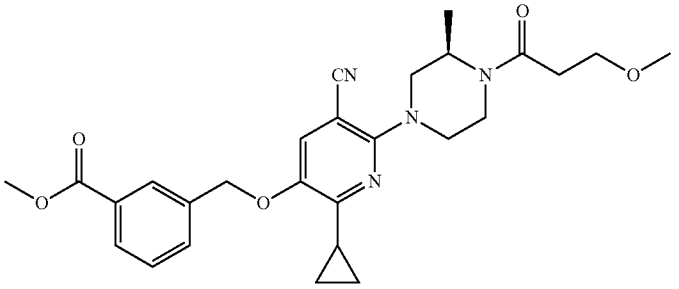
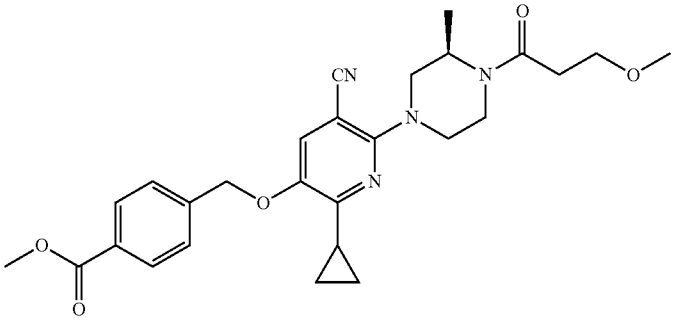
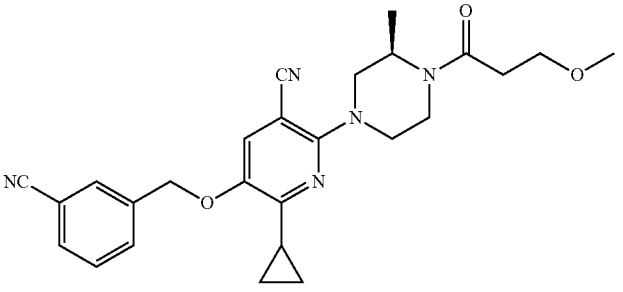
Cpd #	Structure
291	
292	
293	
294	

TABLE 5-continued

Exemplary Compounds of Formula I.

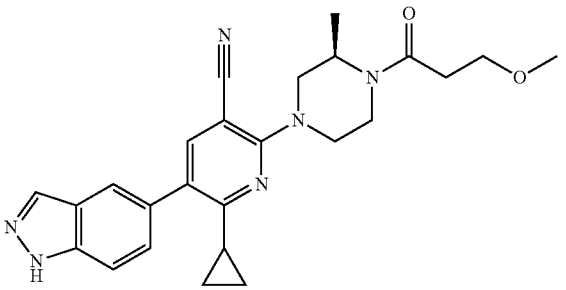
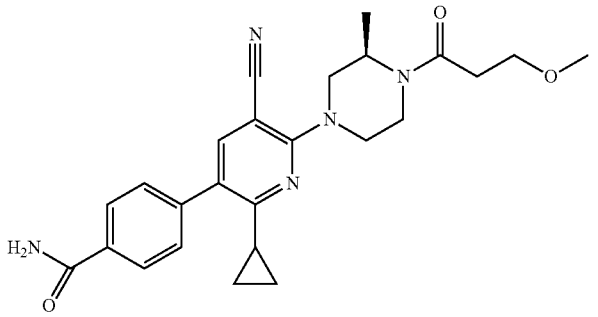
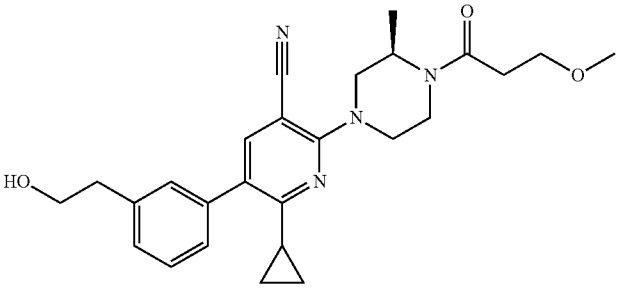
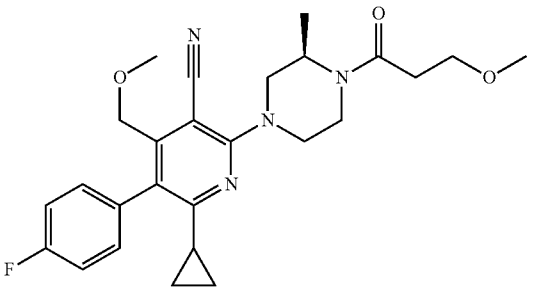
Cpd #	Structure
295	
296	
297	
298	

TABLE 5-continued

Exemplary Compounds of Formula I.

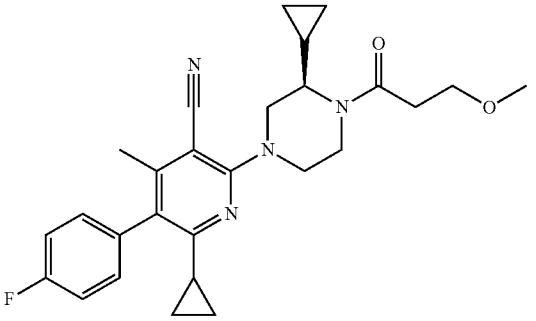
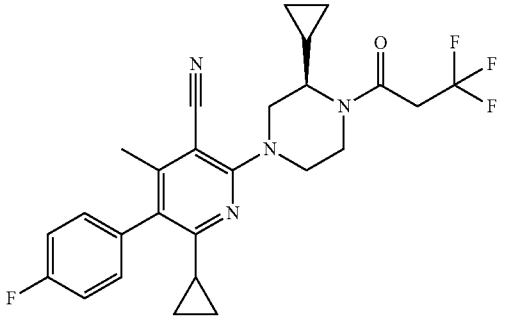
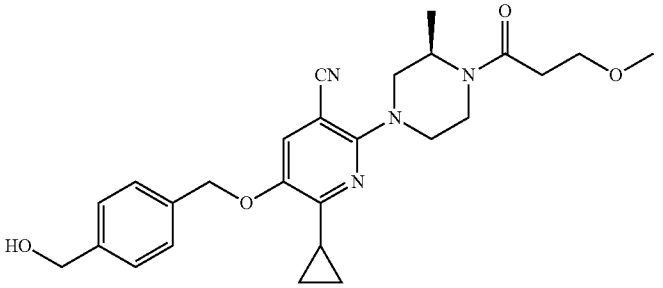
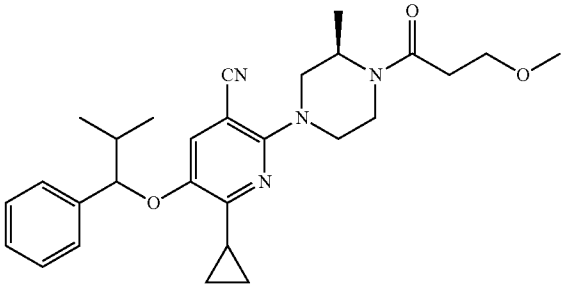
Cpd #	Structure
299	
300	
301	
302	

TABLE 5-continued

Exemplary Compounds of Formula I.

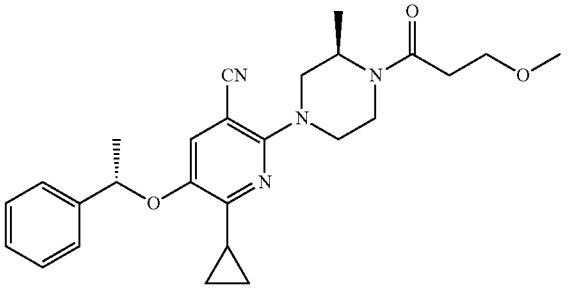
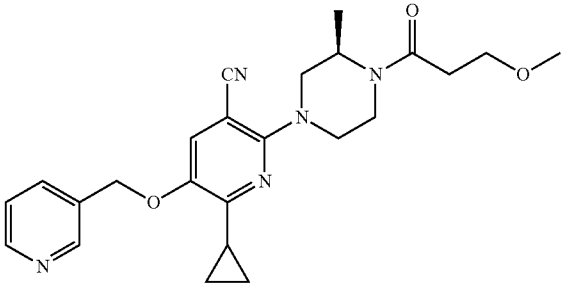
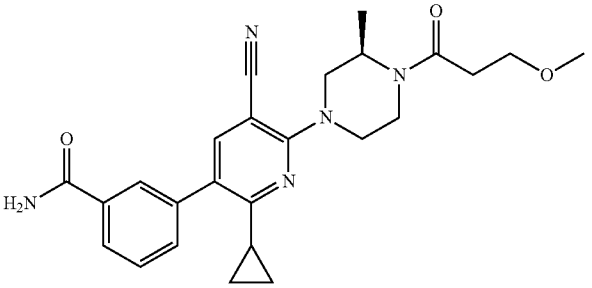
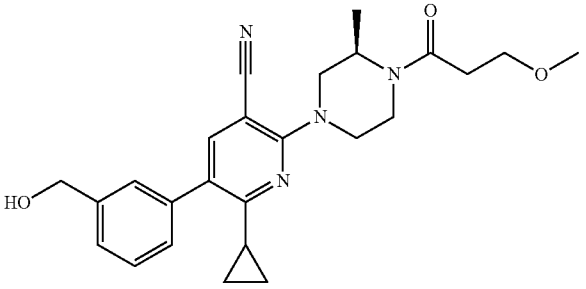
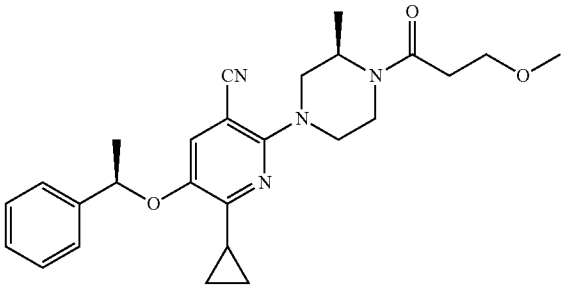
Cpd #	Structure
303	
304	
305	
306	
307	

TABLE 5-continued

Exemplary Compounds of Formula I.

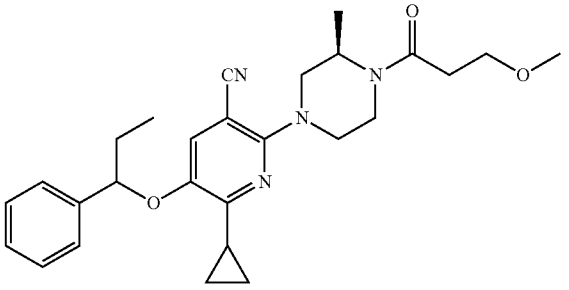
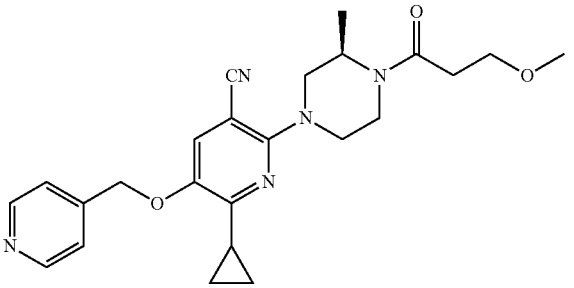
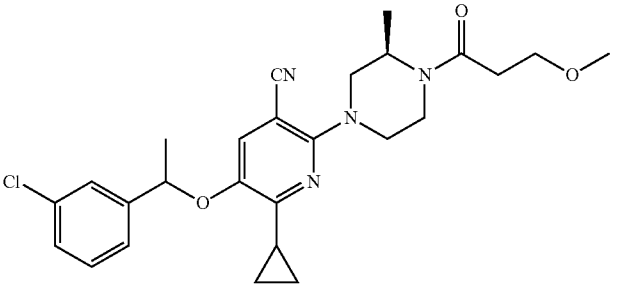
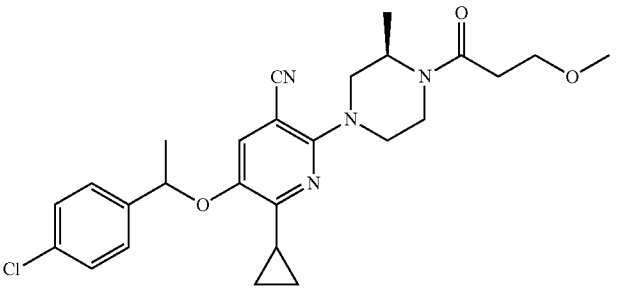
Cpd #	Structure
308	
309	
310	
311	

TABLE 5-continued

Exemplary Compounds of Formula I.

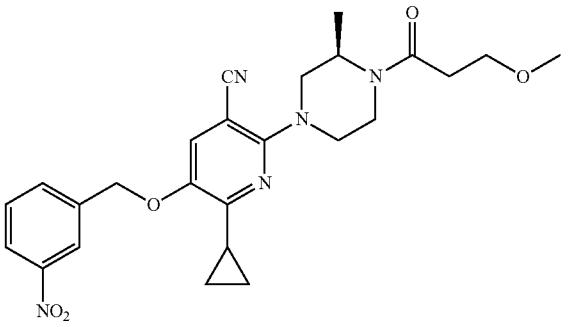
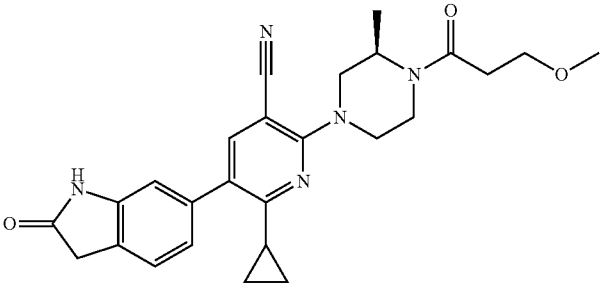
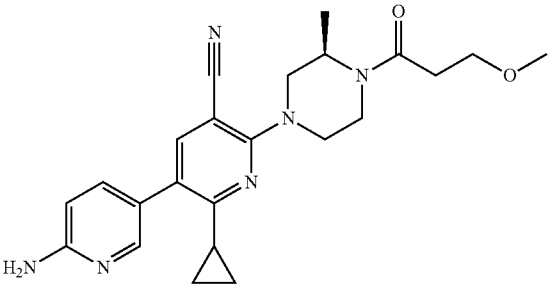
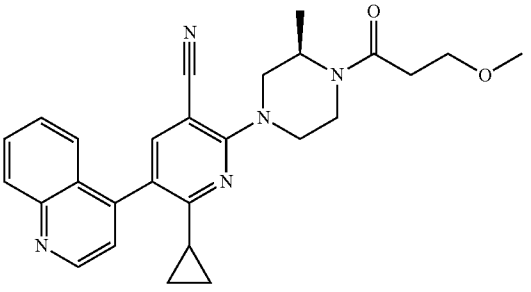
Cpd #	Structure
312	
313	
314	
315	

TABLE 5-continued

Exemplary Compounds of Formula I.

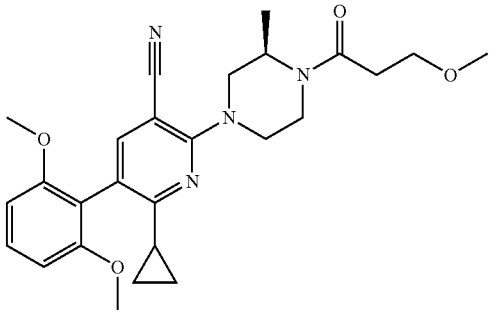
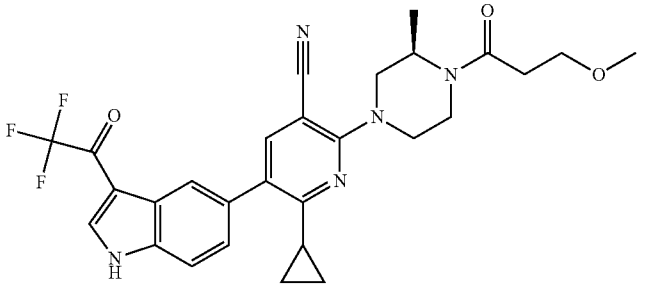
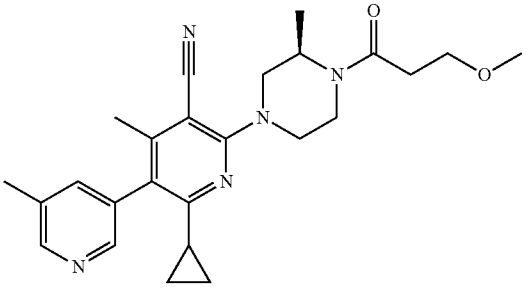
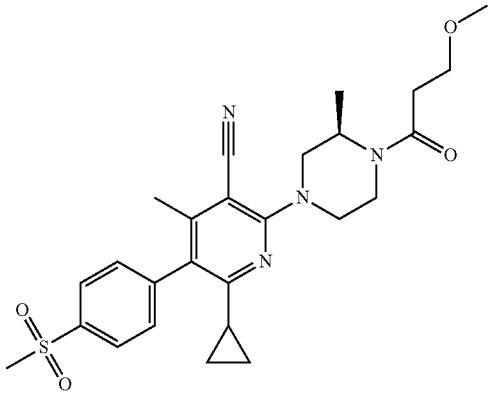
Cpd #	Structure
316	
317	
318	
319	

TABLE 5-continued

Exemplary Compounds of Formula I.

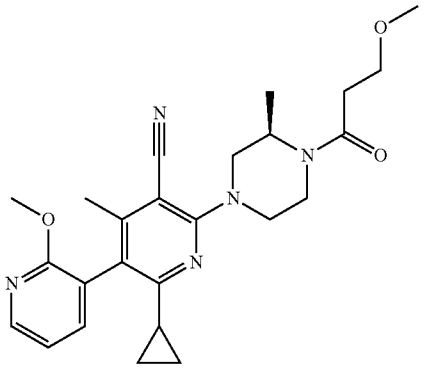
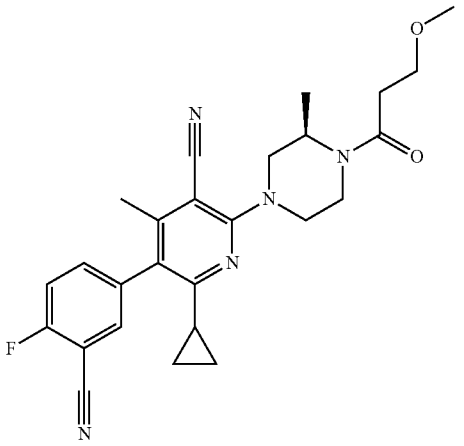
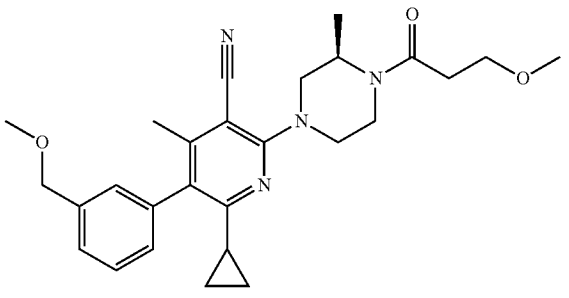
Cpd #	Structure
320	
321	
322	

TABLE 5-continued

Exemplary Compounds of Formula I.

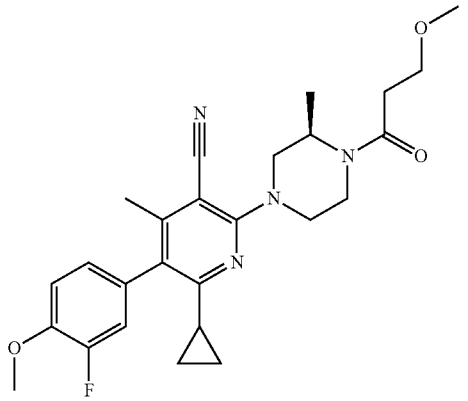
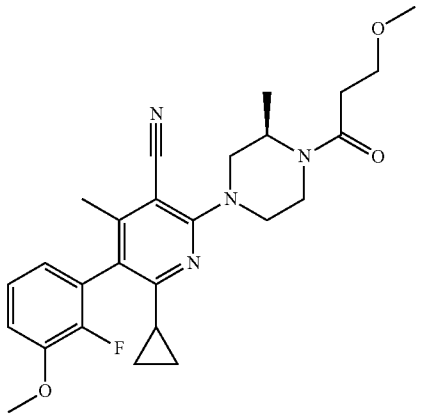
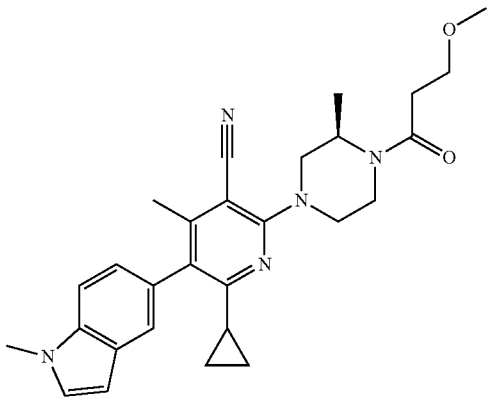
Cpd #	Structure
323	
324	
325	

TABLE 5-continued

Exemplary Compounds of Formula I.

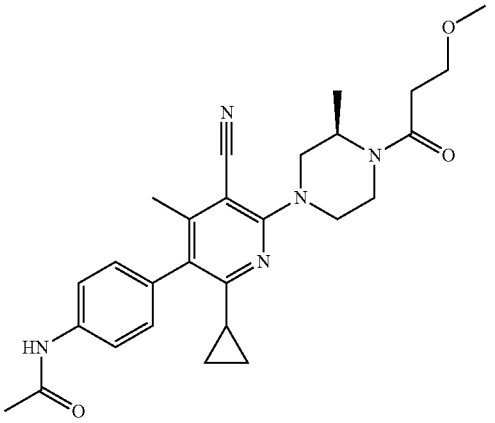
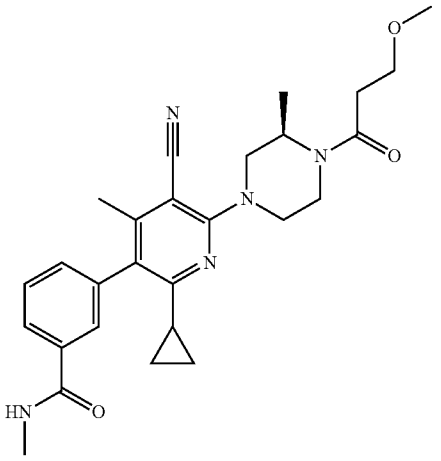
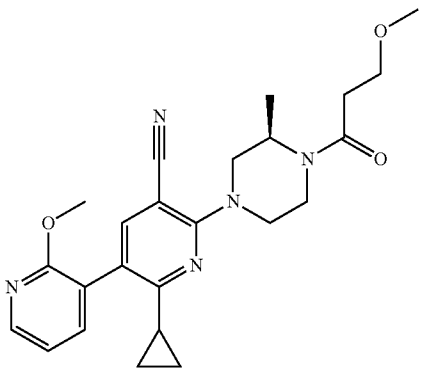
Cpd #	Structure
326	
327	
328	

TABLE 5-continued

Exemplary Compounds of Formula I.

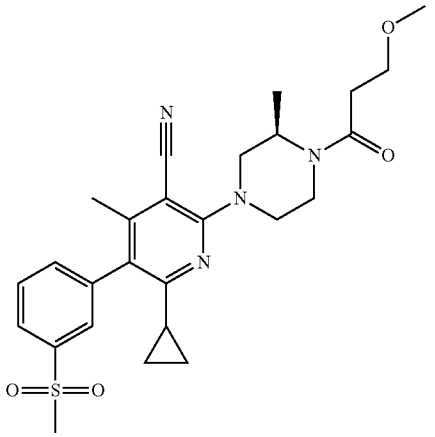
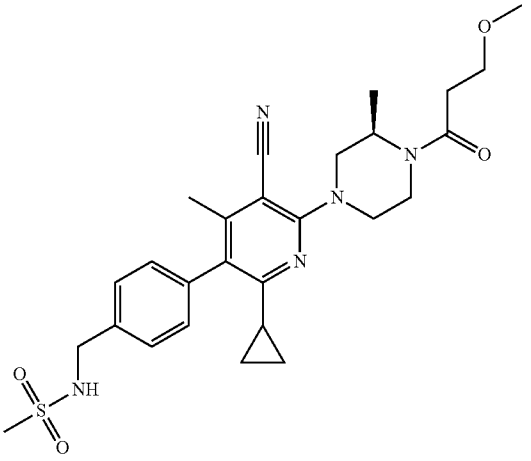
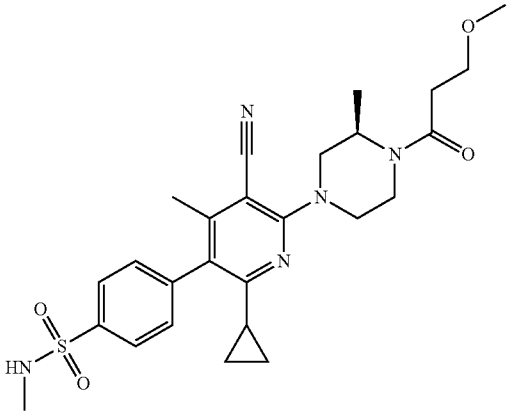
Cpd #	Structure
329	
330	
331	

TABLE 5-continued

Exemplary Compounds of Formula I.

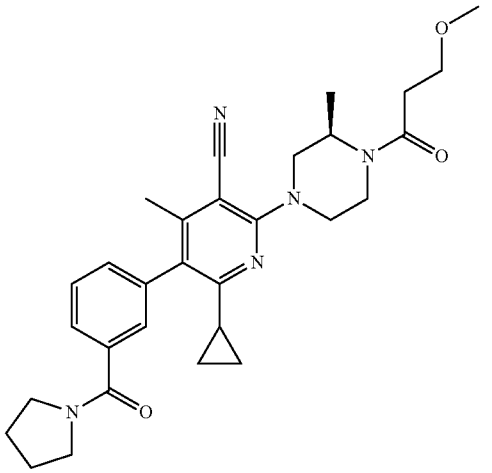
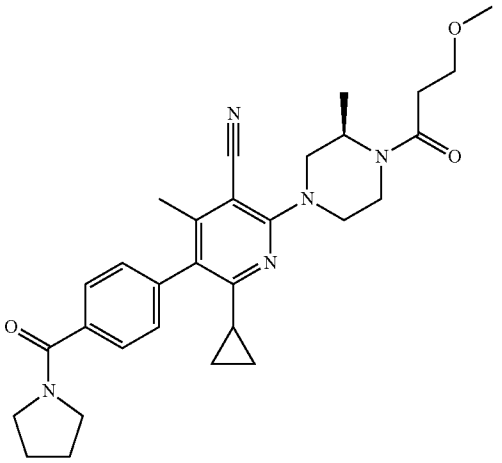
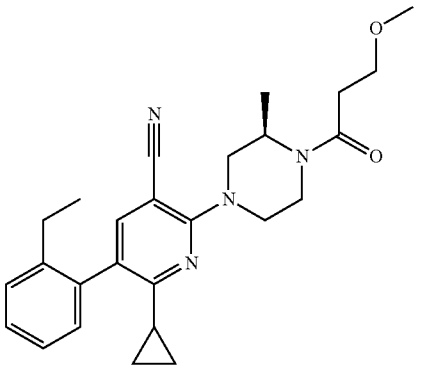
Cpd #	Structure
332	
333	
334	

TABLE 5-continued

Exemplary Compounds of Formula I.

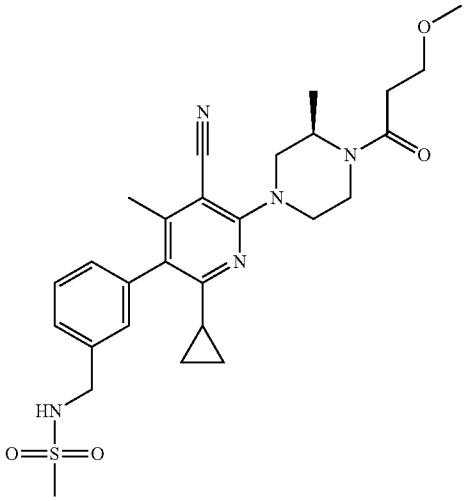
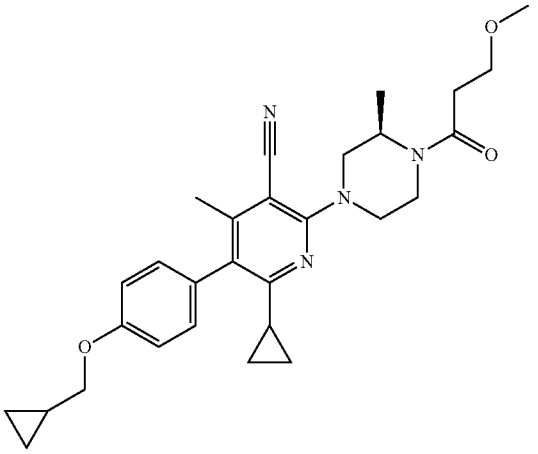
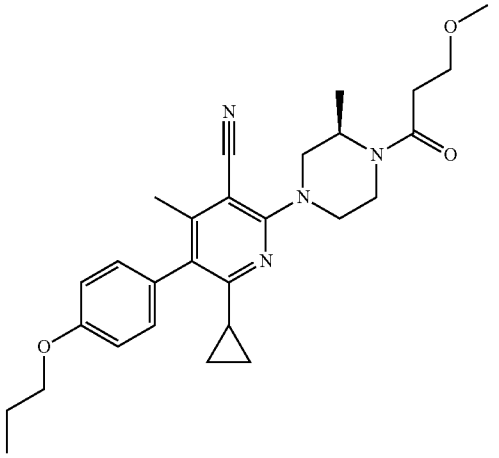
Cpd #	Structure
335	
336	
337	

TABLE 5-continued

Exemplary Compounds of Formula I.

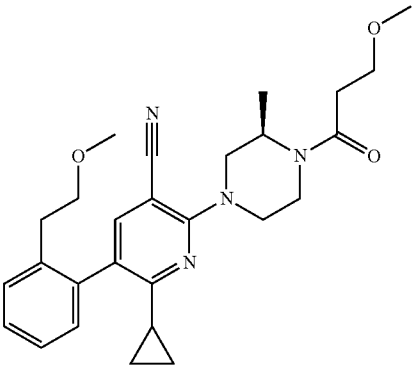
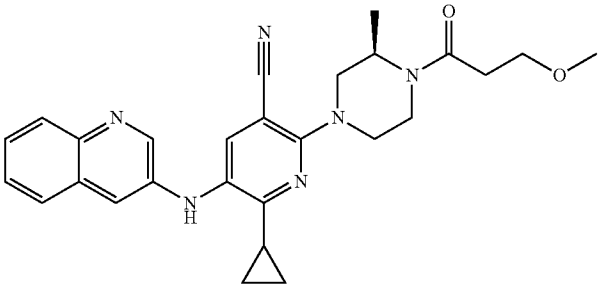
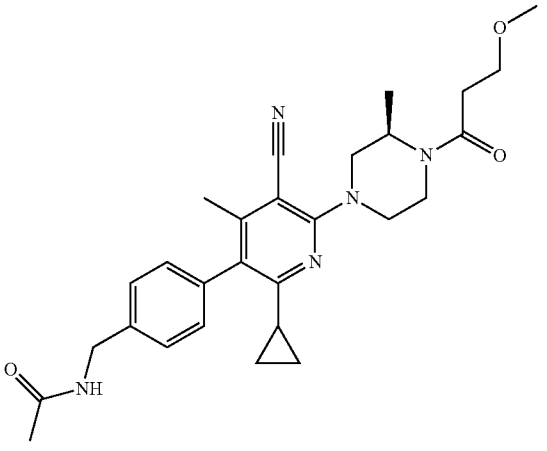
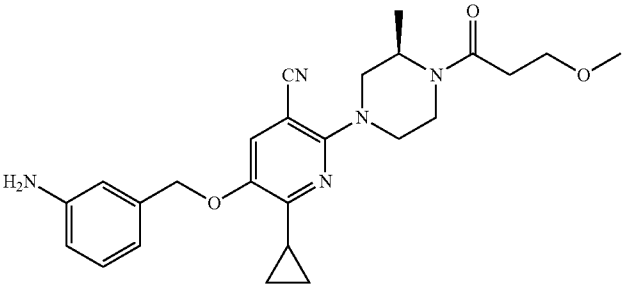
Cpd #	Structure
338	
339	
340	
341	

TABLE 5-continued

Exemplary Compounds of Formula I.

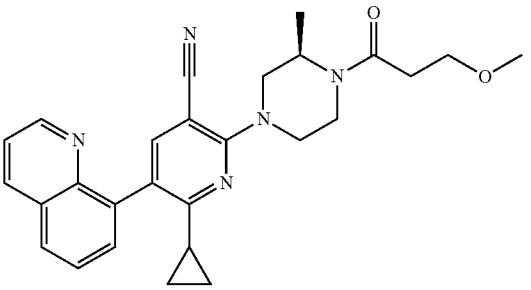
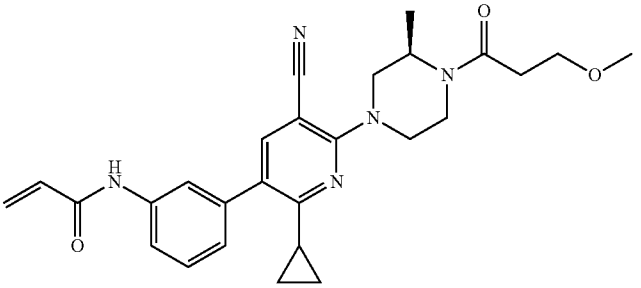
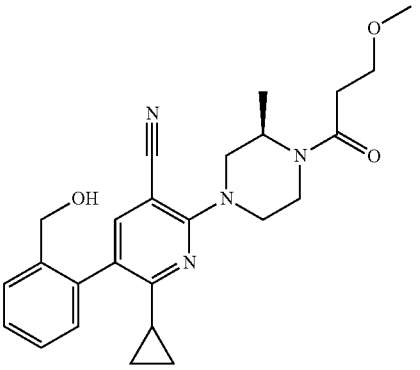
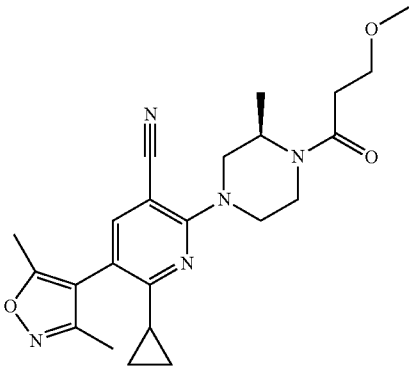
Cpd #	Structure
342	
343	
344	
345	

TABLE 5-continued

Exemplary Compounds of Formula I.

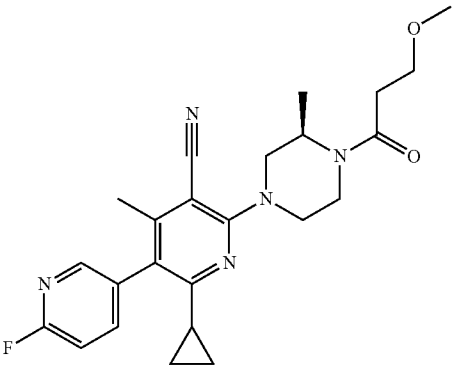
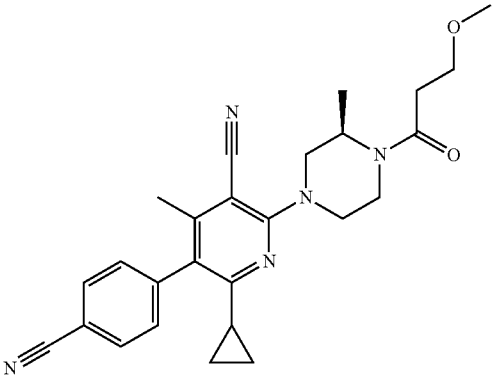
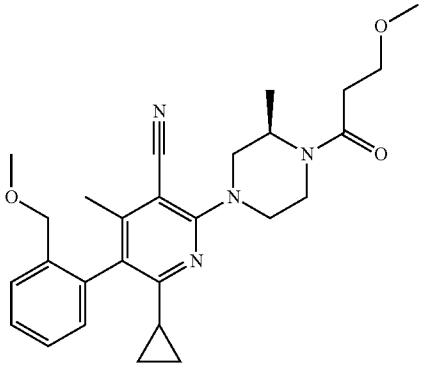
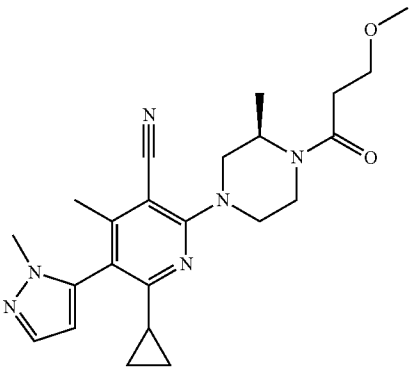
Cpd #	Structure
346	
347	
348	
349	

TABLE 5-continued

Exemplary Compounds of Formula I.

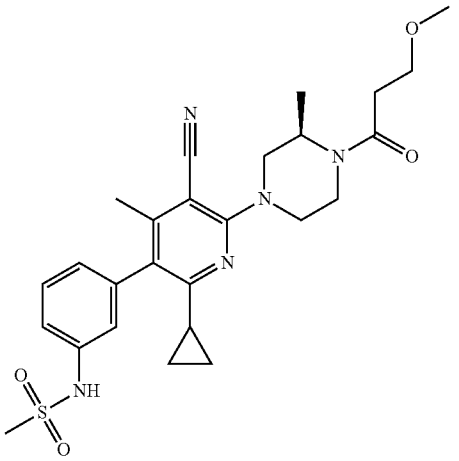
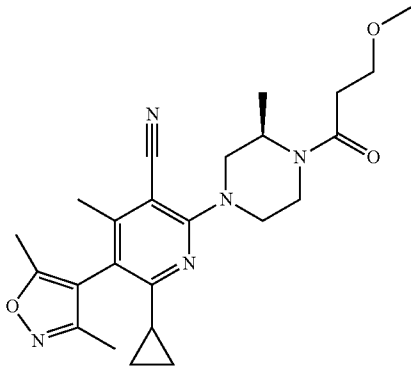
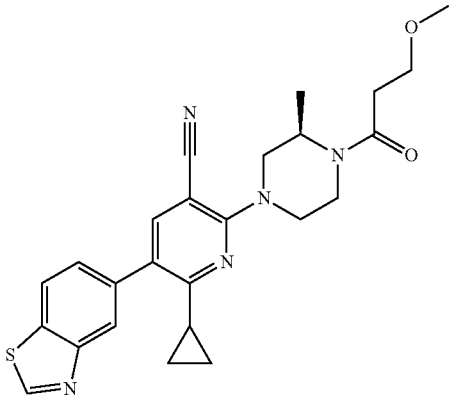
Cpd #	Structure
350	
351	
352	

TABLE 5-continued

Exemplary Compounds of Formula I.

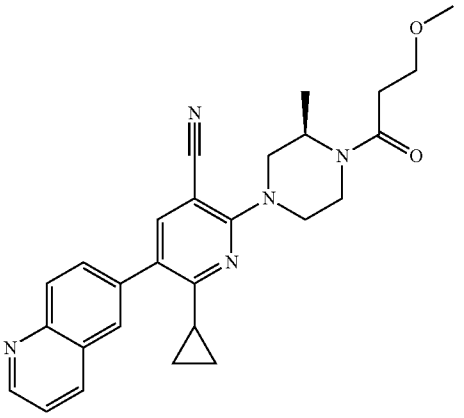
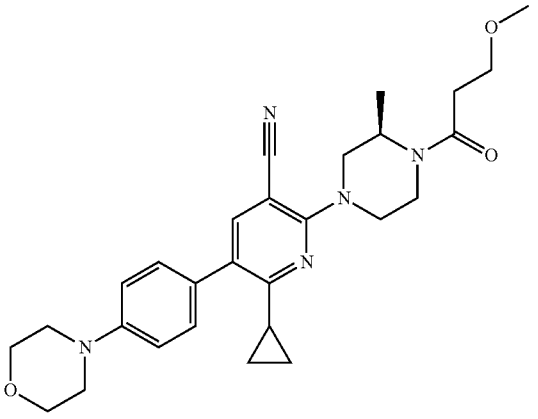
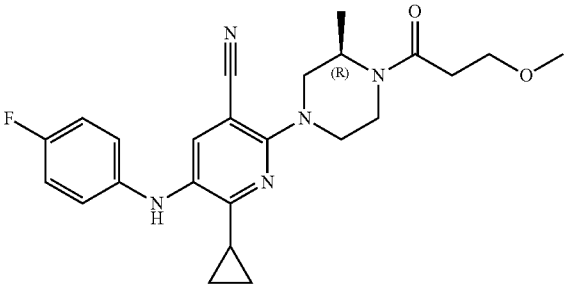
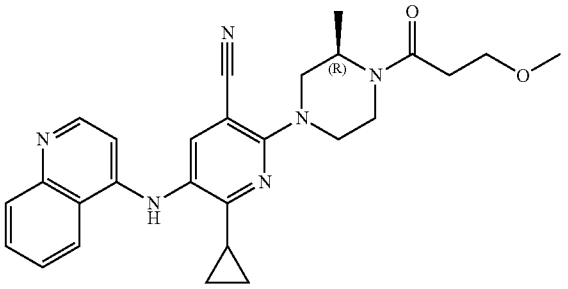
Cpd #	Structure
353	
354	
355	
356	

TABLE 5-continued

Exemplary Compounds of Formula I.

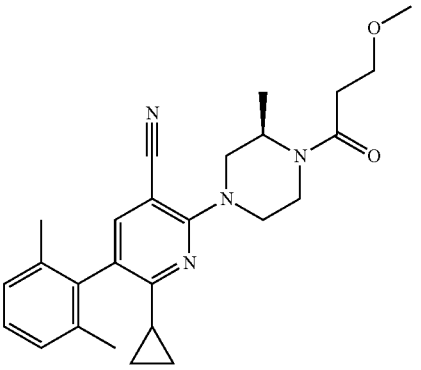
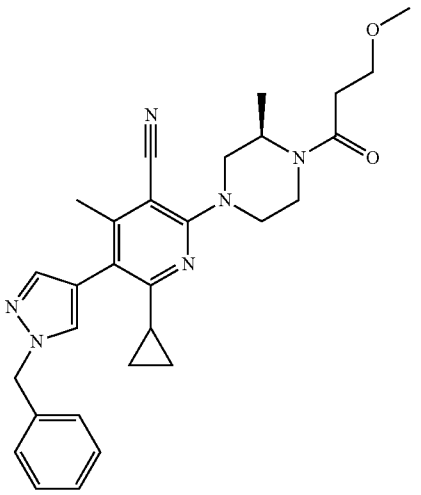
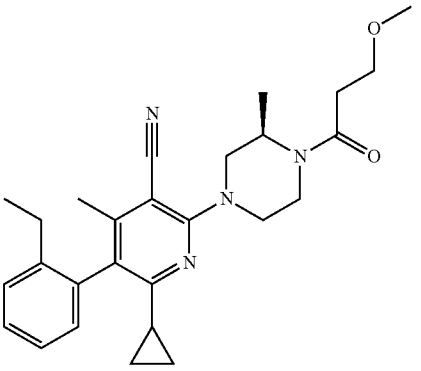
Cpd #	Structure
357	
358	
359	

TABLE 5-continued

Exemplary Compounds of Formula I.

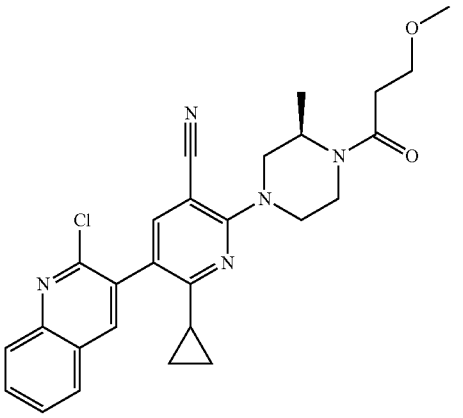
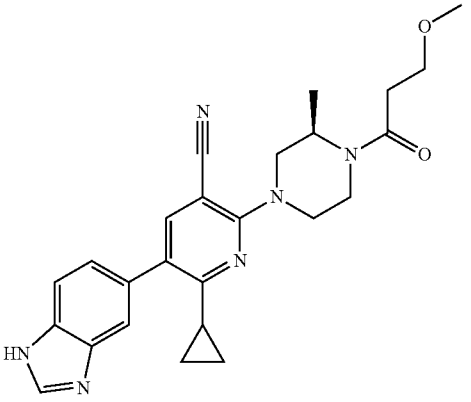
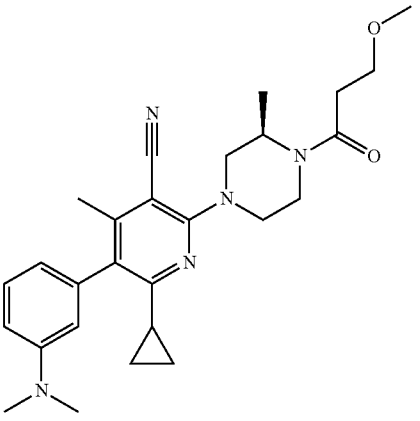
Cpd #	Structure
360	
361	
362	

TABLE 5-continued

Exemplary Compounds of Formula I.

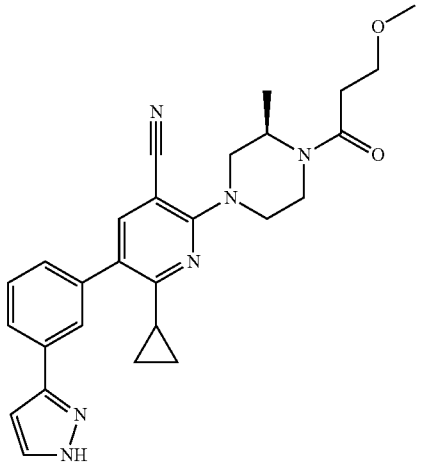
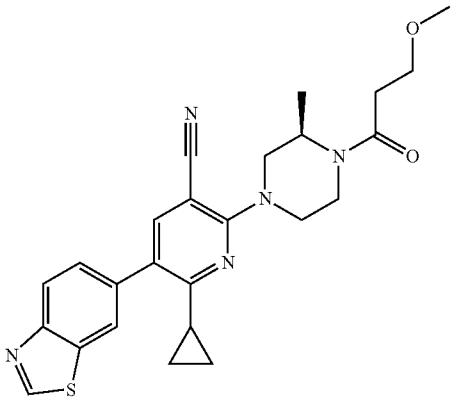
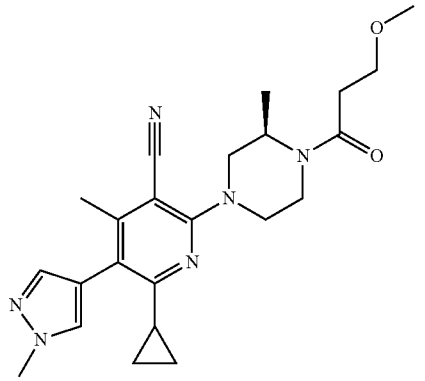
Cpd #	Structure
363	
364	
365	

TABLE 5-continued

Exemplary Compounds of Formula I.

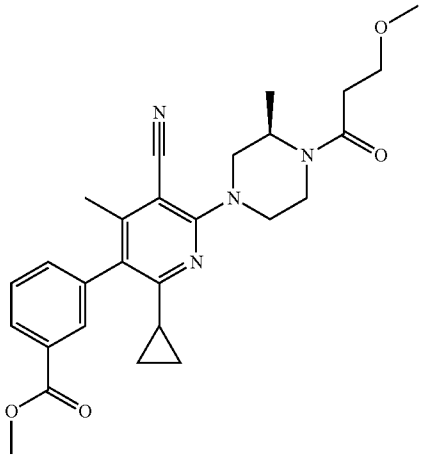
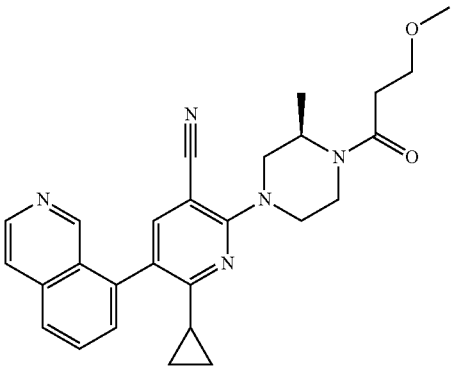
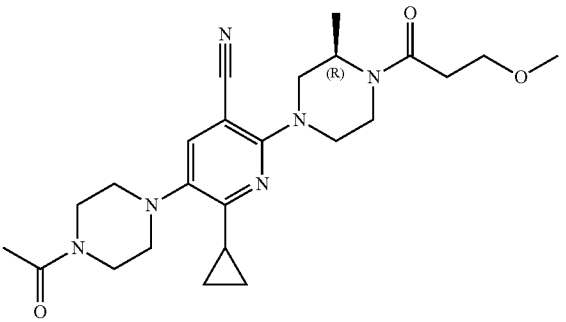
Cpd #	Structure
366	
367	
368	

TABLE 5-continued

Exemplary Compounds of Formula I.

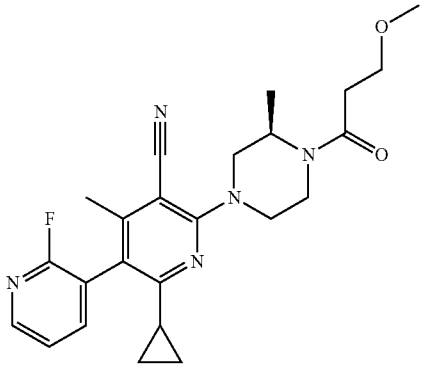
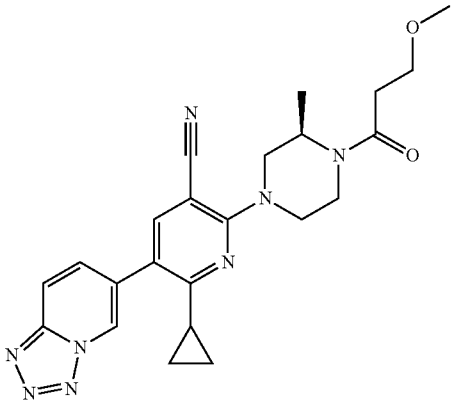
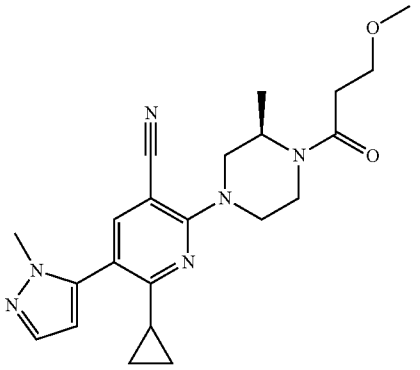
Cpd #	Structure
369	
370	
371	

TABLE 5-continued

Exemplary Compounds of Formula I.

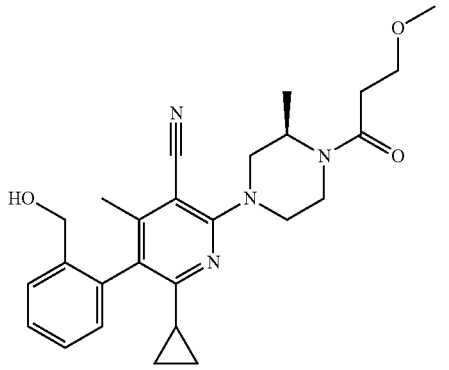
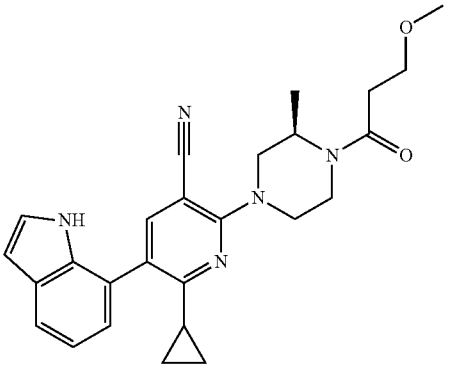
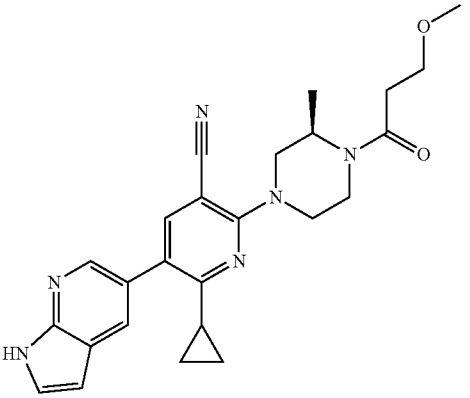
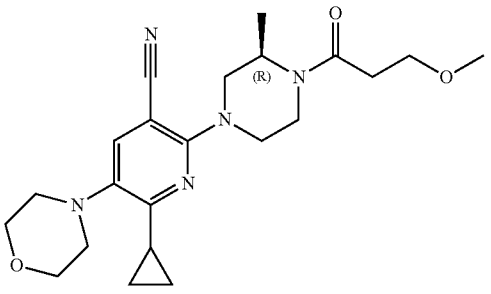
Cpd #	Structure
372	
373	
374	
375	

TABLE 5-continued

Exemplary Compounds of Formula I.

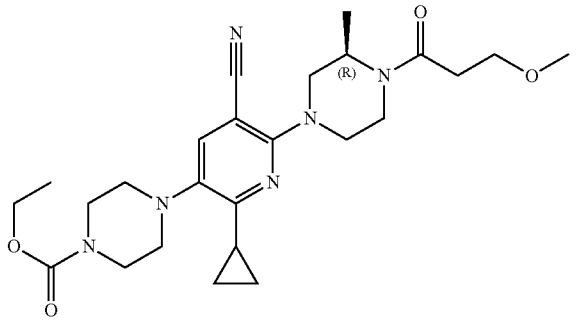
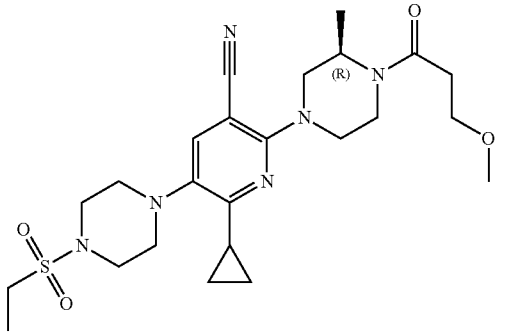
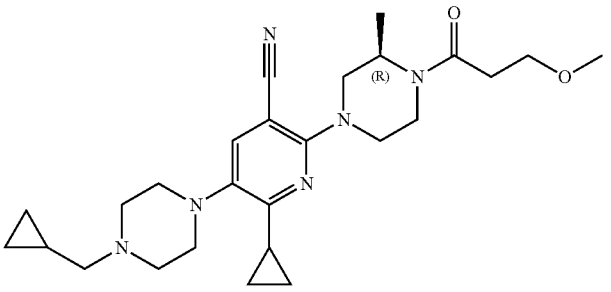
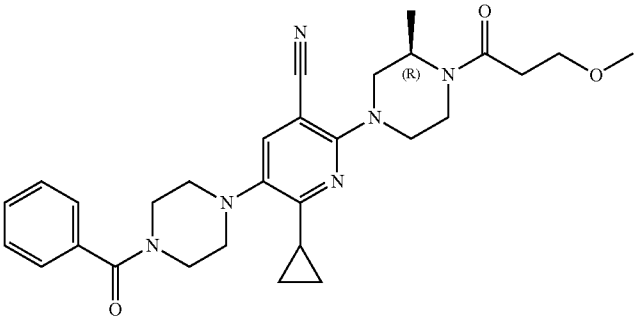
Cpd #	Structure
376	
377	
378	
379	

TABLE 5-continued

Exemplary Compounds of Formula I.

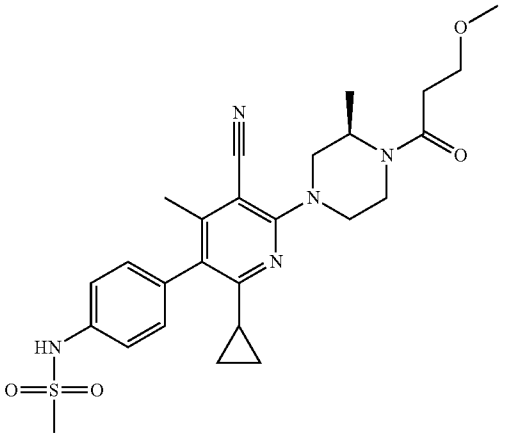
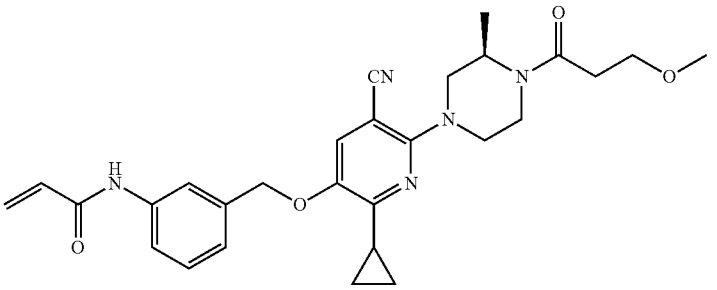
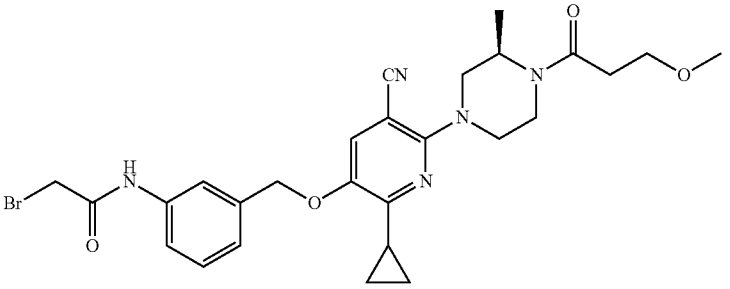
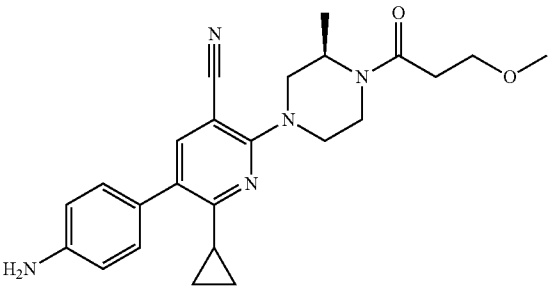
Cpd #	Structure
380	
381	
382	
383	

TABLE 5-continued

Exemplary Compounds of Formula I.

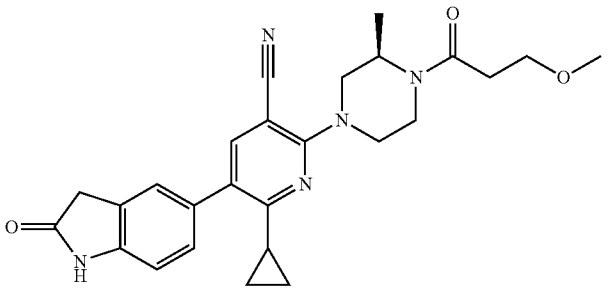
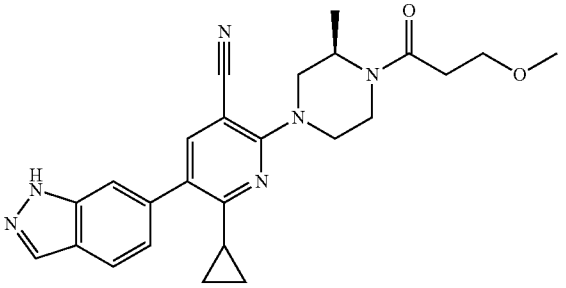
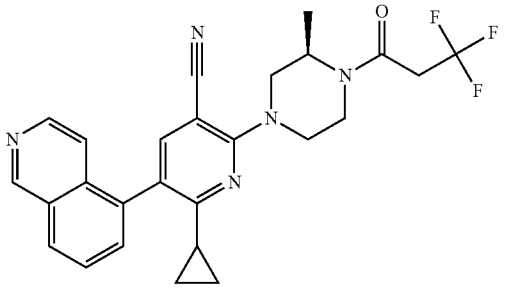
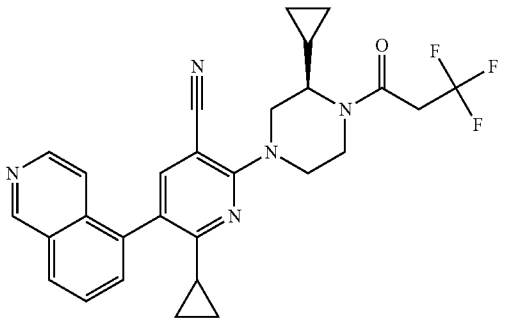
Cpd #	Structure
384	
385	
386	
387	

TABLE 5-continued

Exemplary Compounds of Formula I.

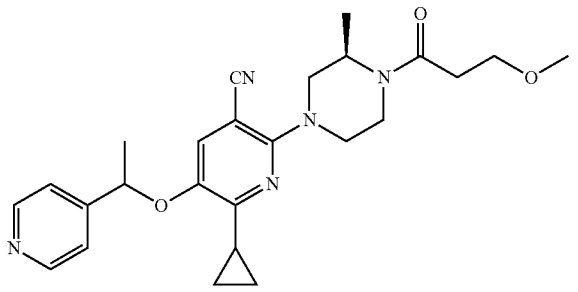
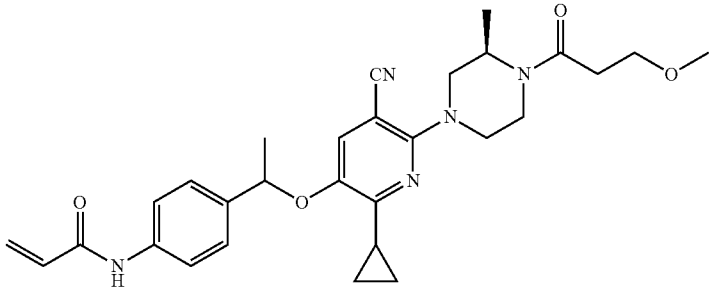
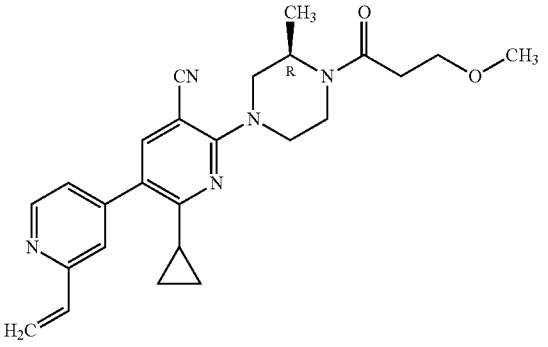
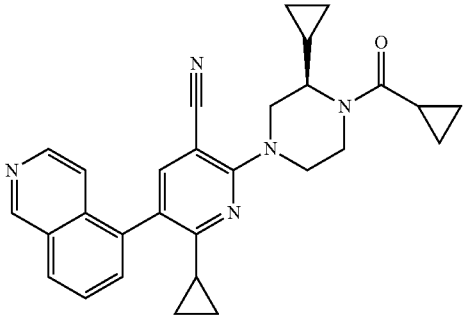
Cpd #	Structure
388	
389	
390	
391	

TABLE 5-continued

Exemplary Compounds of Formula I.

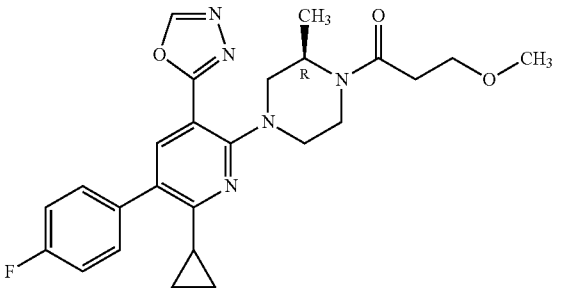
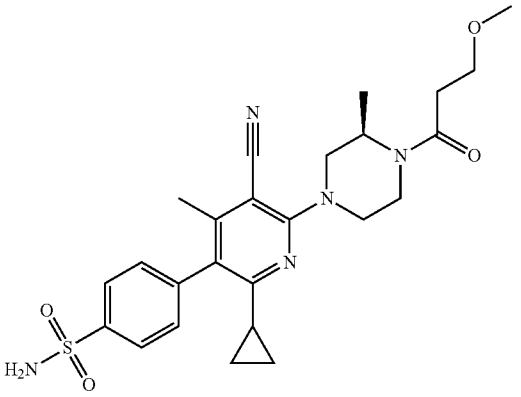
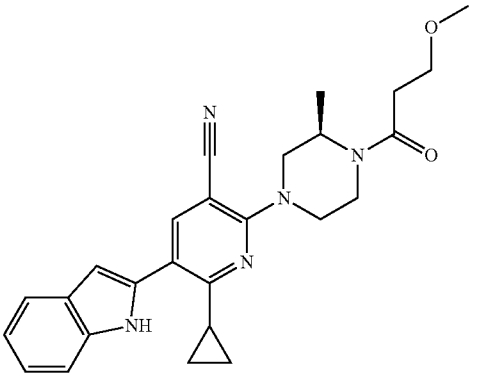
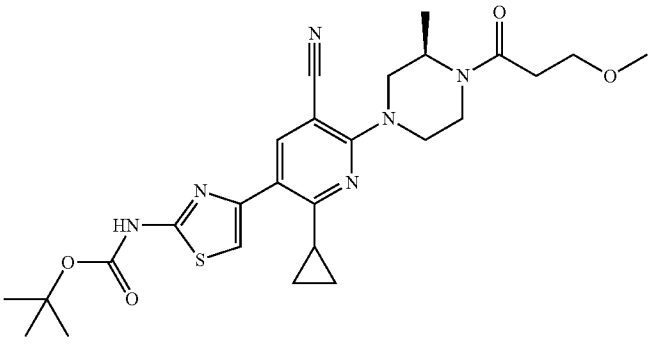
Cpd #	Structure
392	
393	
394	
395	

TABLE 5-continued

Exemplary Compounds of Formula I.

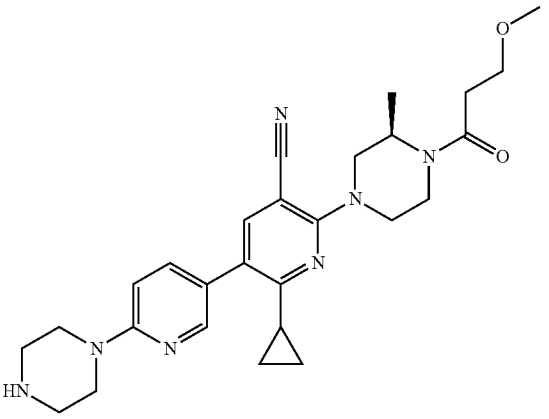
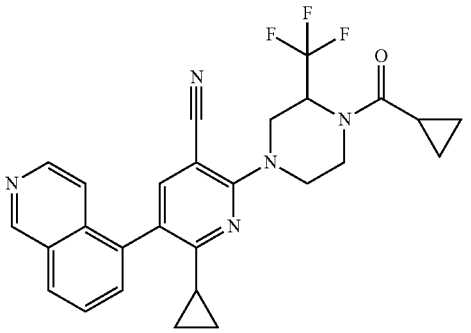
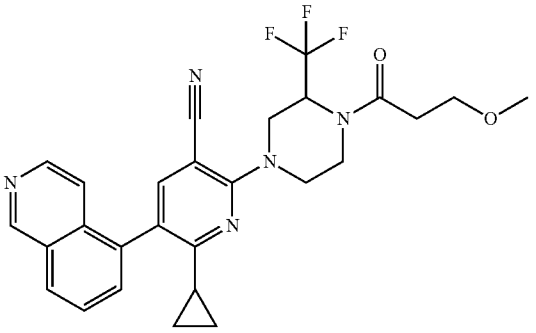
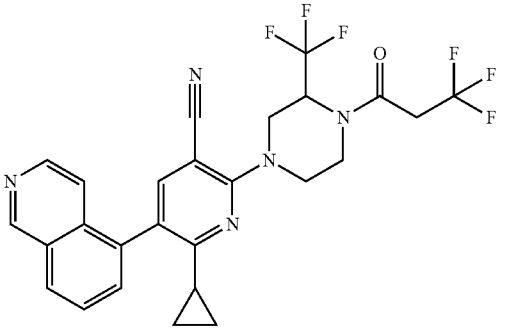
Cpd #	Structure
396	
397	
398	
399	

TABLE 5-continued

Exemplary Compounds of Formula I.

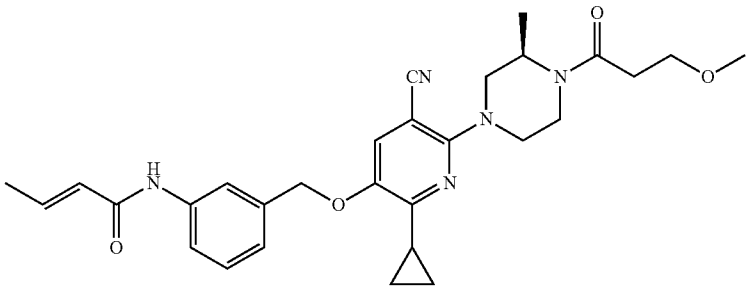
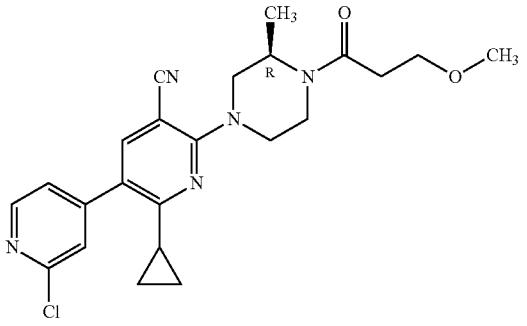
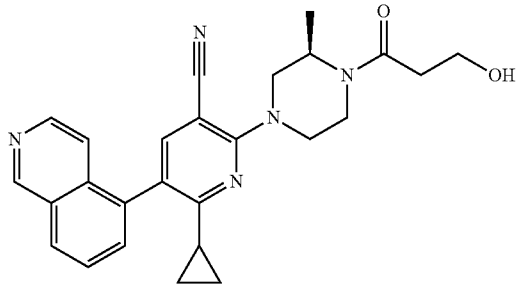
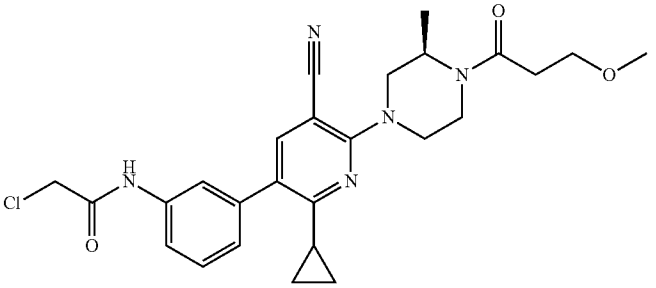
Cpd #	Structure
400	
401	
402	
403	

TABLE 5-continued

Exemplary Compounds of Formula I.

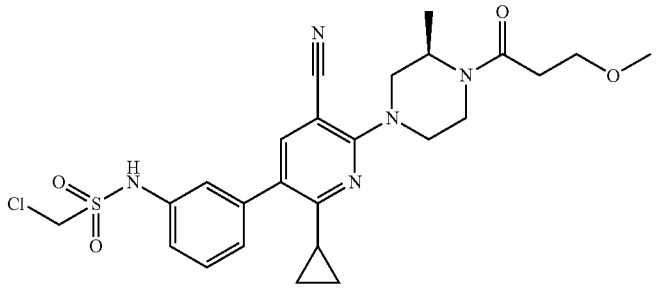
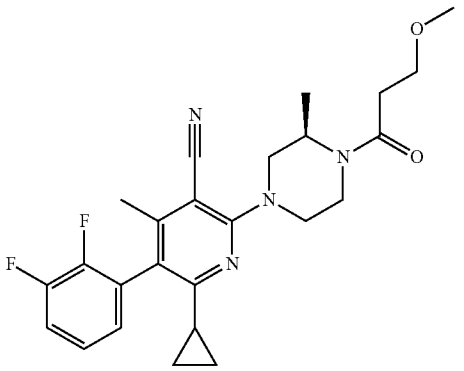
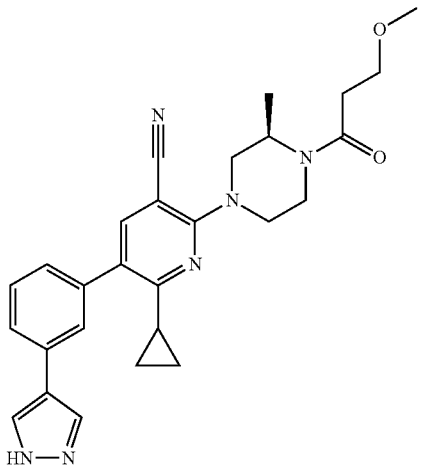
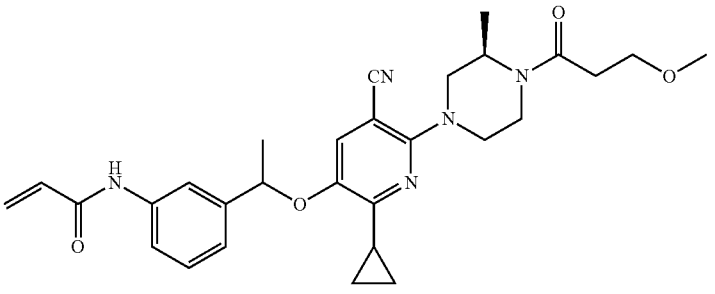
Cpd #	Structure
404	
405	
406	
407	

TABLE 5-continued

Exemplary Compounds of Formula I.

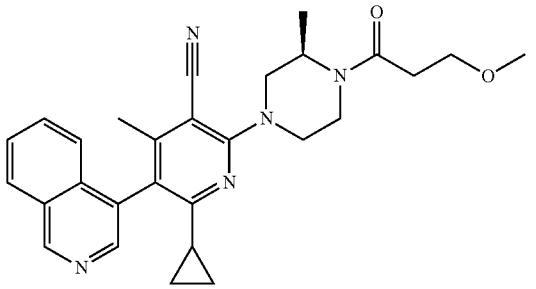
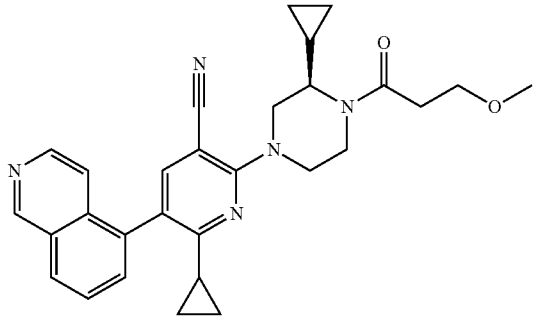
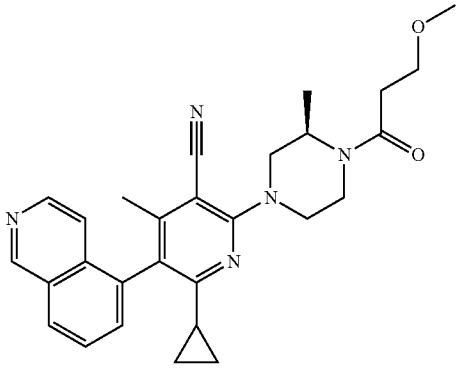
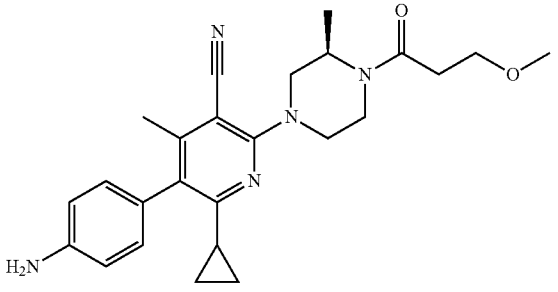
Cpd #	Structure
408	
409	
410	
411	

TABLE 5-continued

Exemplary Compounds of Formula I.

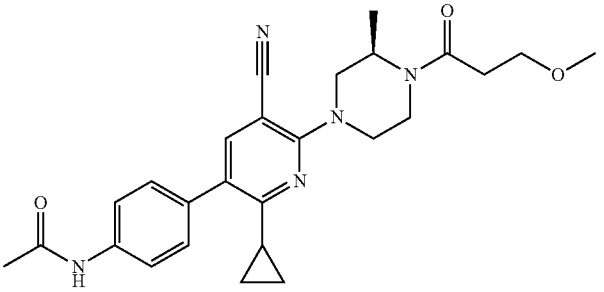
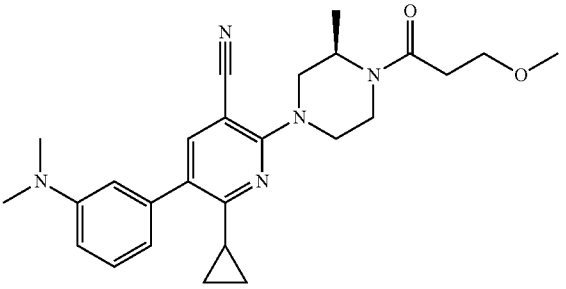
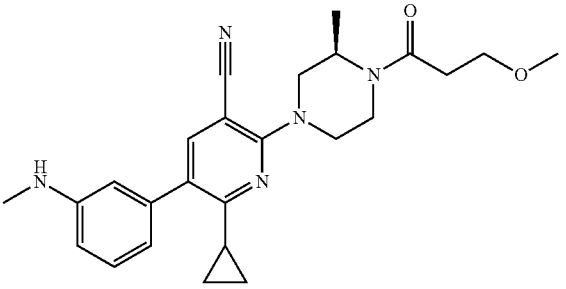
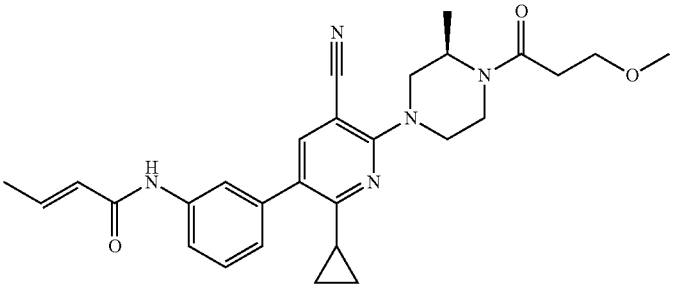
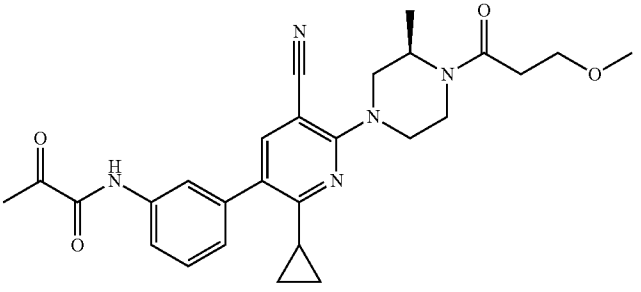
Cpd #	Structure
412	
413	
414	
415	
416	

TABLE 5-continued

Exemplary Compounds of Formula I.

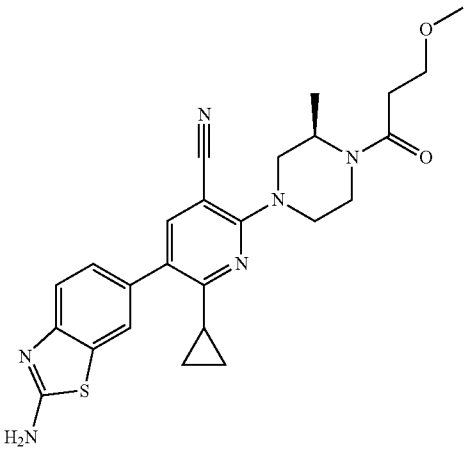
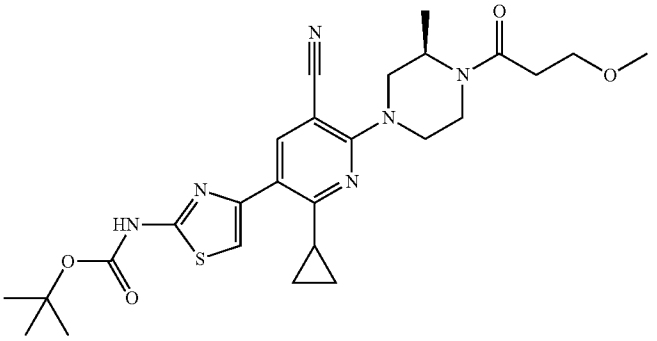
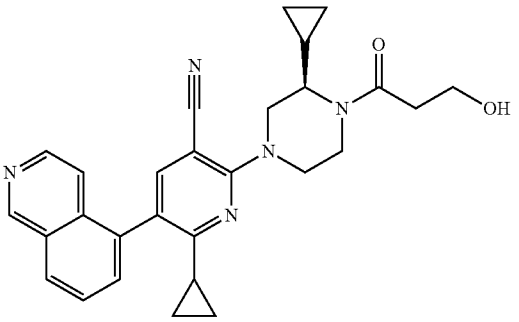
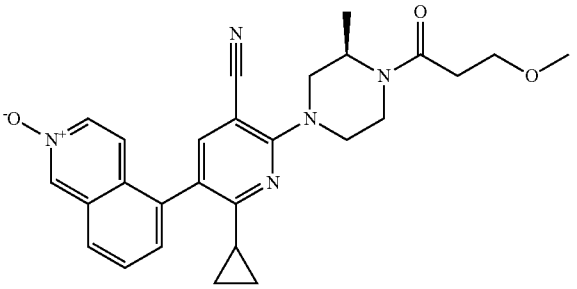
Cpd #	Structure
417	
418	
419	
420	

TABLE 5-continued

Exemplary Compounds of Formula I.

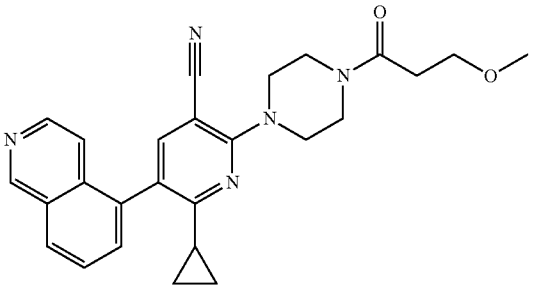
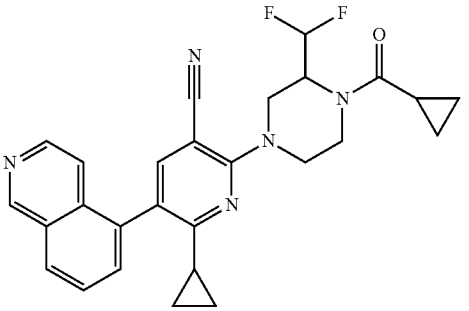
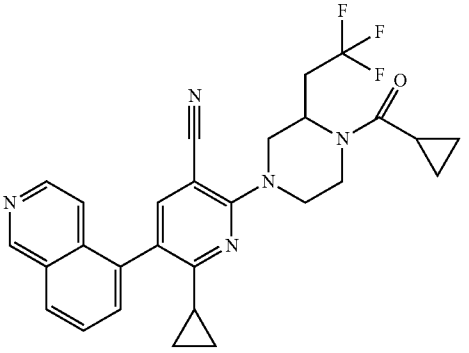
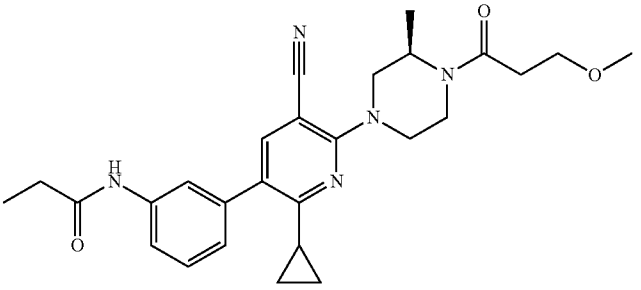
Cpd #	Structure
421	
422	
423	
424	

TABLE 5-continued

Exemplary Compounds of Formula I.

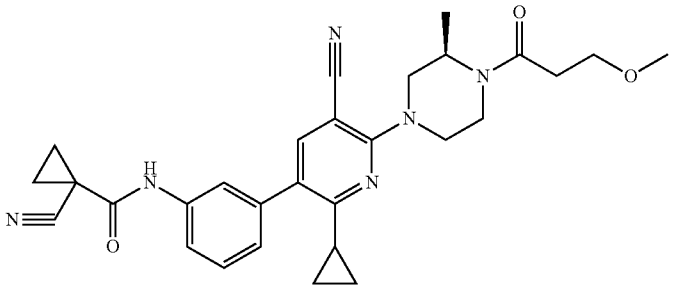
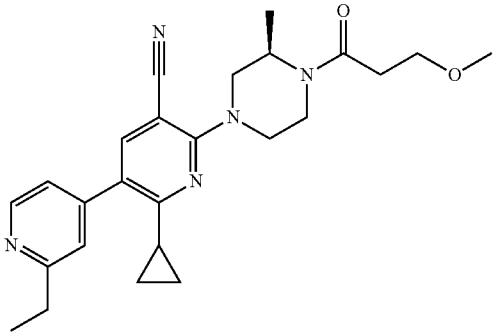
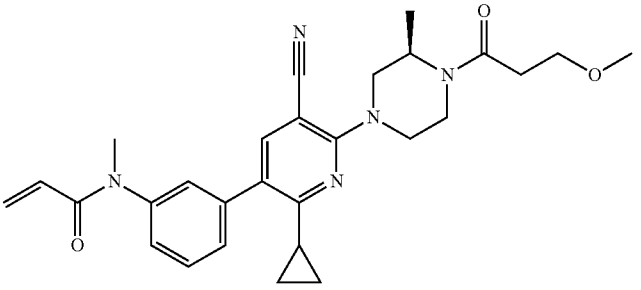
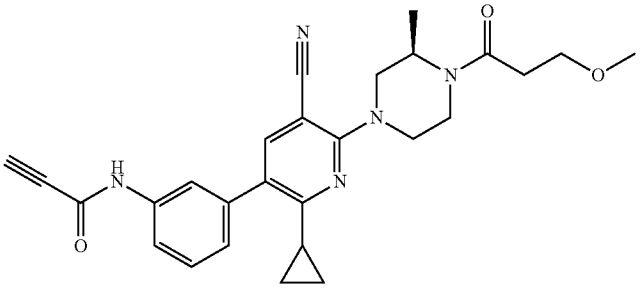
Cpd #	Structure
425	
426	
427	
428	

TABLE 5-continued

Exemplary Compounds of Formula I.

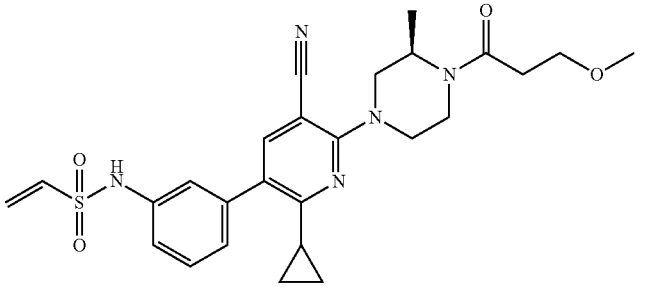
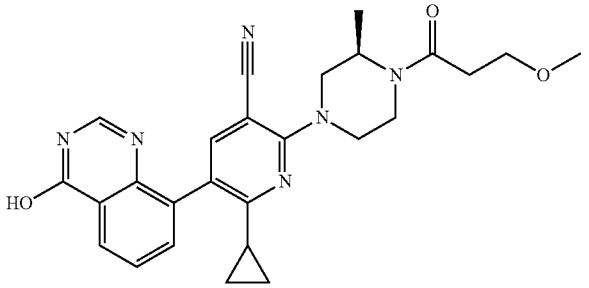
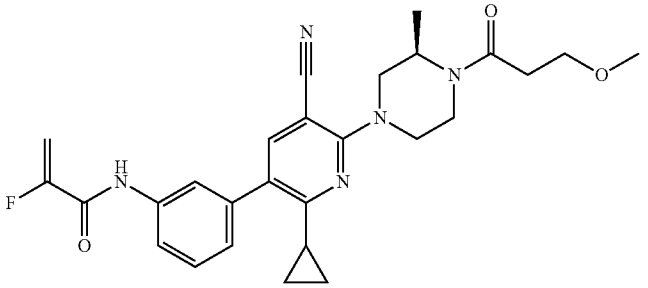
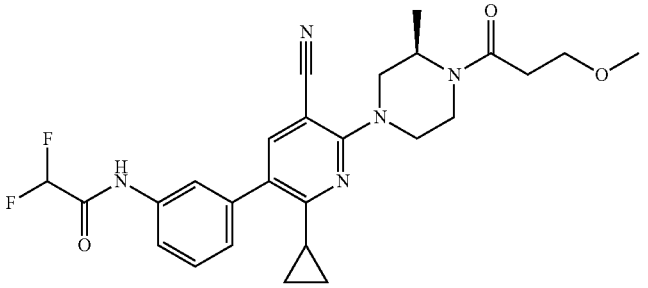
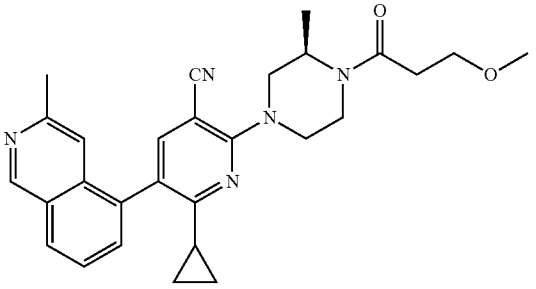
Cpd #	Structure
429	
430	
431	
432	
433	

TABLE 5-continued

Exemplary Compounds of Formula I.

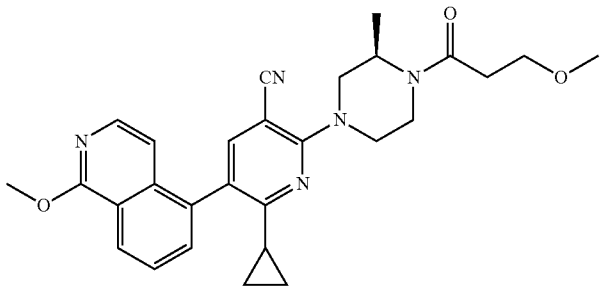
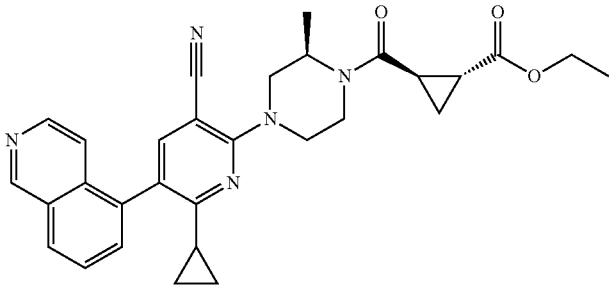
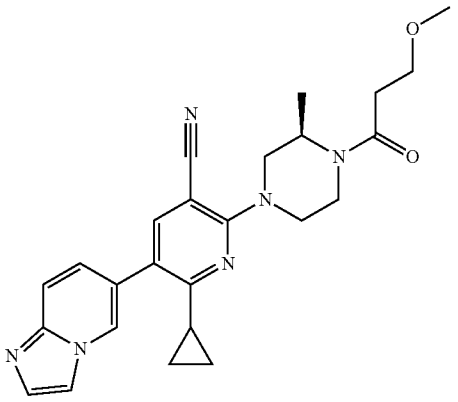
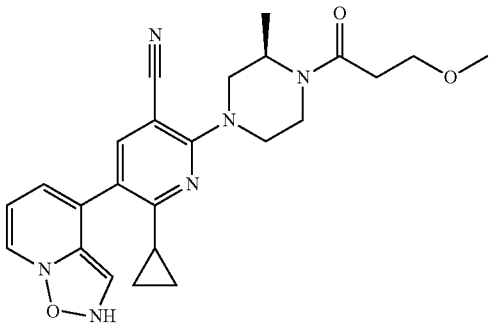
Cpd #	Structure
434	
435	
436	
437	

TABLE 5-continued

Exemplary Compounds of Formula I.

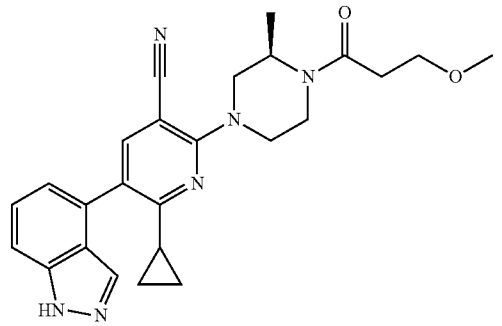
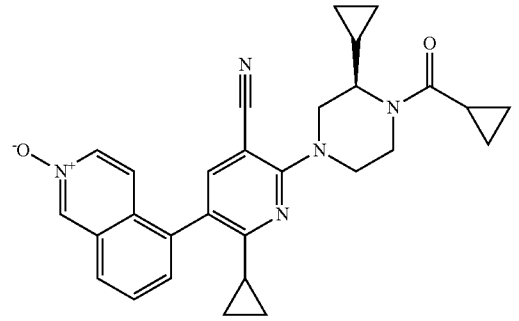
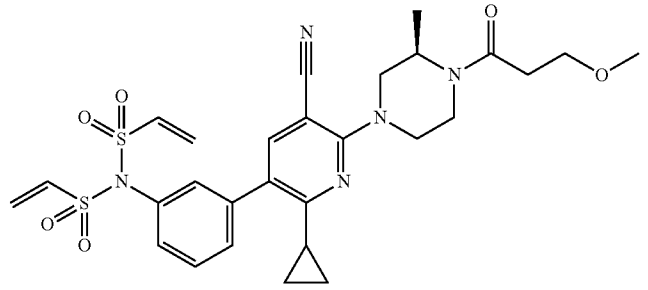
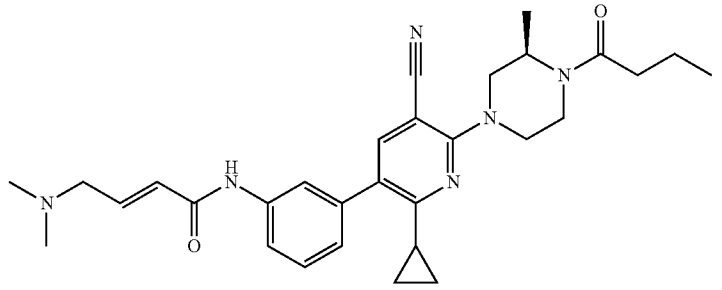
Cpd #	Structure
438	
439	
440	
441	

TABLE 5-continued

Exemplary Compounds of Formula I.

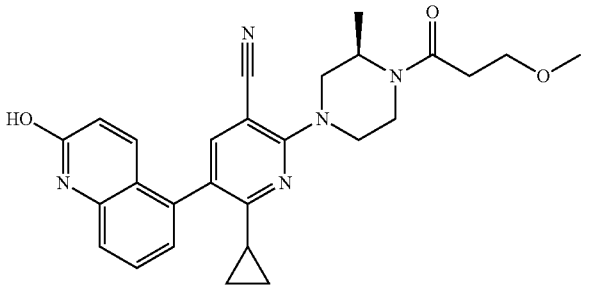
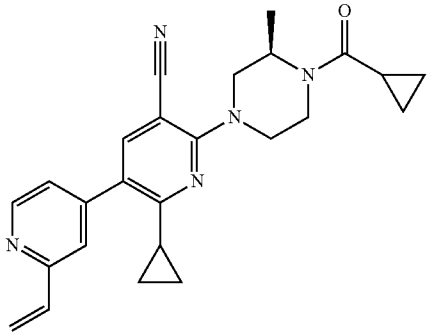
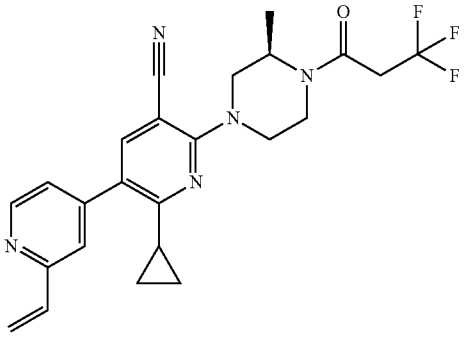
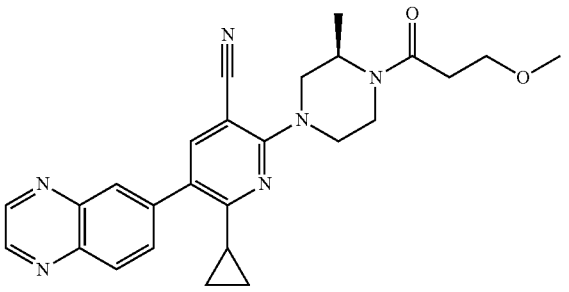
Cpd #	Structure
442	
443	
444	
445	

TABLE 5-continued

Exemplary Compounds of Formula I.

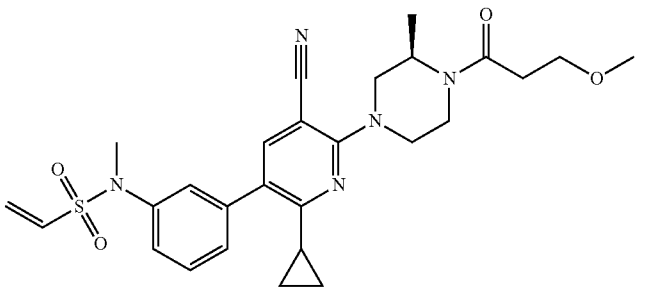
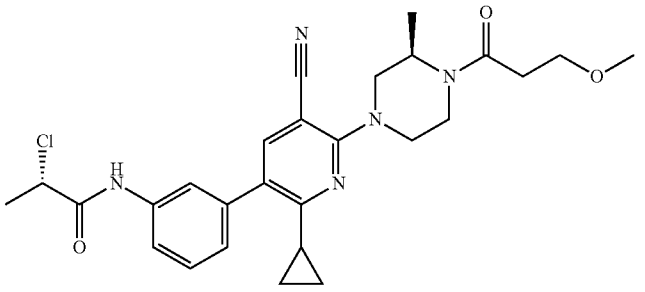
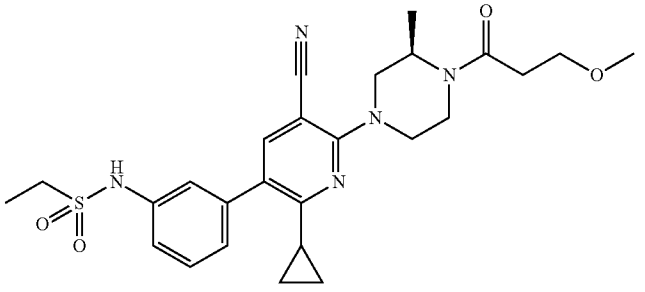
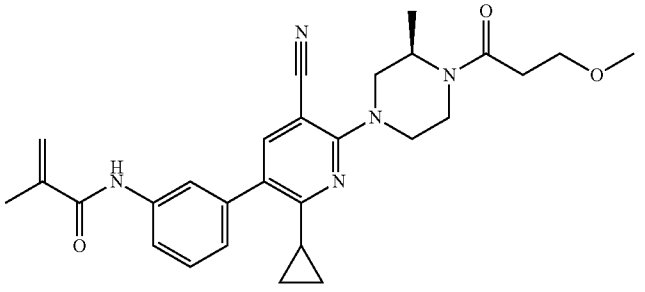
Cpd #	Structure
446	
447	
448	
449	

TABLE 5-continued

Exemplary Compounds of Formula I.

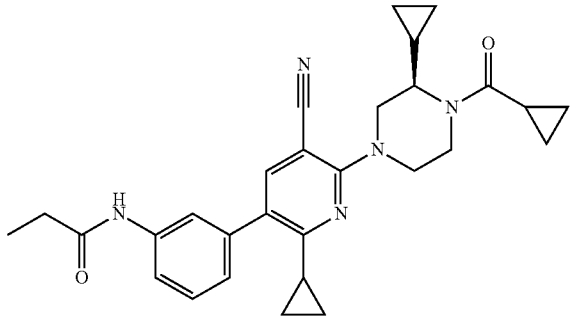
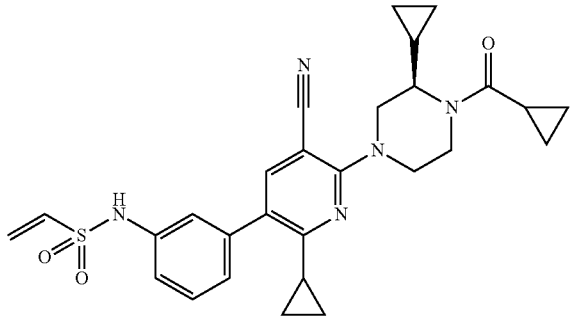
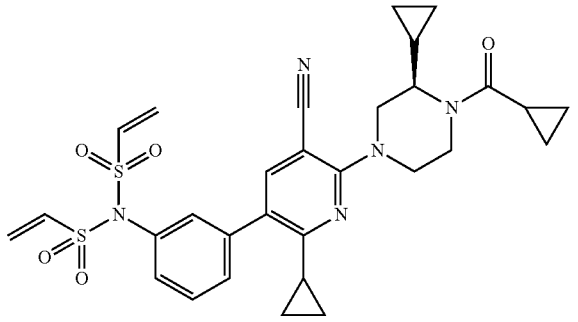
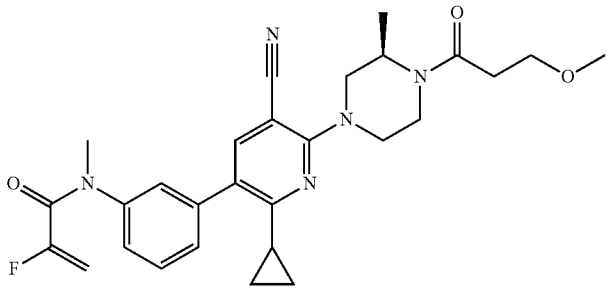
Cpd #	Structure
450	
451	
452	
453	

TABLE 5-continued

Exemplary Compounds of Formula I.

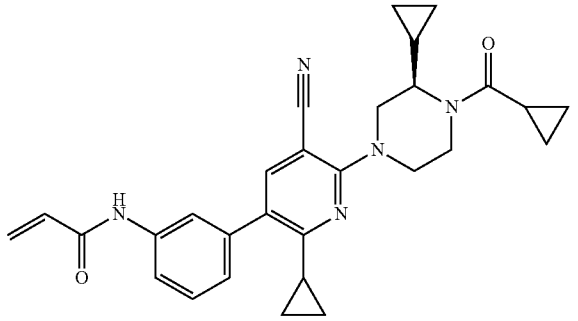
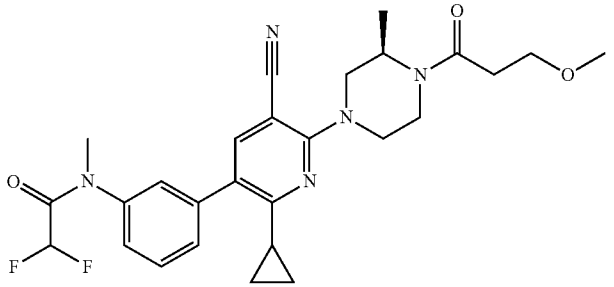
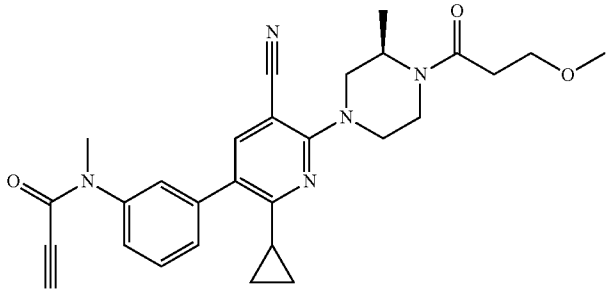
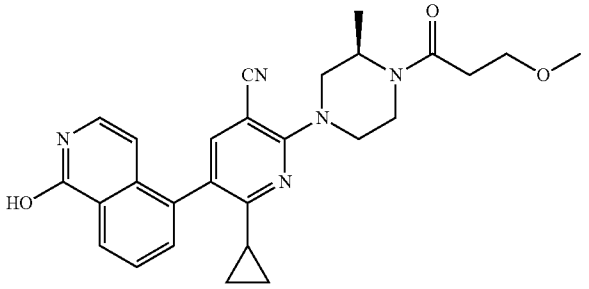
Cpd #	Structure
454	
455	
456	
457	

TABLE 5-continued

Exemplary Compounds of Formula I.

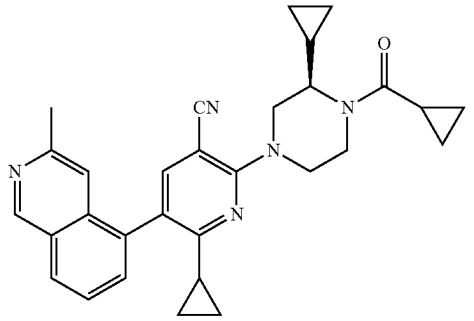
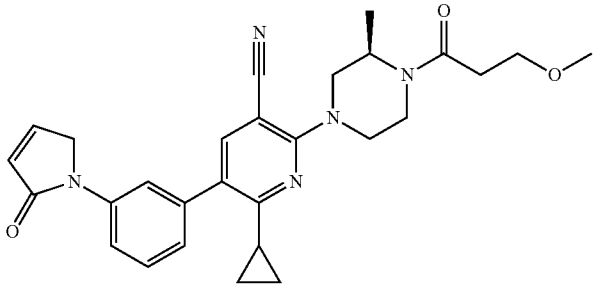
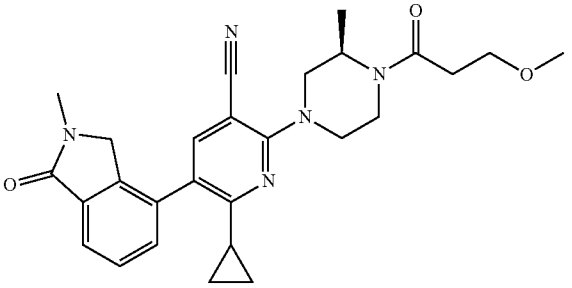
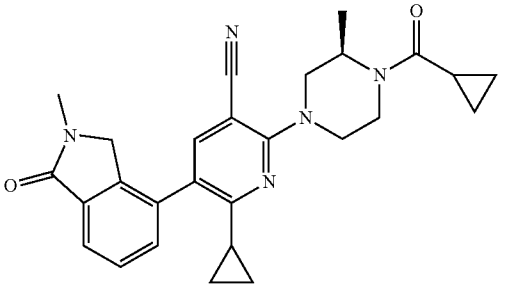
Cpd #	Structure
458	
459	
460	
461	

TABLE 5-continued

Exemplary Compounds of Formula I.

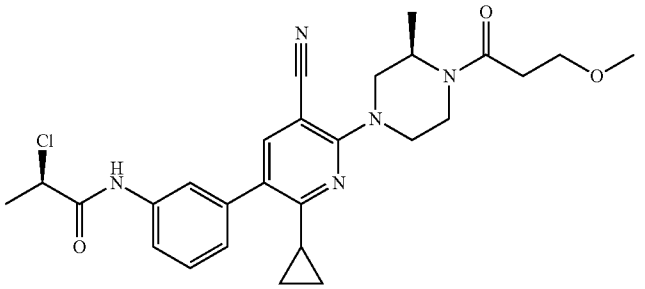
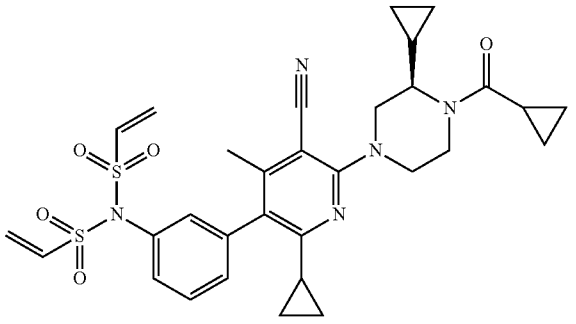
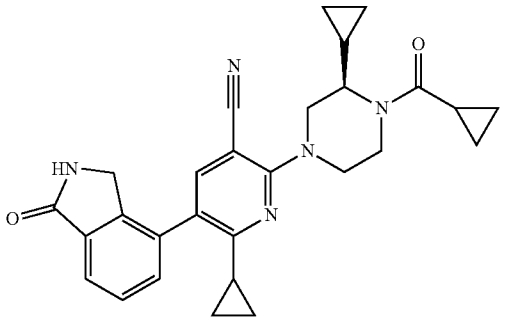
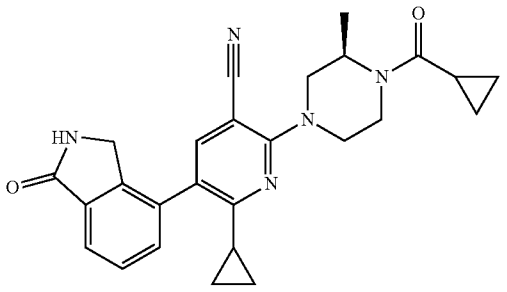
Cpd #	Structure
462	
463	
464	
465	

TABLE 5-continued

Exemplary Compounds of Formula I.

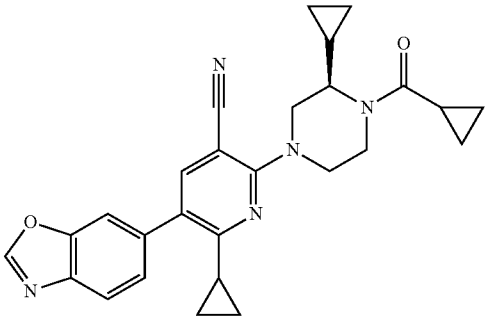
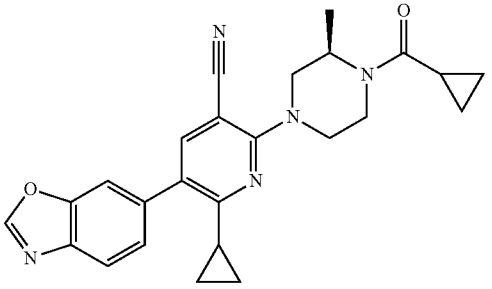
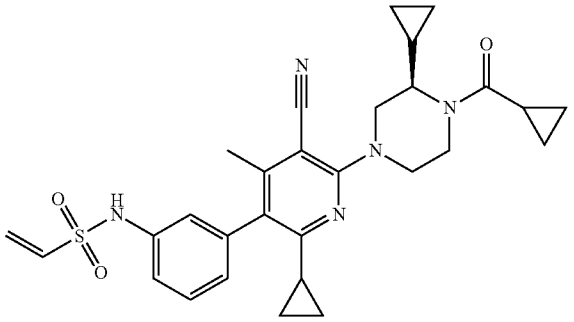
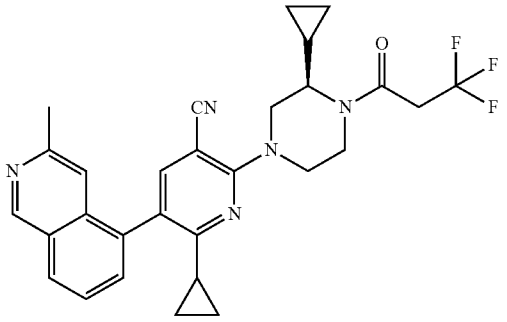
Cpd #	Structure
466	
467	
470	
471	

TABLE 5-continued

Exemplary Compounds of Formula I.

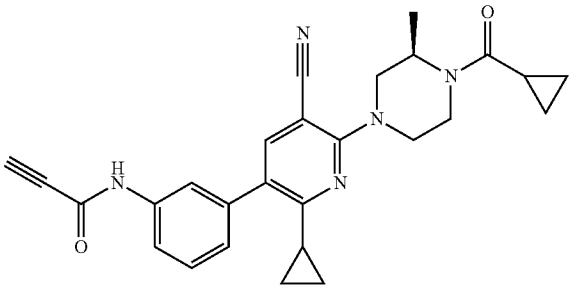
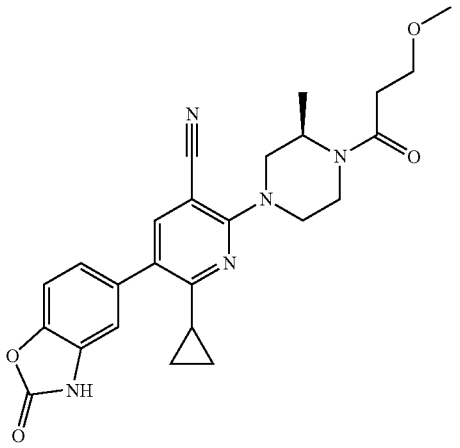
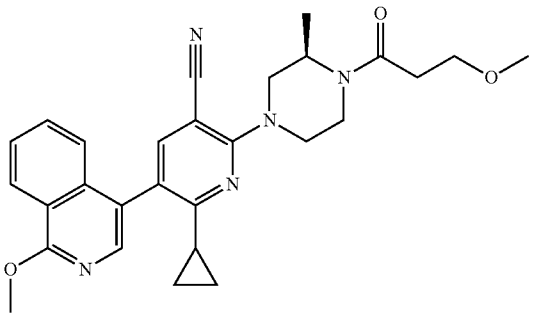
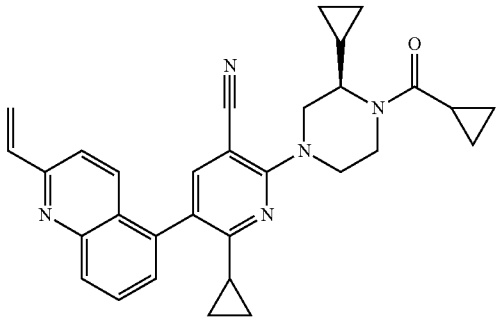
Cpd #	Structure
472	
473	
474	
475	

TABLE 5-continued

Exemplary Compounds of Formula I.

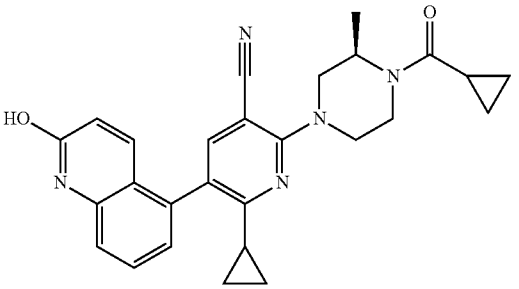
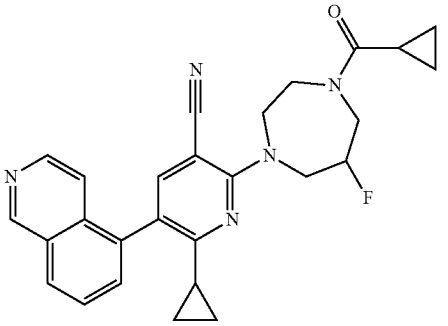
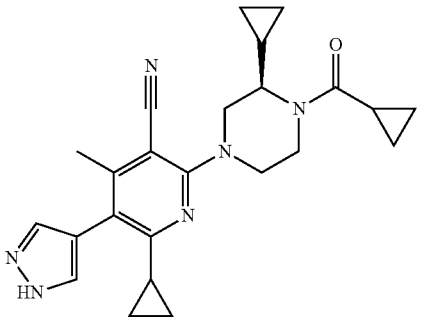
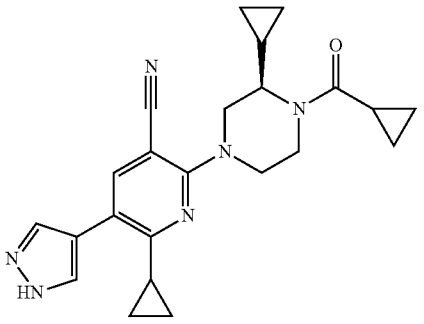
Cpd #	Structure
476	
477	
478	
479	

TABLE 5-continued

Exemplary Compounds of Formula I.

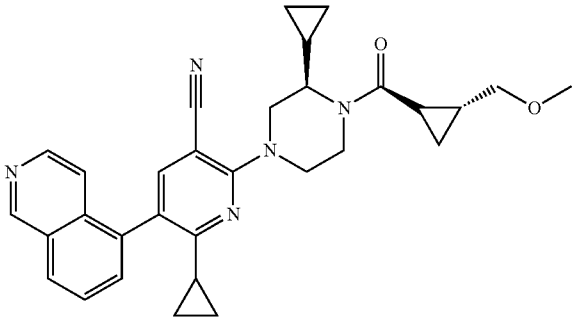
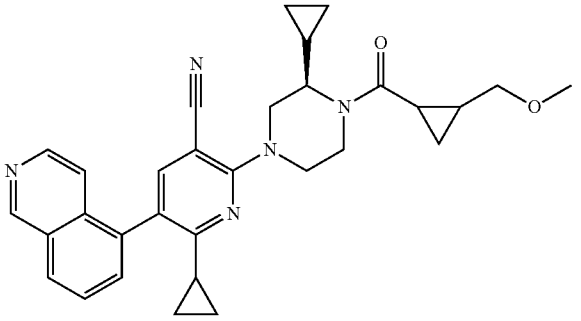
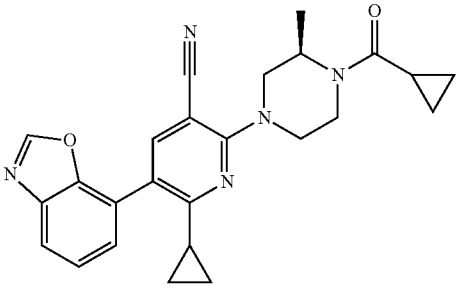
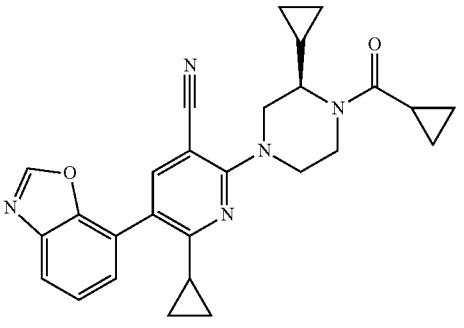
Cpd #	Structure
480	
481	
482	
483	

TABLE 5-continued

Exemplary Compounds of Formula I.

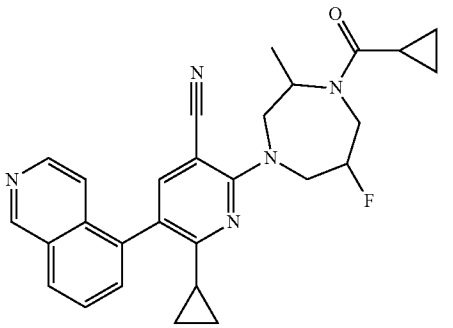
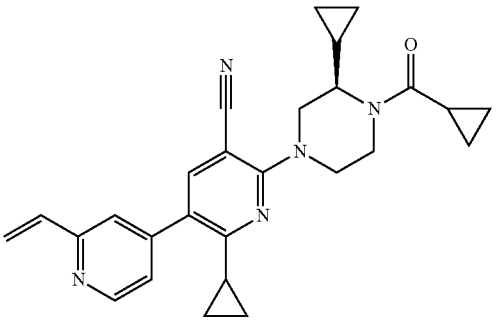
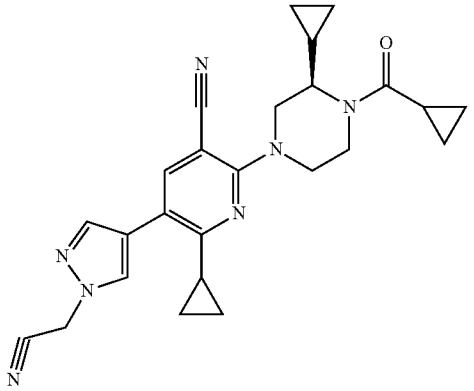
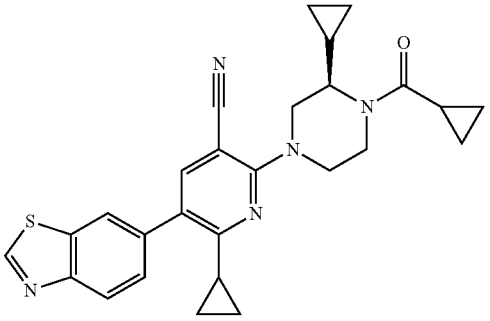
Cpd #	Structure
484	
485	
486	
487	

TABLE 5-continued

Exemplary Compounds of Formula I.

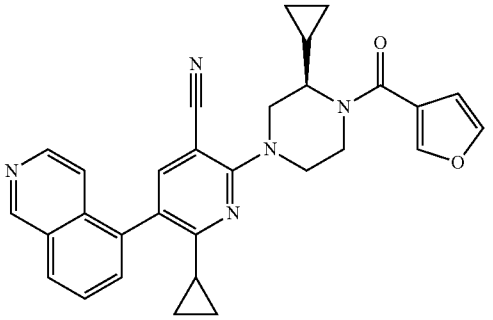
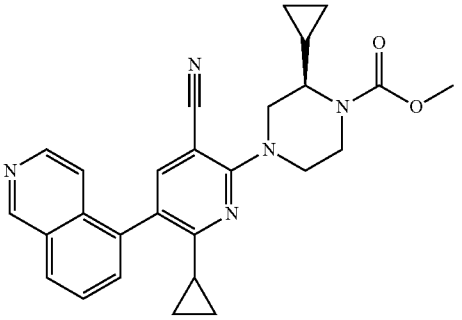
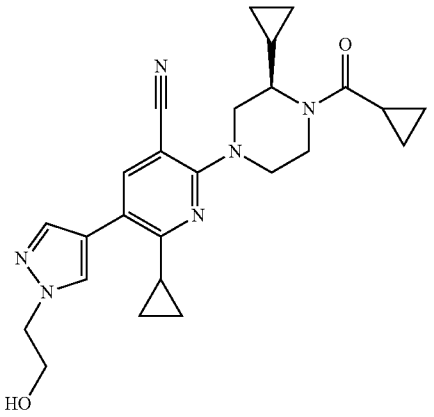
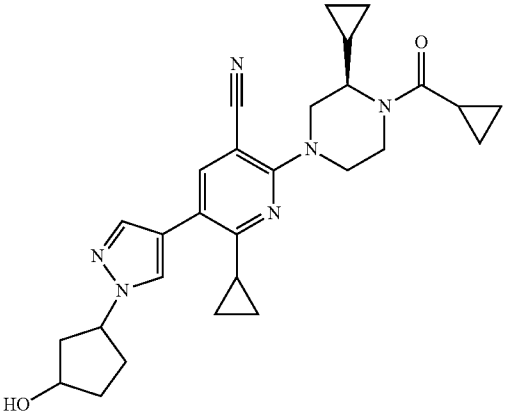
Cpd #	Structure
488	
489	
490	
493	

TABLE 5-continued

Exemplary Compounds of Formula I.

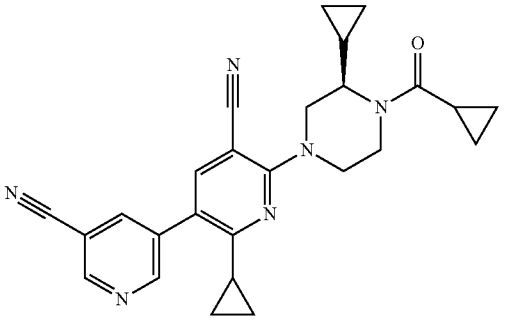
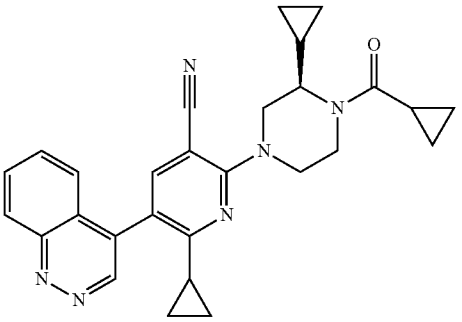
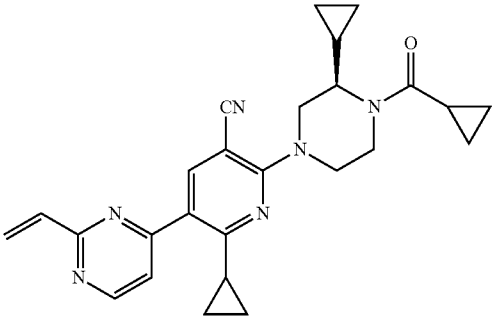
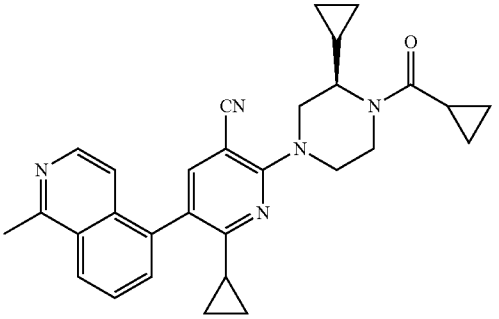
Cpd #	Structure
494	
495	
496	
497	

TABLE 5-continued

Exemplary Compounds of Formula I.

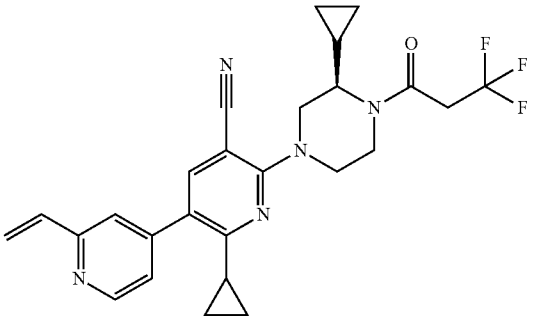
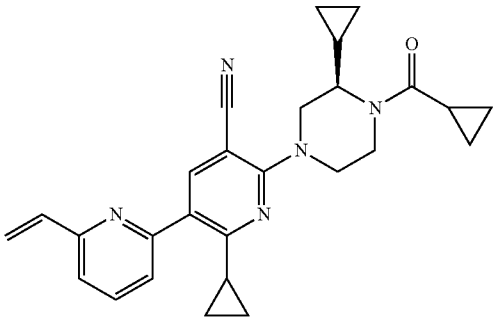
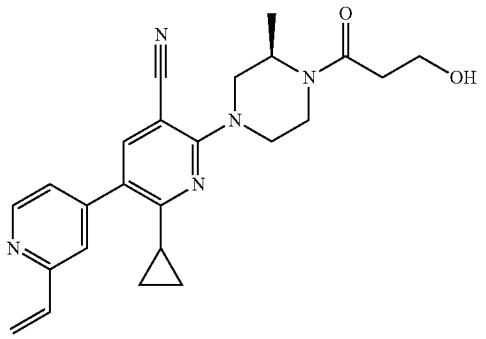
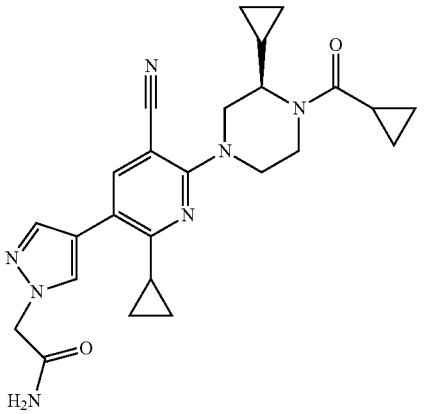
Cpd #	Structure
498	
499	
500	
501	

TABLE 5-continued

Exemplary Compounds of Formula I.

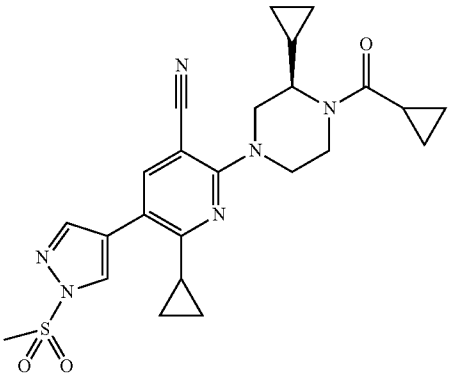
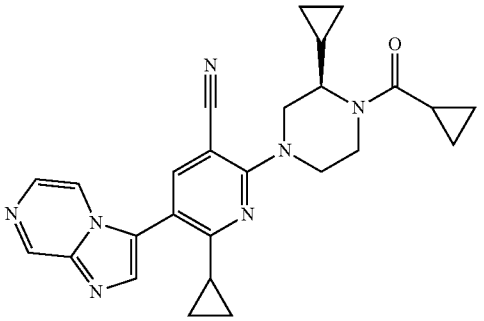
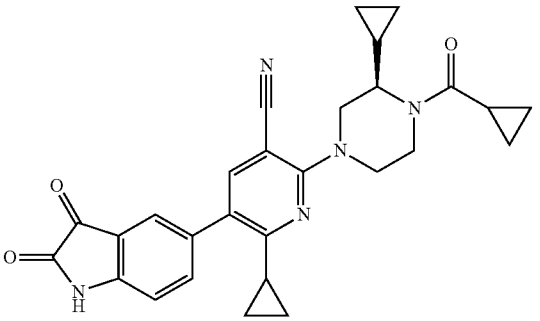
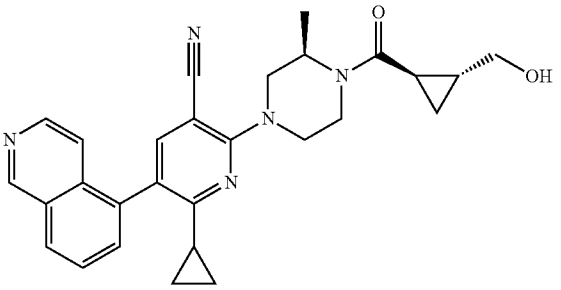
Cpd #	Structure
502	
503	
504	
505	

TABLE 5-continued

Exemplary Compounds of Formula I.

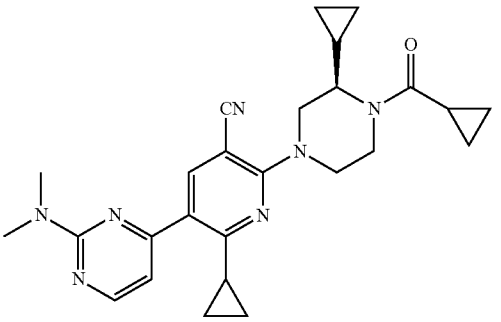
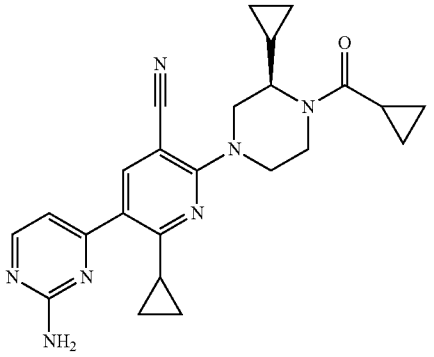
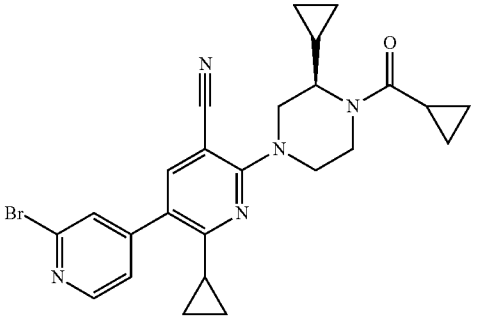
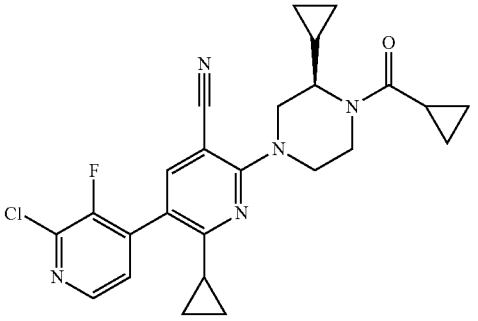
Cpd #	Structure
506	
507	
508	
509	

TABLE 5-continued

Exemplary Compounds of Formula I.

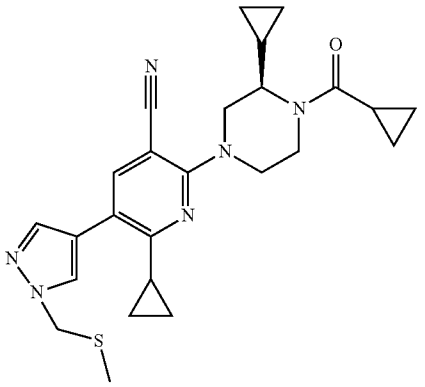
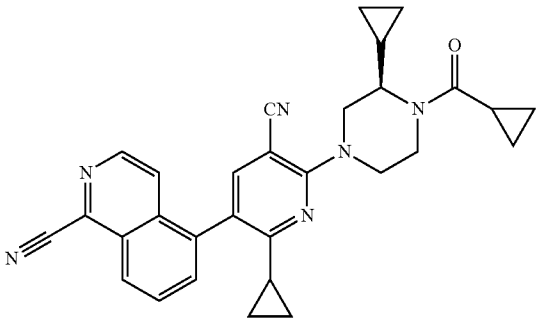
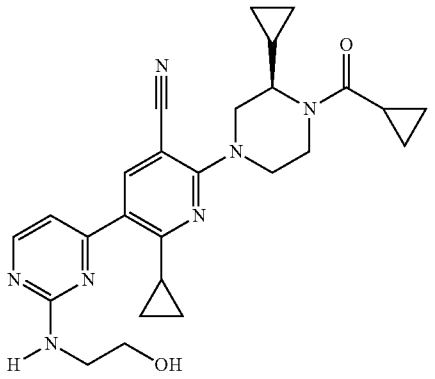
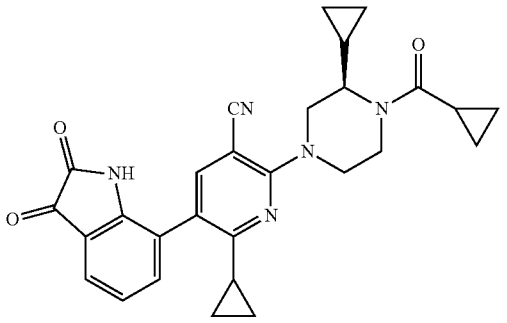
Cpd #	Structure
510	
511	
512	
513	

TABLE 5-continued

Exemplary Compounds of Formula I.

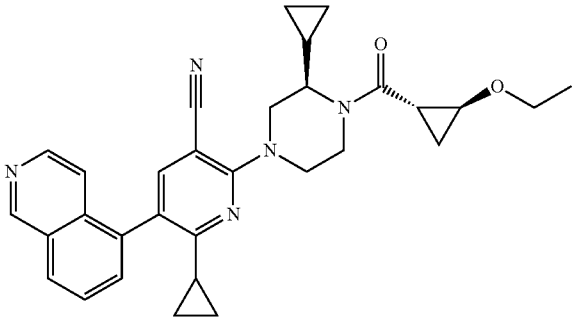
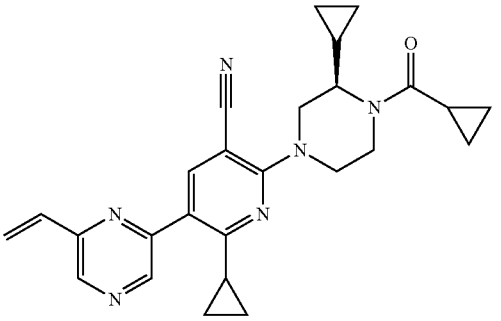
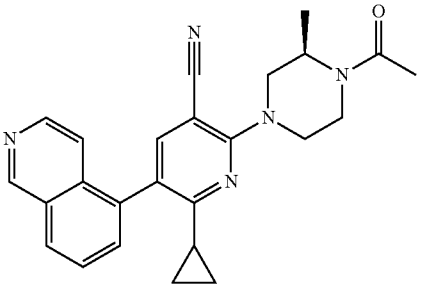
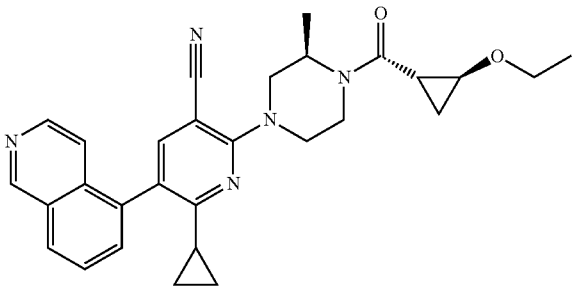
Cpd #	Structure
514	
515	
516	
517	

TABLE 5-continued

Exemplary Compounds of Formula I.

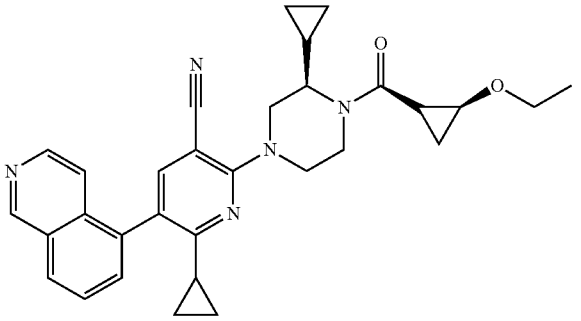
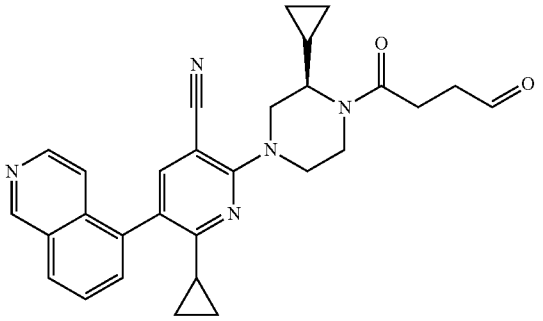
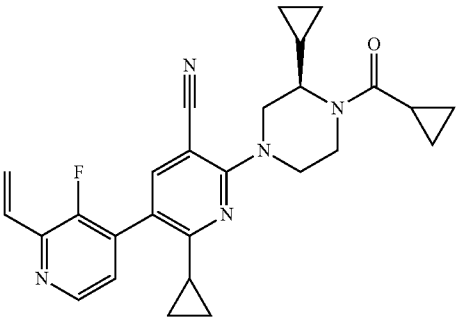
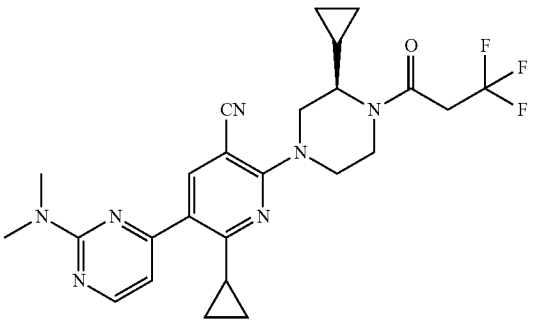
Cpd #	Structure
518	
519	
520	
521	

TABLE 5-continued

Exemplary Compounds of Formula I.

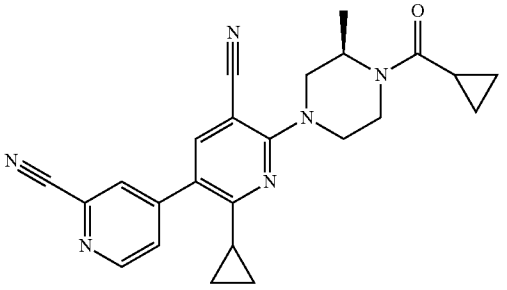
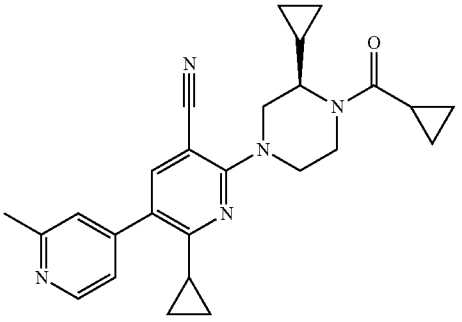
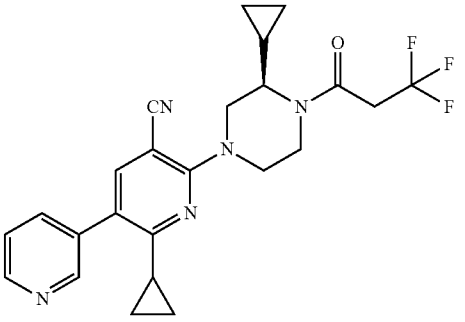
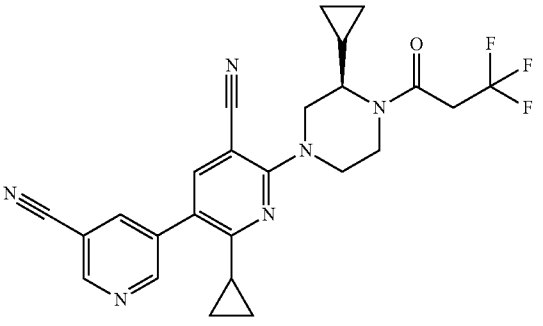
Cpd #	Structure
522	
523	
524	
525	

TABLE 5-continued

Exemplary Compounds of Formula I.

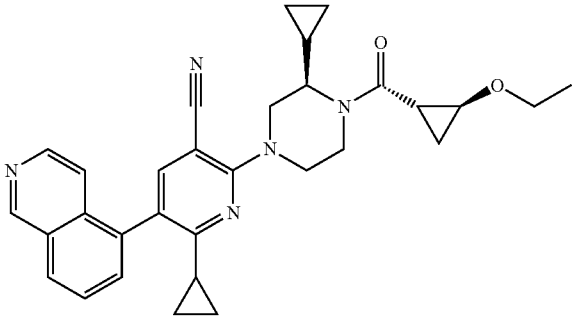
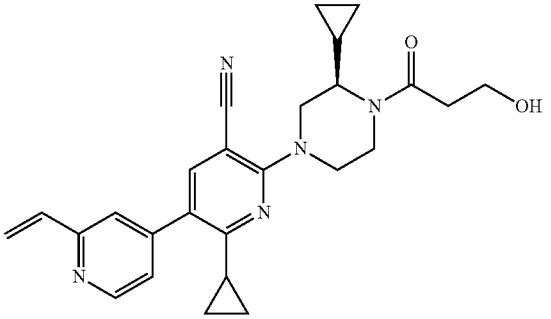
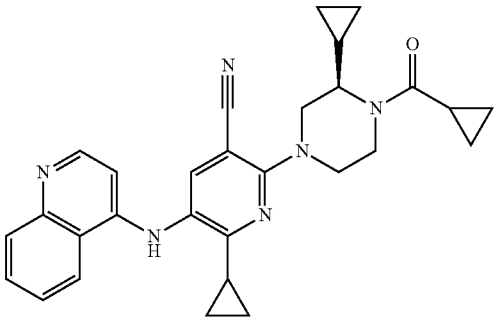
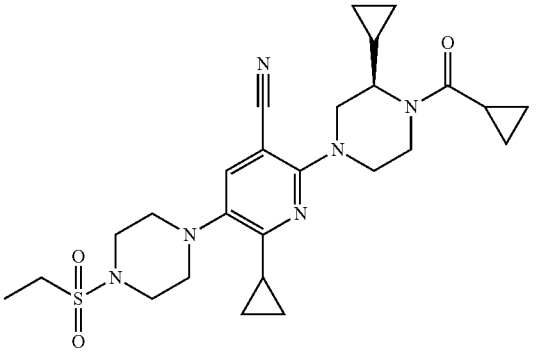
Cpd #	Structure
526	
527	
528	
529	

TABLE 5-continued

Exemplary Compounds of Formula I.

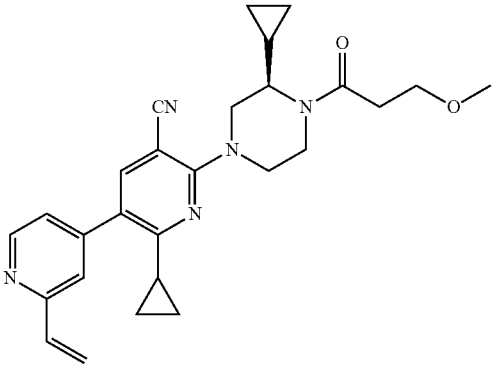
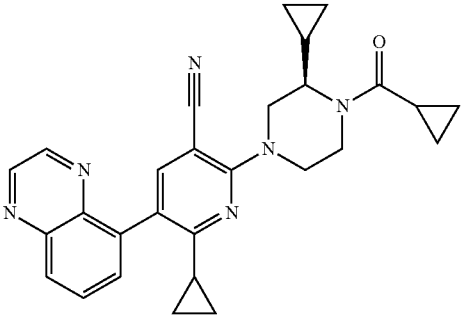
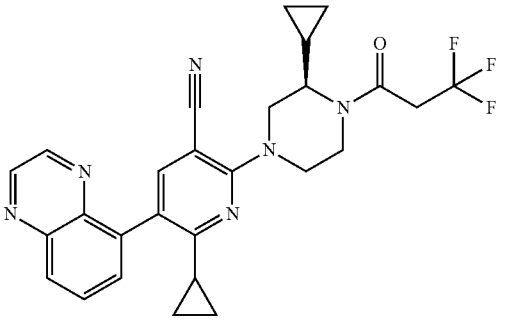
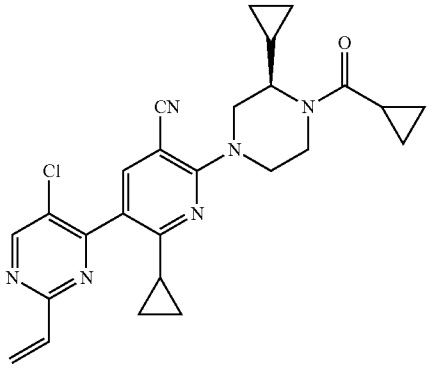
Cpd #	Structure
530	
531	
532	
533	

TABLE 5-continued

Exemplary Compounds of Formula I.

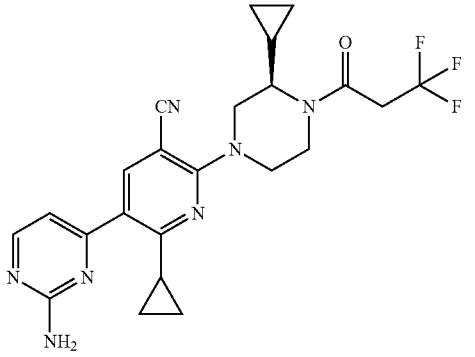
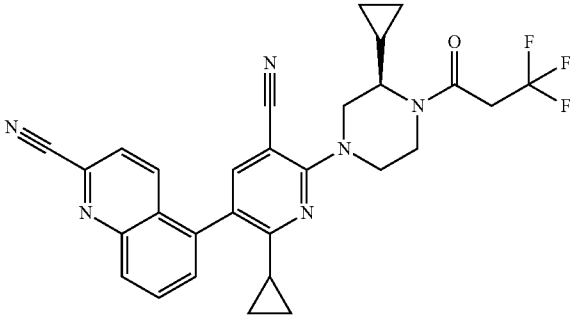
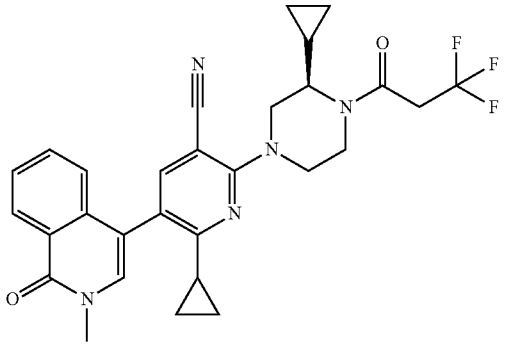
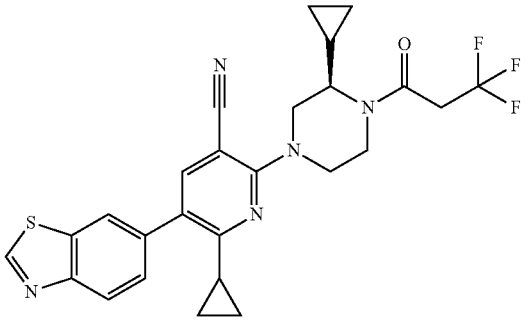
Cpd #	Structure
534	
535	
536	
537	

TABLE 5-continued

Exemplary Compounds of Formula I.

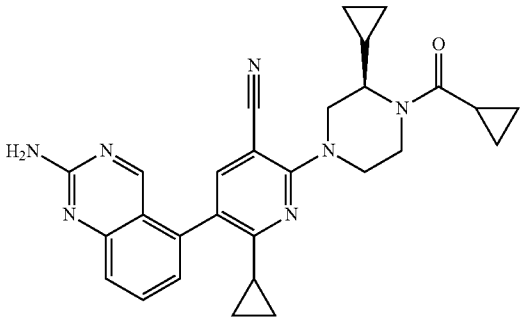
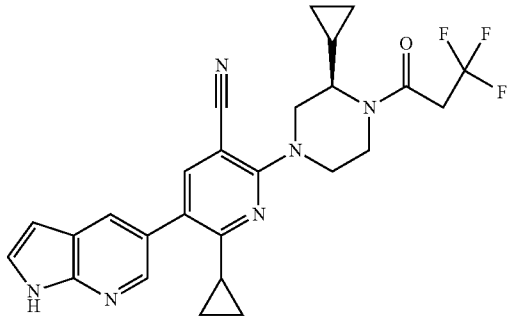
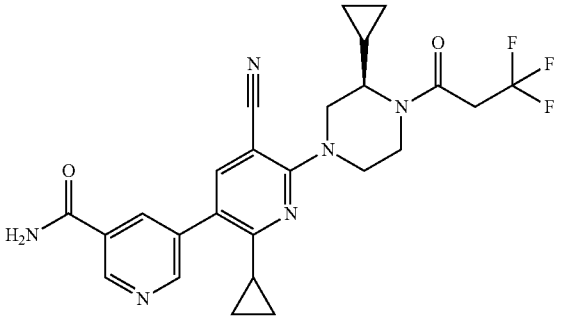
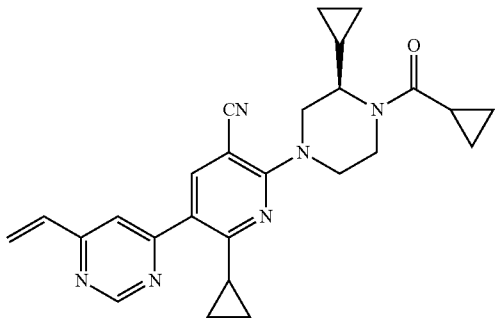
Cpd #	Structure
538	
539	
540	
541	

TABLE 5-continued

Exemplary Compounds of Formula I.

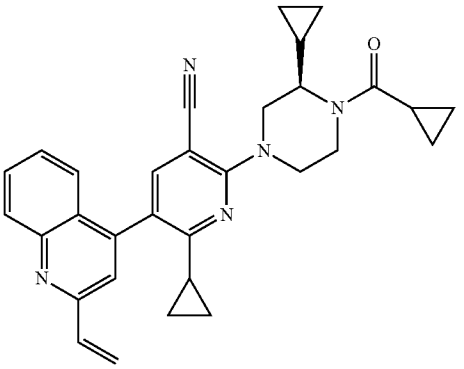
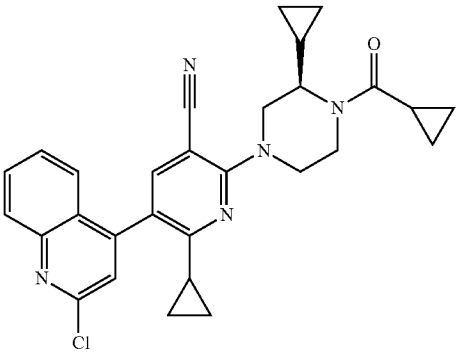
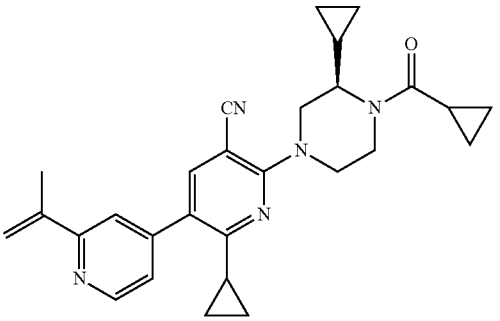
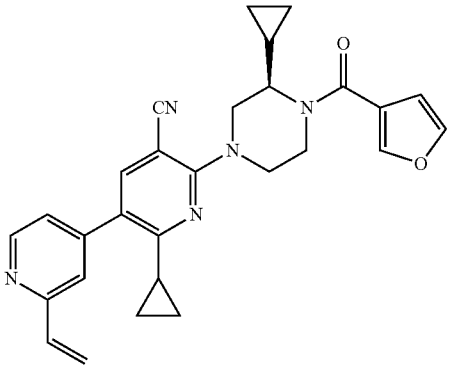
Cpd #	Structure
542	
543	
544	
546	

TABLE 5-continued

Exemplary Compounds of Formula I.

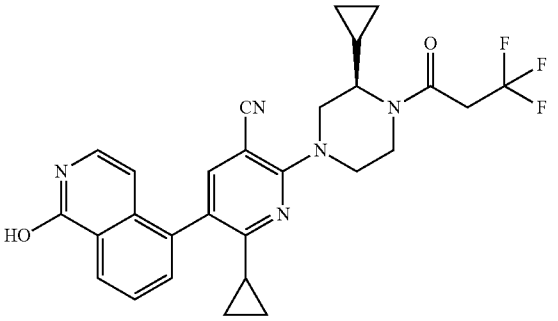
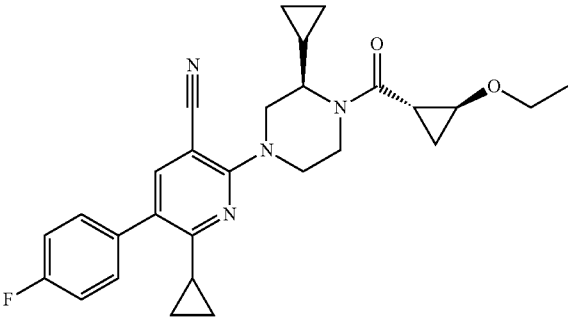
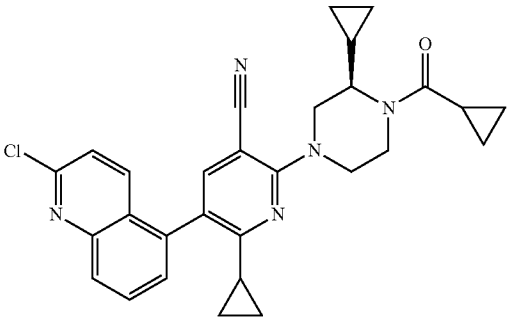
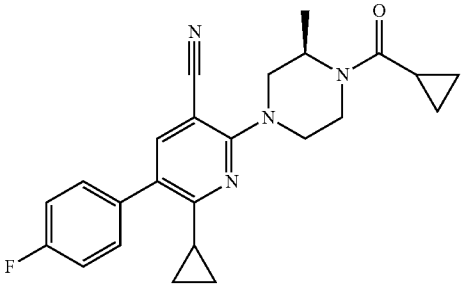
Cpd #	Structure
547	
548	
549	
550	

TABLE 5-continued

Exemplary Compounds of Formula I.

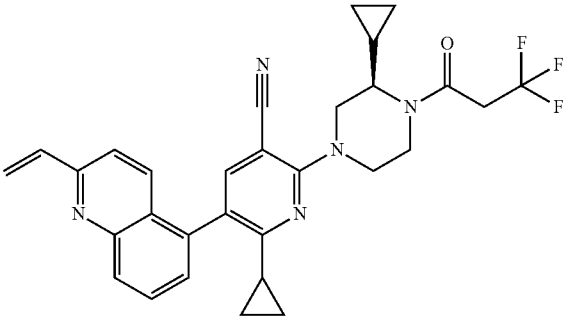
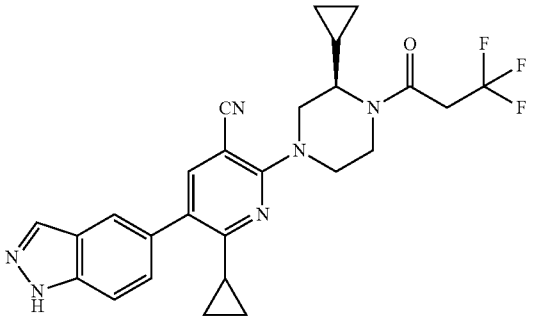
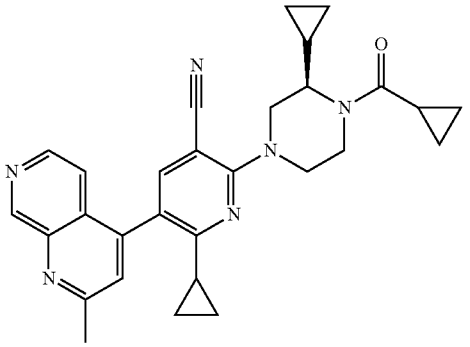
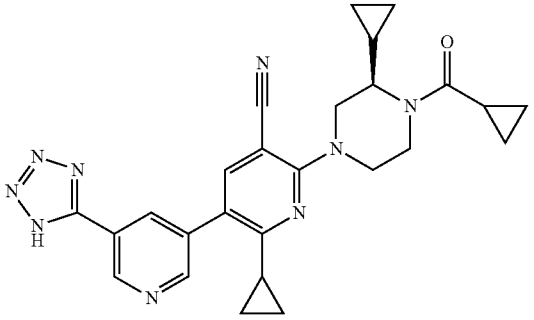
Cpd #	Structure
551	
552	
553	
554	

TABLE 5-continued

Exemplary Compounds of Formula I.

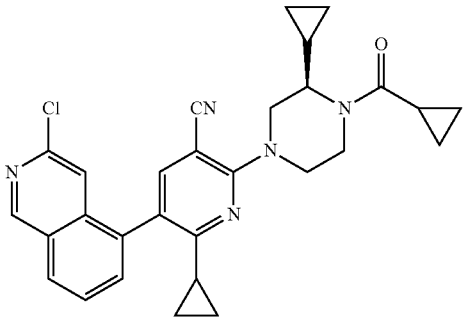
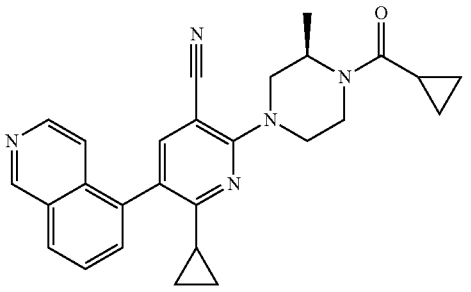
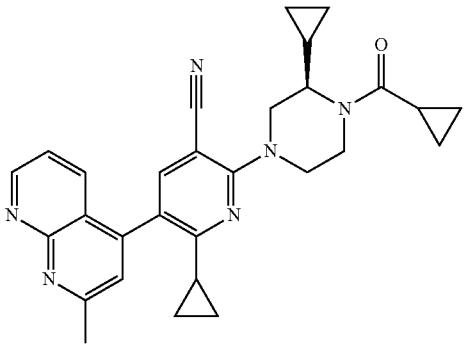
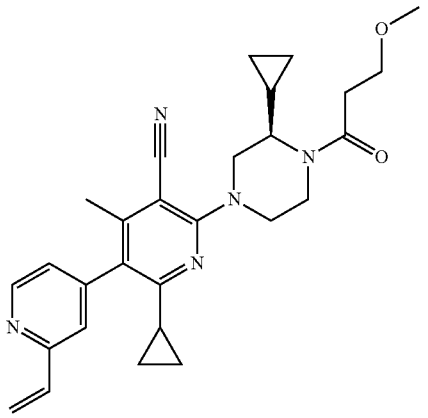
Cpd #	Structure
555	
556	
557	
558	

TABLE 5-continued

Exemplary Compounds of Formula I.

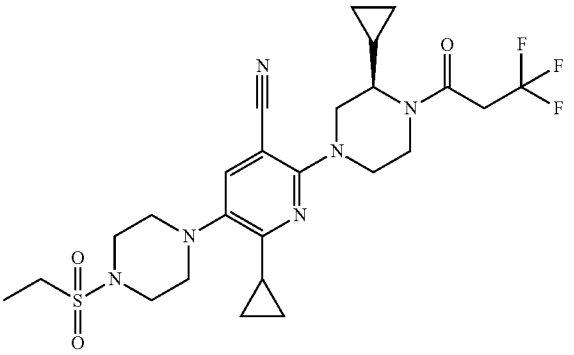
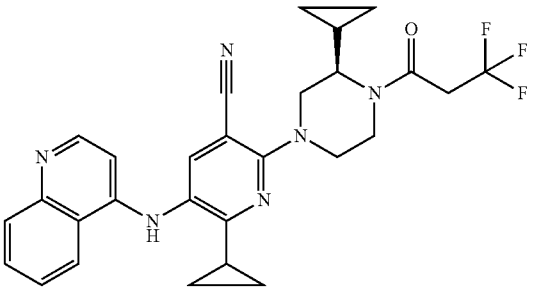
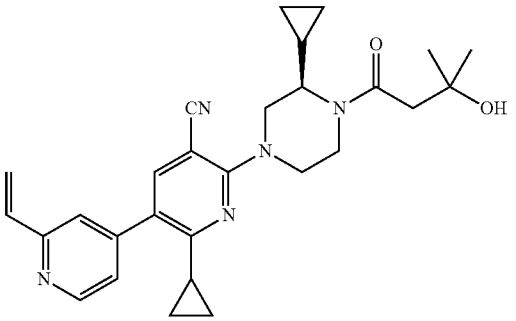
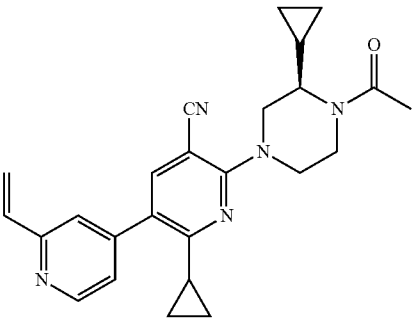
Cpd #	Structure
559	
560	
561	
562	

TABLE 5-continued

Exemplary Compounds of Formula I.

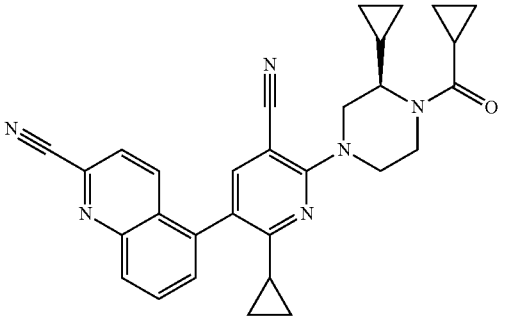
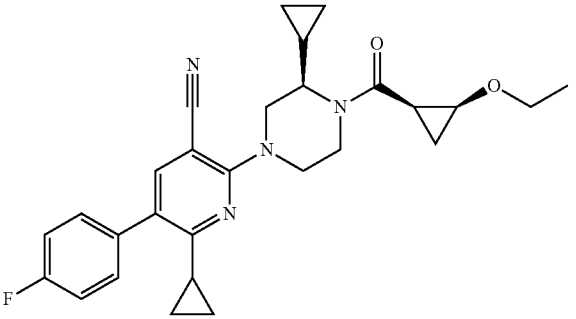
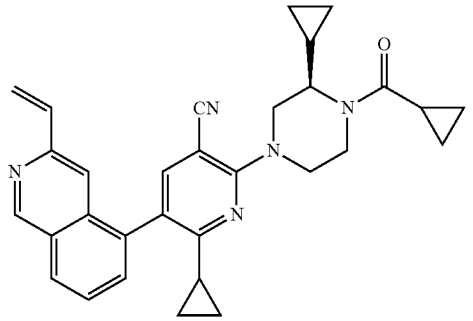
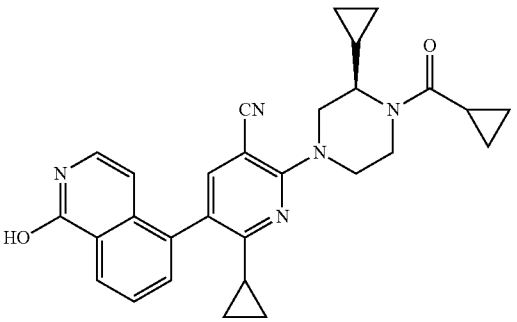
Cpd #	Structure
563	
564	
565	
566	

TABLE 5-continued

Exemplary Compounds of Formula I.

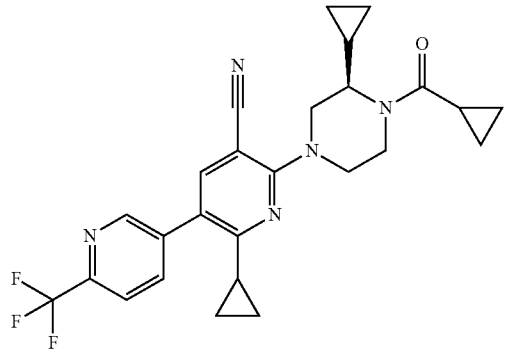
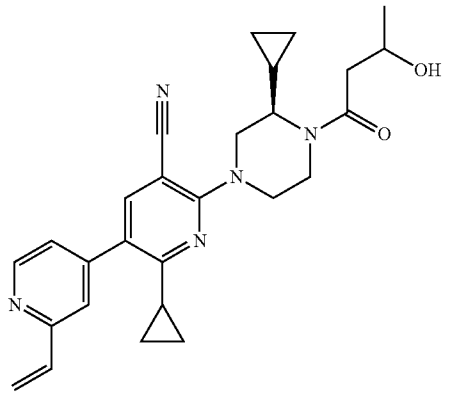
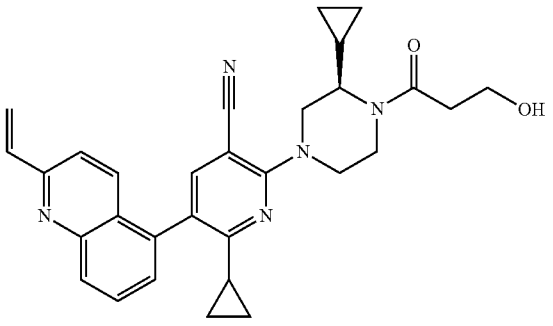
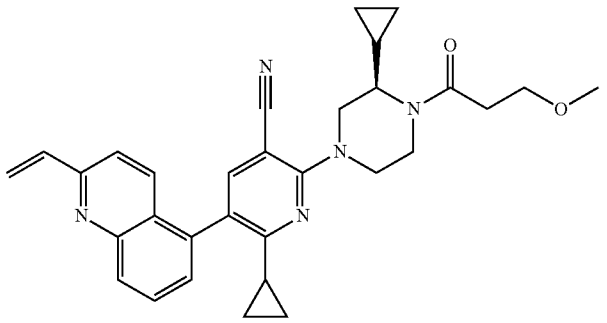
Cpd #	Structure
567	
568	
569	
570	

TABLE 5-continued

Exemplary Compounds of Formula I.

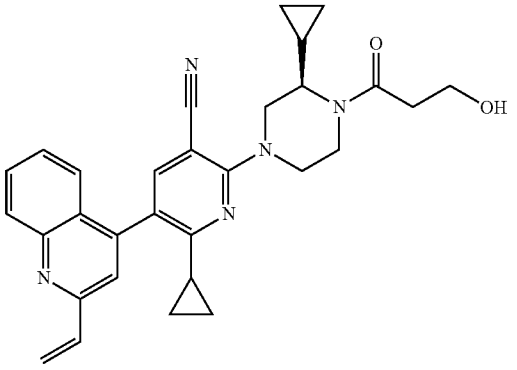
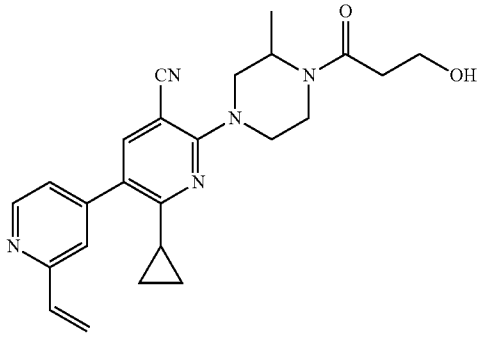
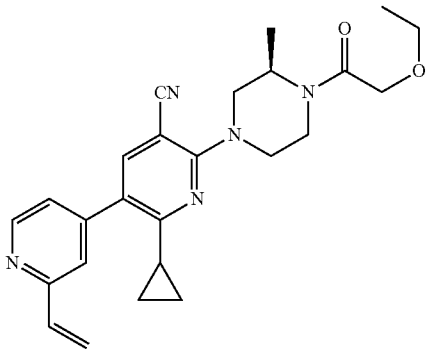
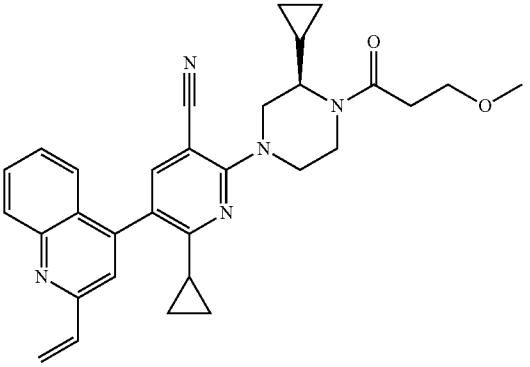
Cpd #	Structure
571	
572	
573	
574	

TABLE 5-continued

Exemplary Compounds of Formula I.

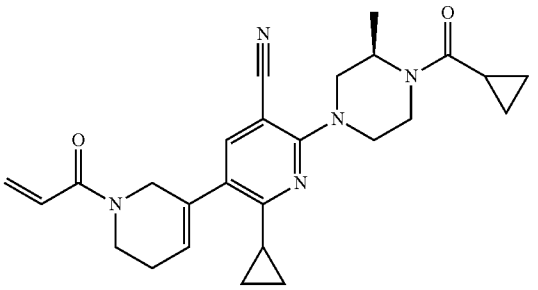
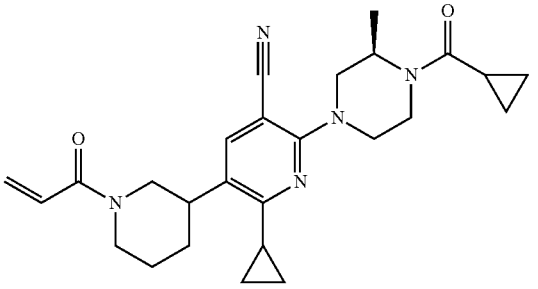
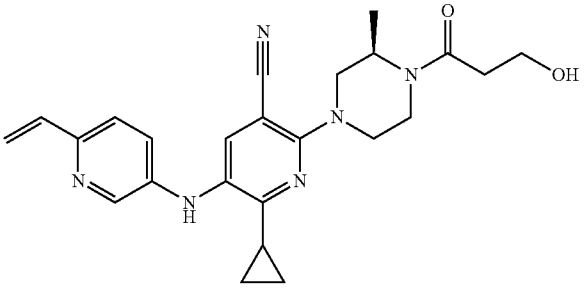
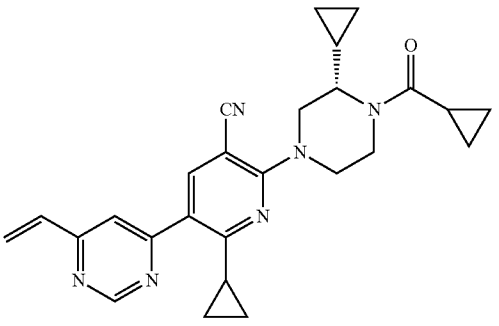
Cpd #	Structure
575	
576	
577	
578	

TABLE 5-continued

Exemplary Compounds of Formula I.

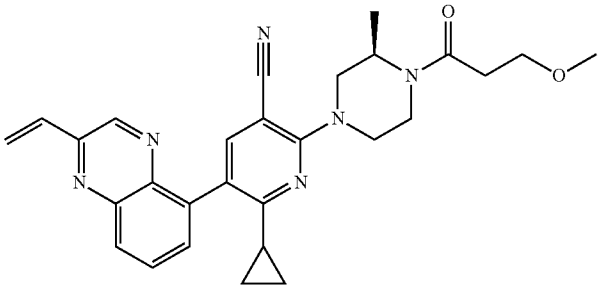
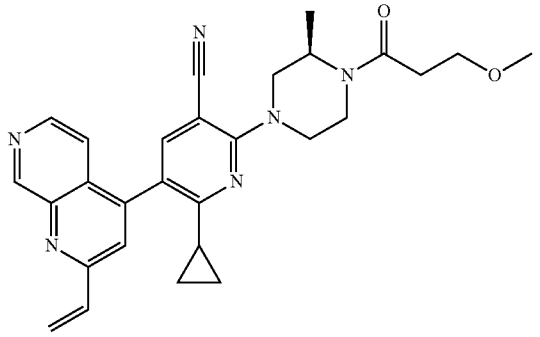
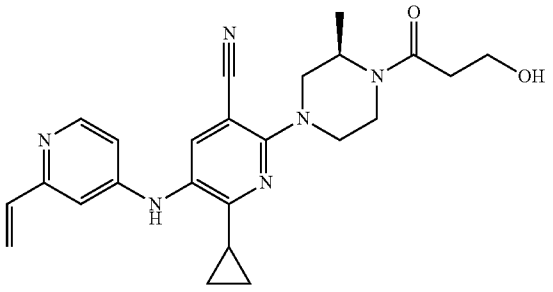
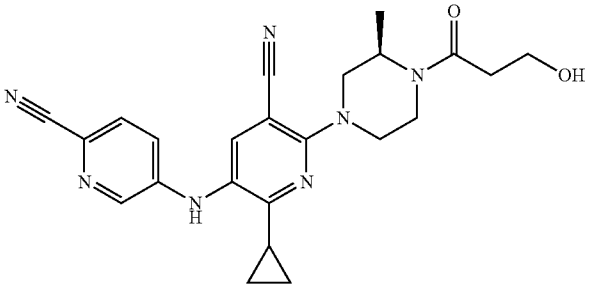
Cpd #	Structure
579	
580	
581	
582	

TABLE 5-continued

Exemplary Compounds of Formula I.

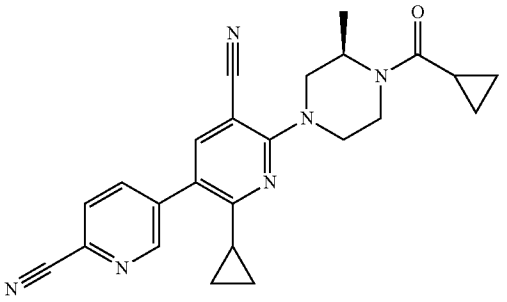
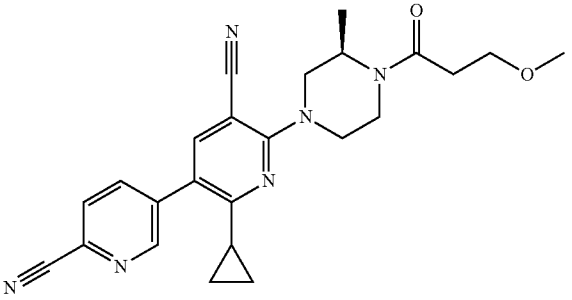
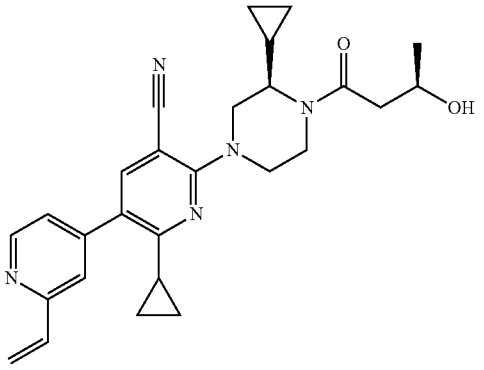
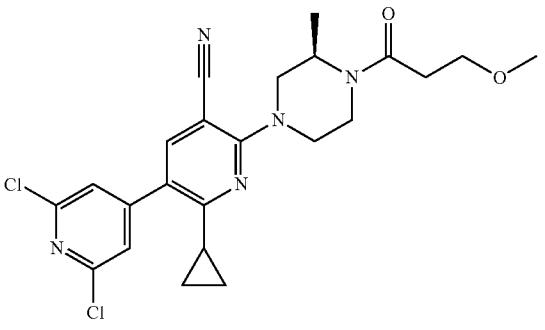
Cpd #	Structure
583	
584	
585	
586	

TABLE 5-continued

Exemplary Compounds of Formula I.

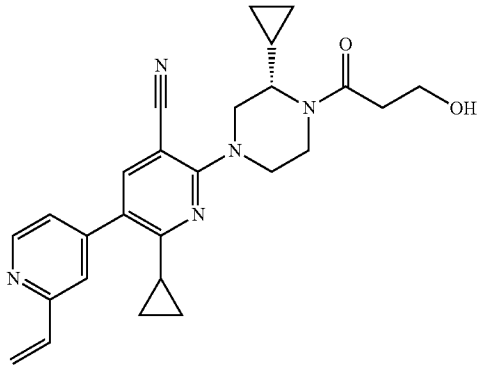
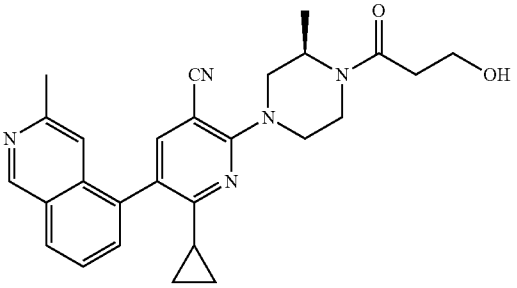
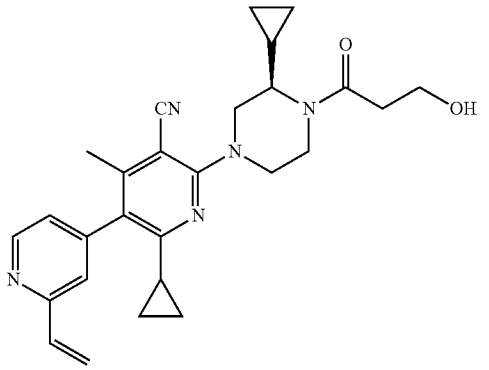
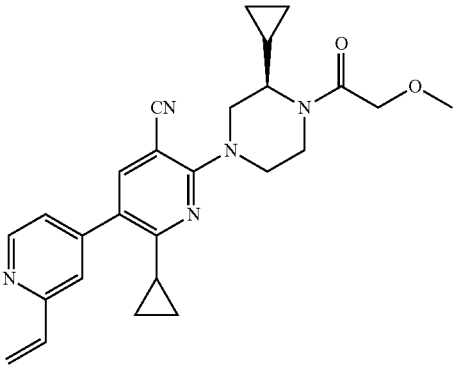
Cpd #	Structure
587	
588	
589	
590	

TABLE 5-continued

Exemplary Compounds of Formula I.

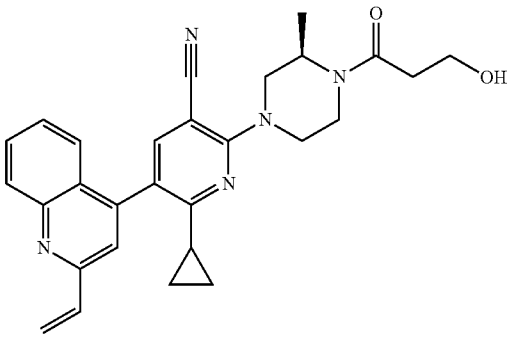
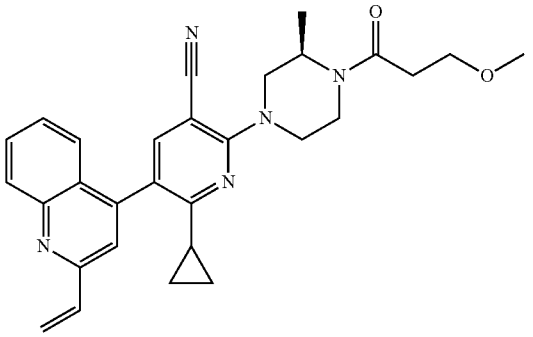
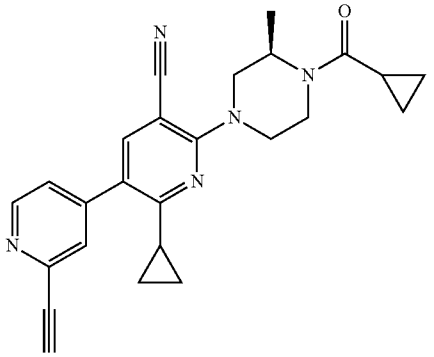
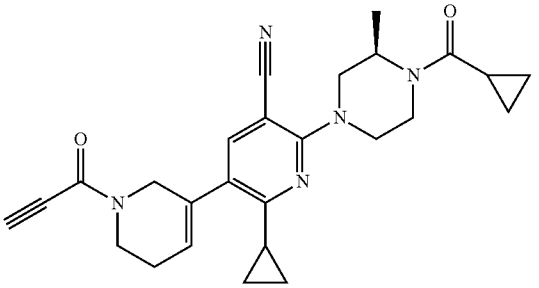
Cpd #	Structure
591	
592	
593	
594	

TABLE 5-continued

Exemplary Compounds of Formula I.

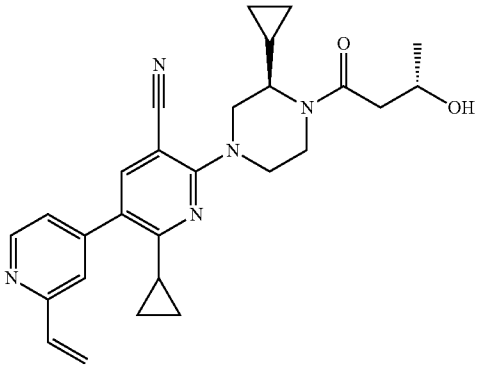
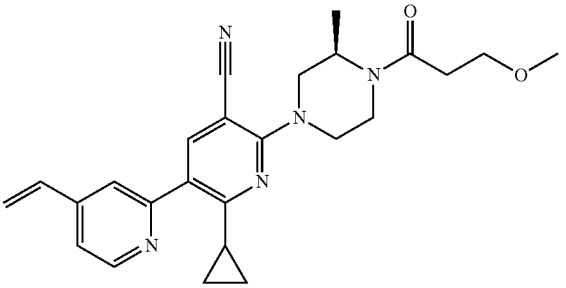
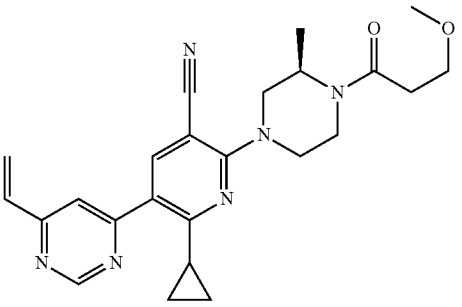
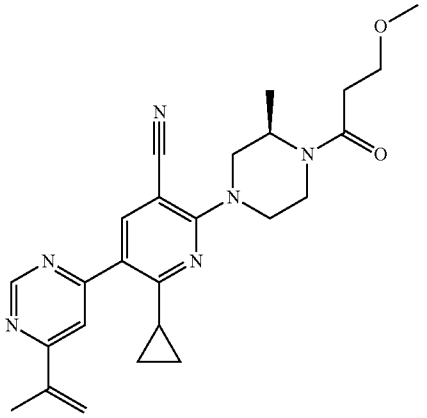
Cpd #	Structure
595	
596	
597	
598	

TABLE 5-continued

Exemplary Compounds of Formula I.

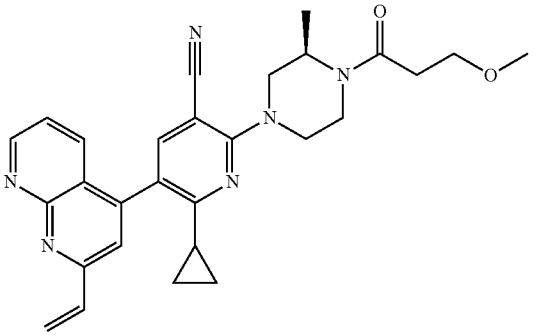
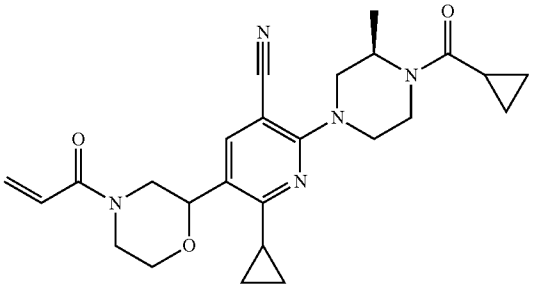
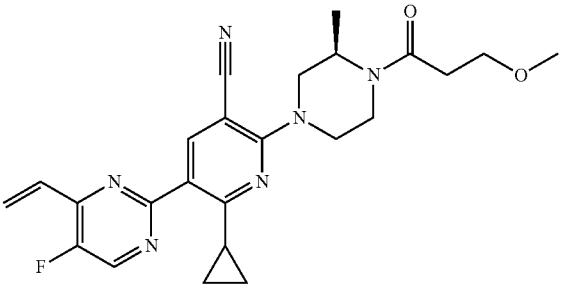
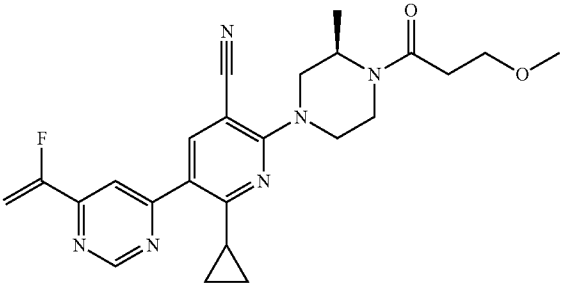
Cpd #	Structure
599	
600	
601	
602	

TABLE 5-continued

Exemplary Compounds of Formula I.

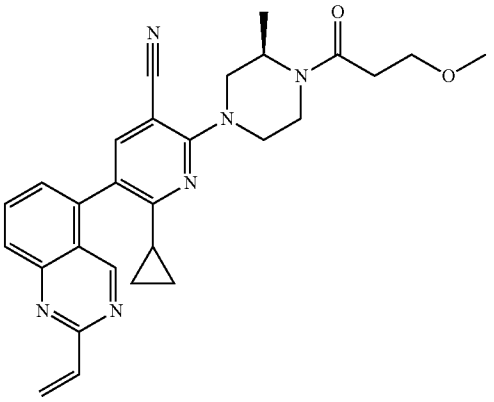
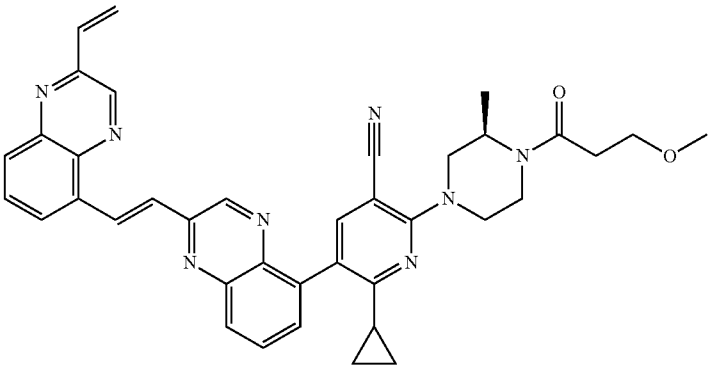
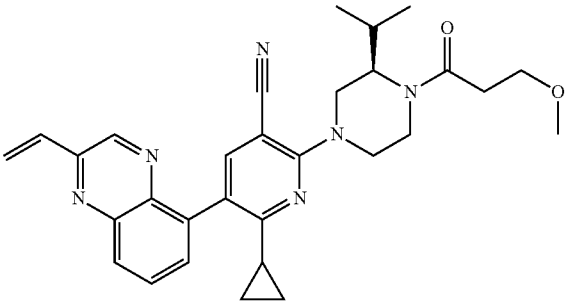
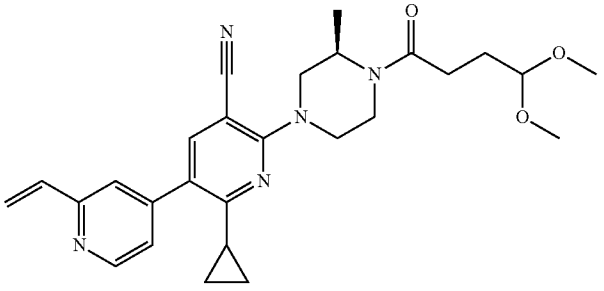
Cpd #	Structure
603	
604	
605	
606	

TABLE 5-continued

Exemplary Compounds of Formula I.

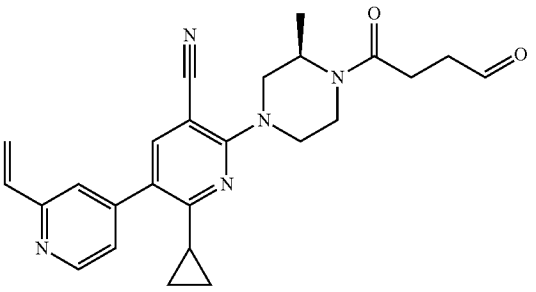
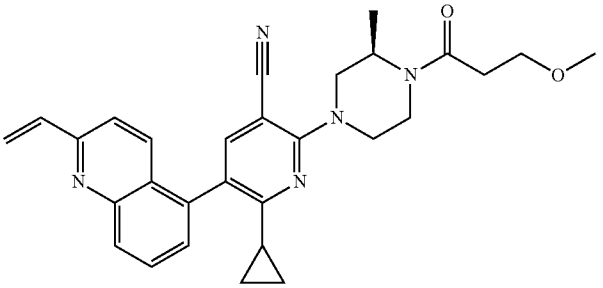
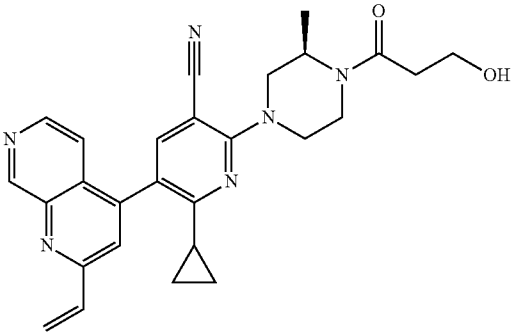
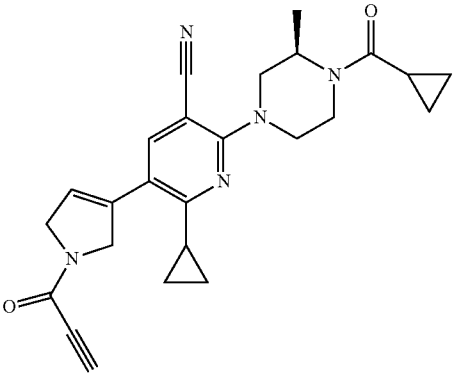
Cpd #	Structure
607	
608	
609	
610	

TABLE 5-continued

Exemplary Compounds of Formula I.

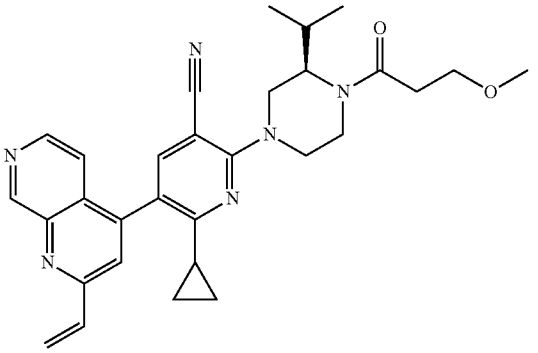
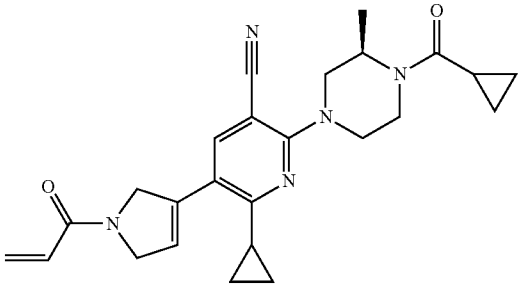
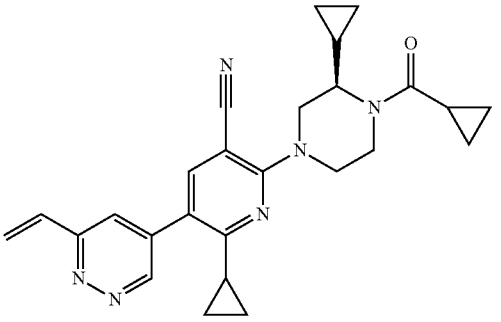
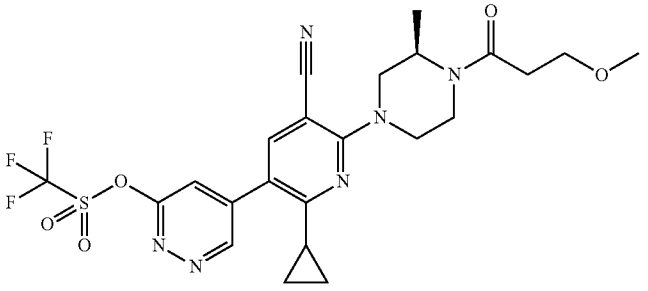
Cpd #	Structure
611	
612	
613	
614	

TABLE 5-continued

Exemplary Compounds of Formula I.

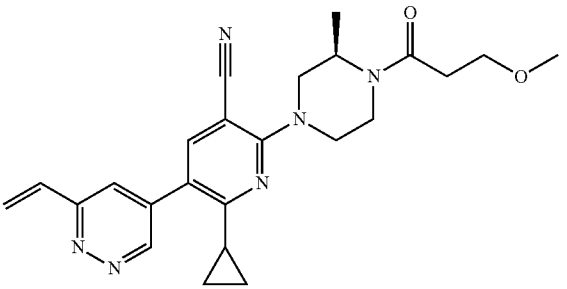
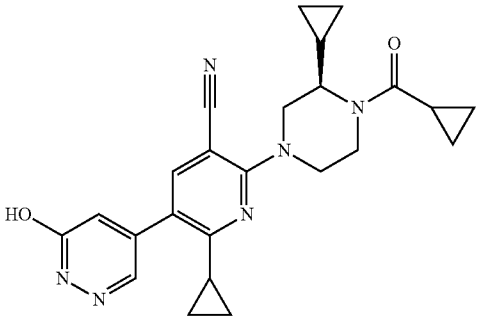
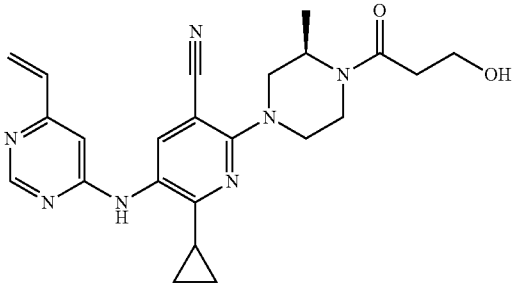
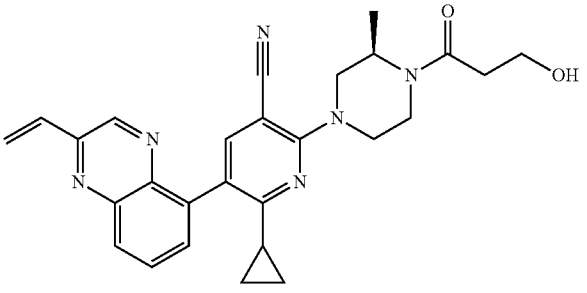
Cpd #	Structure
615	
616	
617	
618	

TABLE 5-continued

Exemplary Compounds of Formula I.

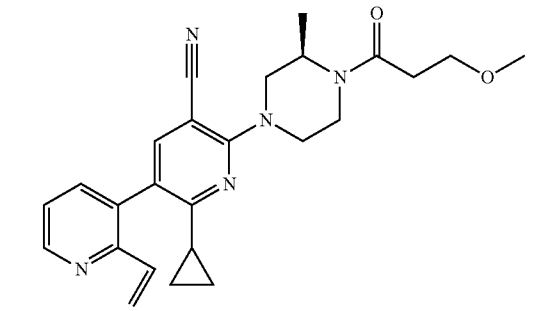
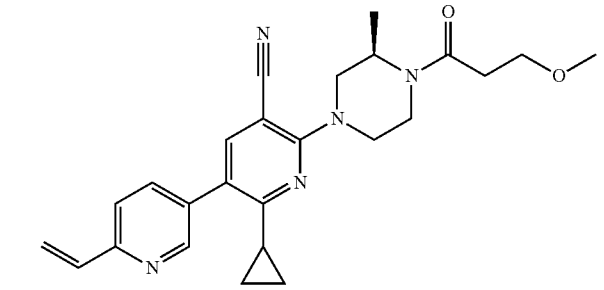
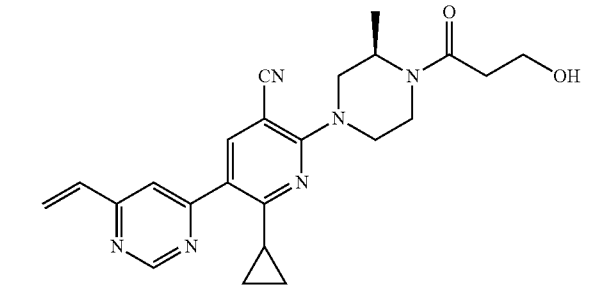
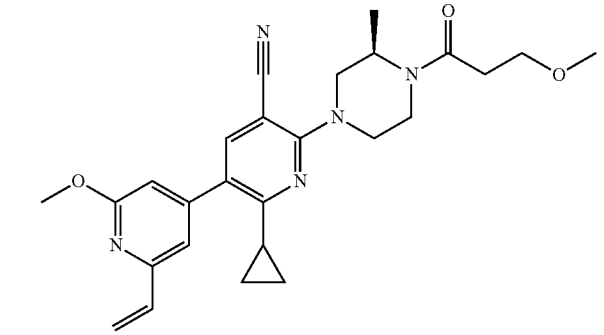
Cpd #	Structure
619	
620	
621	
622	

TABLE 5-continued

Exemplary Compounds of Formula I.

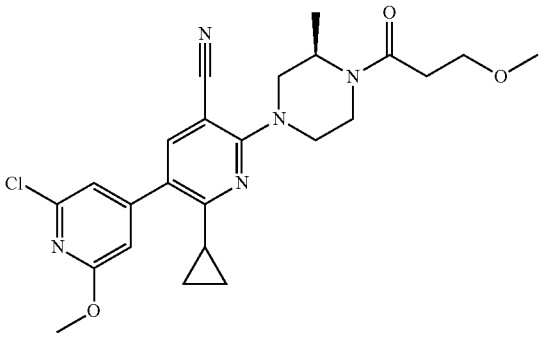
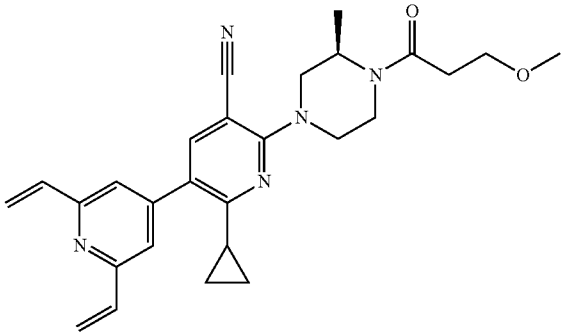
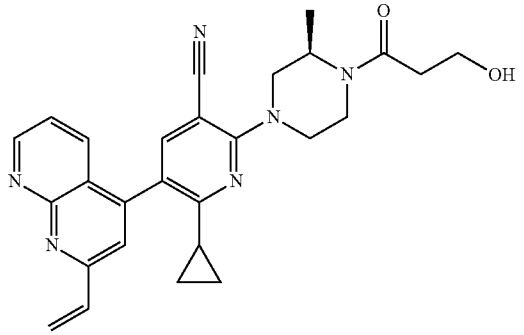
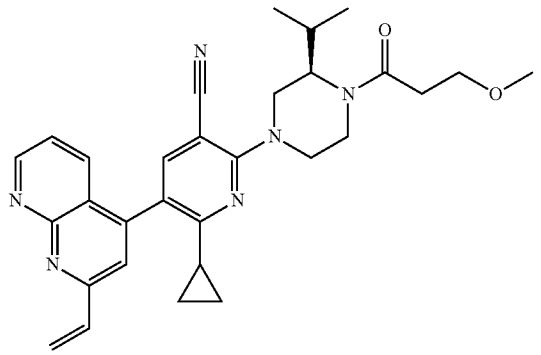
Cpd #	Structure
623	
624	
625	
626	

TABLE 5-continued

Exemplary Compounds of Formula I.

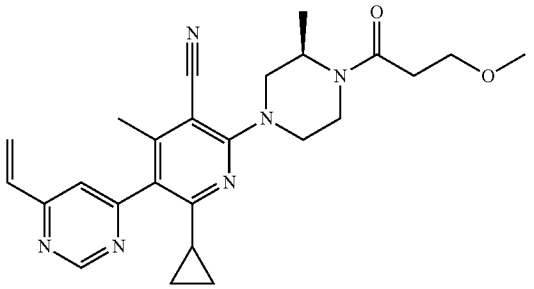
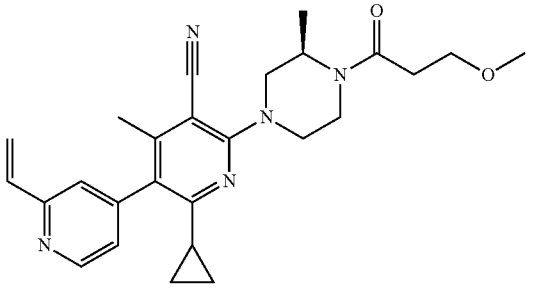
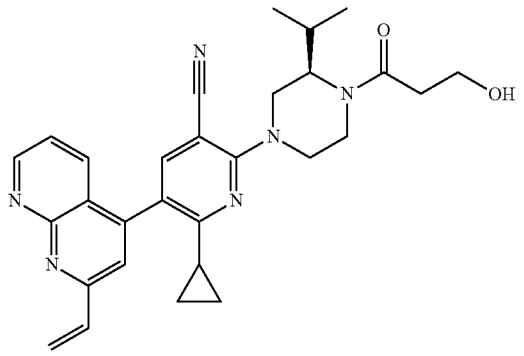
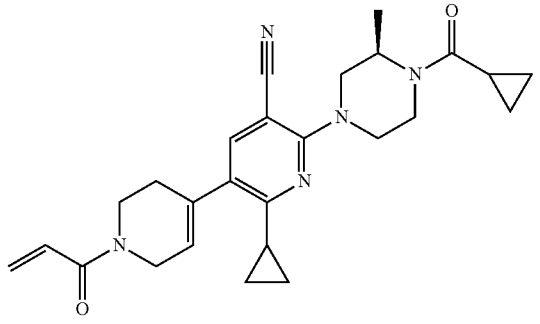
Cpd #	Structure
627	
628	
629	
630	

TABLE 5-continued

Exemplary Compounds of Formula I.

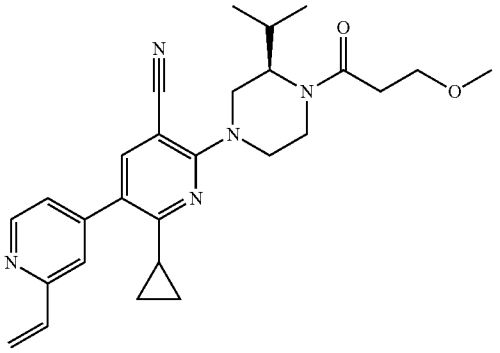
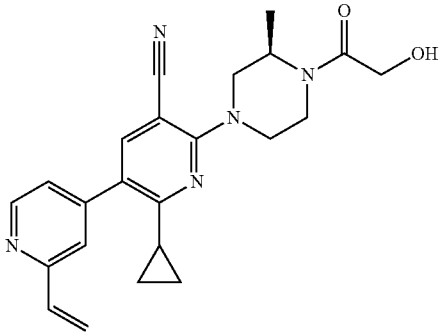
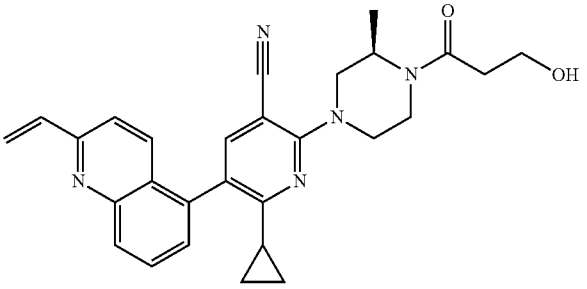
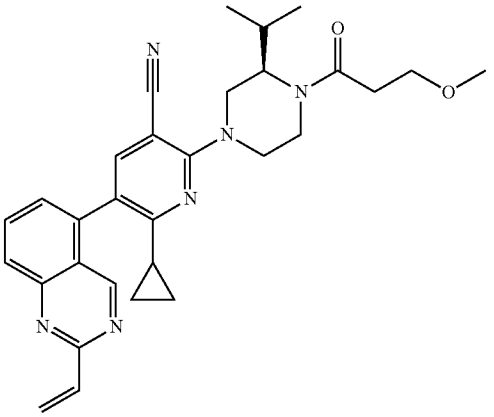
Cpd #	Structure
631	
632	
633	
634	

TABLE 5-continued

Exemplary Compounds of Formula I.

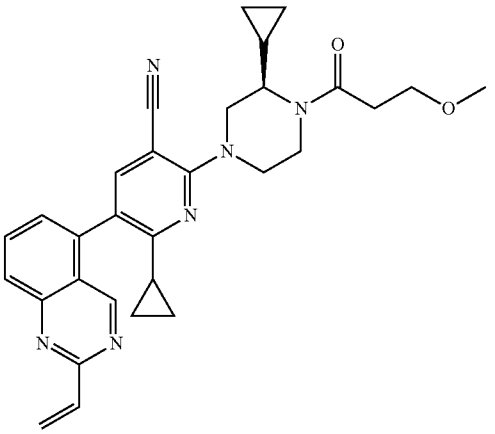
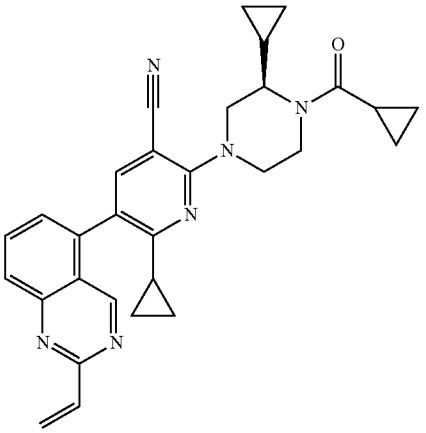
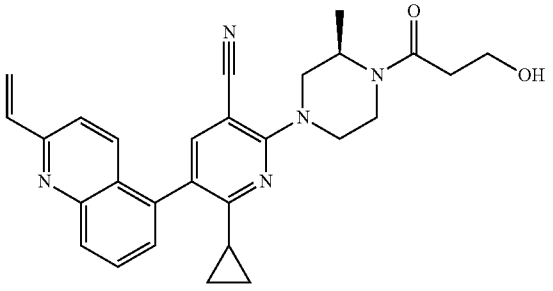
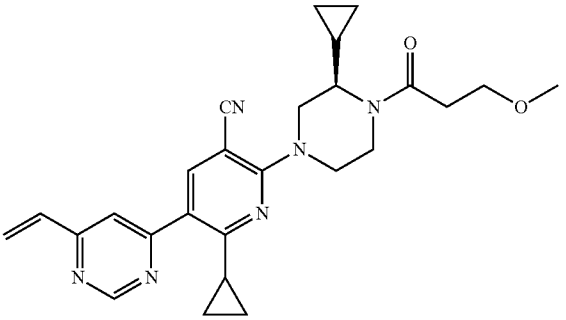
Cpd #	Structure
635	
636	
637	
638	

TABLE 5-continued

Exemplary Compounds of Formula I.

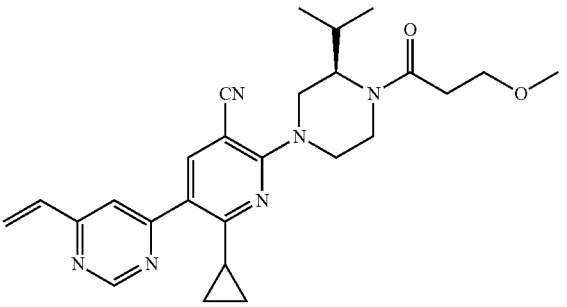
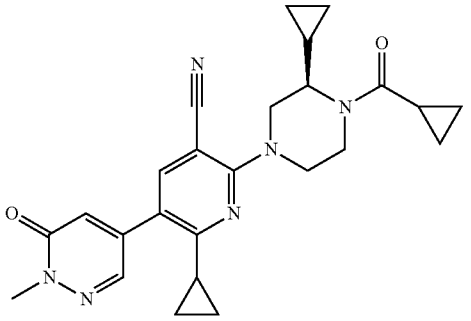
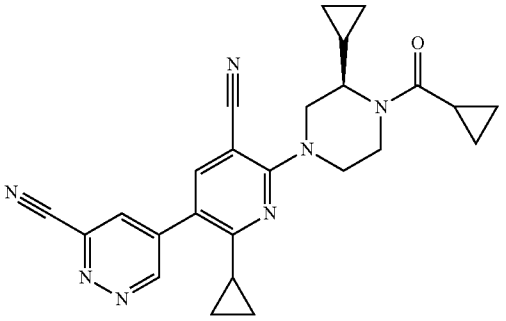
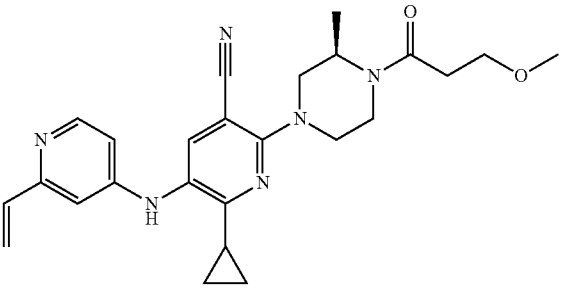
Cpd #	Structure
639	
640	
641	
642	

TABLE 5-continued

Exemplary Compounds of Formula I.

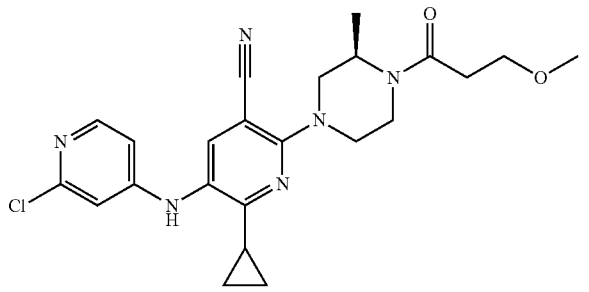
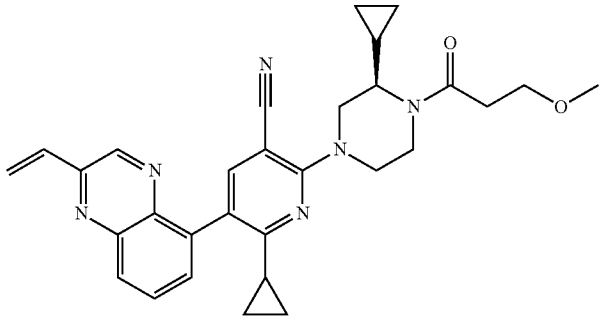
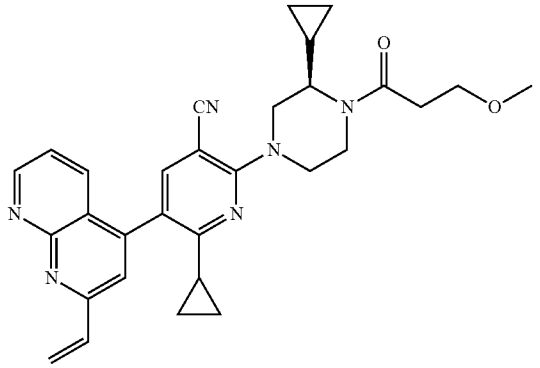
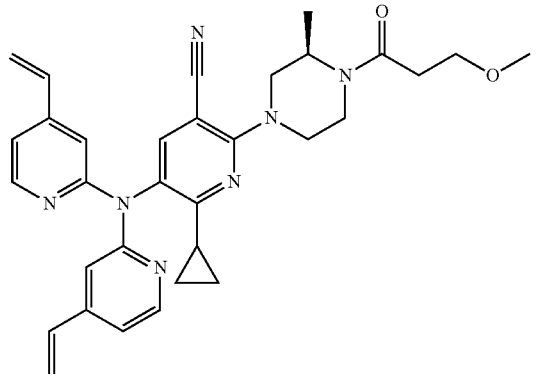
Cpd #	Structure
643	
644	
645	
646	

TABLE 5-continued

Exemplary Compounds of Formula I.

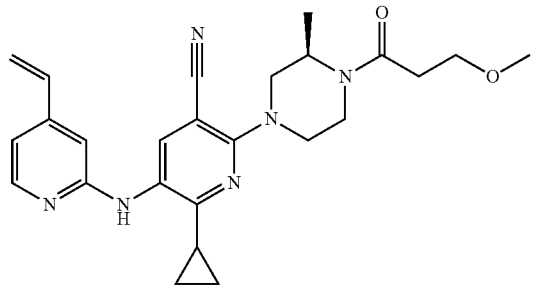
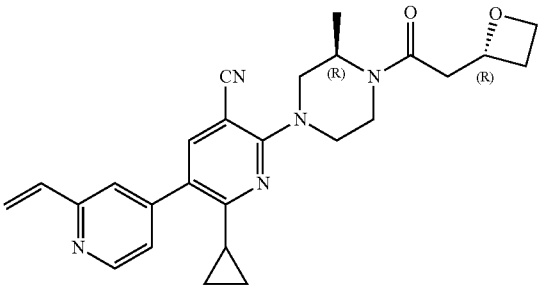
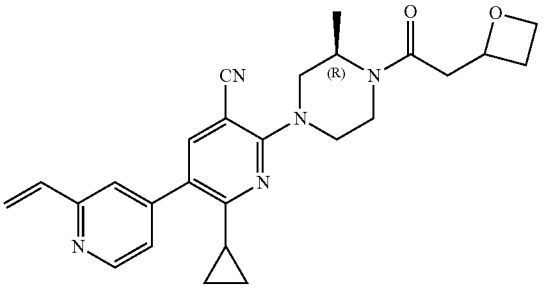
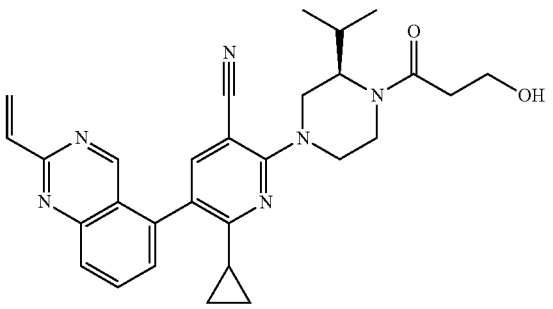
Cpd #	Structure
647	
648	
649	
650	

TABLE 5-continued

Exemplary Compounds of Formula I.

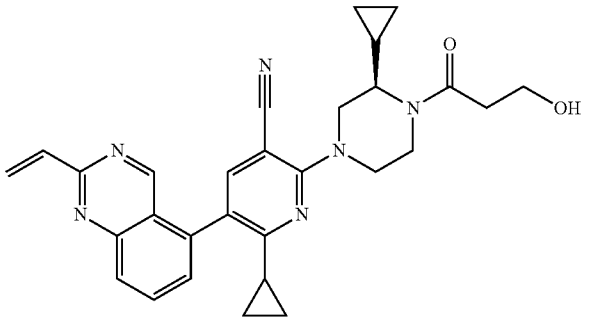
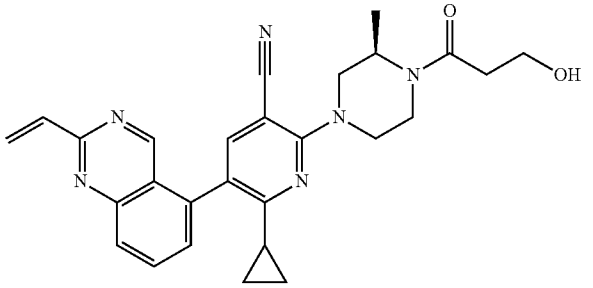
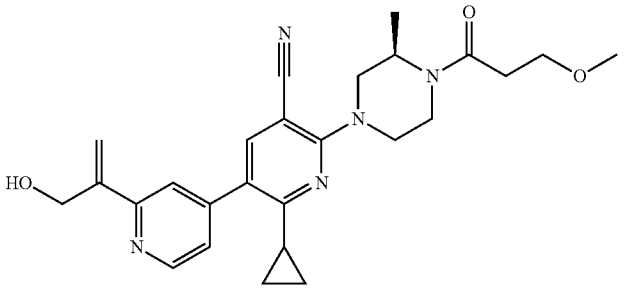
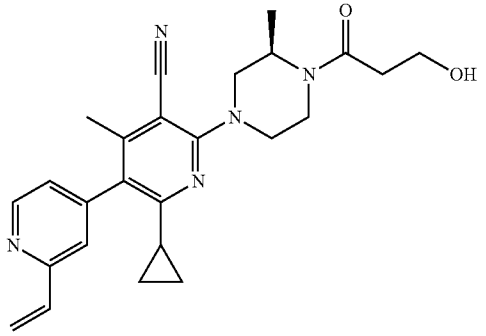
Cpd #	Structure
651	
652	
653	
654	

TABLE 5-continued

Exemplary Compounds of Formula I.

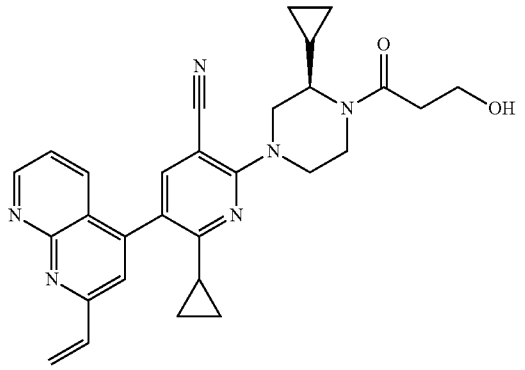
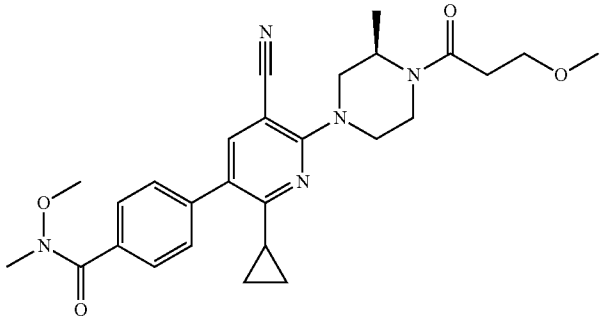
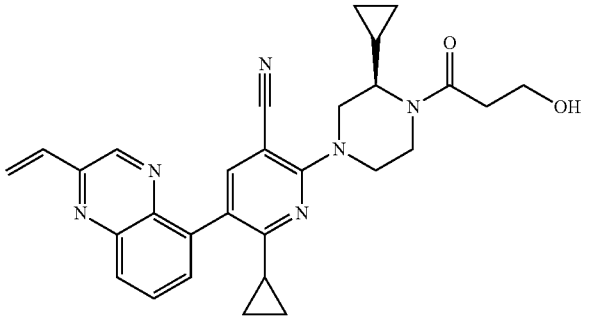
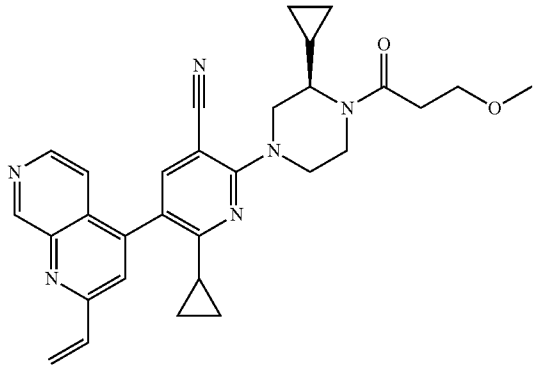
Cpd #	Structure
655	
656	
657	
658	

TABLE 5-continued

Exemplary Compounds of Formula I.

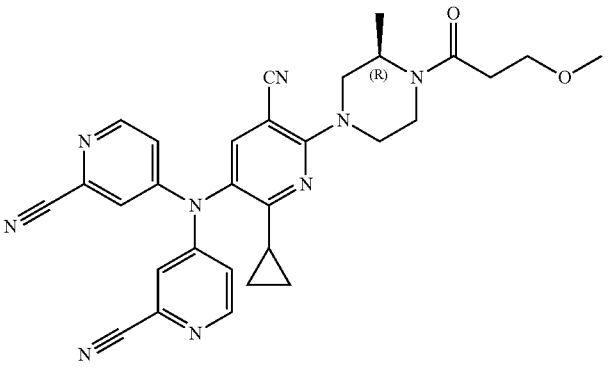
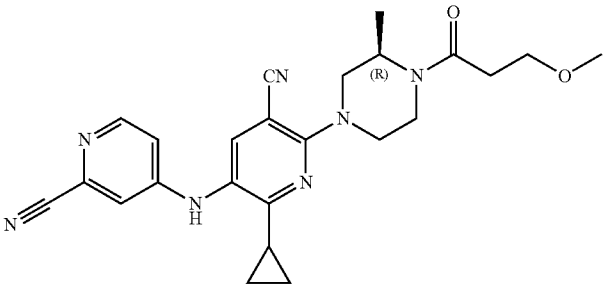
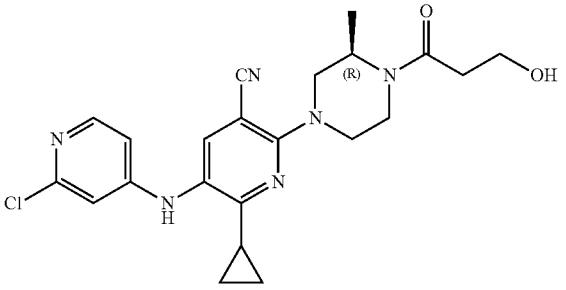
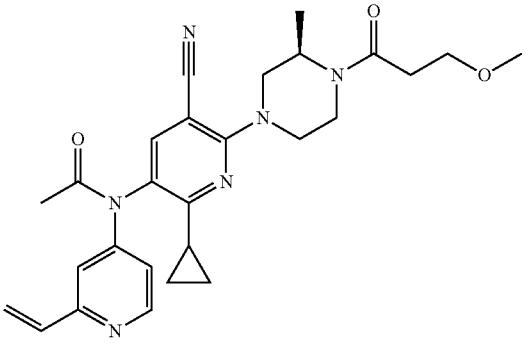
Cpd #	Structure
659	
660	
661	
662	

TABLE 5-continued

Exemplary Compounds of Formula I.

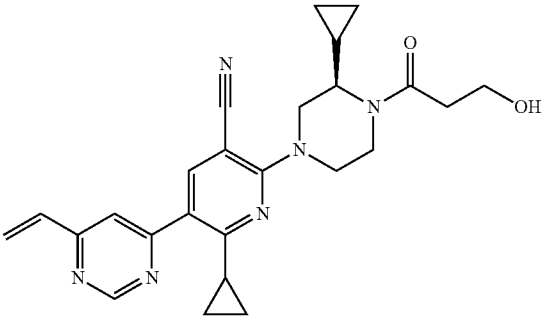
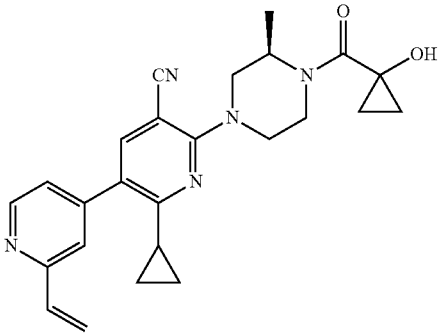
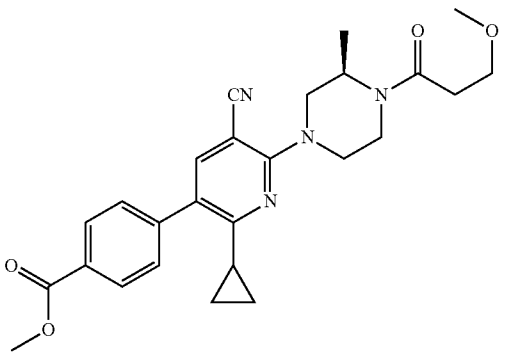
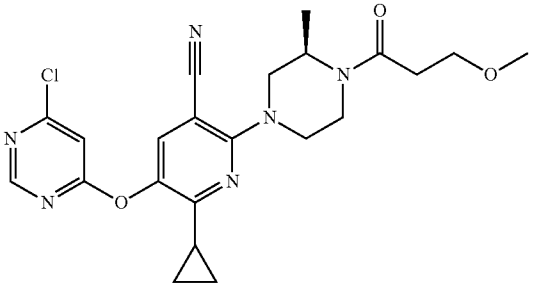
Cpd #	Structure
663	
664	
665	
666	

TABLE 5-continued

Exemplary Compounds of Formula I.

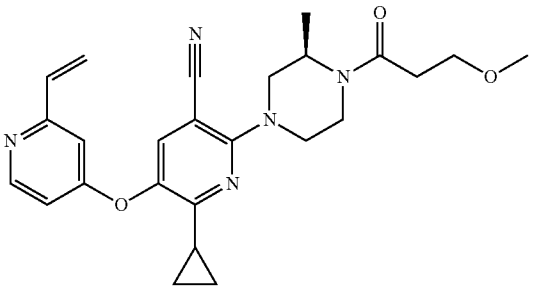
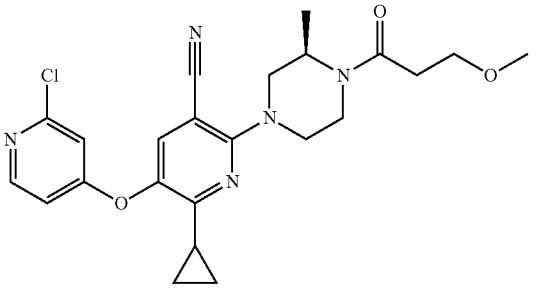
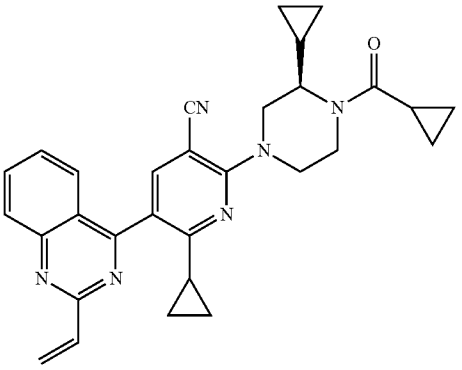
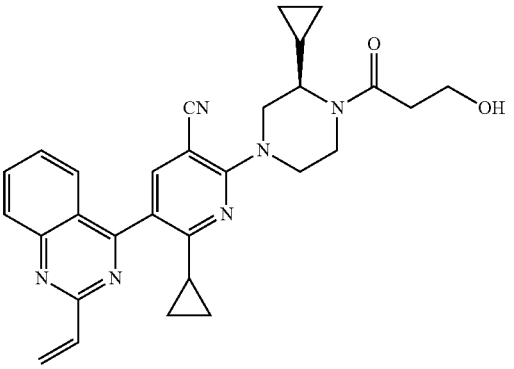
Cpd #	Structure
667	
668	
669	
670	

TABLE 5-continued

Exemplary Compounds of Formula I.

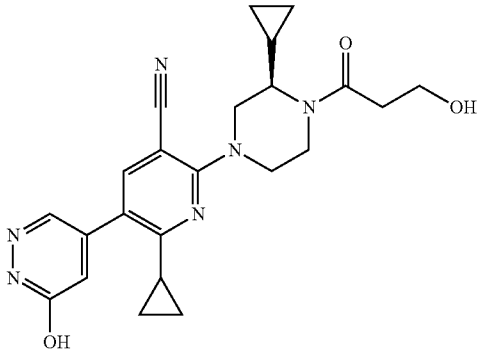
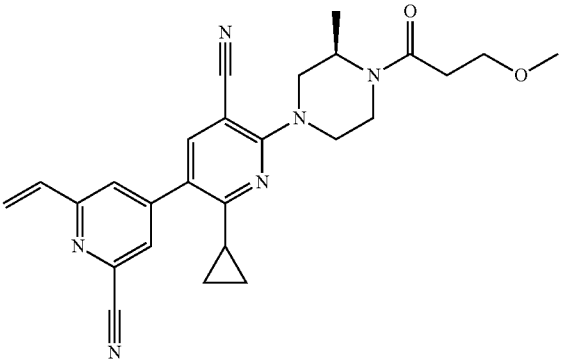
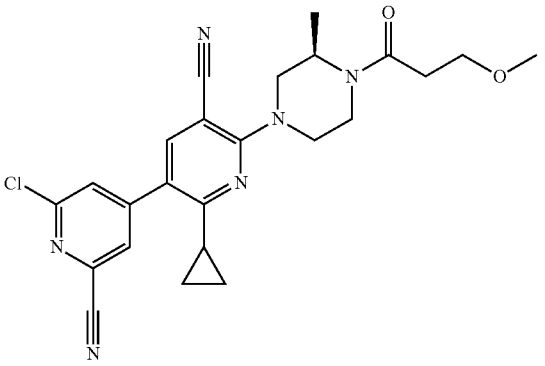
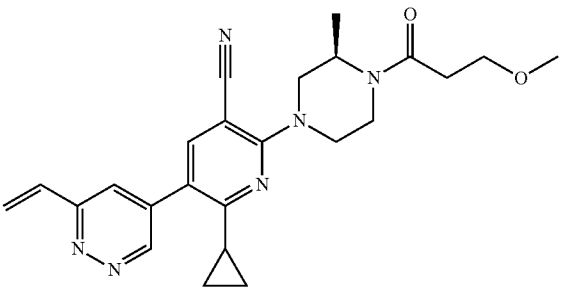
Cpd #	Structure
671	
672	
673	
674	

TABLE 5-continued

Exemplary Compounds of Formula I.

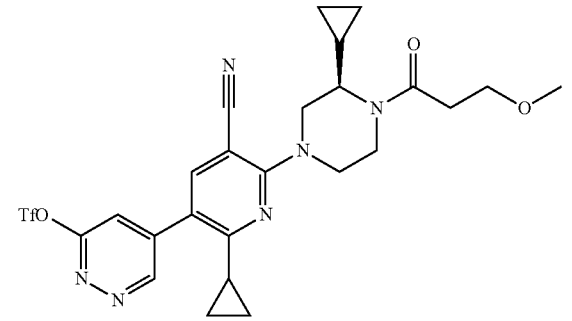
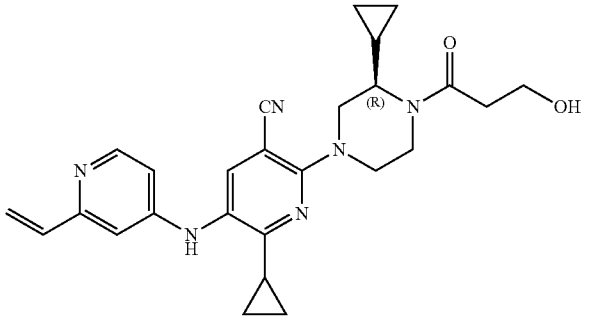
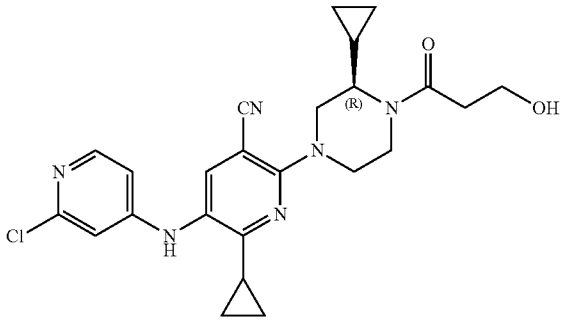
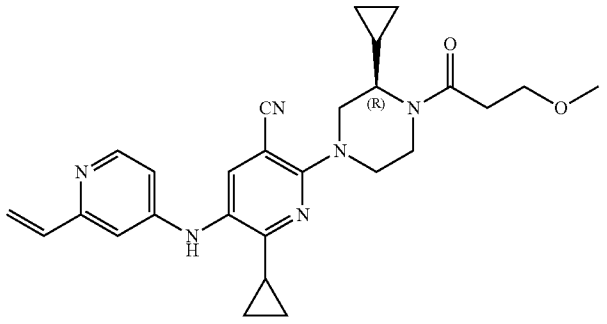
Cpd #	Structure
675	
676	
677	
678	

TABLE 5-continued

Exemplary Compounds of Formula I.

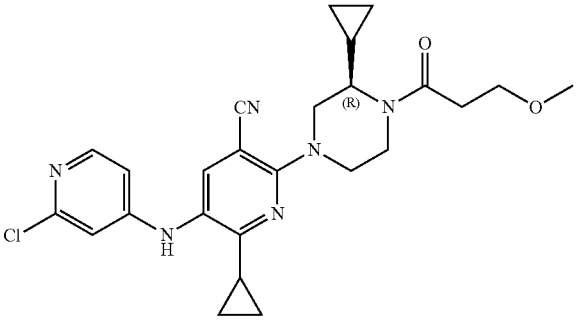
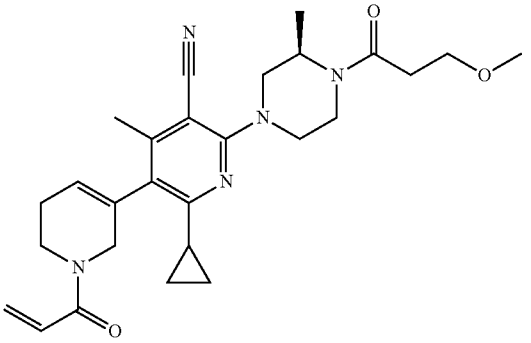
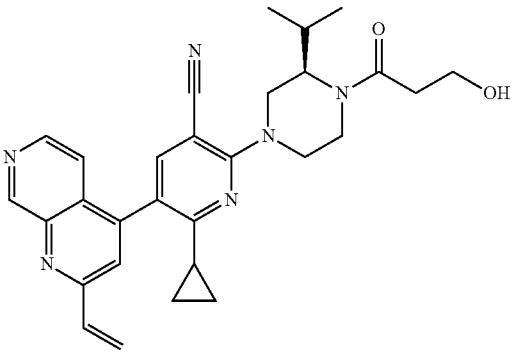
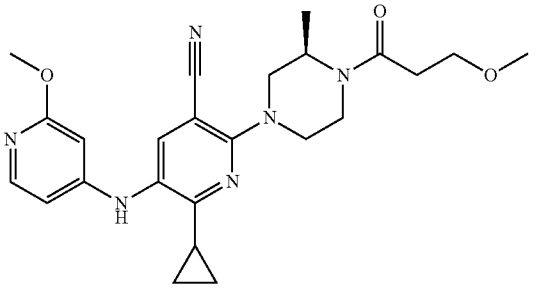
Cpd #	Structure
679	
680	
681	
682	

TABLE 5-continued

Exemplary Compounds of Formula I.

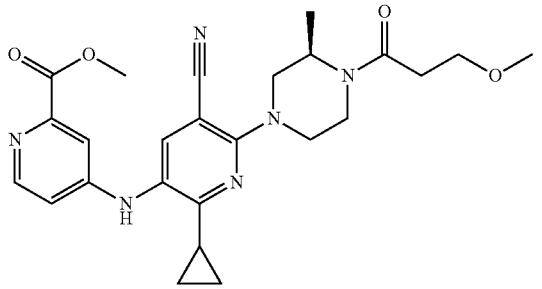
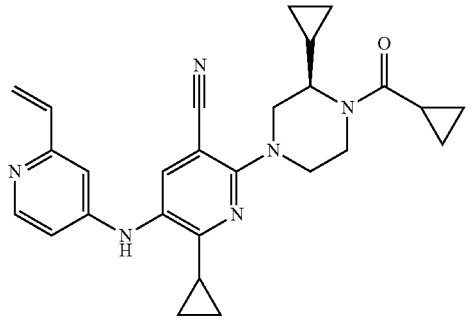
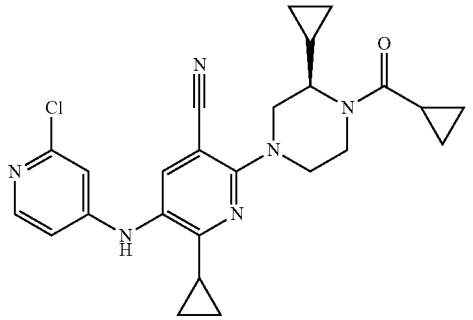
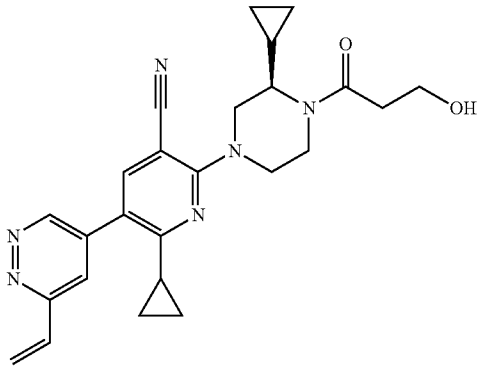
Cpd #	Structure
683	
684	
685	
686	

TABLE 5-continued

Exemplary Compounds of Formula I.

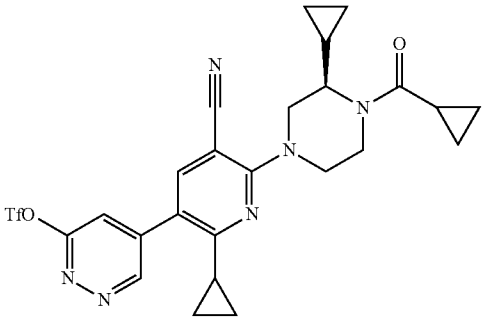
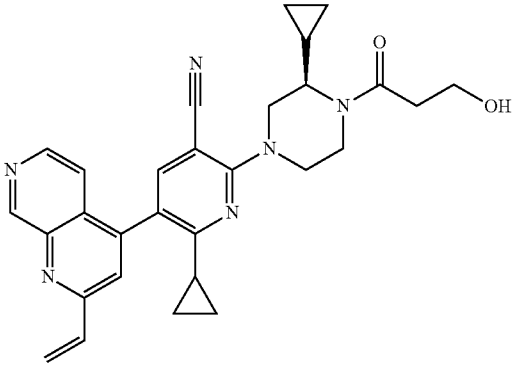
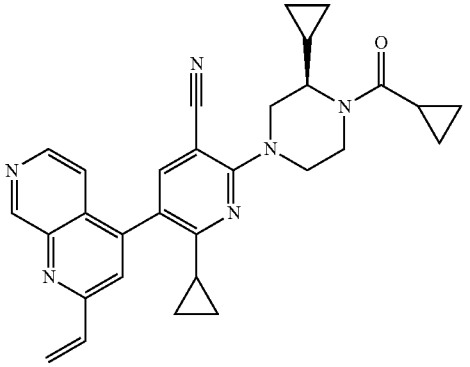
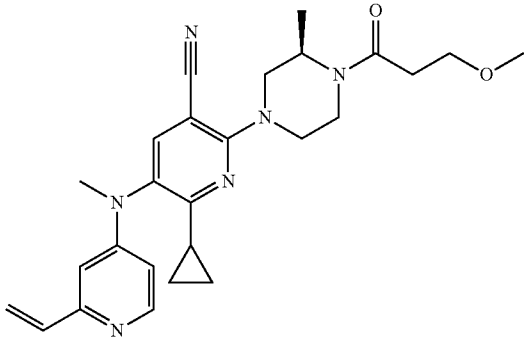
Cpd #	Structure
687	
688	
689	
690	

TABLE 5-continued

Exemplary Compounds of Formula I.

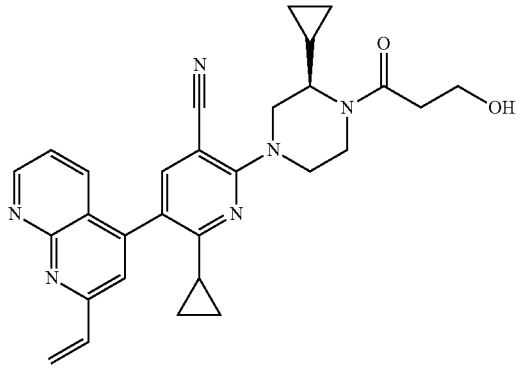
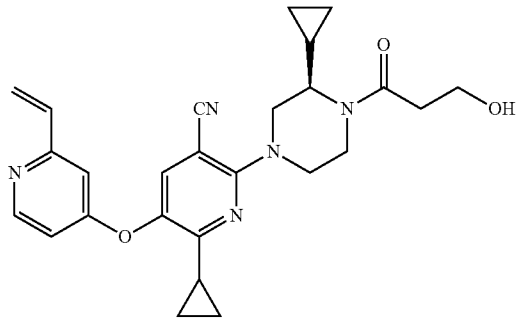
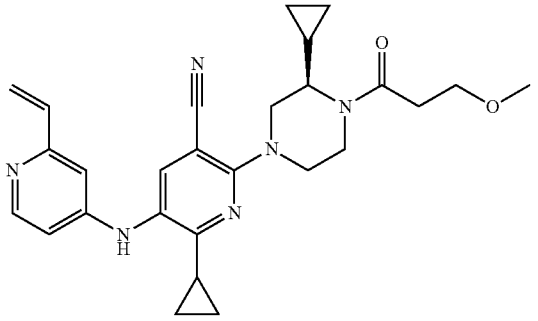
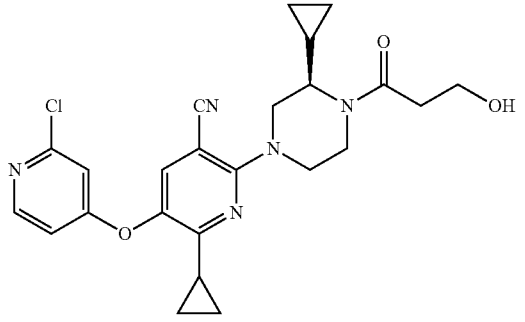
Cpd #	Structure
691	
692	
693	
694	

TABLE 5-continued

Exemplary Compounds of Formula I.

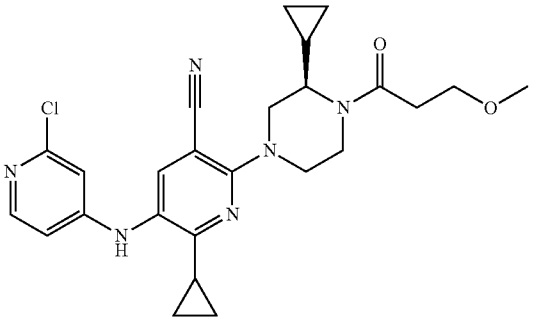
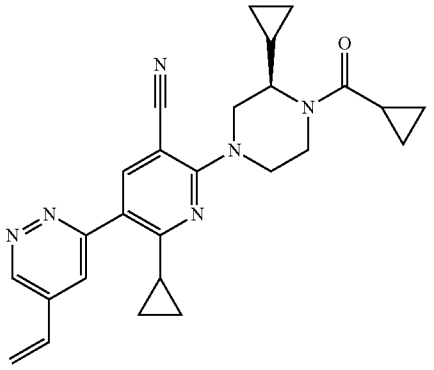
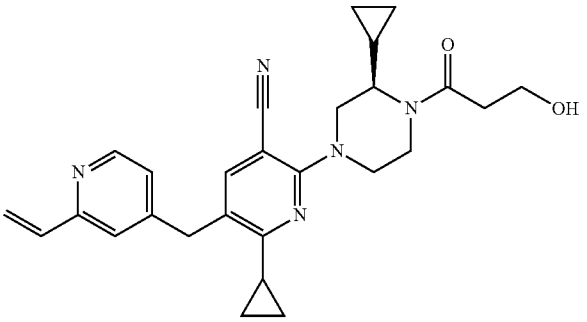
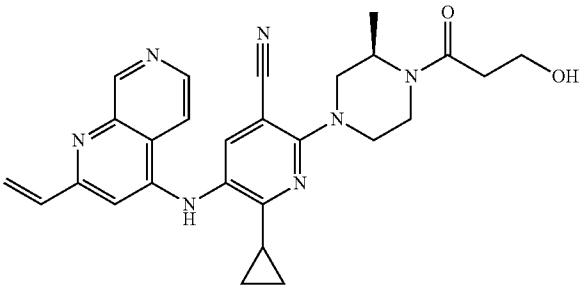
Cpd #	Structure
695	
696	
697	
698	

TABLE 5-continued

Exemplary Compounds of Formula I.

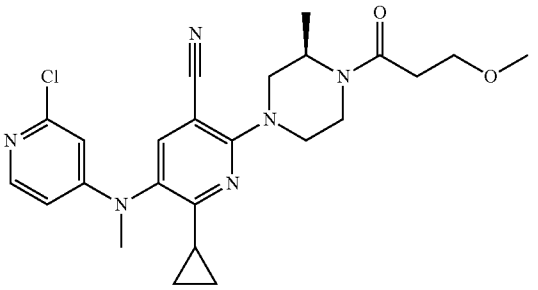
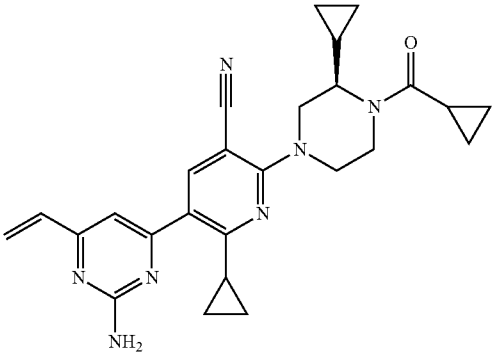
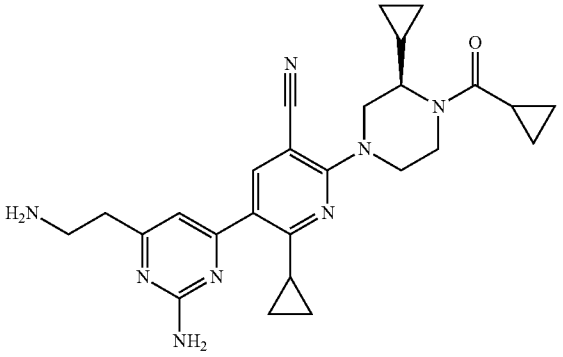
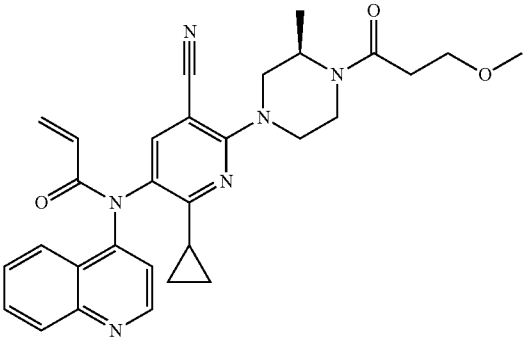
Cpd #	Structure
699	
700	
701	
702	

TABLE 5-continued

Exemplary Compounds of Formula I.

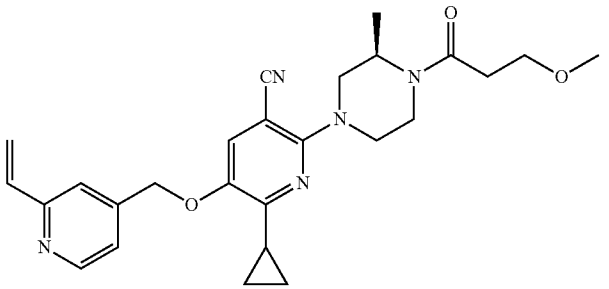
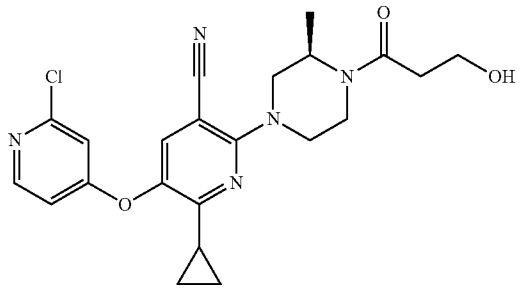
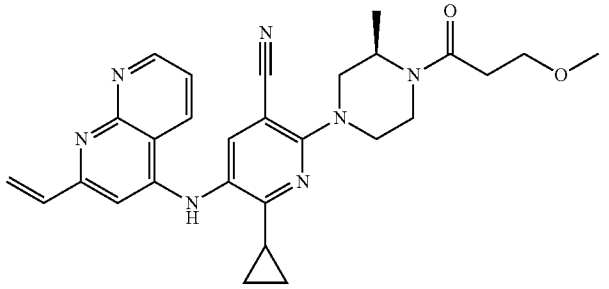
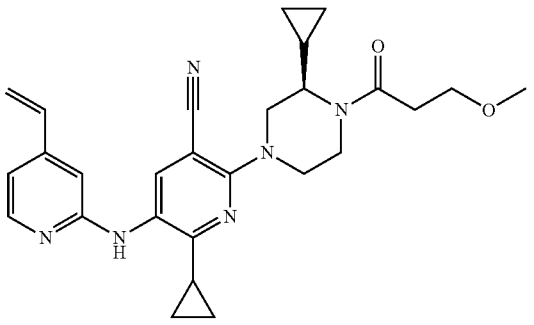
Cpd #	Structure
703	
704	
705	
706	

TABLE 5-continued

Exemplary Compounds of Formula I.

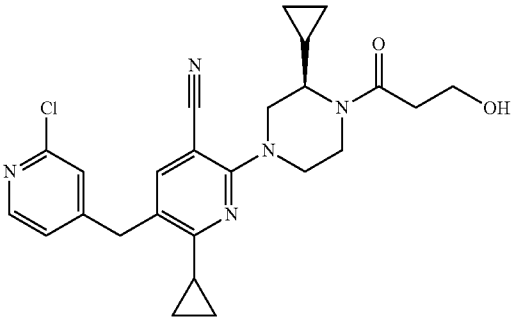
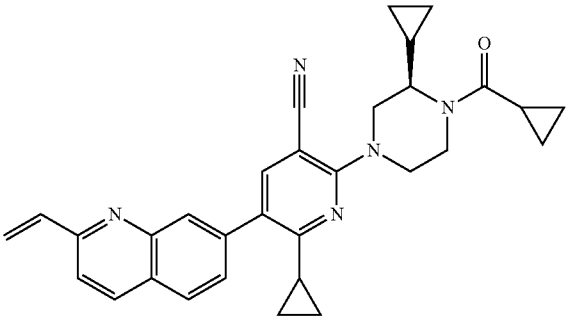
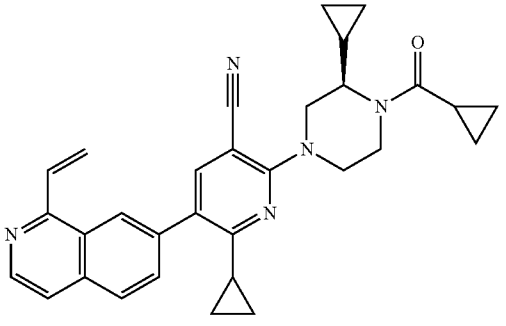
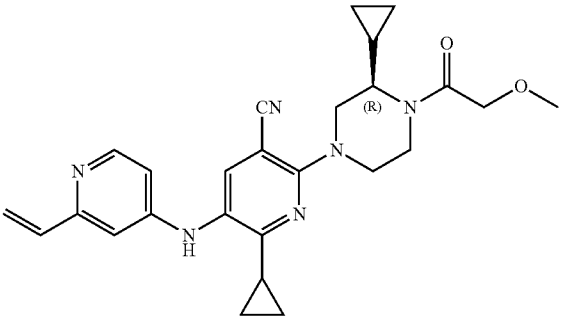
Cpd #	Structure
707	
708	
709	
710	
711	

TABLE 5-continued

Exemplary Compounds of Formula I.

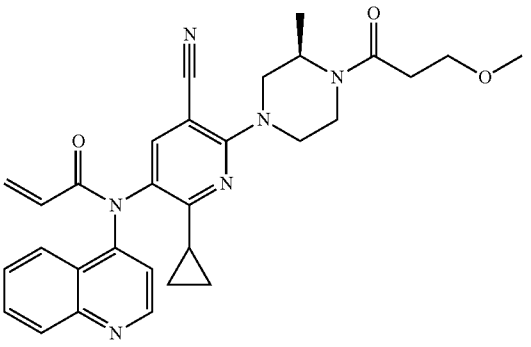
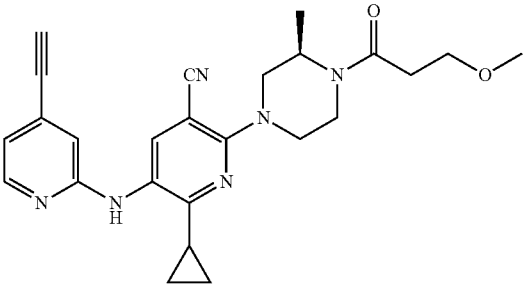
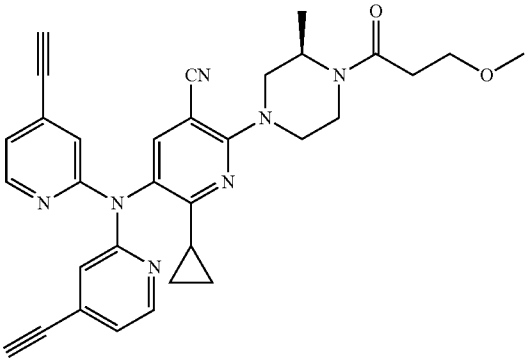
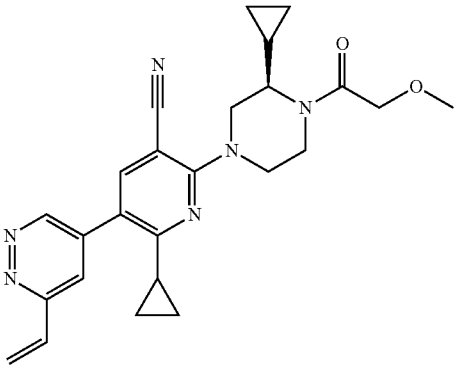
Cpd #	Structure
712	
713	
714	
715	

TABLE 5-continued

Exemplary Compounds of Formula I.

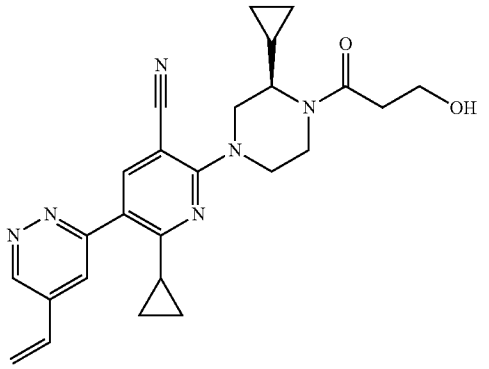
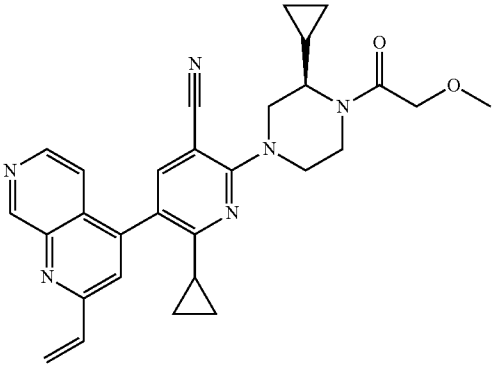
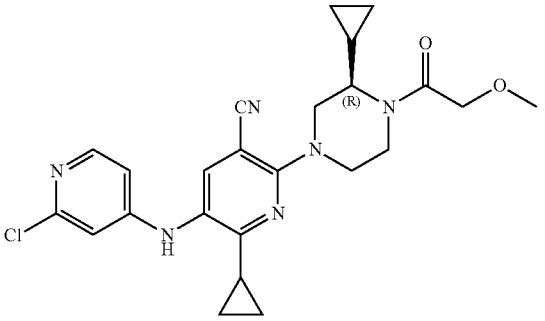
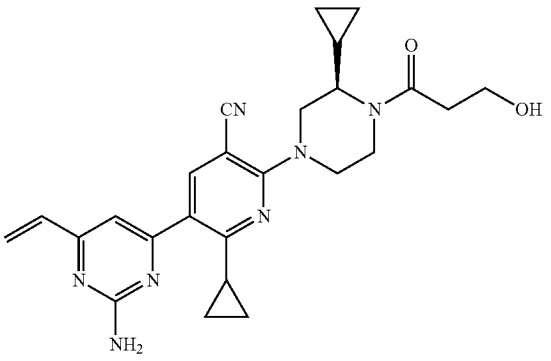
Cpd #	Structure
716	
717	
718	
719	

TABLE 5-continued

Exemplary Compounds of Formula I.

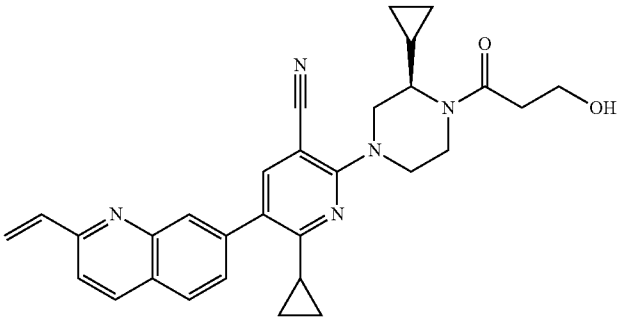
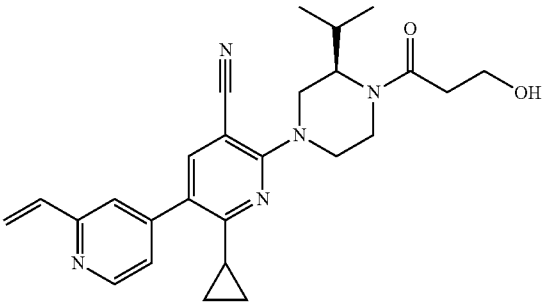
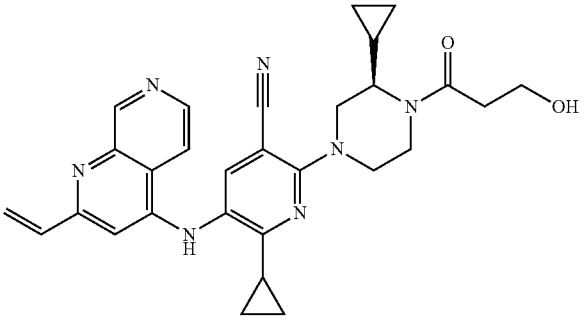
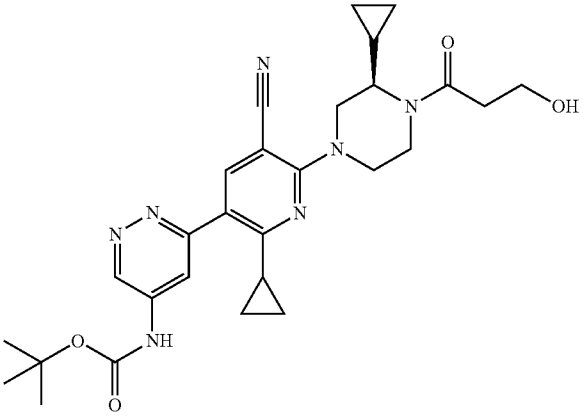
Cpd #	Structure
720	
721	
722	
723	

TABLE 5-continued

Exemplary Compounds of Formula I.

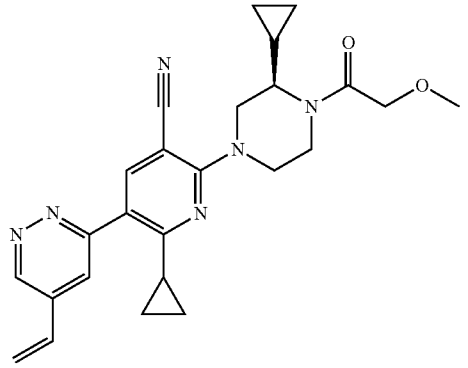
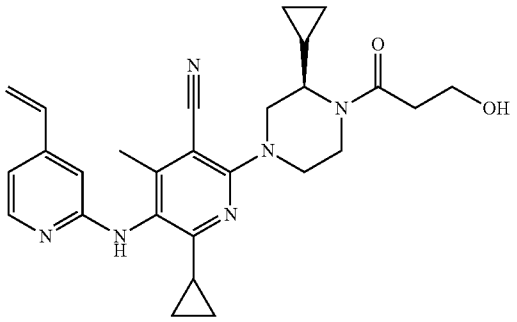
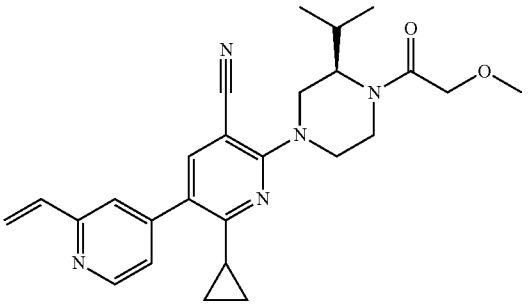
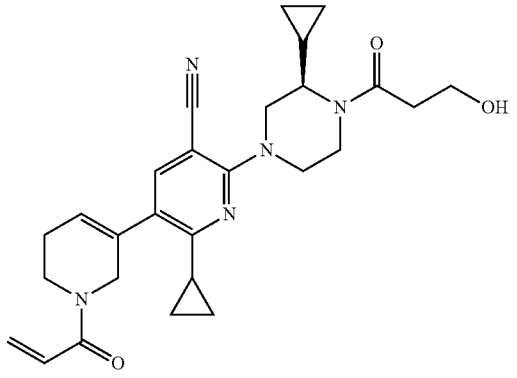
Cpd #	Structure
724	
725	
726	
727	

TABLE 5-continued

Exemplary Compounds of Formula I.

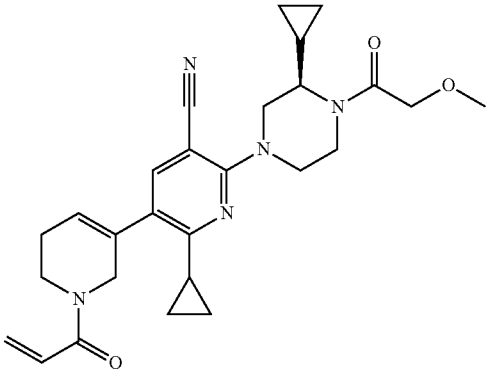
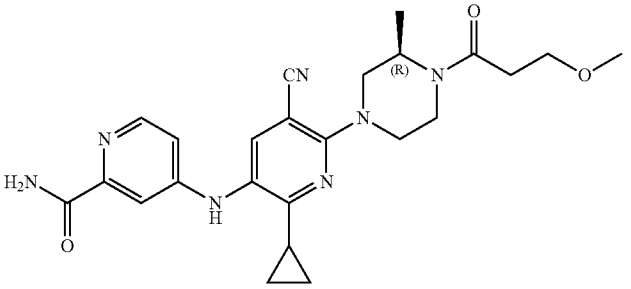
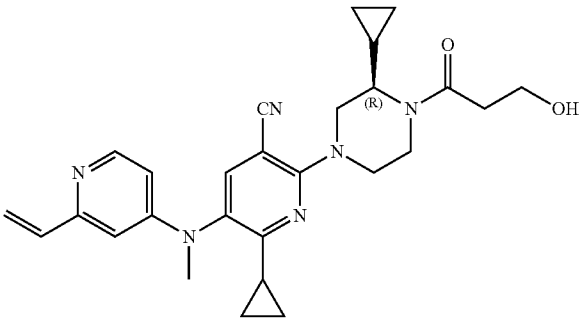
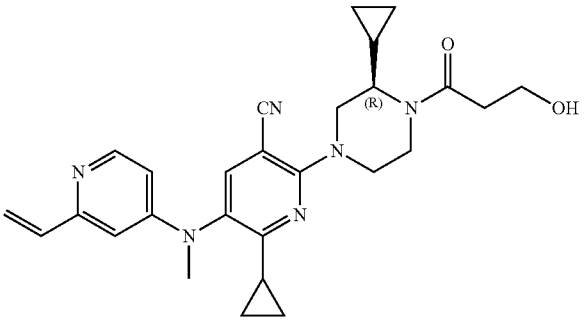
Cpd #	Structure
728	
729	
730	
731	

TABLE 5-continued

Exemplary Compounds of Formula I.

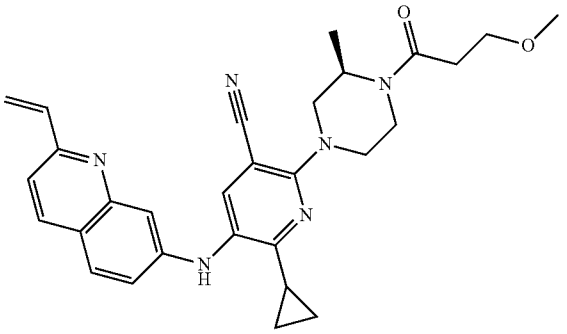
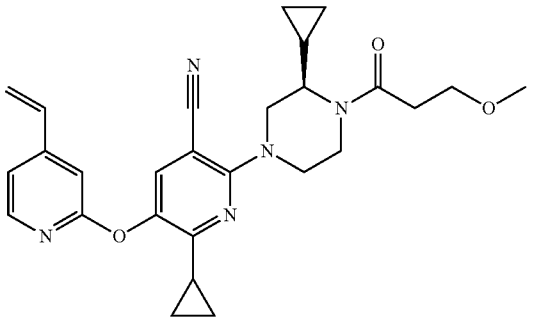
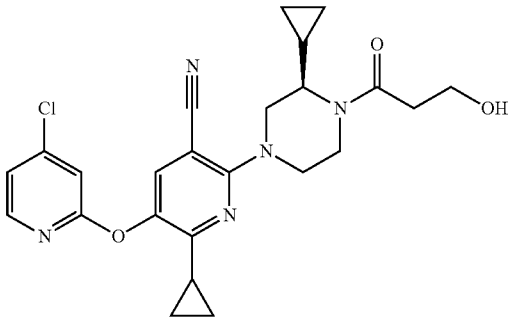
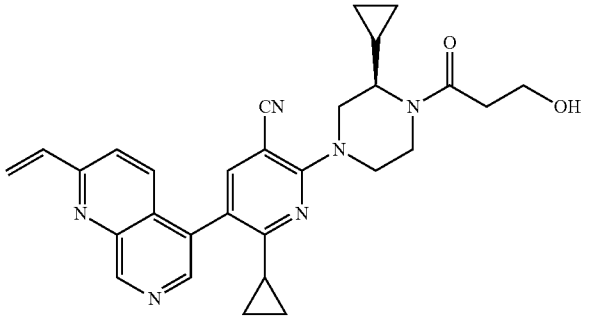
Cpd #	Structure
732	
733	
734	
735	

TABLE 5-continued

Exemplary Compounds of Formula I.

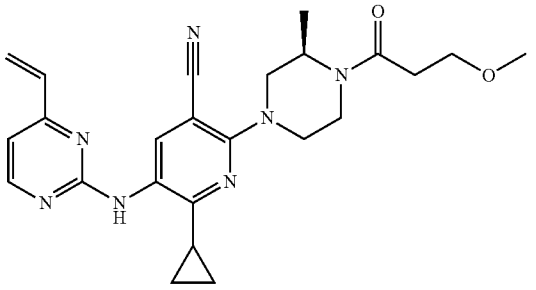
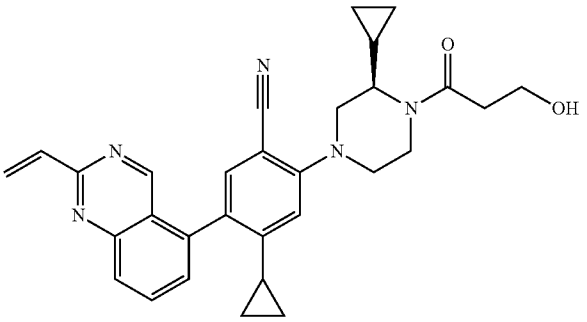
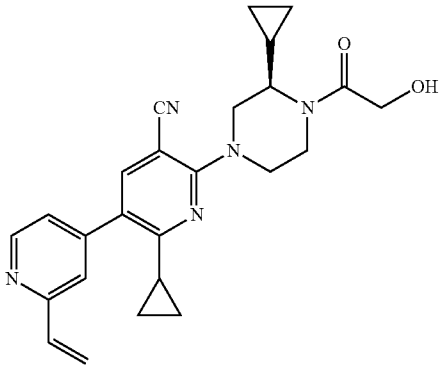
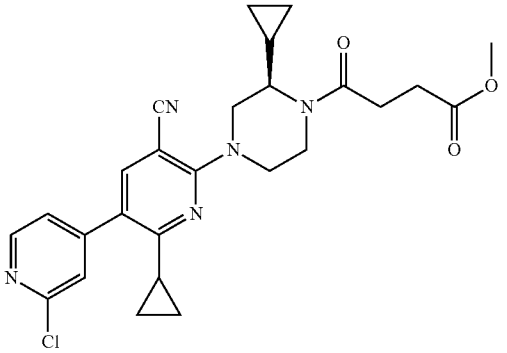
Cpd #	Structure
736	
737	
738	
739	

TABLE 5-continued

Exemplary Compounds of Formula I.

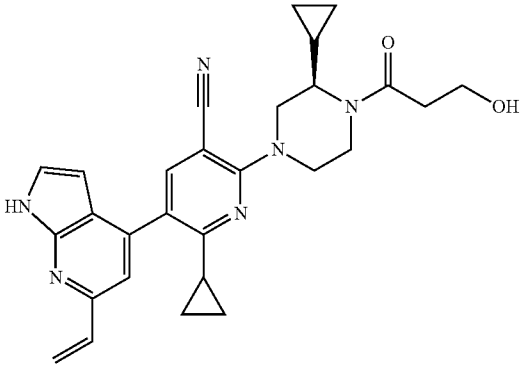
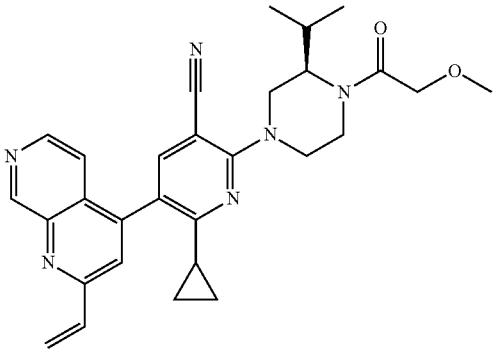
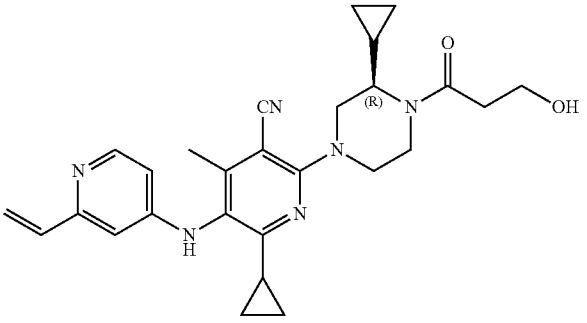
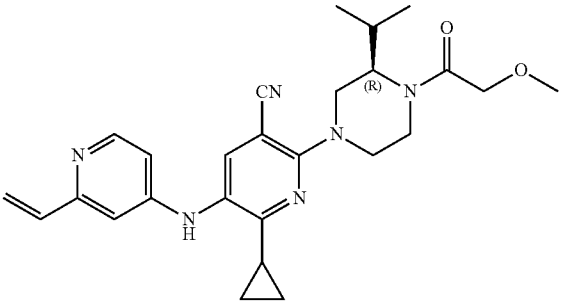
Cpd #	Structure
740	
741	
742	
743	

TABLE 5-continued

Exemplary Compounds of Formula I.

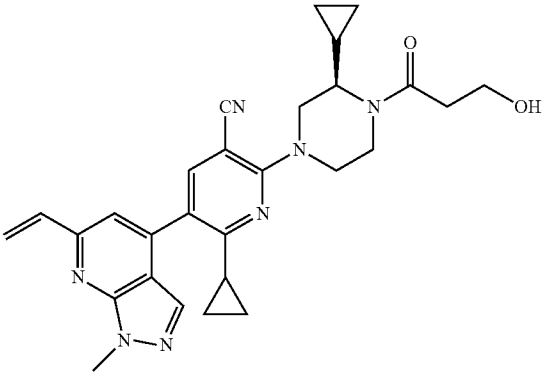
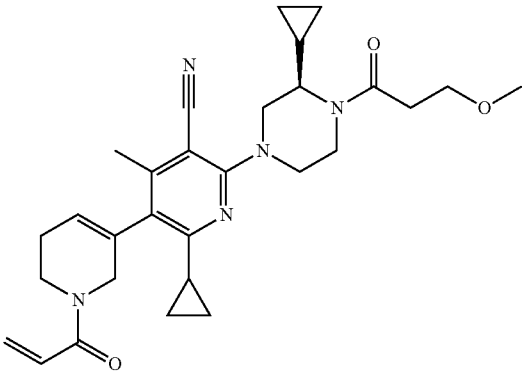
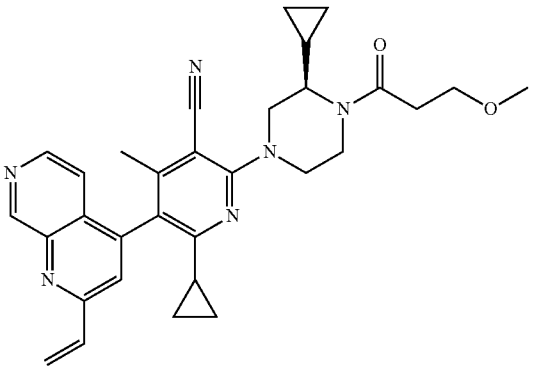
Cpd #	Structure
744	
745	
746	

TABLE 5-continued

Exemplary Compounds of Formula I.

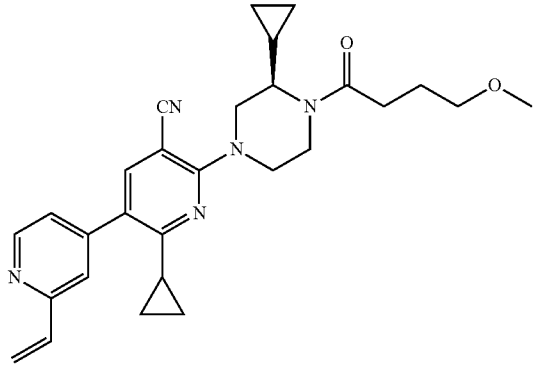
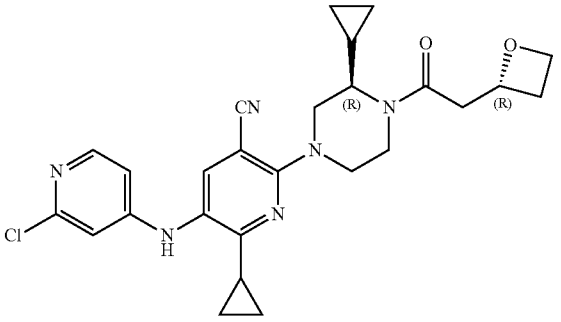
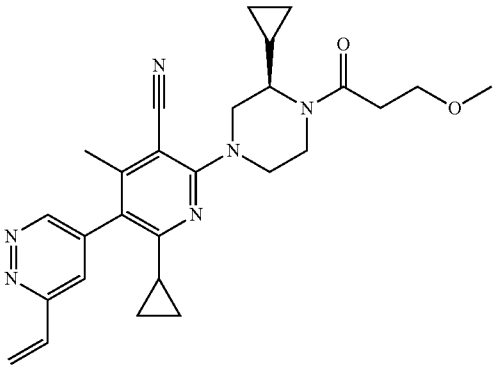
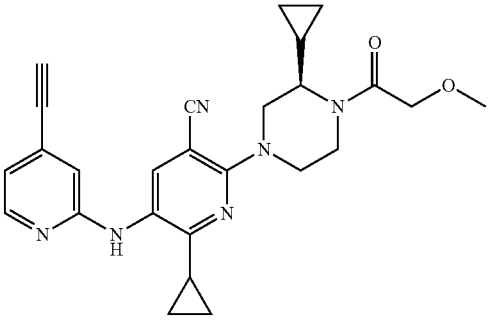
Cpd #	Structure
747	
748	
749	
750	

TABLE 5-continued

Exemplary Compounds of Formula I.

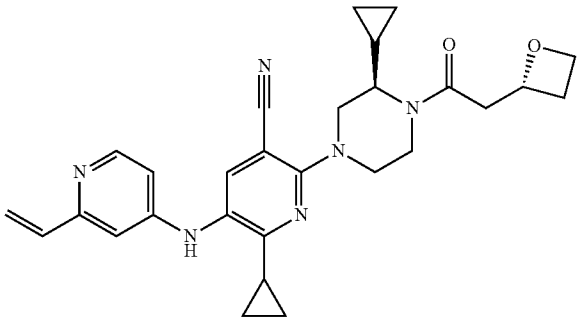
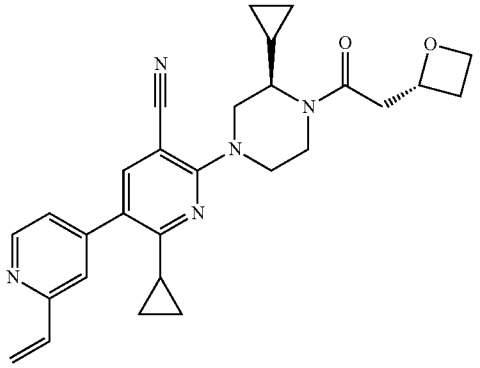
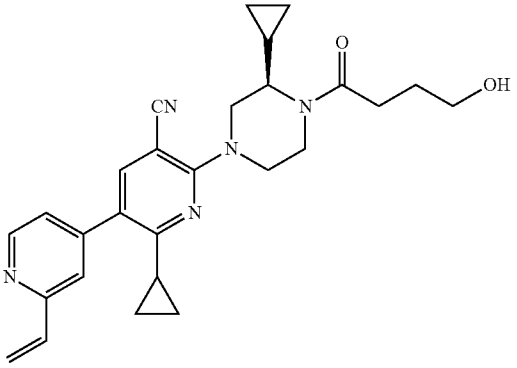
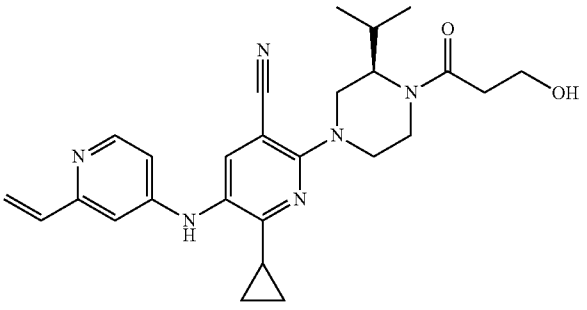
Cpd #	Structure
751	
752	
753	
754	

TABLE 5-continued

Exemplary Compounds of Formula I.

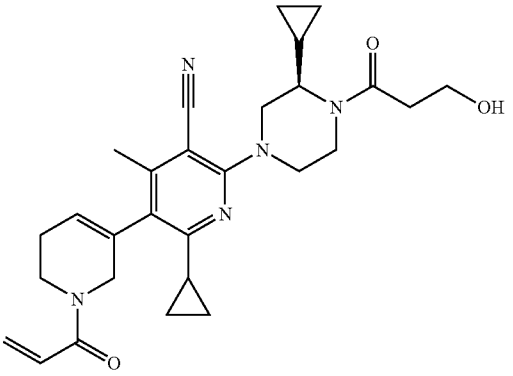
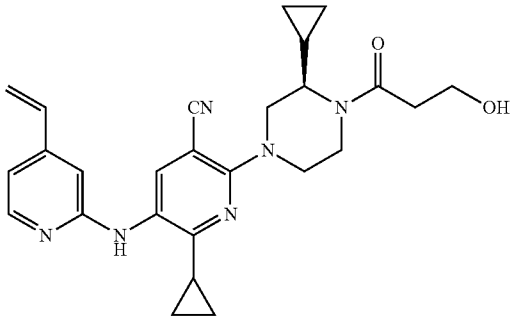
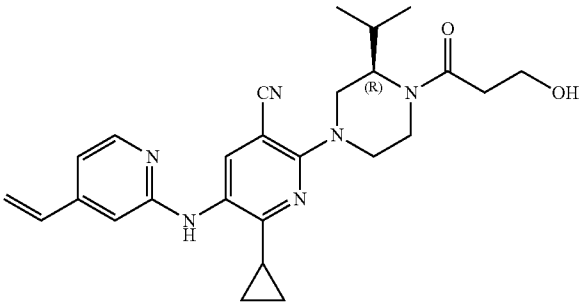
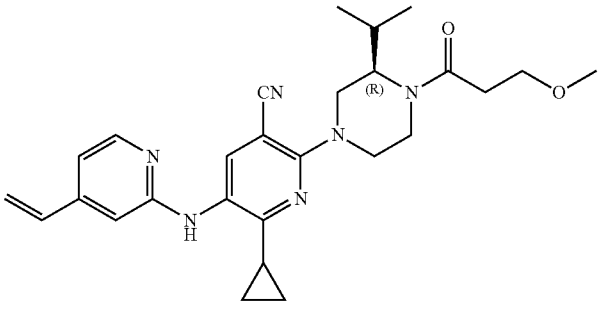
Cpd #	Structure
755	
756	
757	
758	

TABLE 5-continued

Exemplary Compounds of Formula I.

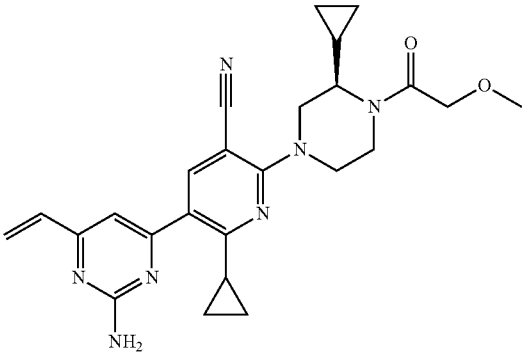
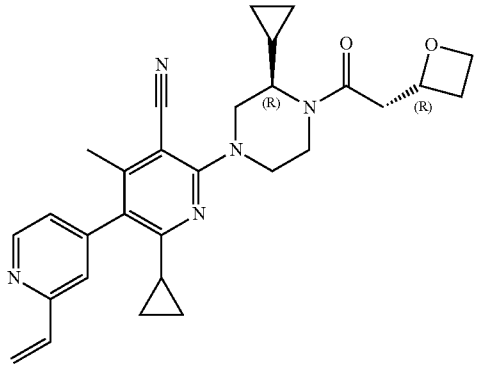
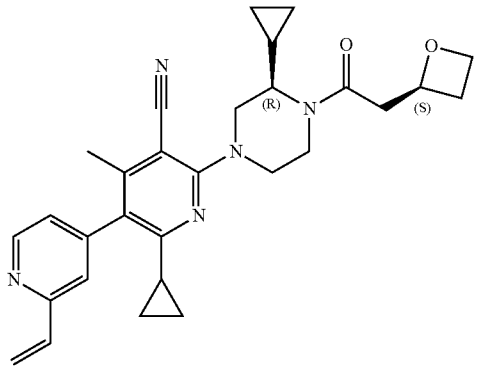
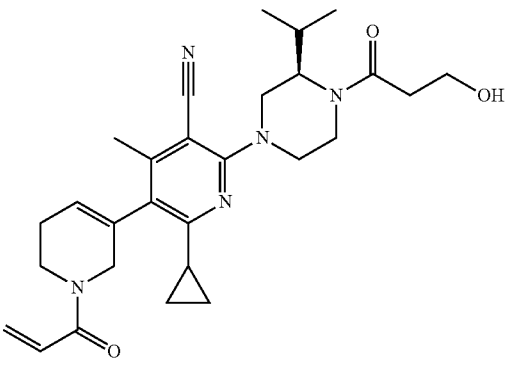
Cpd #	Structure
759	
760	
761	
762	

TABLE 5-continued

Exemplary Compounds of Formula I.

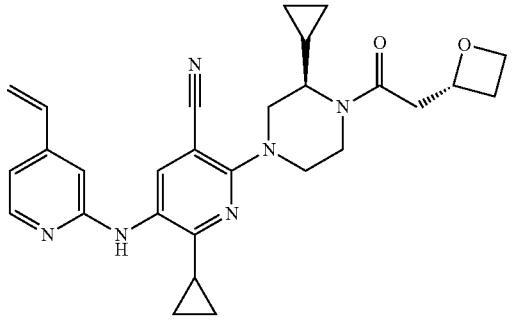
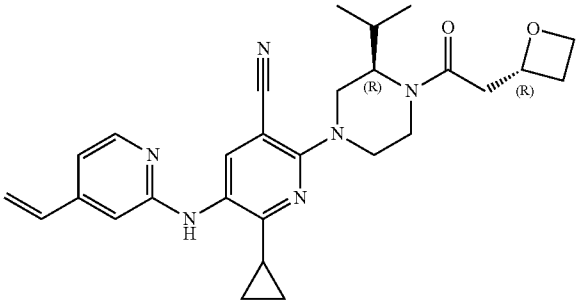
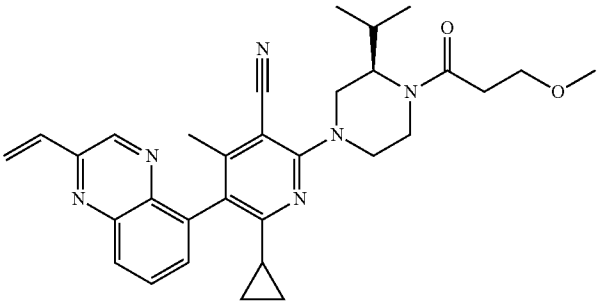
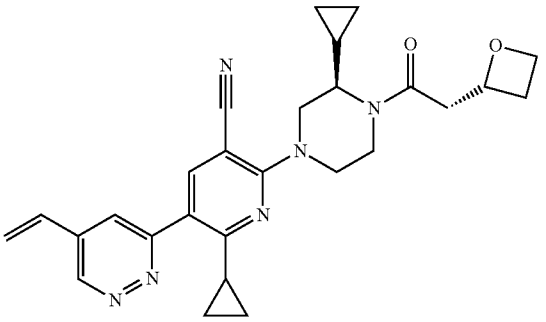
Cpd #	Structure
763	
764	
765	
766	

TABLE 5-continued

Exemplary Compounds of Formula I.

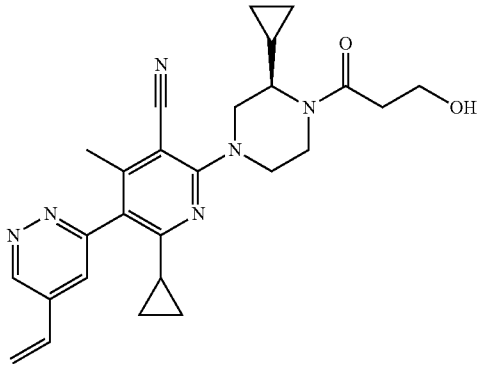
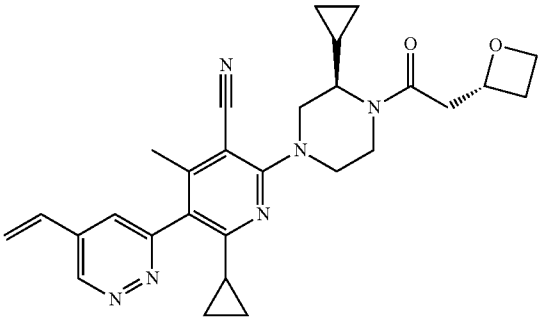
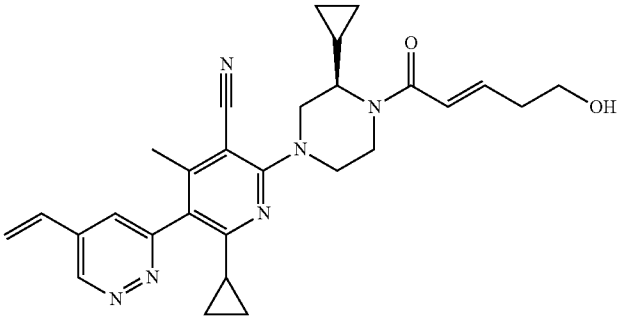
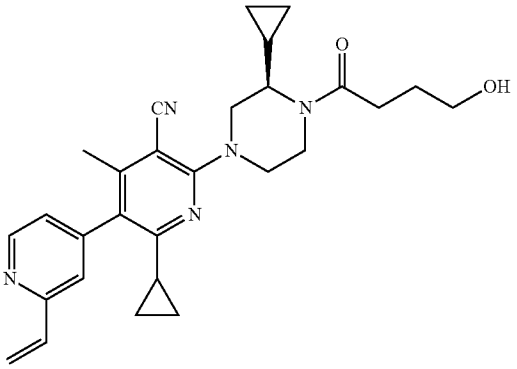
Cpd #	Structure
767	
768	
769	
770	

TABLE 5-continued

Exemplary Compounds of Formula I.

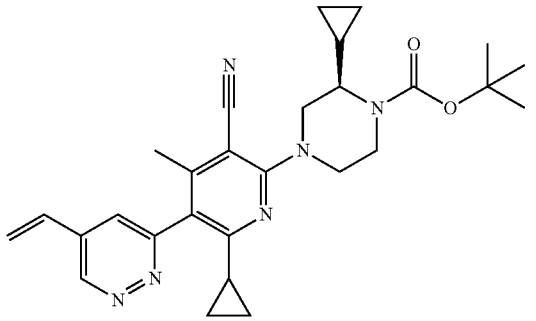
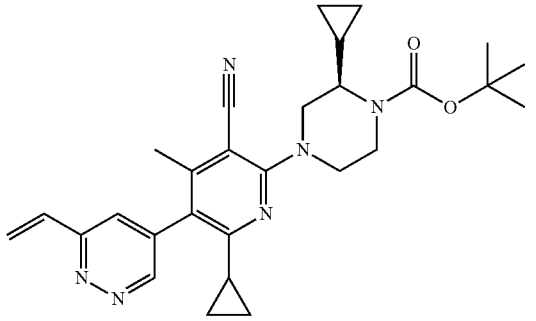
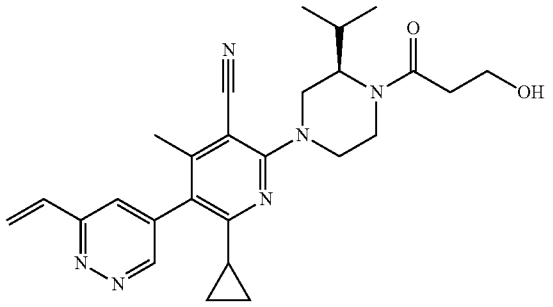
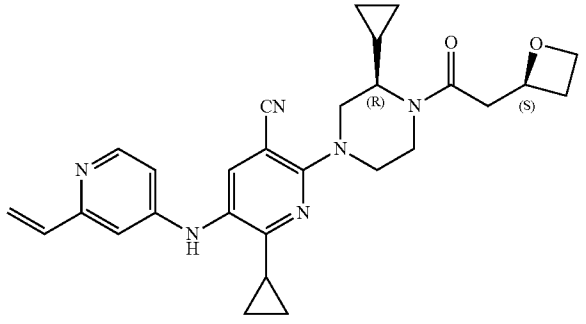
Cpd #	Structure
771	
772	
773	
774	

TABLE 5-continued

Exemplary Compounds of Formula I.

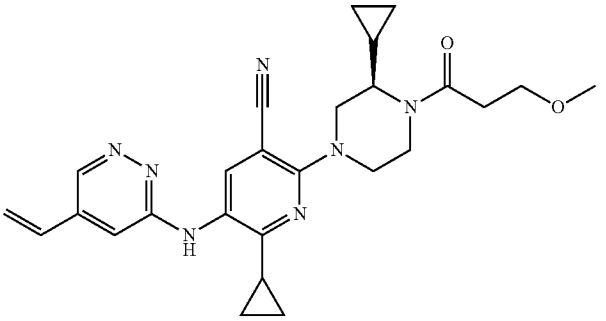
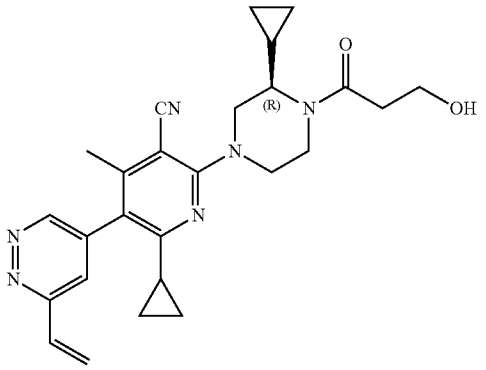
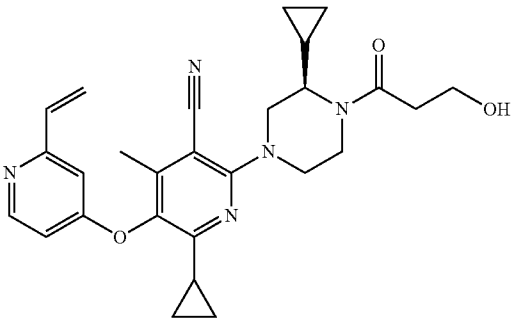
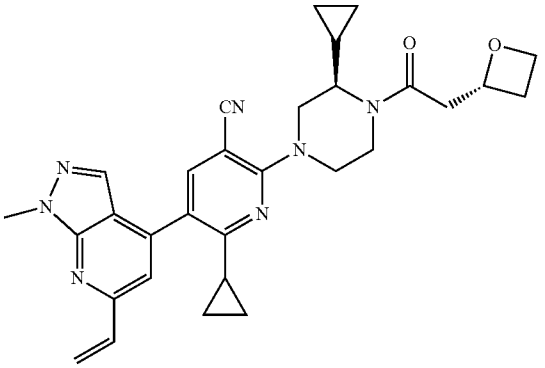
Cpd #	Structure
775	
776	
777	
778	

TABLE 5-continued

Exemplary Compounds of Formula I.

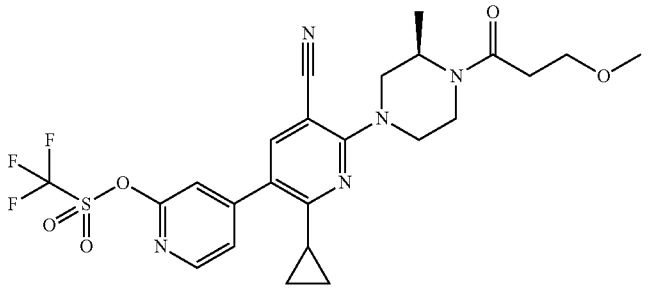
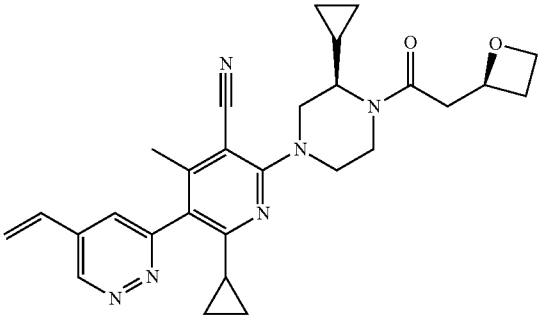
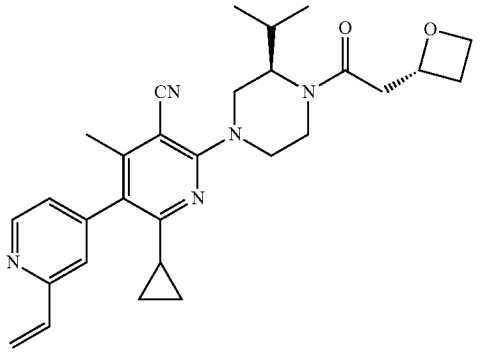
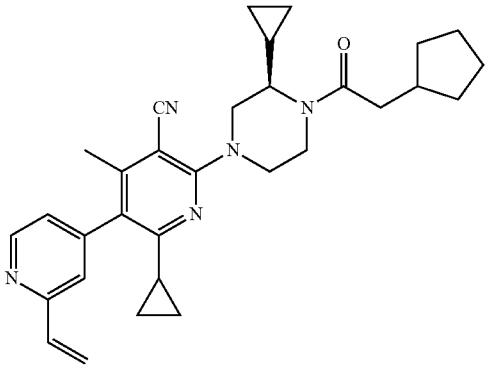
Cpd #	Structure
779	
780	
781	
782	

TABLE 5-continued

Exemplary Compounds of Formula I.

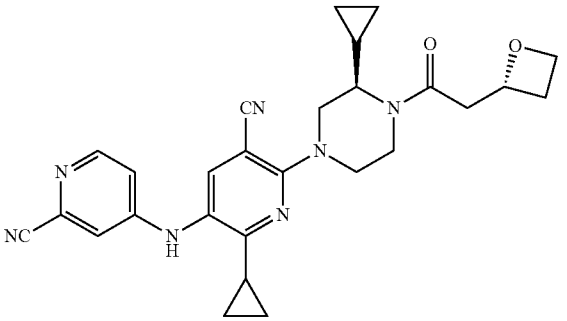
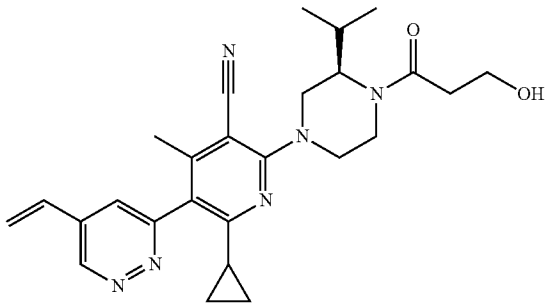
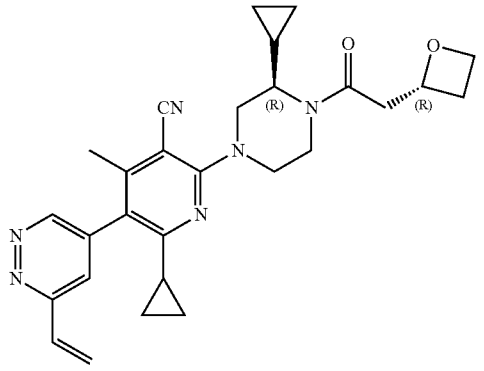
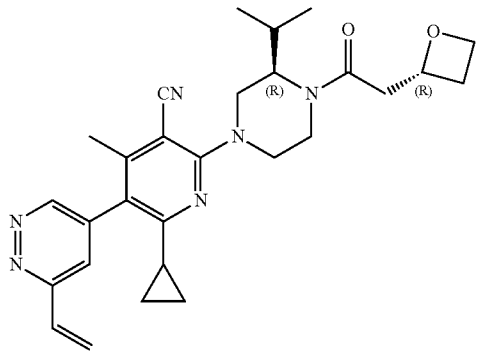
Cpd #	Structure
783	
784	
785	
786	

TABLE 5-continued

Exemplary Compounds of Formula I.

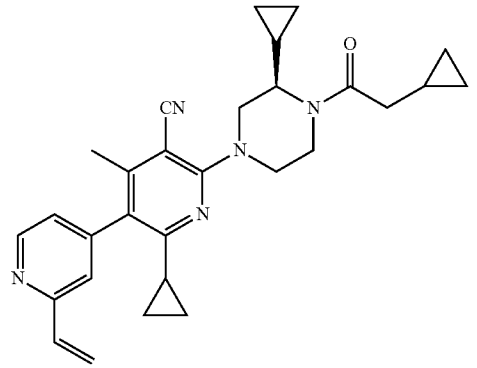
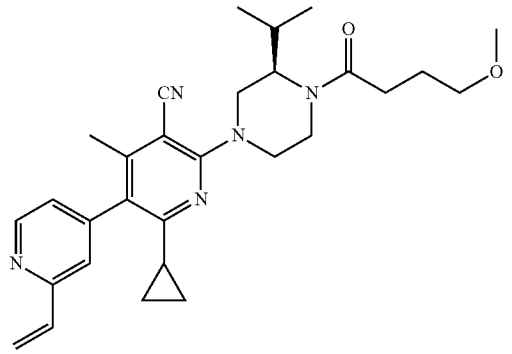
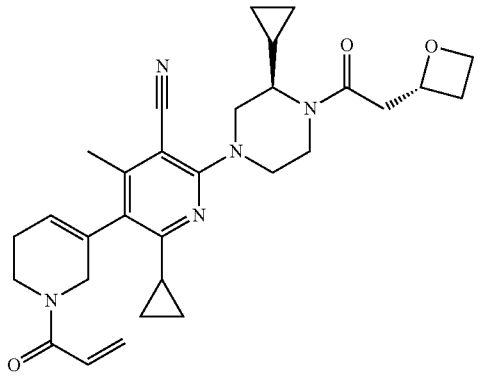
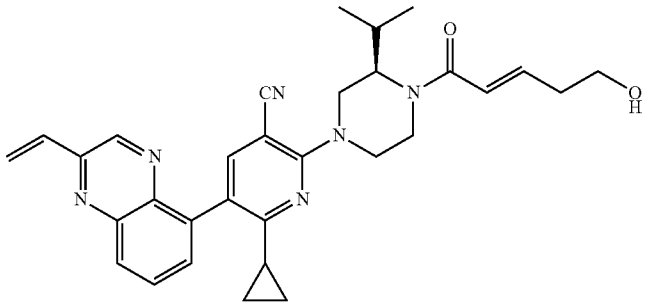
Cpd #	Structure
787	
788	
789	
790	

TABLE 5-continued

Exemplary Compounds of Formula I.

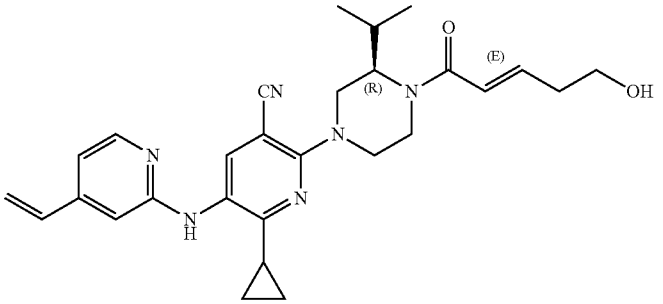
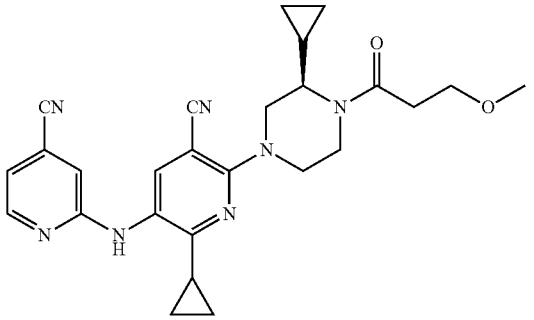
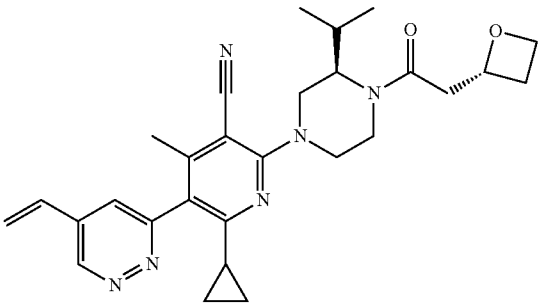
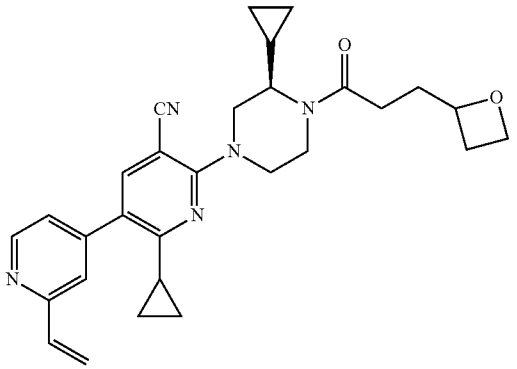
Cpd #	Structure
791	
792	
793	
794	

TABLE 5-continued

Exemplary Compounds of Formula I.

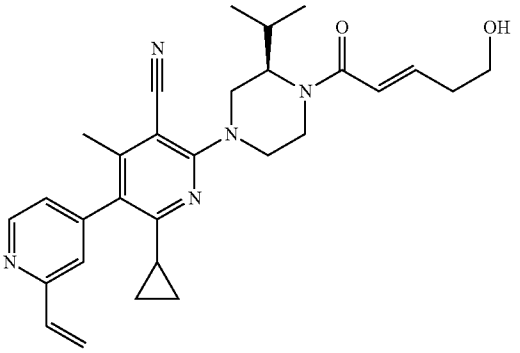
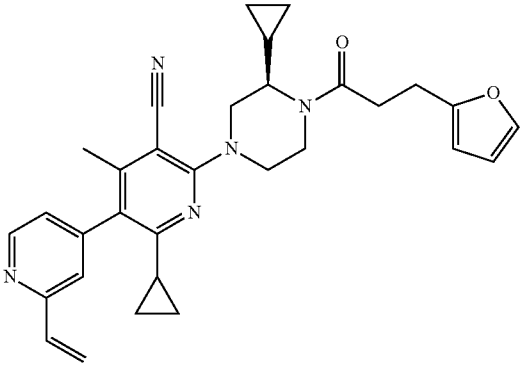
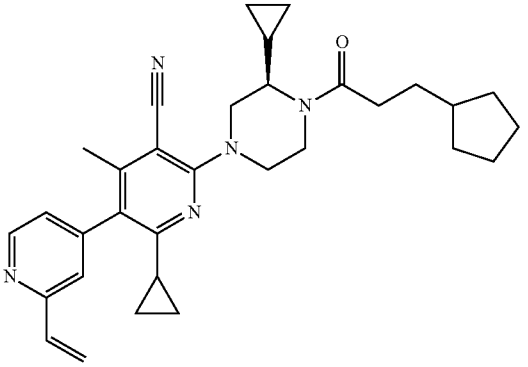
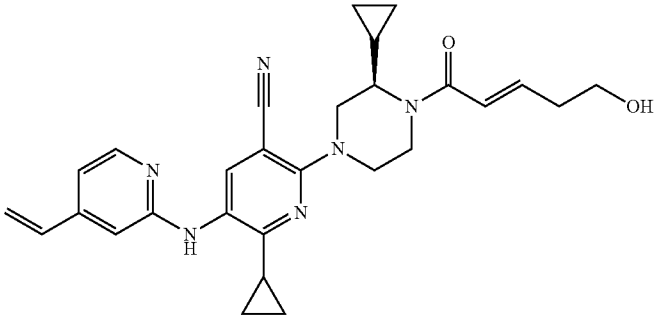
Cpd #	Structure
795	
796	
797	
798	

TABLE 5-continued

Exemplary Compounds of Formula I.

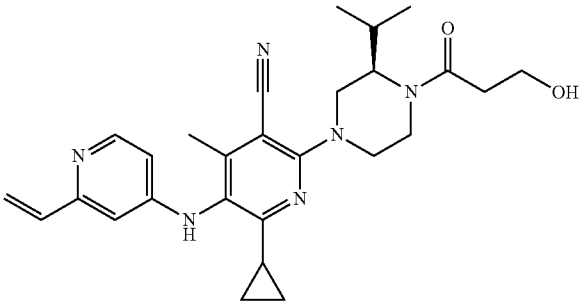
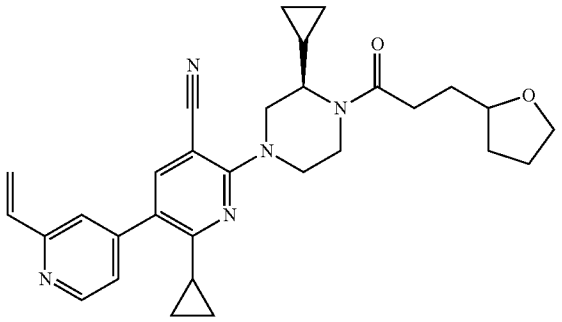
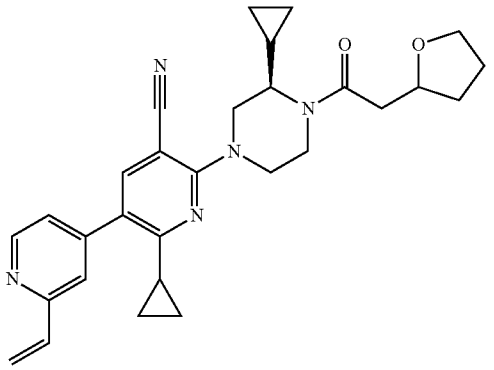
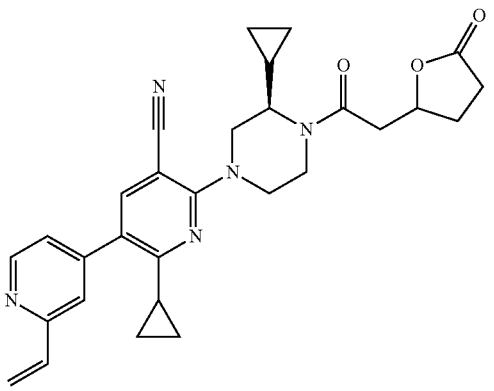
Cpd #	Structure
799	
800	
801	
802	

TABLE 5-continued

Exemplary Compounds of Formula I.

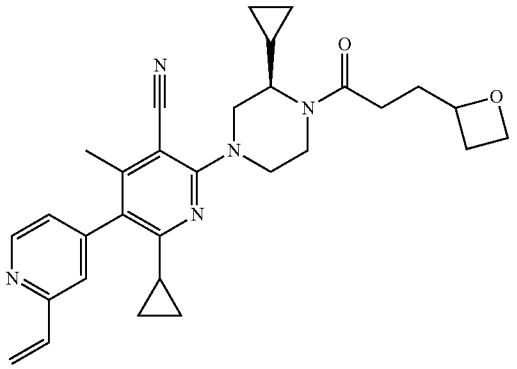
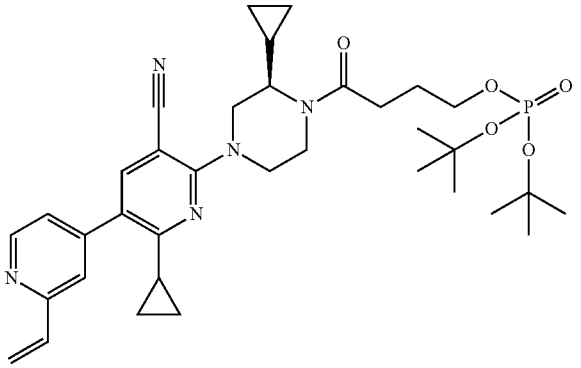
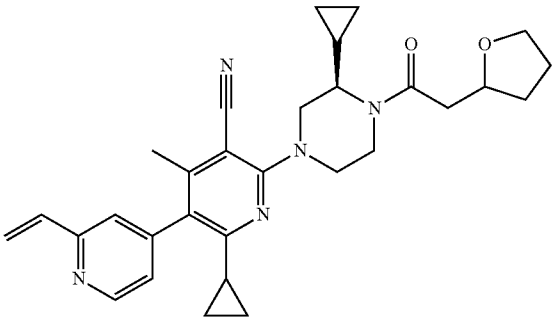
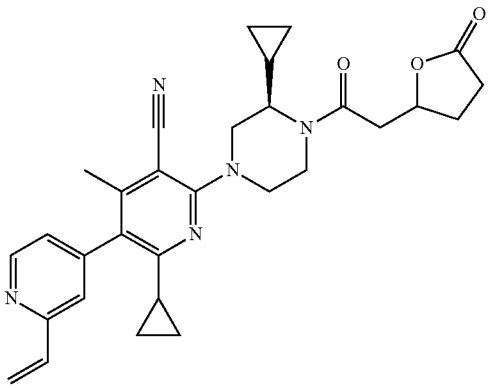
Cpd #	Structure
803	
804	
805	
806	

TABLE 5-continued

Exemplary Compounds of Formula I.

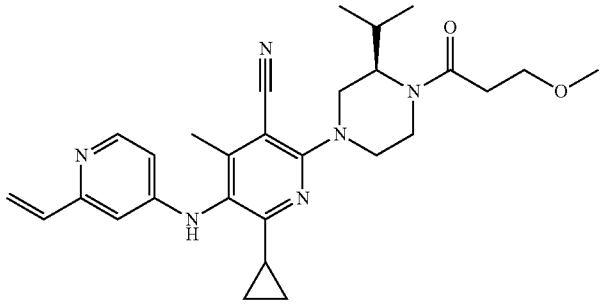
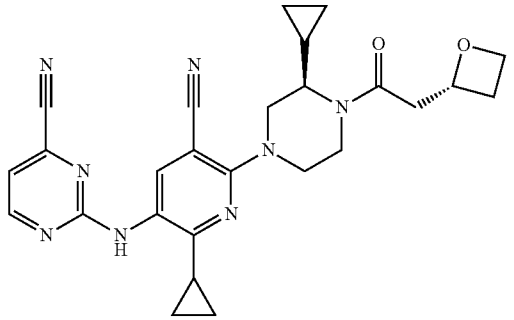
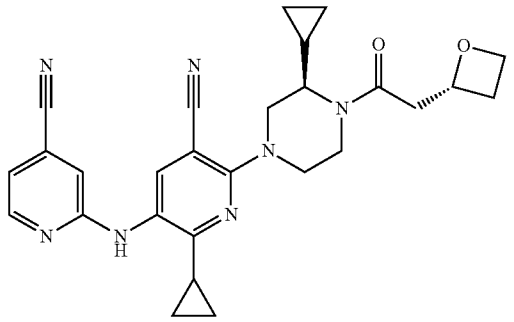
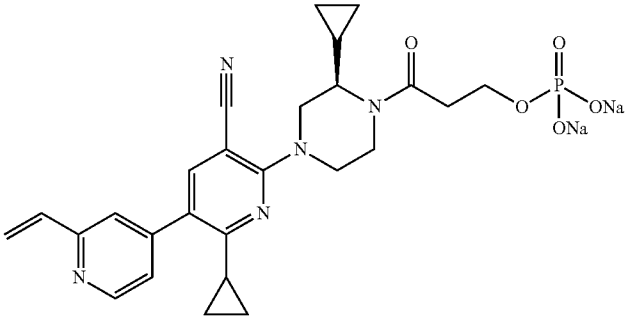
Cpd #	Structure
807	
808	
809	
810	

TABLE 5-continued

Exemplary Compounds of Formula I.

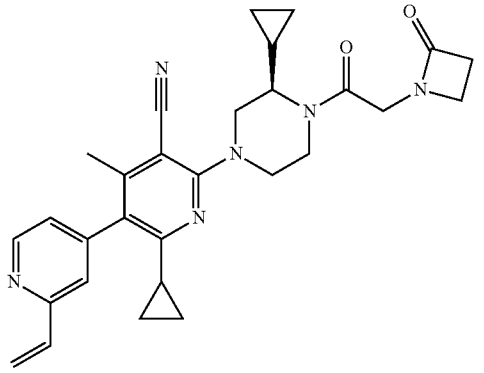
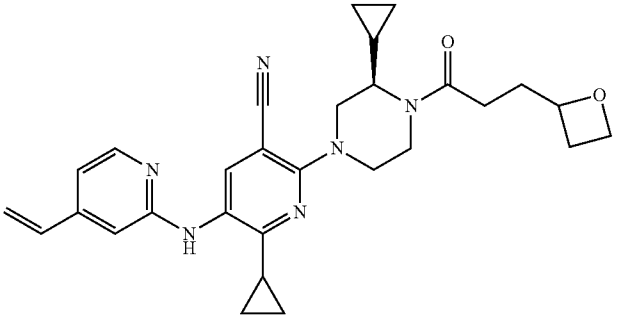
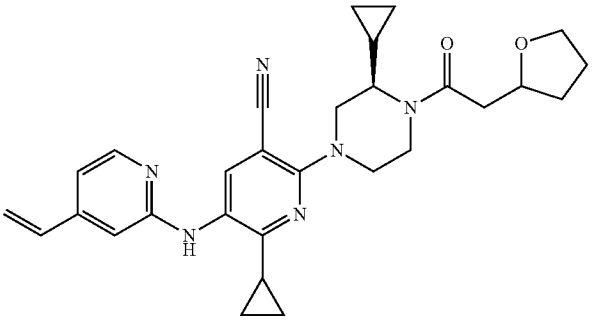
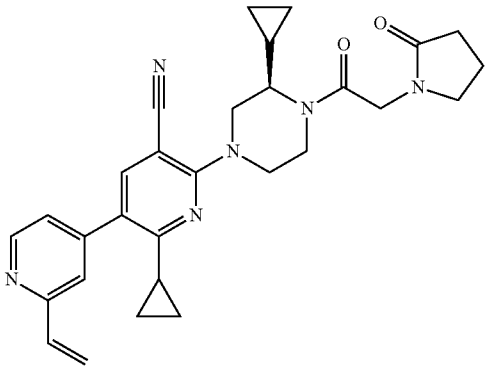
Cpd #	Structure
811	
812	
813	
814	

TABLE 5-continued

Exemplary Compounds of Formula I.

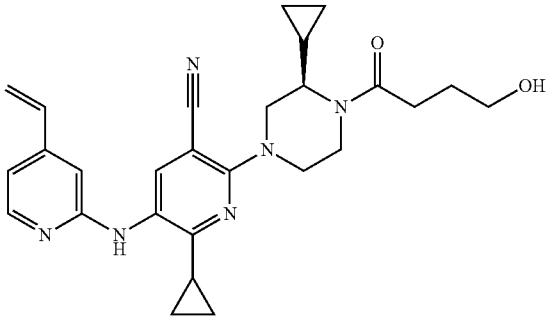
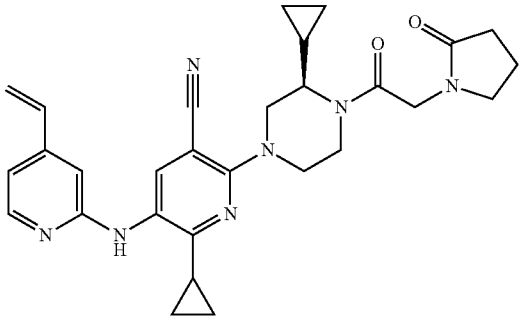
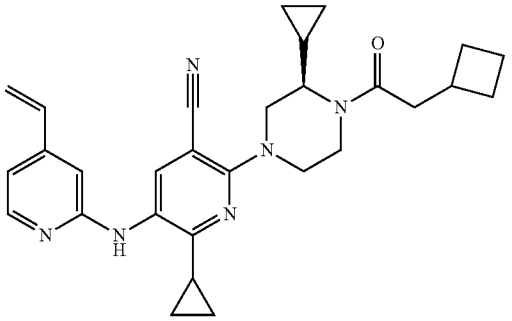
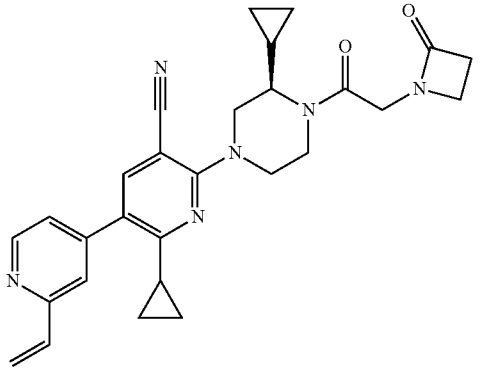
Cpd #	Structure
815	
816	
817	
818	

TABLE 5-continued

Exemplary Compounds of Formula I.

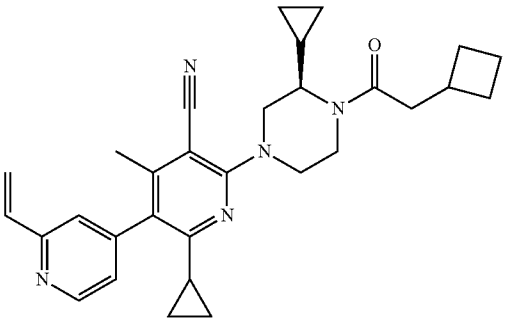
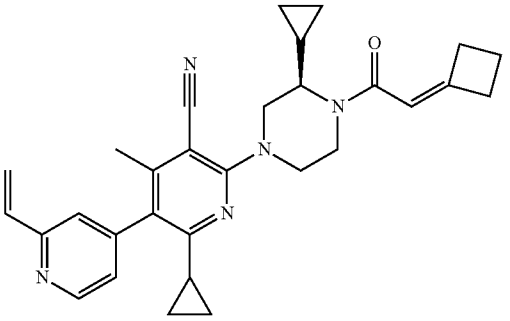
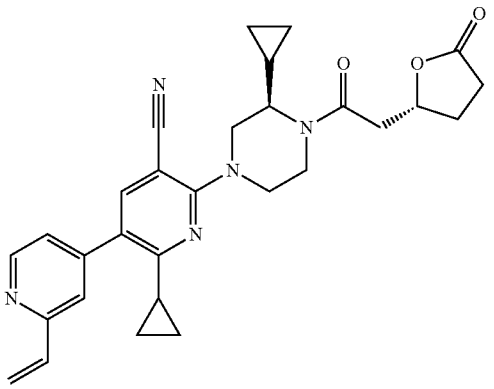
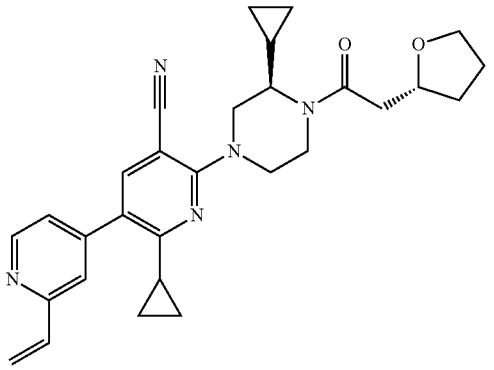
Cpd #	Structure
819	
820	
821	
822	

TABLE 5-continued

Exemplary Compounds of Formula I.

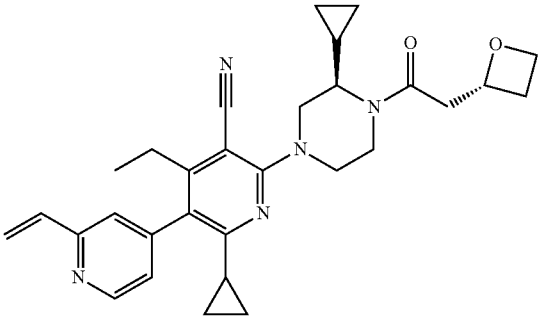
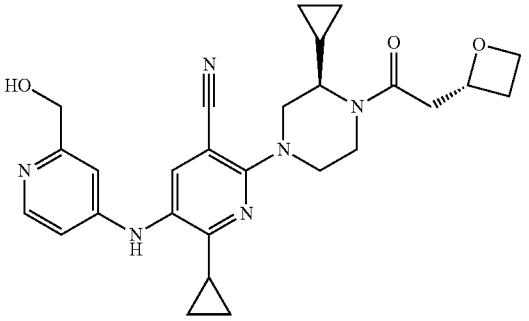
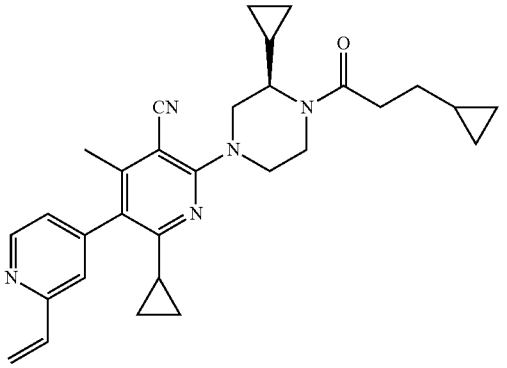
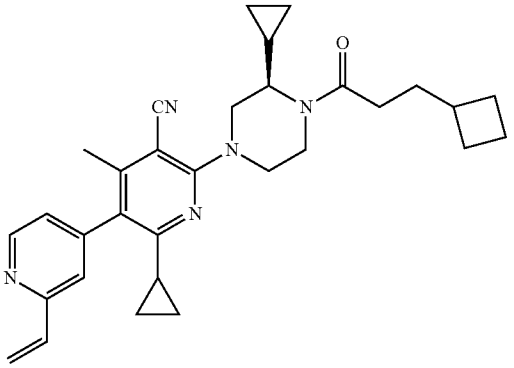
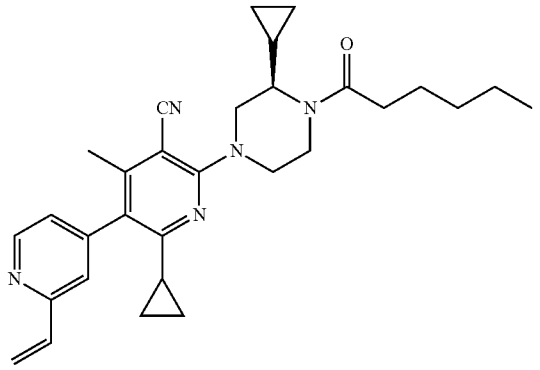
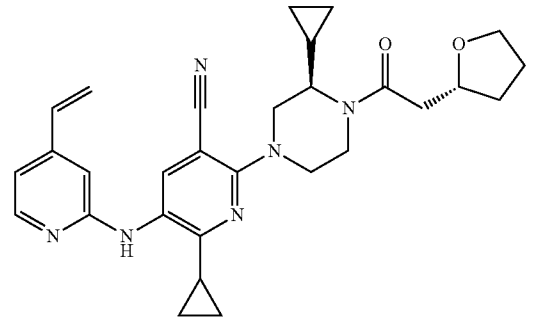
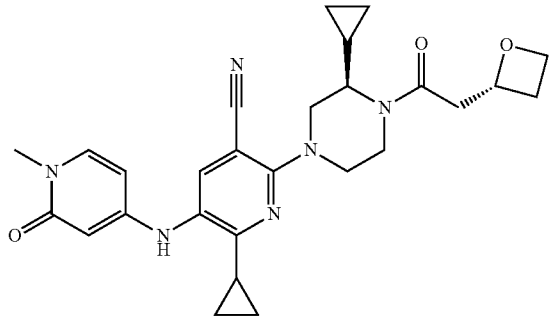
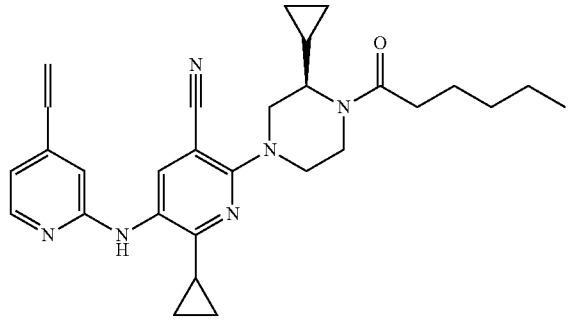
Cpd #	Structure
823	
824	
825	
826	

TABLE 5-continued

Exemplary Compounds of Formula I.

Cpd #	Structure
827	
828	
829	
830	

[0165] The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates, racemic mixtures, scalemic mixtures, and diastereomeric mixtures, as well as single enantiomers or individual stereoisomers that are substantially free from another possible enantiomer or stereoisomer. The term "substantially free of other stereoisomers" as used herein means a preparation enriched in a compound having a selected stereochemistry at one or more selected stereocenters by at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%. The term "enriched" means that at least the designated percentage of a preparation is the compound having a selected stereochemistry at one or more selected stereocenters. Methods of obtaining or synthesizing an individual enantiomer or stereoisomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

[0166] The compounds of Formula I, II and IIa may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D or deuterium), and ^{3}H (T or tritium); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

[0167] Unless otherwise indicated when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

[0168] The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

[0169] It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts." J. Pharm. Sci. Vol. 66, pp. 1-19.

[0170] For example, if the compound is anionic, or has a functional group which may be anionic (e.g., —COOH may be —COO), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^{+} and K^{+}, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^{+}) and substituted ammonium ions (e.g., NH_3R^{+}, NH_2R^{2+}, NHR^{3+}, NR^{+}). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^{+}$.

[0171] If the compound is cationic, or has a functional group that may be cationic (e.g., —NH_2 may be —NH_3^{+}), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

[0172] Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

[0173] Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

Compositions and Routes of Administration

[0174] The compounds utilized in the methods described herein may be formulated together with a pharmaceutically acceptable carrier or adjuvant into pharmaceutically acceptable compositions prior to be administered to a subject. In another embodiment, such pharmaceutically acceptable compositions further comprise additional therapeutic agents in amounts effective for achieving a modulation of disease or disease symptoms, including those described herein.

[0175] The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a subject, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

[0176] Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-α-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

[0177] The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vCompound AGInally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-

toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[0178] The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleCompound AGlnous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0179] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[0180] The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[0181] Topical administration of the pharmaceutical compositions of this invention is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

[0182] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

[0183] The compounds described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

[0184] Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens 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 status, sex, diet, time of

administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

[0185] Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Subjects may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

[0186] The pharmaceutical compositions described above comprising a compound of Structural Formula I, II or IIa or a compound described in any one of the embodiments herein, may further comprise another therapeutic agent useful for treating cancer.

Methods of Use

[0187] Provided is a method for inhibiting a mutant IDH1 activity comprising contacting a subject in need thereof a compound of Structural Formula I, II or IIa, a compound described in any one of the embodiments herein, or a pharmaceutically acceptable salt thereof. In one embodiment, the cancer to be treated is characterized by a mutant allele of IDH1 wherein the IDH1 mutation result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to R(−)-2-hydroxyglutarate in a subject. In one aspect of this embodiment, the mutant IDH1 has an R132X mutation. In one aspect of this embodiment, the R132X mutation is selected from R132H, R132C, R132L, R132V, R132S and R132G. In another aspect, the R132X mutation is R132H or R132C. In yet another aspect, the R132X mutation is R132H.

[0188] Also provided are methods of treating a cancer characterized by the presence of a mutant allele of IDH1 comprising the step of administering to subject in need thereof (a) a compound of Structural Formula I, II or IIa, a compound described in any one of the embodiments herein, or a pharmaceutically acceptable salt thereof, or (b) a pharmaceutical composition comprising (a) and a pharmaceutically acceptable carrier.

[0189] In one embodiment, the cancer to be treated is characterized by a mutant allele of IDH1 wherein the IDH1 mutation result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to R(−)-2-hydroxyglutarate in a patient. In one aspect of this embodiment, the IDH1 mutation is an R132X mutation. In another aspect of this embodiment, the R132X mutation is selected from R132H, R132C, R132L, R132V, R132S and R132G. In another aspect, the R132X mutation is R132H or R132C. A cancer can be analyzed by sequencing cell samples to determine the presence and specific nature of (e.g., the changed amino acid present at) a mutation at amino acid 132 of IDH1.

[0190] Without being bound by theory, applicants believe that mutant alleles of IDH1 wherein the IDH1 mutation result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to R(−)-2-hydroxyglutarate, and in particular R132H mutations of IDH1, characterize a subset of all types of cancers, without regard to their cellular nature or location in the body. Thus, the compounds and methods of this invention are useful to treat any type of cancer that is characterized by the presence of a mutant allele of IDH1 imparting such activity and in particular an IDH1 R132H or R132C mutation.

[0191] In one aspect of this embodiment, the efficacy of cancer treatment is monitored by measuring the levels of 2HG in the subject. Typically levels of 2HG are measured prior to treatment, wherein an elevated level is indicative of the use of the compound of Formula I to treat the cancer. Once the elevated levels are established, the level of 2HG is determined during the course of and/or following termination of treatment to establish efficacy. In certain embodiments, the level of 2HG is only determined during the course of and/or following termination of treatment. A reduction of 2HG levels during the course of treatment and following treatment is indicative of efficacy. Similarly, a determination that 2HG levels are not elevated during the course of or following treatment is also indicative of efficacy. Typically, the these 2HG measurements will be utilized together with other well-known determinations of efficacy of cancer treatment, such as reduction in number and size of tumors and/or other cancer-associated lesions, improvement in the general health of the subject, and alterations in other biomarkers that are associated with cancer treatment efficacy.

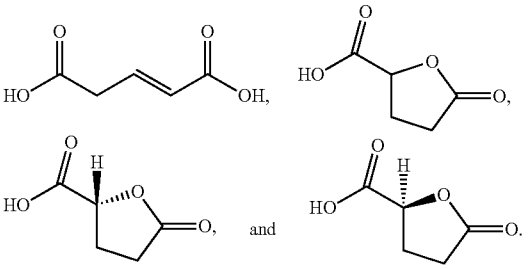
[0192] 2HG can be detected in a sample by LC/MS. The sample is mixed 80:20 with methanol, and centrifuged at 3,000 rpm for 20 minutes at 4 degrees Celsius. The resulting supernatant can be collected and stored at −80 degrees Celsius prior to LC-MS/MS to assess 2-hydroxyglutarate levels. A variety of different liquid chromatography (LC) separation methods can be used. Each method can be coupled by negative electrospray ionization (ESI, −3.0 kV) to triple-quadrupole mass spectrometers operating in multiple reaction monitoring (MRM) mode, with MS parameters optimized on infused metabolite standard solutions. Metabolites can be separated by reversed phase chromatography using 10 mM tributyl-amine as an ion pairing agent in the aqueous mobile phase, according to a variant of a previously reported method (Luo et al. *J Chromatogr A* 1147, 153-64, 2007). One method allows resolution of TCA metabolites: t=0, 50% B; t=5, 95% B; t=7, 95% B; t=8, 0% B, where B refers to an organic mobile phase of 100% methanol. Another method is specific for 2-hydroxyglutarate, running a fast linear gradient from 50%-95% B (buffers as defined above) over 5 minutes. A Synergi Hydro-RP, 100 mm×2 mm, 2.1 μm particle size (Phenomonex) can be used as the column, as described above. Metabolites can be quantified by comparison of peak areas with pure metabolite standards at known concentration. Metabolite flux studies from ^{13}C-glutamine can be performed as described, e.g., in Munger et al. Nat Biotechnol 26, 1179-86, 2008.

[0193] In one embodiment 2HG is directly evaluated.

[0194] In another embodiment a derivative of 2HG formed in process of performing the analytic method is evaluated. By way of example such a derivative can be a derivative formed in MS analysis. Derivatives can include a salt adduct, e.g., a Na adduct, a hydration variant, or a hydration variant which is also a salt adduct, e.g., a Na adduct, e.g., as formed in MS analysis.

[0195] In another embodiment a metabolic derivative of 2HG is evaluated. Examples include species that build up or are elevated, or reduced, as a result of the presence of 2HG, such as glutarate or glutamate that will be correlated to 2HG, e.g., R-2HG.

[0196] Exemplary 2HG derivatives include dehydrated derivatives such as the compounds provided below or a salt adduct thereof:



[0197] In one embodiment the cancer is a tumor wherein at least 30, 40, 50, 60, 70, 80 or 90% of the tumor cells carry an IDH1 mutation, and in particular an IDH1 R132H or R132C mutation, at the time of diagnosis or treatment.

[0198] IDH1 R132X mutations are known to occur in certain types of cancers as indicated in Table 2, below.

TABLE 2

IDH mutations associated with certain cancers

Cancer Type	IDH1 R132X Mutation	Tumor Type
brain tumors	R132H	primary tumor
	R132C	primary tumor
	R132S	primary tumor
	R132G	primary tumor
	R132L	primary tumor
	R132V	primary tumor
fibrosarcoma	R132C	HT1080 fibrosarcoma cell line
Acute Myeloid Leukemia (AML)	R132H	primary tumor
	R132G	primary tumor
	R132C	primary tumor
Prostate cancer	R132H	primary tumor
	R132C	primary tumor
Acute lymphoblastic leukemia (ALL)	R132C	primary tumor
paragangliomas	R132C	primary tumor

[0199] IDH1 R132H mutations have been identified in glioblastoma, acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer, cholangiocarcinomas, chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), colon cancer, and angio-immunoblastic non-Hodgkin's lymphoma (NHL). Accordingly, in one embodiment, the methods described herein are used to treat glioma (glioblastoma), acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer (NSCLC) or eholangiocarcinomas, chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN) or colon cancer in a patient.

[0200] Accordingly in one embodiment, the cancer is a cancer selected from any one of the cancer types listed in Table 2, and the IDH R132X mutation is one or more of the IDH1 R132X mutations listed in Table 2 for that particular cancer type.

[0201] Treatment methods described herein can additionally comprise various evaluation steps prior to and/or following treatment with a compound of Structural Formula I, II or IIa or a compound described in any one of the embodiments described herein.

[0202] In one embodiment, prior to and/or after treatment with a compound of Structural Formula I, II or IIa or a compound described in any one of the embodiments described herein, the method further comprises the step of evaluating the growth, size, weight, invasiveness, stage and/or other phenotype of the cancer.

[0203] In one embodiment, prior to and/or after treatment with a compound of formula I or I-a or a compound described in any one of the embodiments described herein, the method further comprises the step of evaluating the IDH1 genotype of the cancer. This may be achieved by ordinary methods in the art, such as DNA sequencing, immuno analysis, and/or evaluation of the presence, distribution or level of 2HG.

[0204] In one embodiment, prior to and/or after treatment with a compound of formula I or I-a or a compound described in any one of the embodiments described herein, the method further comprises the step of determining the 2HG level in the subject. This may be achieved by pectroscopic analysis, e.g., magnetic resonance-based analysis, e.g., MRI and/or MRS measurement, sample analysis of bodily fluid, such as serum or spinal cord fluid analysis, or by analysis of surgical material, e.g., by mass-spectroscopy.

Combination Therapies

[0205] In some embodiments, the methods described herein comprise the additional step of co-administering to a subject in need thereof a second therapy e.g., an additional cancer therapeutic agent or an additional cancer treatment. Exemplary additional cancer therapeutic agents include for example, chemotherapy, targeted therapy, antibody therapies, immunotherapy, and hormonal therapy. Additional cancer treatments include, for example: surgery, and radiation therapy. Examples of each of these treatments are provided below.

[0206] The term "co-administering" as used herein with respect to an additional cancer therapeutic agents means that the additional cancer therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional cancer therapeutic agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment. The term "co-administering" as used herein with respect to an additional cancer treatment means that the additional cancer treatment may occur prior to, consecutively with, concurrently with or following the administration of a compound of this invention.

[0207] In some embodiments, the additional cancer therapeutic agent is a chemotherapy agent. Examples of chemotherapeutic agents used in cancer therapy include, for example, antimetabolites (e.g., folic acid, purine, and pyrimi-

dine derivatives), alkylating agents (e.g., nitrogen mustards, nitrosoureas, platinum, alkyl sulfonates, hydrazines, triazenes, aziridines, spindle poison, cytotoxic agents, topoisomerase inhibitors and others) and hypomethylating agents (e.g., decitabine (5-aza-deoxycytidine), zebularine, isothiocyanates, azacitidine (5-azacytidine), 5-fluoro-2'-deoxycytidine, 5,6-dihydro-5-azacytidine and others). Exemplary agents include Aclarubicin, Actinomycin, Alitretinoin, Altretamine, Aminopterin, Aminolevulinic acid, Amrubicin, Amsacrine, Anagrelide, Arsenic trioxide, AsparCompound AGlnase, Atrasentan, Belotecan, Bexarotene, bendamustine, Bleomycin, Bortezomib, Busulfan, Camptothecin, Capecitabine, Carboplatin, Carboquone, Carmofur, Carmustine, Celecoxib, Chlorambucil, Chlormethine, Cisplatin, Cladribine, Clofarabine, Crisantaspase, Cyclophosphamide, Cytarabine, Dacarbazine, Dactinomycin, Daunorubicin, Decitabine, Demecolcine, Docetaxel, Doxorubicin, Efaproxiral, Elesclomol, Elsamitrucin, Enocitabine, Epirubicin, Estramustine, Etoglucid, Etoposide, Floxuridine, Fludarabine, Fluorouracil (5FU), Fotemustine, Gemcitabine, Gliadel implants, Hydroxycarbamide, Hydroxyurea, Idarubicin, Ifosfamide, Irinotecan, Irofulven, Ixabepilone, Larotaxel, Leucovorin, Liposomal doxorubicin, Liposomal daunorubicin, Lonidamine, Lomustine, Lucanthone, Mannosulfan, Masoprocol, Melphalan, Mercaptopurine, Mesna, Methotrexate, Methyl aminolevulinate, Mitobronitol, Mitoguazone, Mitotane, Mitomycin, Mitoxantrone, Nedaplatin, Nimustine, Oblimersen, Omacetaxine, Ortataxel, Oxaliplatin, Paclitaxel, Pegaspargase, Pemetrexed, Pentostatin, Pirarubicin, Pixantrone, Plicamycin, Porfimer sodium, Prednimustine, Procarbazine, Raltitrexed, Ranimustine, Rubitecan, Sapacitabine, Semustine, Sitimagene ceradenovec, Strataplatin, Streptozocin, Talaporfin, Tegafur-uracil, Temoporfin, Temozolomide, Teniposide, Tesetaxel, Testolactone, Tetranitrate, Thiotepa, Tiazofurine, Tioguanine, Tipifarnib, Topotecan, Trabectedin, Triaziquone, Triethylenemelamine, Triplatin, Tretinoin, Treosulfan, Trofosfamide, Uramustine, Valrubicin, Verteporfin, Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine, Vorinostat, Zorubicin, and other cytostatic or cytotoxic agents described herein.

[0208] Because some drugs work better together than alone, two or more drugs are often given at the same time. Often, two or more chemotherapy agents are used as combination chemotherapy.

[0209] In some embodiments, the additional cancer therapeutic agent is a differentiation agent. Such differentiation agent includes retinoids (such as all-trans-retinoic acid (ATRA), 9-cis retinoic acid, 13-cis-retinoic acid (13-cRA) and 4-hydroxy-phenretinamide (4-HPR)); arsenic trioxide; histone deacetylase inhibitors HDACs (such as azacytidine (Vidaza) and butyrates (e.g., sodium phenylbutyrate)); hybrid polar compounds (such as hexamethylene bisacetamide ((HMBA)); vitamin D; and cytokines (such as colony-stimulating factors including G-CSF and GM-CSF, and interferons).

[0210] In some embodiments the additional cancer therapeutic agent is a targeted therapy agent. Targeted therapy constitutes the use of agents specific for the deregulated proteins of cancer cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell. Prominent examples are the tyrosine kinase inhibitors such as Axitinib, Bosutinib, Cediranib, aasatinib, erlotinib, imatinib, gefitinib, lapatinib, Lestaurtinib, Nilotinib, Semaxanib, Sorafenib, Sunitinib, and Vandetanib, and also cyclin-dependent kinase inhibitors such as Alvocidib and Seliciclib. Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. Examples include the anti-HER2/neu antibody trastuzumab (HERCEPTIN®) typically used in breast cancer, and the anti-CD20 antibody rituximab and Tositumomab typically used in a variety of B-cell malignancies. Other exemplary antibodies include Cetuximab, Panitumumab, Trastuzumab, Alemtuzumab, Bevacizumab, Edrecolomab, and Gemtuzumab. Exemplary fusion proteins include Aflibercept and Denileukin diftitox. In some embodiments, the targeted therapy can be used in combination with a compound described herein, e.g., a biguanide such as metformin or phenformin, preferably phenformin.

[0211] Targeted therapy can also involve small peptides as "homing devices" which can bind to cell surface receptors or affected extracellular matrix surrounding the tumor. Radionuclides which are attached to these peptides (e.g., RGDs) eventually kill the cancer cell if the nuclide decays in the vicinity of the cell. An example of such therapy includes BEXXAR®.

[0212] In some embodiments, the additional cancer therapeutic agent is an immunotherapy agent. Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the subject's own immune system to fight the tumor. Contemporary methods for generating an immune response against tumors include intravesicular BCG immunotherapy for superficial bladder cancer, and use of interferons and other cytokines to induce an immune response in renal cell carcinoma and melanoma subjects.

[0213] Allogeneic hematopoietic stem cell transplantation can be considered a form of immunotherapy, since the donor's immune cells will often attack the tumor in a graft-versus-tumor effect. In some embodiments, the immunotherapy agents can be used in combination with a compound or composition described herein.

[0214] In some embodiments, the additional cancer therapeutic agent is a hormonal therapy agent. The growth of some cancers can be inhibited by providing or blocking certain hormones. Common examples of hormone-sensitive tumors include certain types of breast and prostate cancers. Removing or blocking estrogen or testosterone is often an important additional treatment. In certain cancers, administration of hormone agonists, such as progestogens may be therapeutically beneficial. In some embodiments, the hormonal therapy agents can be used in combination with a compound or a composition described herein.

[0215] Other possible additional therapeutic modalities include imatinib, gene therapy, peptide and dendritic cell vaccines, synthetic chlorotoxins, and radiolabeled drugs and antibodies.

EXAMPLES

[0216]

ABBREVIATIONS

anhy.—anhydrous
aq.—aqueous
min—minute(s)
mL—milliliter

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ABBREVIATIONS
mmol—millimole(s)
mol—mole(s)
MS—mass spectrometry
NMR—nuclear magnetic resonance
TLC—thin layer chromatography
HPLC—high-performance liquid chromatography
Hz—hertz
δ—chemical shift
J—coupling constant
s—singlet
d—doublet
t—triplet
q—quartet
m—multiplet
br—broad
qd—quartet of doublets
dquin—doublet of quintets
dd—doublet of doublets
dt—doublet of triplets
$CHCl_3$—chloroform
DCM—dichloromethane
DMF—dimethylformamide
Et_2O—diethyl ether
EtOH—ethyl alcohol
EtOAc—ethyl acetate
MeOH—methyl alcohol
MeCN—acetonitrile
PE—petroleum ether
THF—tetrahydrofuran
AcOH—acetic acid
HCl—hydrochloric acid
H_2SO_4—sulfuric acid
NH_4Cl—ammonium chloride
KOH—potassium hydroxide
NaOH—sodium hydroxide
K_2CO_3—potassium carbonate
Na_2CO_3—sodium carbonate
TFA—trifluoroacetic acid
Na_2SO_4—sodium sulfate
$NaBH_4$—sodium borohydride
$NaHCO_3$—sodium bicarbonate
LiHMDS—lithium hexamethyldisilylamide
NaHMDS—sodium hexamethyldisilylamide
LAH—lithium aluminum hydride
$NaBH_4$—sodium borohydride
LDA—lithium diisopropylamide
Et_3N—triethylamine
DMAP—4-(dimethylamino)pyridine
DIPEA—N,N-diisopropylethylamine
NH_4OH—ammonium hydroxide
EDCI—1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBt—1-hydroxybenzotriazole
HATU—O-(7-azabenzotriazol-1-yl)-N,N,N',N',-tetra-methyluronium
BINAP—2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl

[0217] In the following examples, reagents were purchased from commercial sources (including Alfa, Acros, Sigma Aldrich, TCI and Shanghai Chemical Reagent Company), and used without further purification. Flash chromatography was performed on an Ez Purifier III using a column with silica gel particles of 200-300 mesh. Analytical and preparative thin layer chromatography plates (TLC) were HSGF 254 (0.15-0.2 mm thickness, Shanghai Anbang Company, China). Nuclear magnetic resonance (NMR) spectra were obtained on a Brucker AMX-400 NMR (Brucker, Switzerland). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Mass spectra were run with electrospray ionization (ESI) from a Waters LCT TOF Mass Spectrometer (Waters, USA). HPLC chromatographs were recorded on an Compound AGIlent 1200 Liquid Chromatography (Compound AGIlent, USA, column: Ultimate 4.6 mm×50 mm, 5 μm, mobile phase A: 0.1% formic acid in water; mobile phase B: acetonitrile). Microwave reactions were run on an Initiator 2.5 Microwave Synthesizer (Biotage, Sweden).

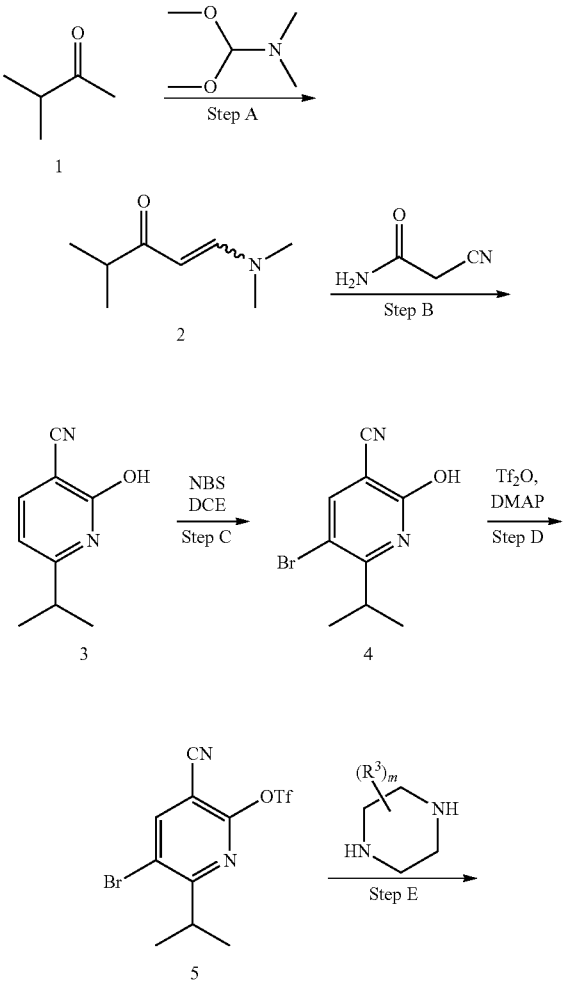
[0218] For exemplary compounds disclosed in this section, the specification of a stereoisomer (e.g., an (R) or (S) stereoisomer) indicates a preparation of that compound such that the compound is enriched at the specified stereocenter by at least about 90%, 95%, 96%, 97%, 98%, or 99%.

Example 1

Preparation of (R)-5-bromo-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[0219] (R)-5-bromo-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (7, wherein R^{1a} is hydrogen; m is 1; R^3 is 3-methyl; and R^8 is methoxyethyl) was prepared according to general Scheme 1, below.

Scheme 1:



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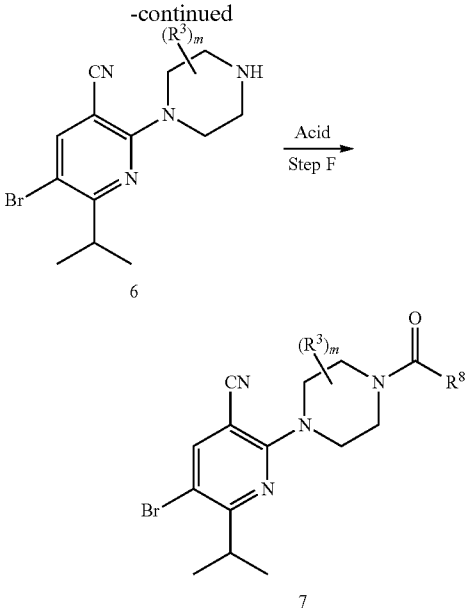


Step A: 1-(dimethylamino)-4-methylpent-1-en-3-one (2)

[0220] To a solution of commerically available 3-methylbutan-2-one (1; 8.613 g, 100 mmol) in 150 mL of anhydrous DMF was added commercially available 1,1-dimethoxy-N,N-dimethylmethanamine (29.80 g, 250 mmol). The resulting mixture was stirred at 100° C. overnight. After removal of DMF and excess of acetal, 14 g of title compound was obtained as a crude product and used in subsequent reaction without further purification. ^{1}H NMR (CHLOROFORM-d) δ 7.57 (d, J=12.8 Hz, 1H), 5.05 (d, J=12.5 Hz, 1H), 2.80-3.10 (m, 6H), 2.56 (dt, J=13.7, 6.8 Hz, 1H), 1.06-1.14 (m, 6H).

Step B: 6-isopropyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3)

[0221] 8.8 g of 1-(dimethylamino)-4-methylpent-1-en-3-one (2; 62 mmol) and 5.3 g of commercially available cyanoacetamide (62 mmol) in 24 mL of H_2O was treated with a premixed buffer solution of 0.7 mL of acetic acid, 1.8 mL of H_2O, and enough piperidine to make the buffer solution basic. The resulting solution was refluxed for 2 hrs and LC-MS showed the formation of desired product. After cooling to room temperature, the mixture was acidified with glacial acetic acid, and a brown yellowish precipitate was formed. The filter cake was washed with H_2O and air-dried to give 6.5 g of title compound. MS (ES) M+H expected 163.1, found 163.0. ^{1}H NMR (DMSO-d_6) δ 12.51 (br. s., 1H), 7.96-8.18 (m, 1H), 6.24 (d, J=7.5 Hz, 1H), 2.83 (spt, J=6.9 Hz, 1H), 1.19 (s, 29H), 1.17 (s, 3H).

Step C: 5-bromo-6-isopropyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (4)

[0222] To a solution of 2-hydroxy-6-isopropylnicotinonitrile (3; 3.0 g, 19 mmol) in 50 mL of DCE was added NBS (5 g, 28 mmol) at room temperature. The reaction mixture was then heated at reflux for 3 hours. After LC-MS showed the completion of reaction, the mixture was cooled to room temperature and poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography (4% MeOH/DCM) afforded 3.9 g of title compound as a brown solid. MS (ES) M+H expected 241.0, found 240.9. ^{1}H NMR (DMSO-d_6) δ 12.58 (br. s., 1H), 8.38 (s, 1H), 3.25-3.32 (m, 1H), 1.23 (s, 3H), 1.21 (s, 3H).

Step D: 5-bromo-3-cyano-6-isopropylpyridin-2-yl trifluoromethanesulfonate (5)

[0223] To a solution of 5-bromo-2-hydroxy-6-isopropylnicotinonitrile (4; 2.0 g, 8 mmol) in 20 mL of methylene chloride was added DMAP (100 mg, 0.8 mmol), and triethylamine (1.01 g, 10 mmol). The mixture was cooled to 0° C. in an ice-water bath, and trifluoromethanesulfonic anhydride (2.82 g, 10 mmol) was added dropwise by syringe. The resulting reaction mixture was stirred at 0° C. for 30 min before it was allowed to warm to room temperature and stirred for additional 2 hours. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% EtOAc/petroleum ether) to afford 2.8 g of title compound. ^{1}H NMR (CHLOROFORM-d) δ 8.22 (s, 1H), 3.57 (spt, J=6.7 Hz, 1H), 1.28 (d, J=6.8 Hz, 6H).

Step E: (R)-5-bromo-6-isopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6)

[0224] A mixture of the above triflate 5 (1.68 g, 4.5 mmol), (R)-2-methylpiperazine (770 mg, 6.77 mmol), and triethylamine (1.9 mL, 13.5 mmol) suspended in 5 mL of MeCN was subjected to microwave reaction at 175° C. for 45 min. After the mixture was concentrated in vacuo, the residue was purified by column chromatography (10% DCM/MeOH) to afford 0.91 g of title compound as a light yellowish solid. MS (ES) M+H expected 323.1, found 323.0. ^{1}H NMR (CHLOROFORM-d) S 7.79 (s, 1H), 4.35-4.40 (m, 0.5H), 4.32-4.35 (m, 1H), 4.30 (t, J=2.4 Hz, 0.5H), 3.37-3.45 (m, 1H), 3.08-3.13 (m, 0.5H), 3.05-3.08 (m, 1H), 3.04 (d, J=2.5 Hz, 0.5H), 2.96-3.01 (m, 1H), 2.89-2.96 (m, 1H), 2.65-2.74 (m, 1H), 1.21 (dd, J=6.8, 0.8 Hz, 6H), 1.13 (d, J=6.3 Hz, 3H).

Step F: (R)-5-bromo-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (7)

[0225] To a 25 mL of round-bottom flask was added (R)-5-bromo-6-isopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6; 680 mg, 2.1 mmol), 3-methoxypropanoic acid (438 mg, 4.2 mmol), HATU (1.6 g, 4.2 mmol), DIPEA (1.1 mL, 6.31 mmol) and 5 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature for 4 hours until TLC showed the completion of the reaction. After washing with Satd. $NaHCO_3$, brine, the combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography purification (20% EtOAc/petroleum ether) afforded 550 mg of title compound as a light yellowish solid. MS (ES) M+H expected 409.1, found 409.0. ^{1}H NMR (CHLOROFORM-d) δ 7.83 (s, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=12.3 Hz, 0.5H), 4.19-4.39 (m, 3H), 3.76-3.85 (m, 0.5H), 3.73 (t, J=6.4 Hz, 2H), 3.50-3.61 (m, 0.5H), 3.37 (s, 3H), 3.25-3.35 (m, 1H), 3.02-3.20 (m, 1H), 2.63-2.80 (m, 1H), 2.51-2.61 (m, 1H), 1.35 (d, J=7.0 Hz, 1.5H), 1.25 (d, J=6.3 Hz, 1.5H), 1.21-1.23 (m, 3H), 1.19-1.21 (m, 3H)

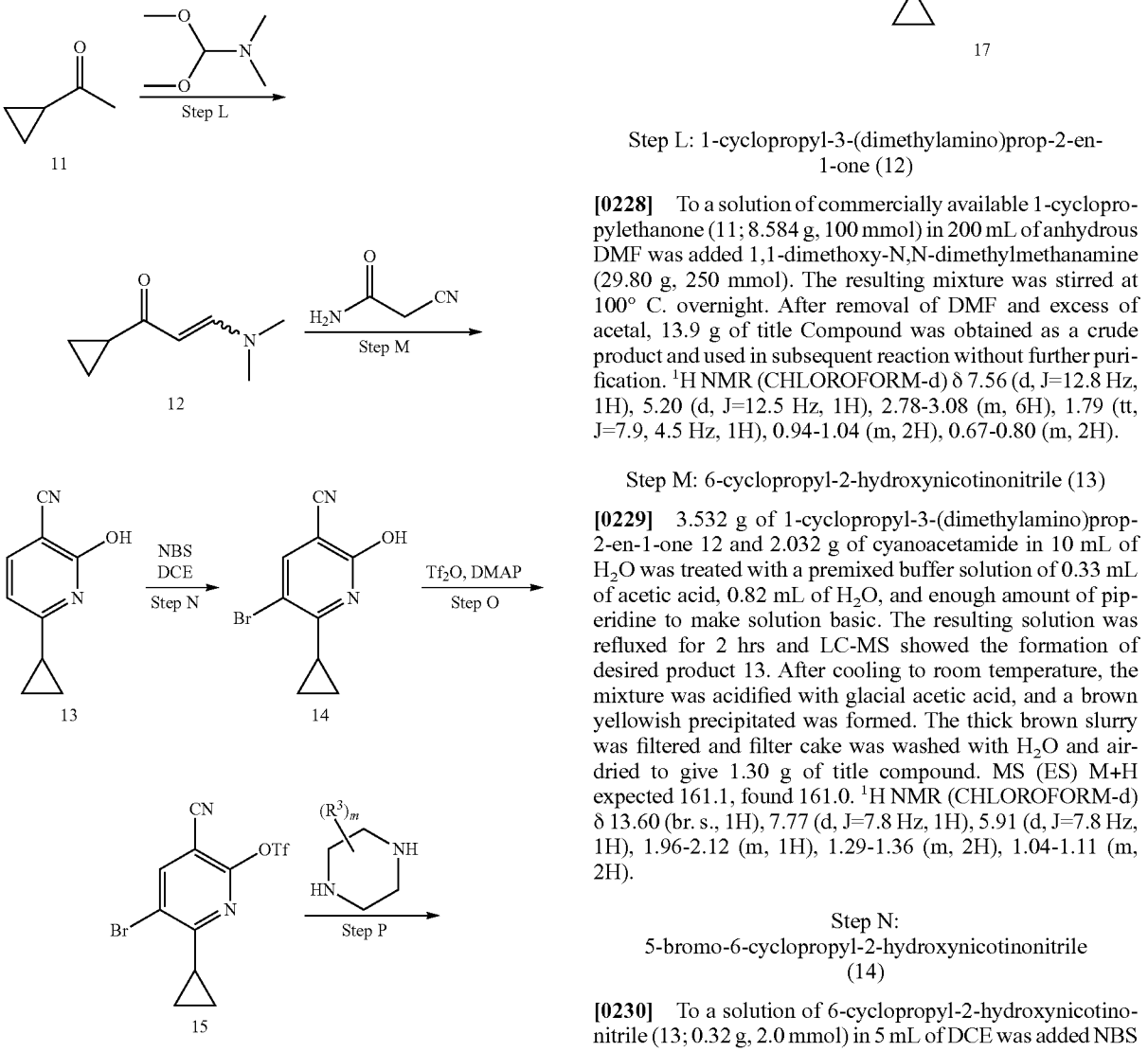
[0226] Other intermediates 7 were prepared by similar steps according to Scheme 1 and either: (1) replacing (R)-2-methylpiperazine in Step E with an alternately substituted or unsubstituted piperazine; and/or (2) replacing 3-methoxypropanoic acid in Step F with an alternate acid.

Example 2

Preparation of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[0227] (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (17; wherein R^{1a} is hydrogen; R^2 is cyclopropyl; m is 1; R^3 is 3-methyl; and R^8 is methoxyethyl) was prepared according to general Scheme 2, below.

Scheme 2:



Step L: 1-cyclopropyl-3-(dimethylamino)prop-2-en-1-one (12)

[0228] To a solution of commercially available 1-cyclopropylethanone (11; 8.584 g, 100 mmol) in 200 mL of anhydrous DMF was added 1,1-dimethoxy-N,N-dimethylmethanamine (29.80 g, 250 mmol). The resulting mixture was stirred at 100° C. overnight. After removal of DMF and excess of acetal, 13.9 g of title Compound was obtained as a crude product and used in subsequent reaction without further purification. ^{1}H NMR (CHLOROFORM-d) δ 7.56 (d, J=12.8 Hz, 1H), 5.20 (d, J=12.5 Hz, 1H), 2.78-3.08 (m, 6H), 1.79 (tt, J=7.9, 4.5 Hz, 1H), 0.94-1.04 (m, 2H), 0.67-0.80 (m, 2H).

Step M: 6-cyclopropyl-2-hydroxynicotinonitrile (13)

[0229] 3.532 g of 1-cyclopropyl-3-(dimethylamino)prop-2-en-1-one 12 and 2.032 g of cyanoacetamide in 10 mL of H_2O was treated with a premixed buffer solution of 0.33 mL of acetic acid, 0.82 mL of H_2O, and enough amount of piperidine to make solution basic. The resulting solution was refluxed for 2 hrs and LC-MS showed the formation of desired product 13. After cooling to room temperature, the mixture was acidified with glacial acetic acid, and a brown yellowish precipitated was formed. The thick brown slurry was filtered and filter cake was washed with H_2O and air-dried to give 1.30 g of title compound. MS (ES) M+H expected 161.1, found 161.0. ^{1}H NMR (CHLOROFORM-d) δ 13.60 (br. s., 1H), 7.77 (d, J=7.8 Hz, 1H), 5.91 (d, J=7.8 Hz, 1H), 1.96-2.12 (m, 1H), 1.29-1.36 (m, 2H), 1.04-1.11 (m, 2H).

Step N: 5-bromo-6-cyclopropyl-2-hydroxynicotinonitrile (14)

[0230] To a solution of 6-cyclopropyl-2-hydroxynicotinonitrile (13; 0.32 g, 2.0 mmol) in 5 mL of DCE was added NBS (0.534 g, 3.0 mmol) at room temperature. The reaction mix-

ture was heated at reflux for 3 hours. After LC-MS showed completion of reaction, the reaction mixture was cooled to room temperature and poured into water. After extraction with methylene chloride (3×5 mL), the combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography (4% MeOH/DCM) afforded 0.45 g of 14. MS (ES) M+H expected 239.0, found 238.9. ^{1}H NMR (CHLOROFORM-d) δ 8.49-8.72 (br. s., 1H), 7.93 (s, 1H), 2.23-2.34 (m, 1H), 1.36-1.42 (m, 2H), 1.29-1.36 (m, 2H).

Step O: 5-bromo-3-cyano-6-cyclopropylpyridin-2-yl trifluoromethanesulfonate (15)

[0231] To a 5-bromo-6-cyclopropyl-2-hydroxynicotinonitrile (14; 0.45 g, 1.882 mmol) in 10 mL of methylene chloride was added DMAP (23.2 mg, 0.19 mmol), and triethylamine (0.247 g, 2.45 mmol). The mixture was cooled to 0° C. in an ice-water bath, and trifluoromethanesulfonic anhydride (0.69 g, 2.45 mmol) was added dropwise via syringe. The resulting reaction mixture was stirred at 0° C. for 30 min before it was allowed to warm to room temperature and stirred for additional 2 hours. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% ethyl acetate/petroleum ether) to afford 537 mg of 15. ^{1}H NMR (CHLOROFORM-d) δ 8.14-8.19 (m, 1H), 2.55-2.66 (m, 1H), 1.30 (dt, J=7.8, 3.1 Hz, 2H), 1.21-1.27 (m, 2H).

Step P: (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (16)

[0232] A mixture of above triflate 15 (1.68 g, 4.6 mmol), (R)-2-methylpiperazine (790 mg, 6.9 mmol), and triethylamine (1.9 mL, 13.8 mmol) suspended in 5 mL of MeCN was subjected to microwave reaction at 175° C. for 60 min. After the mixture was concentrated under reduced pressure, the residue was extracted between ethyl acetate and water. The combined organic layer was then washed with aq. $NaHCO_3$, brine, dried over anhy. Na_2SO_4 and concentrated in vacuo to give 1.26 g of crude 16. MS (ES) M+H expected 321.1, found 321.2. ^{1}H NMR (CHLOROFORM-d) δ 7.78 (s, 1H), 4.14-4.24 (m, 2H), 3.09-3.14 (m, 1H), 3.02-3.07 (m, 1H), 2.96-3.00 (m, 2H), 2.71 (dd, J=12.9, 10.2 Hz, 1H), 2.42-2.52 (m, 1H), 1.16 (d, J=6.3 Hz, 3H), 1.08 (s, 2H), 1.07 (d, J=3.8 Hz, 2H).

Step Q: (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (17)

[0233] To a 25 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (16; 1.26 g, 3.9 mmol), 3-methoxypropanoic acid (0.74 mL, 7.8 mmol), HATU (2.98 g, 7.8 mmol), DIPEA (2 mL, 11.76 mmol) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. Reaction mixture was with Satd. $NaHCO_3$ and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography purification (30% EtOAc/petroleum ether) afforded 1.28 g of title compound as a white solid. MS (ES) M+H expected 407.1, found 407.0. ^{1}H NMR (CHLOROFORM-d) δ 7.78-7.85 (m, 1H), 4.82-4.92 (m, 0.5H), 4.50 (d, J=13.6 Hz, 0.5H), 4.18-4.21 (m, 2H), 4.07-4.16 (m, 1H), 3.75-3.82 (m, 0.5H), 3.70-3.75 (m, 2H), 3.45-3.55 (m, 0.5H), 3.36 (s, 3H), 3.15-3.27 (m, 1H), 2.92-3.14 (m, 1H), 2.67-2.78 (m, 1H), 2.51-2.61 (m, 1H), 2.40-2.51 (m, 1H), 1.34 (d, J=6.8 Hz, 1.5H), 1.25 (d, J=2.5 Hz, 1.5H), 1.09 (d, J=3.5 Hz, 2H), 1.08 (s, 2H).

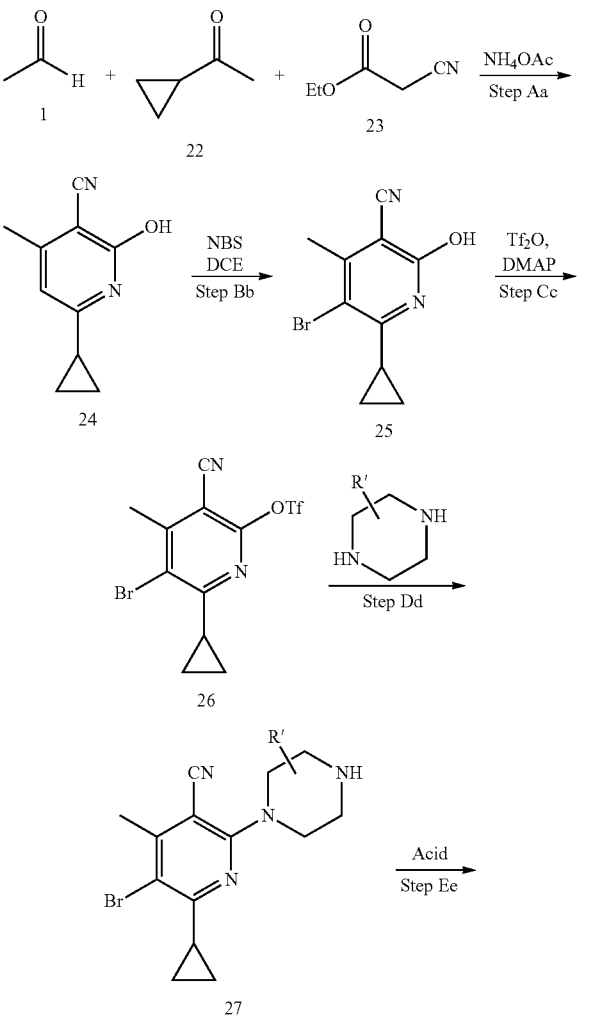
[0234] Other intermediates 17 were similarly prepared according to Scheme 2 by either: (1) replacing (R)-2-methylpiperazine in Step P with an alternately substituted or unsubstituted piperazine; and/or (2) replacing 3-methoxypropanoic acid in Step Q with an alternate acid.

Example 3

Preparation of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[0235] (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (28; wherein R^{1a} is methyl; R^2 is cyclopropyl; m is 1; R^3 is 3-methyl; and R^8 is methoxyethyl) was prepared according to general Scheme 3, below.

Scheme 3:



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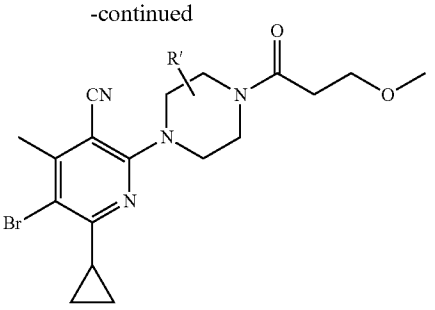


28

Step Aa:
6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (24)

[0236] To a suspension of ammonium acetate (140 g, 1.82 mol) in 400 mL of EtOH was added successively commercially available 1-cyclopropylethanone (22; 22.5 mL, 22.7 mmol), acetaldehyde (21; 10 g, 22.7 mmol), and ethyl cyanoacetate (23; 24.2 mL, 22.7 mmol). The resulting mixture was stirred at reflux temperature for 2 hrs and subsequently at room temperature overnight. After the LC-MS showed the formation of the desired product, the solvent was removed under reduced pressure. Flash column Chromatography (10% MeOH/DCM) afforded 1.3 g of 24 as a white solid. MS (ES) M+H expected 175.1, found 175.1. ^{1}H NMR (DMSO-d6) δ 12.36 (br. s., 1H), 5.93 (s, 1H), 2.26 (s, 3H), 1.81-1.91 (m, 1H), 1.06-1.14 (m, 2H), 0.91-0.95 (m, 2H).

Step Bb: 5-bromo-6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (25)

[0237] To a solution of 6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (24; 2.6 g, 15 mmol) in 10 mL of DCE was added NBS (4 g, 22.5 mmol) at room temperature. The reaction mixture was then heated at reflux for 3 hours. After LC-MS showed the completion of reaction, the mixture was cooled to room temperature and poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography (4% MeOH/DCM) afforded 4 g of 25 as a brown solid. MS (ES) M+H expected 253.0, found 253.0. ^{1}H NMR (CHLOROFORM-d) δ 2.68 (s, 3H), 1.79-1.88 (m, 1H), 1.03-1.09 (m, 2H), 0.93-1.01 (m, 2H).

Step Cc: 5-bromo-3-cyano-6-cyclopropyl-4-methylpyridin-2-yl trifluoromethanesulfonate (26)

[0238] To a solution of 5-bromo-2-hydroxy-6-isopropylnicotinonitrile (25; 4.0 g, 14.6 mmol) in 20 mL of methylene chloride was added DMAP (178 mg, 1.46 mmol), and triethylamine (2.5 mL, 17.5 mmol). The mixture was cooled to 0° C. in an ice-water bath, and trifluoromethanesulfonic anhydride (3.7 mL, 21.9 mmol) was added dropwise by syringe. The resulting reaction mixture was stirred at 0° C. for 30 min then allowed to warm to room temperature and stirred overnight. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% EtOAc/petroleum ether) to afford 1.66 g of 26. ^{1}H NMR (CHLOROFORM-d) δ 2.70 (s, 3H), 2.16-2.20 (m, 1H), 1.23-1.25 (m, 2H), 1.19-1.22 (m, 2H).

Step Dd: (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (27)

[0239] A mixture of above triflate 26 (1.66 g, 4.3 mmol), (R)-2-methylpiperazine (738 mg, 6.46 mmol), and triethylamine (1.8 mL, 12.9 mmol) suspended in 5 mL of MeCN was subjected to microwave reaction at 150° C. for 1 hour. After removal of solvent under reduced pressure, the residue was extracted between EtOAc and water. The organic layer was then washed with satd. aq. $NaHCO_3$ and brine, dried over anhy. Na_2SO_4 and concentrated in vacuo. Flash column chromatography (10% DCM/MeOH) afforded 330 mg of 27 as a light yellowish solid. MS (ES) M+H expected 335.1, found 335.2. ^{1}H NMR (CHLOROFORM-d) δ 4.08-4.16 (m, 0.5H), 4.05-4.08 (m, 1H), 4.01-4.04 (m, 0.5H), 2.99-3.08 (m, 1H), 2.97 (d, J=8.8 Hz, 2H), 2.88-2.95 (m, 1H), 2.58-2.65 (m, 1H), 2.55-2.57 (m, 3H), 1.77 (br. s., 1H), 1.12 (s, 1.5H), 1.10 (s, 1.5H), 1.05-1.09 (m, 2H), 1.00-1.05 (m, 2H).

Step Ee: (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (28)

[0240] To a 50 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (27; 1.12 g, 3.34 mmol), 3-methoxypropanoic acid (0.63 mL, 6.68 mmol), HATU (2.54 g, 6.68 mmol), DIPEA (3.8 g, 10 mmol) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. After washing the reaction mixture with Satd. $NaHCO_3$, brine, the organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Flash column chromatography (20% EtOAc/petroleum ether) afforded 1.7 g of 28 as a yellowish solid. MS (ES) M+H expected 421.1, found 421.3. ^{1}H NMR (CHLOROFORM-d) δ 4.90 (br. s., 0.5H), 4.52 (d, J=13.6 Hz, 0.5H), 4.22 (br. s., 0.5H), 3.95-4.13 (m, 2H), 3.78 (br. s., 0.5H), 3.74 (t, J=5.9 Hz, 2H), 3.50-3.61 (m, 0.5H), 3.38 (s, 3H), 3.07-3.24 (m, 1.5H), 2.90-3.06 (m, 1H), 2.65-2.79 (m, 1H), 2.60 (s, 3H), 2.52-2.63 (m, 1H), 2.17-2.21 (m, 1H), 1.37 (d, J=6.5 Hz, 1.5H), 1.27 (d, J=6.3 Hz, 1.5H), 1.09 (s, 2H), 1.05-1.08 (m, 2H).

[0241] Other intermediates 28 were similarly prepared according to Scheme 3 by either: (1) replacing (R)-2-methylpiperazine in Step Dd with an alternately substituted or unsubstituted piperazine; and/or (2) replacing 3-methoxypropanoic acid in Step Ee with an alternate acid.

Example 4

Preparation of (R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)-nicotinonitrile (Compound 189)

[0242] A mixture of bromide 7 from Example 1 (26 mg, 0.06 mmol), 4-(trifluoromethyl)phenylboronic acid (17 mg, 0.089 mmol), $Pd(PPh_3)_4$ (3 mg, 0.003 mmol), and K_2CO_3 (16 mg, 0.119 mmol) suspended in 1 mL of DMF was subjected to microwave reaction at 150° C. for 45 min. After the reaction, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography to afford 19 mg of Compound 189 as yellowish oil. MS (ES) M+H

expected 475.2, found 475.1. ^{1}H NMR (CHLOROFORM-d) δ 7.70 (d, J=8.0 Hz, 2H), 7.60 (s, 1H), 7.38 (d, J=8.0 Hz, 2H), 4.93 (br. s., 0.5H), 4.56 (d, J=11.0 Hz, 0.5H), 4.44 (d, J=12.3 Hz, 1H), 4.32-4.39 (m, 1H), 4.28 (br. s., 0.5H), 3.83 (d, J=13.3 Hz, 0.5H), 3.68-3.79 (m, 2H), 3.53-3.64 (m, 0.5H), 3.38 (s, 3H), 3.36 (br. s., 0.5H), 3.33 (br. s., 0.5H), 3.10-3.28 (m, 1.5H), 3.07 (dt, J=13.3, 1 Hz, 1H), 2.65-2.80 (m, 1H), 2.52-2.65 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.30 (d, J=6.3 Hz, 1.5H), 1.16 (d, J=6.5 Hz, 6H).

[0243] Other Compounds of Formula II listed below, wherein R^{1b} is aryl or heteroaryl; and R^2 is isopropyl or cyclopropyl were similarly prepared using any of intermediates 7 (Scheme 1), 17 (Scheme 2), or 28 (Scheme 3) as starting material.

(R)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 185)

[0244] ^{1}H NMR (CHLOROFORM-d) δ 7.70 (d, J=8.0 Hz, 2H), 7.61 (s, 1H), 7.47-7.56 (m, 1H), 7.38 (d, J=7.8 Hz, 1H), 7.07 (d, J=3.5 Hz, 1H), 6.48-6.55 (m, 1H), 4.86-4.96 (m, 1H), 4.43-4.59 (m, 2H), 4.38 (dt, J=13.3, 2.0 Hz, 1H), 3.56 (br. s., 1H), 3.46 (dd, J=13.3, 3.8 Hz, 1H), 3.28 (td, J=12.4, 3.4 Hz, 1H), 3.07 (quin, J=6.7 Hz, 1H), 1.47 (d, J=6.8 Hz, 3H), 1.16 (dd, J=6.7, 1.6 Hz, 6H). LC-MS: m/z 483.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 187)

[0245] ^{1}H NMR (CHLOROFORM-d) δ 7.76 (s, 1H), 7.70 (d, J=8.0 Hz, 2H), 7.61 (s, 1H), 7.44-7.49 (m, 1H), 7.38 (d, J=8.0 Hz, 2H), 6.56-6.63 (m, 1H), 4.75 (br. s., 1H), 4.45 (d, J=13.1 Hz, 1H), 4.35-4.42 (m, 2H), 3.42-3.64 (m, 1H), 3.31-3.41 (m, 1H), 3.18 (td, J=12.5, 3.5 Hz, 1H), 3.07 (dt, J=13.2, 6.6 Hz, 1H), 1.44 (d, J=6.8 Hz, 3H), 1.16 (dd, J=6.7, 1.9 Hz, 6H). LC-MS: m/z 483.2 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 188)

[0246] ^{1}H NMR (CHLOROFORM-d) δ 7.69 (d, J=8.3 Hz, 2H), 7.59 (s, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.22 (dd, J=5.1, 1.1 Hz, 1H), 6.95-7.00 (m, 1H), 6.89-6.95 (m, 1H), 4.95 (br. s., 0.5H), 4.59 (d, J=12.8 Hz, 0.5H), 4.19-4.48 (m, 3H), 3.89-4.06 (m, 2H), 3.82 (d, J=13.6 Hz, 0.5H), 3.57 (t, J=11.3 Hz, 0.5H), 3.20-3.38 (m, 1H), 3.08-3.20 (m, 1H), 3.00-3.08 (m, 1H), 1.35 (d, J=6.5 Hz, 1.5H), 1.31 (d, J=6.5 Hz, 1.5H), 1.15 (d, J=6.5 Hz, 6H). LC-MS: m/z 513.1 $(M+H)^+$.

(R)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-m-tolylnicotinonitrile (Compound 190)

[0247] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.51 (d, J=1.0 Hz, 1H), 7.31 (t, J=7.8 Hz, 1H), 7.19 (d, J=7.8 Hz, 1H), 7.01-7.09 (m, 3H), 6.51 (dd, J=3.3, 1.8 Hz, 1H), 4.90 (br. s., 1H), 4.52 (d, J=13.3 Hz, 1H), 4.42 (d, J=13.8 Hz, 1H), 4.30-4.37 (m, 1H), 3.56 (br. s., 1H), 3.41 (dd, J=13.2, 3.6 Hz, 1H), 3.24 (td, J=12.4, 3.3 Hz, 1H), 3.15 (dt, J=13.3, 6.7 Hz, 1H), 2.40 (s, 3H), 1.48 (d, J=6.5 Hz, 3H), 1.15 (dd, J=6.8, 2.3 Hz, 6H). LC-MS: m/z 429.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-m-tolylnicotinonitrile (Compound 191)

[0248] ^{1}H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.61 (s, 1H), 7.46 (t, J=1.6 Hz, 1H), 7.31 (t, J=7.8 Hz, 1H), 7.20 (d, J=7.8 Hz, 1H), 7.00-7.08 (m, 2H), 6.59 (d, J=1.0 Hz, 1H), 4.74 (br. s., 1H), 4.20-4.50 (m, 3H), 3.41-3.61 (m, 1H), 3.32 (dd, J=13.1, 3.0 Hz, 1H), 3.08-3.19 (m, 2H), 2.40 (s, 3H), 1.45 (d, J=6.8 Hz, 3H), 1.08-1.19 (m, 6H). LC-MS: m/z 429.1 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-m-tolylnicotinonitrile (Compound 192)

[0249] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.28-7.35 (m, 1H), 7.16-7.25 (m, 2H), 7.00-7.07 (m, 2H), 6.89-6.99 (m, 2H), 4.94 (br. s., 0.5H), 4.58 (d, J=13.3 Hz, 0.5H), 4.33-4.43 (m, 1H), 4.19-4.33 (m, 2H), 3.90-4.05 (m, 2H), 3.80 (d, J=13.3 Hz, 0.5H), 3.51-3.63 (m, 0.5H), 3.17-3.33 (m, 1H), 3.10-3.17 (m, 1H), 2.99-3.10 (m, 1H), 2.40 (s, 3H), 1.36 (d, J=6.3 Hz, 1.5H), 1.32 (d, J=6.8 Hz, 1.5H), 1.14 (d, J=6.8 Hz, 6H). LC-MS: m/z 459.1 $(M+H)^+$.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-m-tolylnicotinonitrile (Compound 193)

[0250] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.31 (t, J=7.9 Hz, 1H), 7.19 (d, J=7.8 Hz, 1H), 7.01-7.08 (m, 2H), 4.93 (br. s., 0.5H), 4.56 (d, J=13.1 Hz, 0.5H), 4.30-4.44 (m, 2H), 4.19-4.30 (m, 1H), 3.81 (d, J=13.6 Hz, 0.5H), 3.71-3.78 (m, 2H), 3.52-3.65 (m, 0.5H), 3.38 (s, 3H), 3.24-3.36 (m, 1H), 3.10-3.23 (m, 2H), 2.65-2.80 (m, 1H), 2.54-2.64 (m, 1H), 2.40 (s, 3H), 1.41 (d, J=6.5 Hz, 1.5H), 1.31 (d, J=6.8 Hz, 1.5H), 1.15 (d, J=6.5 Hz, 6H). LC-MS: m/z 421.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-isopropylpiperazin-1-yl)-6-isopropyl-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 195)

[0251] ^{1}H NMR (CHLOROFORM-d) δ 7.67-7.84 (m, 3H), 7.57-7.64 (m, 1H), 7.45-7.53 (m, 1H), 7.38 (d, J=8.0 Hz, 2H), 6.58 (s, 1H), 4.84 (d, J=13.6 Hz, 1H), 4.49-4.69 (m, 2H), 3.81-4.22 (m, 1H), 3.22-3.57 (br. s., 3H), 3.07 (dt, J=13.3, 6.7 Hz, 1H), 2.19-2.38 (m, 1H), 1.18 (d, J=6.8 Hz, 3H), 1.14 (d, J=6.8 Hz, 3H), 0.88-1.05 (m, 6H). LC-MS: m/z 511.1 $(M+H)^+$.

(R)-6-isopropyl-2-(3-isopropyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)-nicotinonitrile (Compound 196)

[0252] ^{1}H NMR (CHLOROFORM-d) δ 7.64-7.75 (m, 2H), 7.55-7.62 (m, 1H), 7.37-7.46 (d, J=8.5 Hz, 2H), 7.22 (ddd, J=4.8, 3.2, 1.3 Hz, 1H), 6.87-7.02 (m, 2H), 4.68-4.82 (m, 1.5H), 4.35-4.54 (m, 1.5H), 3.81-4.11 (m, 3H), 3.63 (d, J=10.3 Hz, 0.5H), 3.37-3.53 (m, 0.5H), 3.08-3.20 (m, 1H), 2.96-3.08 (m, 2H), 2.18-2.32 (m, 0.5H), 2.04-2.17 (m, 0.5H), 1.17 (dd, J=6.7, 3.6 Hz, 3H), 1.13 (d, J=6.5 Hz, 3H), 1.08 (dd, J=11.0, 6.5 Hz, 3H), 0.87-0.93 (m, 1.5H), 0.85 (d, J=6.8 Hz, 1.5H). LC-MS: m/z 541.1 $(M+H)^+$.

(R)-6-isopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl) nicotinonitrile (Compound 197)

[0253] ^{1}H NMR (CHLOROFORM-d) δ 7.66-7.76 (m, 2H), 7.59 (d, J=2.3 Hz, 1H), 7.38 (d, J=8.0 Hz, 2H), 4.68-4.84 (m, 1.5H), 4.47-4.5 (s, 1.5H), 3.88 (d, J=13.6 Hz, 0.5H), 3.69-3.82 (m, 2H), 3.61 (d, J=10.3 Hz, 0.5H), 3.42-3.52 (m, 0.5H), 3.38 (d, J=2.8 Hz, 3H), 3.12-3.27 (m, 2H), 3.02-3.12 (m, 1H), 2.90-3.02 (m, 0.5H), 2.53-2.83 (m, 2H), 2.17-2.30 (m, 0.5H), 1.98-2.16 (m, 0.5H), 1.18 (d, J=6.5 Hz, 3H), 1.14 (d, J=6.8 Hz, 3H), 1.08 (dd, J=6.5, 2.8 Hz, 3H), 0.91 (d, J=6.8 Hz, 1.5H), 0.85 (d, J=6.8 Hz, 1.5H). LC-MS: m/z 407.4 $(M+H)^+$.

(R)-5-(4-fluorophenyl)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)nicotinonitrile (Compound 199)

[0254] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.29 (d, J=2.0 Hz, 1H), 7.17-7.24 (m, 2H), 7.08-7.16 (m, 2H), 6.38 (d, J=1.8 Hz, 1H), 4.68 (br. s., 1H), 4.41 (d, J=13.1 Hz, 1H), 4.36 (d, J=13.1 Hz, 1H), 4.20-4.28 (d, J=13.6 Hz, 1H), 3.39-3.59 (m, 1H), 3.25-3.37 (m, 1H), 3.03-3.18 (m, 2H), 2.41 (s, 3H), 1.41 (d, J=6.5 Hz, 3H), 1.14 (dd, J=6.8, 2.3 Hz, 6H). LC-MS: m/z 447.2 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-m-tolylnicotinonitrile (Compound 200)

[0255] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.29 (d, J=2.0 Hz, 2H), 7.17-7.24 (m, 1H), 7.08-7.16 (m, 2H), 6.38 (d, J=1.8 Hz, 1H), 4.68 (br. s., 1H), 4.41 (d, J=13.1 Hz, 1H), 4.36 (d, J=13.1 Hz, 1H), 4.20-4.28 (d, J=13.6 Hz, 1H), 3.39-3.59 (m, 4H), 3.25-3.37 (m, 4H), 3.03-3.18 (m, 8H), 2.41 (s, 11H), 1.41 (d, J=6.5 Hz, 11H), 1.14 (dd, J=6.8, 2.3 Hz, 6H). LC-MS: m/z 443.3 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)-nicotinonitrile (Compound 201)

[0256] ^{1}H NMR (CHLOROFORM-d) δ 7.70 (d, J=8.0 Hz, 2H), 7.57-7.64 (m, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.27-7.32 (m, 1H), 6.35-6.42 (m, 1H), 4.68 (br. s., 1H), 4.34-4.53 (m, 2H), 4.20-4.34 (m, 1H), 3.48 (d, J=4.8 Hz, 1H), 3.28-3.40 (m, 1H), 3.16 (td, J=12.6, 3.4 Hz, 1H), 3.00-3.11 (m, 1H), 2.41 (s, 3H), 1.38-1.48 (m, 3H), 1.16 (dd, J=6.8, 2.3 Hz, 6H). LC-MS: m/z 497.2 $(M+H)^+$.

(R)-6-isopropyl-5-(4-isopropylphenyl)-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)nicotinonitrile (Compound 202)

[0257] ^{1}H NMR (CHLOROFORM-d) δ 7.58-7.65 (m, 1H), 7.28 (d, J=8.3 Hz, 3H), 7.11-7.20 (m, 2H), 6.37 (d, J=2.0 Hz, 1H), 4.59-4.68 (br. s., 1H), 4.30-4.43 (m, 2H), 4.19 (br. s., 1H), 3.40-3.54 (m, 1H), 3.30 (dd, J=12.8, 3.0 Hz, 1H), 3.14-3.22 (m, 1H), 3.06-3.14 (m, 1H), 2.96 (spt, J=6.9 Hz, 1H), 2.41 (s, 3H), 1.39-1.45 (m, 3H), 1.30 (d, J=7.0 Hz, 6H), 1.15 (dd, J=6.8, 3.0 Hz, 6H). LC-MS: m/z 471.3 $(M+H)^+$.

(R)-5-(furan-3-yl)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)nicotinonitrile (Compound 203)

[0258] ^{1}H NMR (CHLOROFORM-d) δ 7.64 (s, 1H), 7.49-7.53 (m, 1H), 7.43-7.47 (m, 1H), 7.29 (d, J=1.8 Hz, 1H), 6.45 (d, J=0.8 Hz, 1H), 6.36 (d, J=1.8 Hz, 1H), 4.68 (br. s., 1H), 4.39 (d, J=13.1 Hz, 1H), 4.34 (d, J=13.1 Hz, 1H), 4.18-4.26 (br. s., 1H), 3.38-3.56 (m, 1H), 3.22-3.35 (m, 2H), 3.11 (td, J=12.6, 3.4 Hz, 1H), 2.36-2.47 (m, 3H), 1.39 (d, J=6.5 Hz, 3H), 1.18 (dd, J=6.7, 1.6 Hz, 6H). LC-MS: m/z 419.2 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-5-(furan-3-yl)-6-isopropylnicotinonitrile (Compound 204)

[0259] ^{1}H NMR (CHLOROFORM-d) δ 7.72-7.77 (m, 1H), 7.64 (s, 1H), 7.50 (t, J=1.8 Hz, 1H), 7.44-7.47 (m, 2H), 6.58 (dd, J=1.8, 0.8 Hz, 1H), 6.45 (dd, J=1.8, 0.8 Hz, 1H), 5.30 (s, 1H), 4.73 (br. s., 1H), 4.38 (s, 1H), 4.41 (s, 1H), 4.31 (t, J=2.1 Hz, 1H), 4.35 (t, J=2.0 Hz, 1H), 3.48 (br. s., 1H), 3.32 (dd, J=9.9, 3.1 Hz, 1H), 3.24-3.30 (m, 1H), 3.14 (td, J=12.5, 3.5 Hz, 1H), 1.42 (d, J=7.0 Hz, 3H), 1.19 (dd, J=6.8, 1.0 Hz, 6H). LC-MS: m/z 405.2 $(M+H)^+$.

(R)-5-(furan-3-yl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 205)

[0260] ^{1}H NMR (CHLOROFORM-d) δ 7.63 (s, 1H), 7.50 (t, J=1.8 Hz, 1H), 7.42-7.47 (m, 1H), 6.44 (dd, J=1.8, 0.8 Hz, 1H), 4.92 (br. s., 0.5H), 4.54 (d, J=13.1 Hz, 0.5H), 4.38 (dd, J=12.2, 2.1 Hz, 1H), 4.17-4.35 (m, 2H), 3.80 (d, J=13.1 Hz, 0.5H), 3.74 (t, J=6.5 Hz, 2H), 3.51-3.62 (m, 0.5H), 3.36-3.39 (m, 3H), 3.23-3.35 (m, 2H), 3.06-3.17 (m, 1H), 2.64-2.80 (m, 1H), 2.51-2.63 (m, 1H), 1.38 (d, J=6.3 Hz, 1.5H), 1.28 (d, J=6.0 Hz, 1.5H), 1.19 (d, J=6.8 Hz, 6H). LC-MS: m/z 397.2 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(4-isopropylphenyl)nicotinonitrile (Compound 206)

[0261] ^{1}H NMR (CHLOROFORM-d) δ 7.72-7.77 (m, 1H), 7.61 (s, 1H), 7.46 (t, J=1.6 Hz, 1H), 7.28 (d, J=8.0 Hz, 2H), 7.12-7.19 (m, 2H), 6.59 (dd, J=1.8, 0.8 Hz, 1H), 4.74 (br. s., 1H), 4.39 (d, J=13.3 Hz, 1H), 4.33 (dt, J=13.2, 1.9 Hz, 2H), 3.49 (br. s., 1H), 3.32 (dd, J=13.2, 3.4 Hz, 1H), 3.08-3.23 (m, 2H), 2.96 (dt, J=13.8, 6.9 Hz, 1H), 1.45 (d, J=6.8 Hz, 3H), 1.30 (d, J=7.0 Hz, 6H), 1.15 (dd, J=6.5, 2.3 Hz, 6H). LC-MS: m/z 457.2 $(M+H)^+$.

(R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 207)

[0262] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.17-7.24 (m, 2H), 7.08-7.16 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.0 Hz, 0.5H), 4.40 (dd, J=12.2, 1.9 Hz, 1H), 4.19-4.35 (m, 2H), 3.82 (d, J=12.5 Hz, 0.5H), 3.69-3.78 (m, 2H), 3.53-3.63 (m, 0.5H), 3.38 (s, 3H), 3.26-3.35 (m, 1H), 3.13-3.22 (m, 1H), 3.03-3.12 (m, 1H), 2.65-2.81 (m, 1H), 2.53-2.64 (m, 1H), 1.40 (d, J=6.3 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.14 (d, J=6.8 Hz, 6H). LC-MS: m/z 425.2 $(M+H)^+$.

(R)-6-isopropyl-5-(4-isopropylphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 208)

[0263] ^{1}H NMR (CHLOROFORM-d) δ 7.59-7.65 (m, 1H), 7.29-7.33 (m, 2H), 7.14-7.22 (m, 2H), 4.95 (br. s., 0.5H), 4.58 (d, J=13.1 Hz, 0.5H), 4.37-4.44 (m, 1H), 4.22-4.37 (m, 2H),

3.83 (d, J=13.3 Hz, 0.5H), 3.70-3.80 (m, 2H), 3.55-3.67 (m, 0.5H), 3.40 (s, 3H), 3.33 (t, J=12.3 Hz, 1H), 3.15-3.25 (m, 2H), 2.98 (quin, J=6.9 Hz, 1H), 2.67-2.83 (m, 1H), 2.55-2.67 (m, 1H), 1.43 (d, J=5.8 Hz, 1.5H), 1.34 (m, 1.5H), 1.32 (d, J=7.0 Hz, 6H), 1.17 (d, J=6.8 Hz, 6H). LC-MS: m/z 449.2 $(M+H)^+$.

(R)-5-(benzofuran-2-yl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 209)

[0264] ^{1}H NMR (CHLOROFORM-d) δ 8.12 (s, 1H), 7.61 (dd, J=7.7, 0.9 Hz, 1H), 7.48-7.56 (m, 1H), 7.32 (td, J=7.7, 1.5 Hz, 1H), 7.24-7.29 (m, 1H), 6.78-6.88 (m, 1H), 4.93 (br. s., 0.5H), 4.38-4.64 (m, 2H), 4.27 (br. s., 0.5H), 3.83 (d, J=12.8 Hz, 1H), 3.75 (br. s., 2H), 3.55 (quin, J=6.7 Hz, 2H), 3.38 (s, 3H), 3.08-3.29 (m, 2H), 2.66-2.83 (m, 1H), 2.60 (br. s., 1H), 1.38 (d, J=6.0 Hz, 1.5H), 1.33 (br. s., 1.5H), 1.28 (d, J=6.5 Hz, 6H). LC-MS: m/z 447.1 $(M+H)^+$.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(pyrimidin-5-yl)nicotinonitrile (Compound 210)

[0265] ^{1}H NMR (CHLOROFORM-d) δ 9.23-9.28 (m, 1H), 8.69 (s, 2H), 7.62 (s, 1H), 4.94 (br. s., 0.5H), 4.56 (d, J=9.5 Hz, 0.5H), 4.37-4.53 (m, 2H), 4.29 (br. s., 0.5H), 3.84 (d, J=13.3 Hz, 0.5H), 3.68-3.79 (m, 2H), 3.52-3.64 (m, 0.5H), 3.40-3.46 (m, 0.5H), 3.38 (s, 3H), 3.20-3.32 (m, 1H), 3.16 (d, J=9.5 Hz, 1H), 2.93-3.04 (m, 1H), 2.65-2.78 (m, 1H), 2.52-2.64 (m, 1H), 1.39 (d, J=6.5 Hz, 1.5H), 1.29 (d, J=6.8 Hz, 1.5H), 1.19 (dd, J=6.7, 1.1 Hz, 6H). LC-MS: m/z 409.2 $(M+H)^+$.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(naphthalen-2-yl)nicotinonitrile (Compound 211)

[0266] ^{1}H NMR (CHLOROFORM-d) δ 7.83-7.97 (m, 3H), 7.66-7.77 (m, 2H), 7.49-7.60 (m, 2H), 7.36 (dd, J=8.4, 1.6 Hz, 1H), 4.94 (br. s., 0.5H), 4.57 (d, J=12.8 Hz, 0.5H), 4.42 (d, J=12.8 Hz, 1H), 4.30-4.38 (m, 1H), 4.27 (br. s., 1H), 3.83 (d, J=13.3 Hz, 0.5H), 3.69-3.79 (m, 2H), 3.54-3.65 (m, 0.5H), 3.39 (s, 3H), 3.29-3.38 (m, 1H), 3.18-3.24 (m, 1H), 3.06-3.17 (m, 1H), 2.66-2.83 (m, 1H), 2.52-2.65 (m, 1H), 1.42 (d, J=7.3 Hz, 1.5H), 1.32 (d, J=6.5 Hz, 1.5H), 1.17 (d, J=6.8 Hz, 6H). LC-MS: m/z 457.1 $(M+H)^+$.

(R)-6-isopropyl-5-(3-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 212)

[0267] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.34 (t, J=7.9 Hz, 1H), 6.92 (dd, J=8.3, 1.8 Hz, 1H), 6.82 (d, J=7.5 Hz, 1H), 6.74-6.79 (m, 1H), 4.93 (br. s., 0.5H), 4.56 (d, J=12.8 Hz, 0.5H), 4.39 (d, J=13.6 Hz, 1H), 4.21-4.34 (m, 2H), 3.84 (s, 3H), 3.79 (d, J=8.0 Hz, 0.5H), 3.70-3.77 (m, 2H), 3.53-3.64 (m, 0.5H), 3.38 (s, 3H), 3.26-3.36 (m, 1H), 3.12-3.22 (m, 2H), 2.65-2.80 (m, 1H), 2.52-2.64 (m, 1H), 1.41 (d, J=1.5 Hz, 4H), 1.31 (d, J=6.5 Hz, 1.5H), 1.10-1.19 (m, 6H). LC-MS: m/z 437.1 $(M+H)^+$.

(R)-2-isopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile (Compound 213)

[0268] ^{1}H NMR (CHLOROFORM-d) δ 8.69 (d, J=5.3 Hz, 2H), 7.61 (s, 1H), 7.22 (d, J=5.5 Hz, 2H), 4.93 (br. s., 0.5H), 4.56 (d, J=9.8 Hz, 0.5H), 4.34-4.51 (m, 2H), 4.28 (br. s., 1H), 3.83 (d, J=13.3 Hz, 0.5H), 3.68-3.79 (m, 2H), 3.58 (t, J=11.0 Hz, 0.5H), 3.38 (s, 3H), 3.14-3.28 (m, 2H), 3.03-3.14 (m, 1H), 2.65-2.83 (m, 1H), 2.52-2.65 (m, 1H), 1.39 (d, J=6.3 Hz, 1.5H), 1.29 (d, J=6.5 Hz, 1.5H), 1.18 (d, J=6.5 Hz, 6H). LC-MS: m/z 408.1 $(M+H)^+$.

(R)-6-isopropyl-5-(4-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 214)

[0269] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.11-7.20 (m, 2H), 6.92-7.01 (m, 2H), 4.92 (br. s., 0.5H), 4.56 (d, J=12.8 Hz, 0.5H), 4.37 (d, J=12.5 Hz, 1H), 4.29 (d, J=13.1 Hz, 2H), 3.86 (s, 3H), 3.81 (d, J=13.6 Hz, 0.5H), 3.75 (br. s., 2H), 3.53-3.64 (m, 0.5H), 3.38 (s, 3H), 3.31 (t, J=13.2 Hz, 1H), 3.11-3.20 (m, 2H), 2.66-2.82 (m, 1H), 2.52-2.64 (m, 1H), 1.41 (d, J=6.0 Hz, 1.5H), 1.31 (d, J=5.8 Hz, 1.5H), 1.14 (d, J=6.8 Hz, 6H). LC-MS: m/z 437.3 $(M+H)^+$.

(R)-5-(4-chlorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 215)

[0270] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.38-7.43 (m, 2H), 7.14-7.20 (m, 2H), 4.93 (br. s., 0.5H), 4.55 (d, J=12.5 Hz, 0.5H), 4.40 (d, J=12.8 Hz, 1H), 4.21-4.36 (m, 2H), 3.82 (d, J=13.6 Hz, 0.5H), 3.69-3.78 (m, 2H), 3.53-3.63 (m, 0.5H), 3.38 (s, 3H), 3.27-3.37 (m, 1H), 3.11-3.23 (m, 1H), 3.02-3.11 (m, 1H), 2.65-2.81 (m, 1H), 2.53-2.64 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.30 (d, J=6.8 Hz, 1.5H), 1.14 (d, J=6.5 Hz, 6H). LC-MS: m/z 441.1 $(M+H)^+$.

5-(4-ethylphenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 216)

[0271] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 7.15 (d, J=8.0 Hz, 2H), 4.93 (br. s., 0.5H), 4.56 (d, J=12.5 Hz, 0.5H), 4.38 (d, J=12.3 Hz, 1H), 4.30 (d, J=12.3 Hz, 2H), 3.81 (d, J=13.3 Hz, 0.5H), 3.75 (br. s., 2H), 3.51-3.64 (m, 0.5H), 3.38 (s, 3H), 3.31 (t, J=13.6 Hz, 1H), 3.12-3.22 (m, 2H), 3.10 (d, J=14.3 Hz, 0.5H), 2.77 (br. s., 0.5H), 2.71 (q, J=7.5 Hz, 2H), 2.61 (br. s., 1H), 1.41 (d, J=6.0 Hz, 1.5H), 1.32 (br. s., 1.5H), 1.29 (t, J=7.5 Hz, 3H), 1.15 (d, J=6.8 Hz, 6H). LC-MS: m/z 435.3 $(M+H)^+$.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(naphthalen-1-yl)nicotinonitrile (Compound 217)

[0272] ^{1}H NMR (CHLOROFORM-d) δ 7.92 (t, J=7.4 Hz, 2H), 7.63 (s, 1H), 7.49-7.57 (m, 2H), 7.39-7.47 (m, 2H), 7.27-7.34 (m, 1H), 4.96 (br. s., 0.5H), 4.59 (d, J=12.5 Hz, 0.5H), 4.45 (d, J=13.3 Hz, 1H), 4.32-4.41 (m, 1H), 4.30 (br. s., 1H), 3.85 (d, J=13.6 Hz, 0.5H), 3.70-3.81 (m, 2H), 3.55-3.67 (m, 0.5H), 3.39 (s, 3H), 3.07-3.27 (m, 2H), 2.67-2.76 (m, 2H), 2.53-2.66 (m, 1H), 1.45 (d, J=5.5 Hz, 1.5H), 1.36 (d, J=6.5 Hz, 1.5H), 1.06 (d, J=6.5 Hz, 6H). LC-MS: m/z 457.3 $(M+H)^+$.

(R)-5-(3-chlorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 218)

[0273] ^{1}H NMR (CHLOROFORM-d) δ 7.56-7.61 (m, 1H), 7.35-7.39 (m, 2H), 7.21-7.25 (m, 1H), 7.11-7.14 (m, 1H),

4.93 (br. s., 0.5H), 4.55 (d, J=11.8 Hz, 0.5H), 4.42 (d, J=12.5 Hz, 1H), 4.29-4.37 (m, 1H), 4.26 (br. s., 1H), 3.82 (d, J=13.6 Hz, 0.5H), 3.68-3.78 (m, 2H), 3.53-3.65 (m, 0.5H), 3.38 (s, 3H), 3.28-3.37 (m, 1H), 3.12-3.24 (m, 1H), 3.04-3.12 (m, 1H), 2.65-2.80 (m, 1H), 2.50-2.64 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.15 (d, J=6.5 Hz, 6H). LC-MS: m/z 441.2 $(M+H)^+$.

(R)-5-(3,4-dimethylphenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 220)

[0274] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.18 (d, J=7.5 Hz, 1H), 7.00 (s, 1H), 6.97 (dd, J=7.7, 1.6 Hz, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J=13.1 Hz, 0.5H), 4.32-4.42 (m, 1H), 4.29 (d, J=12.8 Hz, 1H), 3.78-3.85 (m, 0.5H), 3.71-3.77 (m, 2H), 3.53-3.64 (m, 0.5H), 3.38 (s, 3H), 3.24-3.35 (m, 1H), 3.17 (dt, J=13.3, 6.7 Hz, 2H), 3.01-3.12 (m, 1H), 2.65-2.80 (m, 1H), 2.53-2.63 (m, 1H), 2.31 (d, J=3.0 Hz, 6H), 1.40 (d, J=6.5 Hz, 1.5H), 1.31 (d, J=6.8 Hz, 1.5H), 1.14 (d, J=6.5 Hz, 6H). LC-MS: m/z 435.4 $(M+H)^+$.

(R)-5-(3-fluoro-4-methylphenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 221)

[0275] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.23 (t, J=8.0 Hz, 1H), 6.90-6.95 (m, 1H), 6.89 (dd, J=5.8, 1.3 Hz, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.21-4.45 (m, 3H), 3.81 (d, J=13.3 Hz, 0.5H), 3.70-3.77 (m, 2H), 3.52-3.63 (m, 0.5H), 3.38 (s, 3H), 3.26-3.37 (m, 1H), 3.10-3.18 (m, 2H), 2.65-2.80 (m, 1H), 2.53-2.63 (m, 1H), 2.33 (d, J=1.5 Hz, 3H), 1.40 (d, J=6.5 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.15 (d, J=6.8 Hz, 6H). LC-MS: m/z 439.4 $(M+H)^+$.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-phenylnicotinonitrile (Compound 222)

[0276] ^{1}H NMR (CHLOROFORM-d) δ 7.56-7.61 (m, 1H), 7.35-7.39 (m, 3H), 7.21-7.25 (m, 2H), 4.93 (br. s., 0.5H), 4.55 (d, J=11.8 Hz, 0.5H), 4.42 (d, J=12.5 Hz, 1H), 4.29-4.37 (m, 1H), 4.26 (br. s., 1H), 3.82 (d, J=13.6 Hz, 0.5H), 3.68-3.78 (m, 2H), 3.53-3.65 (m, 0.5H), 3.38 (s, 3H), 3.28-3.37 (m, 1H), 3.12-3.24 (m, 1H), 3.04-3.12 (m, 1H), 2.65-2.80 (m, 1H), 2.50-2.64 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.15 (d, J=6.5 Hz, 6H). LC-MS: m/z 407.4 $(M+H)^+$.

(R)-5-(3,4-dimethoxyphenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 223)

[0277] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 6.92 (d, J=8.3 Hz, 1H), 6.78 (dd, J=8.2, 1.9 Hz, 1H), 6.73 (d, J=2.0 Hz, 1H), 4.88-4.96 (m, 0.5H), 4.55 (d, J=13.1 Hz, 0.5H), 4.18-4.46 (m, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.78-3.86 (m, 0.5H), 3.71-3.78 (m, 2H), 3.52-3.64 (m, 0.5H), 3.38 (s, 3H), 3.31 (t, J=10.8 Hz, 1H), 3.10-3.22 (m, 2H), 2.65-2.80 (m, 1H), 2.52-2.64 (m, 1H), 1.33 (s, 1.5H), 1.28 (s, 1.5H), 1.16 (d, J=6.8 Hz, 6H). LC-MS: m/z 467.3 $(M+H)^+$.

(R)-5-(benzo[d][1,3]-dioxol-5-yl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 224)

[0278] ^{1}H NMR (CHLOROFORM-d) δ 7.57 (s, 1H), 6.83-6.90 (m, 1H), 6.64-6.73 (m, 2H), 6.02 (s, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.5 Hz, 0.5H), 4.20-4.43 (m, 3H), 3.81 (d, J=12.8 Hz, 0.5H), 3.74 (t, J=6.3 Hz, 2H), 3.53-3.64 (m, 0.5H), 3.38 (s, 3H), 3.25-3.36 (m, 1H), 3.10-3.22 (m, 2H), 2.64-2.80 (m, 1H), 2.52-2.64 (m, 1H), 1.40 (d, J=6.0 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.14 (d, J=6.8 Hz, 6H). LC-MS: m/z 451.3 $(M+H)^+$.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-(trifluoromethoxy)phenyl) nicotinonitrile (Compound 230)

[0279] ^{1}H NMR (CHLOROFORM-d) δ 7.58-7.63 (m, 1H), 7.42-7.51 (m, 1H), 7.22-7.26 (m, 1H), 7.18 (dd, J=7.8, 1.3 Hz, 1H), 7.11 (s, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J=11.8 Hz, 0.5H), 4.27-4.46 (m, 3H), 3.78-3.88 (m, 0.5H), 3.75 (t, J=6.4 Hz, 2H), 3.50-3.64 (m, 0.5H), 3.38 (s, 3H), 3.29-3.36 (m, 1H), 3.13-3.24 (m, 1H), 3.07 (dt, J=13.3, 6.7 Hz, 1H), 2.65-2.81 (m, 1H), 2.52-2.64 (m, 1H), 1.40 (d, J=6.3 Hz, 1.5H), 1.30 (d, J=6.3 Hz, 1.5H), 1.16 (d, J=6.5 Hz, 6H). LC-MS: m/z 491.3 $(M+H)^+$.

(R)-5-(3-fluorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 231)

[0280] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.39 (td, J=8.0, 6.1 Hz, 1H), 7.05-7.13 (m, 1H), 7.02 (d, J=7.8 Hz, 1H), 6.95 (dt, J=9.4, 2.1 Hz, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J=11.8 Hz, 0.5H), 4.26-4.45 (m, 3H), 3.82 (d, J=13.1 Hz, 0.5H), 3.75 (t, J=6.1 Hz, 2H), 3.51-3.64 (m, 0.5H), 3.38 (s, 3H), 3.27-3.35 (m, 1H), 3.16-3.23 (m, 1H), 3.09-3.14 (m, 1H), 2.65-2.81 (m, 1H), 2.60 (t, J=5.9 Hz, 1H), 1.40 (d, J=6.3 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.15 (d, J=6.8 Hz, 6H). LC-MS: m/z 443.3 $(M+H)^+$.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4-(trifluoromethoxy)phenyl) nicotinonitrile (Compound 232)

[0281] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.27 (s, 4H), 4.93 (br. s., 0.5H), 4.49-4.61 (m, 9.5H), 4.26-4.47 (m, 3H), 3.82 (d, J=13.6 Hz, 0.5H), 3.72-3.77 (m, 2H), 3.51-3.65 (m, 0.5H), 3.38 (s, 3H), 3.28-3.36 (m, 1H), 3.13-3.23 (m, 1H), 3.08 (dt, J=13.3, 6.7 Hz, 1H), 2.65-2.80 (m, 1H), 2.60 (t, J=5.9 Hz, 1H), 1.40 (d, J=6.0 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.16 (d, J=6.5 Hz, 6H). LC-MS: m/z 491.3 $(M+H)^+$.

(R)-5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 233)

[0282] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.27 (s, 4H), 4.93 (br. s., 0.5H), 4.49-4.61 (m, 0.5H), 4.26-4.47 (m, 3H), 3.82 (d, J=13.6 Hz, 0.5H), 3.72-3.77 (m, 2H), 3.51-3.65 (m, 0.5H), 3.38 (s, 3H), 3.28-3.36 (m, 1H), 3.13-3.23 (m, 1H), 3.08 (dt, J=13.3, 6.7 Hz, 1H), 2.65-2.80 (m, 1H), 2.60 (t, J=5.9 Hz, 1H), 1.40 (d, J=6.0 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.16 (d, J=6.5 Hz, 6H). LC-MS: m/z 465.3 $(M+H)^+$.

(R)-6-isopropyl-5-(isoquinolin-4-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 234)

[0283] ^{1}H NMR (CHLOROFORM-d) δ 9.33 (s, 1H), 8.37 (s, 1H), 8.06-8.16 (m, 1H), 7.64-7.69 (m, 2H), 7.45-7.50 (m, 2H), 4.96 (br. s., 0.5H), 4.58 (br. s., 0.5H), 4.31-4.54 (m, 3H), 3.86 (d, J=12.5 Hz, 0.5H), 3.76 (t, J=6.4 Hz, 2H), 3.56-3.67

(m, 0.5H), 3.42 (d, J=3.8 Hz, 1H), 3.36-3.40 (m, 3H), 3.08-3.33 (m, 1H), 2.65-2.78 (m, 2H), 2.54-2.64 (m, 1H), 1.44 (d, J=4.5 Hz, 1.5H), 1.35 (d, J=6.0 Hz, 1.5H), 1.05-1.11 (m, 6H). LC-MS: m/z 458.2 $(M+H)^+$.

(R)-6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 219)

[0284] ^{1}H NMR (CHLOROFORM-d) δ 7.57 (s, 1H), 7.31-7.39 (m, 2H), 7.27 (s, 1H), 7.10-7.18 (m, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.6 Hz, 0.5H), 4.07-4.33 (m, 3H), 3.77-3.84 (m, 0.5H), 3.71-3.76 (m, 2H), 3.48-3.60 (m, 0.5H), 3.36-3.41 (m, 3H), 3.25 (t, J=10.4 Hz, 1H), 3.06-3.18 (m, 1H), 2.63-2.79 (m, 1H), 2.51-2.62 (m, 1H), 1.95-2.07 (m, 1H), 1.38 (d, J=6.5 Hz, 1.5H), 1.28 (d, J=6.8 Hz, 1.5H), 1.12-1.18 (m, 2H), 0.91-0.97 (m, 2H). LC-MS: m/z 423.3 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-m-tolylnicotinonitrile (Compound 225)

[0285] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.30-7.36 (m, 1H), 7.14-7.22 (m, 3H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 3.80-4.36 (m, 3H), 3.80 (br. s., 0.5H), 3.74 (t, J=6.3 Hz, 2H), 3.50-3.61 (m, 0.5H), 3.37 (s, 3H), 3.19-3.29 (m, 1H), 3.07-3.17 (m, 1H), 2.63-2.80 (m, 1H), 2.53-2.62 (m, 1H), 2.41 (s, 3H), 2.03-2.13 (m, 1H), 1.39 (d, J=5.8 Hz, 1.5H), 1.29 (d, J=6.5 Hz, 1.5H), 1.11-1.17 (m, 2H), 0.89-0.97 (m, 2H). LC-MS: m/z 419.3 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4-(trifluoromethyl)phenyl) nicotinonitrile (Compound 226)

[0286] ^{1}H NMR (CHLOROFORM-d) δ 7.71 (d, J=8.0 Hz, 2H), 7.60 (s, 1H), 7.52 (d, J=8.0 Hz, 2H), 4.82-4.95 (m, 0.5H), 4.53 (d, J=12.8 Hz, 0.5H), 4.17-4.39 (m, 3H), 3.80 (d, J=13.6 Hz, 0.5H), 3.74 (t, J=6.3 Hz, 2H), 3.49-3.62 (m, 0.5H), 3.37 (s, 3H), 3.24-3.33 (m, 1H), 3.03-3.15 (m, 1H), 2.63-2.80 (m, 1H), 2.51-2.62 (m, 1H), 1.93-2.02 (m, 1H), 1.38 (d, J=6.5 Hz, 1.5H), 1.28 (d, J=3.5 Hz, 1.5H), 1.14-1.20 (m, 2H), 0.93-0.99 (m, 2H). LC-MS: m/z 473.3 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4-(trifluoromethoxy)phenyl)nicotinonitrile (Compound 227)

[0287] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.41-7.44 (m, 1H), 7.38-7.41 (m, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=11.5 Hz, 0.5H), 4.12-4.34 (m, 3H), 3.81 (br. s., 0.5H), 3.74 (t, J=6.3 Hz, 2H), 3.55 (t, J=11.4 Hz, 0.5H), 3.37 (s, 3H), 3.26 (br. s., 1H), 3.11 (br. s., 1H), 2.63-2.78 (m, 1H), 2.58 (d, J=5.8 Hz, 1H), 1.95-2.05 (m, 1H), 1.38 (d, J=5.8 Hz, 1.5H), 1.28 (d, J=5.8 Hz, 1.5H), 1.13-1.18 (m, 2H), 0.93-0.99 (m, 2H). LC-MS: m/z 489.2 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-(trifluoromethoxy)phenyl)-nicotinonitrile (Compound 228)

[0288] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.48 (t, J=7.9 Hz, 1H), 7.33 (d, J=7.8 Hz, 1H), 7.27 (br. s., 1H), 7.21-7.26 (m, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=12.8 Hz, 0.5H), 4.17-4.36 (m, 3H), 3.77-3.86 (m, 0.5H), 3.74 (t, J=6.1 Hz, 2H), 3.51-3.62 (m, 0.5H), 3.37 (s, 3H), 3.28 (t, J=8.9 Hz, 1H), 3.12 (d, J=10.8 Hz, 1H), 2.64-2.80 (m, 1H), 2.52-2.63 (m, 1H), 1.96-2.04 (m, 1H), 1.35-1.42 (m, 1.5H), 1.28 (d, J=5.5 Hz, 1.5H), 1.14-1.20 (m, 2H), 0.93-1.01 (m, 2H). LC-MS: m/z 489.2 $(M+H)^+$.

(R)-6-cyclopropyl-5-(3-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 229)

[0289] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.41 (td, J=7.8, 6.1 Hz, 1H), 7.14-7.19 (m, 1H), 7.04-7.13 (m, 2H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 4.12-4.34 (m, 3H), 3.77-3.85 (m, 0.5H), 3.74 (t, J=6.1 Hz, 2H), 3.48-3.61 (m, 0.5H), 3.37 (s, 3H), 3.26 (t, J=9.4 Hz, 1H), 3.06-3.16 (m, 1H), 2.64-2.79 (m, 1H), 2.51-2.62 (m, 1H), 1.99-2.08 (m, 1H), 1.38 (d, J=6.0 Hz, 1.5H), 1.28 (d, J=6.5 Hz, 1.5H), 1.12-1.19 (m, 2H), 0.93-0.99 (m, 2H). LC-MS: m/z 423.3 $(M+H)^+$.

(R)-6-cyclopropyl-5-(3-fluoro-4-methylphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 235)

[0290] ^{1}H NMR (CHLOROFORM-d) δ 7.57 (s, 1H), 7.21-7.26 (m, 1H), 7.06 (s, 1H), 7.01-7.05 (m, 1H), 4.89 (br. s., 0.5H), 4.52 (d, J=12.8 Hz, 0.5H), 4.11-4.33 (m, 3H), 3.80 (br. s., 0.5H), 3.74 (t, J=6.3 Hz, 2H), 3.49-3.60 (m, 0.5H), 3.36-3.41 (m, 3H), 3.25 (t, J=9.8 Hz, 1H), 3.03-3.15 (m, 1H), 2.63-2.79 (m, 1H), 2.51-2.61 (m, 1H), 2.32 (d, J=1.5 Hz, 3H), 2.01-2.09 (m, 1H), 1.38 (d, J=6.0 Hz, 1.5H), 1.26-1.30 (m, 1.5H), 1.12-1.17 (m, 2H), 0.92-0.97 (m, 2H). LC-MS: m/z 437.3 $(M+H)^+$.

(R)-6-cyclopropyl-5-(3-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 236)

[0291] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.32-7.38 (m, 1H), 6.94-6.99 (m, 1H), 6.87-6.94 (m, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.1 Hz, 0.5H), 4.18-4.26 (m, J=12.7 Hz, 3H), 3.84 (s, 3H), 3.81 (d, J=5.5 Hz, 0.5H), 3.74 (t, J=6.1 Hz, 2H), 3.55 (t, J=11.0 Hz, 0.5H), 3.37 (s, 3H), 3.25 (t, J=10.2 Hz, 1H), 3.03-3.15 (m, 1H), 2.63-2.79 (m, 1H), 2.51-2.62 (m, 1H), 2.05-2.15 (m, 1H), 1.39 (d, J=6.0 Hz, 1.5H), 1.29 (d, J=6.3 Hz, 1.5H), 1.11-1.18 (m, 2H), 0.91-0.96 (m, 2H). LC-MS: m/z 435.3 $(M+H)^+$.

(R)-6-cyclopropyl-5-(3,4-dimethoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 237)

[0292] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 6.92-6.95 (m, 2H), 6.88 (s, 1H), 4.89 (br. s., 0.5H), 4.53 (d, J=14.1 Hz, 0.5H), 4.16-4.30 (m, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.78-3.84 (m, 0.5H), 3.71-3.77 (m, 2H), 3.55 (br. s., 0.5H), 3.37 (s, 1H), 3.24 (br. s., 1H), 3.03-3.09 (m., 1H), 2.66-2.79 (m, 1H), 2.59 (br. s., 1H), 2.08-2.15 (m, 1.5H), 1.38 (br. s., 1.5H), 1.13-1.17 (m, 2H), 0.93 (dd, J=8.0, 3.3 Hz, 2H). LC-MS: m/z 465.1 $(M+H)^+$.

(R)-6-cyclopropyl-5-(isoquinolin-4-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 242)

[0293] ^{1}H NMR (DMSO-d_6) δ 7.47 (dd, J=5.0, 3.0 Hz, 1H), 7.17 (dd, J=2.8, 1.3 Hz, 1H), 7.00 (dd, J=5.0, 1.3 Hz, 1H), 4.91 (br. s., 0.5H), 4.55 (d, J=10.8 Hz, 0.5H), 3.98-4.27 (m, 3H), 3.75 (q, J=6.0 Hz, 2.5H), 3.53-3.63 (m, 0.5H), 3.40 (s,

3H), 3.11-3.25 (m, 1H), 2.94-3.06 (m, 1H), 2.69-2.81 (m, 1H), 2.67 (d, J=7.3 Hz, 1H), 2.25 (s, 3H), 1.71-1.78 (m, 1H), 1.42 (d, J=6.5 Hz, 1.5H), 1.32 (d, J=6.8 Hz, 1.5H), 1.06-1.08 (m, 2H), 0.83-0.88 (m, 2H). LC-MS: m/z 456.2 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(thiophen-3-yl)nicotinonitrile (Compound 246)

[0294] ^{1}H NMR (CHLOROFORM-d) δ 7.64 (s, 1H), 7.41 (dd, J=4.8, 3.0 Hz, 1H), 7.29 (dd, J=3.0, 1.3 Hz, 1H), 7.18 (dd, J=5.0, 1.3 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.6 Hz, 0.5H), 4.14-4.32 (m, 2.5H), 3.67-3.84 (m, 2.5H), 3.55 (br. s., 0.5H), 3.18-3.34 (m, 1H), 2.96-3.18 (m, 1.5H), 2.50-2.71 (m, 2H), 2.12-2.23 (m, 1H), 1.34-1.41 (m, 1.5H), 1.24-1.30 (m, 1.5H), 1.12-1.18 (m, 2H), 0.92-1.02 (m, 2H). LC-MS: m/z 411.3 $(M+H)^+$.

(R)-5-(benzo[b]thiophen-2-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 247)

[0295] ^{1}H NMR (CHLOROFORM-d) δ 7.82-7.87 (m, 1H), 7.78-7.82 (m, 1H), 7.77 (s, 1H), 7.33-7.42 (m, 2H), 7.32 (s, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=12.8 Hz, 0.5H), 4.24-4.39 (m, 3H), 3.70-3.80 (m, 2.5H), 3.35-3.41 (m, 3H), 3.29 (t, J=9.8 Hz, 1H), 3.03-3.20 (m, 1.5H), 2.63-2.78 (m, 1H), 2.52-2.63 (m, 1H), 2.34-2.44 (m, 1H), 1.37 (d, J=6.0 Hz, 1.5H), 1.23-1.29 (m, 1.5H), 1.15-1.21 (m, 2H), 0.95-1.06 (m, 2H). LC-MS: m/z 461.3 $(M+H)^+$.

(R)-5-(3-chloro-4-fluorophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 248)

[0296] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.45 (dd, J=6.9, 1.9 Hz, 1H), 7.22-7.28 (m, 2H), 4.92 (br. s., 0.5H), 4.54 (d, J=12.8 Hz, 0.5H), 4.16-4.37 (m, 3H), 3.70-3.81 (m, 2.5H), 3.50-3.64 (m, 0.5H), 3.37-3.42 (m, 3H), 3.28 (t, J=10.2 Hz, 1H), 3.12 (d, J=11.0 Hz, 1H), 2.65-2.87 (m, 1H), 2.55-2.65 (m, 1H), 1.94-2.05 (m, 1H), 1.39 (d, J=6.5 Hz, 1.5H), 1.28 (d, J=4.0 Hz, 1.5H), 1.14-1.21 (m, 2H), 0.94-1.03 (m, 2H). LC-MS: m/z 457.3 $(M+H)^+$.

(R)-6-cyclopropyl-5-(2-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 249)

[0297] ^{1}H NMR (CHLOROFORM-d) δ 7.62 (s, 1H), 7.37-7.45 (m, 1H), 7.30-7.36 (m, 1H), 7.22-7.27 (m, 1H), 7.19 (t, J=9.0 Hz, 1H), 4.92 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.19-4.37 (m, 3H), 3.78-3.86 (m, 0.5H), 3.70-3.78 (m, 2H), 3.51-3.61 (m, 0.5H), 3.39 (s, 3H), 3.27 (t, J=12.5 Hz, 1H), 3.02-3.16 (m, 1H), 2.65-2.82 (m, 1H), 2.54-2.64 (m, 1H), 1.83-1.90 (m, 1H), 1.41 (d, J=6.3 Hz, 1.5H), 1.30 (d, J=6.8 Hz, 1.5H), 1.12-1.19 (m, 2H), 0.92-0.98 (m, 2H). LC-MS: m/z 423.3 $(M+H)^+$.

(R)-6-cyclopropyl-5-(2,4-difluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 250)

[0298] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.26-7.35 (m, 1H), 6.91-7.04 (m, 2H), 4.92 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.18-4.37 (m, 3H), 3.78-3.85 (m, 0.5H), 3.71-3.78 (m, 2H), 3.51-3.62 (m, 0.5H), 3.39 (s, 3H), 3.23-3.33 (m, 1H), 3.14 (d, J=10.5 Hz, 1H), 2.65-2.80 (m, 1H), 2.53-2.63 (m, 1H), 1.77-1.85 (m, 1H), 1.40 (d, J=6.3 Hz, 1.5H), 1.30 (d, J=6.5 Hz, 1.5H), 1.11-1.19 (m, 2H), 0.96 (dd, J=7.8, 3.0 Hz, 2H). LC-MS: m/z 441.3 $(M+H)^+$.

(R)-2-cyclopropyl-6-methoxy-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,3'-bipyridine-5-carbonitrile (Compound 252)

[0299] ^{1}H NMR (CHLOROFORM-d) δ 8.18 (d, J=2.3 Hz, 1H), 7.60 (dd, J=8.5, 2.5 Hz, 1H), 7.56 (s, 1H), 6.83 (d, J=8.5 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 4.15-4.36 (m, 3H), 3.96-4.02 (m, 3H), 3.76-3.86 (m, 0.5H), 3.74 (t, J=6.3 Hz, 2H), 3.53-3.61 (m, 0.5H), 3.37 (s, 3H), 3.21-3.31 (m, 1H), 3.12 (d, J=11.3 Hz, 1H), 2.63-2.80 (m, 1H), 2.51-2.62 (m, 1H), 1.93-2.04 (m, 1H), 1.38 (d, J=6.0 Hz, 1.5H), 1.28 (d, J=6.3 Hz, 1.5H), 1.12-1.19 (m, 2H), 0.92-1.00 (m, 2H). LC-MS: m/z 436.2 $(M+H)^+$.

(R)-6-cyclopropyl-5-(1H-indol-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 253)

[0300] ^{1}H NMR (CHLOROFORM-d) δ 8.28 (br. s., 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.46 (d, J=8.3 Hz, 1H), 7.29 (t, J=2.8 Hz, 1H), 7.20 (dd, J=8.3, 1.8 Hz, 1H), 6.60 (t, J=2.1 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.12-4.33 (m, 3H), 3.81 (br. s., 0.5H), 3.75 (t, J=6.4 Hz, 2H), 3.51-3.63 (m, 0.5H), 3.38 (s, 3H), 3.22 (d, J=14.1 Hz, 1H), 3.01-3.17 (m, 1H), 2.66-2.81 (m, 1H), 2.62 (t, J=5.8 Hz, 1H), 2.11-2.21 (m, 1H), 1.41 (d, J=5.5 Hz, 1.5H), 1.31 (d, J=6.3 Hz, 1.5H), 1.11-1.17 (m, 2H), 0.87-0.94 (m, 2H). LC-MS: m/z 444.3 $(M+H)^+$.

(R)-6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 241)

[0301] ^{1}H NMR (CHLOROFORM-d) δ 7.17 (s, 2H), 7.16 (d, J=1.8 Hz, 2H), 4.90 (br. s., 0.51H), 4.53 (d, J=13.3 Hz, 0.5H), 4.03-4.22 (m, 3H), 3.79 (br. s., 0.5H), 3.74 (t, J=6.3 Hz, 2H), 3.52-3.63 (m, 0.5H), 3.38 (s, 3H), 3.16-3.25 (m, 1H), 2.92-3.08 (m, 1H), 2.64-2.79 (m, 1H), 2.51-2.63 (m, 1H), 2.18 (s, 3H), 1.56-1.63 (m, 1H), 1.41 (d, J=6.5 Hz, 1.5H), 1.31 (d, J=6.5 Hz, 1.5H), 1.03-1.09 (m, 2H), 0.79-0.84 (m, 2H). LC-MS: m/z 437.2 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-m-tolylnicotinonitrile (Compound 243)

[0302] ^{1}H NMR (DMSO-d_6) δ 7.36 (t, J=7.5 Hz, 1H), 7.22 (d, J=7.5 Hz, 1H), 6.97-7.04 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.3 Hz, 0.5H), 4.24 (br. s., 0.5H), 4.03-4.19 (m, 2H), 3.76 (s, 0.5H), 3.75 (s, 2H), 3.55-3.64 (m, 0.5H), 3.40 (s, 3H), 3.11-3.26 (m, 1H), 2.93-3.08 (m, 1H), 2.68-2.80 (m, 1H), 2.61 (d, J=11.0 Hz, 1H), 2.42 (s, 3H), 2.20 (s, 3H), 1.62-1.71 (m, 1H), 1.43 (d, J=6.5 Hz, 1.5H), 1.34 (d, J=6.0 Hz, 1.5H), 1.01-1.11 (m, 2H), 0.80-0.85 (m, 2H). LC-MS: m/z 433.3 $(M+H)^+$.

(R)-6-cyclopropyl-5-(3-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 251)

[0303] ^{1}H NMR (CHLOROFORM-d) δ 7.37 (t, J=7.8 Hz, 1H), 6.93 (dd, J=8.3, 2.5 Hz, 1H), 6.78 (d, J=7.5 Hz, 1H), 6.74 (s, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=12.8 Hz, 0.5H), 3.96-

4.21 (m, 3H), 3.83 (s, 3H), 3.71-3.77 (m, 2H), 3.52-3.63 (m, 1H), 3.37 (s, 3H), 3.09-3.25 (m, 1H), 2.89-3.04 (m, 1H), 2.63-2.79 (m, 1H), 2.59 (br. s., 1H), 2.16-2.29 (m, 3H), 1.63-1.72 (m, 1H), 1.41 (d, J=6.3 Hz, 1.5H), 1.29-1.33 (m, 1.5H), 1.06 (d, J=7.3 Hz, 2H), 0.78-0.84 (m, 2H). LC-MS: m/z 449.3 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(4-(trifluoromethoxy)-phenyl)nicotinonitrile (Compound 255)

[0304] ^{1}H NMR (CHLOROFORM-d) δ 7.31-7.36 (m, J=8.0 Hz, 2H), 7.23-7.28 (m, J=8.3 Hz, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=13.8 Hz, 0.5H), 4.01-4.22 (m, 2.5H), 3.69-3.85 (m, 2.5H), 3.53-3.67 (m, 0.5H), 3.36-3.43 (m, 3H), 3.12-3.28 (m, 1.5H), 2.94-3.12 (m, 1H), 2.66-2.83 (m, 1H), 2.61 (br. s., 1H), 2.16-2.22 (m, 3H), 1.54-1.65 (m, 1H), 1.39-1.46 (m, 1.5H), 1.32 (d, J=6.3 Hz, 1.5H), 1.03-1.12 (m, 2H), 0.80-0.89 (m, 2H). LC-MS: m/z 503.3 $(M+H)^+$.

6-cyclopropyl-5-(2,4-difluorophenyl)-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-nicotinonitrile (Compound 256)

[0305] ^{1}H NMR (CHLOROFORM-d) δ 7.16-7.25 (m, 1H), 6.93-7.07 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=13.3 Hz, 0.5H), 4.03-4.30 (m, 2.5H), 3.71-3.86 (m, 2.5H), 3.51-3.67 (m, 0.5H), 3.40 (s, 3H), 3.12-3.30 (m, 1.5H), 2.95-3.11 (m, 1H), 2.73 (td, J=15.3, 7.3 Hz, 1H), 2.54-2.64 (m, 1H), 2.18-2.25 (m, 3H), 1.53-1.61 (m, 1H), 1.39-1.47 (m, 1.5H), 1.32 (t, J=5.8 Hz, 1.5H), 1.03-1.17 (m, 2H), 0.82-0.93 (m, 2H). LC-MS: m/z 455.4 $(M+H)^+$.

(R)-6-cyclopropyl-5-(3-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 257)

[0306] ^{1}H NMR (CHLOROFORM-d) δ 7.41-7.51 (m, 1H), 7.12 (td, J=8.5, 2.5 Hz, 1H), 7.01 (d, J=7.5 Hz, 1H), 6.95 (d, J=9.0 Hz, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.04-4.22 (m, 2.5H), 3.72-3.84 (m, 2.5H), 3.53-3.67 (m, 0.5H), 3.40 (s, 3H), 3.12-3.29 (m, 1.5H), 2.93-3.11 (m, 1H), 2.66-2.83 (m, 1H), 2.61 (d, J=6.3 Hz, 1H), 2.16-2.25 (m, 3H), 1.57-1.64 (m, 1H), 1.43 (d, J=6.5 Hz, 1.5H), 1.33 (d, J=6.8 Hz, 1.5H), 1.08 (t, J=4.6 Hz, 2H), 0.80-0.91 (m, 2H). LC-MS: m/z 437.4 $(M+H)^+$.

(R)-6-cyclopropyl-5-(3-fluoro-4-methylphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 258)

[0307] ^{1}H NMR (CHLOROFORM-d) δ 7.23-7.33 (m, 2H), 6.89 (s, 1H), 6.87 (d, J=3.5 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.23 (br. s., 1H), 4.01-4.21 (m, 1.5H), 3.70-3.84 (m, 2.5H), 3.50-3.66 (m, 0.5H), 3.39 (s, 3H), 3.10-3.28 (m, 1.5H), 2.92-3.09 (m, 1H), 2.65-2.81 (m, 1H), 2.53-2.64 (m, 1H), 2.32-2.39 (m, 3H), 2.20 (s, 3H), 1.60-1.70 (m, 1H), 1.39-1.47 (m, 1.5H), 1.30-1.35 (m, 1.5H), 1.07 (t, J=4.6 Hz, 2H), 0.83 (dt, J=7.5, 3.5 Hz, 2H). LC-MS: m/z 451.4 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(napthalen-2-yl) nicotinonitrile (Compound 259)

[0308] ^{1}H NMR (DMSO-d_6) δ 7.96 (d, J=8.5 Hz, 1H), 7.91-7.95 (m, 1H), 7.88 (dd, J=6.1, 3.4 Hz, 1H), 7.71 (s, 1H), 7.53-7.59 (m, 2H), 7.34 (dd, J=8.4, 1.4 Hz, 1H), 4.94 (br. s., 0.5H), 4.57 (d, J=13.3 Hz, 0.5H), 4.05-4.32 (m, 3H), 3.83 (br. s., 0.5H), 3.77 (t, J=6.3 Hz, 2H), 3.56-3.67 (m, 0.5H), 3.41 (s, 3H), 3.17-3.29 (m, 1H), 2.96-3.12 (m, 1H), 2.67-2.83 (m, 1H), 2.55-2.65 (m, 1H), 2.23 (s, 3H), 1.63-1.71 (m, 1H), 1.45 (d, J=5.8 Hz, 1.5H), 1.35 (d, J=5.5 Hz, 1.5H), 1.05-1.14 (m, 2H), 0.77-0.83 (m, 2H). LC-MS: m/z 469.4 $(M+H)^+$.

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-3,4'-bipyridine-5-carbonitrile (Compound 260)

[0309] ^{1}H NMR (DMSO-d_6) δ 8.87 (br. s., 2H), 7.86 (br. s., 2H), 4.94 (br. s., 0.5H), 4.71 (s, 0.5H), 4.31-4.35 (s, 3H), 3.82 (br. s., 0.5H), 3.71-3.79 (m, 2H), 3.58 (br. s., 0.5H), 3.40 (s, 3H), 3.21 (br. s., 1H), 3.14 (br. s., 1H), 2.68 (br. s., 1H), 2.61 (br. s., 1H), 2.04 (br. s., 1H), 1.45 (d, J=5.8 Hz, 1.5H), 1.35 (d, J=5.5 Hz, 1.5H), 1.05-1.14 (m, 2H), 0.77-0.83 (m, 2H). LC-MS: m/z 420.5 $(M+H)^+$.

(R)-5-(benzo[d][1,3]dioxol-5-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 261)

[0310] ^{1}H NMR (DMSO-d_6) δ 6.91 (d, J=8.0 Hz, 1H), 6.62-6.71 (m, 2H), 6.03-6.10 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=13.6 Hz, 0.5H), 4.03-4.24 (m, 3H), 3.80 (br. s., 0.5H), 3.76 (t, J=6.1 Hz, 2H), 3.59 (t, J=11.7 Hz, 0.5H), 3.39 (s, 3H), 3.18-3.25 (m, 1H), 2.92-3.08 (m, 1H), 2.65-2.80 (m, 1H), 2.54-2.65 (m, 1H), 2.22 (s, 3H), 1.68-1.77 (m, 1H), 1.42 (d, J=6.5 Hz, 1.5H), 1.33 (d, J=6.5 Hz, 1.5H), 1.06 (t, J=5.3 Hz, 2H), 0.84 (t, J=6.1 Hz, 2H) LC-MS: m/z 463.3 $(M+H)^+$.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(thiophen-3-yl) nicotinonitrile (Compound 262)

[0311] ^{1}H NMR (DMSO-d_6) δ 7.47 (dd, J=5.0, 3.0 Hz, 1H), 7.17 (dd, J=2.8, 1.3 Hz, 1H), 7.00 (dd, J=5.0, 1.3 Hz, 1H), 4.91 (br. s., 0.5H), 4.55 (d, J=10.8 Hz, 0.5H), 3.98-4.27 (m, 3H), 3.75 (q, J=6.0 Hz, 2.5H), 3.53-3.63 (m, 0.5H), 3.40 (s, 3H), 3.11-3.25 (m, 1H), 2.94-3.06 (m, 1H), 2.69-2.81 (m, 1H), 2.67 (d, J=7.3 Hz, 1H), 2.25 (s, 3H), 1.71-1.78 (m, 1H), 1.42 (d, J=6.5 Hz, 1.5H), 1.32 (d, J=6.8 Hz, 1.5H), 1.06-1.08 (m, 2H), 0.83-0.88 (m, 2H). LC-MS: m/z 425.3 $(M+H)^+$.

Example 5

Preparation of (R)-5-benzyl-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 239)

[0312] A mixture of the bromide 7 from Example 1 (20 mg, 0.049 mmol) and $PdCl_2$(dppf) CH_2Cl_2 (4 mg, 0.005 mmol) in 1 mL of dry THF was stirred at room temperature for 5 min under nitrogen atmosphere. Benzyl zinc bromide (2 mL of 0.5M solution in THF, 0.098 mmol) was then added via a transfer needle, and the resulting reaction mixture was then refluxed for 4 h before the volatile was evaporated under reduced pressure. The black solid was applied to the top of a flash silica gel column, which was eluted with CH_2Cl_2 and then 8:1 CH_2Cl_2-EtOAc to obtain 5.1 mg of Compound 239 as a reddish solid. MS (ES) M+H expected 421.3, found 421.2. ^{1}H NMR (CHLOROFORM-d) δ 7.43 (s, 1H), 7.28-7.36 (m, 2H), 7.19-7.25 (m, 1H), 7.08 (d, J=7.0 Hz, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.6 Hz, 0.5H), 4.16-4.36 (m, 3H), 3.91 (s, 2H), 3.79 (br. s., 0.5H), 3.73 (t, J=6.5 Hz, 2H),

3.51-3.61 (m, 0.5H), 3.37 (s, 3H), 3.22-3.30 (m, 1H), 3.12-3.21 (m, 1H), 2.63-2.78 (m, 1H), 2.51-2.61 (m, 1H), 1.38 (d, J=5.8 Hz, 1.5H), 1.28-1.32 (m, 1.5H), 1.12 (d, J=6.5 Hz, 6H). Other Compounds of Formula II listed below, wherein R^{1b} is alkyl, —CH_2-aryl or —CH_2-heteroaryl; and R^2 is isopropyl or cyclopropyl were similarly prepared using any of intermediates 7 (Scheme 1), 17 (Scheme 2), or 28 (Scheme 3) as starting material.

(R)-5-benzyl-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 245)

[0313] ^{1}H NMR (CHLOROFORM-d) δ 7.29-7.35 (m, 2H), 7.24 (d, J=7.5 Hz, 1H), 7.09 (d, J=7.3 Hz, 2H), 4.91 (br. s., 0.5H), 4.54 (d, J=14.1 Hz, 0.5H), 4.22 (br. s., 0.5H), 4.16 (s, 2H), 4.09 (d, J=15.6 Hz, 1.5H), 3.97-4.05 (m, 1H), 3.69-3.82 (m, 2H), 3.53-3.63 (m, 1H), 3.36-3.42 (m, 3H), 3.15 (t, J=13.9 Hz, 1H), 2.90-3.05 (m, 1H), 2.66-2.81 (m, 1H), 2.54-2.63 (m, 1H), 2.40 (s, 3H), 2.04 (dd, J=8.0, 4.8 Hz, 1H), 1.42 (d, J=6.8 Hz, 1.5H), 1.35 (br. s., 1.5H), 1.07-1.15 (m, 2H), 0.90-0.92 (m, 2H). LC-MS: m/z 433.3 $(M+H)^+$.

Example 6

Preparation of (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(methyl(2-(methylamino)ethyl)amino)nicotinonitrile (Compound 238)

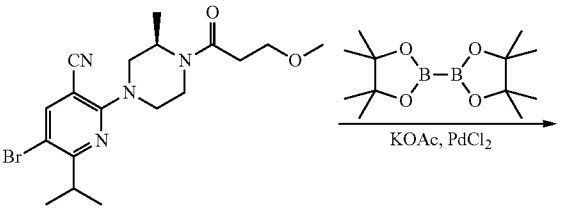
[0314] (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(methyl(2-(methylamino)ethyl)amino)nicotinonitrile (Compound 238) was prepared by mixing bromide 7 (30 mg, 0.074 mmol), CuI (0.7 mg, 0.004 mmol), K_2CO_3 (20 mg, 0.147 mmol), and N1, N2-dimethylethane-1,2-diamine (3.25 mg, 0.035 mmol) in a 5 mL microwave tube capped with a rubber septum. The tube was placed under vacuum and refilled with nitrogen three times. Piperidine (19 mg, 0.22 mmol) and DMSO (1 mL) were added to the tube and the rubber septum was quickly replaced with microwave tube cap. The reaction was heated in an oil bath at 120° C. overnight before it was cooled, diluted with EtOAc, and filtered through a pad of Celite. The EtOAc was removed on a rotary evaporator. Compound 238 was obtained in 10 mg of quantity via preparative TLC (DCM: MeOH/10:1) separation. MS (ES) M+H expected 417.3, found 417.5. ^{1}H NMR (CHLOROFORM-d) δ 7.56 (s, 1H), 4.91 (br. s., 0.5H), 4.53 (d, J=12.3 Hz, 6.5H), 4.02-4.31 (m, 3H), 3.67-3.83 (m, 3H), 3.47-3.64 (m, 2H), 3.34-3.41 (m, 3H), 3.16-3.30 (m, 1H), 2.93-3.13 (m, 4H), 2.74-2.84 (m, 2H), 2.61 (s, 3H), 2.53 (s, 3H), 1.39 (d, J=5.8 Hz, 1.5H), 1.30-1.34 (m, 1.5H), 1.17 (d, J=6.5 Hz, 6H).

Example 7

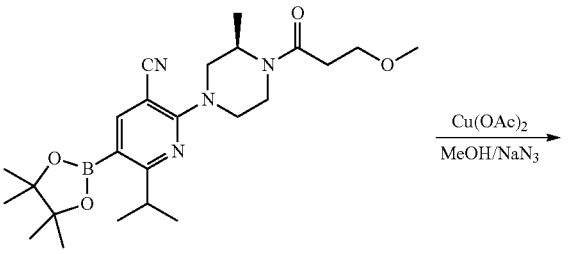
Preparation of (R)-5-amino-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[0315] (R)-5-amino-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile was prepared according to Scheme 4.

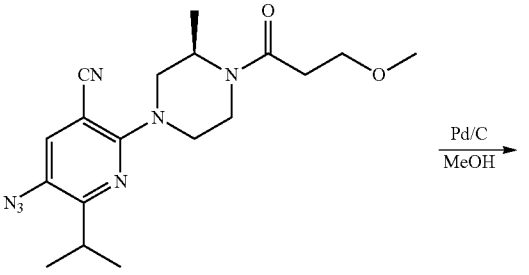
Scheme 4:



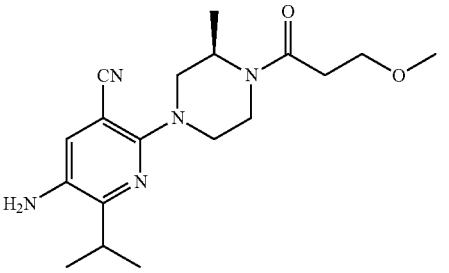
7



30



31



32

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (30)

[0316] To a solution of (R)-5-bromo-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

(7; 747 mg, 1.8 mmol) in DMF (8 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2, T-bi(1,3,2 dioxaborolane) (563 mg, 2.2 mmol) and KOAc (538 mg, 5.5 mmol). The resulting mixture was stirred at room temperature for 5 min before addition of $PdCl_2(dppf)$. CH_2Cl_2 (45 mg, 0.03 mmol). After flushing with nitrogen, the reaction mixture was heated at 85° C. for 18 hours. LC-MS analysis indicated starting material still present, the temperature was raised to 120° C. and stirred overnight. After cooling, the reaction mixture was diluted with water, and extracted with methylene chloride. The organic layer was then washed with brine, dried over anhy. Na_2SO_4, and concentrated in vacuo. Column chromatography (25% EtOAc/petroleum ether) afforded 334 mg of 30 as a white solid. MS (ES) M+H expected 457.3, found 457.4. ^1H NMR (CHLOROFORM-d) δ 8.16 (s, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=12.3 Hz, 0.5H), 4.19-4.39 (m, 3H), 3.76-3.85 (m, 0.5H), 3.73 (t, J=6.4 Hz, 2H), 3.50-3.61 (m, 0.5H), 3.37 (s, 3H), 3.25-3.35 (m, 1H), 3.02-3.20 (m, 1H), 2.63-2.80 (m, 1H), 2.51-2.61 (m, 1H), 1.45 (d, J=7.0 Hz, 1.5H), 1.35 (d, J=6.3 Hz, 1.5H), 1.34 (s, 12H), 1.19-1.21 (dd, J=6.8, 2.0 Hz, 3H), 1.23-1.25 (d, J=6.8 Hz, 3H).

(R)-5-azido-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (31)

[0317] To a solution of above boronate 30 (10 mg, 0.022 mmol) and $Cu(OAc)_2.H_2O$ (0.5 mg, 0.0025 mmol) in MeOH (0.2 mL) was added slowly NaN_3 (2.4 mg, 0.037 mmol) with stirring. After the addition, the reaction mixture was heated to 50° C. and stirred overnight. After cooling and dilution with water, the reaction mixture was extracted with methylene chloride. The organic layer was then washed with brine, dried over anhy. Na_2SO_4, and concentrated in vacuo. Column chromatography (25% ethyl acetate/petroleum ether) afforded 3.7 mg of 31 as a yellowish solid. MS (ES) M+H expected 372.2, found 372.3.

—(R)-5-amino-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (32)

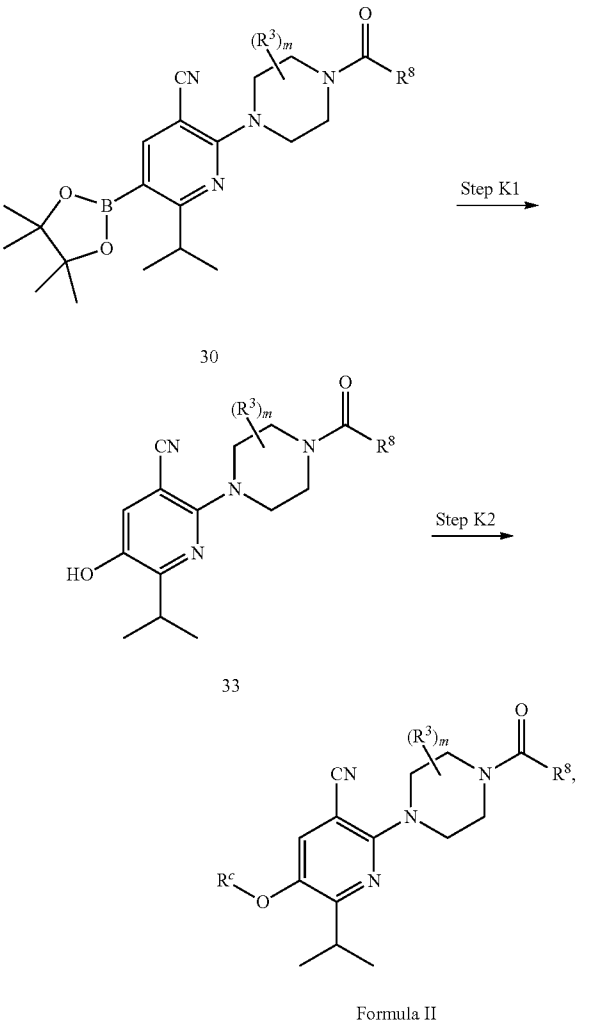
[0318] To a solution of above azide 31 (10 mg, 0.027 mmol) in 1 mL of MeOH was added 10% Pd/C (0.5 mg). The resulting mixture was purged with hydrogen and stirred at room temperature for 1 h under hydrogen atmosphere. After LC-MS analysis showed the formation of desired product, the reaction mixture was filtered, the filtrate was concentrated in vacuo. Column chromatography (25% EtOAc/petroleum ether) afforded 9 mg of 32 as a pink solid. MS (ES) M+H expected 346.2, found 346.1. ^1H NMR (CHLOROFORM-d) δ 7.25 (s, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.1 Hz, 0.5H), 4.20 (br. s., 1H), 3.95-4.07 (m, 1H), 3.93 (br. s., 1H), 3.75 (br. s., 0.5H), 3.73 (t, J=6.4 Hz, 2H), 3.52-3.63 (m, 0.5H), 3.37 (s, 3H), 3.02-3.21 (m, 2H), 2.88-3.02 (m, 1H), 2.62-2.78 (m, 1H), 2.59 (t, J=5.8 Hz, 1H), 1.41 (d, J=5.8 Hz, 1.5H), 1.31-1.32 (m, 1.5H), 1.26 (s, 6H).

Example 8

Preparation of (R)-5-(benzyloxy)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 254)

[0319] Compound 254 was prepared according to general Scheme 5, below:

Scheme 5:



wherein R^c is —CH_2-aryl or —CH_2-heteroaryl.

Step K-1: (R)-5-hydroxy-6-isopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile

[0320] To a solution of boronate 30 from Example 7 (30 mg, 0.066 mmol) in 15 mL of THF, at room temperature, was added aq. NaOH solution (2.86 g, 0.07 mmol). After stirring for 5 min, a solution of 30% of H_2O_2 (2.43 mg, 0.07 mmol) was added. The reaction mixture was allowed to stir at room temperature for additional 30 min before it was adjusted to neutral pH and concentrated in vacuo. Column chromatography (50% EtOAc/petroleum ether) afforded 21 mg of 33. MS

(ES) M+H expected 347.2, found 347.3. ^{1}H NMR (METHANOL-d_4) δ 7.26 (s, 1H), 4.82 (br. s., 0.5H), 4.47 (d, J=13.1 Hz, 0.5H), 4.39 (br. s., 0.5H), 3.95 (d, J=13.1 Hz, 0.5H), 3.79-3.92 (m, 2H), 3.55-3.74 (m, 3H), 3.36 (s, 3H), 3.10-3.23 (m, 1H), 2.95-3.10 (m, 1H), 2.81-2.93 (m, 1H), 2.71-2.81 (m, 1H), 2.59-2.69 (m, 1H), 1.45 (d, J=6.8 Hz, 1.5H), 1.36 (br. s., 1.5H), 1.23 (d, J=6.8 Hz, 6H).

Step K-2: (R)-5-(benzyloxy)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 254)

[0321] To a solution of (R)-5-hydroxy-6-isopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (33; 15 mg, 0.043 mmol) in 1 mL of THF was added 60% NaH (2.1 mg, 0.052 mmol) at 0° C. After stirring at room temperature for 30 min, benzyl bromide (8.9 mg, 0.052 mmol) was then added. The reaction mixture was stirred at 0° C. for 30 min and then at room temperature overnight. After the reaction mixture was concentrated, preparative TLC separation of the crude (50% ethyl acetate/petroleum ether) afforded 6.5 mg of Compound 254 as a yellowish solid. MS (ES) M+H expected 437.3, found 437.4. ^{1}H NMR (CHLOROFORM-d) δ 7.33-7.43 (m, 5H), 7.23 (s, 1H), 5.02 (s, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.3 Hz, 0.5H), 4.21 (br. s., 0.5H), 4.02-4.09 (m, 1H), 3.90-4.02 (m, 1H), 3.65-3.85 (m, 3H), 3.51-3.61 (m, 0.5H), 3.42-3.51 (m, 1H), 3.37 (s, 3H), 3.09-3.23 (m, 1H), 2.91-3.07 (m, 1H), 2.63-2.78 (m, 1H), 2.51-2.62 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.31 (d, J=6.5 Hz, 1.5H), 1.20 (d, J=6.8 Hz, 6H).

[0322] Other Compounds of Formula II listed below, wherein R^{1b} is —O—CH_2-aryl or —O—CH_2-heteroaryl; and R^2 is isopropyl or cyclopropyl were similarly prepared according to Scheme 5 by replacing (R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile 30 with alternate boronates prepared from any of intermediates 7 (Scheme 1), 17 (Scheme 2), or 28 (Scheme 3) using similar procedures set forth in Example 7 to prepare 30.

(R)-5-(benzyloxy)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 254)

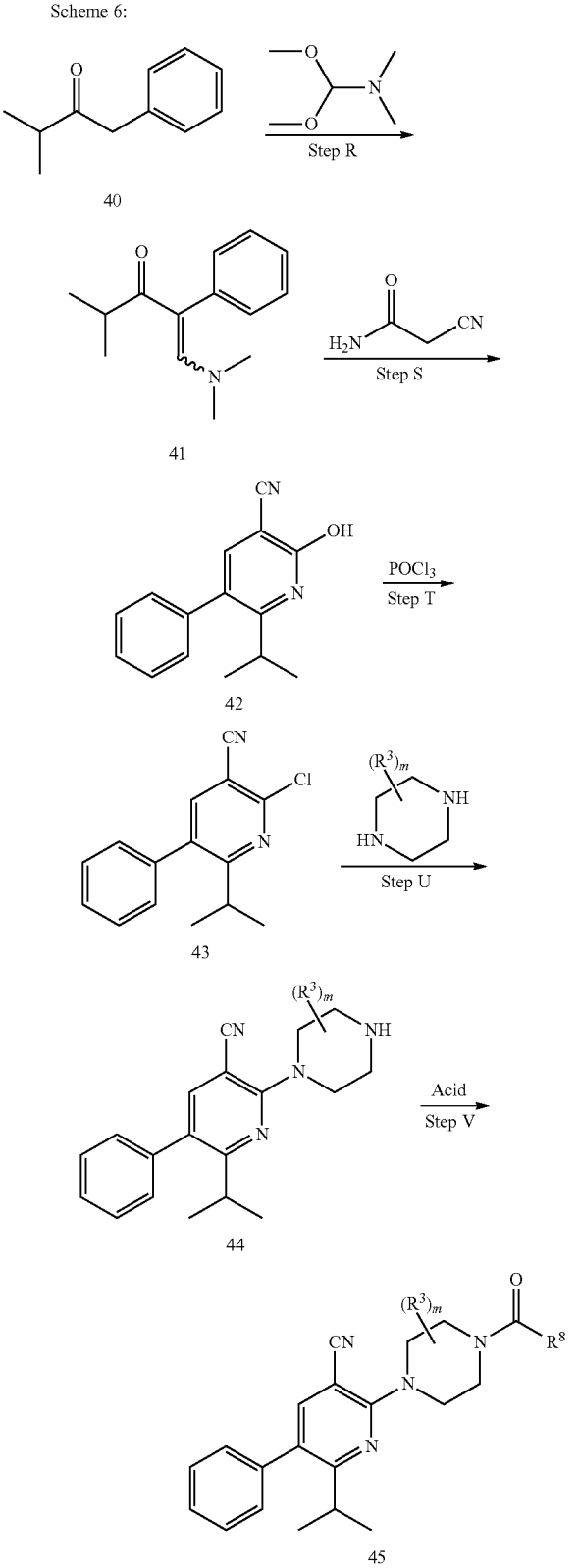
[0323] 1H NMR (CHLOROFORM-d) δ 7.33-7.43 (m, 5H), 7.23 (s, 1H), 5.02 (s, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.3 Hz, 0.5H), 4.21 (br. s., 0.5H), 4.02-4.09 (m, 1H), 3.90-4.02 (m, 1H), 3.65-3.85 (m, 3H), 3.51-3.61 (m, 0.5H), 3.42-3.51 (m, 1H), 3.37 (s, 3H), 3.09-3.23 (m, 1H), 2.91-3.07 (m, 1H), 2.63-2.78 (m, 1H), 2.51-2.62 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.31 (d, J=6.5 Hz, 1.5H), 1.20 (d, J=6.8 Hz, 6H). LC-MS: m/z 437.4 $(M+H)^+$.

Example 9

Preparation of (R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 164)

[0324] Compound 164 (45, wherein m is 1; R^3 is 3-methyl; and R^8 is 2-methylfuran-3-yl) was prepared according to the general scheme set forth below in general Scheme 6.

Scheme 6:



Step R: 1-(dimethylamino)-4-methyl-2-phenylpent-1-en-3-one (41)

[0325] To a solution of 3-methyl-1-phenylbutan-2-one (40; 3.38 g, 20 mmol) in 40 mL of anhydrous DMF was added 1,1-dimethoxy-N,N-dimethylmethanamine (5.958 g, 50 mmol). The resulting mixture was stirred at 100° C. overnight. After removal of DMF and excess of acetal, 4.3 g of 41 was obtained as a crude product and used in subsequent reaction without further purification. MS (ES) M+H expected 218.2, found 218.0.

Step S: 2-hydroxy-6-isopropyl-5-phenylnicotinonitrile (42)

[0326] To a 20 mL of anhydrous DMF solution containing 960 mg of sodium hydride (22 mmol, 60% dispersion in mineral oil) was added dropwise a solution of crude 1-(dimethylamino)-4-methyl-2-phenylpent-1-en-3-one (41; 4.3 g, 20 mmol DMF solution), cyano acetamide (1.72 g, 20 mmol), and 2 mL of MeOH in 35 mL of DMF. After the addition was completed, the resulting mixture was stirred at 80° C. overnight. After removal of DMF under reduced pressure, the residue was re-dissolved in methylene chloride and washed with water, and brine. The organic layer was then dried over anhy. Na_2SO_4 and concentrated in vacuo. Flash column chromatography (1:10 ethyl acetate/petroleum ether) afforded 3.84 g of 42 as a white solid. MS (ES) M+H expected 239.1, found 239.0. ^{1}H NMR (DMSO-d_6) δ 8.03 (s, 1H), 7.43-7.50 (m, 2H), 7.37-7.43 (m, 1H), 7.30-7.33 (m, 1H), 7.29 (s, 1H), 2.85-2.97 (m, 1H), 1.21 (s, 3H), 1.20 (s, 3H).

Step T. 2-chloro-6-isopropyl-5-phenylnicotinonitrile (43)

[0327] A mixture of 2-hydroxy-6-isopropyl-5-phenylnicotinonitrile (42; 2.3 g, 10 mmol), 5 mL of phosphoryl trichloride and one drop of DMF were heated to reflux overnight until LC-MS indicated the complete conversion to the product. After evaporation of excess of phosphoryl trichloride under reduced pressure, the residue was re-dissolved in methylene chloride and neutralized carefully with satd. aq. $NaHCO_3$ and washed subsequently with 1N HCl and brine. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Flash column chromatography (1:5 ethyl acetate/petroleum ether) afforded 2.4 g of 43 as a yellowish solid. MS (ES) M+H expected 257.1, found 257.0. ^{1}H NMR (CHLOROFORM-d) δ 7.76-7.82 (m, 1H), 7.43-7.54 (m, 3H), 7.28 (br. s., 1H), 7.22-7.26 (m, 1H), 3.20 (spt, J=6.7 Hz, 1H), 1.22 (s, 3H), 1.20 (s, 3H).

Step U: (R)-6-isopropyl-2-(3-methylpiperazin-1-yl)-5-phenylnicotinonitrile (44)

[0328] A mixture of above chloride 43 (192.5 mg, 0.75 mmol), (R)-2-methylpiperazine (187.8 mg, 1.875 mmol), and triethylamine (0.261 mL, 1.875 mmol) suspended in 2 mL of acetonitrile was subjected to microwave reaction at 175° C. for 45 min. After the reaction mixture was concentrated in vacuo, the residue was purified by flash column chromatography to give 184 mg of 44 as yellowish oil. MS (ES) M+H expected 321.2, found 321.1. ^{1}H NMR (CHLOROFORM-d) δ 7.56-7.66 (m, 1H), 7.34-7.51 (m, 3H), 7.19-7.28 (m, 2H), 4.31-4.59 (m, 2H), 3.11-3.27 (m, 3H), 3.01-3.11 (m, 2H), 2.84 (dd, J=12.8, 10.3 Hz, 1H), 1.22 (d, J=6.3 Hz, 3H), 1.15 (dd, J=6.7, 1.1 Hz, 6H).

Step V: (R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 164)

[0329] In a 5-mL of amber glass vial was placed (R)-6-isopropyl-2-(3-methylpiperazin-1-yl)-5-phenyl-nicotinonitrile (50 mg, 0.156 mmol), 2-methylfuran-3-carboxylic acid (39 mg, 0.312 mmol), EDCI (60 mg, 0.312 mmol), HOBt (42 mg, 0.312 mmol), triethylamine (40 mg, 0.312 mmol) and 2 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight. The mixture was quenched with 1 N HCl aqueous solution, extracted with EtOAc three times. The combined organic layer was washed with satd. $NaHCO_3$ and brine, dried over anhy. Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (EtOAc: petroleum ether/100:20) to afford 28 mg of the title compound as a white solid. MS (ES) M+H expected 429.2, found 429.1. ^{1}H NMR (METHANOL-d_4) δ 7.59-7.67 (m, 1H), 7.37-7.50 (m, 3H), 7.31 (d, J=2.0 Hz, 1H), 7.21-7.28 (m, 2H), 6.39 (d, J=2.0 Hz, 1H), 4.70 (br. s., 1H), 4.29-4.50 (m, 2H), 4.23 (br. s., 1H), 3.49 (br. s., 1H), 3.33 (dd, J=12.9, 3.1 Hz, 1H), 3.08-3.23 (m, 2H), 2.40-2.47 (m, 3H), 1.43 (d, J=6.8 Hz, 3H), 1.16 (dd, J=6.8, 2.8 Hz, 6H).

[0330] Other Compounds of Formula II listed below, wherein R^{1a} is hydrogen; R^{1b} is optionally substituted phenyl; were similarly prepared according to Scheme 6 by replacing one or more of: (1) methyl-1-phenylbutan-2-one (40) with an alternate phenyl ketone as starting material; (2) (R)-2-methylpiperazine with an alternate piperazine in Step U; and (3) 2-methylfuran-3-carboxylic acid with an alternate acid in Step V.

2-(4-(furan-2-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 109)

[0331] ^{1}H NMR (CHLOROFORM-d) δ 7.65 (s, 1H), 7.53-7.58 (m, 1H), 7.38-7.49 (m, 3H), 7.24-7.28 (m, 2H), 7.10 (d, J=3.3 Hz, 1H), 6.54 (dd, J=3.3, 1.8 Hz, 1H), 4.03 (br. s., 4H), 3.89 (dd, J=6.4, 3.6 Hz, 4H), 3.17 (dt, J=13.4, 6.7 Hz, 1H), 1.18 (d, J=6.5 Hz, 6H). LC-MS: m/z 401.1 $(M+H)^+$.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 119)

[0332] ^{1}H NMR (CHLOROFORM-d) δ 7.62-7.69 (m, 1H), 7.54 (d, J=0.8 Hz, 1H), 7.40-7.47 (m, 3H), 7.23-7.28 (m, 2H), 7.08 (d, J=3.5 Hz, 1H), 6.53 (dd, J=3.5, 1.8 Hz, 1H), 4.93 (br. s., 1H), 4.54 (d, J=12.8 Hz, 1H), 4.45 (d, J=12.3 Hz, 1H), 4.37 (d, J=13.3 Hz, 1H), 3.58 (br. s., 1H), 3.44 (dd, J=13.3, 3.8 Hz, 1H), 3.27 (td, J=12.4, 3.4 Hz, 1H), 3.16 (dt, J=13.3, 6.7 Hz, 1H), 1.50 (d, J=6.8 Hz, 3H), 1.17 (dd, J=6.7, 1.9 Hz, 6H). LC-MS: m/z 414.9 $(M+H)^+$.

2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 120)

[0333] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.64 (s, 1H), 7.40-7.51 (m, 4H), 7.24-7.28 (m, 2H), 6.61 (d, J=1.3 Hz, 1H), 4.76 (br. s., 1H), 4.33-4.52 (m, 3H), 3.51 (s, 1H), 3.35 (dd, J=13.2, 3.1 Hz, 1H), 3.12-3.22 (m, 2H), 1.47 (d, J=6.8 Hz, 3H), 1.17 (dd, J=6.5, 2.0 Hz, 6H). LC-MS: m/z 414.9 $(M+H)^+$.

2-(4-(furan-3-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 124)

[0334] ^{1}H NMR (CHLOROFORM-d) δ 7.76-7.81 (m, 1H), 7.65 (s, 1H), 7.36-7.51 (m, 4H), 7.23-7.28 (m, 2H), 6.62 (dd,

J=1.9, 0.9 Hz, 1H), 3.91 (br. s., 4H), 3.84 (br. s., 4H), 3.17 (dt, J=13.4, 6.6 Hz, 1H), 1.17 (d, J=6.8 Hz, 6H). LC-MS: m/z 401.1 $(M+H)^+$.

2-(4-(1H-indole-3-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 125)

[0335] ^{1}H NMR (CHLOROFORM-d) δ 8.97 (br. s., 1H), 7.74-7.81 (m, 1H), 7.64 (s, 1H), 7.53 (br. s., 1H), 7.38-7.50 (m, 4H), 7.28-7.31 (m, 1H), 7.24-7.28 (m, 3H), 3.94 (br. s., 4H), 3.85 (br. s., 4H), 3.16 (dt, J=13.2, 6.6 Hz, 1H), 1.17 (d, J=6.5 Hz, 6H). LC-MS: m/z 450.2 $(M+H)^+$.

6-isopropyl-5-phenyl-2-(4-(2-phenylacetyl)piperazin-1-yl)nicotinonitrile (Compound 126)

[0336] ^{1}H NMR (CHLOROFORM-d) δ 7.62 (s, 1H), 7.41-7.47 (m, 3H), 7.38-7.41 (m, 1H), 7.37 (s, 1H), 7.34-7.36 (m, 1H), 7.32 (s, 1H), 7.30 (s, 1H), 7.25 (d, J=1.5 Hz, 1H), 7.24 (s, 1H), 3.84-3.89 (m, 2H), 3.83 (s, 2H), 3.73-3.78 (m, 2H), 3.64-3.68 (m, 2H), 3.58-3.63 (m, 2H), 3.15 (dt, J=13.3, 6.7 Hz, 1H), 1.15 (d, J=6.5 Hz, 6H). LC-MS: m/z 425.1 $(M+H)^+$.

6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 139)

[0337] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.37-7.51 (m, 4H), 7.33-7.37 (m, 2H), 7.29-7.33 (m, 2H), 7.22-7.27 (m, 2H), 4.62 (d, J=13.6 Hz, 0.5H), 4.42 (d, J=12.5 Hz, 0.5H), 4.19-4.35 (m, 2H), 3.81 (br. s., 1H), 3.76 (d, J=13.1 Hz, 0.5H), 3.49 (t, J=12.0 Hz, 0.5H), 2.91-3.29 (m, 3H), 1.31 (br. s., 3H), 1.15 (d, J=6.8 Hz, 6H). LC-MS: m/z 439.2 $(M+H)^+$.

2-((3S,5R)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 140)

[0338] ^{1}H NMR (CHLOROFORM-d) δ 7.61-7.64 (m, 1H), 7.41-7.48 (m, 3H), 7.38-7.41 (m, 1H), 7.37 (s, 1H), 7.34-7.36 (m, 1H), 7.32 (s, 1H), 7.30 (s, 1H), 7.27 (d, J=1.8 Hz, 1H), 7.23-7.26 (m, 1H), 4.90 (br. s., 1H), 4.46 (br. s., 2H), 4.20 (br. s., 1H), 3.82 (s, 2H), 3.12-3.22 (m, 2H), 3.11 (br. s., 1H), 1.43 (d, J=7.0 Hz, 6H), 1.16 (d, J=6.8 Hz, 6H). LC-MS: m/z 453.1 $(M+H)^+$.

2-((3S,5R)-4-(furan-3-carbonyl)-3,5-dimethylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 141)

[0339] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (dd, J=1.5, 0.8 Hz, 1H), 7.65 (s, 1H), 7.47-7.49 (m, 1H), 7.45-7.47 (m, 1H), 7.44 (s, 1H), 7.40-7.43 (m, 1H), 7.24-7.28 (m, 2H), 6.65 (dd, J=1.9, 0.9 Hz, 1H), 4.71 (br. s., 2H), 4.47 (s, 1H), 4.50 (s, 1H), 3.27 (dd, J=12.9, 4.1 Hz, 2H), 3.18 (dt, J=13.3, 6.7 Hz, 1H), 1.55 (d, J=7.0 Hz, 6H), 1.18 (d, J=6.5 Hz, 6H). LC-MS: m/z 429.2 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 143)

[0340] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.39-7.47 (m, 3H), 7.34-7.39 (m, 2H), 7.29-7.33 (m, 2H), 7.22-7.28 (m, 3H), 4.98 (br. s., 0.5H), 4.62 (d, J=13.8 Hz, 0.5H), 4.42 (d, J=12.0 Hz, 0.5H), 4.15-4.35 (m, 2H), 3.81 (br. s., 2H), 3.72-3.79 (m, 0.5H), 3.49 (t, J=11.3 Hz, 0.5H), 3.29 (d, J=10.0 Hz, 0.5H), 3.04-3.21 (m, 2.5H), 2.88-3.01 (m, 0.5H), 1.27-1.34 (m, 3H), 1.15 (d, J=6.5 Hz, 6H). LC-MS: m/z 439.2 $(M+H)^+$.

(S)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 144)

[0341] ^{1}H NMR (CHLOROFORM-d) δ 7.74-7.80 (m, 1H), 7.64 (s, 1H), 7.36-7.52 (m, 4H), 7.27 (dd, J=7.9, 6.4 Hz, 2H), 6.59-6.64 (m, 1H), 4.76 (br. s., 1H), 4.20-4.50 (m, 3H), 3.51 (br. s., 1H), 3.35 (dd, J=13.3, 3.3 Hz, 1H), 3.06-3.24 (m, 2H), 1.47 (d, J=6.8 Hz, 3H), 1.17 (dd, J=6.5, 2.0 Hz, 6H). LC-MS: m/z 415.2 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 145)

[0342] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.29-7.47 (m, 7H), 7.22-7.28 (m, 3H), 4.98 (br. s., 0.5H), 4.62 (d, J=13.6 Hz, 0.5H), 4.42 (d, J=12.8 Hz, 0.5H), 4.15-4.37 (m, 2H), 3.80-3.85 (m, 2H), 3.76 (d, J=12.8 Hz, 0.5H), 3.49 (t, J=11.2 Hz, 0.5H), 3.25-3.37 (m, 0.5H), 3.02-3.23 (m, 2.5H), 2.88-3.01 (m, 0.5H), 1.26-1.35 (m, 3H), 1.15 (d, J=6.8 Hz, 6H). LC-MS: m/z 439.2 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 150)

[0343] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (dd, J=1.5, 1.0 Hz, 1H), 7.63-7.66 (m, 1H), 7.38-7.50 (m, 4H), 7.23-7.28 (m, 2H), 6.61 (dd, J=1.8, 0.8 Hz, 1H), 4.76 (br. s., 1H), 4.30-4.51 (m, 3H), 3.52 (br. s., 1H), 3.35 (dd, J=13.2, 3.6 Hz, 1H), 3.06-3.24 (m, 2H), 1.47 (d, J=6.8 Hz, 3H), 1.17 (dd, J=6.8, 2.0 Hz, 6H). LC-MS: m/z 415.1 $(M+H)^+$.

2-(4-(furan-3-carbonyl)-3-phenylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 153)

[0344] ^{1}H NMR (CHLOROFORM-d) δ 7.59-7.74 (m, 1H), 7.56 (s, 1H), 7.33-7.50 (m, 8H), 7.29 (d, J=7.3 Hz, 1H), 7.17-7.25 (m, 2H), 6.54 (br. s., 1H), 5.74 (br. s., 1H), 4.79 (br. s., 1H), 4.51 (br. s., 1H), 4.33 (d, J=9.5 Hz, 1H), 3.95 (d, J=11.5 Hz, 1H), 3.58 (br. s., 2H), 3.12 (spt, J=6.6 Hz, 1H), 1.08-1.18 (m, 6H). LC-MS: m/z 477.1 $(M+H)^+$.

2-(4-(furan-3-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 159)

[0345] ^{1}H NMR (CHLOROFORM-d) δ 7.72 (br. s., 1H), 7.48-7.60 (m, 5H), 7.46 (br. s., 3H), 7.40 (br. s., 2H), 7.27 (br. s., 1H), 7.20 (d, J=6.8 Hz, 1H), 6.77 (s, 1H), 6.59 (s, 1H), 5.14-5.37 (m, 1H), 4.25 (br. s., 2H), 3.87 (br. s., 3H), 3.64 (br. s., 1H), 2.81-2.95 (m, 1H), 1.16 (d, J=6.5 Hz, 3H), 1.06 (d, J=6.3 Hz, 3H). LC-MS: m/z 477.2 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 165)

[0346] ^{1}H NMR (METHANOL-d_4) δ 7.62 (s, 1H), 7.35-7.57 (m, 3H), 7.21-7.28 (m, 3H), 6.87-7.11 (m, 2H), 4.60 (d, J=13.3 Hz, 1H), 4.29-4.37 (m, 2H), 3.98 (s, 2H), 3.59 (t, J=11.4 Hz, 1H), 3.04-3.27 (m, 4H), 1.36 (dd, J=15.2, 5.9 Hz, 3H), 1.16 (d, J=6.5 Hz, 6H). LC-MS: m/z 445.0 $(M+H)^+$.

2-(4-(furan-2-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 166)

[0347] ^{1}H NMR (CHLOROFORM-d) δ 7.54-7.56 (m, 2H), 7.52 (br. s., 3H), 7.43 (br. s., 2H), 7.24-7.30 (m, 3H), 7.20 (d, J=7.3 Hz, 1H), 7.08 (d, J=3.3 Hz, 1H), 6.77 (s, 1H), 6.52 (br. s., 1H), 5.31-5.37 (br. s., 1H), 4.40 (br. s., 1H), 4.32 (br. s., 1H), 3.85-4.03 (m, 2H), 3.79 (d, J=13.1 Hz, 1H), 3.68 (d, J=4.8 Hz, 1H), 2.87 (dt, J=13.4, 6.8 Hz, 1H), 1.15 (d, J=6.8 Hz, 3H), 1.06 (d, J=6.5 Hz, 3H). LC-MS: m/z 477.2 $(M+H)^+$.

2-(4-(1H-indole-3-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 168)

[0348] ^{1}H NMR (CHLOROFORM-d) δ 9.09 (br. s., 1H), 7.76 (br. s., 1H), 7.51 (s, 2H), 7.55 (s, 3H), 7.39 (br. s., 3H), 7.29 (s, 2H), 7.33 (s, 1H), 7.24 (br. s., 3H), 6.77 (br. s., 1H), 5.29 (br. s., 1H), 4.30 (d, J=11.5 Hz, 1H), 4.18 (br. s., 1H), 3.93 (br. s., 3H), 3.64 (br. s., 1H), 2.89 (br. s., 1H), 1.16 (d, J=5.8 Hz, 3H), 1.07 (d, J=5.8 Hz, 3H). LC-MS: m/z 526.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-isopropylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 170)

[0349] ^{1}H NMR (CHLOROFORM-d) δ 7.74 (br. s., 1H), 7.61 (s, 1H), 7.47 (t, J=1.6 Hz, 1H), 7.35-7.46 (m, 3H), 7.20-7.26 (m, 2H), 6.58 (s, 1H), 4.79 (d, J=12.8 Hz, 1H), 4.54-4.68 (br. s., 1H), 4.45 (br. s., 1H), 3.8-4.07 (m, 1H), 3.56-3.74 (m, 1H), 3.19 (br. s., 1H), 3.06-3.18 (m, 3H), 1.52-1.59 (m, 3H), 1.40-1.48 (m, 3H), 1.17 (d, J=6.8 Hz, 3H), 1.13 (d, J=6.8 Hz, 3H). LC-MS: m/z 443.1 $(M+H)^+$.

(R)-2-(3-ethyl-4-(furan-3-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 171)

[0350] ^{1}H NMR (CHLOROFORM-d) δ 7.74 (s, 1H), 7.58-7.65 (m, 1H), 7.35-7.50 (m, 4H), 7.20-7.26 (m, 2H), 6.58 (dd, J=1.8, 0.8 Hz, 1H), 5.02 (s, 1H), 4.69 (br. s., 1H), 4.50 (d, J=13.1 Hz, 1H), 4.41 (d, J=12.3 Hz, 1H), 4.23-4.31 (br. s., 1H), 3.46-3.86 (m, 2H), 3.27 (dd, J=13.3, 3.3 Hz, 1H), 3.10-3.21 (m, 2H), 1.79-1.96 (m, 2H), 1.54 (d, J=6.5 Hz, 1.5H), 1.45 (d, J=6.5 Hz, 1.5H), 1.15 (dd, J=6.8, 3.5 Hz, 6H). LC-MS: m/z 429.1 $(M+H)^+$.

(R)-2-(3-ethyl-4-(furan-2-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 172)

[0351] ^{1}H NMR (CHLOROFORM-d) δ 7.59-7.64 (m, 1H), 7.51 (dd, J=1.8, 0.8 Hz, 1H), 7.36-7.46 (m, 3H), 7.21-7.26 (m, 2H), 7.02-7.10 (m, 1H), 6.51 (dd, J=3.5, 1.8 Hz, 1H), 4.71 (br. s., 1H), 4.38-4.60 (m, 3H), 3.50 (br. s., 1H), 3.35 (dd, J=13.3, 3.5 Hz, 1H), 3.22 (td, J=12.5, 3.4 Hz, 1H), 3.08-3.18 (m, 1H), 1.90-2.06 (m, 1H), 1.83 (dquin, J=14.2, 7.2 Hz, 1H), 1.15 (dd, J=6.7, 3.1 Hz, 6H), 0.97 (t, J=7.4 Hz, 3H). LC-MS: m/z 429.1 $(M+H)^+$.

(R)-2-(3-ethyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 173)

[0352] ^{1}H NMR (CHLOROFORM-d) δ 7.58-7.66 (m, 1H), 7.35-7.47 (m, 3H), 7.29 (d, J=2.0 Hz, 1H), 7.21-7.26 (m, 2H), 6.32-6.41 (m, 1H), 4.59-4.80 (m, 1H), 4.50 (d, J=13.1 Hz, 1H), 4.42 (br. s., 1H), 3.91-3.97 (br. s., 1H), 3.45-3.65 (m, 1H), 3.27 (dd, J=13.1, 3.3 Hz, 1H), 3.05-3.19 (m, 2H), 2.41 (s, 3H), 1.86-1.95 (m, 1H), 1.79 (dt, J=14.1, 7.0 Hz, 1H), 1.15 (dd, J=6.8, 2.0 Hz, 6H), 0.87-0.99 (m, 3H). LC-MS: m/z 443.1 $(M+H)^+$.

(R)-2-(3-ethyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 174)

[0353] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.35-7.49 (m, 3H), 7.17-7.25 (m, 3H), 6.92-6.99 (m, 2H), 4.75 (br. s., 0.5H), 4.59-4.71 (m, 0.5H), 4.30-4.50 (m, 2H), 3.79-4.07 (m, 3H), 3.46-3.56 (m, 0.5H), 3.17-3.30 (m, 0.5H), 2.97-3.17 (m, 3H), 1.78-1.89 (m, 1H), 1.69-1.78 (m, 1H), 1.10-1.16 (m, 6H), 0.90-0.97 (m, 3H). LC-MS: m/z 459.1 $(M+H)^+$.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-5,6-diphenylnicotinonitrile (Compound 117)

[0354] Compound 117 was synthesized was synthesized was synthesized using 1,2-diphenylethanone as starting material.

[0355] ^{1}H NMR (CHLOROFORM-d) δ 7.87 (s, 1H), 7.53 (dd, J=1.5, 0.8 Hz, 1H), 7.37-7.44 (m, 2H), 7.27-7.35 (m, 6H), 7.12-7.19 (m, 2H), 7.06-7.12 (m, 1H), 6.53 (dd, J=3.4, 1.9 Hz, 1H), 4.94 (br. s., 1H), 4.53 (t, J=11.7 Hz, 2H), 4.36-4.46 (m, 1H), 3.62 (br. s., 1H), 3.44-3.54 (m, 1H), 3.26-3.37 (m, 1H), 1.52 (d, J=6.5 Hz, 3H). LC-MS: m/z 448.9 $(M+H)^+$.

2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-5,6-diphenylnicotinonitrile (Compound 118)

[0356] Compound 118 was synthesized using 1,2-diphenylethanone as starting material.

[0357] ^{1}H NMR (CHLOROFORM-d) δ 7.88 (s, 1H), 7.77 (s, 1H), 7.48 (s, 1H), 7.38 (d, J=8.0 Hz, 2H), 7.27-7.33 (m, 6H), 7.13-7.16 (m, 2H), 6.61 (s, 1H), 4.71-4.79 (br. s., 1H), 4.47-4.50 (s, 1H), 4.38 (s, 1H), 4.41 (s, 1H), 3.48-3.64 (m, 1H), 3.38-3.42 (m, 1H), 3.21 (td, J=12.4, 3.0 Hz, 1H), 1.49 (d, J=6.5 Hz, 3H). LC-MS: m/z 448.9 $(M+H)^+$.

2-(4-(furan-3-carbonyl)piperazin-1-yl)-5,6-diphenylnicotinonitrile (Compound 122)

[0358] Compound 122 was synthesized using 1,2-diphenylethanone as starting material.

[0359] ^{1}H NMR (CHLOROFORM-d) δ 7.88 (s, 1H), 7.78 (s, 1H), 7.47-7.51 (m, 1H), 7.37-7.42 (m, 2H), 7.27-7.35 (m, 6H), 7.15 (dd, J=6.5, 3.0 Hz, 2H), 6.62 (s, 1H), 3.92 (br. s., 4H), 3.89 (br. s., 4H). LC-MS: m/z 435.1 $(M+H)^+$.

5,6-diphenyl-2-(4-(2-phenylacetyl)piperazin-1-yl) nicotinonitrile (Compound 123)

[0360] Compound 123 was synthesized using 1,2-diphenylethanone as starting material. ^{1}H NMR (CHLOROFORM-d) δ 7.85 (s, 1H), 7.34-7.39 (m, 4H), 7.28-7.33 (m, 8H), 7.22-7.26 (m, 1H), 7.13 (dd, J=6.5, 3.0 Hz, 2H), 3.85-3.91 (m, 2H), 3.79-3.84 (m, 4H), 3.66 (s, 4H). LC-MS: m/z 459.1 $(M+H)^+$.

(R)-5-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 161)

[0361] Compound 161 was synthesized using 1-(3-fluorophenyl)-3-methylbutan-2-one as starting material.

[0362] ^{1}H NMR (CHLOROFORM-d) δ 7.73-7.79 (m, 1H), 7.61 (s, 1H), 7.47 (t, J=1.6 Hz, 1H), 7.35-7.44 (m, 1H),

7.06-7.13 (m, 1H), 7.00-7.04 (m, 1H), 6.96 (dt, J=9.3, 2.1 Hz, 1H), 6.54-6.63 (m, 1H), 4.61-4.90 (m, 1H), 4.41 (s, 0.5H), 4.44 (s, 0.5H), 4.19-4.39 (m, 2H), 3.42-3.49 (br. s., 1H), 3.34 (dd, J=13.2, 3.1 Hz, 1H), 3.14-3.23 (m, 1H), 3.06-3.14 (m, 1H), 1.44 (d, J=6.8 Hz, 3H), 1.15 (dd, J=6.8, 1.8 Hz, 6H). LC-MS: m/z 433.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(2-methoxyphenyl)nicotinonitrile (Compound 175)

[0363] Compound 175 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

[0364] ^{1}H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.56 (s, 1H), 7.46 (t, J=1.5 Hz, 1H), 7.34-7.41 (m, 1H), 7.06-7.12 (m, 1H), 7.01 (t, J=7.3 Hz, 1H), 6.96 (d, J=8.3 Hz, 1H), 6.55-6.62 (m, 1H), 4.74 (br. s., 1H), 4.18-4.46 (m, 3H), 3.77 (s, 3H), 3.49 (br. s., 1H), 3.31 (dd, J=13.2, 3.1 Hz, 1H), 3.14 (td, J=12.5, 3.0 Hz, 1H), 2.86 (quin, J=6.7 Hz, 1H), 1.46 (d, J=6.8 Hz, 3H), 1.15 (br. s., 3H), 1.04 (br. s., 3H). LC-MS: m/z 445.2 $(M+H)^+$.

(R)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(2-methoxyphenyl)nicotinonitrile (Compound 176)

[0365] Compound 176 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

[0366] ^{1}H NMR (CHLOROFORM-d) δ 7.56 (s, 1H), 7.50-7.53 (m, 1H), 7.34-7.41 (m, 1H), 7.07-7.13 (m, 1H), 7.03-7.06 (m, 1H), 6.99-7.02 (m, 1H), 6.96 (d, J=8.3 Hz, 1H), 6.51 (dd, J=3.3, 1.8 Hz, 1H), 4.90 (br. s., 1H), 4.51 (d, J=13.6 Hz, 1H), 4.41 (d, J=13.8 Hz, 1H), 4.34 (d, J=13.3 Hz, 1H), 3.77 (s, 3H), 3.57 (d, J=10.5 Hz, 1H), 3.39 (dd, J=13.1, 3.5 Hz, 1H), 3.23 (td, J=12.4, 3.1 Hz, 1H), 2.86 (dt, J=13.3, 6.7 Hz, 1H), 1.49 (d, J=6.5 Hz, 3H), 1.16 (br. s., 3H), 1.05 (br. s., 3H). LC-MS: m/z 445.2 $(M+H)^+$.

(R)-6-isopropyl-5-(2-methoxyphenyl)-2-(3-methyl-4-(2-(thiophen-2-acetyl)piperazin-1-yl)nicotinonitrile (Compound 177)

[0367] Compound 177 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

[0368] ^{1}H NMR (CHLOROFORM-d) δ 7.54 (s, 1H), 7.33-7.41 (m, 1H), 7.20-7.24 (m, 1H), 7.05-7.11 (m, 1H), 6.98-7.04 (m, 1H), 6.89-6.98 (m, 3H), 4.94 (br. s., 0.5H), 4.58 (d, J=12.8 Hz, 0.2H), 4.17-4.46 (m, 3H), 3.91-4.04 (m, 2H), 3.76 (s, 3H), 3.56 (t, J=11.2 Hz, 0.5H), 3.27 (d, J=12.8 Hz, 0.5H), 3.13-3.23 (m, 1H), 2.98-3.11 (m, 1H), 2.85 (dt, J=13.3, 6.7 Hz, 1H), 1.33-1.39 (m, 3H), 1.15 (br. s., 3H), 1.04 (br. s., 3H). LC-MS: m/z 475.2 $(M+H)^+$.

(R)-6-isopropyl-5-(2-methoxyphenyl)-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)nicotino-nitrile (Compound 178)

[0369] Compound 178 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

[0370] ^{1}H NMR (CHLOROFORM-d) δ 7.52-7.59 (m, 1H), 7.34-7.41 (m, 1H), 7.29 (d, J=1.8 Hz, 1H), 7.08 (dd, J=7.3, 1.8 Hz, 1H), 7.01 (t, J=7.2 Hz, 1H), 6.96 (d, J=8.3 Hz, 1H), 6.38 (d, J=1.8 Hz, 1H), 4.69 (br. s., 1H), 4.29-4.43 (m, 2H), 4.00-4.29 (m, 1H), 3.77 (s, 3H), 3.46 (br. s., 1H), 3.24-3.39 (m, 1H), 3.11 (td, J=12.5, 3.0 Hz, 1H), 2.86 (spt, J=6.6 Hz, 1H), 2.41 (s, 3H), 1.43 (d, J=6.8 Hz, 3H), 1.12-1.19 (m, 3H), 1.04 (br. s., 3H). LC-MS: m/z 459.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-p-tolylnicotinonitrile (Compound 179)

[0371] Compound 179 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

[0372] ^{1}H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.60 (s, 1H), 7.44-7.49 (m, 1H), 7.24 (d, J=7.8 Hz, 2H), 7.13 (d, J=8.0 Hz, 2H), 6.55-6.62 (m, 1H), 4.74 (br. s., 1H), 4.20-4.49 (m, 3H), 3.38-3.57 (m, 1H), 3.31 (dd, J=13.1, 3.0 Hz, 1H), 3.07-3.22 (m, 2H), 2.37-2.46 (m, 3H), 1.45 (d, J=6.8 Hz, 3H), 1.07-1.20 (m, 6H). LC-MS: m/z 429.1 $(M+H)^+$.

(R)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-p-tolylnicotinonitrile (Compound 180)

[0373] Compound 180 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

[0374] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.50-7.53 (m, 1H), 7.24 (d, J=7.8 Hz, 2H), 7.13 (d, J=8.0 Hz, 2H), 7.05 (d, J=3.5 Hz, 1H), 6.46-6.55 (m, 1H), 4.90 (br. s., 1H), 4.51 (d, J=13.6 Hz, 1H), 4.42 (d, J=14.1 Hz, 1H), 4.33 (dt, J=13.3, 2.0 Hz, 1H), 3.57 (d, J=10.3 Hz, 1H), 3.40 (dd, J=13.2, 3.6 Hz, 1H), 3.18-3.30 (m, 1H), 3.09-3.18 (m, 1H), 2.41 (s, 3H), 1.48 (d, J=6.8 Hz, 3H), 1.07-1.20 (m, 6H). LC-MS: m/z 429.2 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-(thiophen-2-yl) acetyl)piperazin-1-yl)-5-p-tolylnicotinonitrile (Compound 181)

[0375] Compound 181 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

[0376] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.20-7.25 (m, 3H), 7.12 (d, J=7.8 Hz, 2H), 6.88-7.00 (m, 2H), 4.94 (br. s., 0.5H), 4.58 (d, J=13.1 Hz, 0.5H), 4.32-4.43 (m, 1H), 4.27 (s, 1H), 4.30 (s, 1H), 3.91-4.05 (m, 2H), 3.80 (d, J=13.6 Hz, 0.5H), 3.51-3.63 (m, 0.5H), 3.20-3.33 (m, 1H), 3.11-3.20 (m, 1H), 2.98-3.10 (m, 1H), 2.41 (s, 3H), 1.36 (d, J=6.3 Hz, 1.5H), 1.32 (d, J=6.8 Hz, 1.5H), 1.13 (d, J=6.5 Hz, 6H). LC-MS: m/z 459.1 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-p-tolylnicotinonitrile (Compound 182)

[0377] Compound 182 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

[0378] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.28-7.32 (m, 1H), 7.24 (d, J=8.0 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 6.36-6.41 (m, 1H), 4.69 (br. s., 1H), 4.38 (d, J=13.3 Hz, 1H), 4.33 (d, J=13.1 Hz, 1H), 4.23 (d, J=12.0 Hz, 1H), 3.46 (br. s., 1H), 3.26-3.34 (m, 1H), 3.13-3.21 (m, 1H), 3.05-3.13 (m, 1H), 2.41 (s, 6H), 1.41 (d, J=6.8 Hz, 3H), 1.14 (dd, J=6.7, 3.4 Hz, 6H). LC-MS: m/z 443.2 $(M+H)^+$.

(R)-6-isopropyl-5-(2-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 183)

[0379] Compound 183 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

[0380] ^{1}H NMR (CHLOROFORM-d) δ 7.55 (s, 1H), 7.34-7.42 (m, 1H), 7.05-7.12 (m, 1H), 6.99-7.05 (m, 1H), 6.96 (d,

J=8.3 Hz, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J=13.1 Hz, 0.5H), 4.19-4.43 (m, 3H), 3.82 (d, J=7.5 Hz, 0.5H), 3.76 (s, 3H), 3.70-3.76 (m, 2H), 3.54-3.64 (m, 0.5H), 3.38 (s, 3H), 3.30 (t, J=13.3 Hz, 1H), 3.02-3.22 (m, 1H), 2.82-2.92 (m, 1H), 2.66-2.80 (m, 1H), 2.53-2.65 (m, 1H), 1.42 (d, J=6.5 Hz, 1.5H), 1.32 (d, J=6.5 Hz, 1.5H), 1.16 (br. s., 3H), 1.05 (br. s., 3H). LC-MS: m/z 437.1 $(M+H)^+$.

(S)-5-(2-ethoxyphenyl)-2-(4-(furan-2-carbonyl)-2-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 184)

[0381] Compound 184 was synthesized using 1-(2-ethoxyphenyl)-3-methylbutan-2-one as starting material.

[0382] ^{1}H NMR (CHLOROFORM-d) δ 7.55 (s, 1H), 7.48-7.53 (m, 1H), 7.31-7.38 (m, 1H), 7.05-7.11 (m, 2H), 6.96-7.02 (m, 1H), 6.94 (d, J=8.3 Hz, 1H), 6.45-6.56 (m, 1H), 4.77 (br. s., 1H), 4.53 (d, J=11.3 Hz, 1H), 4.36 (d, J=13.3 Hz, 1H), 4.23-4.33 (m, 1H), 4.02 (q, J=6.8 Hz, 2H), 3.38-3.67 (m, 3H), 2.84-2.97 (m, 1H), 1.36 (d, J=6.8 Hz, 3H), 1.27-1.30 (m, 3H), 1.24-1.27 (m, 6H). LC-MS: m/z 459.1 $(M+H)^+$.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-p-tolylnicotinonitrile (Compound 198)

[0383] Compound 198 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

[0384] ^{1}H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.23 (d, J=7.8 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.21-4.42 (m, 3H), 3.81 (d, J=13.8 Hz, 0.5H), 3.69-3.77 (m, 62H), 3.53-3.64 (m, 0.5H), 3.38 (s, 3H), 3.31 (t, J=12.3 Hz, 1H), 3.11-3.19 (m, 2H), 2.65-2.81 (m, 1H), 2.54-2.63 (m, 1H), 2.41 (s, 3H), 1.40 (d, J=6.3 Hz, 1.5H), 1.31 (d, J=6.5 Hz, 1.5H), 1.14 (d, J=6.8 Hz, 6H). LC-MS: m/z 421.1 $(M+H)^+$.

(R)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5,6-diphenylnicotinonitrile (Compound 240)

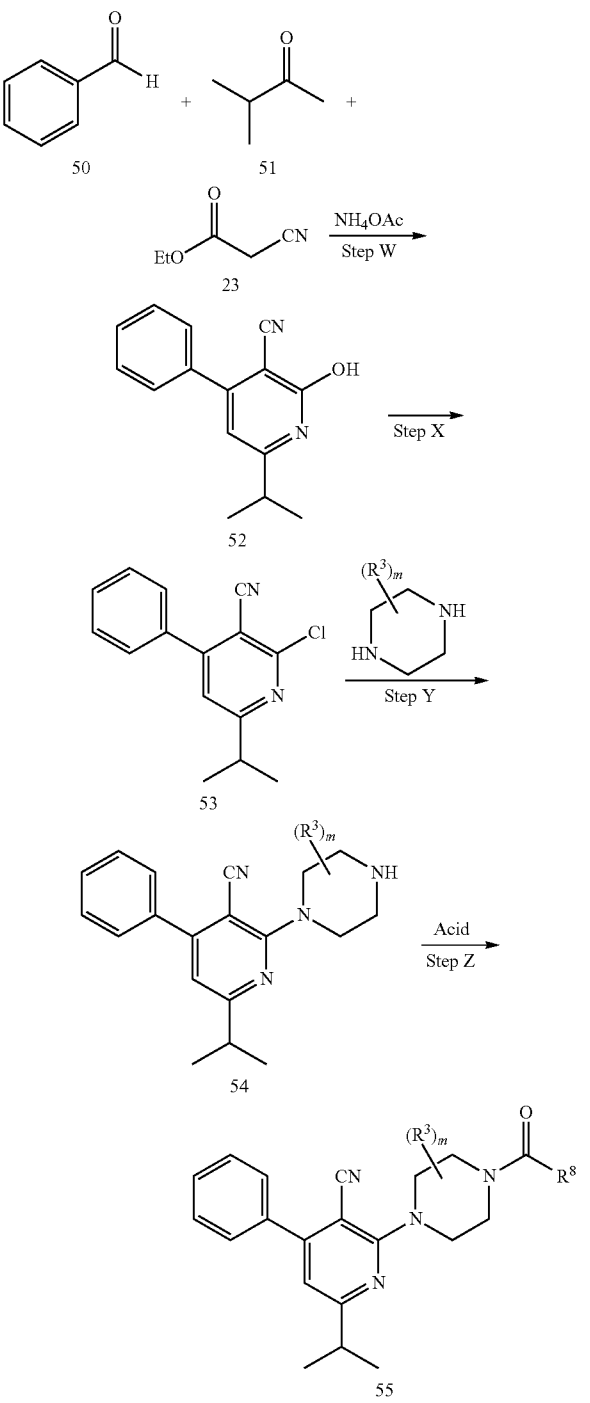
[0385] Compound 240 was synthesized using 1,2-diphenylethanone as starting material. ^{1}H NMR (CHLOROFORM-d) δ 7.84 (s, 1H), 7.33-7.40 (m, 2H), 7.26-7.33 (m, 4H), 7.20-7.25 (m, 2H), 7.08-7.16 (m, 2H), 4.94 (br. s., 0.5H), 4.56 (d, J=12.8 Hz, 0.5H), 4.38-4.49 (m, 1H), 4.23-4.38 (m, 2H), 3.77-3.90 (m, 1H), 3.74 (t, J=6.0 Hz, 2H), 3.54-3.64 (m, 0.5H), 3.37 (s, 3H), 3.34 (d, J=6.3 Hz, 0.5H), 3.19-3.26 (m, 1H), 3.06-3.19 (m, 1H), 2.66-2.78 (m, 1H), 2.55-2.63 (m, 1H), 1.39-1.46 (m, 1.5H), 1.33 (d, J=6.0 Hz, 1.5H). LC-MS: m/z 441.3 $(M+H)^+$.

Example 10

Preparation of (R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 130)

[0386] Compound 130 (55, wherein m is 1, R^3 is methyl; and R^8 is furan-3-yl) was synthesized according to general Scheme 7.

Scheme 7.



Step W:
2-hydroxy-6-isopropyl-4-phenylnicotinonitrile (52)

[0387] To a suspension of ammonium acetate (31.46 g, 0.4 mol) in 200 mL of EtOH was added successively the 3-methyl-2-butanone (51; 5.38 mL, 50 mmol), benzaldehyde (50; 5.21 g, 50 mmol), and ethyl cyanoacetate (23; 5.6 mL, 50

mmol). The resulting mixture was stirred at reflux temperature for 3 hrs and subsequently at room temperature overnight. After the LC-MS showed the formation of the desired product, the precipitate formed was filtered and washed with EtOH (10 mL×3 times) and hexane (10 mL×3 times). After air-drying, 2.18 g of 52 was obtained as a white solid. MS (ES) M+H expected 239.1, found 239.0. ^{1}H NMR (CHLOROFORM-d) δ 7.61-7.70 (m, 2H), 7.51-7.58 (m, 3H), 6.33 (s, 1H), 3.06 (dt, J=13.8, 6.9 Hz, 1H), 1.42 (d, J=7.0 Hz, 6H).

Step X: 2-chloro-6-isopropyl-4-phenylnicotinonitrile (53)

[0388] A mixture of 2-hydroxy-6-isopropyl-4-phenylnicotinonitrile 52; (0.702 g, 2.94 mmol), 7 mL of phosphoryl trichloride and one drop of DMF were heated to reflux overnight until LC-MS indicated the complete conversion to the product. After evaporation of excess of phosphoryl trichloride under reduced pressure, the residue was re-dissolved in methylene chloride and neutralized carefully with satd. aq. $NaHCO_3$ and washed subsequently with 1N HCl and brine. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Flash column chromatography (1:5 ethyl acetate/petroleum ether) afforded 717 mg of 53 as a yellowish solid. MS (ES) M+H expected 257.1, found 257.0. ^{1}H NMR (CHLOROFORM-d) δ 7.52-7.64 (m, 5H), 7.26 (s, 1H), 3.09-3.21 (m, 1H), 1.37 (d, J=7.0 Hz, 6H).

Step Y: (R)-6-isopropyl-2-(3-methylpiperazin-1-yl)-4-phenylnicotinonitrile (54)

[0389] A mixture of above chloride 53 (192.6 mg, 0.75 mmol), (R)-2-methylpiperazine (150 mg, 1.5 mmol), and triethylamine (0.21 mL, 1.5 mmol) suspended in 1.5 mL of acetonitrile was subjected to microwave reaction at 175° C. for 45 min. After the reaction mixture was concentrated in vacuo, the residue was purified by flash column chromatography to give 197 mg of 54 as yellowish oil. MS (ES) M+H expected 321.2, found 321.1. ^{1}H NMR (CHLOROFORM-d) δ 7.54-7.60 (m, 2H), 7.47-7.53 (m, 3H), 6.71 (s, 1H), 4.21-4.35 (m, 2H), 3.03-3.18 (m, 4H), 2.99 (dt, J=13.8, 6.9 Hz, 1H), 2.78 (dd, J=12.7, 10.2 Hz, 1H), 1.30 (d, J=7.0 Hz, 6H), 1.15-1.20 (m, 3H).

Step Z: (R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 130)

[0390] In a 5-mL of amber glass vial was placed (R)-6-isopropyl-2-(3-methylpiperazin-1-yl)-4-phenyl-nicotinonitrile (54; 32 mg, 0.1 mmol), furan-3-carboxylic acid (22.4 mg, 0.312 mmol), EDCI (38.2 mg, 0.2 mmol), HOBt (27 mg, 0.2 mmol), triethylamine (35 μL, 0.2 mmol) and 1.5 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight. The mixture was quenched with 1 N HCl aqueous solution, extracted with EtOAc three times. The combined organic layer was washed with satd. $NaHCO_3$ and brine, dried over anhy. Na_2SO_4, and concentrated in vacuo. The crude product was purified by preparative TLC (EtOAc: petroleum ether/20:100) to afford 23 mg of Compound 130 as a light yellowish solid. MS (ES) M+H expected 415.2, found 415.1. ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.55-7.58 (m, 2H), 7.50-7.53 (m, 3H), 7.48 (t, J=1.6 Hz, 1H), 6.79 (s, 1H), 6.60-6.62 (m, 1H), 4.76 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J=13.1 Hz, 1H), 3.56 (br. s., 1H), 3.34 (dd, J=12.9, 3.6 Hz, 1H), 3.17 (td, J=12.5, 3.5 Hz, 1H), 3.01 (spt, J=6.9 Hz, 1H), 1.47 (d, J=6.8 Hz, 3H), 1.31 (d, J=6.8 Hz, 6H).

[0391] Other Compounds of Formula II listed below, wherein R^{1a} is optionally substituted phenyl; and R^{1b} is hydrogen; were similarly prepared by general Scheme 7 replacing one or more of: (1) 3-methyl-2-butanone (51) with an alternate ketone as starting material; (2) benzaldehyde (50) with an alternate aldehyde as starting material; (3) (R)-2-methylpiperazine with an alternate piperazine in Step Y; and (4) 2-methylfuran-3-carboxylic acid with an alternate acid in Step Z. In addition, a compound wherein R^{1a} is isopropyl; R^{1b} is hydrogen and R^2 is phenyl was also prepared by the same method of general Scheme 7.

2-(4-benzoylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 100)

[0392] ^{1}H NMR (DMSO-d_6) δ 7.54-7.59 (m, 2H), 7.50-7.54 (m, 3H), 7.47 (s, 5H), 6.80 (s, 1H), 4.01 (br. s., 2H), 3.74-3.89 (m, 3H), 3.66 (br. s., 3H), 3.01 (quin, J=6.8 Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H). LC-MS: m/z 411.1 $(M+H)^+$.

2-((3S,5R)-4-benzoyl-3,5-dimethylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 101)

[0393] ^{1}H NMR (DMSO-d_6) δ 7.53-7.58 (m, 2H), 7.49-7.53 (m, 3H), 7.40-7.47 (m, 5H), 6.79 (s, 1H), 4.54 (br. s., 2H), 4.24 (s, 1H), 4.27 (s, 1H), 3.28 (dd, J=13.1, 4.3 Hz, 2H), 3.01 (dt, J=13.6, 6.9 Hz, 1H), 1.52 (d, J=6.8 Hz, 6H), 1.31 (d, J=7.0 Hz, 6H). LC-MS: m/z 439.1 $(M+H)^+$.

2-((3S,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 102)

[0394] ^{1}H NMR (CHLOROFORM-d) δ 7.54-7.61 (m, 2H), 7.45-7.54 (m, 4H), 7.08 (d, J=3.5 Hz, 1H), 6.78 (s, 1H), 6.52 (dd, J=3.5, 1.8 Hz, 1H), 4.90 (br. s., 2H), 4.30 (s, 1H), 4.34 (s, 1H), 3.32 (dd, J=12.9, 4.4 Hz, 2H), 3.01 (quin, J=6.9 Hz, 1H), 1.60 (d, J=7.0 Hz, 6H), 1.31 (d, J=7.0 Hz, 6H). LC-MS: m/z 429.1 $(M+H)^+$.

2-(4-(furan-2-carbonyl)piperazin-1-yl)-4-isopropyl-6-phenylnicotinonitrile (Compound 103)

[0395] Compound 103 was synthesized using isobutyraldehyde and acetophenone as starting materials.

[0396] ^{1}H NMR (DMSO-d_6) δ 8.02-8.08 (m, 2H), 7.50-7.56 (m, 2H), 7.46-7.50 (m, 2H), 7.30 (s, 1H), 7.08 (dd, J=3.4, 0.6 Hz, 1H), 6.53 (dd, J=3.3, 1.8 Hz, 1H), 4.05 (br. s., 4H), 3.79-3.85 (m, 4H), 3.40 (dt, J=13.7, 6.8 Hz, 1H), 1.38 (d, J=6.8 Hz, 6H). LC-MS: m/z 400.8 $(M+H)^+$.

2-(4-(furan-2-carbonyl)piperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 104)

[0397] Compound 104 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0398] ^{1}H NMR (CHLOROFORM-d) δ 7.51-7.57 (m, 1H), 7.43-7.51 (m, 1H), 7.23-7.28 (m, 1H), 7.03-7.11 (m, 3H), 6.75 (s, 1H), 6.53 (dd, J=3.0, 1.5 Hz, 1H), 4.02 (br. s., 4H), 3.89 (s, 3H), 3.74-3.82 (m, 4H), 3.00 (dt, J=13.8, 6.9 Hz, 1H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 430.9 $(M+H)^+$.

2-(4-benzoylpiperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 105)

[0399] Compound 105 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0400] ^{1}H NMR (DMSO-d_6) δ 7.43-7.50 (m, 6H), 7.25 (dd, J=7.4, 1.6 Hz, 1H), 7.07-7.10 (m, 1H), 7.02-7.06 (m, 1H), 6.75 (s, 1H), 3.99 (br. s., 2H), 3.87 (s, 3H), 3.78 (br. s., 2H), 3.64 (br. s., 4H), 2.99 (dt, J=13.8, 6.9 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H). LC-MS: m/z 440.8 $(M+H)^+$.

2-(4-(1H-indole-3-carbonyl)piperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 106)

[0401] Compound 106 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0402] ^{1}H NMR (CHLOROFORM-d) δ 9.02 (br. s., 1H), 7.73-7.80 (m, 1H), 7.41-7.51 (m, 3H), 7.21-7.28 (m, 3H), 7.01-7.11 (m, 2H), 6.75 (s, 1H), 3.94 (br. s., 4H), 3.87 (s, 3H), 3.75 (br. s., 4H), 3.02 (dt, J=13.7, 6.8 Hz, 1H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 480 $(M+H)^+$.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 107)

[0403] ^{1}H NMR (CHLOROFORM-d) δ 7.55-7.60 (m, 2H), 7.48-7.54 (m, 4H), 7.06 (dd, J=3.5, 0.8 Hz, 1H), 6.77 (s, 1H), 6.52 (dd, J=3.5, 1.8 Hz, 1H), 4.91 (br. s., 1H), 4.52 (d, J=13.6 Hz, 1H), 4.29-4.36 (m, 1H), 4.23 (dt, J=13.1, 2.1 Hz, 1H), 3.62 (br. s., 1H), 3.43 (dd, J=13.1, 3.8 Hz, 1H), 3.26 (td, J=12.4, 3.5 Hz, 1H), 3.00 (quin, J=6.9 Hz, 1H), 1.50 (d, J=6.8 Hz, 3H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 415.1 $(M+H)^+$.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-4-isopropyl-6-phenylnicotinonitrile (Compound 108)

[0404] Compound 108 was synthesized using benzaldehyde and 3-methylbutan-2-one as starting materials.

[0405] ^{1}H NMR (CHLOROFORM-d) δ 8.00-8.08 (m, 2H), 7.50-7.57 (m, 2H), 7.45-7.50 (m, 2H), 7.29 (s, 1H), 7.07 (dd, J=3.5, 0.5 Hz, 1H), 6.52 (dd, J=3.5, 1.8 Hz, 1H), 4.94 (br. s., 1H), 4.54 (d, J=13.3 Hz, 1H), 4.34 (dd, J=12.5, 2.3 Hz, 1H), 4.24 (dt, J=13.1, 2.1 Hz, 1H), 3.65 (br. s., 1H), 3.41-3.46 (m, 1H), 3.38-3.41 (m, 1H), 3.25 (td, J=12.4, 3.3 Hz, 1H), 1.53 (d, J=6.8 Hz, 3H), 1.38 (d, J=6.8 Hz, 6H). LC-MS: m/z 415.1 $(M+H)^+$.

2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 110)

[0406] ^{1}H NMR (CHLOROFORM-d) δ 8.00-8.06 (m, 2H), 7.77 (s, 1H), 7.50 (br. s., 1H), 7.48 (d, J=4.3 Hz, 3H), 7.30 (s, 1H), 6.61 (s, 1H), 4.78 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J=13.1 Hz, 1H), 3.58 (br. s., 1H), 3.40 (quin, J=6.9 Hz, 1H), 3.33 (dd, J=12.9, 3.1 Hz, 1H), 3.17 (td, J=12.4, 3.3 Hz, 1H), 1.50 (d, J=6.8 Hz, 3H), 1.38 (d, J=6.8 Hz, 6H). LC-MS: m/z 415.0 $(M+H)^+$.

2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-isopropyl-6-phenylnicotinonitrile (Compound III)

[0407] Compound III was synthesized using benzaldehyde and 3-methylbutan-2-one as starting materials.

[0408] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.53-7.61 (m, 2H), 7.49-7.53 (m, 3H), 7.47 (s, 1H), 6.79 (s, 4H), 6.61 (s, 1H), 4.71-4.76 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J=13.1 Hz, 1H), 3.56 (br. s., 1H), 3.34 (dd, J=13.1, 3.3 Hz, 1H), 3.17 (td, J=12.5, 3.4 Hz, 1H), 3.00 (dt, J=13.7, 6.8 Hz, 1H), 1.47 (d, J=6.8 Hz, 3H), 1.29 (d, J=7.3 Hz, 6H). LC-MS: m/z 414.9 $(M+H)^+$.

2-(4-(furan-3-carbonyl)piperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 113)

[0409] Compound 113 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0410] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.42-7.53 (m, 2H), 7.25 (dd, J=7.5, 1.5 Hz, 1H), 7.02-7.13 (m, 2H), 6.76 (s, 1H), 6.59-6.66 (m, 1H), 3.90 (br. s., 4H), 3.88 (s, 3H), 3.73 (br. s., 4H), 3.00 (dt, J=13.7, 6.8 Hz, 1H), 1.30 (d, J=6.8 Hz, 6H). LC-MS: m/z 431.0 $(M+H)^+$.

4-(3-fluorophenyl)-2-(4-(furan-2-carbonyl)piperazin-1-yl)-6-isopropylnicotinonitrile (Compound 114)

[0411] Compound 114 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0412] ^{1}H NMR (CHLOROFORM-d) δ 7.42-7.56 (m, 2H), 7.36 (dq, J=7.7, 0.9 Hz, 1H), 7.17-7.27 (m, 2H), 7.09 (dd, J=3.4, 0.9 Hz, 1H), 6.76 (s, 1H), 6.53 (dd, J=3.5, 1.8 Hz, 1H), 4.03 (br. s., 4H), 3.83 (dd, J=6.3, 4.0 Hz, 4H), 2.95-3.10 (m, 1H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 419.1 $(M+H)^+$.

4-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)piperazin-1-yl)-6-isopropylnicotinonitrile (Compound 115)

[0413] Compound 115 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0414] ^{1}H NMR (CHLOROFORM-d) δ 7.77-7.80 (m, 1H), 7.45-7.53 (m, 2H), 7.36 (dt, J=7.7, 1.2 Hz, 1H), 7.17-7.28 (m, 2H), 6.77 (s, 1H), 6.62 (dd, J=1.9, 0.6 Hz, 1H), 3.92 (br. s., 4H), 3.77 (br. s., 4H), 2.92-3.10 (m, 1H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 419.0 $(M+H)^+$.

2-(4-(1H-indole-3-carbonyl)piperazin-1-yl)-4-(3-fluorophenyl)-6-isopropylnicotinonitrile (Compound 116)

[0415] Compound 116 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0416] ^{1}H NMR (CHLOROFORM-d) δ 7.75 (d, J=7.0 Hz, 1H), 7.40-7.63 (m, 3H), 7.36 (d, J=7.8 Hz, 1H), 7.17-7.28 (m, 3H), 6.77 (s, 1H), 3.94 (br. s., 4H), 3.79 (br. s., 4H), 3.67 (s, 1H), 3.02-3.13 (m, 1H), 1.32 (d, J=6.8 Hz, 6H). LC-MS: m/z 468.1 $(M+H)^+$.

6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-4-phenylnicotinonitrile (Compound 121)

[0417] ^{1}H NMR (CHLOROFORM-d) δ 7.48-7.58 (m, 5H), 7.33-7.39 (m, 3H), 7.30 (d, J=1.5 Hz, 1H), 7.25-7.28 (m, 1H), 6.75 (s, 1H), 4.71 (s, 1H), 4.27 (br. s., 1H), 4.09-4.20 (m, 2H), 3.80 (br. s., 2H), 3.52 (s, 1H), 3.19-3.26 (s, 1H), 3.06-3.15 (m, 1H), 2.98 (dt, J=13.7, 6.8 Hz, 1H), 1.40 (s, 3H), 1.30 (d, J=4.5 Hz, 19H). LC-MS: m/z 439.2 $(M+H)^+$.

4-(3-fluorophenyl)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 127)

[0418] Compound 127 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0419] ^{1}H NMR (CHLOROFORM-d) δ 7.44-7.58 (m, 2H), 7.31-7.40 (m, 1H), 7.14-7.27 (m, 2H), 7.07 (d, J=3.5 Hz, 1H), 6.74 (s, 1H), 6.53 (dd, J=3.5, 1.8 Hz, 1H), 4.92 (br. s., 1H),

4.52 (d, J=13.6 Hz, 1H), 4.34 (d, J=10.5 Hz, 1H), 4.24 (dt, J=13.1, 2.1 Hz, 1H), 3.62 (br. s., 1H), 3.45 (dd, J=13.3, 3.8 Hz, 1H), 3.28 (td, J=12.4, 3.4 Hz, 1H), 3.01 (dt, J=13.6, 6.9 Hz, 1H), 1.44-1.54 (m, 3H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 433.0 $(M+H)^+$.

4-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 128)

[0420] Compound 128 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0421] ^{1}H NMR (CHLOROFORM-d) δ 7.73-7.81 (m, 1H), 7.44-7.56 (m, 2H), 7.35 (dt, J=8.0, 1.1 Hz, 1H), 7.12-7.27 (m, 2H), 6.75 (s, 1H), 6.61 (dd, J=1.8, 0.8 Hz, 1H), 4.77 (br. s., 1H), 4.31 (d, J=12.0 Hz, 2H), 4.23 (d, J=13.1 Hz, 1H), 3.57 (br. s., 1H), 3.36 (d, J=10.0 Hz, 1H), 3.19 (td, J=12.4, 3.5 Hz, 1H), 3.01 (dt, J=13.5, 6.9 Hz, 1H), 1.46 (d, J=6.8 Hz, 3H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 433.1 $(M+H)^+$.

2-(4-(1H-indole-3-carbonyl)-3-methylpiperazin-1-yl)-4-(3-fluorophenyl)-6-isopropylnicotinonitrile (Compound 129)

[0422] Compound 129 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0423] ^{1}H NMR (CHLOROFORM-d) δ 8.85 (s, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.40-7.54 (m, 3H), 7.35 (d, J=7.8 Hz, 1H), 7.15-7.28 (m, 4H), 6.74 (s, 1H), 4.84 (br. s., 1H), 4.28 (t, J=15.3 Hz, 3H), 3.59 (d, J=11.8 Hz, 1H), 3.41 (d, J=11.0 Hz, 1H), 3.21 (t, J=10.8 Hz, 1H), 3.00 (dt, J=13.8, 6.9 Hz, 1H), 1.45 (d, J=6.5 Hz, 3H), 1.30 (d, J=6.8 Hz, 6H). LC-MS: m/z 482.2 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 130)

[0424] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.55-7.58 (m, 2H), 7.50-7.53 (m, 3H), 7.48 (t, J=1.6 Hz, 1H), 6.79 (s, 1H), 6.60-6.62 (m, 1H), 4.76 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J=13.1 Hz, 1H), 3.56 (br. s., 1H), 3.34 (dd, J=12.9, 3.6 Hz, 1H), 3.17 (td, J=12.5, 3.5 Hz, 1H), 3.01 (spt, J=6.9 Hz, 1H), 1.47 (d, J=6.8 Hz, 3H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 415.1 $(M+H)^+$.

(R)-6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-4-phenylnicotinonitrile (Compound 131)

[0425] ^{1}H NMR (CHLOROFORM-d) δ 7.52-7.57 (m, 2H), 7.47-7.52 (m, 3H), 7.29-7.41 (m, 4H), 7.24-7.28 (m, 1H), 6.75 (s, 1H), 4.98 (br. s., 0.5H), 4.62 (d, J=13.3 Hz, 0.5H), 4.28 (d, J=13.1 Hz, 1H), 4.06-4.20 (m, 2H), 3.81 (br. s., 2H), 3.70-3.79 (m, 0.5H), 3.54 (t, J=11.3 Hz, 0.5H), 3.18-3.33 (m, 1H), 3.03-3.17 (m, 1H), 2.99 (dt, J=13.8, 6.9 Hz, 1H), 1.33 (br. s., 3H), 1.29 (d, J=7.0 Hz, 6H). LC-MS: m/z 439.1 $(M+H)^+$.

(S)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 132)

[0426] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.54-7.59 (m, 2H), 7.49-7.54 (m, 3H), 7.48 (t, J=1.6 Hz, 1H), 6.79 (s, 1H), 6.59-6.63 (m, 1H), 4.76 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J=13.3 Hz, 1H), 3.57 (br. s., 1H), 3.34 (dd, J=13.2, 3.6 Hz, 1H), 3.17 (td, J=12.5, 3.4 Hz, 1H), 3.01 (spt, J=6.9 Hz, 1H), 1.47 (d, J=6.8 Hz, 3H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 415.1 $(M+H)^+$.

(S)-6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-4-phenylnicotinonitrile (Compound 133)

[0427] ^{1}H NMR (CHLOROFORM-d) δ 7.53-7.56 (m, 2H), 7.47-7.53 (m, 3H), 7.33-7.39 (m, 2H), 7.29-7.33 (m, 2H), 7.24-7.28 (m, 1H), 6.75 (s, 1H), 4.98 (br. s., 0.5H), 4.62 (d, J=13.3 Hz, 0.5H), 4.28 (d, J=12.8 Hz, 1H), 4.08-4.20 (m, 2H), 3.81 (br. s., 2H), 3.70-3.79 (m, 0.5H), 3.54 (t, J=11.3 Hz, 0.5H), 3.17-3.32 (m, 1H), 3.10 (t, J=12.7 Hz, 1H), 2.98 (dt, J=13.7, 6.8 Hz, 1H), 1.31-1.35 (m, 3H), 1.29 (d, J=7.0 Hz, 6H). LC-MS: m/z 439.1 $(M+H)^+$.

4-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)-3,5-dimethylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 134)

[0428] Compound 134 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0429] ^{1}H NMR (DMSO-d_6) δ 7.77 (s, 1H), 7.45-7.53 (m, 2H), 7.35 (d, J=8.3 Hz, 1H), 7.17-7.25 (m, 2H), 6.76 (s, 1H), 6.65 (d, J=1.0 Hz, 1H), 4.71 (br. s., 1H), 4.31 (d, J=12.8 Hz, 2H), 3.50-3.69 (m, 1H), 3.27 (dd, J=13.2, 4.4 Hz, 2H), 3.01 (quin, J=7.0 Hz, 1H), 1.56 (d, J=7.0 Hz, 6H), 1.32 (s, 3H), 1.30 (s, 3H). LC-MS: m/z 447.1 $(M+H)^+$.

2-(3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)-4-(3-fluorophenyl)-6-isopropylnicotinonitrile (Compound 135)

[0430] Compound 135 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0431] ^{1}H NMR (CHLOROFORM-d) δ 7.43-7.55 (m, 1H), 7.12-7.40 (m, 8H), 6.74 (s, 1H), 4.90 (br. s., 1H), 4.26 (br. s., 3H), 3.82 (s, 2H), 3.14 (br. s., 2H), 3.00 (dt, J=13.8, 6.9 Hz, 1H), 1.44 (d, J=6.8 Hz, 6H), 1.30 (d, J=6.8 Hz, 6H). LC-MS: m/z 471.1 $(M+H)^+$.

4-(3-fluorophenyl)-2-(4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 136)

[0432] Compound 136 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0433] ^{1}H NMR (CHLOROFORM-d) δ 7.45-7.55 (m, 2H), 7.32-7.38 (m, 1H), 7.15-7.28 (m, 2H), 7.08 (d, J=3.5 Hz, 1H), 6.74 (s, 1H), 6.52 (dd, J=3.5, 1.8 Hz, 1H), 4.90 (br. s., 2H), 4.34 (d, J=13.1 Hz, 2H), 3.33 (dd, J=13.1, 4.5 Hz, 2H), 2.93-3.08 (m, 1H), 1.59 (d, J=7.0 Hz, 6H), 1.31 (d, J=6.8 Hz, 6H). LC-MS: m/z 447.0 $(M+H)^+$.

6-cyclohexyl-2-(4-(furan-2-carbonyl)piperazin-1-yl)-4-phenylnicotinonitrile (Compound 137)

[0434] Compound 137 was synthesized using benzaldehyde and 1-cyclohexylethanone as starting materials.

[0435] ^{1}H NMR (CHLOROFORM-d) δ 7.46-7.61 (m, 6H), 7.08 (dd, J=3.4, 0.9 Hz, 1H), 6.78 (s, 1H), 6.53 (dd, J=3.4, 1.9 Hz, 1H), 4.03 (br. s., 4H), 3.76-3.86 (m, 4H), 2.66 (tt, J=11.6, 3.3 Hz, 1H), 1.92-2.00 (m, 2H), 1.83-1.91 (m, 2H), 1.74-1.82 (m, 1H), 1.55 (qd, J=12.3, 2.8 Hz, 2H), 1.41 (qt, J=12.6, 3.1 Hz, 2H), 1.25-1.35 (m, 1H). LC-MS: m/z 441.0 $(M+H)^+$.

6-cyclohexyl-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-phenylnicotinonitrile (Compound 138)

[0436] Compound 138 was synthesized using benzaldehyde and 1-cyclohexylethanone as starting materials.

[0437] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.43-7.61 (m, 6H), 6.77 (s, 1H), 6.61 (s, 1H), 4.76 (br. s., 1H), 4.29 (d, J=12.3 Hz, 2H), 4.20 (d, J=13.1 Hz, 1H), 3.56 (br. s., 1H), 3.33 (dd, J=13.2, 3.1 Hz, 1H), 3.16 (td, J=12.5, 3.1 Hz, 1H), 2.56-2.72 (m, 1H), 1.95 (d, J=12.5 Hz, 2H), 1.87 (d, J=12.8 Hz, 2H), 1.78 (d, J=12.8 Hz, 1H), 1.49-1.60 (m, 2H), 1.46 (d, J=6.5 Hz, 3H), 1.35-1.44 (m, 2H), 1.25-1.34 (m, 1H). LC-MS: m/z 455.1 $(M+H)^+$.

6-cyclohexyl-2-((3S,5R)-4-(furan-3-carbonyl)-3,5-dimethylpiperazin-1-yl)-4-phenylnicotinonitrile (Compound 142)

[0438] Compound 142 was synthesized using benzaldehyde and 1-cyclohexylethanone as starting materials.

[0439] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.54-7.58 (m, 2H), 7.49-7.53 (m, 3H), 7.48 (t, J=1.6 Hz, 1H), 6.79 (s, 1H), 6.65 (d, J=2.0 Hz, 1H), 4.73 (br. s., 2H), 4.27 (d, J=13.1 Hz, 2H), 3.25 (dd, J=13.1, 4.5 Hz, 2H), 2.66 (tt, J=11.6, 3.4 Hz, 1H), 1.95 (d, J=12.5 Hz, 2H), 1.84-1.92 (m, 2H), 1.78 (d, J=12.5 Hz, 1H), 1.57 (d, J=7.0 Hz, 6H), 1.49-1.54 (m, 2H), 1.38-1.47 (m, 2H), 1.31-1.37 (m, 1H). LC-MS: m/z 469.1 $(M+H)^+$.

6-isopropyl-4-(2-methoxyphenyl)-2-(4-(2-phenylacetyl)piperazin-1-yl)nicotinonitrile (Compound 146)

[0440] Compound 146 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0441] ^{1}H NMR (CHLOROFORM-d) δ 7.42-7.48 (m, 1H), 7.28-7.40 (m, 5H), 7.23 (dd, J=7.5, 1.8 Hz, 1H), 7.01-7.10 (m, 2H), 6.73 (s, 1H), 3.83-3.90 (m, 5H), 3.82 (s, 2H), 3.62-3.70 (m, 4H), 3.49-3.56 (m, 2H), 2.91-3.03 (m, 1H), 1.29 (d, J=6.8 Hz, 6H). LC-MS: m/z 455.2 $(M+H)^+$.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 147)

[0442] Compound 147 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0443] ^{1}H NMR (CHLOROFORM-d) δ 7.52 (dd, J=1.8, 0.8 Hz, 1H), 7.41-7.48 (m, 1H), 7.25 (dd, J=7.5, 1.8 Hz, 1H), 7.00-7.16 (m, 3H), 6.73 (s, 1H), 6.52 (dd, J=3.5, 1.8 Hz, 1H), 4.91 (br. s., 1H), 4.51 (d, J=12.3 Hz, 1H), 4.32 (d, J=12.5 Hz, 1H), 4.22 (dt, J=13.2, 2.0 Hz, 1H), 3.88 (s, 3H), 3.62 (br. s., 1H), 3.39 (dd, J=13.2, 3.6 Hz, 1H), 3.22 (td, J=12.4, 3.5 Hz, 1H), 3.00 (dt, J=13.7, 6.8 Hz, 1H), 1.49 (d, J=6.8 Hz, 3H), 1.30 (d, J=6.8 Hz, 6H). LC-MS: m/z 455.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 148)

[0444] Compound 148 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0445] ^{1}H NMR (CHLOROFORM-d) δ 7.76 (dd, J=1.5, 0.8 Hz, 1H), 7.40-7.51 (m, 2H), 7.22-7.28 (m, 1H), 7.01-7.11 (m, 2H), 6.70-6.76 (m, 1H), 6.61 (dd, J=1.8, 0.8 Hz, 1H), 4.75 (br. s., 1H), 4.16-4.45 (m, 3H), 3.88 (s, 3H), 3.55 (br. s., 1H), 3.31 (dd, J=12.9, 3.4 Hz, 1H), 3.14 (td, J=12.5, 3.4 Hz, 1H), 3.00 (dt, J=13.7, 6.8 Hz, 1H), 1.46 (d, J=7.0 Hz, 3H), 1.30 (d, J=6.8 Hz, 6H). LC-MS: m/z 445.2 $(M+H)^+$.

6-isopropyl-4-(2-methoxyphenyl)-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)nicotinonitrile (Compound 149)

[0446] Compound 149 was synthesized using 3-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0447] ^{1}H NMR (CHLOROFORM-d) δ 7.41-7.49 (m, 1H), 7.29-7.40 (m, 4H), 7.20-7.28 (m, 2H), 7.01-7.09 (m, 2H), 6.71 (s, 1H), 4.97 (br. s., 1H), 4.60 (d, J=13.3 Hz, 1H), 4.25 (br. s., 1H), 4.16 (d, J=13.3 Hz, 1H), 3.87 (s, 3H), 3.64-3.81 (m, 2H), 3.53 (t, J=11.4 Hz, 1H), 3.14-3.29 (m, 1H), 2.85-3.14 (m, 2H), 1.62 (s, 3H), 1.29 (s, 6H). LC-MS: m/z 469.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-(3-methoxyphenyl)nicotinonitrile (Compound 151)

[0448] Compound 151 was synthesized using 3-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0449] ^{1}H NMR (CHLOROFORM-d) δ 7.76 (dd, J=1.5, 0.8 Hz, 1H), 7.38-7.50 (m, 2H), 7.00-7.17 (m, 3H), 6.76-6.81 (m, 1H), 6.61 (dd, J=1.9, 0.9 Hz, 1H), 4.76 (br. s., 1H), 4.29 (d, J=12.8 Hz, 2H), 4.21 (d, J=13.1 Hz, 1H), 3.84-3.92 (m, 3H), 3.56 (br. s., 1H), 3.33 (dd, J=13.2, 3.6 Hz, 1H), 3.17 (td, J=12.5, 3.4 Hz, 1H), 3.00 (dt, J=13.7, 6.8 Hz, 1H), 1.47 (d, J=6.8 Hz, 3H), 1.30 (d, J=7.0 Hz, 6H). LC-MS: m/z 445.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-(3-hydroxyphenyl)-6-isopropylnicotinonitrile (Compound 152)

[0450] Compound 152 was synthesized using 3-hydroxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0451] ^{1}H NMR (CHLOROFORM-d) δ 7.74-7.81 (m, 1H), 7.41-7.51 (m, 1H), 7.34 (t, J=7.9 Hz, 1H), 7.11 (s, 1H), 7.05 (d, J=7.5 Hz, 1H), 6.97 (dd, J=8.2, 2.4 Hz, 1H), 6.79 (s, 1H), 6.57-6.64 (m, 1H), 4.79 (br. s., 1H), 4.15-4.44 (m, 3H), 3.59 (br. s., 1H), 3.34 (d, J=10.5 Hz, 1H), 3.17 (td, J=12.5, 3.1 Hz, 1H), 2.93-3.04 (m, 1H), 1.47 (d, J=6.8 Hz, 3H), 1.27-1.31 (m, 6H). LC-MS: m/z 431.2 $(M+H)^+$.

2-(4-(furan-3-carbonyl)-3-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 154)

[0452] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (br. s., 1H), 7.50-7.54 (m, 2H), 7.46-7.50 (m, 3H), 7.37-7.43 (m, 3H), 7.34 (t, J=7.7 Hz, 2H), 7.22-7.27 (m, 1H), 6.67 (s, 1H), 6.52 (br. s., 1H), 5.75 (br. s., 1H), 4.57 (br. s., 2H), 4.29 (d, J=11.5 Hz, 1H), 4.00 (d, J=11.0 Hz, 1H), 3.60-3.74 (m, 1H), 3.55 (d, J=10.5 Hz, 1H), 2.94 (dt, J=13.6, 6.8 Hz, 1H), 1.25-1.27 (m, 3H), 1.23 (d, J=7.0 Hz, 3H). LC-MS: m/z 477.1 $(M+H)^+$.

2-(4-(furan-2-carbonyl)-3-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 155)

[0453] ^{1}H NMR (CHLOROFORM-d) δ 7.51-7.55 (m, 2H), 7.46-7.50 (m, 4H), 7.45 (d, J=7.5 Hz, 2H), 7.33 (t, J=7.5 Hz, 2H), 7.20-7.25 (m, 1H), 6.92-7.07 (m, 1H), 6.68 (s, 1H), 6.45 (br. s., 4H), 5.95 (t, J=4.5 Hz, 1H), 4.63 (s, 1H), 4.66 (s, 1H), 4.33 (d, J=11.0 Hz, 1H), 4.06 (dd, J=13.6, 4.0 Hz, 1H), 3.69 (br. s., 1H), 3.56-3.65 (m, 1H), 2.97 (dt, J=13.7, 6.8 Hz, 1H), 1.24-1.28 (m, 6H). LC-MS: m/z 477.1 $(M+H)^+$.

(R)-4-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 156)

[0454] Compound 156 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

[0455] ^{1}H NMR (CHLOROFORM-d) δ 7.77 (dd, J=1.5, 1.0 Hz, 1H), 7.43-7.53 (m, 2H), 7.35 (dq, J=7.7, 0.9 Hz, 1H), 7.12-7.28 (m, 2H), 6.67-6.80 (m, 1H), 6.61 (dd, J=1.9, 0.9 Hz, 1H), 4.76 (br. s., 1H), 4.17-4.45 (m, 3H), 3.56 (br. s., 1H), 3.36 (dd, J=13.1, 3.5 Hz, 1H), 3.18 (td, J=12.5, 3.5 Hz, 1H), 2.95-3.07 (m, 1H), 1.46 (d, J=6.8 Hz, 3H), 1.29-1.32 (m, 6H). LC-MS: m/z 433.1 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-(2-hydroxyphenyl)-6-isopropylnicotinonitrile (Compound 157)

[0456] Compound 157 was synthesized using 2-hydroxybenzaldehyde and 3-methylbutan-2-one as starting materials.

[0457] ^{1}H NMR (CHLOROFORM-d) δ 8.01 (dd, J=8.2, 1.4 Hz, 1H), 7.73-7.77 (m, 1H), 7.50-7.60 (m, 1H), 7.46 (t, J=1.6 Hz, 1H), 7.31-7.37 (m, 2H), 7.21 (s, 1H), 6.60 (dd, J=1.6, 0.6 Hz, 1H), 4.71 (br. s., 1H), 4.25 (br. s., 1H), 4.07 (d, J=13.3 Hz, 1H), 3.98 (d, J=13.8 Hz, 1H), 3.71 (br. s., 1H), 3.45-3.56 (m, 1H), 3.15-3.26 (m, 1H), 3.06 (dt, J=13.7, 6.8 Hz, 1H), 1.32-1.37 (m, 9H). LC-MS: m/z 432.2 $(M+H)^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-o-tolylnicotinonitrile (Compound 158)

[0458] Compound 158 was synthesized using 2-methylbenzaldehyde and 3-methylbutan-2-one as starting materials.

[0459] ^{1}H NMR (CHLOROFORM-d) δ 7.72-7.79 (m, 1H), 7.47 (t, J=1.6 Hz, 1H), 7.29-7.40 (m, 3H), 7.19 (d, J=6.8 Hz, 1H), 6.65 (s, 1H), 6.60 (dd, J=1.9, 0.9 Hz, 1H), 4.75 (br. s., 1H), 4.17-4.46 (m, 3H), 3.42-3.67 (m, 1H), 3.34 (dd, J=13.1, 3.5 Hz, 1H), 3.16 (td, J=12.5, 3.5 Hz, 1H), 2.92-3.03 (m, 1H), 2.24 (s, 3H), 1.45 (d, J=6.3 Hz, 3H), 1.30 (d, J=6.8 Hz, 6H). LC-MS: m/z 429.1 $(M+H)^+$.

2-(4-(furan-3-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 160)

[0460] ^{1}H NMR (CHLOROFORM-d) δ 7.69 (br. s., 1H), 7.64 (s, 1H), 7.45 (br. s., 2H), 7.36-7.44 (m, 4H), 7.31 (br. s., 2H), 7.16-7.26 (m, 3H), 6.57 (br. s., 1H), 5.37 (br. s., 1H), 4.15 (d, J=9.8 Hz, 2H), 3.96 (d, J=8.8 Hz, 4H), 2.98-3.12 (m, 1H), 1.13 (d, J=6.8 Hz, 6H). LC-MS: m/z 477.2 $(M+H)^+$.

(R)-2-(3-cyano-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylpyridin-4-yl)phenyl acetate (Compound 162)

[0461] Compound 162 was synthesized from (R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-(2-hydroxyphenyl)-6-isopropylnicotinonitrile (Compound 157) by reaction with acetyl chloride.

[0462] ^{1}H NMR (METHANOL-d_4) δ 7.76 (s, 1H), 7.39-7.58 (m, 3H), 7.31 (t, J=1.9 Hz, 1H), 7.24 (dd, J=7.7, 1.9 Hz, 1H), 6.78 (s, 1H), 6.61 (d, J=1.3 Hz, 1H), 4.76 (br. s., 1H), 4.17-4.44 (m, 3H), 3.56 (br. s., 1H), 3.34 (dd, J=12.9, 3.4 Hz, 1H), 3.17 (td, J=12.5, 3.5 Hz, 1H), 2.93-3.06 (m, 1H), 2.27-2.43 (m, 3H), 1.46 (d, J=6.8 Hz, 3H), 1.30 (d, J=7.0 Hz, 6H). LC-MS: m/z 473.1 $(M+H)^+$.

(R)-4-(2-ethoxyphenyl)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 163)

[0463] Compound 163 was synthesized from (R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-(2-hydroxyphenyl)-6-isopropylnicotinonitrile (Compound 157) by treatment with NaH/DMF followed by ethyl bromide quench.

[0464] ^{1}H NMR (METHANOL-d_4) δ 7.76 (s, 1H), 7.37-7.51 (m, 2H), 6.98-7.16 (m, 3H), 6.79 (s, 1H), 6.57-6.64 (m, 1H), 4.76 (br. s., 1H), 4.17-4.45 (m, 3H), 4.12 (q, J=7.0 Hz, 2H), 3.56 (br. s., 1H), 3.34 (dd, J=12.9, 3.6 Hz, 1H), 3.17 (td, J=12.4, 3.3 Hz, 1H), 3.00 (quin, J=6.9 Hz, 1H), 1.47 (dt, J=6.8, 3.5 Hz, 6H), 1.30 (d, J=6.8 Hz, 6H). LC-MS: m/z 459.1 $(M+H)^+$.

2-(4-(furan-2-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 167)

[0465] ^{1}H NMR (CHLOROFORM-d) δ 7.64 (s, 1H), 7.52 (s, 1H), 7.36-7.48 (m, 5H), 7.31 (br. s., 2H), 7.22 (d, J=6.5 Hz, 3H), 7.07 (d, J=3.0 Hz, 1H), 6.52 (br. s., 1H), 5.37-5.59 (br. s., 1H), 4.17 (br. s., 3H), 3.98 (br. s., 2H), 3.92 (br. s., 1H), 3.00-3.12 (m, 1H), 1.13 (d, J=6.5 Hz, 3H), 0.79 (br. s., 3H). LC-MS: m/z 477.1 $(M+H)^+$.

2-(4-(1H-indole-3-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 169)

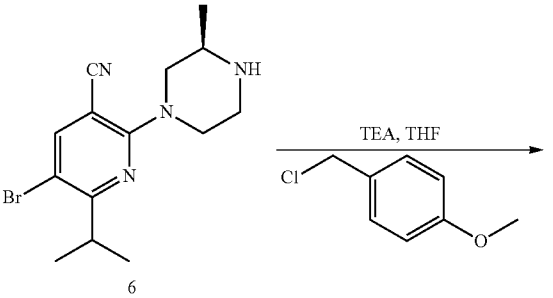
[0466] ^{1}H NMR (CHLOROFORM-d) δ 9.00 (br. s., 1H), 7.71 (d, J=6.3 Hz, 1H), 7.64 (s, 1H), 7.42 (d, J=7.3 Hz, 6H), 7.24-7.34 (m, 4H), 7.22 (d, J=6.3 Hz, 4H), 5.53 (br. s., 1H), 4.13-4.35 (m, 2H), 4.01 (br. s., 2H), 3.76-3.96 (m, 2H), 3.00-3.13 (m, 1H), 1.14 (d, J=6.5 Hz, 3H), 0.80 (d, J=6.5 Hz, 3H). LC-MS: m/z 526.1 $(M+H)^+$.

Example 11

Preparation of (R)-methyl 5-(4-fluorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinate (Compound 244)

[0467] Compound 244 was prepared according to Scheme 8.

Scheme 8.



6

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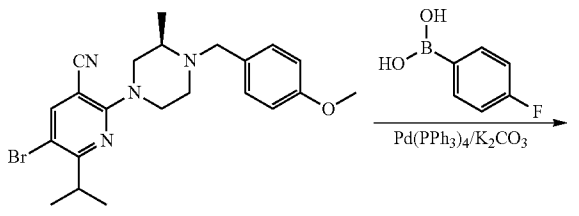

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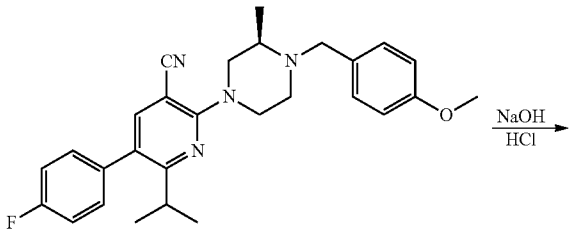

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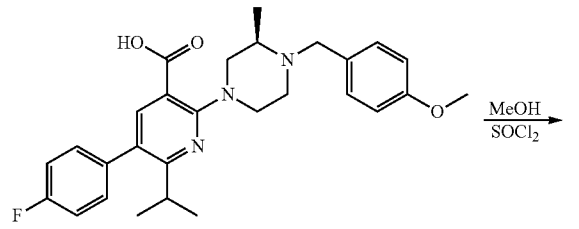
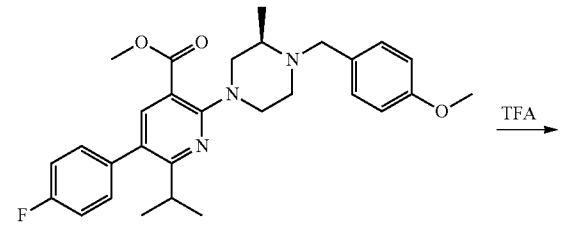
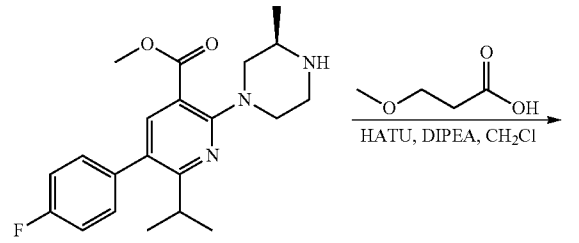
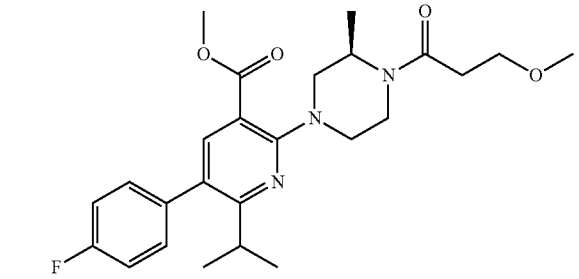


60



61





Compound 244

Step 1: (R)-5-bromo-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinonitrile (58)

[0468] To a solution of (R)-5-bromo-6-isopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6; Example 1; 1 g, 3.10 mmol) and triethylamine (375 mg, 3.72 mmol) in 20 mL THF was added 1-(chloromethyl)-4-methoxybenzene (485 mg, 3.10 mmol) dropwise at 0° C. The reaction mixture was stirred at 0° C. for 4 hrs before warmed up to room temperature and quenched by adding 20 mL of water. Solvent was removed under reduced pressure and the residue was extracted with EtOAc (3×20 mL). The combined organic layer was then washed with brine, dried over anhy. Na_2SO_4 and concentrated in vacuo. Flash column chromatography separation (20% EtOAc/petroleum ether) then afforded 1.3 g of 58 as thick brown oil. MS (ES) M+H expected 443.1, found 443.2

Step 2: (R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinonitrile (59)

[0469] To a solution of (R)-5-bromo-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)-nicotinonitrile (58; 1 g, 2.18 mmol) and 4-fluorophenylboronic acid (610 mg, 4.36 mmol) in 5 mL of DMF was added $Pd(PPh_3)_4$ (340 mg 0.218 mmol) and K_2CO_3 (360 mg, 2.62 mmol) under nitrogen protection. The reaction was subjected to microwave reaction at 150° C. for 1 hour. After dilution with 20 mL of water, the mixture was extracted with EtOAc (3×20 mL). The combined organic layer was washed with brine, dried over anhy. Na_2SO_4 and concentrated in vacuo. Flash column chromatography separation (20% EtOAc/petroleum ether) then afforded 600 mg of 59 as thick brown oil. MS (ES) M+H expected 459.3, found 459.2.

Step 3: (R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinic acid (60)

[0470] To a solution of (R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methyl-piperazin-1-yl)nicotinonitrile (600 mg, 1.31 mmol) in 20 mL of ethanol was added 20 mL 50% aq. NaOH solution. The reaction mixture was heated to 120° C. overnight, and then acidified with 2N aq. HCl to pH<6. Ethanol was removed under reduced pressure and the residue was washed with water several times and filtered. After air-drying, 500 mg of crude title compound was obtained as a yellowish solid. MS (ES) M+H expected 478.2, found 478.2.

Step 4: (R)-methyl-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl) nicotinate (61)

[0471] To a 25 mL of round-bottom flask was charged with 10 mL of methanol. After cooling at 0° C., 1 mL of thionyl chloride was added dropwise and the solution was stirred at room temperature for 30 min, before adding (R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxy-benzyl)-3-methylpiperazin-1-yl)nicotinic acid (500 mg, 1.05 mmol) slowly. The resulting mixture was then heated to reflux temperature for 2 hrs. After removing the volatile under reduced pressure, 500 mg of crude title compound was obtained and used without further purification. MS (ES) M+H expected 492.3, found 492.2.

Step 5: (R)-methyl 5-(4-fluorophenyl)-6-isopropyl-2-(3-methylpiperazin-1-yl)nicotinate (62)

[0472] (R)-methyl-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinate (61; 500 mg, 1.02 mmol) was dissolved in 15 mL of 2,2,2-trifluoroacetic acid. The mixture was heated to reflux overnight. After removal of excess of TFA under reduced pressure, the residue was re-dissolved in methylene chloride and washed with satd. $NaHCO_3$, brine. The organic layer was then dried over anhy. Na_2SO_4, and concentrated in vacuo. 300 mg of title compound was obtained as yellowish oil and used subsequently without further purification. MS (ES) M+H expected 372.2, found 372.2.

Step 6: (R)-methyl 5-(4-fluorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinate (Compound 244)

[0473] ^{1}H NMR (CHLOROFORM-d) δ 7.84 (s, 1H), 7.20-7.25 (m, 2H), 7.06-7.15 (m, 2H), 4.86 (br. s., 0.5H), 4.43 (d, J=12.5 Hz, 0.5H), 4.21 (d, J=6.0 Hz, 0.5H), 3.92 (d, J=13.1 Hz, 0.5H), 3.87 (s, 3H), 3.81 (d, J=16.3 Hz, 1H), 3.74 (t, J=6.7 Hz, 3H), 3.64 (br. s., 1H), 3.37 (s, 3H), 3.18-3.34 (m, 1H), 2.96-3.15 (m, 2H), 2.64-2.80 (m, 1H), 2.60 (br. s., 1H), 1.34-1.40 (m, 1.5H), 1.29-1.32 (m, 1.5H), 1.17 (d, J=6.8 Hz, 3H), 1.12 (d, J=6.5 Hz, 3H). LC-MS: m/z 458.2 $(M+H)^+$.

Example 12

Assays for IDH1 R132H Inhibitors

[0474] Assays were conducted in a volume of 76 μl assay buffer (150 mM NaCl, 10 mM $MgCl_2$, 20 mM Tris pH 7.5, 0.03% bovine serum albumin) as follows in a standard 384-well plate: To 25 ul of substrate mix (8 uM NADPH, 2 mM aKG), 1 μl of test compound was added in DMSO. The plate was centrifuged briefly, and then 25 μl of enzyme mix was added (0.2 μg/ml IDH1 R132H) followed by a brief centrifugation and shake at 100 RPM. The reaction was incubated for 50 minutes at room temperature, then 25 μl of detection mix (30 μM resazurin, 36 μg/ml) was added and the mixture further incubated for 5 minutes at room temperature. The conversion of resazurin to resorufin was detected by fluorescent spectroscopy at Ex544 Em590 c/o 590.

[0475] Certain of the compounds of Formula I set forth in Tables 1 and 5 were tested in this assay and the results set forth below in Table 3. As used in Table 3, "A" refers to an inhibitory activity against IDH1 R132H with an $IC_{50} \leq 1.0$ μM; "B" refers to an inhibitory activity against IDH1 R132H with an IC_{50} greater than 1 μM and ≤5 μM; "C" refers to an inhibitory activity against IDH1 R132H with an IC_{50} greater than 5 μM and ≤15 μM.

TABLE 3

IDH1 R132H Inhibition by Compounds of Formula I.

Cmpd No.	IC_{50}
100	C
101	B
102	B
103	C
104	C
105	B
106	C
107	B

TABLE 3-continued

IDH1 R132H Inhibition by Compounds of Formula I.

Cmpd No.	IC_{50}
108	C
109	C
110	B
111	C
113	C
114	B
115	B
116	C
117	C
118	C
119	C
120	B
121	C
122	C
123	C
124	C
125	C
126	B
127	C
128	B
129	C
130	B
131	B
132	B
133	B
134	B
135	B
136	C
137	C
138	B
139	B
140	B
141	C
142	B
143	B
144	B
145	B
146	C
147	C
148	B
149	B
150	B
151	B
152	B
153	C
154	C
155	C
156	B
157	C
158	B
159	C
160	C
161	B
162	B
163	B
164	B
165	B
166	C
167	B
168	B
169	B
170	B
171	B
172	C
173	B
174	B
175	B
176	B
177	B
178	B
179	B
180	B
181	B

TABLE 3-continued

IDH1 R132H Inhibition by Compounds of Formula I.

Cmpd No.	IC_{50}
182	A
183	B
184	B
185	B
187	A
188	B
189	B
190	C
191	A
192	B
193	B
195	B
196	B
197	B
198	B
199	B
200	B
201	B
202	B
203	B
204	B
205	B
206	B
207	A
208	B
209	B
210	C
211	B
212	A
213	B
214	B
215	B
216	B
217	B
218	B
219	A
220	B
221	B
222	A
223	A
224	A
225	A
226	A
227	A
228	B
229	A
230	B
231	B
232	B
233	B
234	A
235	A
236	A
237	B
238	B
239	B
240	B
241	A
242	A
243	A
244	B
245	B
246	A
247	B
248	A
249	A
250	A
251	A
252	A
253	A
254	B
255	A
256	A

TABLE 3-continued

IDH1 R132H Inhibition by Compounds of Formula I.

Cmpd No.	IC_{50}
257	A
258	A
259	A
260	A
261	A
262	A

[0476] Certain of the compounds of Formula I set forth in Table 5 were tested in this assay and the assay in Example 13 and the results set forth below in Table 4. As used in Table 4, "A1" refers to an inhibitory activity against IDH1 R132H with an $IC_{50} \leq 0.5$ μM or an IC_{50} for inhibition of 2-HG production ≤0.5 μM; "B1" refers to an inhibitory activity against IDH1 R132H with an IC_{50} greater than 0.5 μM and ≤1 μM or an IC_{50} for inhibition of 2-HG production greater than 0.5 μM and ≤1 μM; "C1" refers to an inhibitory activity against IDH1 R132H with an IC_{50} greater than 1 μM and ≤10 μM or an IC_{50} for inhibition of 2-HG production greater than 1 μM and ≤10 μM; and "D1" refers to an inhibitory activity against IDH1 R132H with an IC_{50} greater than 10 μM or an IC_{50} for inhibition of 2-HG production greater than 10 μM.

TABLE 4

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
263	A1	B1	C1
264	B1	C1	C1
265	A1	C1	C1
266	A1	C1	C1
267	B1	C1	C1
268	B1	C1	C1
269	A1	C1	C1
270	B1	C1	C1
271	A1	C1	C1
272	B1	C1	C1
273	B1		
274	B1	C1	C1
275	A1	C1	C1
276	A1	C1	C1
277	A1	C1	C1
278	B1	C1	C1
279	B1	C1	C1
280	A1	C1	C1
281	B1		
282	B1		
283	A1	B1	C1
284	B1		
285	A1	B1	C1
286	A1	A1	A1
287	A1	C1	C1
288	A1	A1	A1
289	A1		
290	A1		
291	B1		
292	A1	B1	C1
293	A1	C1	C1
294	A1	B1	B1
295	A1	B1	B1
296	A1	B1	B1
297	A1	B1	C1
298	B1		
299	A1	B1	B1
300	B1		
301	A1	C1	C1

TABLE 4-continued

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
302	A1	C1	C1
303	A1	C1	C1
304	A1	C1	B1
305	B1		
306	B1		
307	A1	C1	C1
308	A1	C1	C1
309	A1	B1	B1
310	B1		
311	B1		
312	A1	B1	C1
313	A1	C1	B1
314	B1		
315	A1	A1	B1
316	B1		
317	B1		
318	A1		
319	A1		
320	A1	B1	A1
321	A1	B1	A1
322	A1		
323	A1	B1	B1
324	B1		
325	A1	A1	A1
326	A1	B1	A1
327	B1		
328	A1		
329	B1		
330	A1	A1	A1
331	A1		
332	B1		
333	A1		
334	B1		
335	A1	B1	A1
336	B1		
337	B1		
338	A1		
339	B1		
340	A1	B1	B1
341	A1		
342	A1	A1	A1
343	A1	A1	A1
344	B1		
345	A1	C1	B1
346	A1	C1	B1
347	A1	A1	A1
348	A1		
349	B1		
350	A1	C1	B1
351	A1	C1	B1
352	A1	C1	B1
353	A1	B1	B1
354	B1		
355	B1		
356	A1	C1	C1
357	B1		
358	A1		
359	A1		
360	A1	C1	C1
361	A1	C1	B1
362	A1		
363	A1	C1	B1
364	A1	B1	A1
365			
366			
367			
368	B1		
369	B1		
370	B1		
371	B1		
372	A1		
373	A1	C1	B1

TABLE 4-continued

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
374	A1	C1	B1
375	B1		
376	A1	C1	B1
377	A1	B1	A1
378	A1		
379	B1		
380	A1	B1	B1
381	A1	A1	A1
382	A1	A1	B1
383	A1	C1	C1
384	A1	B1	B1
385	B1		
386	A1	C1	B1
387	A1	A1	A1
388	A1	C1	B1
389	A1	A1	A1
390	A1	A1	A1
391	A1	B1	B1
392	A1		
393	A1	C1	B1
394	B1		
395	B1		
396	A1		
397	A1		
398	A1	C1	B1
399	B1		
400	B1	C1	C1
401	B1	C1	C1
402	A1		
403	A1	B1	B1
404	B1		
405	A1		
406	A1	C1	C1
407	A1	A1	A1
408	A1	B1	A1
409	A1	A1	A1
410	A1	A1	A1
411	A1	B1	B1
412	A1	C1	B1
413	B1		
414	B1		
415	A1	C1	C1
416	B1	C1	B1
417	A1	A1	A1
418	A1	A1	A1
419	A1	A1	A1
420	A1	C1	C1
421	B1		
422	B1		
423	B1		
424	A1	B1	B1
425	B1	C1	C1
426	B1	C1	C1
427	A1	A1	A1
428	A1	A1	B1
429	A1	C1	C1
430	C1		
431	B1	B1	B1
432	B1	C1	C1
433	A1	A1	A1
434	A1	C1	C1
435	B1		
436	A1	B1	B1
437	B1		
438	A1	C1	B1
439	A1	A1	
440	A1		
441	B1		
442	A1	A1	A1
443	A1	A1	A1
444	A1	A1	A1
445	A1	C1	

TABLE 4-continued

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
446	A1	A1	C1
447	B1	C1	C1
448	A1	C1	C1
449	B1	C1	C1
450	B1		
451	A1	C1	C1
452	A1	C1	C1
453	A1	B1	A1
454	A1	A1	A1
455	B1		
456	A1	A1	A1
457	A1	B1	B1
458	A1	B1	B1
459	A1	A1	A1
460	A1		
461	B1		
462	B1	C1	C1
463	A1	C1	C1
464	B1		
465	B1		
466	A1	C1	B1
467	B1		
468	A1	C1	C1
469	A1	C1	C1
470	A1	C1	C1
471	A1		
472	A1	A1	A1
473	A1	C1	B1
474	A1		/
475	A1	B1	A1
476	A1	B1	A1
477	B1		
478	B1		
479	B1		
480	A1	A1	A1
481	A1	A1	A1
482	A1		
483	A1	C1	B1
484	B1		
485	A1	A1	A1
486	B1		
487	A1		
488	A1	A1	B1
489	B1		
490	B1		
491	A1	B1	
492	B1	B1	
493	B1		
494	A1		
495	B1		
496	B1	B1	A1
497	A1		
498	A1	A1	A1
499	B1	C1	C1
500	A1	A1	A1
501	B1		
502	B1		
503	A1		
504	B1		
505	A1		
506	B1		
507	B1		
508	A1	A1	A1
509	B1		
510	B1		
511	A1	B1	
512	A1		
513	B1		
514	A1	A1	
515	B1	C1	
516	A1	B1	
517	A1	B1	

TABLE 4-continued

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
518	A1	A1	A1
519	B1		
520	B1	A1	
521	A1		
522	B1	C1	
523	B1		
524	A1		
525	A1		
526	B1	A1	A1
527	A1	A1	A1
528	A1	B1	A1
529	A1	B1	
530	A1	A1	A1
531	A1		
532	A1		
533	B1	C1	
534	A1		
535	A1	A1	
536	A1	A1	
537	A1	B1	
538	A1		
539	A1	C1	
540	A1		
541	A1	A1	A1
542	A1	A1	A1
543	B1		
544	A1	B1	
545	B1		
546	A1	A1	A1
547	A1	A1	A1
548	B1		
549	A1		
550	B1	A1	A1
551	A1	A1	A1
552	A1		
553	A1	A1	
554	A1		
555	A1	B1	
556	A1		
557	A1	B1	
558	A1	A1	A1
559	A1	C1	
560	A1	C1	
561	A1	A1	A1
562	A1	A1	A1
563	A1	A1	
564	A1		
565	A1	B1	B1
566	A1	B1	
567	B1		
568	A1	A1	A1
569	A1	A1	
570	A1	A1	
571	A1	A1	
572	A1	A1	
573	A1	A1	A1
574	A1	A1	
575	A1	A1	
576	B1	A1	
577	A1	A1	
578	A1	A1	
579	A1	A1	A1
580	A1	A1	A1
581	A1	A1	A1
582	A1	C1	
583	B1		
584	B1		
585	A1	A1	A1
586	A1		
587	A1	A1	A1
588	A1	A1	
589	A1	A1	A1

TABLE 4-continued

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
590	A1	A1	A1
591	A1	A1	A1
592	A1	A1	A1
593	B1		
594	A1	A1	
595	A1	A1	A1
596	A1	A1	
597	A1	A1	A1
598	A1	B1	
599	A1	A1	A1
600	B1	B1	
601	A1		
602	A1	A1	
603	A1	A1	A1
604	A1	A1	
605	A1	A1	A1
606	A1	A1	
607	A1	A1	
608	A1	A1	A1
609	A1	A1	A1
610	A1	A1	A1
611	A1	A1	A1
612	A1	A1	A1
613	A1	A1	A1
614	A1		
615	A1	A1	A1
616	A1		
617	A1	A1	A1
618	A1	A1	A1
619	A1	A1	
620	A1	A1	
621	A1	A1	B1
622	B1	C1	
623	B1		
624	A1	A1	
625	A1	A1	A1
626	A1	A1	A1
627	A1	A1	A1
628	A1	A1	A1
629	A1	A1	A1
630	B1		
631	A1	A1	A1
632	A1		
633	A1	A1	A1
634	A1	A1	A1
635	A1	A1	A1
636	A1	A1	A1
637	A1	A1	A1
638	A1	A1	A1
639	A1	A1	A1
640	A1		
641	A1		
642	A1	A1	A1
643	A1	A1	B1
644	A1	A1	A1
645	A1	A1	A1
646	A1		
647	A1	A1	A1
648	A1	A1	A1
649	A1	A1	A1
650	A1		A1
651	A1		A1
652	A1	A1	A1
653	A1	A1	
654	A1	A1	A1
655	A1	A1	
656	B1		
657	A1	A1	A1
658	A1		A1
659	A1		
660	A1	A1	A1
661	A1		

TABLE 4-continued

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
662	A1	A1	
663	A1	A1	A1
664	A1	A1	
665	A1		
666	A1	A1	A1
667	A1	A1	A1
668	A1	B1	
669	A1	A1	
670	A1	A1	A1
671	A1		
672	B1	C1	
673	B1		
674	A1	A1	A1
675	A1	C1	B1
676	A1	A1	A1
677	A1	A1	
678	A1	A1	A1
679	A1	A1	
680	A1	A1	
681	A1	A1	A1
682	A1		
683	A1		
684	A1	A1	
685	C1		
686	A1	A1	A1
687	A1		B1
688	A1	A1	A1
689	A1	A1	A1
690	A1	A1	A1
691	A1	A1	A1
692	A1	A1	A1
693	A1	A1	A1
694	A1	B1	A1
695	A1	A1	A1
696	A1	A1	A1
697	A1	A1	A1
698	A1	A1	A1
699	A1		
700		A1	A1
701	A1		
702	A1	C1	C1
703	A1	A1	A1
704	A1		
705	A1	A1	A1
706	A1	A1	A1
707	A1	A1	A1
708	A1		C1
709	A1	A1	A1
710	A1	A1	A1
711	A1	A1	A1
712	A1	C1	
713	A1	A1	A1
714	A1	A1	A1
715	A1	A1	A1
716	A1	A1	A1
717	A1	A1	A1
718	A1	B1	A1
719	A1	A1	A1
720	A1	A1	A1
721	A1	A1	A1
722	A1	A1	A1
723	A1		
724	A1	A1	A1
725	A1	A1	A1
726	A1	A1	A1
727	A1	A1	A1
728	A1	A1	A1
729	A1		
730	A1	A1	A1
731	A1		
732	A1	A1	A1
733	A1	B1	A1

TABLE 4-continued

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
734	A1		
735	A1	A1	A1
736	A1	A1	A1
737	A1	B1	B1
738	A1	A1	A1
739	A1		
740	A1	A1	A1
741	A1	A1	A1
742	A1	A1	A1
743	A1	A1	A1
744	A1	A1	A1
745	A1	A1	A1
746	A1	A1	A1
747	A1	A1	A1
748	A1	A1	A1
749	A1	A1	A1
750	A1	A1	A1
751	A1	A1	A1
752	A1	A1	A1
753	A1	A1	A1
754	A1	A1	A1
755	A1	A1	A1
756	A1	A1	A1
757	A1		A1
758	A1		A1
759	A1		A1
760	A1	A1	A1
761	A1	A1	A1
762	A1	A1	A1
763	A1	A1	A1
764	A1	A1	A1
765	A1	A1	A1
766	A1	A1	A1
767	A1	A1	A1
768	A1	A1	A1
769	A1	A1	A1
770	A1	A1	A1
771	A1	A1	A1
772	B1		
773	A1		A1
774	A1	A1	A1
775	A1	A1	A1
776	A1	A1	A1
777	A1	A1	A1
778	A1	A1	A1
779	C1		
780	A1		
781	A1	A1	A1
782	A1	A1	A1
783		A1	A1
784	A1	A1	A1
785	A1	A1	A1
786	A1	A1	A1
787	A1	A1	A1
788	A1	A1	A1
789	A1	A1	A1
790	A1		
791	A1		
792	A1	C1	C1
793	A1	A1	A1
794	A1	A1	A1
795	A1		
796	A1	A1	A1
797	A1	A1	A1
798	A1		
799	A1	A1	A1
800	A1	A1	A1
801	A1	A1	A1
802	A1		
803	A1	A1	A1
804	A1	A1	B1
805	A1	A1	A1

TABLE 4-continued

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
806	A1	A1	A1
807	A1	A1	
808	A1	A1	
809	A1	A1	
810	B1	A1	A1
811	A1	A1	A1
812	A1	A1	A1
813	A1	A1	A1
814	B1		
815	A1	A1	
816	B1		
817	A1	A1	
818	A1	A1	
819	A1	A1	
820	A1		
821	A1		
822	A1	A1	
823	A1	A1	
824	A1		
825	A1		
826	A1		
827	A1		
828	A1		
829	A1		
830	A1		

[0477] In some embodiments, the invention provides a compound selected from any one of compound numbers 182, 187, 191, 207, 212, 219, 222, 223, 224, 225, 226, 227, 229, 234, 235, 236, 241, 242, 243, 246, 248, 249, 250, 251, 252, 253, 255, 256, 257, 258, 259, 260, 261, and 262.

[0478] In some embodiments, the invention provides a compound selected from any one of compound numbers 263, 265, 266, 269, 271, 275, 276, 277, 280, 283, 285, 286, 287, 288, 289, 290, 292, 293, 294, 295, 296, 297, 299, 301, 302, 303, 304, 307, 308, 309, 312, 313, 315, 318, 319, 320, 321, 322, 323, 325, 326, 328, 330, 331, 333, 335, 338, 340, 341, 342, 343, 345, 346, 347, 348, 350, 351, 352, 353, 356, 358, 359, 360, 361, 362, 363, 364, 372, 373, 374, 376, 377, 378, 380, 381, 382, 383, 384, 386, 387, 388, 389, 390, 391, 392, 393, 396, 397, 398, 402, 403, 405, 406, 407, 408, 409, 410, 411, 412, 415, 417, 418, 419, 420, 424, 427, 428, 429, 433, 434, 436, 438, 439, 440, 442, 443, 444, 445, 446, 448, 451, 452, 453, 454, 456, 457, 458, 459, 460, 463, 466, 468, 469, 470, 471, 472, 473, 474, 475, 476, 480, 481, 482, 483, 485, 487, 488, 491, 494, 497, 498, 500, 503, 505, 508, 511, 512, 514, 516, 517, 518, 521, 524, 525, 527, 528, 529, 530, 531, 532, 534, 535, 536, 537, 538, 539, 540, 541, 542, 544, 546, 547, 549, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 568, 569, 570, 571, 572, 573, 574, 575, 577, 578, 579, 580, 581, 582, 585, 586, 587, 588, 589, 590, 591, 592, 594, 595, 596, 597, 598, 599, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 624, 625, 626, 627, 628, 629, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742,

743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 773, 774, 775, 776, 777, 778, 780, 781, 782, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 811, 812, 813, 815, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, and 830.

Example 13

Cellular Assays for IDH1m (R132H or R132C) Inhibitors

[0479] Cells (e.g., HT1080 or U87MG) and are grown in T125 flasks in DMEM containing 10% FBS, 1× penicillin/streptomycin and 500 ug/mL G418. They are harvested by trypsin and seeded into 96 well white bottom plates at a density of 5000 cell/well in 100 ul/well in DMEM with 10% FBS. No cells are plates in columns 1 and 12. Cells are incubated overnight at 37° C. in 5% CO2. The next day compounds are made up at 2× concentration and 100 ul are added to each cell well. The final concentration of DMSO is 0.2% and the DMSO control wells are plated in row G. The plates are then placed in the incubator for 48 hours. At 48 hours, 100 μl of media is removed from each well and analyzed by LC-MS for 2-HG concentrations. The cell plate is placed back in the incubator for another 24 hours. At 72 hours post compound addition, 10 mL/plate of Promega Cell Titer Glo reagent is thawed and mixed. The cell plate is removed from the incubator and allowed to equilibrate to room temperature. Then 100 ul of reagent is added to each well of media. The cell plate is then placed on an orbital shaker for 10 minutes and then allowed to sit at room temperature for 20 minutes. The plate is then read for luminescence with an integration time of 500 ms.

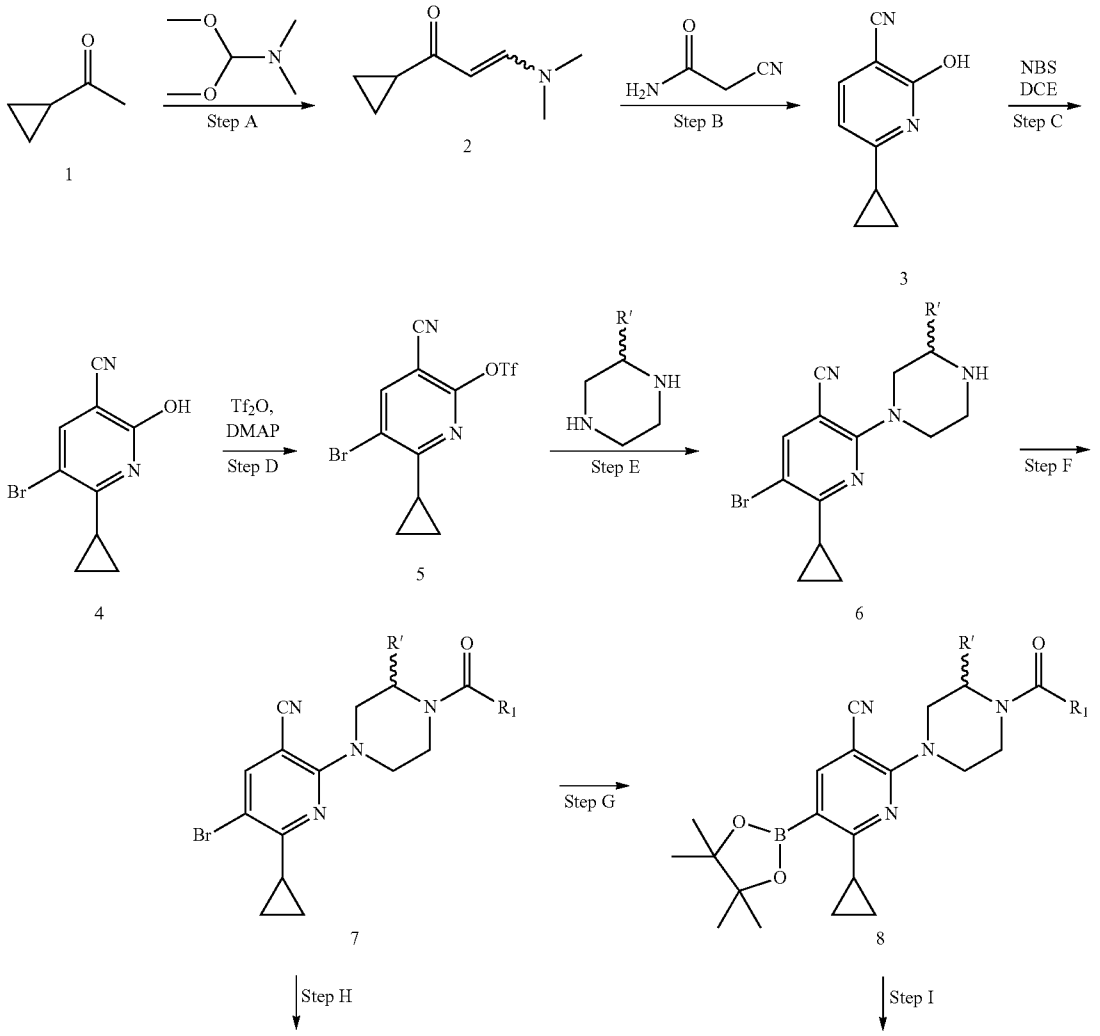
[0480] The IC_{50} for inhibition of 2-HG production (concentration of test compound to reduce 2HG production by 50% compared to control) in these two cell lines for various compounds of formula I is set forth in Table 4 above.

Example 14

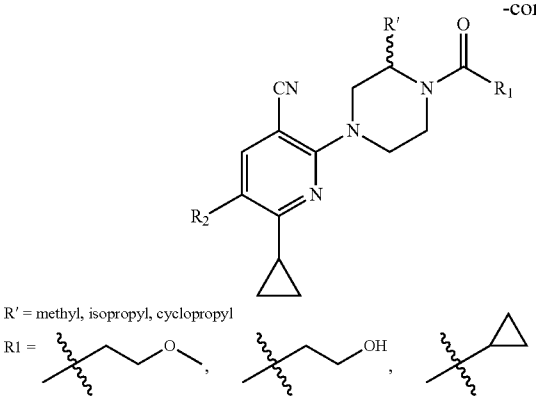
Preparation of 2,3,5,6-Tetrasubstituted Pyridines

General procedure 1

[0481]

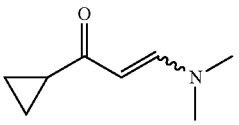


-continued



Step A: 1-cyclopropyl-3-(dimethylamino)prop-2-en-1-one (2)

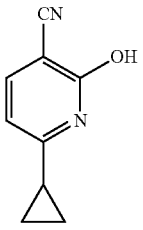
[0482]



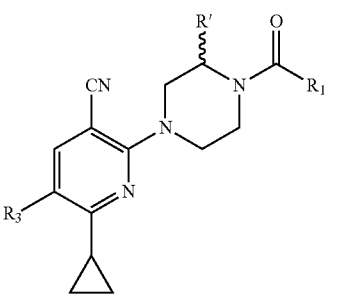
[0483] To a solution of 1-cyclopropylethanone (100 g, 1.2 mol) in anhydrous DMF (1300 mL) Was added DMFDMA (300 g, 2.5 mol). The resulting mixture was stirred at 100° C. overnight. The solvent was removed in vacuum to give crude 2 (110 g) as yellow solid. ^{1}H NMR (CHLOROFORM-d) δ 7.56 (d, J=12.8 Hz, 1H), 5.20 (d, J=12.5 Hz, 1H), 2.78-3.08 (m, 6H), 1.79 (tt, J=7.9, 4.5 Hz, 1H), 0.94-1.04 (m, 2H), 0.67-0.80 (m, 2H).

Step B: 6-cyclopropyl-2-hydroxynicotinonitrile (3)

[0484]

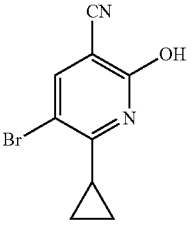


[0485] To a mixture of 1-cyclopropyl-3-dimethylamino-propenone (315 g, 2.3 mol) and cyanoacetamide (270 g, 2.3 mol) in a buffer solution of 47.4 mL of acetic acid and 1485 mL of water was added piperidine to adjust to pH 9. The mixture was then heated at reflux for 2 hours, cooled and acidified by 6N HCl to pH 5 below 25 degree. The yellow precipitate was filtered, washed with water and dried to give 3 as a white solid (561 g). MS (ES) M+H expected 161.1, found 161.0. ^{1}H NMR (CHLOROFORM-d) δ 13.60 (br. s., 1H), 7.77 (d, J=7.8 Hz, 1H), 5.91 (d, J=7.8 Hz, 1H), 1.96-2.12 (m, 1H), 1.29-1.36 (m, 2H), 1.04-1.11 (m, 2H).



Step C: 5-bromo-6-cyclopropyl-2-hydroxynicotinonitrile (4)

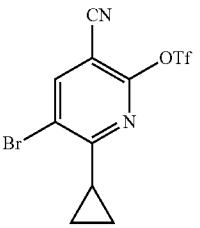
[0486]



[0487] A mixture of 6-cyclopropyl-2-hydroxynicotinonitrile (561 g, 3.6 mol) and NBS (624 g, 5.4 mol) in DCE (4500 mL) was heated at reflux for 3 hrs. The mixture was cooled to room temperature and the precipitate was filtered, washed with water and dried to give crude 4 (473 g) as a white solid. MS (ES) M+H expected 239.0, found 238.9. ^{1}H NMR (CHLOROFORM-d) δ 8.49-8.72 (br. s., 1H), 7.93 (s, 1H), 2.23-2.34 (m, 1H), 1.36-1.42 (m, 2H), 1.29-1.36 (m, 2H).

Step D: 5-bromo-3-cyano-6-cyclopropylpyridin-2-yl trifluoromethanesulfonate (5)

[0488]



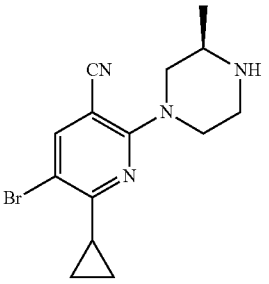
[0489] To a 1 L flask were added 5-bromo-4-cyclopropyl-2-hydroxybenzonitrile (47.6 g, 0.2 mol), pyridine (32 g, 0.4 mol) and Cat. DMAP (500 mg) in DCM (300 mL), and the mixture was cooled to 0° C., and trifluoromethanesulfonic anhydride (59 g, 0.21 mol) in DCM (100 mL) was added dropwise. After addition, the mixture was stirred for another 1 h. TLC (PE:EtOAc=10:1) showed conversion of starting

material to product. After reaction, diluted with DCM (300 mL), and washed with 1N HCl. The organic layer was dried over Na_2SO_4 and concentrated in vacuo afforded the title compound (70 g) as a yellow solid. ^{1}H NMR (CHLOROFORM-d) δ 8.14-8.19 (m, 1H), 2.55-2.66 (m, 1H), 1.30 (dt, J=7.8, 3.1 Hz, 2H), 1.21-1.27 (m, 2H).

Step E: Exemplified by (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6-1) (R'=methyl)

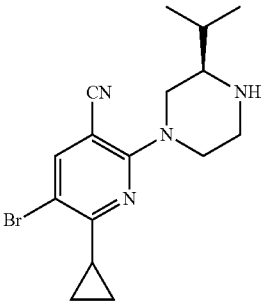
[0490]

6-1



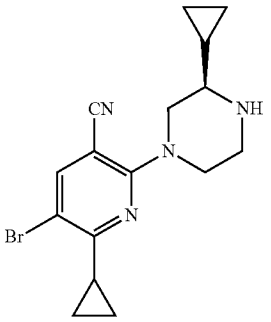
[0491] A mixture of above triflate 5 (1.68 g, 4.6 mmol), (R)-2-methylpiperazine (790 mg, 6.9 mmol), and triethylamine (1.9 mL, 13.8 mmol) suspended in 5 mL of MeCN was heated at 70° C. for 2 h. After the mixture was concentrated under reduced pressure, the residue was extracted between ethyl acetate and water. The combined organic layer was then washed with aq. $NaHCO_3$, brine, dried over anhy. Na_2SO_4 and concentrated in vacuo to give 1.26 g of crude title compound. MS (ES) M+H expected 321.1, found 321.2. ^{1}H NMR (CHLOROFORM-d) δ 7.78 (s, 1H), 4.14-4.24 (m, 2H), 3.09-3.14 (m, 1H), 3.02-3.07 (m, 1H), 2.96-3.00 (m, 2H), 2.71 (dd, J=12.9, 10.2 Hz, 1H), 2.42-2.52 (m, 1H), 1.16 (d, J=6.3 Hz, 3H), 1.08 (s, 2H), 1.07 (d, J=3.8 Hz, 2H).

6-2



[0492] (R)-5-bromo-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)nicotinonitrile (6-2) (R'=isopropyl) was synthesized by the same procedure described above except using (R)-2-isopropylpiperazine instead of (R)-2-methylpiperazine. MS (ES) M+H expected 349.1, found 349.2. ^{1}H NMR (CHLOROFORM-d) δ 7.79 (s, 1H), 4.14-4.24 (m, 2H), 3.09-3.14 (m, 1H), 3.02-3.07 (m, 1H), 2.96-3.00 (m, 2H), 2.71 (dd, 1H), 2.12-2.22 (m, 1H), 1.26 (d, 6H), 1.08 (d, 2H), 1.07 (d, 2H).

6-3

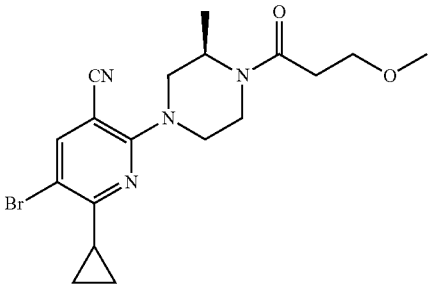


[0493] (R)-5-bromo-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile (6-3) (R'=cyclopropyl) was synthesized by the same procedure described above except using (R)-2-cyclopropylpiperazine (building block 1) instead of (R)-2-methylpiperazine. MS (ES) M+H expected 347.1, found 349.1. ^{1}H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 4.14-4.24 (m, 2H), 3.09-3.14 (m, 1H), 3.02-3.07 (m, 1H), 2.96-3.00 (m, 2H), 2.71 (dd, 1H), 2.12-2.24 (m, 1H), 1.25 (d, 2H), 1.16 (d, 2H), 1.08 (d, 2H), 1.07 (d, 2H).

Step F, method 1: Exemplified by (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (7-1) (R'=methyl, R1=c)

[0494]

7-1

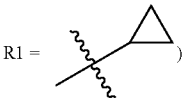


[0495] To a 25 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6-1) (1.26 g, 3.9 mmol), 3-methoxypropanoic acid (0.74 mL, 7.8 mmol), HATU (2.98 g, 7.8 mmol), DIPEA (2 mL, 11.76 mmol) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. Reaction mixture was with satd. $NaHCO_3$ and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography purification (30% EtOAc/petroleum ether) afforded 1.28 g of title compound as a white solid. MS (ES) M+H expected 407.1, found 407.0. ^{1}H NMR (CHLOROFORM-d) δ 7.78-7.85 (m, 1H), 4.82-4.92 (m, 0.5H), 4.50 (d, J=13.6 Hz, 0.5H), 4.18-4.21 (m, 2H), 4.07-4.16 (m, 1H), 3.75-3.82 (m, 0.5H), 3.70-3.75 (m, 2H), 3.45-3.55 (m, 0.5H), 3.36 (s, 3H), 3.15-3.27 (m, 1H), 2.92-3.14 (m, 1H), 2.67-2.78 (m, 1H), 2.51-2.61 (m,

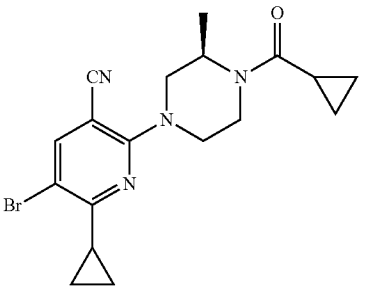
1H), 2.40-2.51 (m, 1H), 1.34 (d, J=6.8 Hz, 1.5H), 1.25 (d, J=2.5 Hz, 1.5H), 1.09 (d, J=3.5 Hz, 2H), 1.08 (s, 2H).

Step F, Method 2: Exemplified by (R)-5-bromo-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (7-2) (R'=methyl,

[0496]



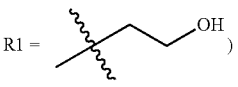
7-2



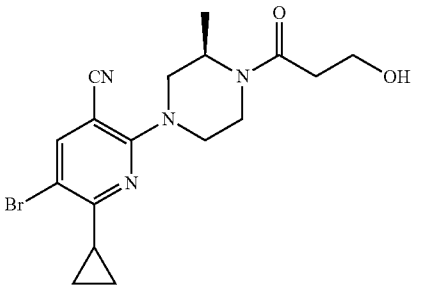
[0497] To a 25 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6-1) (1 g, 3.2 mmol), cyclopropanecarbonyl chloride (0.4 mL, 3.3 mmol), DIPEA (0.4 mL, 3.4 mmol) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. Reaction mixture was with Satd. $NaHCO_3$ and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography purification (10% EtOAc/petroleum ether) afforded 1.1 g of title compound as a white solid. MS (ES) M+H expected 389.1, found 389.0. ^{1}H NMR (CHLOROFORM-d) δ 7.85 (s, 1H), 4.18-4.21 (m, 2H), 4.07-4.16 (m, 1H), 3.70-3.75 (m, 2H), 3.15-3.27 (m, 1H), 2.92-3.14 (m, 1H), 2.67-2.78 (m, 1H), 2.51-2.61 (m, 1H), 2.40-2.51 (m, 1H), 1.34 (d, J=6.8 Hz, 1.5H), 1.25 (d, J=2.5 Hz, 1.5H), 1.25-1.36 (m, 4H), 1.09 (d, 2H), 1.08 (d, 2H).

Step F, method 3: Exemplified by (R)-5-bromo-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (7-3) (R'=methyl,

[0498]

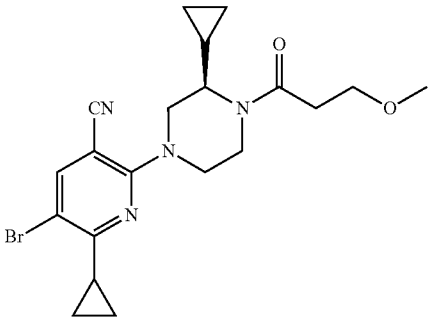


7-3



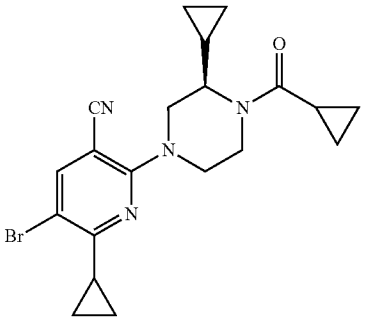
[0499] To a 25 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6-1) (2 g, 6.2 mmol), sodium 2-carboxyethanolate (0.70 g, 6.4 mmol), DIPEA (2 mL, 11.5 mmol) and 10 mL of DMF. The resulting reaction mixture was stirred at room temperature for 5 h until TLC showed the completion of the reaction. Reaction mixture was washed with water and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography purification (50% EtOAc/petroleum ether) afforded 1.2 g of title compound as a white solid. MS (ES) M+H expected 393.1, found 393.1. ^{1}H NMR (CHLOROFORM-d) δ 7.85 (m, 1H), 4.88-4.97 (m, 0.5H), 4.75 (d, J=13.6 Hz, 0.5H), 4.29-4.48 (m, 2H), 4.11-4.20 (m, 1H), 3.70-3.75 (m, 2H), 3.45-3.55 (m, 2H), 3.15-3.27 (m, 1H), 2.92-3.14 (m, 1H), 2.67-2.78 (m, 1H), 2.51-2.61 (m, 1H), 2.40-2.51 (m, 1H), 1.34 (d, J=6.8 Hz, 1.5H), 1.25 (d, J=2.5 Hz, 1.5H), 1.09 (d, J=3.5 Hz, 2H), 1.08 (s, 2H).

7-4



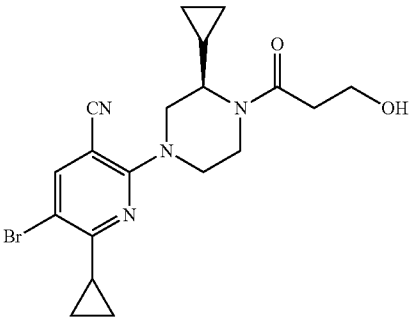
[0500] (R)-5-bromo-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (7-4) was synthesized by method 1 in step F except using 6-3 as the starting material instead of 6-1. MS (ES) M+H expected 433.1, found 433.3.

7-5



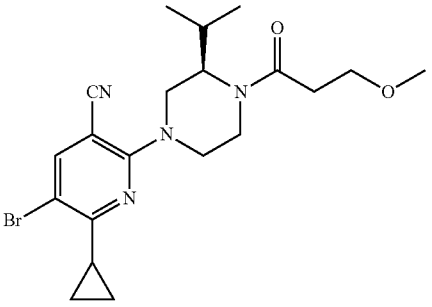
[0501] (R)-5-bromo-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (7-5) was synthesized by method 2 in step F except using 6-3 as the starting material instead of 6-1. MS (ES) M+H expected 415.1, found 415.1.

7-6



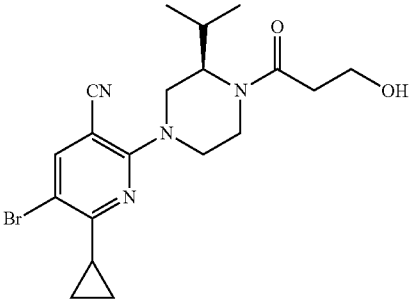
[0502] (R)-5-bromo-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile (7-6) was synthesized by method 3 in step F except using 6-3 as the starting material instead of 6-1. MS (ES) M+H expected 419.1, found 419.1. ^{1}H NMR (CHLOROFORM-d) δ 7.85 (m, 1H), 4.87-4.97 (m, 0.5H), 4.77 (d, J=13.6 Hz, 0.5H), 4.29-4.48 (m, 2H), 4.11-4.20 (m, 1H), 3.70-3.75 (m, 2H), 3.45-3.55 (m, 2H), 3.15-3.27 (m, 1H), 2.92-3.14 (m, 1H), 2.67-2.78 (m, 1H), 2.51-2.61 (m, 1H), 2.40-2.51 (m, 1H), 1.34 (d, J=6.8 Hz, 2H), 1.25 (d, 2H), 1.09 (d, J=3.5 Hz, 2H), 1.08 (s, 2H).

7-7



[0503] (R)-5-bromo-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (7-7) was synthesized by method 1 in step F except using 6-2 as the starting material instead of 6-1. MS (ES) M+H expected 434.1, found 435.1.

7-8

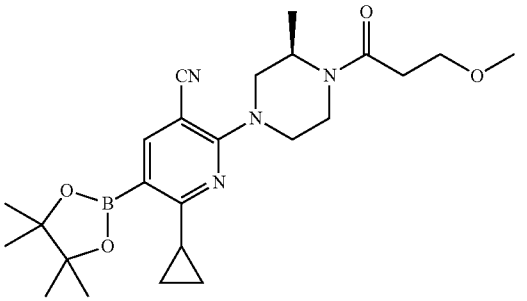


[0504] (R)-5-bromo-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)nicotinonitrile (7-8) was synthesized by method 1 in step F except using 6-2 as the starting material instead of 6-1. MS (ES) M+H expected 421.1, found 421.6.

Step G, method 1: Exemplified by (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinonitrile (8-1) (R'=methyl, R1=c)

[0505]

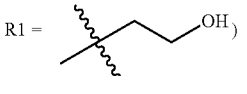
8-1



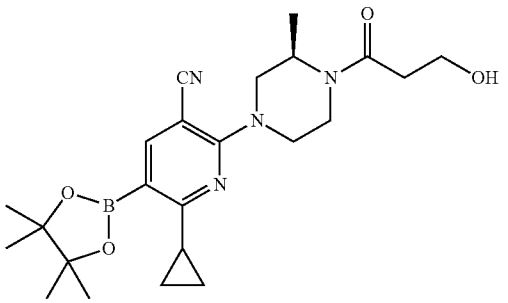
[0506] To a solution of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (7-1) (747 mg, 1.8 mmol) in DMF (8 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2 dioxaborolane) (563 mg, 2.2 mmol) and KOAc (538 mg, 5.5 mmol). The resulting mixture was stirred at room temperature for 5 min before addition of $PdCl_2(dppf).CH_2Cl_2$ (45 mg, 0.03 mmol). After flushing with nitrogen, the reaction mixture was heated at 85° C. for 18 hours. After cooling, the reaction mixture was diluted with water, and extracted with methylene chloride. The organic layer was then washed with brine, dried over anhy. Na_2SO_4, and concentrated in vacuo. Column chromatography (25% EtOAc/petroleum ether) afforded 334 mg of title compound as a white solid. MS (ES) M+H expected 455.3, found 455.2.

Step G, method 2: Exemplified by (R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) nicotinonitrile (R'=methyl,

[0507]



8-2



[0508] 1.4 g of (R)-5-bromo-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (7-3) (3.3 mmol), 2.12 g of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (8.34 mmol), 0.7 g of KOAc (7.4 mmol), 154 mg of Xphos (0.32 mmol) and 308 mg of $Pd_2(dba)_3$ (0.33 mmol) in 20 mL of dioxane in a round bottom flask was stirred under N_2 at 75° C. overnight. Then the mixture was cooled to room temperature. Concentrated, purified by column chromatography (petroleum ether: ethyl acetate from 3:1 to 1:1) to give 670 mg of title compound. MS (ES) M+H expected 441.2, found 441.2.

General procedure 1, Step H: Exemplified by (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(thiophen-2-yl)nicotinonitrile (Compound 273)

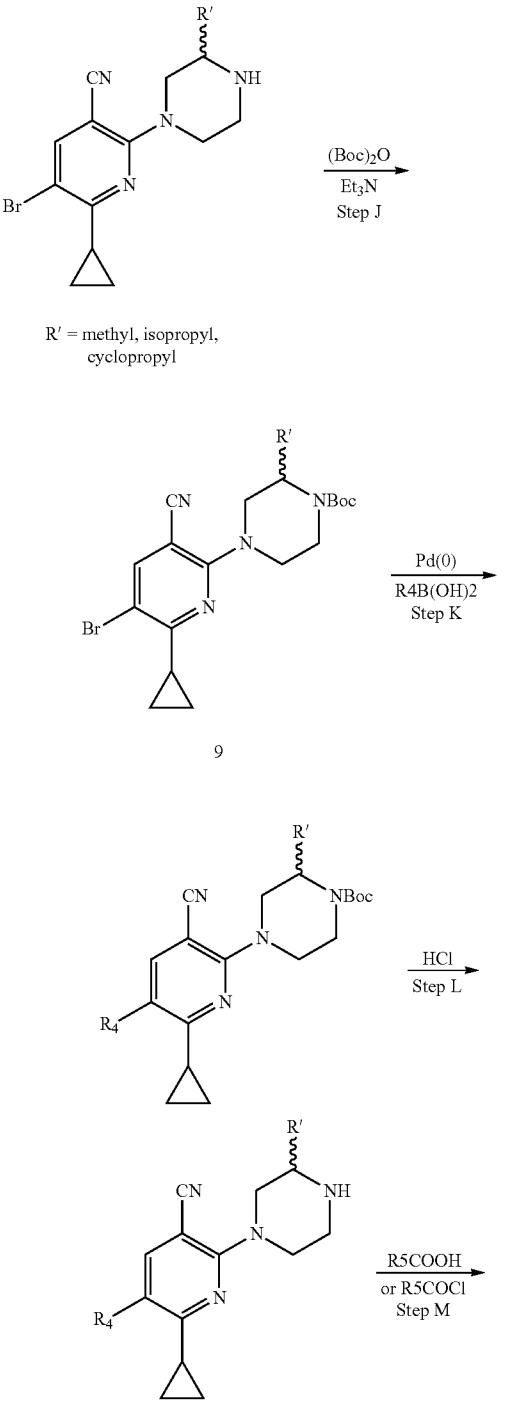
[0509] A mixture of 7-1 (26 mg, 0.06 mmol), thiophen-2-ylboronic acid (14 mg, 0.089 mmol), $Pd(PPh_3)_4$ (3 mg, 0.003 mmol), and K_2CO_3 (16 mg, 0.119 mmol) suspended in 1 mL of DMF was subjected to microwave reaction at 150° C. for 45 min. After the reaction was complete, the reaction mixture was concentrated in vacuo, and the residue was purified by column Chromatography to afford 19 mg of title compound as yellowish oil. ^{1}H NMR (CHLOROFORM-d) δ 7.70 (s, 1H), 7.38 (dd, J=3.9, 2.4 Hz, 1H), 7.07-7.14 (m, 2H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 4.15-4.41 (m, 2.5H), 3.67-3.89 (m, 2.5H), 3.47-3.63 (m, 0.5H), 3.34-3.43 (m, 3H), 3.20-3.33 (m, 1H), 2.99-3.17 (m, 1.5H), 2.63-2.81 (m, 1H), 2.50-2.62 (m, 1H), 2.26-2.36 (m, 1H), 1.37 (d, J=6.3 Hz, 1.5H), 1.27 (d, J=6.8 Hz, 1.5H), 1.10-1.18 (m, 2H), 0.94-1.05 (m, 2H). LC-MS: m/z 411.1 $(M+H)^+$.

Step I: Exemplified by(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinazolin-5-yl)nicotinonitrile (Compound 603)

[0510] To a solution of 8-1 (95 mg, 0.197 mmol), 5-chloro-2-vinylquinazoline (25 mg, 0.131 mmol), Xphos (7 mg, 0.013 mmol), $Pd_2(dba)_3$ (6 mg, 0.007 mmol) and $K_3PO_4.H_2O$ (105 mg, 0.393 mmol) was stirred at 100° C. for 16 hours, the mixture was partitioned between EtOAc and water, the organic was washed with water, brine and concentrated to give the crude which was purified by column chromatography to give 25 mg of the product. ^{1}H NMR (CHLOROFORM-d) δ 9.16 (d, J=3.0 Hz, 1H), 8.05 (d, J=8.5 Hz, 1H), 7.95 (dd, J=8.5, 7.3 Hz, 1H), 7.66 (s, 1H), 7.45-7.58 (m, 1H), 7.06 (dd, J=17.2, 10.4 Hz, 1H), 6.80 (dd, J=17.3, 1.5 Hz, 1H), 5.80-5.96 (m, 1H), 4.87-5.02 (m, 0.5H), 4.56 (d, J=12.0 Hz, 0.5H), 4.35-4.44 (m, 2.5H), 3.84 (d, J=12.8 Hz, 0.5H), 3.69-3.79 (m, 2H), 3.52-3.65 (m, 0.5H), 3.30-3.43 (m, 4H), 3.05-3.24 (m, 1.5H), 2.65-2.81 (m, 1H), 2.48-2.64 (m, 1H), 1.50-1.59 (m, 1H), 1.30-1.44 (m, 3H), 1.13-1.22 (m, 2H), 0.84-0.89 (m, 2H). LC-MS: m/z 483.2 $(M+H)^+$

General Procedure 2

[0511]



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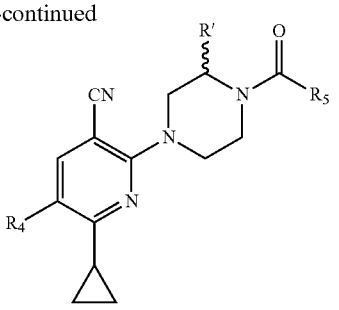
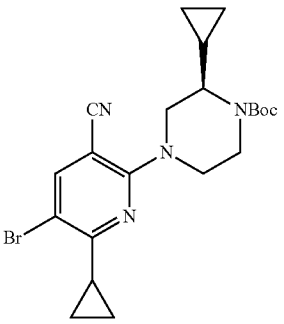


Step J: Exemplified by (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiper-azine-1-carboxylate (9-1, R'=cyclopropyl)

[0512]

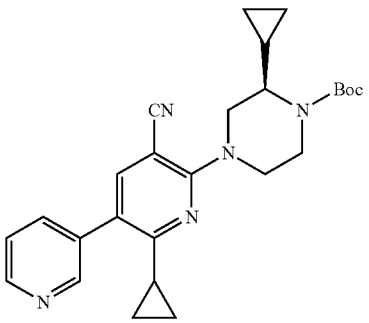
9-1



[0513] To a solution of 6-3 (1 g, 2.24 mmol) in DCM (8 mL) was added $(Boc)_2O$ (0.5 g, 2.26 mmol) and Et_3N (0.1 mL). The resultant solution was stirred at room temperature for 2 h. The reaction mixture was diluted with water. The organic layer was then washed with brine, dried over anhy. Na_2SO_4, and concentrated in vacuo to give the title compound as a white solid (1.5 g), which can be used directly for the next step. ^1H NMR (CHLOROFORM-d) δ 7.85 (s, 1H), 4.14-4.24 (m, 2H), 3.29-3.34 (m, 1H), 3.12-3.18 (m, 1H), 2.96-3.00 (m, 2H), 2.71 (dd, 1H), 2.12-2.24 (m, 1H), 1.5 (s, 9H), 1.25 (d, 2H), 1.16 (d, 2H), 1.08 (d, 2H), 1.07 (d, 2H).

Step K: Exemplified by (R)-tert-butyl 4-(5-cyano-2-cyclopropyl-[3,3'-bipyridin]-6-yl)-2-cyclopropyl piperazine-1-carboxylate (R'=cyclopropyl, R4=3-pyridinyl)

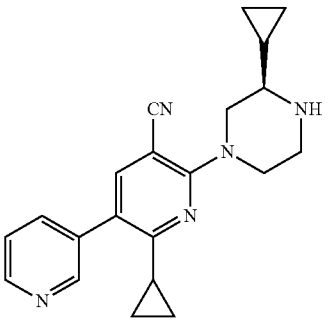
[0514]



[0515] To a solution of (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (150 mg, 0.33 mmol) in 2 mL of dioxane and 0.5 mL water was added pyridin-3-ylboronic acid (45.6 mg, 0.37 mmol), Pd(dppf)Cl2 (24 mg, 0.033 mmol), CsF (100 mg, 0.66 mmol). The resulting mixture was stirred at 100° C. under N2 atmosphere and microwaved for 1 h. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% EtOAc/petroleum ether) to afford 100 mg title compound. MS (ES) M+H expected 446.2, found 446.3.

Step L: Exemplified by (R)-2-cyclopropyl-6-(3-cyclopropylpiperazin-1-yl)-[3,3'-bipyridine]-5-carbonitrile (R'=cyclopropyl, R4=3-pyridinyl)

[0516]



[0517] To a solution of (R)-tert-butyl 4-(5-cyano-2-cyclopropyl-[3,3'-bipyridin]-6-yl)-2-cyclopropyl piperazine-1-carboxylate (100 mg, 0.22 mmol) in 3 mL of DCM was added TFA (1 mL). The resulting mixture was stirred at room temperature for 2 h. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and basified with Na_2CO_3 solution to pH=8. Then the solution was extracted with DCM (10 mL×3). The organic layer was dried and concentrated and purified by Prep-HPLC (5% DCM/MeOH) to get 70 mg title compound. MS (ES) M+H expected 346.2, found 346.2.

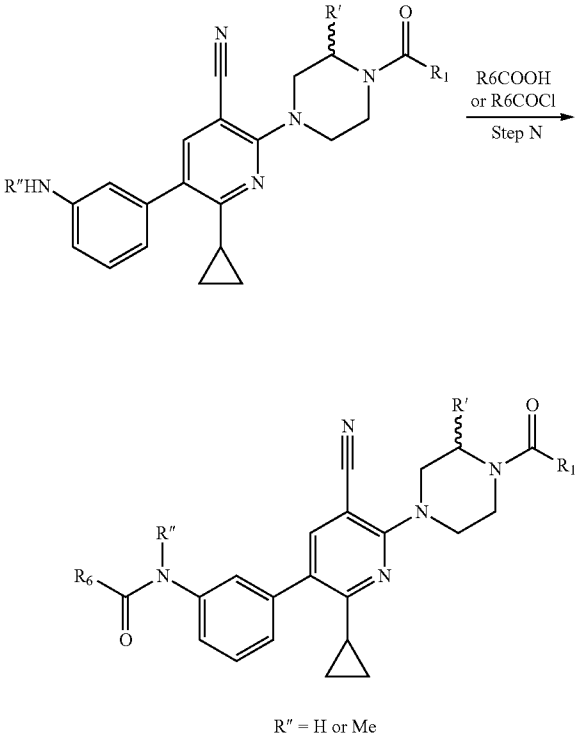
General Procedure 2, Step M: Exemplified by (R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-[3,3'-bipyridine]-5-carbonitrile (Compound 524)

[0518] To a solution of (R)-2-cyclopropyl-6-(3-cyclopropylpiperazin-1-yl)-[3,3'-bipyridine]-5-carbonitrile (70 mg, 0.2 mmol) in 10 mL DCM was added 3,3,3-trifluoropropanoic acid (31 mg, 0.24 mmol), and triethylamine (1 mL), HOBT (54 mg, 0.4 mmol), EDCI (76.8 mg, 0.4 mmol). The resulting reaction mixture was stirred at r.t. overnight. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by Prep-HPLC (50% EtOAc/petroleum ether) to get 25 mg title compound. ^1H NMR (CHLOROFORM-d) δ 8.56-8.77 (m, 2H), 7.77 (d, J=7.8 Hz, 1H), 7.65 (s, 1H), 7.44 (dd, J=7.7, 4.9 Hz, 1H), 4.56 (d, J=13.1 Hz, 1H), 4.44 (d, J=13.1 Hz, 1H), 4.12 (br. s., 1H), 3.63-3.86 (m, 2H), 3.32 (d, J=9.3 Hz, 2H), 3.20 (d, J=13.1 Hz, 1H), 3.11 (d, J=11.8 Hz, 1H), 1.99 (td, J=8.0, 3.8 Hz, 1H), 1.11-1.23 (m, 3H), 1.01 (dd, J=7.5, 3.5

Hz, 2H), 0.77-0.95 (m, 2H), 0.66 (br. s., 1H), 0.50 (d, J=5.0 Hz, 2H) LC-MS: m/z 4 456.4 $(M+H)^+$.

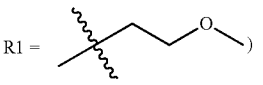
General Procedure 3

[0519]



Method 1: Exemplified by (R)-2-chloro-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetamide (Compound 403) (R"=H,

[0520]



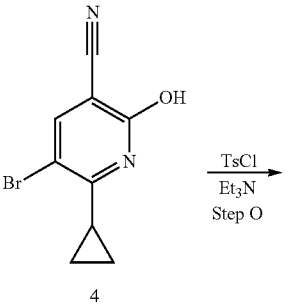
[0521] To a solution of (R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methyl piperazin-1-yl) nicotinonitrile (50 mg, 0.119 mmol) and 2-chloroacetyl chloride (15 mg, 0.131 mmol) in 2 ml of DCM was added dropwise TEA (24 mg, 0.238 mmol) at 0° C., then the mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 20 mg of the product. ^1H NMR (CHLOROFORM-d) δ 8.34 (s, 1H), 7.66-7.75 (m, 1H), 7.62 (s, 1H), 7.50-7.55 (m, 1H), 7.42-7.48 (m, 1H), 7.22 (d, J=7.8 Hz, 1H), 4.92 (s, 0.5H), 4.50-4.54 (m, 0.5H), 4.29-4.33 (m, 1H), 4.26 (m, 1H), 4.21-4.25 (m, 0.5H), 3.71-3.84 (m, 2.5H), 3.52-3.57 (m, 0.5H), 3.39 (s, 3H), 3.21-3.32 (m, 1H), 3.13 (d, J=11.3 Hz, 1H), 3.05 (d, J=12.3 Hz, 0.5H), 2.66-2.81 (m, 1H), 2.54-2.65 (m, 1H), 2.07-2.12 (m, 1H), 1.40 (d, J=6.3 Hz, 1H), 1.28-1.31 (m, 2H), 1.14-1.19 (m, 2H), 0.94-1.00 (m, 2H). LC-MS: m/z 496.2 $(M+H)^+$.

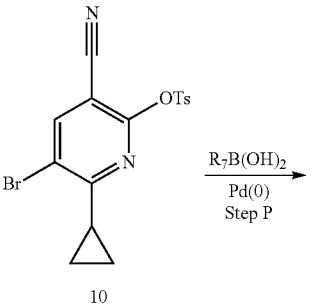
Method 2: Exemplified by (R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propionamide (Compound 424)

[0522] To a 25 mL of round-bottom flask was added (R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methyl piperazin-1-yl)nicotinonitrile (50 mg, 0.119 mmol), propionic acid (0.1 mL), HATU (20 mg), DIPEA (0.05 mL) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. Reaction mixture was with satd. $NaHCO_3$ and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography purification (30% EtOAc/petroleum ether) afforded 45 mg of title compound as a white solid. ^1H NMR (CHLOROFORM-d) 7.75 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.49 (d, J=8.0 Hz, 1H), 7.37 (t, J=7.8 Hz, 1H), 7.11 (d, J=7.5 Hz, 1H), 4.89 (s, 0.5H), 4.52 (d, J=13.3 Hz, 0.5H), 4.14-4.35 (m, 2.5H), 3.67-3.85 (m, 2.5H), 3.49-3.62 (m, 0.5H), 3.37 (s, 3H), 3.17-3.32 (m, 1H), 2.93-3.17 (m, 1.5H), 2.63-2.81 (m, 1H), 2.52-2.63 (m, 1H), 2.37-2.49 (m, 2H), 2.05-2.13 (m, 1H), 1.38 (d, J=6.5 Hz, 1H), 1.22-1.31 (m, 5H), 1.14 (dt, J=7.4, 3.6 Hz, 2H), 0.88-1.01 (m, 2H). LC-MS: m/z 476.3 $(M+H)^+$.

General Procedure 4

[0523]





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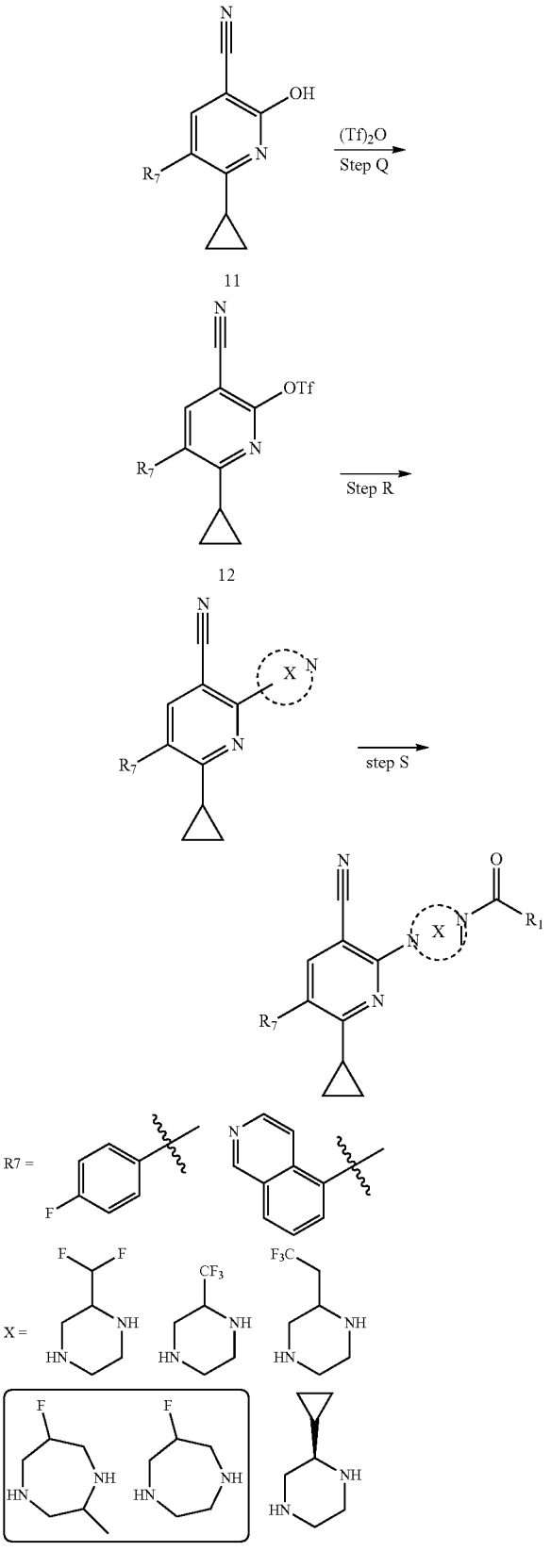


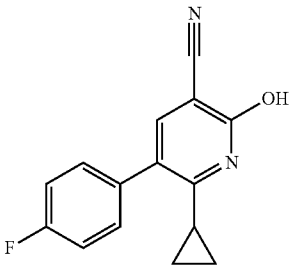
Step O: 5-bromo-3-cyano-6-cyclopropylpyridin-2-yl 4-methylbenzenesulfonate (10)

[0524] To a solution of 4 (2.37 g, 10 mmol) in THF (20 mL) was added TsCl (1.9 g, 11 mmol) and Et_3N (1 mL). The reaction was stirred at room temperature for 2 h. The resultant solution was partitioned between DCM and water. The organic layer was dried over Na_2SO_4 and concentrated to give the crude which was purified by column chromatography to give 2.6 g of 10. ^1H NMR (CHLOROFORM-d) δ 7.86 (s, 1H), 7.35-7.46 (m, 2H), 7.11-7.25 (m, 2H), 1.99-2.17 (m, 1H), 1.21-1.38 (m, 2H), 1.00-1.20 (m, 2H). LC-MS: m/z 393.0 $(M+H)^+$.

Step P: Exemplified by 6-cyclopropyl-5-(4-fluorophenyl)-2-hydroxynicotinonitrile (1H)

[0525]

11-1

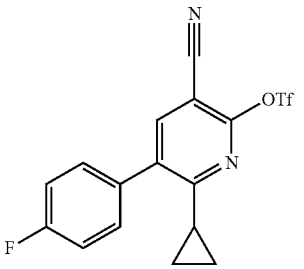


[0526] A mixture of 10 (2.6 g, 11 mmol), 4-fluorophenylboronic acid (1.4 g, 10 mmol), $Pd(PPh_3)_4$ (30 mg), and K_2CO_3 (16 mg, 0.119 mmol) suspended in 10 mL of DMF was subjected to microwave reaction at 150° C. for 45 min. After the reaction, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography to afford 1.9 g of title compound as a yellow solid. LC-MS: m/z 255.0 $(M+H)^+$

Step Q

[0527]

12-1



[0528] 3-cyano-6-cyclopropyl-5-(4-fluorophenyl)pyridin-2-yl trifluoromethanesulfonate. ^1H NMR (CHLOROFORM-d) δ: 7.87 (s, 1H), 7.32-7.57 (m, 2H), 7.13-7.24 (m, 2H), 1.99-2.17 (m, 1H), 1.21-1.38 (m, 2H), 1.00-1.20 (m, 2H). LC-MS: m/z 387.1 $(M+H)^+$.

Step R

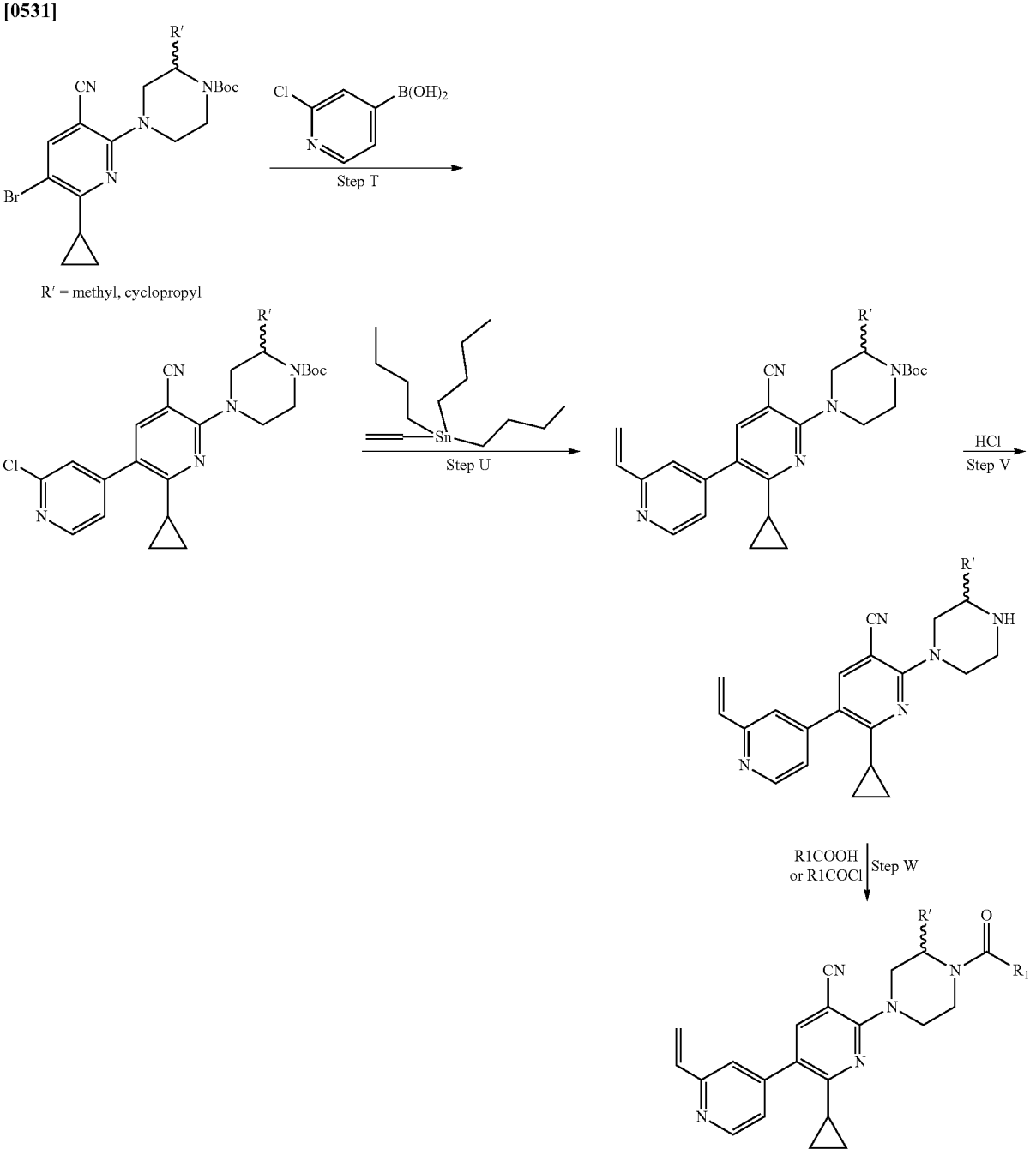
[0529] The same procedure as General procedure 1, step E except using 12-1 as the starting material instead of 5 and the suitable building blocks described in the "building block" section.

Step S

[0530] The same procedure as General procedure 1, step G except using the suitable building blocks described in the "building block" section.

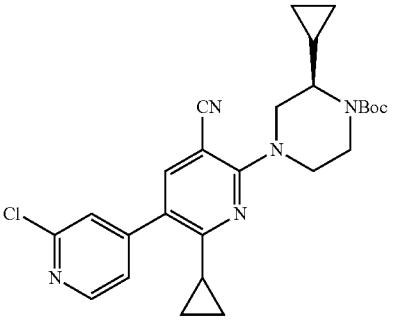
General Procedure 5

[0531]



Step T: Exemplified by (R)-tert-butyl 4-(2'-chloro-5-cyano-2-cyclopropyl-3,4'-bipyridin-6-yl)-2-cyclopropylpiperazine-1-carboxylate

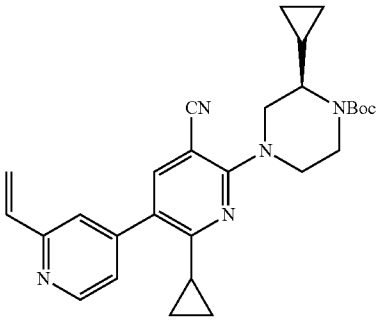
[0532]



[0533] To a 25 mL flask was added with 9-1 (1000 mg 2.235 mmol), 2-chloropyridin-4-ylboronic acid (457 mg, 2.906 mmol), $Pd(PPh_3)_4$ (120 mg, 0.1 mmol), K_2CO_3 (926 mg, 6.705 mmol), and 4 mL DMF. The resultant mixture was stirred at 150° C. for 5 h. After washing with satd. $NaHCO_3$, brine, the combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography purification (20% EtOAc/petroleum ether) afforded 640 mg of title compound. ^1H NMR (CHLOROFORM-d) δ 8.48 (d, J=5.0 Hz, 1H), 7.62 (s, 1H), 7.39-7.47 (m, 1H), 7.32 (dd, J=5.1, 1.3 Hz, 1H), 4.59 (d, J=12.9 Hz, 1H), 4.45 (d, J=13.2 Hz, 1H), 4.09 (d, J=13.5 Hz, 1H), 3.50 (d, J=9.1 Hz, 1H), 3.34-3.43 (m, 1H), 3.27 (dd, J=13.2, 3.8 Hz, 1H), 3.11 (td, J=12.5, 3.7 Hz, 1H), 1.94-2.06 (m, 1H), 1.77 (br. s., 2H), 1.50 (s, 9H), 1.34 (br. s., 1H), 1.04 (dd, J=7.9, 3.2 Hz, 2H), 0.56-0.63 (m, 2H), 0.50 (dd, J=8.5, 3.5 Hz, 1H), 0.32-0.42 (m, 1H).

Step U: Exemplified by (R)-tert-butyl-4-(5-cyano-2-cyclopropyl-2'-vinyl-3,4'-bipyridin-6-yl)-2-cyclopropyl piperazine-1-carboxylate

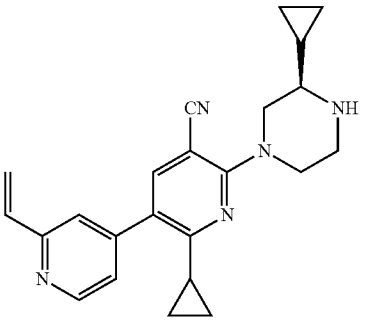
[0534]



[0535] To a flask was added with (R)-tert-butyl 4-(2'-chloro-5-cyano-2-cyclopropyl-3,4'-bipyridin-6-yl)-2-cyclopropylpiperazine-1-carboxylate (640 mg 1.33 mmol), tributyl(vinyl)stannane (550 mg, 1.73 mmol), $Pd(PPh_3)_4$ (120 mg, 0.1 mmol), K_2CO_3 (460 mg, 3.33 mmol), and 4 mL DMF. The resultant mixture was stirred at 150° C. for 5 h. After washing with satd. $NaHCO_3$, brine, the combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography purification (20% EtOAc/petroleum ether) afforded the compound. LC-MS: m/z 472.2 $(M+H)^+$.

Step V: (R)-2-cyclopropyl-6-(3-cyclopropylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[0536]



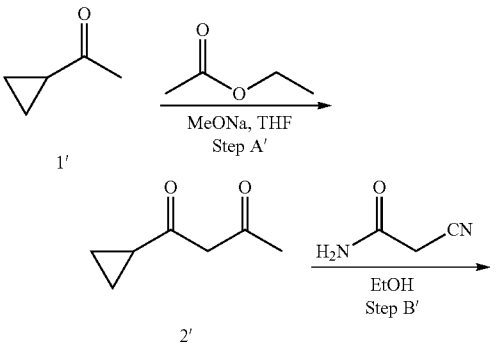
[0537] To a flask was added (R)-tert-butyl 4-(5-cyano-2-cyclopropyl-2'-vinyl-3,4'-bipyridin-6-yl)-2-cyclopropylpiperazine-1-carboxylate and 12 mL EtOH/HCl (1M). The resulting reaction mixture was stirred at 0° C. for 30 minutes until TLC showed the completion of the reaction, which was concentrated in vacuo to afford a product as light yellowish solid. ^1H NMR (CHLOROFORM-d) δ: 8.65 (d, J=5.0 Hz, 1H), 7.62 (s, 1H), 7.38 (s, 1H), 7.23 (dd, J=5.0, 1.8 Hz, 1H), 6.89 (dd, J=17.3, 10.9 Hz, 1H), 6.29 (dd, J=17.6, 1.2 Hz, 1H), 5.57 (dd, J=10.9, 1.2 Hz, 1H), 4.50 (d, J=12.9 Hz, 1H), 4.36 (d, J=13.2 Hz, 1H), 3.28 (br. s., 1H), 3.22 (d, J=12.3 Hz, 1H), 3.10 (br. s., 1H), 2.95 (br. s., 1H), 1.96-2.06 (m, 1H), 1.21 (t, J=4.1 Hz, 1H), 0.95-1.07 (m, 3H), 0.92 (br. s., 1H), 0.62 (d, J=7.9 Hz, 2H), 0.40 (d, J=4.7 Hz, 2H).

Step W

[0538] The same procedure as General procedure 1, step G except using the suitable building blocks described in the "building block" section.

General Procedure 6

[0539]



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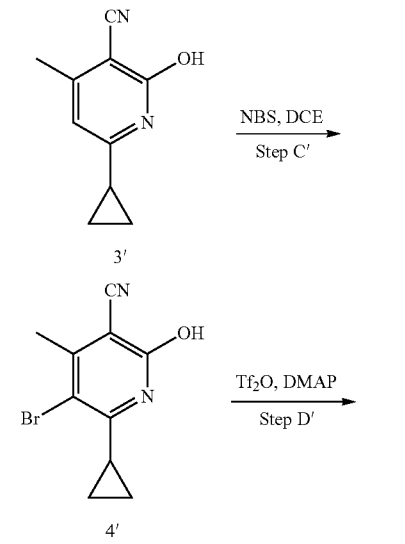

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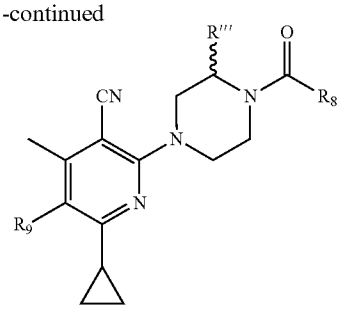
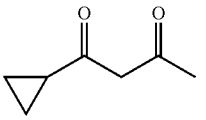


Step A': 1-cyclopropylbutane-1,3-dione

[0540]

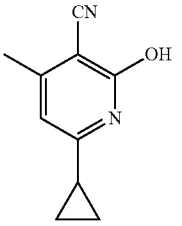


[0541] A mixture of CH3ONa (75.65 g, 1.25 mol) and 1-cyclopropylethanone (105.0 g, 1.25 mol) in THF (1000 mL) was stirred at 35° C. for 1 h and followed by addition of ethyl acetate (110.0 g, 1.25 mol) dropwise. After stirring at 50° C. for 4 hrs, the solvent was removed under reduced pressure and the residue was dissolved in H2O (500 mL) and adjusted to pH 3.5 with citric acid. The mixture was extracted by ethyl acetate (500 mL×3). The combined organic layers were concentrated in vacuum to give 1-cyclopropylbutane-1, 3-dione (110.0 g, yield 69%) as a yellow oil. ^{1}H NMR (CHLOROFORM-d) δ 0.83-0.95 (m, 2H), 1.06-1.10 (m, 2H), 1.54-1.63 (m, 1H), 2.00 (s, 3H).

Step B':
6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile

[0542]

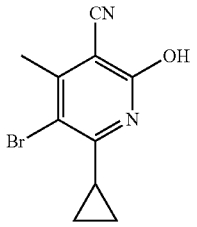
3'



[0543] A mixture of 1-cyclopropylbutane-1,3-dione (126.0 g, 1.0 mol) and 2-cyanoacetamide (88.0 g, 1.0 mol) and piperidine (60 mL) in EtOH (1500 mL) was stirred at reflux for 4 hrs. The reaction mixture was filtered, washed with PE (200 mL) and dried in vacuum to give 6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (90.0 g, 52%) as a white solid. ^{1}H NMR (DMSO-d6) δ 12.36 (br. s., 1H), 5.93 (s, 1H), 2.26 (s, 3H), 1.81-1.91 (m, 1H), 1.06-1.14 (m, 2H), 0.91-0.95 (m, 2H).

Step C': 5-bromo-6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile

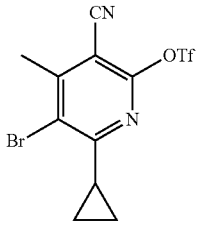
[0544]



[0545] A mixture of 6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (90.0 g, 0.52 mol) and NBS (100.0 g, 0.57 mol) in DCE (1500 mL) was stirred at reflux temperature for 4 hrs. The reaction mixture was filtered and the residue was washed with DCE (200 mL) and dried in vacuum to give 5-bromo-6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (100.0 g, 76%) as a white solid. MS (ES) M+H expected 253.0, found 253.0. ^{1}H NMR (CHLOROFORM-d) δ 2.68 (s, 3H), 1.79-1.88 (m, 1H), 1.03-1.09 (m, 2H), 0.93-1.01 (m, 2H).

Step D': 5-bromo-3-cyano-6-cyclopropyl-4-methylpyridin-2-yl trifluoromethane-sulfonate

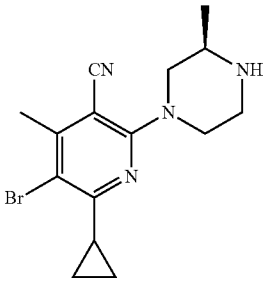
[0546]



[0547] To a solution of 5-bromo-2-hydroxy-6-isopropylnicotinonitrile (40 g, 0.15 mol) in 200 mL of methylene chloride was added DMAP (1.78 g, 14.6 mmol), and triethylamine (25 mL, 175 mmol). The mixture was cooled to 0° C. in an ice-water bath, and trifluoromethanesulfonic anhydride (37 mL, 0.21 mol) was added dropwise by syringe. The resulting reaction mixture was stirred at 0° C. for 30 min then allowed to warm to room temperature and stirred overnight. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% EtOAc/petroleum ether) to afford 55 g of title compound. ^{1}H NMR (CHLOROFORM-d). 2.70 (s, 3H), 2.16-2.20 (m, 1H), 1.23-1.25 (m, 2H), 1.19-1.22 (m, 2H)

Step E': Exemplified by (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (R'"=methyl)

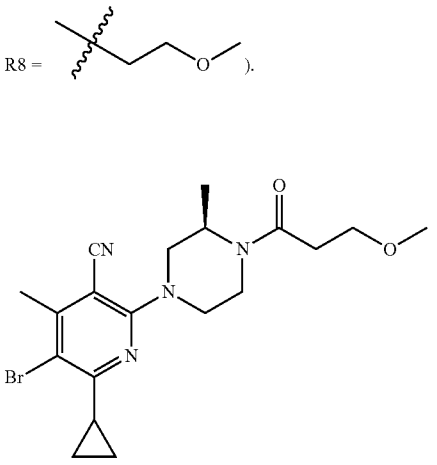
[0548]



[0549] A mixture of 5-bromo-3-cyano-6-cyclopropyl-4-methylpyridin-2-yl trifluoromethanesulfonate (50.0 g, 0.13 mol) and (R)-2-methylpiperazine (15.6 g, 0.16 mol) and Et3N (26.0 g, 0.26 mol) in THF (500 mL) was stirred at 80° C. overnight. The resulting mixture concentrated in vacuum to give (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (34.8 g, 80%) as a white solid. ^{1}H NMR (CHLOROFORM-d) δ 4.08-4.16 (m, 0.5H), 4.05-4.08 (m, 1H), 4.01-4.04 (m, 0.5H), 2.99-3.08 (m, 1H), 2.97 (d, J=8.8 Hz, 2H), 2.88-2.95 (m, 1H), 2.58-2.65 (m, 1H), 2.55-2.57 (m, 3H), 1.77 (br. s., 1H), 1.12 (s, 1.5H), 1.10 (s, 1.5H), 1.05-1.09 (m, 2H), 1.00-1.05 (m, 2H).

Step F': preparation of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (R'"=methyl,

[0550]



[0551] A mixture of (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methyl piperazin-1-yl)nicotinonitrile (34.8 g, 0.1 mol) and 3-methoxypropanoic acid (16.0 g, 0.15 mol) in pyridine (500 mL) was stirred at 0° C. for 30 min, and followed by addition of $POCl_3$ (28.7 g, 0.19 mol) dropwise. The resulting mixture was stirred at 20° C. for 2 hrs. The reaction mixture was concentrated and purified by chromatography to

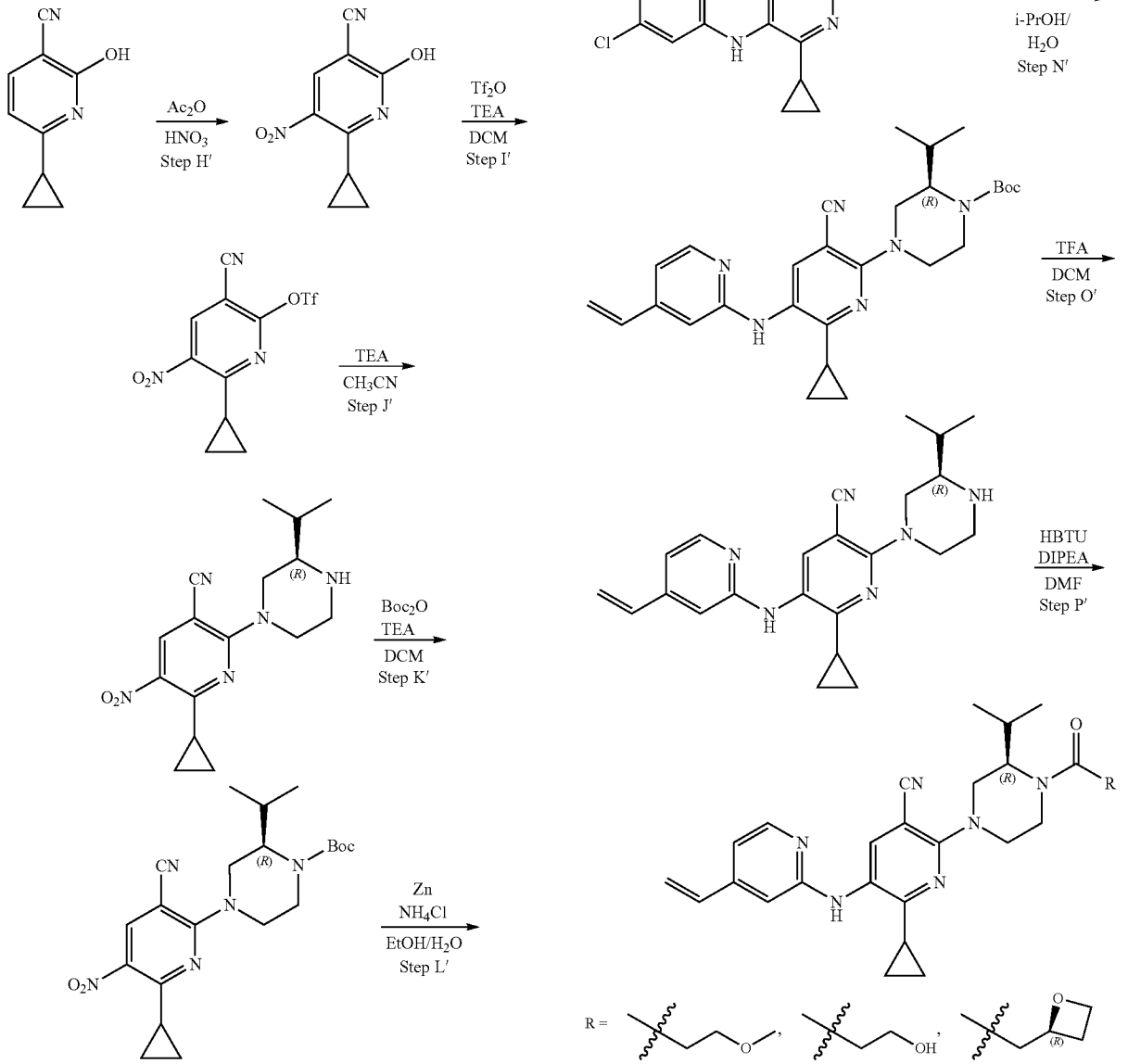
give (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (25.0 g, 59%) as yellow oil.

[0552] ^{1}H NMR (CHLOROFORM-d) δ 4.90 (br. s., 0.5H), 4.52 (d, J=13.6 Hz, 0.5H), 4.22 (br. s., 0.5H), 3.95-4.13 (m, 2H), 3.78 (br. s., 0.5H), 3.74 (t, J=5.9 Hz, 2H), 3.50-3.61 (m, 0.5H), 3.38 (s, 3H), 3.07-3.24 (m, 1.5H), 2.90-3.06 (m, 1H), 2.65-2.79 (m, 1H), 2.60 (s, 3H), 2.52-2.63 (m, 1H), 2.17-2.21 (m, 1H), 1.37 (d, J=6.5 Hz, 1.5H), 1.27 (d, J=6.3 Hz, 1.5H), 1.09 (s, 2H), 1.05-1.08 (m, 2H).

[0553] Step G' was similar to Step H in general procedure 1.

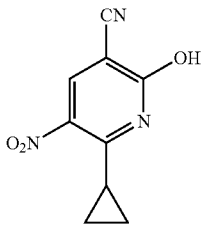
General Procedure 7

[0554]



Step H':
6-cyclopropyl-2-hydroxy-5-nitronicotinonitrile

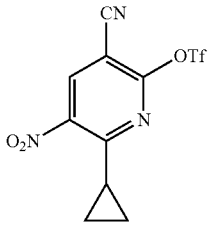
[0555]



[0556] To a solution of 6-cyclopropyl-2-hydroxynicotinonitrile (20 g, 0.125 mmol) in Ac_2O (110 mL) was added dropwise HNO_3 (15 mL) at 0° C.~40° C. for 30 mins. After the addition, the reaction mixture was stirred at r.t. for 3 hrs. The mixture was cooled to 0° C. and the solid was collected by filtration. The solid was washed with brine dried under vacuum to give the title compound (15.5 g, 60.4%) as a pale yellow solid. ^{1}H NMR (CHLOROFORM-d) δ10.71 (s, 1H), 8.68 (s, 1H), 3.13 (tt, J=8.6, 5.6 Hz, 1H), 1.57-1.52 (m, 2H), 1.44-1.37 (m, 2H). LC-MS: m/z 205.9 $(M+H)^+$

Step I': 3-cyano-6-cyclopropyl-5-nitropyridin-2-yl trifluoromethanesulfonate

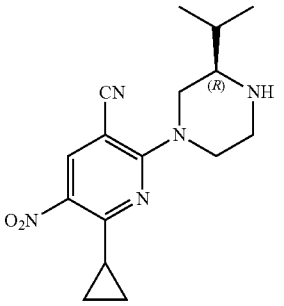
[0557]



[0558] To a solution of 6-cyclopropyl-2-hydroxy-5-nitronicotinonitrile (7.6 g, 37.7 mmol) in DCM (150 mL) was added DMAP (30.0 mg) and TEA (7.5 g, 74.1 mmol) at r.t. Then Tf_2O (15.7 g, 55.6 mmol) was added dropwise to the above solution at −40° C. for 30 min. The reaction mixture was stirred at −40° C. for 2 hs. The mixture was quenched with water at −40° C. The mixture was then extracted with EtOAc (50 mL×2). The combined organic layer was washed with brine, dried over Na_2SO_4. The organic phase was filtered and the filtrate was concentrated in vacuum to give the title compound (12.5 g, crude) as a pale yellow solid. LC-MS: m/z 337.5 $(M+H)^+$

Step J': (R)-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)-5-nitronicotinonitrile

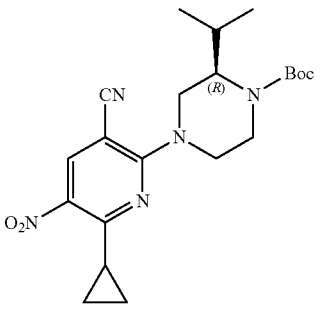
[0559]



[0560] To a solution of 3-cyano-6-cyclopropyl-5-nitropyridin-2-yl trifluoromethanesulfonate (10.9 g, 32.3 mmol) and (R)-2-isopropylpiperazine (3.45 g, 27.0 mmol) in CH_3CN (100 mL) was added TEA (6.5 g, 64.7 mmol) at r.t. The reaction mixture was heated and stirred at 85° C. for 3 hrs. The mixture was concentrated in vacuo and the residue was extracted with EtOAc (50 mL×2). The combined organic layer was washed with brine, dried over Na_2SO_4. The organic phase was filtered and the filtrate was concentrated in vacuum to give the title compound (8.5 g, crude) as a brown solid. LC-MS: m/z 316.6 $(M+H)^+$

Step K': (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-nitropyridin-2-yl)-2-isopropylpiperazine-1-carboxylate

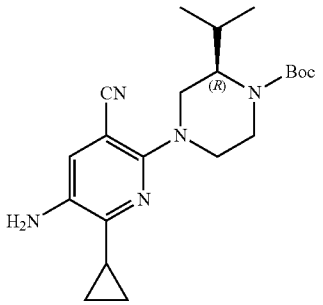
[0561]



[0562] To a solution of (R)-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)-5-nitronicotinonitrile (8.52 g, 26.2 mmol) and Boc anhydride (8.5 g, 39.3 mmol) in DCM (50 mL) was added TEA (3.9 g, 39.3 mmol) at r.t. The reaction mixture was stirred at 30° C. for 3 hrs. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM:MeOH) to afford the title compound (10.4 g, 95%) as a yellow liquid. ^{1}H NMR (CHLOROFORM-d) δ 8.51 (s, 1H), 4.74 (d, J=13.7 Hz, 1H), 4.55 (d, J=13.1 Hz, 1H), 3.88 (s, 1H), 3.37-3.23 (m, 2H), 3.11 (ddd, J=10.5, 7.7, 5.7 Hz, 2H), 1.86 (tdd, J=13.3, 8.5, 4.9 Hz, 1H), 1.49 (s, 9H), 1.27 (d, J=2.3 Hz, 2H), 1.26-1.17 (m, 4H), 1.01 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.8 Hz, 3H).

Step L': (R)-tert-butyl 4-(5-amino-3-cyano-6-cyclopropylpyridin-2-yl)-2-isopropylpiperazine-1-carboxylate

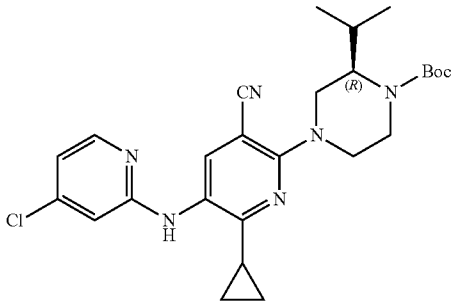
[0563]



[0564] To a solution of (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-nitropyridin-2-yl)-2-isopropylpiperazine-1-carboxylate (19 g, 45.8 mmol) in EtOH (200 mL) and H_2O (100 mL) was added Zinc (30 g, 458 mmol) and NH_4Cl (24.5 g, 458 mmol) at r.t. The reaction mixture was stirred at 40° C. overnight. The mixture was filtered through a pad of silica and the filtrate was extracted with EtOAc (100 mL×2). The combined organic layer was washed with brine, dried over Na_2SO_4. The organic phase was filtered and the filtrate was concentrated in vacuum to give the title compound (13.1 g, 74.3%) as a yellow solid. ^1H NMR (CHLOROFORM-d) δ: 7.10 (d, J=2.9 Hz, 1H), 4.02 (t, J=19.0 Hz, 3H), 3.81 (t, J=16.8 Hz, 3H), 3.13 (td, J=12.8, 2.4 Hz, 1H), 2.99-2.86 (m, 2H), 2.25 (tt, J=12.9, 6.5 Hz, 1H), 1.97-1.83 (m, 1H), 1.49 (d, J=2.2 Hz, 9H), 1.13-1.06 (m, 2H), 1.06-1.01 (m, 2H), 0.98 (t, J=9.2 Hz, 3H), 0.87 (t, J=6.6 Hz, 3H). LC-MS: m/z 386.6 $(M+H)^+$

Step M': (R)-tert-butyl 4-(5-((4-chloropyridin-2-yl)amino)-3-cyano-6-cyclopropylpyridin-2-yl)-2-isopropylpiperazine-1-carboxylate

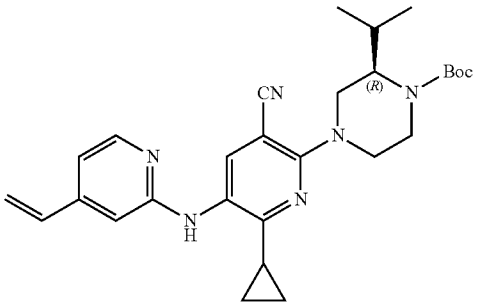
[0565]



[0566] To a solution of (R)-tert-butyl 4-(5-amino-3-cyano-6-cyclopropylpyridin-2-yl)-2-isopropylpiperazine-1-carboxylate (600 mg, 81.6 mmol) and 2-bromo-4-chloropyridine (390.3 mg, 2.03 mmol) in 1,4-dioxane (15 mL) was added $Pd_2(dba)_3$ (142.7 mg, 0.156 mmol) and Xantphos (135.3 mg, 0.234 mmol) and Cs_2CO_3 (1.02 g, 3.12 mmol) at r.t. under N_2. The resulting mixture was heated and stirred at 115° C. under N_2 in microwave for 1 h. The solvent was removed in vacuum and the residue was purified via reverse phase silica gel column chromatography (MeOH:H_2O) to afford the title compound (137 mg, 18%) as a pale yellow solid. ^1H NMR (CHLOROFORM-d) δ: 8.07 (d, J=5.4 Hz, 1H), 7.72 (d, J=3.3 Hz, 1H), 6.75 (dd, J=5.5, 1.7 Hz, 1H), 6.39 (d, J=1.6 Hz, 1H), 6.25 (s, 1H), 4.45 (d, J=13.2 Hz, 1H), 4.26 (d, J=9.2 Hz, 1H), 4.21-3.61 (m, 2.5H), 3.11 (dt, J=13.5, 6.8 Hz, 2.5H), 2.22-1.98 (m, 2H), 1.52-1.47 (m, 9H), 1.28 (s, 1H), 1.14 (dt, J=8.1, 4.5 Hz, 1H), 1.08 (dd, J=9.7, 4.7 Hz, 1H), 1.01 (dd, J=10.9, 5.2 Hz, 4H), 0.90 (d, J=6.8 Hz, 3H). LC-MS: m/z 497.6 $(M+H)^+$

Step N': (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-((4-vinylpyridin-2-yl)amino)pyridin-2-yl)-2-isopropylpiperazine-1-carboxylate

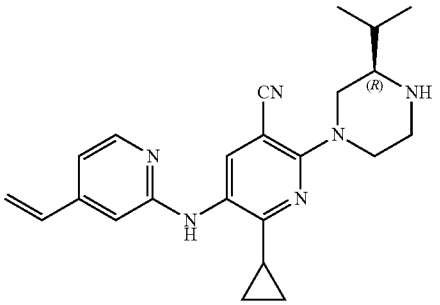
[0567]



[0568] To a solution of (R)-tert-butyl 4-(5-((4-chloropyridin-2-yl)amino)-3-cyano-6-cyclopropylpyridin-2-yl)-2-isopropylpiperazine-1-carboxylate (600 mg, 1.21 mmol) in isopropanol (15 mL) and H_2O (3 mL) was added Vinyltrifluoroboric acid potassium salt (324.2 mg, 2.42 mmol), $Pd(dppf)Cl_2$ (98.7 mg, 0.121 mmol) and DIPEA (312.2 mg, 2.42 mmol) at r.t. under N_2. The reaction mixture was heated and stirred at 125° C. under N_2 in microwave for 1.5 h. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM: MeOH) to afford the title compound (513 mg, 87%) as a yellow solid. LC-MS: m/z 489.6 $(M+H)^+$

Step O': (R)-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[0569]



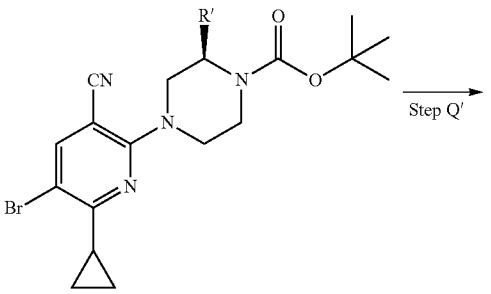
[0570] To a solution of (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-((4-vinylpyridin-2-yl)amino)pyridin-2-yl)-2-isopropylpiperazine-1-carboxylate (513 mg, 1.05 mmol) in anhydrous DCM (10 mL) was added TFA (5 mL) at r.t. The reaction mixture was stirred at r.t. for 2 hs. The solvent was removed in vacuum and the residue was adjusted to pH>7.0. The residue mixture was extracted with EtOAc (15 mL×2). The combined organic layer was washed with brine, dried over Na_2SO_4. The organic phase was filtered and the filtrate was concentrated in vacuum to give out the title compound (crude, 406 mg) as a yellow liquid. ^{1}H NMR (CHLOROFORM-d) δ: 7.99 (d, J=6.6 Hz, 1H), 7.72 (s, 1H), 7.04 (dd, J=6.6, 1.3 Hz, 1H), 6.64 (dd, J=17.4, 10.8 Hz, 1H), 6.47 (s, 1H), 6.12 (d, J=17.5 Hz, 1H), 5.81 (d, J=10.8 Hz, 1H), 5.24 (s, 1H), 4.59 (d, J=13.9 Hz, 1H), 4.45 (d, J=14.3 Hz, 1H), 3.63-3.48 (m, 2H), 3.30 (dd, J=14.1, 11.1 Hz, 2H), 3.18 (s, 1H), 2.15-2.01 (m, 2H), 1.28 (d, J=4.8 Hz, 1H), 1.16 (dd, J=10.2, 6.9 Hz, 8H), 1.12-1.09 (m, 1H). LC-MS: m/z 389.5 $(M+H)^+$

Step P': (R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile (Compound 757)

[0571] To a solution of (R)-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile (300 mg, 0.77 mmol) in DMF (15 mL) was added sodium 3-hydroxypropanoate (208.8 mg, 1.55 mmol), HATU (442.5 mg, 1.2 mmol) and DIPEA (200 mg, 1.55 mmol) at r.t. The reaction mixture was stirred at r.t. for 3 hs. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM: MeOH) to afford the title compound (138 mg, 38.8%) as a pale yellow solid. ^{1}H NMR (CHLOROFORM-d) δ: 8.12 (d, J=5.4 Hz, 1H), 7.85 (d, J=5.5 Hz, 1H), 6.84 (d, J=5.4 Hz, 1H), 6.59 (dd, J=17.6, 10.8 Hz, 1H), 6.46 (s, 1H), 6.42 (s, 1H), 5.91 (d, J=17.5 Hz, 1H), 5.48 (d, J=10.9 Hz, 1H), 4.69 (d, J=10.4 Hz, 0.5H), 4.44 (d, J=12.6 Hz, 1.5H), 4.31-4.23 (m, 1H), 3.93 (s, 2H), 3.75 (d, J=13.5 Hz, 0.5H), 3.51-3.38 (m, 2H), 3.14-2.97 (m, 2H), 2.61 (dt, J=5.7, 4.8 Hz, 2H), 2.36-2.25 (m, 0.5H), 2.19 (ddd, J=12.9, 8.1, 4.9 Hz, 1H), 1.29 (t, J=16.6 Hz, 1H), 1.18-0.97 (m, 7H), 0.95-0.88 (m, 1.5H), 0.86 (d, J=6.8 Hz, 1.5H). LC-MS: m/z 461.6 $(M+H)^+$

General Procedure 8

[0572]



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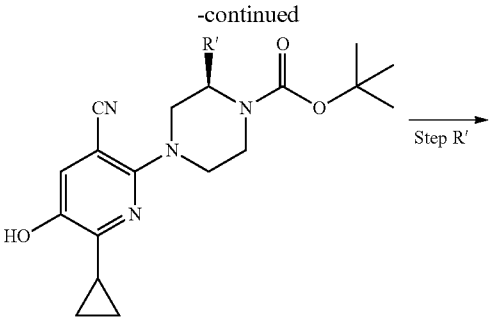

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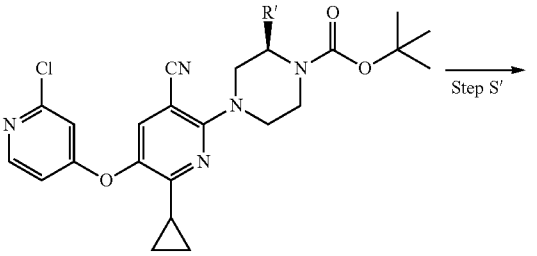

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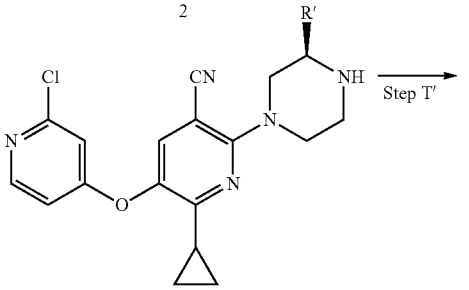

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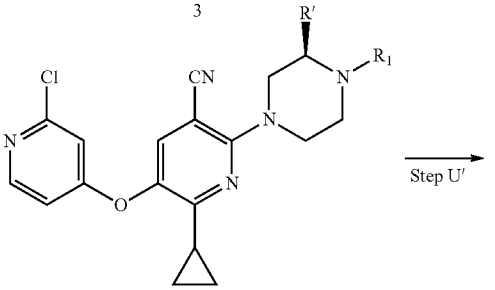

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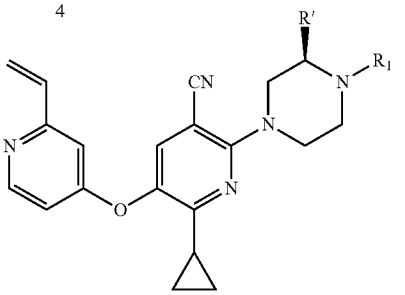
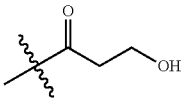
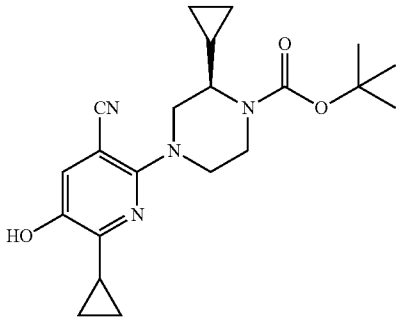


R' = cyclopropyl or methyl

R1 = 

Step Q': ((R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-hydroxypyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate

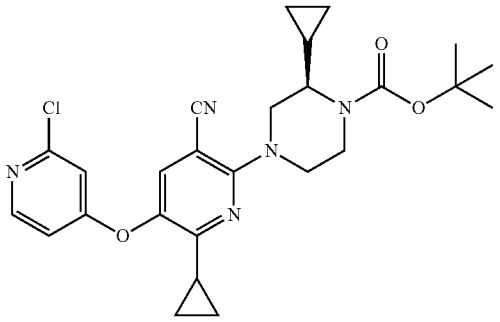
[0573]



[0574] To a mixture of (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (0.35 g, 1.0 mmol), potassium hydroxide (0.22 g, 4 mmol) in a 50 mL flask was added $Pd_2(dba)_3$ (0.092 g, 0.1 mmol), t-Bu-Xphos (0.082 g, 0.2 mol). Then 10 mL 1,4-dioxane and 1.0 mL water was added, the mixture was stirred at 80° C. for 16 hours, cooled and acidified with 2N HCl to pH 6 (temperature held below 25° C.). Then the mixture was extracted with ethyl acetate (15 mL×2), the organic phase was combined and concentrated to give brown oil, which was further purified by silica gel chromatography (PE:EA=3:1), to give 0.16 g of (1) as a white solid (41% yield). LC-MS: m/z 386.0 $(M+H)^+$

Step R': (R)-tert-butyl 4-(5-(2-chloropyridin-4-yloxy)-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate

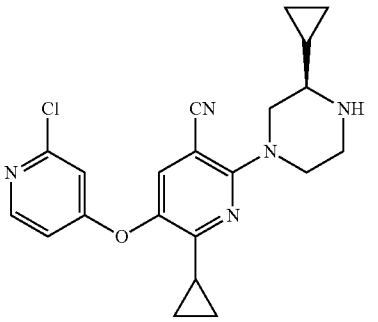
[0575]



[0576] A mixture of (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropyl piperazine-1-carboxylate (0.16 g, 0.41 mol), 2-chloro-4-iodopyridine (0.15 g, 0.62 mol), 9 mg Cu(I)Br (0.06 mmol) and 12 mg 2,2,6,6-tetramethylheptane-3,5-dione (0.06 mmol), 0.28 g Cs_2CO_3 was heated under microwave in 4 mL DMSO for 30 min. The mixture was cooled to room temperature and washed with water and purified by silica gel chromatography (DCM:MeOH=20:1) to give 0.10 g of (2) as a yellow solid (52% yield). LC-MS: m/z 486.0 $(M+H)^+$

Step S': (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile

[0577]



[0578] A mixture of (R)-tert-butyl 4-(5-(2-chloropyridin-4-yloxy)-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (0.10 g, 0.21 mmol) and TFA (0.35 mL) was stirred in DCM (10 mL) for 2 hrs. The solvent was removed and the residue was basified with $NaHCO_3$ solution and extracted with DCM (10 mL), the organic phase was separated and concentrated to give a yellow solid (3) (0.075 g, 0.19 mmol, crude yield 90%). LC-MS: m/z 397.1 $(M+H)^+$

Step T': (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile (Compound 694)

[0579] A mixture of (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile (0.35 g, 0.88 mmol), sodium 3-hydroxypropanoate (0.10 g, 0.88 mmol), HATU (0.50 g, 1.32 mmol) and 0.23 g DIEA (1.76 mmol) was stirred in 8 mL DMF for 4 hrs. Then the mixture was quenched by adding 6 mL water and extracted with EA (15 mL×2), the organic phase was combined and concentrated to give a yellow oil, which was further purified by silica gel chromatography (DCM:MeOH=20:1) to give 0.10 g of product as a yellow solid (52% yield). ^1H NMR (CHLOROFORM-d) δ: 8.30 (d, J=5.6 Hz, 1H), 7.48-7.49 (m, 0.5H), 6.81 (dt, J=5.6, 2.0 Hz, 2H), 4.70 (s, 1H), 4.41 (d, J=13.0 Hz, 1H), 4.29 (d, J=13.0 Hz, 1H), 4.12 (dd, J=18.6, 7.4 Hz, 1H), 3.93 (s, 2H), 3.84-3.67 (m, 1H), 3.18 (d, J=12.8 Hz, 1H), 3.13-2.99 (m, 1H), 2.61 (s, 2H), 2.32-2.22 (m, 0.5H), 2.02 (t, J=4.6 Hz, 1H), 1.35 (s, 1H), 1.29 (d, J=9.4 Hz, 3H), 1.14 (dd, J=7.4, 3.0 Hz, 2H), 1.04 (dt, J=7.9, 3.1 Hz, 2H), 0.66-0.67 (m, 2H), 0.46-0.51 (m, 2H). LC-MS: m/z 468.1 $(M+H)^+$

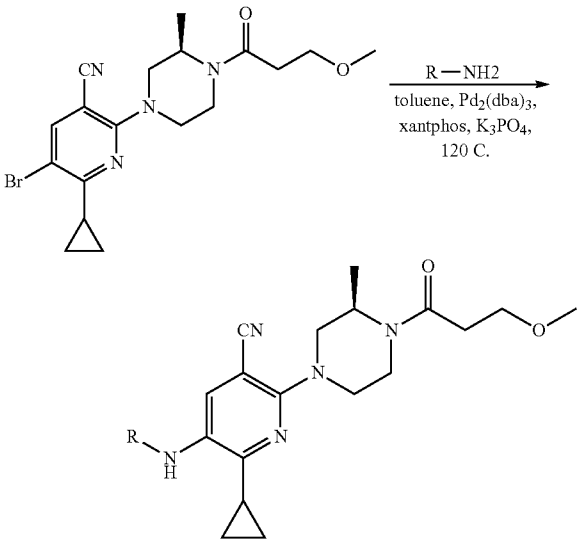
Step U': (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylpyridin-4-yloxy)nicotinonitrile (Compound 692)

[0580] A mixture of (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxy propanoyl)piperazin-1-yl)nicotinonitrile (4) 0.35 g, (0.75 mmol), potassium trifluoro(vinyl)borate (0.15 g, 1.1 mmol), $PdCl_2dppf$ (80 mg, 0.075 mmol) and DIEA (0.24 mL, 1.5 mmol) was heated in isopropanol at reflux at 85° C. under nitrogen for 5 hrs. Then mixture was then concentrated under reduced pressure to give a yellow solid which was further purified by silica chromatography (PE/EA/MeOH=150/120/8) to give 0.19 g

of product as a white solid (55% yield). ^{1}H NMR (CHLOROFORM-d) δ: 8.47 (d, J=5.6 Hz, 1H), 7.48-7.49 (m, 0.5H), 6.86 (d, J=2.3 Hz, 1H), 6.77 (dd, J=17.4, 10.8 Hz, 1H), 6.66 (dd, J=5.6, 2.4 Hz, 1H), 6.22 (dd, J=17.4, 0.9 Hz, 1H), 5.53 (dd, J=10.8, 0.8 Hz, 1H), 4.68 (d, J=11.7 Hz, 1H), 4.38 (d, J=12.9 Hz, 1H), 4.30-4.22 (m, 1H), 4.15-4.04 (m, 1H), 3.92 (s, 2H), 3.75 (d, J=20.7 Hz, 1H), 3.47 (d, J=21.7 Hz, 1H), 3.25-3.12 (m, 1H), 3.09-2.95 (m, 1H), 2.60 (s, 2H), 2.32-2.22 (m, 0.5H), 2.11-2.05 (m, 1H), 1.37 (d, J=20.5 Hz, 1H), 1.27 (d, J=2.0 Hz, 1H), 1.16-1.10 (m, 2H), 1.01 (ddd, J=10.1, 6.7, 3.3 Hz, 2H), 0.65 (t, J=33.7 Hz, 2H), 0.45-0.48 (m, 2H). LC-MS: m/z 460.1 $(M+H)^+$

General Procedure 9

[0581]



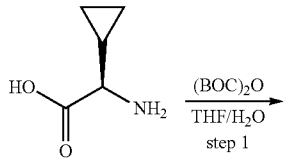
[0582] Core 7-1 (120 mg, 0.295 mmol) and amine (0.295 mmol) were dissolved in toluene (2 mL). K3PO4 (125.0 mg, 0.590 mmol), Xantphos (cat.) and Pd2(dba)3(cat.) were added to above mixture under N2. The mixture was shaken at 120° C. for 16 hrs. The crude product was purified by prep-HPLC.

Example 15

Building Blocks Syntheses

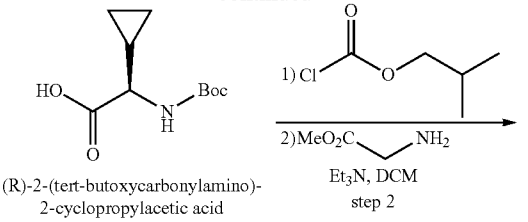
Building Block 1: (R)-2-cyclopropylpiperazine

[0583]

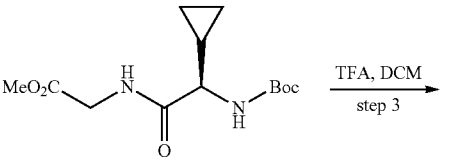


(R)-2-amino-2-cyclopropylacetic acid

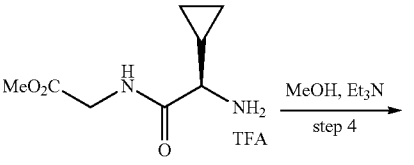
-continued



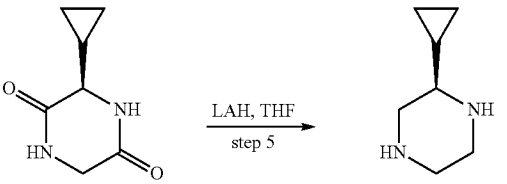
(R)-2-(tert-butoxycarbonylamino)-2-cyclopropylacetic acid



(R)-methyl 2-(2-(tert-butoxycarbonylamino)-2-cyclopropylacetamido)acetate



(R)-methyl 2-(2-amino-2-cyclopropylacetamido)acetate



(R)-3-cyclopropylpiperazine-2,5-dione

(R)-2-cyclopropylpiperazine

Step 1

[0584] To a solution of (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinazolin-5-yl)nicotinonitrile (100 g, 0.87 mol) in water (1250 ml), $NaHCO_3$ (175 g, 2.08 mol) was add at room temperature, then a solution of $(Boc)_2O$ in THF (1250 mL) was added and the reaction mixture was heated to reflux overnight. Then the resulting mixture was concentrated to remove THF under reduced pressure. EtOAc (1250 mL) was added to the residue and the resulting mixture was cooled to 5° C. and then adjusted to pH 3 with saturated aqueous $NaHSO_4$. The layers were separated and the aqueous was extracted with EtOAc (1000 mL×3). The combined EtOAc layers were washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to give (R)-2-(tert-butoxycarbonylamino)-2-cyclopropylacetic acid (165 g, yield 88%). ^{1}H NMR (MeOD 400 MHz) 3.16-3.14 (d, J=8.8, 1H), 1.11 (s, 9H), 0.73-0.78 (m, 1H), 0.28-0.2 (m, 3H), 0.18-0.15 (m, 1H) 100 ee %.

Step 2

[0585] Isobutyl chloroformate (81.6 g, 0.6 mol.) was added over 1 hr to a stirred mixture of (R)-2-(tert-butoxycarbonylamino)-2-cyclopropylacetic acid (129 g, 0.6 mol.) and Et_3N (67 g, 0.66 mol.) in DCM (1000 mL) at 0° C.-5° C. and the reaction mixture was stirred 1 hr at 0° C.-5° C. In a separate flask, a mixture of glycine methyl ester hydrochloride (82.8 g, 0.66 mol.), Et_3N (73 g, 0.72 mol.) and DCM (1000 mL) was stirred for 1 hr and the mixture was then added to the flask over 2 hrs. After the addition was complete, the mixture was stirred overnight at room temperature for 40 hrs and then washed with water and brine, dried with Na_2SO_4, concentrated under reduced pressure and the residue was purified by column chromatography to give (R)-methyl 2-(2-(tert-butoxycarbonylamino)-2-cyclopropyl acetamido)acetate (100 g, yield 58%) as white solid. 100 ee %. ^1H NMR (DMSO 400 MHz) δ 8.2-8.16 (t, J=5.6, 1H), 6.66-6.86 (d, J=8.8, 9H), 3.71-3.92 (m, 2H), 3.62 (s, 3H), 3.46-3.51 (t, J=8.4, 1H), 1.36 (s, 9H), 0.97-1.01 (m, 1H), 0.38-0.44 (m, 3H), 0.25-0.28 (m, 1H).

Step 3

[0586] To a solution of (R)-methyl 2-(2-(tert-butoxycarbonylamino)-2-cyclopropylacetamido) acetate (290 g, 1.014 mol) in DCM (1740 mL), TFA (870 mL) was added dropwise at 0° C. The reaction solution was stirred overnight at room temperature. The resulting solution was concentrated under reduced pressure to give (R)-methyl 2-(2-amino-2-cyclopropylacetamido) acetate (511 g crude).

Step 4

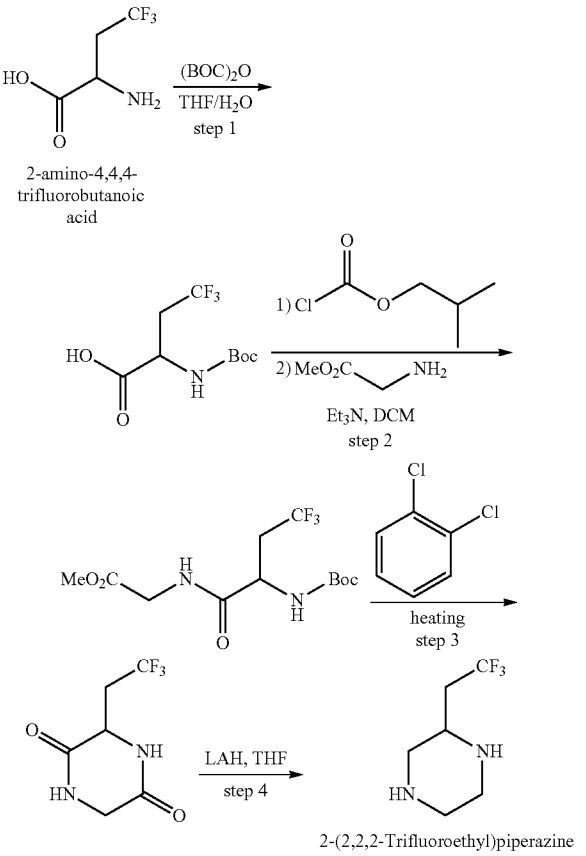
[0587] To a solution (R)-methyl 2-(2-amino-2-cyclopropylacetamido)acetate (255.5 g crude, 0.507 mol) in MeOH (1250 ml), Et_3N (750 ml, 10.78 mol) was added was added dropwise at 0° C. Then the reaction solution was stirred two days at room temperature. The resulting mixture was filtered and the precipitate was washed with MTBE and dried by high vacuum to give (R)-3-cyclopropylpiperazine-2,5-dione (60 g, yield 76.9%). ^1H NMR (DMSO 400 MHz) δ 7.98 (s, 1H), 7.74 (s, 1H), 3.68-6.64 (d, J=17.6, 1H), 3.30-3.36 (m, 1H), 2.9-2.93 (dd, J=3.2, 1H), 0.87-0.92 (m, 1H), 0.21-0.27 (m, 3H), 0.18-0.21 (m, 1H).

Step 5

[0588] To a suspension mixture of (R)-3-cyclopropylpiperazine-2,5-dione (30 g, 0.195 mmol) in THF (1000 mL), $AlLiH_4$ (45 g, 1.184 mol) was added in portions over 1.5 hrs at 0° C. Then the reaction mixture was heated to 70° C. overnight. After cooling, water (45 mL) was added dropwise at 0° C. and then a solution of KOH (45 mL, 1%) was added dropwise at 0° C. The resulting mixture was filtered and the residue was washed with EtOAc and MeOH (3:1) and the filtrate was concentrated under reduced pressure to give crude product. Then the crude product was washed with DCM and the filtrate was concentrated under reduced pressure to give (R)-2-cyclopropylpiperazine (18.5 g, yield 75.5%). 99.5 ee %. ^1H NMR (MeOD 400 MHz) δ 2.9-2.96 (m, 1H), 2.8-2.88 (m, 1H), 2.7-2.8 (m, 1H), 2.55-2.68 (m, 2H), 2.4-2.5 (q, J=10.4, 1H), 1.65-1.73 (m, 1H), 0.55-0.67 (m, 1H), 0.35-0.45 (m, 2H), 0.05-0.25 (m, 2H).

Building Block 2: 2-(2,2,2-trifluoroethyl)piperazine

[0589]



Step 1

[0590] To a solution of 2-amino-4,4,4-trifluorobutanoic acid (450 mg, 3 mmol) in 5 mL H_2O and 5 mL THF was added $NaHCO_3$ (504 mg, 6 mmol), followed by a solution of di-tert-butyl dicarbonate (650 mg, 3 mmol) in THF (3 mL). The resulting mixture was stirred at 80° C. overnight. After removal of THF, poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. 723 mg of 2-(tert-butoxycarbonylamino)-4,4,4-trifluorobutanoic acid was obtained as a crude product and used in subsequent reaction without further purification. MS (ES) M+H expected 258, found 258. ^1H NMR (CHLOROFORM-d) δ 5.25 (d, J=7.8 Hz, 1H), 4.40-4.67 (m, 1H), 2.60-2.90 (m, 2H), 1.46 (s, 9H).

Step 2

[0591] To a 25 mL of round-bottom flask was added 2-(tert-butoxycarbonylamino)-4,4,4-trifluorobutanoic acid (723 mg, 2.8 mmol), Et_3N (560 mg, 5.6 mmol), isobutyl carbonochloridate (380 g, 2.8 mmol) in 5 mL methylene chloride. The resulting reaction mixture was stirred at 0° C. for 0.5 hours. And methyl 2-aminoacetate (352 mg, 2.8 mmol) was added. The resulting mixture was stirred at room temperature overnight. After washing with Satd. $NaHCO_3$, brine, the com-

bined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. 900 mg of methyl 2-(2-(tert-butoxycarbonylamino)-4,4,4-trifluorobutanamido)acetate was obtained as a crude product and used in subsequent reaction without further purification. MS (ES) M+H expected 329.1, found 329.0. ^{1}H NMR (CHLOROFORM-d) δ 7.11 (br. s., 1H), 5.28 (br. s., 1H), 4.44-4.67 (m, 1H), 3.84-4.07 (m, 2H), 3.69-3.83 (s, 3H), 2.72-2.95 (m, 1H), 2.42-2.64 (m, 1H), 1.38-1.50 (m, 9H).

Step 3

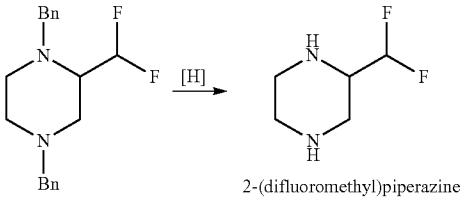
[0592] A mixture of methyl 2-(2-(tert-butoxycarbonylamino)-4,4,4-trifluorobutanamido)acetate (900 mg, 2.7 mmol) in 5 mL 1,2-dichlorobenzene was heated to 180° C. overnight. The mixture was cooled down and was added MTBE (5 mL). A brown yellowish precipitate was formed. The filter cake was washed with MTBE and air-dried to give 200 mg of 3-(2,2,2-trifluoroethyl)piperazine-2,5-dione. ^{1}H NMR (DMSO-d6) δ 8.28 (d, J=9.3 Hz, 2H), 4.00-4.26 (m, 1H), 3.68-3.87 (m, 2H), 2.66-2.88 (m, 2H).

Step 4

[0593] To a flask was added 3-(2,2,2-trifluoroethyl)piperazine-2,5-dione (200 mg, 1 mmol) in TH F(5 mL), and LAH (2.5 mL, 6 mmol) was added dropwise under N_2 at 0° C. And the mixture was heated to 65° C. overnight. After reaction, the mixture was cooled down. And 0.23 mL H_2O was added followed by 0.2×3 mL 10% NaOH and 0.46 mL H_2O, and the mixture was filtered. The cake washed with EtOAc. The organic phase was concentrated to give 2-(2,2,2-trifluoroethyl)piperazine 140 mg, which was used without further purification. 1H NMR (CHLOROFORM-d) δ 2.75-3.02 (m, 7H), 2.52 (dd, J=11.7, 9.9 Hz, 1H), 2.10-2.17 (m, 2H).

Building Block 3: 2-(difluoromethyl)piperazine

[0594]

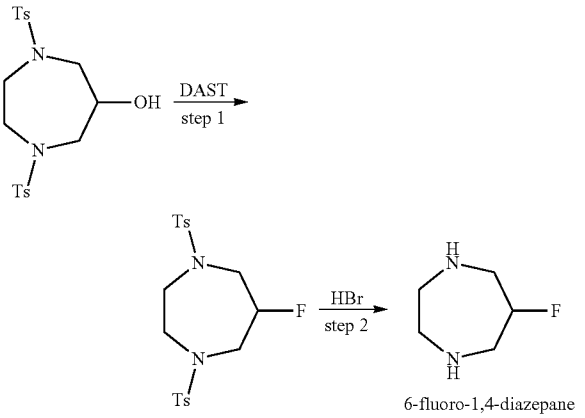


2-(difluoromethyl)piperazine

[0595] To a solution of 1,4-dibenzyl-2-(difluoromethyl) piperazine (synthesized according to *Synthetic Communications,* 2011, vol. 41, #14, 2031-2035)(80 mg, 0.253 mmol) in 40 mL of EtOH was added $Pd(OH)_2/C$ (15 mg). The resulting mixture was hydrogenated under 50 Psi at r.t. for two days. The reaction mixture was filtered, and the filtrate was concentrated to afford 2-(difluoromethyl)piperazine, which was used directly without further purification. LC-MS: m/z 137.1 $(M+H)^+$

Building Block 4: 6-fluoro-1,4-diazepane

[0596]



6-fluoro-1,4-diazepane

Step 1

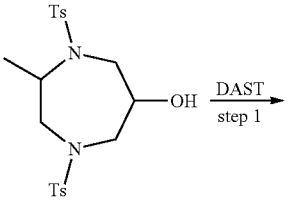
[0597] To a solution of 1,4-ditosyl-1,4-diazepan-6-ol (synthesized according to *Synthesis,* 2003, 2, 223-226) (200 mg, 0.47 mmol) in 5 mL of DCM was added DAST (190 mg, 1.18 mmol). The resulting mixture was stirred at r.t. overnight. The reaction mixture was quenched with aq $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic phases were dried and concentrated. The residue was purified by prep-TLC to afford 6-fluoro-1,4-ditosyl-1,4-diazepane (120 mg). ^{1}H NMR (CHLOROFORM-d) δ 7.66-7.71 (m, 4H), 7.34 (d, J=8.0 Hz, 4H), 5.02-4.92 (m, 1H), 3.60 (dd, J=18.1, 5.3 Hz, 4H), 3.34-3.53 (m, 4H), 2.46 (s, 6H).

Step 2

[0598] A suspension of 6-fluoro-1,4-ditosyl-1,4-diazepane (82 mg, 0.19 mmol) in HOAc—HBr (3 mL, 30 wt %) was heated to 100° C. for 3 mins in a pressure tube using microwave irradiation. The solvent was removed in vacuum and the residue triturated with Et_2O, washed with Et_2O to give 6-fluoro-1,4-diazepane, which was used directly without further purification. LC-MS: m/z 119.1 $(M+H)^+$

Building Block 5: 6-fluoro-2-methyl-1,4-diazepane

[0599]



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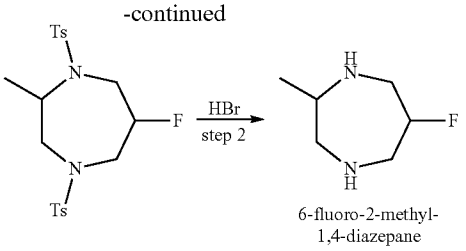


Step 1

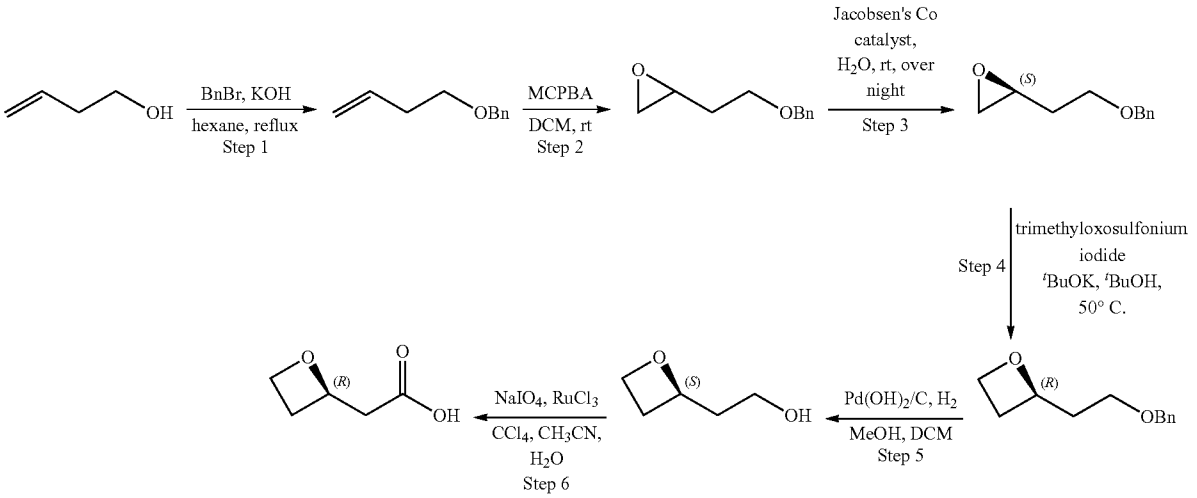
[0600] 6-fluoro-2-methyl-1,4-ditosyl-1,4-diazepane (120 mg) was obtained from 2-methyl-1,4-ditosyl-1,4-diazepan-6-ol (synthesized according to *Synthesis,* 2003, 2, 223-226) (200 mg, 0.47 mmol) (200 mg) by the method similar to 6-fluoro-1,4-ditosyl-1,4-diazepane. ^{1}H NMR (CHLOROFORM-d) δ 7.62-7.75 (m, 4H), 7.30-7.37 (m, 4H), 5.00-4.84 (m, 1H), 4.09-4.37 (m, 2H), 3.73-3.95 (m, 1H), 3.37-3.62 (m, 2H), 3.12-3.32 (m, 1H), 3.05 (ddd, J=13.6, 7.2, 4.0 Hz, 1H), 2.43-2.46 (m, 6H), 1.05-1.14 (m, 3H).

Step 2

[0601] 6-fluoro-2-methyl-1,4-diazepane was obtained from 6-fluoro-2-methyl-1,4-ditosyl-1,4-diazepane by the method similar to 6-fluoro-1,4-ditosyl-1,4-diazepane. LC-MS: m/z 133.1 $(M+H)^+$

Building Block 6: 2-(oxetan-2-yl)acetic acid

[0602]



Step 1

[0603] A mixture of 3-buten-1-ol (18.03 g, 0.25 mol), TEA (2.4 mL, 0.02 mol) and sodium hydroxide (15 g, 0.38 mol) in hexane (200 mL) was stirred at 50° C. for 0.5 h. Benzyl bromide (32.7 mL, 0.27 mol) in hexane (50 mL) was added dropwise over a period of 0.5 h. Afterwards, the resulting mixture was heated to reflux overnight (oil temperature: 85° C.). The precipitate was removed via filtration and washed with ethyl acetate twice. The combined organic phase was washed with brine and dried over sodium sulfate. Such obtained product was pure enough for the next reaction step. Yield: 38.21 g, 94.2%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.29 (m, 6H), 5.89 (ddt, J=17.0, 10.1, 6.7 Hz, 1H), 5.21-5.03 (m, 2H), 4.56 (s, 2H), 3.57 (t, J=6.8 Hz, 2H), 2.43 (qd, J=6.7, 1.1 Hz, 2H).

Step 2

[0604] To solution of ((but-3-en-1-yloxy)methyl)benzene (38.21 g, 0.24 mol) in dichloromethane (400 mL) was added mCPBA (77.15 g, 0.38 mol) at −20° C. as solid in portions. Afterwards, the resulting suspension was allowed to warm to rt and stirred overnight. The precipitate was filtered off and washed with dichloromethane. Afterwards, the combined organic phase was washed with saturated NaHCO3 and Na2SO3 and brine. The white precipitate was occurred while removing solvents under reduced pressure. More n-hexane was added and the most appeared white solid was filtered off. This procedure was repeated third times. The crude product was subjected to column chromatography on silica gel using a mixture of ethyl acetate with petroleum ether as eluent (EtOAc:PE=1/50 to 1/5) to afford the title compound. Yield: 35.26 g, 84.0%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 4.56 (s, 2H), 3.73-3.59 (m, 2H), 3.15-3.06 (m, 1H), 2.85-2.77 (m, 1H), 2.55 (dd, J=5.0, 2.7 Hz, 1H), 1.95 (dddd, J=13.4, 7.2, 6.2, 4.7 Hz, 1H), 1.81 (dq, J=14.3, 5.9 Hz, 1H). LC-MS: m/z 220.0 $(M+CH_3CN)^+$.

Step 3

[0605] To a round bottom flask charged with HOAc (60.1 mg, 1.0 mol %) in toluene (20 mL) was added Jacobsen salen Co(II) catalyst (0.30 g, 0.5 mol %) at rt and the resulting solution was stirred at rt for 0.5 h while the flask is open to air in order to absorb oxygen. The volatiles were removed under reduced pressure to give rise to a dark solid. Racemic epoxide (17.82 g, 100 mmol) was added neat, followed by the addition of distilled water (1.0 mL, 56 mmol) dropwise at 0° C. The resulting reaction mixture was allowed to warm to it slowly and stirred at it overnight. The reaction mixture was diluted with n-hexane and then passed through a pad of celite.

Epoxide was obtained by using petroleum ether and diol was obtained by using a mixture of methanol with dichloromethane (1/30). The obtained epoxide (red oil) was distilled and the desired product was obtained at 145-165° C. (oil temperature); similarly, the diol was obtained at 185-205° C. (oil temperature). Yield of epoxide: 7.83 g, 43.9%, pale yellow oil; Yield of diol: 8.46 g, 43.1%, bright yellow oil. For chiral epoxide: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 4.56 (s, 2H), 3.73-3.59 (m, 2H), 3.15-3.06 (m, 1H), 2.85-2.77 (m, 1H), 2.55 (dd, J=5.0, 2.7 Hz, 1H), 1.95 (dddd, J=13.4, 7.2, 6.2, 4.7 Hz, 1H), 1.81 (dq, J=14.3, 5.9 Hz, 1H). LC-MS: m/z 220.0 $(M+CH_3CN)^+$. For chiral diol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 4.53 (s, 2H), 3.94 (s, 1H), 3.86-3.41 (m, 5H), 3.18 (s, 1H), 1.91-1.66 (m, 2H). LC-MS: m/z 219.0 $(M+Na)^+$. ee>99%.

Step 4

[0606] A mixture of potassium tert-butoxide (1.68 g, 15 mmol) and trimethyloxosulphonium iodide (3.30 g, 15 mmol) in tert-butoxide (35 mL) was stirred at 50° C. for 1 h. A solution of chiral epoxide (0.89 g, 5 mmol) in tert-butoxide (15 mL) was added dropwise while keeping the temperature around 50° C. Afterwards, the resulting reaction mixture was stirred at 50° C. overnight. The precipitate was removed via filtration and washed with ethyl acetate. The combined organic phase was dried under reduced pressure and diluted with ethyl acetate. The diluted solution was washed with brine and dried over sodium sulfate. The crude product was subjected to column chromatography on silica gel using EtOAc:PE=1/10 as eluent to afford the title compound. Yield: 0.55 g, 57.7%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 5.09-4.94 (m, 1H), 4.70 (dd, J=14.0, 7.8 Hz, 1H), 4.62-4.38 (m, 3H), 3.67-3.51 (m, 2H), 2.72 (dq, J=13.9, 7.8 Hz, 1H), 2.43 (dt, J=10.7, 7.6 Hz, 1H), 2.16 (td, J=13.3, 5.8 Hz, 1H), 2.02 (td, J=13.6, 6.0 Hz, 1H). LC-MS: m/z 234.1 $(M+CH3CN)^+$. ee>99%.

Step 5

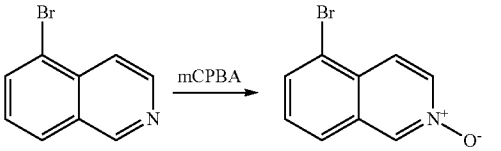
[0607] A mixture of (R)-2-(2-(benzyloxy)ethyl)oxetane (4.35 g, 22.63 mmol) and palladium hydroxide on carbon (20%, with 50% of water, 0.80 g, 2.5 mol %) in methanol (50 mL) and dichloromethane (15 mL) was stirred at rt overnight with an input of hydrogen gas. The precipitate was removed via filtration through a pad of celite and washed with dichloromethane. The combined organic phase was dried using water pump at 30° C. and was confirmed pure enough for the next reaction. Yield: 2.28 g, 98.7%; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (qd, J=7.5, 4.6 Hz, 1H), 4.70 (td, J=8.0, 6.0 Hz, 1H), 4.57 (dt, J=9.1, 5.9 Hz, 1H), 3.82 (ddd, J=11.8, 7.3, 4.6 Hz, 1H), 3.74 (ddd, J=11.1, 6.5, 4.9 Hz, 1H), 3.11-2.77 (m, 1H), 2.77-2.62 (m, 1H), 2.45 (ddt, J=11.0, 9.1, 7.4 Hz, 1H), 2.13-1.98 (m, 1H), 1.91 (ddt, J=14.3, 7.3, 4.7 Hz, 1H). ee>99%.

Step 6

[0608] To a mixture of oxetane (3.10 g, 30.48 mmol), sodium periodate (19.56 g, 91.44 mmol), water (30 mL), acetonitrile (60 mL) and carbon tetrachloride (30 mL) was added ruthenium trichloride plus three water (79.7 mg, 1 mol %) at 0-5° C. Afterwards, the resulting mixture was allowed to warm to rt and stirred at this temperature for 2 h. The precipitate was removed via filtration through a pad of celite and washed with diethyl ether (around 100 mL×5). The combined organic phase was washed with brine (50 mL×3) and then dried using water pump at 35° C. and was confirmed pure enough for the next reaction. Yield: 2.26 g, 63.8%; light yellow oil. ^{1}H NMR (400 MHz, methanol-d4) δ 5.26-5.15 (m, 1H), 4.69 (ddd, J=8.3, 7.8, 5.9 Hz, 1H), 4.58 (dt, J=9.2, 5.9 Hz, 1H), 2.88-2.70 (m, 3H), 2.51 (ddt, J=11.2, 9.1, 7.3 Hz, 1H). ee>99%.

Building Block 7: 5-bromoisoquinoline 2-oxide

[0609]

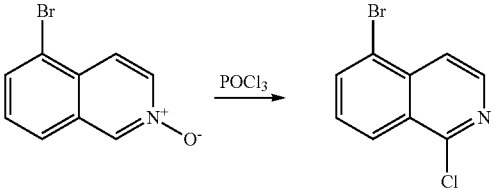


5-bromoisoquinoline 2-oxide

[0610] To a solution of 5-bromoisoquinoline (1.5 g, 7.2 mmol) in dichloromethane (20 mL) was added mCPBA (1.5 g, 8.6 mmol) at room temperature all at once. The reaction mixture was stirred at room temperature for 2 h. Then the mixture was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4. The solvent was removed and the residue was purified by column chromatography over silica gel (EtOAc) to give 0.97 g of title compound as a pale yellow solid. ^{1}H NMR (CHLOROFORM-d) δ 8.71-8.80 (m, 1H), 8.22 (dd, J=7.3, 1.5 Hz, 1H), 8.06 (d, J=7.3 Hz, 1H), 7.81-7.91 (m, 1H), 7.70 (d, J=8.2 Hz, 1H), 7.43-7.54 (m, 1H). LC-MS: m/z 222.9 $(M+H)^+$

Building Block 8: 5-bromo-1-chloroisoquinoline

[0611]

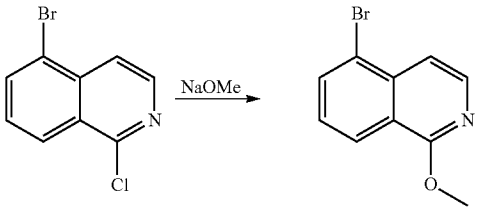


5-bromo-1-chloroisoquinoline

[0612] To a solution of 5-bromoisoquinoline 2-oxide (0.4 g, 2.4 mmol) in $CHCl_3$ (10 mL) was added $POCl_3$ (0.7 mL, 3 eq). Then the mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was poured into ice-water, neutralized with saturated NaHCO3 (aq), extracted with EtOAc. The solvent was removed and 0.45 g crude product was obtained which was used in next step with further purification. ^{1}H NMR (CHLOROFORM-d) δ 8.33-8.44 (m, 2H), 8.02-8.08 (m, 1H), 8.00 (d, J=5.6 Hz, 1H), 7.52-7.61 (m, 1H). LC-MS: m/z 242.9 $(M+H)^+$.

Building Block 9: 5-bromo-1-methoxyisoquinoline

[0613]

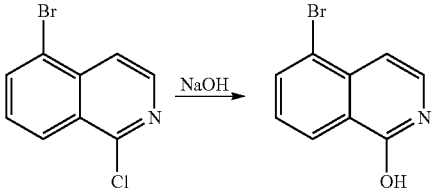


5-bromo-1-methoxyisoquinoline

[0614] To a solution of 5-bromo-1-chloroisoquinoline (1.2 g, 5.0 mmol) in methanol (10 mL) was added NaOMe (324 mg, 6.0 mmol). The mixture was refluxed for 2 h. The solvent was removed and the residue was purified by column chromatography over silica gel (10-20% EtOAc/petroleum ether) to obtain 600 mg of title compound as a white solid. ^{1}H NMR (DMSO-d_6) δ 8.26 (d, J=8.3 Hz, 1H), 8.12 (d, J=6.0 Hz, 1H), 7.95 (dd, J=7.5, 1.0 Hz, 1H), 7.58 (d, J=6.0 Hz, 1H), 7.41 (t, J=7.9 Hz, 1H), 4.17 (s, 3H). LC-MS: m/z 237.0 $(M+H)^+$

Building Block 10: 5-bromo-1-methoxyisoquinoline

[0615]

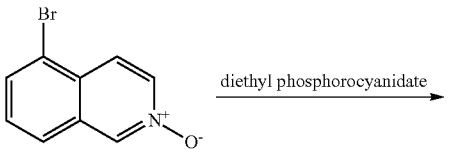


5-bromoisoquinolin-1-ol

[0616] To a suspension of 5-bromo-1-chloroisoquinoline (300 mg, 1.2 mmol) in water (10 mL) was added NaOH (240 mg, 6 mmol). The mixture was refluxed for 2 h. After cooling to room temperature, the pH of the mixture was adjusted to 7 with 2N HCl. The precipitate was filtered and dried to get 205 mg crude product as a white solid which was used directly in next step. LC-MS: m/z 222.9 $(M+H)^+$

Building Block 11: 5-bromo-1-methoxyisoquinoline

[0617]



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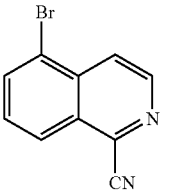
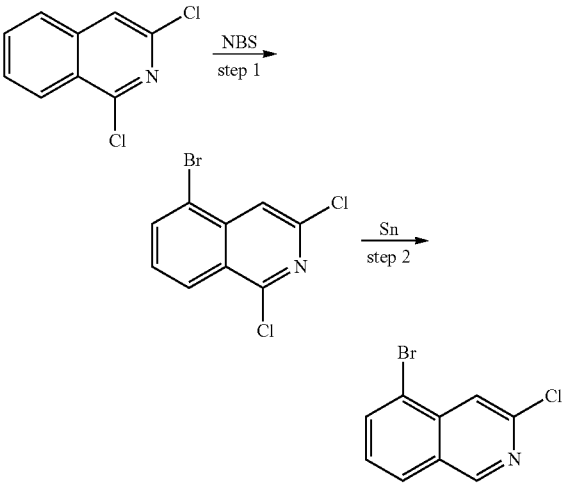


5-bromoisoquinoline-1-carbonitrile

[0618] A mixture of 5-bromoisoquinoline 2-oxide (224 mg, 1.0 mmol), diethyl phosphorocyanidate (489 mg, 3.0 mmol) and Et3N (101 mg, 1.0 mmol) in CH3CN (5 mL) was heated at 150° C. for 1.5 h in a microwave oven. After cooling to room temperature, the precipitate was filtered and dried to obtain 110 mg product as a yellow solid. ^{1}H NMR (CHLOROFORM-d) δ 8.79 (d, J=5.8 Hz, 1H), 8.38 (d, J=8.5 Hz, 1H), 8.29 (d, J=5.8 Hz, 1H), 8.14 (d, J=7.5 Hz, 1H), 7.70 (t, J=7.9 Hz, 1H). LC-MS: m/z 231.9 $(M+H)^+$

Building Block 12: 5-bromo-3-chloroisoquinoline

[0619]



5-bromo-3-chloroisoquinoline

Step 1

[0620] To a solution of 1,3-dichloroisoquinoline (4 g, 20.2 mmol) in CH3CN (100 mL) was added H2SO4 (4 mL), followed by NBS (4.4 g, 24.2 mmol). The mixture was stirred at room temperature for 90 h. Then the precipitate was collected by filtration, washed with water, dried to afford 3.4 g of 5-bromo-1,3-dichloroisoquinoline as a pale yellow solid. ^{1}H NMR (CHLOROFORM-d) δ 8.33 (d, J=8.5 Hz, 1H), 8.03-8.10 (m, 2H), 7.56 (dd, J=8.4, 7.7 Hz, 1H). LC-MS: m/z 276.9 $(M+H)^+$

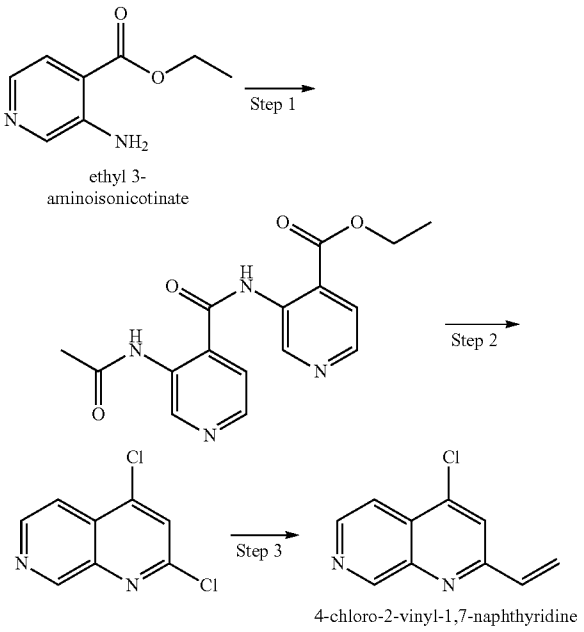
Step 2

[0621] To a suspension of 5-bromo-1,3-dichloroisoquinoline (3 g, 10.8 mmol) in AcOH (30 mL) and conc. HCl (6 mL) was added Sn powder (3.86 g, 32.4 mmol). The mixture was stirred at 60° C. for 20 min. After cooling to room tempera-

ture, the mixture was neutralized with NaOH (aq), filtered through celite. The filtrate was extracted with EtOAc (2×30 mL). The solvent was removed and the residue was purified by column chromatography over silica gel (5-10% EtOAc/petroleum ether) to afford 0.8 g of 5-bromo-3-chloroisoquinoline as a white solid. ^{1}H NMR (CHLOROFORM-d) δ 9.04 (s, 1H), 8.04 (s, 1H), 7.90-8.02 (m, 2H), 7.47 (t, J=7.9 Hz, 1H).

Building Block 13:
4-chloro-2-vinyl-1,7-naphthyridine

[0622]



Step 1

[0623] To a stirred solution of ethyl-2-aminonicotinate (1 g, 6.02 mmol) and ethyl acetate (13 g, 147.7 mmol) in 15 mL of anhydrous THF was added sodium tert-butoxide (1.45 g, 15.1 mmol) portionwise over 1 min. The resulting mixture was stirred at room temperature for 40 mins and at 100° C. for 4 hours. After this time the reaction was cooled to r.t. and evaporated in vacuo. The resulting solid was dissolved in water (20 mL) and neutralized to pH 7 with 1.0M aqueous HCl. The resulting solid was filtered and dried under vacuum overnight to give ethyl 3-(3-acetamidoisonicotinamido) isonicotinate as a tan solid (0.58 g, 59%). LC-MS: m/z 329.1 $(M+H)^+$ ^{1}H NMR (CHLOROFORM-d) δ: 11.96 (s, 1H), 10.74 (br. s., 1H), 10.12 (s, 1H), 9.99 (s, 1H), 8.56 (d, J=5.3 Hz, 1H), 8.59 (d, J=5.0 Hz, 1H), 7.89-7.96 (m, 1H), 7.66 (d, J=5.3 Hz, 1H), 4.51 (q, J=7.0 Hz, 2H), 2.24-2.33 (m, 3H), 2.19 (s, 2H), 1.43-1.54 (t, 3H).

Step 2

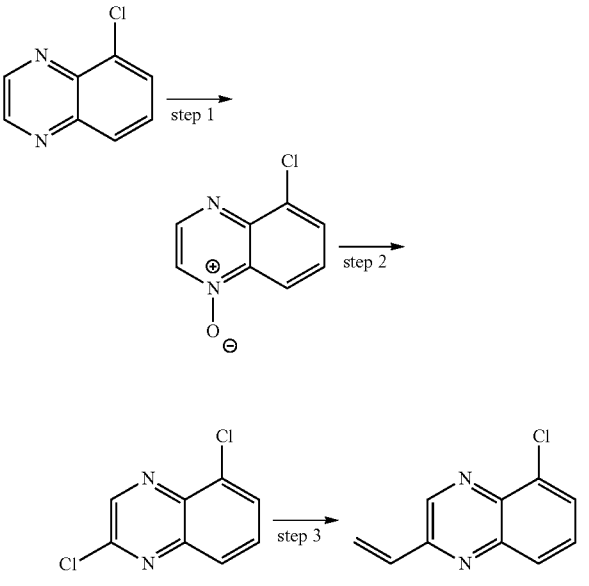
[0624] A stirred solution of ethyl 3-(3-acetamidoisonicotinamido)isonicotinate (400 mg, 2.47 mmol) in phosphorus oxychloride (2.5 mL) was heated to 120° C. for 3 hours. After this time the reaction was cooled to r.t. and evaporated in vacuo. The resulting residue was carefully basified to pH>10 with an aqueous solution of Na_2CO_3 and the resulting solid was filtered, washed with water and dried under vacuum to give 2,4-dichloro-1,7-naphthyridine (200 mg, 83%). ^{1}H NMR (CHLOROFORM-d) δ: 9.48 (s, 1H), 8.79 (d, J=5.9 Hz, 1H), 8.01 (d, J=5.9 Hz, 1H), 7.74 (s, 1H). LC-MS: m/z 200 $(M+H)^+$

Step 3

[0625] To 5 mg $PdCl_2$(dppf). CH_2Cl_2 in a reaction tube under nitrogen were added 3 mL isopropanol, 1 mL water, 93.6 mg (0.8 mmol) DIPEA, 52 mg (0.39 mmol) potassium vinyl trifluoroborate and 78 mg (0.39 mmol) 4-chloro-2-vinyl-1,7-naphthyridine. The reaction solution was heated to 100° C. for half hour under microwave irradiation. The reaction mixture was extracted into ethyl acetate, washed several times with water and purified by prepTLC (petrol: ethyl acetate=1:1) to give 4-chloro-2-vinyl-1,7-naphthyridine 50 mg (66.8%). ^{1}H NMR (CHLOROFORM-d) δ: 9.51 (d, J=0.6 Hz, 1H), 8.70 (d, J=5.6 Hz, 1H), 7.98-8.04 (m, 1H), 7.89 (s, 1H), 7.02 (dd, J=17.6, 10.9 Hz, 1H), 6.41 (d, J=17.6 Hz, 1H), 5.83 (d, J=11.2 Hz, 1H). LC-MS: m/z 191.6 $(M+H)^+$

Building Block 14: 5-chloro-2-vinylquinoxaline

[0626]



Step 1

[0627] To a solution of 5-chloroquinoxaline (1.4 g, 8.54 mmol) in 50 mL of dichloromethane was added mCPBA (1.62 g, 9.39 mmol). The resulting mixture was stirred at room temperature overnight. After removal of dichloromethane, the crude product obtained was purified by doing column chromatography (100% DCM) to afford 1.5 g of 5-chloroquinoxaline 1-oxide as a white solid.

Step 2

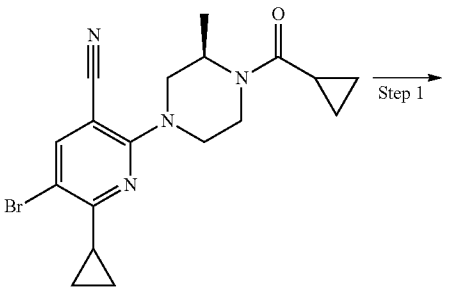
[0628] To a solution of 5-chloroquinoxaline 1-oxide (450 mg, 2.5 mmol) in 5 mL of chloroform was added $POCl_3$ (1.9 g, 12.5 mmol) slowly. The resulting mixture was heated to 80° C. and held stirring at 80° C. overnight. After removal of chloroform and excess $POCl_3$, the crude product obtained was purified by doing column chromatography (5% PE/EA) to afford 240 mg of 2,5-dichloroquinoxaline as a white solid. MS (ES) M+H expected 198, found 199. ^{1}H NMR (CHLOROFORM-d) δ: 8.89 (s, 1H), 7.98 (d, 1H), 7.92 (d, 1H), 7.76 (t, 1H).

Step 3

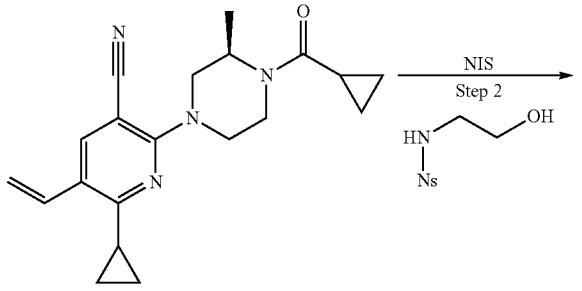
[0629] To a flask was added 2,5-dichloroquinoxaline (315 mg, 1.59 mmol), potassium trifluoro(vinyl)borate (234 mg, 1.75 mmol), $PdCl_2DPPF$ (130 mg, 0.16 mmol), K_2CO_3 (442 mg, 3.18 mmol), propan-2-ol (4 mL), and H_2O (1 mL), the mixture was degassed with N_2, then heated to 90° C. with stirring for about 3 hrs. TLC (5% PE/EA) showed the consumption of the starting material and new spot appeared. The mixture was then filtered through celite, the cake was washed with ethyl acetate. The filtrate was concentrated in vacuo, the residue was purified by column chromatography (1-5% PE/EA) to afford 256 mg of 5-chloro-2-vinylquinoxaline as a white solid. ^{1}H NMR (CHLOROFORM-d) δ: 9.10 (s, 1H), 8.02 (d, 1H), 7.85 (d, 1H), 7.71 (t, 1H), 7.09 (q, 1H), 6.57 (d, 1H), 5.89 (d, 1H). MS (ES) M+H expected 190, found 191.

Building Block 15: 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(morpholin-2-yl)nicotinonitrile

[0630]



7-2



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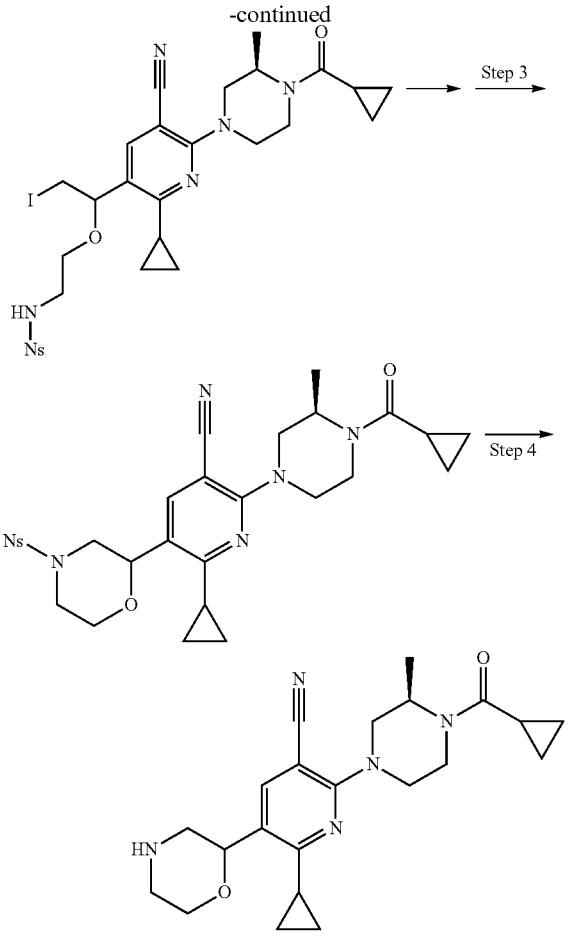


Step 1

[0631] A mixture of 7-2 (500 mg, 1.28 mmol), Potassium vinyltrifluoroborate (258 mg, 1.93 mmol), TEA (650 mg, 6.4 mmol) and $Pd(dppf)Cl_2$(52 mg, 0.064 mmol) in i-PrOH and water was heated at 100° C. under microwave irradiation for 0.5 hr. The reaction mixture was concentrated and the residue was purified by column chromatography (50% PE/EA) to afford 420 mg of title compound. ^{1}H NMR (CHLOROFORM-d) δ 7.80 (s, 1H), 6.99 (dd, J=17.3, 10.8 Hz, 1H), 5.58 (dd, J=17.3, 0.8 Hz, 1H), 5.36 (dd, J=11.0, 0.8 Hz, 1H), 4.86 (br. s., 0.5H), 4.53 (br. s., 0.5H), 4.44 (br. s., 0.5H), 4.09-4.29 (m, 2.5H), 3.65 (br. s., 0.5H), 3.41 (br. s., 0.5H), 3.12-3.24 (m, 2H), 2.14-2.26 (m, 1H), 1.76 (br. s., 1H), 1.25-1.42 (m, 3H), 1.10-1.17 (m, 2H), 0.96-1.10 (m, 4H), 0.82 (dd, J=7.8, 1.8 Hz, 2H).

Step 2

[0632] A mixture of (R)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-vinylnicotinonitrile (200 mg, 0.59 mmol), N-(2-hydroxyethyl)-4-nitrobenzenesulfonamide (174 mg, 0.71 mmol, synthesized in accordance with Organic Letters, 2011, 13, #4, p. 728-731), and NIS (159 mg, 0.71 mmol) suspended in 10 mL of MeCN was stirred at r.t. for 2 hrs. After the mixture was concentrated in vacuo, the residue was purified by column chromatography (50% PE/EA) to afford 100 mg of N-(2-(1-(5-cyano-6-((R)-4-(cy-

clopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropyl pyridin-3-yl)-2-iodoethoxy)ethyl)-4-nitrobenzenesulfonamide as a light yellowish solid. ^{1}H NMR (CHLOROFORM-d) δ 8.36-8.45 (m, J=8.8 Hz, 2H), 8.08-8.17 (m, J=8.8 Hz, 2H), 7.60 (s, 1H), 5.57 (br. s., 1H), 4.83 (br. s., 0.5H), 4.60-4.71 (m, 1H), 4.53 (br. s., 0.5H), 4.40 (br. s., 0.5H), 4.19-4.34 (m, 2.5H), 3.54-3.72 (m, 1H), 3.15-3.48 (m, 8H), 1.88-1.98 (m, 1H), 1.75 (br. s., 1H), 1.34-1.40 (m, 3H), 1.00-1.18 (m, 6H), 0.81 (d, J=7.8 Hz, 2H).

Step 3

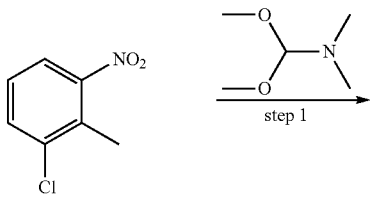
[0633] A mixture of N-(2-(1-(5-cyano-6-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)-2-iodoethoxy)ethyl)-4-nitrobenzenesulfonamide (100 mg, 0.14 mmol), K_2CO_3 (97 mg, 0.71 mmol) in 10 mL of MeCN was stirred at r.t. overnight. After the mixture was filtered, the filtrate was concentrated and the residue was purified by column chromatography (50% PE/EA) to afford 66 mg of 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(4-((4-nitrophenyl)sulfonyl) morpholin-2-yl)nicotinonitrile as a light yellowish solid. ^{1}H NMR (CHLOROFORM-d) δ 8.39-8.49 (m, J=8.5 Hz, 2H), 7.90-8.02 (m, J=8.3 Hz, 2H), 7.70 (s, 1H), 4.91 (dd, J=10.2, 2.1 Hz, 1H), 4.84 (br. s., 0.5H), 4.52 (br. s., 0.5H), 4.42 (br. s., 0.5H), 4.16 (dd, J=11.8, 2.5 Hz, 4H), 3.86-4.00 (m, 2H), 3.76 (d, J=11.5 Hz, 1H), 3.61 (br. s., 0.5H), 3.14-3.38 (m, 3H), 2.52-2.69 (m, 1H), 1.97-2.09 (m, 1H), 1.74 (br. s., 1H), 1.28-1.48 (m, 3H), 1.19-1.25 (m, 2H), 1.11-1.19 (m, 2H), 1.04-1.11 (m, 2H), 0.81 (d, J=7.5 Hz, 2H).

Step 4

[0634] A mixture of 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(4-((4-nitrophenyl) sulfonyl)morpholin-2-yl)nicotinonitrile (50 mg, 0.075 mmol), butane-1-thiol (3 d) and $LiOH.H_2O$(20 mg) in 10 mL of MeCN was stirred at r.t. overnight. After the mixture was filtered, the filtrate was concentrated and the residue was purified by column chromatography (10% DCM/MeOH) to afford 21 mg of 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(morpholin-2-yl)nicotinonitrile. ^{1}H NMR (CHLOROFORM-d) δ 7.81 (br. s., 1H), 4.96 (br. s., 1H), 4.34-4.63 (m, 1H), 4.14 (br. s., 3H), 3.97 (br. s., 1H), 3.46 (br. s., 3H), 3.32 (br. s., 2H), 3.09 (br. s., 3H), 2.75 (br. s., 1H), 2.09 (br. s., 1H), 1.74 (br. s., 1H), 1.26 (br. s., 5H), 1.03 (br. s., 4H), 0.80 (br. s., 2H).

Building Block 16: 5-chloro-2-vinylquinazoline

[0635]



1-chloro-2-methyl-3-nitrobenzene

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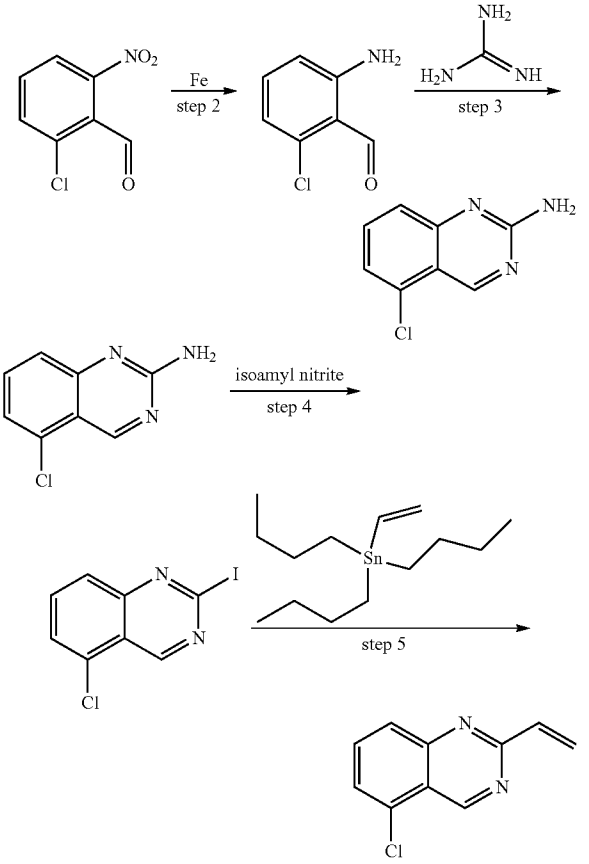


5-chloro-2-vinylquinazoline

Step 1

[0636] To a solution of 1-chloro-2-methyl-3-nitrobenzene (10.0 g, 58.3 mmol) in 150 mL of anhydrous DMF was added 1,1-dimethoxy-N,N-dimethylmethanamine (21.0 g, 175 mmol). The resulting mixture was stirred at 140° C. for 16 hours. After cooling to 0° C., the mixture was added slowly a solution of $NaIO_4$ (37.4 g, 175 mmol) in H_2O and DMF. The mixture was stirred for another 6 hours. The mixture was filtered and partitioned between EtOAc and water. The organic layer was washed with water and dried over Na_2SO_4 and concentrated to give the crude which was purified by column to afford 6.5 g of 2-chloro-6-nitrobenzaldehyde. ^{1}H NMR (CHLOROFORM-d) δ 10.39 (s, 1H), 7.95-8.04 (m, 1H), 7.74-7.80 (m, 1H), 7.64 (t, J=8.0 Hz, 1H). LC-MS: m/z 186.0 $(M+H)^+$

Step 2

[0637] To a solution of 2-chloro-6-nitrobenzaldehyde (1 g, 0.0054 mmol) in ethanol was added Fe (1.8 g, 0.032 mmol), AcOH (10 ml) and 2N aqueous HCl (5 mL). The resulting mixture was stirred at 25° C. for 2 hours. The mixture was filtered and the filtrate was partitioned between DCM and water, the organic layer was washed with water and brine, concentrated to give 2-amino-6-chlorobenzaldehyde under 25° C. which was without purification for next step. LC-MS: m/z 156.01 (M+H).

Step 3

[0638] The mixture of compound 2-amino-6-chlorobenzaldehyde (2.8 g, 0.018 mol), guanidine (3.43 g, 0.36 mol) and Na_2CO_3 (3.82 g, 0.36 mol) in naphthalene was stirred at 180° C. for 2 hours. After cooling to room temperature, the mixture was filtered and the solid was washed with water and DCM to give the yellow solid 5-chloroquinazolin-2-amine which was used without purification for next step. ^{1}H NMR (DMSO-d6) δ9.28 (s, 1H), 7.65 (dd, J=8.5, 7.8 Hz, 1H), 7.39 (d, J=8.5 Hz, 1H), 7.31 (d, J=7.5 Hz, 1H), 7.16 (s, 2H). LC-MS: m/z 180.0 (M+H).

Step 4

[0639] The mixture of 5-chloroquinazolin-2-amine (2.2 g, 12.2 mmol), isoamyl nitrite (4.30 g, 36.7 mmol), CuI (1.17 g, 6.12 mmol) and CH_2I_2 (16.4 g, 61.2 mmol) in THF was stirred at 60° C. for 72 hours. After cooling to room temperature, the mixture was filtered and the filtrate was partitioned between EtOAc and water, the organic layer was washed with water and brine, dried over Na_2SO_4. Then the organic layer was concentrate to give the crude which was purified by column to give 5-chloro-2-iodoquinazoline as yellow solid. ^{1}H NMR (CHLOROFORM-d) δ 9.46 (s, 1H), 7.93 (d, J=8.5 Hz, 1H), 7.86 (dd, J=8.5, 7.5 Hz, 1H), 7.72 (dd, J=7.4, 1.1 Hz, 1H).

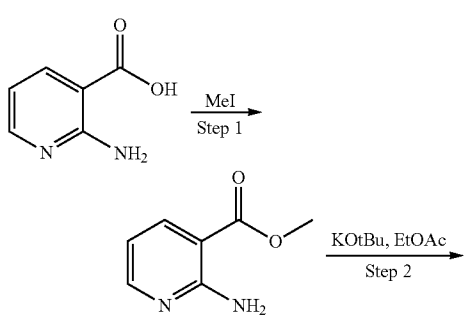
[0640] LC-MS: m/z 291.1 (M+H).

Step 5

[0641] The mixture of 5-chloro-2-iodoquinazoline (1.3 g, 4.48 mmol), potassium vinyltrifluoroborate (600 mg, 4.48 mmol), $Pd(dppf)Cl_2$ (165 mg, 0.224 mmol) and CsF (2.04 g, 13.4 mmol) in dioxane/H_2O was stirred at 80° C. for 16 hours. After cooling to room temperature, the mixture was partitioned between EtOAc and water. The organic layer was washed with water, brine and dried over Na_2SO_4, concentrated to give the crude which was purified by column to give 500 mg of 5-chloro-2-vinylquinazoline as yellow solid. ^{1}H NMR (CHLOROFORM-d) δ 9.75 (s, 1H), 7.93 (d, J=8.5 Hz, 1H), 7.80 (t, J=8.0 Hz, 1H), 7.63 (d, J=7.5 Hz, 1H), 7.06 (dd, J=17.2, 10.4 Hz, 1H), 6.85 (dd, J=17.3, 1.8 Hz, 1H), 5.90 (dd, J=10.5, 1.5 Hz, 1H). LC-MS: m/z 191.0 (M+H).

Building Block 17:
4-chloro-2-vinyl-1,8-naphthyridine

[0642]



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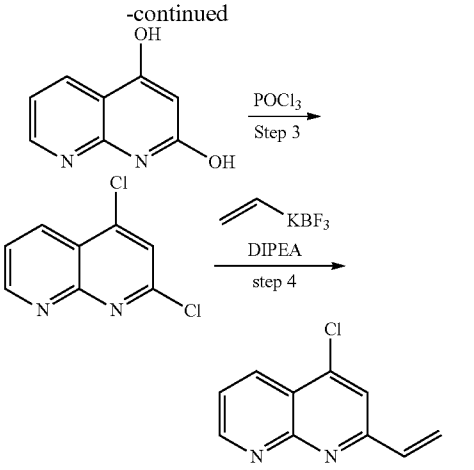


4-chloro-2-vinyl-1,8-naphthyridine

Step 1

[0643] A mixture of 25 g of 2-aminonicotinic acid (0.18 mol), 25 g of K_2CO_3 (0.18 mol) in 250 mL of DMF was stirred at 140° C. for 30 minutes, then cooled to 10° C. in ice/H_2O, 11 mL of MeI (0.18 mol) was added at 10° C. dropwise, the mixture was stirred at room temperature overnight. The mixture was filtered, the filtrate was concentrated, residue was dissolved in EtOAc, and filtered again through a pad of silica gel, the filtrate was concentrated to give 15 g of methyl 2-aminonicotinate. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 7.67 (d, J=7.0 Hz, 1H), 7.69 (d, J=7.8 Hz, 1H), 7.60-7.44 (m, 1H), 3.54 (br. s., 3H).

Step 2

[0644] To methyl 2-aminonicotinate (7.48 g, 49 mmol) in EtOAc/THF (150 mL/150 mL) was added 13.8 g of KtOBu (123 mmol) in portions slowly at room temperature, and the mixture was stirred at room temperature for 50 minutes before it was refluxed for 4 hours. After cooling to room temperature, the mixture was concentrated, the residue was dissolved in 200 mL of H_2O, pH was adjusted to pH=7 with 1N HCl with vigorous stirring, the resulting suspension was filtered, the solid obtained was dried in vacuum to give 7 g of 1,8-naphthyridine-2,4-diol.

Step 3

[0645] A mixture of 8.0 g of 1,8-naphthyridine-2,4-diol (49 mmol) in 80 mL of $POCl_3$ was refluxed for 1.5 hour, excessive $POCl_3$ was removed under reduced pressure, the residue was poured into satd $NaHCO_3$ slowly with vigorous stirring, the mixture was extracted with EtOAc, and the organic layers were dried over Na_2SO_4, concentrated to give 2 g of 2,4-dichloro-1,8-naphthyridine, which was used in the subsequent reaction without further purification. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 9.21-9.12 (m, 1H), 8.59 (dd, J=1.8, 8.3 Hz, 1H), 7.67-7.58 (m, 2H).

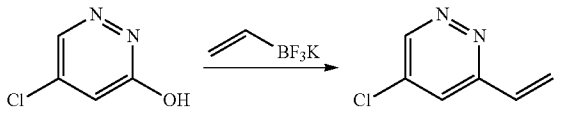
Step 4

[0646] 100 mg of 2,4-dichloro-1,8-naphthyridine (0.5 mmol), 68 mg of potassium vinyltrifluoroborate (0.5 mmol), 130 mg of DIPEA (1 mmol) in iPrOH/H_2O (3 mL/1 mL) was

added $Pd(dppf)_2Cl_2$, then the mixture was stirred at 105° C. in a sealed tube for 1 hour. When TLC (Petroleum ether: Ethyl acetate=3:1) indicated the completion of the reaction, the mixture was cooled to room temperature, filtered through a pad of celite, the filtrate was concentrated to give 120 mg of crude 4-chloro-2-vinyl-1,8-naphthyridine, and was used in the subsequent reaction without further purification. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 9.17 (dd, J=1.8, 4.3 Hz, 1H), 8.58 (dd, J=1.9, 8.4 Hz, 1H), 7.62-7.49 (m, 2H), 7.13-6.94 (m, 1H), 6.52 (d, J=17.6 Hz, 1H), 5.81 (d, J=10.8 Hz, 1H).

Building Block 18: 5-chloro-3-vinylpyridazine

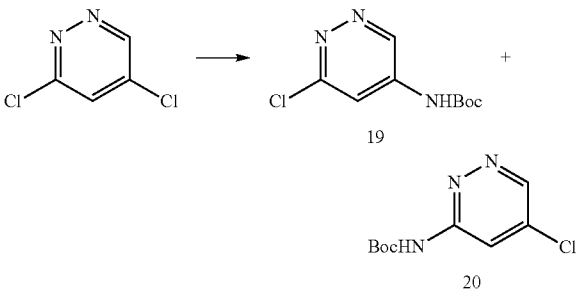
[0647]



[0648] The mixture of 5-chloropyridazin-3-ol (500 mg, 3.36 mmol), potassium vinyltrifluoroborate (450 mg, 3.36 mmol), $Pd(dppf)Cl_2$ (124 mg, 0.168 mmol) and CsF (1.5 g, 10.07 mmol) in dioxane/H_2O (8 mL/2 mL) was stirred at 100° C. for 16 hours. The mixture was diluted with EtOAc (50 mL) and filtered. The filtrate was partitioned between EtOAc (50 mL) and water (30 mL), the organic layer was washed with water (30 mL), brine and dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 200 mg of the product. ^{1}H NMR (CHLOROFORM-d) δ 9.06 (d, J=2.3 Hz, 1H), 7.60 (d, J=2.3 Hz, 1H), 7.02 (dd, J=17.8, 11.0 Hz, 1H), 6.32 (d, J=17.6 Hz, 1H), 5.77 (d, J=10.9 Hz, 1H). LC-MS: m/z 141.0 $(M+H)^+$

Building Block 19 and 20: tert-butyl 6-chloropyridazin-4-ylcarbamate and tert-butyl 5-chloropyridazin-3-ylcarbamate

[0649]



[0650] The mixture of 3,5-dichloropyridazine (400 mg, 2.68 mmol), BocNH2 (314 mg, 2.68 mmol), Pd(dppf)Cl2 (99 mg, 0.134 mmol), Xantphos (155 mg, 0.268 mmol) and Cs_2CO_3 (2.61 g, 8.05 mmol) in toluene was stirred at 80° C. for 16 hours. The mixture was diluted with EtOAc (50 mL) and filtered. The filtrate was partitioned between EtOAc (50 mL) and water (30 mL), the organic layer was washed with water (30 mL), brine and dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 150 mg of the product 19 and 120 mg of 20.

tert-butyl 6-chloropyridazin-4-ylcarbamate

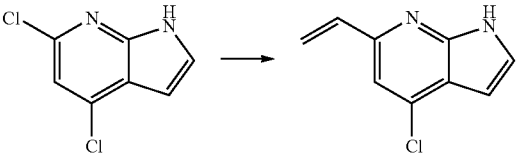
[0651] ^{1}H NMR (CHLOROFORM-d) δ 8.86 (d, J=2.0 Hz, 1H), 8.37 (d, J=2.3 Hz, 1H), 8.12 (br. s., 1H), 1.56 (s, 9H). LC-MS: m/z 230.1 $(M+H)^+$

tert-butyl 5-chloropyridazin-3-ylcarbamate

[0652] ^{1}H NMR (CHLOROFORM-d) δ 8.94 (s, 1H), 8.04 (s, 1H), 7.37 (br. s., 1H), 1.48-1.63 (s, 9H). LC-MS: m/z 230.1 $(M+H)^+$

Building Block 21: 4-chloro-6-vinyl-1H-pyrrolo[2,3-b]pyridine

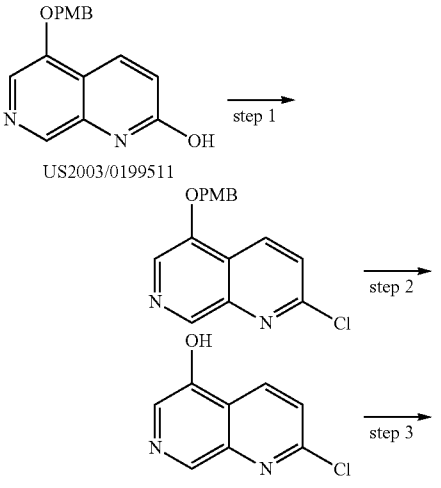
[0653]



[0654] To a solution of 4,6-dichloro-1H-pyrrolo[2,3-b]pyridine (20 mg, 0.1 mmol), potassium vinyl trifluoroborate (13 mg, 0.1 mmol), 5 mg $PdCl_2(dppf)$. CH_2Cl_2 and CsF (45 mg, 0.3 mmol) in dioxane/H_2O (5:1) 3 mL was stirred at 100° C. for 1 hours. Then the mixture was partitioned between EtOAc and water, the organic was washed with water, brine and concentrated to give the crude which was purified by column to give 14 mg of the product. ^{1}H NMR (CHLOROFORM-d) δ: 11.19 (br. s., 1H), 7.39 (br. s., 1H), 7.28 (s, 2H), 6.91 (dd, J=17.3, 10.9 Hz, 1H), 6.62 (br. s., 1H), 6.21 (d, J=17.3 Hz, 1H), 5.55 (d, J=10.9 Hz, 1H). LC-MS: m/z 179.6 $(M+H)^+$

Building Block 22: 2-vinyl-1,7-naphthyridin-5-yl trifluoromethanesulfonate

[0655]



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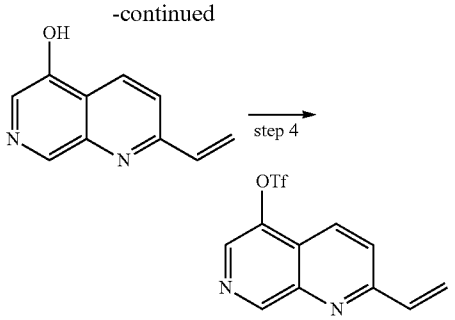


2-vinyl-1,7-naphthyridin-5-yl trifluoromethanesulfonate

Step 1

[0656] To a suspension of 5-(4-methoxybenzyloxy)-1,7-naphthyridin-2-ol (180 mg, 0.64 mmol) in DMF (5 mL) was added $POCl_3$ (293 mg, 1.92 mmol). The mixture was heated at 45° C. for 6 h. After cooling to room temperature, the reaction mixture was poured into ice-water, neutralized with NaHCO3, extracted with EtOAc (3×20 mL). The organic layer washed with water (20 mL) and brine (20 mL). The solvent was removed and 150 mg crude product was obtained which was used in next step without further purification. LC-MS: m/z 300 $(M+H)^+$

Step 2

[0657] To a solution of 2-chloro-5-(4-methoxybenzyloxy)-1,7-naphthyridine (150 mg, 0.5 mmol) in EtOH (10 mL) was added 1N HCl (2.5 mL). Then the mixture was heated at 90° C. for 2 h. After cooling to room temperature, 190 mg of K_2CO_3 was added and followed 10 mL of methanol. The mixture was stirred vigorously for 1 h at which time silica gel was added. The solvent was removed and the residue was purified by column chromatography (5% methanol/dichloromethane) to give 70 mg of title compound (83%). LC-MS: m/z 180 $(M+H)^+$

Step 3

[0658] A mixture of 2-chloro-1,7-naphthyridin-5-ol (70 mg, 0.39 mmol), Potassium vinyltrifluorobrate (104 mg, 0.78 mmol), Pd(dppf)Cl2 (32 mg, 0.039 mmol) and CsF (119 mg, 0.78 mmol) in dioxane:H_2O=5:1 (5 ml+1 ml) was purged with N2 for three times. Then the mixture was heated at 100° C. for 2 h. The solvent was removed and the residue was purified by column chromatography (5% methanol/dichloromethane) to give 30 mg of title compound (45%).

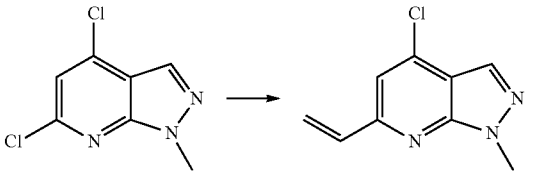
[0659] LC-MS: m/z 173 $(M+H)^+$

Step 4

[0660] To a solution of 2-vinyl-1,7-naphthyridin-5-ol (30 mg, 0.17 mmol) and Et3N (35 mg, 0.34 mmol) in dichloromethane (3 mL) was added Tf2O (59 mg, 0.21 mmol) at 0° C. Then the temperature was raised to room temperature and stirred for 2 h. The solvent was removed and the residue was purified by prep. TLC (EtOAc/petroleum ether=3/7) to give 10 mg of title compound (20%). LC-MS: m/z 305 $(M+H)^+$

Building Block 23: 4-chloro-1-methyl-6-vinyl-1H-pyrazolo[3,4-b]pyridine

[0661]

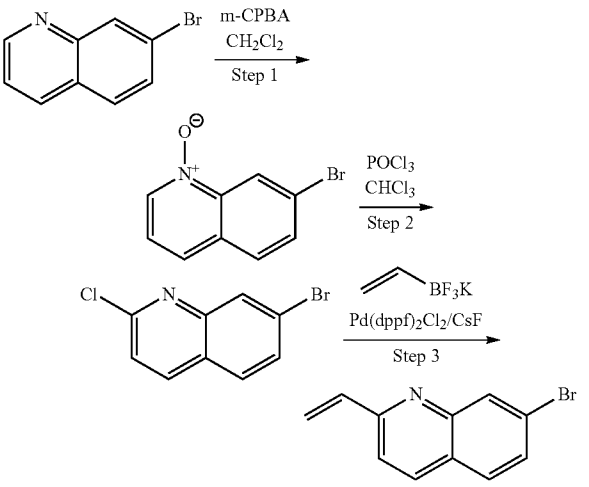


WO2010/59788

[0662] A mixture of 4,6-dichloro-1-methyl-1H-pyrazolo [3,4-b]pyridine (0.8 g, 4.0 mmol), Potassium vinyltrifluorobrate (540 mg, 4.0 mmol), Pd(dppf)Cl2 (98 mg, 0.12 mmol) and CsF (1.22 g, 8 mmol) in dioxane:H2O=5:1 (10 mL+2 mL) was purged with N2 three times. Then the mixture was heated at 100° C. for 2 h. The solvent was removed and the residue was purified by column chromatography (30% EtOAc/petroleum ether) to give 500 mg of title compound (65%). ^{1}H NMR (CHLOROFORM-d) δ 8.03 (s, 1H), 7.24 (s, 1H), 6.89 (dd, J=17.5, 10.7 Hz, 1H), 6.36 (d, J=17.3 Hz, 1H), 5.64 (d, J=10.9 Hz, 1H), 4.16 (s, 3H). LC-MS: m/z 193 $(M+H)^+$

Building Block 24: 7-bromo-2-vinylquinoline

[0663]



Step 1

[0664] 7-bromoquinoline 1-oxide: to a solution of 7-bromoquinoline (1.04 g, 5 mmol) in 20 mL of DCM was added m-Chloroperbenzoic acid (1.01 g, 5 mmol) at room temperature. The reaction mixture was then stirred at room temperature overnight. After LC-MS showed the completion of reaction, the mixture was poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography (hexane/ethyl acetate=3/1) afforded 1.0 g of title compound as a white solid. LC-MS: m/z 225.1 $(M+H)^+$

Step 2

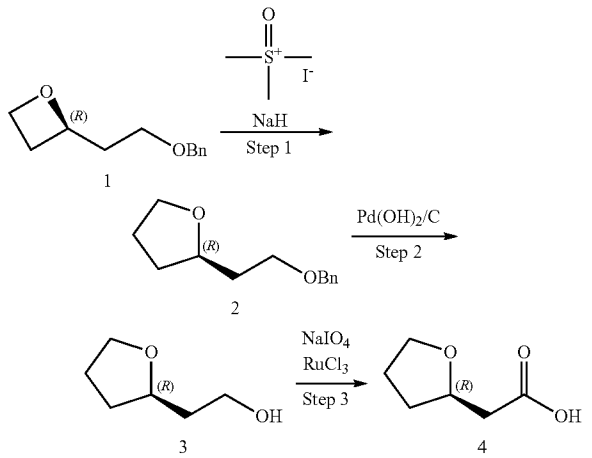
[0665] 7-bromo-2-chloroquinoline: to a solution of 7-bromoquinoline 1-oxide (1.0 g, 4.5 mmol) in 20 mL of chloroform was added Phosphorus oxychloride (3.42 g, 22 mmol) at room temperature. The reaction mixture was then heated at reflux for 3 hours. After LC-MS showed the completion of reaction, the mixture was poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography (hexane/ethyl acetate=3/1) afforded 0.75 g of title compound as a white solid. LC-MS: m/z 244.1 $(M+H)^+$

Step 3

[0666] 7-bromo-2-vinylquinoline: to a solution of 7-bromo-2-chloroquinoline (0.75 g, 3 mmol) in 1,4-dioxane (10 mL) was added Potassium vinyltrifluoroborate (0.42 g, 3 mmol), dichlorobis (triphenylphosphine) palladium (II) (143 mg) and Cesium fluoride (1.40 g, 9 mmol), and the mixture was stirred at 100° C. for 10 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate=4/1) afforded 0.42 g of title compound as a white solid. LC-MS: m/z 234.9 $(M+H)^+$

Building Block 25:
(R)-2-(tetrahydrofuran-2-yl)acetic acid

[0667]



Step 1

[0668] (R)-2-(2-(benzyloxy)ethyl)tetrahydrofuran: to a well stirred suspension of 1.28 g (52 mmol) of NaH in dry diglyme (15 mL) was added 6.86 g (31.2 mmol) of trimethylsulfoxonium iodide at room temperature. The mixture was gently heated to 120° C., and compound 1 (Step 4 product in building block 6 scheme) (1 g, 5.2 mmol) in diglyme (3 mL) was added in one portion. The reaction mixture was stirred at 120° for 4 hours, cooled, carefully quenched with water, and extracted three times with n-hexane. The combined extracts were washed with water and brine and dried over Na2SO4. Removal of solvent and purification by chromatography on silica gel gave the compound 2 (0.5 g, 46%). ^{1}H NMR (CHLOROFORM-d) δ 7.34-7.42 (m, 4H), 7.26-7.34 (m, 1H), 4.43-4.63 (m, 2H), 3.91-4.05 (m, 1H), 3.83-3.91 (m, 1H), 3.74 (td, J=7.9, 6.5 Hz, 1H), 3.62 (t, J=6.6 Hz, 2H), 1.96-2.05 (m, 1H), 1.73-1.95 (m, 4H), 1.52 (dd, J=11.9, 8.7 Hz, 1H).

Step 2

[0669] (R)-2-(tetrahydrofuran-2-yl)ethanol: to a solution of compound 2 (0.3 g, 1.45 mmol) in MeOH (15 mL) was added 10% $Pd(OH)_2$/C (20 mg). The reaction mixture was purged with hydrogen and stirred under an atmosphere of hydrogen for 2 d. The black suspension was passed through a plug of celite eluting with MeOH, then the solution was concentrated to yield the desired product as colorless oil (0.15 g, 89%). ^{1}H NMR (CHLOROFORM-d, 400 MHz): δ 4.00-4.08 (m, 1H), 3.86-4.00 (m, 1H), 3.66-3.86 (m, 3H), 2.87 (br. s., 1H), 1.98-2.10 (m, 1H), 1.84-1.98 (m, 2H), 1.70-1.84 (m, 2H), 1.46-1.63 ppm (m, 1H).

Step 3

[0670] (R)-2-(tetrahydrofuran-2-yl)acetic acid: to a mixture of compound 3 (0.15 g, 1.3 mmol), sodium periodate (0.72 G, 2.6 mmol), water (10 mL), acetonitrile (20 mL) and carbon tetrachloride (20 mL) was added ruthenium trichloride (29 mg, 10 mol %) at 0-5° C. Afterwards, the resulting mixture was allowed to warm to rt and stirred at this temperature for 2 h. The precipitate was removed via filtration through a pad of celite and washed with diethylether (around 100 mL×5). The combined organic phase was washed with brine (50 mL×3) and then dried under reduced pressure to get the compound 4 (60 mg, contain about 8% of the byproduct). ^{1}H NMR (CHLOROFORM-d, 400 MHz): δ 4.19-4.33 (m, 1H), 3.89-4.06 (m, 1H), 3.83 (td, J=7.8, 6.5 Hz, 1H), 2.62 (dd, J=6.5, 1.5 Hz, 2H), 2.07-2.23 (m, 1H), 1.89-2.06 (m, 2H), 1.54-1.72 (m, 1H).

Example 16

The Following Compounds were Made Following Methods Analogous to Those for Compound 273

(R)-5-(2-cyanophenyl)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (Compound 274; General procedure 1, Step H)

[0671] ^{1}H NMR (CHLOROFORM-d) δ 7.76-7.82 (m, 1H), 7.69 (td, J=7.7, 1.4 Hz, 1H), 7.58-7.63 (m, 1H), 7.52 (td, J=7.7, 1.1 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H), 4.56-4.79 (m, 1.5H), 4.44 (t, J=10.3 Hz, 1.5H), 3.86 (d, J=13.8 Hz, 0.5H), 3.70-3.79 (m, 2H), 3.51-3.65 (m, 0.5H), 3.34-3.49 (m, 3.5H), 3.03-3.24 (m, 2H), 2.87-3.00 (m, 0.5H), 2.53-2.82 (m, 2H), 2.05-2.29 (m, 1H), 1.63-1.77 (m, 1H), 1.26 (br. s., 1H), 0.93-1.23 (m, 7H), 0.87-0.92 (m, 1.5H), 0.84 (d, J=6.8 Hz, 1.5H). LC-MS: m/z 458.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-methoxyphenyl)nicotinonitrile (Compound 275; General procedure 1, Step H)

[0672] ^{1}H NMR (CHLOROFORM-d) δ 7.58 (d, J=2.5 Hz, 1H), 7.39 (td, J=7.9, 1.8 Hz, 1H), 7.18-7.25 (m, 1H), 7.04 (td, J=7.4, 1.0 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H), 4.69 (d, J=12.8 Hz,

0.5H), 4.49-4.60 (m, 1H), 4.44 (d, J=10.5 Hz, 0.5H), 4.25-4.38 (m, 1H), 3.79-3.89 (m, 4H), 3.68-3.78 (m, 2H), 3.51-3.63 (m, 0.5H), 3.34-3.42 (m, 3H), 2.90-3.16 (m, 2.5H), 2.53-2.82 (m, 2H), 2.09-2.36 (m, 1H), 1.75-1.88 (m, 1H), 1.02-1.18 (m, 5H), 0.79-0.96 (m, 5H). LC-MS: m/z 463.2 $(M+H)^+$

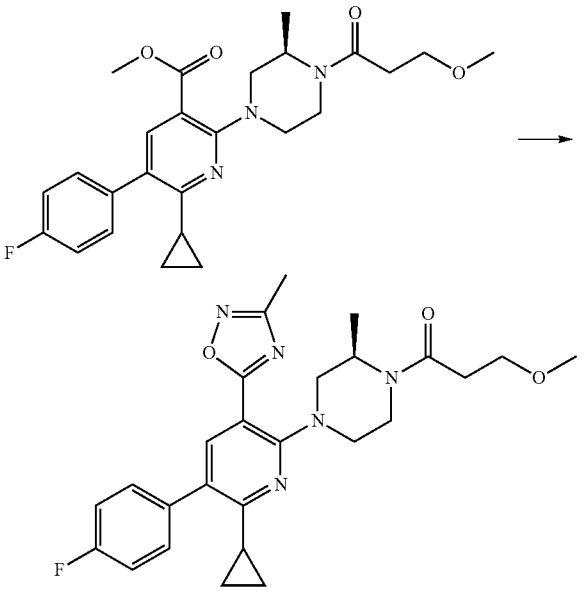
COMPOUND AGI-0007758/NB162-086 (General Procedure 1, Step H)

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-(trifluoromethoxy)phenyl)nicotinonitrile (Compound 276; General procedure 1, Step H)

[0673] ^{1}H NMR (CHLOROFORM-d) δ 7.54 (d, J=2.0 Hz, 1H), 7.43-7.48 (m, 1H), 7.33-7.41 (m, 3H), 4.69 (d, J=13.3 Hz, 0.5H), 4.60 (t, J=13.3 Hz, 1H), 4.41 (dd, J=16.8, 13.3 Hz, 1.5H), 3.85 (d, J=13.3 Hz, 0.5H), 3.70-3.79 (m, 2H), 3.52-3.62 (m, 0.5H), 3.35-3.49 (m, 3.5H), 3.03-3.23 (m, 2H), 2.89-3.02 (m, 0.5H), 2.53-2.82 (m, 2H), 1.67-1.78 (m, 1H), 1.04-1.12 (m, 5H), 0.77-0.98 (m, 6H). LC-MS: m/z 517.2 $(M+H)^+$

(R)-1-(4-(6-cyclopropyl-5-(4-fluorophenyl)-3-(3-methyl-1,2,4-oxadiazol-5-yl)pyridin-2-yl)-2-methylpiperazin-1-yl)-3-methoxypropan-1-one (Compound 831)

[0674]



[0675] To a solution of N'-hydroxyacetimidamide (221 mg, 2 mmol) hydrochloride in 10 mL anhydrous THF was added NaH (48 mg, 2 mmol). The reaction mixture was heated reflux for 0.5 h and (R)-methyl 6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinate (455 mg, 1 mmol) was added to this solution. The reaction was continued reflux for 2 h. The reaction was cooled down to RT and filtered. The filtrate was concentrated to dryness and 120 mg product was obtained by prep-TLC. ^{1}H NMR (CHLOROFORM-d) δ 7.99 (s, 1H), 7.33-7.49 (m, 2H), 7.05-7.23 (m, 2H), 4.85 (br. s., 0.5H), 4.42 (d, J=13.1 Hz, 0.5H), 4.17 (br. s., 0.5H), 3.77-3.93 (m, 2H), 3.47-3.77 (m, 6H), 3.37 (s, 4H), 3.06-3.26 (m, 2H), 2.81-3.06 (m, 1H), 2.51-2.80 (m, 3H), 2.31-2.49 (m, 3H), 1.87-2.11 (m, 1H), 1.28-1.43 (m, 1.5H), 1.15-1.28 (m, 3.5H), 1.12 (br. s., 1H), 0.80-1.06 (m, 2H).

(R)-5-(3-cyanophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 283; General procedure 1, Step H)

[0676] ^{1}H NMR (CHLOROFORM-d) δ 7.66-7.71 (m, 2H), 7.62-7.65 (m, 1H), 7.55-7.60 (m, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J=12.8 Hz, 0.5H), 4.18-4.40 (m, 2.5H), 3.67-3.88 (m, 2.5H), 3.46-3.62 (m, 0.5H), 3.38 (s, 3H), 3.24-3.35 (m, 1H), 2.99-3.20 (m, 1.5H), 2.64-2.81 (m, 1H), 2.49-2.63 (m, 1H), 1.85-1.97 (m, 1H), 1.38 (d, J=6.5 Hz, 1.5H), 1.27 (d, J=6.5 Hz, 1.5H), 1.14-1.21 (m, 2H), 0.94-1.04 (m, 2H). LC-MS: m/z 430.2 $(M+H)^+$

(R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 285; General procedure 1, Step H)

[0677] ^{1}H NMR (CHLOROFORM-d) δ 7.57-7.60 (m, 1H), 7.22 (t, J=7.8 Hz, 1H), 6.77 (d, J=7.8 Hz, 1H), 6.68-6.74 (m, 2H), 4.89 (br. s., 0.5H), 4.52 (d, J=13.3 Hz, 0.5H), 4.09-4.31 (m, 2.5H), 3.67-3.81 (m, 2.5H), 3.47-3.60 (m, 0.5H), 3.37 (s, 3H), 3.18-3.29 (m, 1H), 2.95-3.16 (m, 1.5H), 2.63-2.78 (m, 1H), 2.52-2.61 (m, 1H), 2.09-2.17 (m, 1H), 1.38 (d, J=6.5 Hz, 1.5H), 1.28 (d, J=6.8 Hz, 1.5H), 1.06-1.16 (m, 2H), 0.88-0.99 (m, 2H). LC-MS: m/z 420.1 $(M+H)^+$

(R)-6-cyclopropyl-5-(isoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 286; General procedure 1, Step H)

[0678] ^{1}H NMR (CHLOROFORM-d) δ 9.34 (s, 1H), 8.53 (d, J=6.0 Hz, 1H), 8.06 (d, J=8.0 Hz, 1H), 7.68-7.75 (m, 1H), 7.61-7.68 (m, 2H), 7.43 (t, J=5.6 Hz, 1H), 4.94 (br. s., 0.5H), 4.57 (d, J=13.1 Hz, 0.5H), 4.18-4.47 (m, 2.5H), 3.69-3.86 (m, 2.5H), 3.54-3.67 (m, 0.5H), 3.37-3.44 (m, 3H), 3.34 (dd, J=13.1, 6.3 Hz, 1H), 3.04-3.25 (m, 1.5H), 2.67-2.78 (m, 1H), 2.54-2.67 (m, 1H), 1.48-1.58 (m, 1H), 1.39-1.47 (m, 1.5H), 1.29-1.39 (m, 1.5H), 1.09-1.21 (m, 2H), 0.75-0.89 (m, 2H). LC-MS: m/z 456.1 $(M+H)^+$

(R)-6-cyclopropyl-5-(1H-indol-4-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 287; General procedure 1, Step I)

[0679] ^{1}H NMR (CHLOROFORM-d) δ 8.40 (br. s., 1H), 7.74 (s, 1H), 7.44 (d, J=8.3 Hz, 1H), 7.24-7.29 (m, 1H), 7.02-7.10 (m, 1H), 6.37-6.45 (m, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J=13.6 Hz, 0.5H), 4.17-4.39 (m, 2.5H), 3.71-3.86 (m, 2.5H), 3.51-3.65 (m, 0.5H), 3.35-3.44 (m, 3H), 3.20-3.32 (m, 1H), 2.98-3.17 (m, 1.5H), 2.66-2.81 (m, 1H), 2.54-2.64 (m, 1H), 1.94-2.04 (m, 1H), 1.40-1.46 (m, 1.5H), 1.32 (d, J=6.5 Hz, 1.5H), 1.08-1.17 (m, 2H), 0.80-0.91 (m, 2H). LC-MS: m/z 444.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinolin-5-yl)nicotinonitrile (Compound 288; General procedure 1, Step H)

[0680] ^{1}H NMR (CHLOROFORM-d) δ 8.97 (dd, J=4.1, 1.6 Hz, 1H), 8.23 (d, J=8.5 Hz, 1H), 7.94-8.05 (m, 1H), 7.82 (dd, J=8.5, 7.0 Hz, 1H), 7.61-7.66 (m, 1H), 7.48-7.55 (m,

1H), 7.40-7.48 (m, 1H), 4.83-5.06 (m, 0.5H), 4.56 (d, J=13.1 Hz, 0.5H), 4.15-4.43 (m, 2.5H), 3.69-3.91 (m, 2.5H), 0.57 (d, J=10.5 Hz, 0.5H), 3.36-3.45 (m, 3H), 3.33 (dd, J=13.1, 3.5 Hz, 1H), 3.01-3.26 (m, 1.5H), 2.65-2.82 (m, 1H), 2.52-2.64 (m, 1H), 1.48-1.56 (m, 1H), 1.39-1.47 (m, 1.5H), 1.29-1.38 (m, 1.5H), 1.07-1.18 (m, 2H), 0.74-0.91 (m, 2H). LC-MS: m/z 456.1 $(M+H)^+$

(R)-6-cyclopropyl-5-(1H-indol-6-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 289; General procedure 1, Step I)

[0681] ^{1}H NMR (CHLOROFORM-d) δ 8.41 (br. s., 1H), 7.69 (d, J=8.0 Hz, 1H), 7.66 (s, 1H), 7.39 (s, 1H), 7.27-7.30 (m, 1H), 7.13 (dd, J=8.0, 1.5 Hz, 1H), 6.60 (t, J=2.1 Hz, 1H), 4.91 (br. s., 0.5H), 4.53 (d, J=13.6 Hz, 0.5H), 4.13-4.32 (m, 2.5H), 3.68-3.84 (m, 2.5H), 3.49-3.65 (m, 0.5H), 3.38 (s, 3H), 3.17-3.31 (m, 1H), 2.93-3.16 (m, 1.5H), 2.64-2.82 (m, 1H), 2.53-2.63 (m, 1H), 2.13-2.23 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.30 (d, J=6.8 Hz, 1.5H), 1.09-1.17 (m, 2H), 0.84-0.98 (m, 2H).

[0682] LC-MS: m/z 444.2 $(M+H)^+$

(R)-6-cyclopropyl-5-(4-fluoronaphthalen-1-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 290; General procedure 1, Step H)

[0683] ^{1}H NMR (CHLOROFORM-d) δ 8.19 (d, J=8.0 Hz, 1H), 7.50-7.65 (m, 4H), 7.30-7.37 (m, 1H), 7.22 (dd, J=10.2, 7.9 Hz, 1H), 4.93 (br. s., 0.5H), 4.56 (d, J=13.3 Hz, 0.5H), 4.15-4.42 (m, 2.5H), 3.69-3.90 (m, 2.5H), 3.50-3.68 (m, 0.5H), 3.36-3.43 (m, 3H), 3.24-3.34 (m, 1H), 3.00-3.23 (m, 1.5H), 2.65-2.85 (m, 1H), 2.55-2.64 (m, 1H), 1.54-1.61 (m, 1H), 1.40-1.48 (m, 1.5H), 1.33 (dd, J=6.3, 3.5 Hz, 1.5H), 1.07-1.18 (m, 2H), 0.72-0.85 (m, 2H). LC-MS: m/z 473.1 $(M+H)^+$

(R)-methyl 2-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetate (Compound 291; General procedure 1, Step H)

[0684] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.36-7.45 (m, 1H), 7.25-7.34 (m, 3H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.1 Hz, 0.5H), 4.26 (t, J=12.5 Hz, 2.5H), 3.64-3.85 (m, 7H), 3.50-3.61 (m, 0.5H), 3.38 (s, 3H), 3.19-3.30 (m, 1H), 2.93-3.18 (m, 2H), 2.63-2.81 (m, 1H), 2.49-2.63 (m, 1H), 2.02-2.12 (m, 1H), 1.39 (d, J=6.3 Hz, 1.5H), 1.28 (d, J=6.5 Hz, 1.5H), 1.10-1.20 (m, 2H), 0.89-1.00 (m, 2H). LC-MS: m/z 477.1 $(M+H)^+$

(R)-6-cyclopropyl-5-(1H-indazol-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 295; General procedure 2, Step M)

[0685] ^{1}H NMR (CHLOROFORM-d) δ 8.14 (br. s., 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.59 (d, J=8.5 Hz, 1H), 7.42 (dd, J=8.7, 1.4 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.12-4.39 (m, 2.5H), 3.69-3.89 (m, 2.5H), 3.50-3.64 (m, 0.5H), 3.38 (s, 3H), 3.20-3.33 (m, 1H), 2.97-3.20 (m, 1.5H), 2.66-2.82 (m, 1H), 2.52-2.64 (m, 1H), 1.99-2.14 (m, 1H), 1.36-1.46 (m, 1.5H), 1.30 (d, J=6.8 Hz, 1.5H), 1.13-1.21 (m, 2H), 0.90-0.99 (m, 2H). LC-MS: m/z 445.4 $(M+H)^+$

(R)-4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)benzamide (Compound 296; General procedure 1, Step H)

[0686] ^{1}H NMR (CHLOROFORM-d) δ 7.84-7.96 (m, J=8.5 Hz, 2H), 7.57-7.66 (m, 1H), 7.45-7.56 (m, 2H), 6.27 (br. s., 1H), 5.99 (br. s., 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.3 Hz, 0.5H), 4.14-4.38 (m, 2.5H), 3.70-3.87 (m, 2.5H), 3.47-3.62 (m, 0.5H), 3.33-3.43 (m, 3H), 3.27 (t, J=10.3 Hz, 1H), 2.99-3.21 (m, 1.5H), 2.64-2.83 (m, 1H), 2.50-2.64 (m, 1H), 1.95-2.09 (m, 1H), 1.38 (d, J=6.3 Hz, 1.5H), 1.25-1.31 (m, 1.5H), 1.13-1.21 (m, 2H), 0.92-1.02 (m, 2H). LC-MS: m/z 448.5 $(M+H)^+$

(R)-6-cyclopropyl-5-(3-(2-hydroxyethyl)phenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 297; General procedure 1, Step H)

[0687] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.35-7.42 (m, 1H), 7.23-7.27 (m, 3H), 4.89 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 4.14-4.31 (m, 2.5H), 3.91 (t, J=6.7 Hz, 2H), 3.68-3.83 (m, 2.5H), 3.49-3.61 (m, 0.5H), 3.37 (s, 3H), 3.19-3.29 (m, 1H), 2.97-3.18 (m, 1.5H), 2.91-2.97 (m, 2H), 2.64-2.81 (m, 1H), 2.52-2.62 (m, 1H), 2.02-2.14 (m, 1H), 1.39 (d, J=6.3 Hz, 1.5H), 1.27-1.32 (m, 1.5H), 1.08-1.19 (m, 2H), 0.89-1.02 (m, 2H). LC-MS: m/z 449.6 $(M+H)^+$

(R)-3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)benzamide (Compound 305; General procedure 1, Step H)

[0688] ^{1}H NMR (METHANOL-d_4) δ 7.96 (t, J=1.5 Hz, 1H), 7.91 (dt, J=7.7, 1.6 Hz, 1H), 7.81 (s, 1H), 7.62-7.67 (m, 1H), 7.56-7.62 (m, 1H), 4.82 (br. s., 0.5H), 4.38-4.48 (m, 1H), 4.16-4.29 (m, 2H), 3.97 (d, J=13.6 Hz, 0.5H), 3.68-3.76 (m, 2H), 3.54-3.67 (m, 0.5H), 3.36 (s, 4H), 3.05-3.26 (m, 1.5H), 2.72-2.89 (m, 1H), 2.57-2.70 (m, 1H), 1.99-2.10 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.29 (d, J=6.8 Hz, 1.5H), 1.20 (dq, J=4.4, 3.1 Hz, 2H), 0.93-1.04 (m, 2H). LC-MS: m/z 448.3 $(M+H)^+$

(R)-6-cyclopropyl-5-(3-(hydroxymethyl)phenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 306; General procedure 1, Step H)

[0689] ^{1}H NMR (METHANOL-d_4) δ 7.71 (br. s., 1H), 7.37-7.48 (m, 3H), 7.32 (d, J=7.5 Hz, 1H), 4.80 (br. s., 1H), 4.68 (s, 3H), 4.36-4.51 (m, 1H), 4.13-4.30 (m, 2H), 3.95 (d, J=13.6 Hz, 0.5H), 3.67-3.78 (m, 2H), 3.50-3.65 (m, 0.5H), 3.27-3.35 (m, 2.5H), 2.99-3.20 (m, 1.5H), 2.70-2.84 (m, 1H), 2.61-2.67 (m, 1H), 2.06-2.13 (m, 1H), 1.40 (d, J=6.5 Hz, 1.5H), 1.28 (d, J=6.8 Hz, 1.5H), 1.12-1.24 (m, 2H), 0.96 (dd, J=7.3, 3.5 Hz, 2H). LC-MS: m/z 435.3 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-oxoindolin-6-yl)nicotinonitrile (Compound 313; General procedure 1, Step H)

[0690] ^{1}H NMR (CHLOROFORM-d) δ 8.40 (s, 1H), 7.53-7.64 (m, 1H), 7.29 (d, J=7.8 Hz, 1H), 6.98-7.07 (m, 1H), 6.87-6.93 (m, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.4 Hz, 0.5H), 4.13-4.37 (m, 2.5H), 3.68-3.88 (m, 2.5H), 3.49-3.65 (m, 2.5H), 3.34-3.43 (m, 3H), 3.20-3.31 (m, 1H), 2.95-3.18 (m, 1.5H), 2.51-2.81 (m, 2H), 2.02-2.15 (m, 1H), 1.38-1.40

(m, 1.5H), 1.26-1.31 (m, 1.5H), 1.07-1.20 (m, 2H), 0.90-1.04 (m, 2H). LC-MS: m/z 460.2 $(M+H)^+$

(R)-6'-amino-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,3'-bipyridine-5-carbonitrile (Compound 314; General procedure 1, Step H)

[0691] ^{1}H NMR (CHLOROFORM-d) δ 8.10 (d, J=2.0 Hz, 1H), 7.54 (s, 1H), 7.44-7.50 (m, 1H), 6.55-6.64 (m, 1H), 4.89 (br. s., 0.5H), 4.72 (br. s., 2H), 4.52 (d, J=13.3 Hz, 0.5H), 4.15-4.31 (m, 2.5H), 3.69-3.85 (m, 2.5H), 3.49-3.63 (m, 0.5H), 3.34-3.43 (m, 3H), 3.19-3.31 (m, 1H), 2.96-3.17 (m, 1.5H), 2.51-2.81 (m, 2H), 1.99-2.08 (m, 1H), 1.23-1.41 (m, 3H), 1.11-1.18 (m, 2H), 0.90-0.99 (m, 2H). LC-MS: m/z 421.4 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinolin-4-yl)nicotinonitrile (Compound 315; General procedure 1, Step H)

[0692] ^{1}H NMR (CHLOROFORM-d) δ 8.99 (d, J=4.5 Hz, 1H), 8.23 (d, J=8.5 Hz, 1H), 7.78 (t, J=7.5 Hz, 1H), 7.61-7.71 (m, 2H), 7.53-7.61 (m, 1H), 7.36 (d, J=4.0 Hz, 1H), 4.93 (br. s., 0.5H), 4.56 (d, J=12.5 Hz, 0.5H), 4.25-4.45 (m, 2.5H), 3.68-3.91 (m, 2.5H), 3.57 (d, J=9.3 Hz, 0.5H), 3.29-3.45 (m, 4H), 3.01-3.27 (m, 1.5H), 2.65-2.84 (m, 1H), 2.51-2.65 (m, 1H), 1.54 (td, J=8.2, 4.1 Hz, 1H), 1.42 (d, J=5.5 Hz, 1.5H), 1.32 (t, J=5.0 Hz, 1.5H), 1.05-1.21 (m, 2H), 0.74-0.92 (m, 2H). LC-MS: m/z 456.0 $(M+H)^+$

(R)-6-cyclopropyl-5-(2,6-dimethoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 316; General procedure 1, Step H)

[0693] ^{1}H NMR (CHLOROFORM-d) δ 7.51-7.57 (m, 1H), 7.30-7.38 (m, 1H), 6.65 (d, J=8.3 Hz, 2H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.6 Hz, 0.5H), 4.11-4.34 (m, 2.5H), 3.67-3.84 (m, 8.5H), 3.47-3.62 (m, 0.5H), 3.32-3.43 (m, 3H), 2.95-3.24 (m, 2.5H), 2.63-2.84 (m, 1H), 2.51-2.63 (m, 1H), 1.65-1.72 (m, 1H), 1.41 (d, J=6.5 Hz, 1.5H), 1.31 (d, J=6.8 Hz, 1.5H), 1.00-1.12 (m, 2H), 0.75-0.86 (m, 2H). LC-MS: m/z 465.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)nicotinonitrile (Compound 317; General procedure 1, Step H)

[0694] ^{1}H NMR (CHLOROFORM-d) δ 8.44 (s, 1H), 8.10-8.18 (m, 1H), 7.67 (s, 1H), 7.56 (d, J=8.5 Hz, 1H), 7.37 (d, J=8.3 Hz, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.17-4.39 (m, 2.5H), 3.69-3.88 (m, 2.5H), 3.52-3.69 (m, 0.5H), 3.35-3.45 (m, 3H), 3.22-3.35 (m, 1H), 0.98-3.20 (m, 1.5H), 2.54-2.82 (m, 2H), 2.04-2.13 (m, 1H), 1.38-1.47 (m, 1.5H), 1.31 (d, J=6.5 Hz, 1.5H), 1.14-1.19 (m, 2H), 0.90-0.97 (m, 2H). LC-MS: m/z 540.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinolin-8-yl)nicotinonitrile (Compound 342; General procedure 1, Step H)

[0695] ^{1}H NMR (CHLOROFORM-d) δ 8.94 (dd, J=4.1, 1.6 Hz, 1H), 8.23 (dd, J=8.3, 1.8 Hz, 1H), 7.90 (dd, J=8.2, 1.4 Hz, 1H), 7.73 (s, 1H), 7.66-7.71 (m, 1H), 7.59-7.66 (m, 1H), 7.45 (dd, J=8.3, 4.3 Hz, 1H), 4.92 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.13-4.38 (m, 2.5H), 3.68-3.87 (m, 2.5H), 3.50-3.64 (m, 0.5H), 3.38 (s, 3H), 3.24 (t, J=12.8 Hz, 1H), 2.96-3.17 (m, 1.5H), 2.52-2.82 (m, 2H), 1.59-1.68 (m, 1H), 1.43 (d, J=6.5 Hz, 1.5H), 1.33 (d, J=6.5 Hz, 1.5H), 1.07 (br. s., 2H), 0.78 (br. s., 2H)

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetamide (Compound 284; General procedure 3, step N, method 1)

[0696] ^{1}H NMR (CHLOROFORM-d) δ 7.64 (s, 1H), 7.58 (s, 2H), 7.46 (d, J=8.0 Hz, 1H), 7.38 (t, J=7.8 Hz, 1H), 7.12 (d, J=7.8 Hz, 1H), 4.89 (br. s., 0.5H), 4.52 (d, J=13.3 Hz, 0.5H), 4.11-4.36 (m, 2.5H), 3.67-3.86 (m, 2.5H), 3.54 (t, J=10.9 Hz, 0.5H), 3.33-3.43 (m, 3H), 3.18-3.31 (m, 1H), 2.94-3.17 (m, 1.5H), 2.63-2.79 (m, 1H), 2.51-2.63 (m, 1H), 2.17-2.28 (m, 3H), 2.06-2.14 (m, 1H), 1.38 (d, J=6.5 Hz, 1.5H), 1.27 (d, J=7.0 Hz, 1.5H), 1.08-1.17 (m, 2H), 0.91-1.00 (m, 2H). LC-MS: m/z 462.2 $(M+H)^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acrylamide (Compound 343; General procedure 3, Step N, method 1)

[0697] ^{1}H NMR (CHLOROFORM-d) δ 7.70-7.79 (m, 2H), 7.54-7.63 (m, 2H), 7.41 (t, J=7.9 Hz, 1H), 7.16 (d, J=7.5 Hz, 1H), 6.48 (dd, J=16.8, 1.0 Hz, 1H), 6.31 (dd, J=16.8, 10.0 Hz, 1H), 5.81 (dd, J=10.2, 1.1 Hz, 1H), 4.91 (br. s., 1H), 4.54 (d, J=13.1 Hz, 0.5H), 4.12-4.36 (m, 2.5H), 3.69-3.88 (m, 2.5H), 3.49-3.65 (m, 0.5H), 3.38 (s, 3H), 3.20-3.33 (m, 1H), 2.96-3.17 (m, 1.5H), 2.54-2.81 (m, 2H), 2.07-2.16 (m, 1H), 1.39 (d, J=6.5 Hz, 1.5H), 1.25-1.35 (m, 1.5H), 1.15 (quin, J=3.6 Hz, 2H), 0.89-1.02 (m, 2H). LC-MS: m/z 474.6 $(M+H)^+$ (R,E)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)but-2-enamide (Compound 415; General procedure 3, Step N, method 2)

[0698] ^{1}H NMR (CHLOROFORM-d) δ 7.64-7.76 (m, 2H), 7.60-7.63 (m, 1H), 7.49-7.53 (m, 1H), 7.37-7.44 (m, 1H), 7.30-7.35 (m, 1H), 7.14 (d, J=7.8 Hz, 1H), 6.95-7.10 (m, 1H), 5.99 (dd, J=15.1, 1.8 Hz, 1H), 4.92 (s, 0.5H), 4.54 (d, J=12.8 Hz, 0.5H), 4.20-4.32 (m, 2.5H), 3.76 (t, J=6.3 Hz, 2H), 3.50-3.62 (m, 0.5H), 3.39 (s, 3H), 3.18-3.34 (m, 1.5H), 2.97-3.16 (m, 1.5H), 2.65-2.80 (m, 1H), 2.53-2.65 (m, 1H), 2.09-2.16 (m, 1H), 1.95 (dd, J=6.8, 1.5 Hz, 3H), 1.40 (d, J=6.3 Hz, 1H), 1.29-1.31 (m, 2H), 1.12-1.19 (m, 2H), 0.92-1.01 (m, 2H)

[0699] LC-MS: m/z 487.3 $(M+H)^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-2-oxopropanamide (Compound 416; General procedure 3, step N, method 2)

[0700] ^{1}H NMR (CHLOROFORM-d) δ 7.38-7.66 (m, 4H), 7.32 (dd, J=3.9, 1.9 Hz, 1H), 7.12-7.25 (m, 1H), 4.89 (s, 0.5H), 4.52 (d, J=10.8 Hz, 0.5H), 4.22-4.34 (m, 2H), 4.10-4.22 (m, 0.5H), 3.66-3.85 (m, 2.5H), 3.55 (d, J=3.5 Hz, 0.5H), 3.39 (d, J=1.5 Hz, 3H), 3.20-3.31 (m, 1H), 3.10-3.14 (m, 1.5H), 2.97-3.09 (m, 1H), 2.66-2.80 (m, 1H), 2.53-2.64 (m, 1H), 1.97-2.07 (m, 1H), 1.55-1.58 (m, 3H), 1.35-1.42 (m, 2H), 1.10-1.17 (m, 1H), 1.05-1.10 (m, 1H), 0.73-0.96 (m, 4H). LC-MS: m/z 490.2 $(M+H)^+$

(R)-2-chloro-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetamide (Compound 403; General procedure 3, Step N, method 1)

[0701] ^{1}H NMR (CHLOROFORM-d) δ 8.34 (s, 1H), 7.66-7.75 (m, 1H), 7.62 (s, 1H), 7.50-7.55 (m, 1H), 7.42-7.48 (m, 1H), 7.22 (d, J=7.8 Hz, 1H), 4.92 (s, 0.5H), 4.50-4.54 (m, 0.5H), 4.29-4.33 (m, 1H), 4.26 (m, 1H), 4.21-4.25 (m, 0.5H), 3.71-3.84 (m, 2.5H), 3.52-3.57 (m, 0.5H), 3.39 (s, 3H), 3.21-3.32 (m, 1H), 3.13 (d, J=11.3 Hz, 1H), 3.05 (d, J=12.3 Hz, 0.5H), 2.66-2.81 (m, 1H), 2.54-2.65 (m, 1H), 2.07-2.12 (m, 1H), 1.40 (d, J=6.3 Hz, 1H), 1.28-1.31 (m, 2H), 1.14-1.19 (m, 2H), 0.94-1.00 (m, 2H). LC-MS: m/z 495.2 (M+H)$^+$

(R)-1-chloro-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)methanesulfonamide (Compound 404; General procedure 3, Step N, method 1)

[0702] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.44-7.52 (m, 1H), 7.36-7.41 (m, 1H), 7.29-7.36 (m, 2H), 7.11 (br. s., 1H), 4.92 (s, 1H), 4.45-4.63 (m, 2.5H), 4.18-4.40 (m, 2.5H), 3.66-3.89 (m, 2.5H), 3.50-3.57 (m, 0.5H), 3.39 (s, 3H), 3.29 (t, J=10.2 Hz, 1H), 2.99-3.20 (m, 1.5H), 2.65-2.83 (m, 1H), 2.52-2.64 (m, 1H), 1.99-2.06 (m, 1H), 1.40 (d, J=6.3 Hz, 1H), 1.30 (s, 2H), 1.15-1.22 (m, 2H), 0.96-1.03 (m, 2H). LC-MS: m/z 531.2 (M+H)$^+$

(R)-2-chloro-N-(3-(5-cyano-2-cyclopropyl-6-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propanamide (Compound 462; General procedure 3, Step N, method 2)

[0703] ^{1}H NMR (CHLOROFORM-d) δ 8.54 (s, 1H), 7.67-7.73 (m, 1H), 7.60 (s, 1H), 7.49-7.57 (m, 1H), 7.38-7.45 (m, 1H), 7.14-7.22 (m, 1H), 4.90 (br. s., 0.5H), 4.44-4.64 (m, 1.5H), 4.16-4.37 (m, 2.5H), 3.68-3.86 (m, 2.5H), 3.50-3.63 (m, 0.5H), 3.37 (s, 3H), 3.19-3.32 (m, 1H), 2.96-3.17 (m, 1.5H), 2.53-2.78 (m, 2H), 2.05-2.12 (m, 1H), 1.83 (d, J=7.0 Hz, 3H), 1.39 (d, J=6.5 Hz, 1.5H), 1.28 (dd, J=6.9, 2.6 Hz, 1.5H), 1.10-1.19 (m, 2H), 0.90-1.02 (m, 2H). LC-MS: m/z 510.2 (M+H)$^+$

(R)—N-(4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetamide (Compound 412; General procedure 1, Step H)

[0704] ^{1}H NMR (CHLOROFORM-d) δ 7.55-7.67 (m, 3H), 7.31-7.44 (m, 3H), 4.91 (s, 0.5H), 4.54 (d, J=13.6 Hz, 0.5H), 4.14-4.33 (m, 2.5H), 3.65-3.93 (m, 2.5H), 3.46-3.65 (m, 0.5H), 3.39 (s, 3H), 3.20-3.30 (m, 1H), 2.98-3.19 (m, 1.5H), 2.51-2.81 (m, 1H), 2.16-2.31 (m, 3H), 1.98-2.13 (m, 1H), 1.24-1.44 (m, 4H), 1.08-1.18 (m, 2H), 0.84-0.99 (m, 2H). LC-MS: m/z 462.6 (M+H)$^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propionamide (Compound 424; General procedure 3, Step N, method 2)

[0705] ^{1}H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.49 (d, J=8.0 Hz, 1H), 7.37 (t, J=7.8 Hz, 1H), 7.11 (d, J=7.5 Hz, 1H), 4.89 (s, 0.5H), 4.52 (d, J=13.3 Hz, 0.5H), 4.14-4.35 (m, 2.5H), 3.67-3.85 (m, 2.5H), 3.49-3.62 (m, 0.5H), 3.37 (s, 3H), 3.17-3.32 (m, 1H), 2.93-3.17 (m, 1.5H), 2.63-2.81 (m, 1H), 2.52-2.63 (m, 1H), 2.37-2.49 (m, 2H), 2.05-2.13 (m, 1H), 1.38 (d, J=6.5 Hz, 1H), 1.22-1.31 (m, 5H), 1.14 (dt, J=7.4, 3.6 Hz, 2H), 0.88-1.01 (m, 2H). LC-MS: m/z 476.3 (M+H)$^+$

(R)-1-cyano-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)cyclopropanecarboxamide (Compound 425; General procedure 3, Step N, method 2)

[0706] ^{1}H NMR (CHLOROFORM-d) δ 8.11 (s, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.42-7.50 (m, 2H), 7.19-7.25 (m, 1H), 4.92 (s, 0.5H), 4.55 (d, J=12.3 Hz, 0.5H), 4.17-4.39 (m, 2.5H), 3.71-3.76 (m, 2.5H), 3.55-3.58 (m, 0.5H), 3.36-3.46 (m, 3H), 3.21-3.33 (m, 1H), 3.14 (d, J=13.3 Hz, 1.5H), 3.05 (d, J=12.0 Hz, 1H), 2.63-3.75 (s, 1H), 2.61-3.63 (m, 1H), 2.02-2.12 (m, 1H), 1.81-1.91 (m, 2H), 1.66 (q, J=4.5 Hz, 2H), 1.40 (d, J=5.5 Hz, 1H), 1.25-1.33 (m, 2H), 1.12-1.20 (m, 2H), 0.92-1.01 (m, 2H). LC-MS: m/z 513.2 (M+H)$^+$

Compound 427 (General Procedure 3, Step N, method 1)

[0707] ^{1}H NMR (CHLOROFORM-d) δ 7.62 (s, 1H), 7.47-7.56 (m, 1H), 7.35-7.44 (m, 1H), 7.18-7.25 (m, 2H), 6.42 (dd, J=16.8, 2.0 Hz, 1H), 6.16 (dd, J=16.6, 10.3 Hz, 1H), 5.57 (dd, J=10.2, 1.6 Hz, 1H), 4.92 (d, J=12.8 Hz, 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.13-4.41 (m, 3H), 3.69-3.90 (m, 3H), 3.58 (d, J=9.3 Hz, 1H), 3.39 (s, 3H), 3.42 (s, 3H), 3.29 (t, J=9.5 Hz, 1H), 3.01-3.21 (m, 2H), 2.65-2.80 (m, 1H), 2.47-2.65 (m, 1H), 1.88-2.07 (m, 1H), 1.65 (br. s., 3H), 1.35-1.44 (m, 2H), 1.25-1.35 (m, 2H), 1.09-1.25 (m, 2H), 0.92-1.09 (m, 2H). LC-MS: m/z 488.2 (M+H)$^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propiolamide (Compound 428; General procedure 3, Step N, Method 2)

[0708] ^{1}H NMR (CHLOROFORM-d) δ 7.63-7.69 (m, 2H), 7.61 (s, 1H), 7.41-7.50 (m, 2H), 7.20 (d, J=7.3 Hz, 1H), 4.92 (s, 0.5H), 4.54 (d, J=11.8 Hz, 0.5H), 4.12-4.40 (m, 2.5H), 3.72-3.79 (m, 2.5H), 3.51-3.57 (m, 0.5H), 3.40 (s, 3H), 3.23-3.32 (m, 1H), 3.14 (d, J=13.1 Hz, 1H), 3.05 (d, J=11.0 Hz, 1H), 2.99 (s, 1H), 2.65-2.81 (m, 1H), 2.54-2.65 (m, 1H), 2.05-2.13 (m, 1H), 1.40 (d, J=6.5 Hz, 1H), 1.14-1.19 (m, 2H), 0.95-1.01 (m, 2H), 0.88-0.93 (m, 2H).

[0709] LC-MS: m/z 472.2 (M+H)$^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)ethenesulfonamide (Compound 429; General procedure 3, Step N, method 1)

[0710] To a solution of (R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile (20 mg, 0.048 mmol) and 2-chloroethanesulfonyl chloride (8.6 mg, 0.052 mmol) in 5 ml of DCM was added dropwised TEA (15 mg, 0.143 mmol) at 0° C., then the resulting mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 15 mg of the product. ^{1}H NMR (CHLOROFORM-d) δ 7.55-7.61 (m, 1H), 7.37-7.46 (m, 1H), 7.15-7.26 (m, 3H), 6.70 (d, J=12.8 Hz, 1H), 6.62 (dd, J=16.4, 9.9 Hz, 1H), 6.34 (d, J=16.3 Hz, 1H), 6.02 (d, J=9.8 Hz, 1H), 4.92

(s, 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.19-4.37 (m, 2.5H), 3.73-3.79 (m, 3H), 3.52-3.61 (m, 0.5H), 3.39 (s, 3H), 3.28 (t, J=10.4 Hz, 1H), 3.02-3.14 (m, 1H), 2.65-2.80 (m, 1H), 2.55-2.64 (m, 1H), 1.98-2.07 (m, 1H), 1.27 (s, 3H), 1.14-1.19 (m, 2H), 0.95-1.01 (m, 2H).

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-2-fluoroacrylamide (Compound 431; General procedure 3, Step N, method 2)

[0711] ^{1}H NMR (CHLOROFORM-d) δ 8.19 (d, J=4.5 Hz, 1H), 7.75 (s, 1H), 7.61 (s, 1H), 7.57 (dd, J=8.0, 1.3 Hz, 1H), 7.43 (t, J=7.9 Hz, 1H), 7.16-7.23 (m, 1H), 5.84 (dd, J=18.0 Hz, J=3.3 Hz, 0.5H), 5.21-5.35 (m, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 4.10-4.38 (m, 2.5H), 3.66-3.86 (m, 2.5H), 3.50-3.64 (m, 0.5H), 3.38 (s, 3H), 3.19-3.33 (m, 1H), 2.95-3.18 (m, 1.5H), 2.56-2.78 (m, 2H), 2.04-2.16 (m, 1H), 1.39 (d, J=6.3 Hz, 1.5H), 1.28 (d, J=6.8 Hz, 1.5H), 1.11-1.22 (m, 2H), 0.91-1.03 (m, 2H). LC-MS: m/z 492.7 $(M+H)^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-2,2-difluoroacetamide (Compound 432; General procedure 3, Step N, method 2)

[0712] ^{1}H NMR (CHLOROFORM-d) δ 8.79 (br. s., 1H), 7.77 (s, 1H), 7.55-7.65 (m, 2H), 7.44 (t, J=7.9 Hz, 1H), 7.22 (d, J=7.8 Hz, 1H), 6.05 (t, J=56.0 Hz, 1H), 4.89 (br. s., 0.5H), 4.51 (d, J=13.3 Hz, 0.5H), 4.08-4.37 (m, 2.5H), 3.66-3.88 (m, 2.5H), 3.49-3.63 (m, 0.5H), 3.36 (s, 3H), 2.96-3.25 (m, 2.5H), 2.81 (s, 6H), 2.50-2.79 (m, 2H), 2.03-2.13 (m, 1H), 1.32-1.45 (m, 1.5H), 1.27 (d, J=6.8 Hz, 1.5H), 1.10-1.17 (m, 2H), 0.91-1.02 (m, 2H)

[0713] LC-MS: m/z 498.8 $(M+H)^+$

(R)-5-(4-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 383; General procedure 1, Step H)

[0714] ^{1}H NMR (CHLOROFORM-d) δ 7.53-7.62 (m, 1H), 7.11-7.21 (m, 2H), 6.70-6.83 (m, 2H), 4.89 (br. s., 0.5H), 4.52 (d, J=13.6 Hz, 0.5H), 4.04-4.28 (m, 2.5H), 3.64-3.88 (m, 4.5H), 3.47-3.64 (m, 0.5H), 3.30-3.43 (m, 3H), 3.14-3.27 (m, 1H), 2.92-3.14 (m, 1.5H), 2.50-2.79 (m, 2H), 2.08-2.15 (m, 1H), 1.34-1.43 (m, 1.5H), 1.28-1.30 (m, 1.5H), 1.06-1.15 (m, 2H), 0.84-0.95 (m, 2H). LC-MS: m/z 420.1 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-oxoindolin-5-yl)nicotinonitrile (Compound 384; General procedure 1, Step H)

[0715] ^{1}H NMR (CHLOROFORM-d) δ 8.22 (s, 1H), 7.50-7.64 (m, 1H), 7.21-7.26 (m, 2H), 6.85-7.03 (m, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.6 Hz, 0.5H), 4.10-4.37 (m, 2.5H), 3.68-3.86 (m, 2.5H), 3.48-3.64 (m, 2.5H), 3.35-3.44 (m, 3H), 3.19-3.31 (m, 1H), 2.94-3.17 (m, 1.5H), 2.52-2.82 (m, 2H), 1.99-2.09 (m, 1H), 1.39 (d, J=6.5 Hz, 1.5H), 1.28 (d, J=6.8 Hz, 1.5H), 1.09-1.20 (m, 2H), 0.91-0.99 (m, 2H). LC-MS: m/z 460.5 $(M+H)^+$

(R)-6-cyclopropyl-5-(1H-indazol-6-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 385; General procedure 1, Step H)

[0716] ^{1}H NMR (CHLOROFORM-d) δ 8.14 (br. s., 1H), 7.82 (d, J=8.3 Hz, 1H), 7.66 (s, 1H), 7.50 (s, 1H), 7.16-7.24 (m, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J=12.5 Hz, 0.5H), 4.16-4.39 (m, 2.5H), 3.69-3.85 (m, 2.5H), 3.50-3.65 (m, 0.5H), 3.38 (s, 3H), 3.20-3.32 (m, 1H), 2.98-3.14 (m, 1.5H), 2.52-2.82 (m, 2H), 2.04-2.13 (m, 1H), 1.28-1.43 (m, 3H), 0.91-0.98 (m, 2H), 0.81-0.89 (m, 2H).

[0717] LC-MS: m/z 445.5 $(M+H)^+$

(R)-6-cyclopropyl-5-(isoquinolin-5-yl)-2-(3-methyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)nicotinonitrile (Compound 386; General procedure 2, Step M)

[0718] ^{1}H NMR (CHLOROFORM-d) δ 9.30-9.40 (m, 1H), 8.49-8.58 (m, 1H), 8.06 (d, J=8.3 Hz, 1H), 7.67-7.75 (m, 1H), 7.62-7.67 (m, 2H), 7.36-7.45 (m, 1H), 4.95 (br. s., 0.5H), 4.58-4.61 (m, 0.5H), 4.27-4.49 (m, 2H), 4.14 (br. s., 0.5H), 3.59-3.73 (m, 1H), 3.11-3.39 (m, 4.5H), 1.45-1.55 (m, 2.5H), 1.37 (dd, J=6.4, 4.4 Hz, 1.5H), 1.07-1.19 (m, 2H), 0.77-0.87 (m, 2H). LC-MS: m/z 480.1 $(M+H)^+$

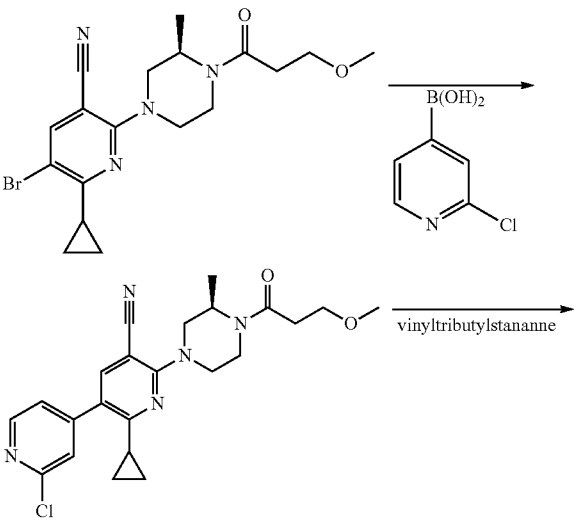
[0719] (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 387; General procedure 2, Step M)

[0720] ^{1}H NMR (CHLOROFORM-d) δ 9.40 (br. s., 1H), 8.56 (d, J=4.5 Hz, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.72-7.78 (m, 1H), 7.64-7.71 (m, 2H), 7.46 (dd, J=12.5, 5.8 Hz, 1H), 4.58 (dt, J=13.1, 2.1 Hz, 1H), 4.47 (d, J=12.0 Hz, 1H), 4.09-4.26 (m, 0.5H), 3.80-3.86 (m, 1.5H), 3.08-3.44 (m, 5H), 1.49-1.57 (m, 1H), 1.33 (br. s., 1H), 1.08-1.22 (m, 2H), 0.82-0.91 (m, 2H), 0.41-0.72 (m, 4H).

[0721] LC-MS: m/z 506.7 $(M+H)^+$

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 390)

[0722]



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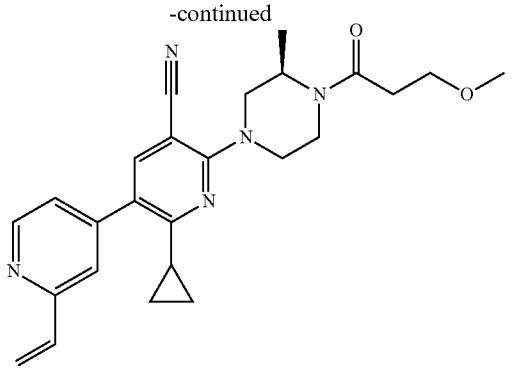


[0723] A mixture of 7-1 (410 mg, 1.01 mmol), 2-chloropyridin-4-ylboronic acid (237 mg, 0.95 mmol), K_2CO_3 (414 mg, 3.03 mmol) and $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) in DMF (2 mL) was stirred at 150° C. in the microwave reactor for 1 h. The resultant mixture was partitioned between EtOAc and water, the organic phase was washed with water, brine and concentrated and purified by prepTLC (PE:EA=1:1) to give 375 mg of (R)-2'-chloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile. ^{1}H NMR (CHLOROFORM-d) δ 8.34-8.61 (m, 1H), 7.60 (s, 1H), 7.39 (d, J=1.0 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=11.8 Hz, 0.5H), 4.21-4.41 (m, 2.5H), 3.68-3.91 (m, 2.5H), 3.54 (d, J=4.0 Hz, 1H), 3.25-3.45 (m, 4H), 2.95-3.25 (m, 1H), 2.63-2.92 (m, 1H), 2.42-2.63 (m, 1H), 1.87-2.07 (m, 1H), 1.36 (d, J=6.5 Hz, 1.5H), 1.11-1.31 (m, 3.5H), 0.81-1.11 (m, 2H). LC-MS: m/z 440.1 $(M+H)^+$

[0724] A mixture of (R)-2'-chloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile (40 mg, 0.09 mmol), vinyl tributyl stananne (30 mg, 0.09 mmol), KOAc (10 mg) and $Pd(PPh_3)_4$ (5 mg) in DMF (2 mL) was stirred at 120° C. in the microwave reactor for 20 min. The resulting mixture was concentrated and purified by prepTLC (PE: EA=1:1) to give 25 mg of the title product. ^{1}H NMR (CHLOROFORM-d) δ 8.64 (d, J=5.0 Hz, 1H), 7.63 (s, 1H), 7.31-7.45 (m, 1H), 7.22 (dd, J=5.0, 1.8 Hz, 1H), 6.87 (dd, J=17.6, 10.8 Hz, 1H), 6.27 (dd, J=17.6, 1.0 Hz, 1H), 5.41-5.71 (m, 1H), 4.90 (m, 0.5H), 5.51 (m, 6.5H), 4.16-4.44 (m, 3H), 3.74 (t, J=6.1 Hz, 3H), 3.38 (s, 4H), 3.31 (d, J=4.0 Hz, 1H), 3.14 (br. s., 2H), 2.59 (t, J=6.0 Hz, 2H), 1.86-2.06 (m, 1H), 1.38 (d, J=6.3 Hz, 1.5H), 1.24-1.33 (m, 1.5H), 1.10-1.24 (m, 2H), 0.83-1.10 (m, 2H). LC-MS: m/z 432.6 $(M+H)^+$

(R)-2'-chloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile (Compound 401)

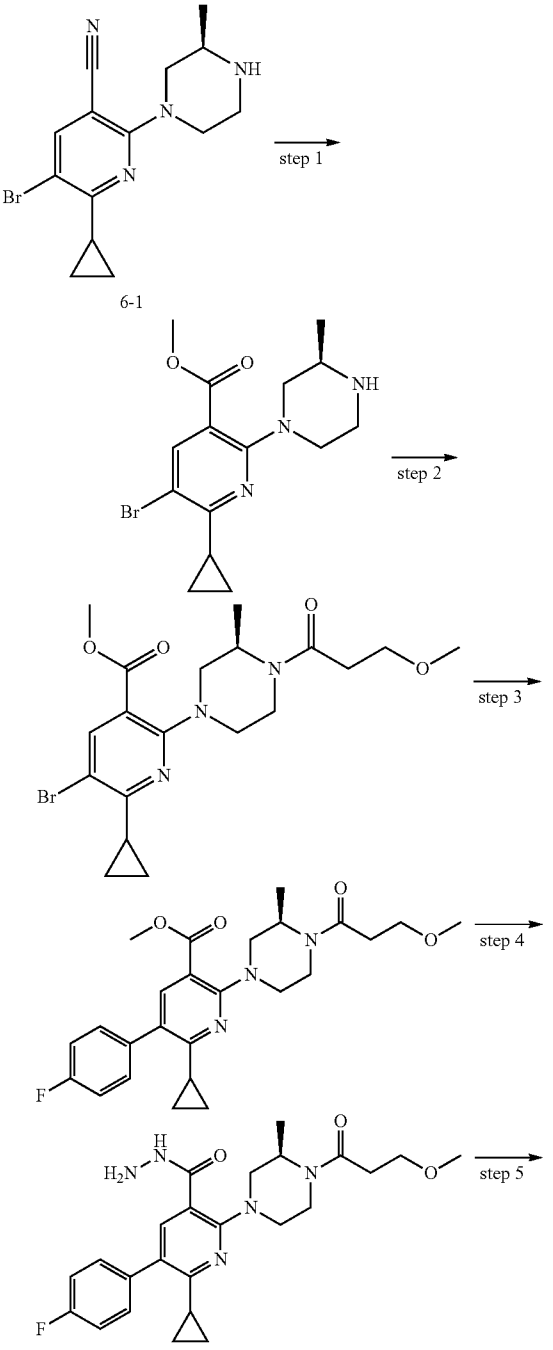
[0725] ^{1}H NMR (CHLOROFORM-d) δ 8.34-8.61 (m, 1H), 7.60 (s, 1H), 7.39 (d, J=1.0 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=11.8 Hz, 0.5H), 4.21-4.41 (m, 2.5H), 3.68-3.91 (m, 2.5H), 3.54 (d, J=4.0 Hz, 1H), 3.25-3.45 (m, 4H), 2.95-3.25 (m, 1H), 2.63-2.92 (m, 1H), 2.42-2.63 (m, 1H), 1.87-2.07 (m, 1H), 1.36 (d, J=6.5 Hz, 1.5H), 1.11-1.31 (m, 3.5H), 0.81-1.11 (m, 2H). LC-MS: m/z 440.1 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 391; General procedure 1, Step H)

[0726] ^{1}H NMR (CHLOROFORM-d) δ 9.41 (s, 1H), 8.54 (d, J=5.3 Hz, 1H), 8.11 (d, J=8.0 Hz, 1H), 7.68-7.81 (m, 2H), 7.61-7.67 (m, 1H), 7.45-7.56 (m, 1H), 4.58 (d, J=11.5 Hz, 1H), 4.46 (d, J=13.1 Hz, 1H), 3.49-4.23 (m, 2.5H), 3.16-3.33 (m, 2.5H), 1.58-1.69 (m, 1H), 1.42-1.54 (m, 1H), 1.17 (t, J=4.9 Hz, 2H), 1.00-1.10 (m, 3H), 0.76-0.87 (m, 4H), 0.69 (br. s., 1H), 0.41-0.62 (m, 3H); LC-MS: m/z 464.2 $(M+H)^+$

(R)-1-(4-(6-cyclopropyl-5-(4-fluorophenyl)-3-(1,3,4-oxadiazol-2-yl)pyridin-2-yl)-2-methylpiperazin-1-yl)-3-methoxypropan-1-one (Compound 392)

[0727]



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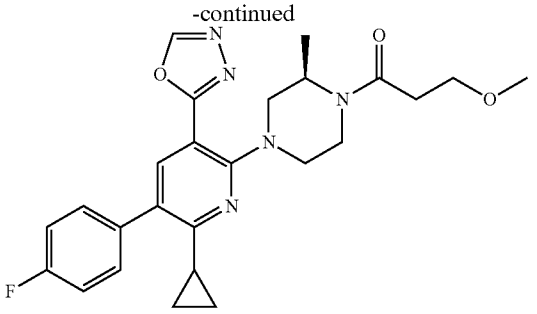


Step 1

[0728] (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (2 g, 6.3 mmol) was dissolved in MeOH (5 mL) and NaOH (20% wt aq, 10 mL) and the reaction solution was heated to reflux overnight. The resultant solution was concentrated and then dissolved in MeOH (10 mL), treated with $SOCl_2$ (0.1 ml) and then heated to reflux for 2 h. The resulting solution was concentrated, washed with brine and exacted with EA (50 mL). The organic phase was dried, concentrated and purified with flash column (EA:PE=1:3) to give (R)-methyl 5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinate as a white solid (804 mg, 50% yield).

Step 2

[0729] Following the same procedure as General procedure 1, step F, method 1.

Step 3

[0730] Following the same procedure as General procedure 1, step H.

Step 4

[0731] (R)-methyl6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinate (500 mg, 1.1 mmol) and 2 mL hydrazine hydrate was dissolved in 10 mL ethanol. The reaction mixture was heated reflux overnight and cooled down to rt. The mixture was filtered and the residue was washed with cold ethanol. 200 mg title compound was obtained without further purification.

Step 5

[0732] (R)-6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotine-hydrazide (200 mg, 0.44 mmol) was dissolved in trimethoxymethane (25 mL). The reaction mixture was heated to reflux overnight. The rest of trimethoxymethane was removed under reduced pressure and purified by prep-TLC to give 50 mg of title compound. ^{1}H NMR (CHLOROFORM-d) δ 9.33 (s, 1H), 8.51 (d, J=6.0 Hz, 1H), 8.10 (s, 1H), 8.02 (d, J=7.8 Hz, 1H), 7.62-7.89 (m, 2H), 7.27 (s, 1H), 4.63-4.78 (m, 2H), 4.47-4.63 (m, 1H), 3.55-3.84 (m, 3H), 3.39 (s, 4H), 3.19 (dd, J=13.3, 3.5 Hz, 1H), 2.91-3.12 (m, 2H), 2.66-2.88 (m, 3H), 2.44-2.66 (m, 2H), 1.28-1.43 (m, 1.5H), 1.15-1.28 (m, 3.5H), 1.12 (br. s., 1H), 0.80-1.06 (m, 2H); LC-MS: m/z 466.2 (M+H).

2-(4-(cyclopropanecarbonyl)-3-(trifluoromethyl) piperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl) nicotinonitrile (Compound 397; General procedure 4, Step R and S)

[0733] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (s, 1H), 8.54 (t, J=6.4 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.60-7.76 (m, 3H), 7.35-7.49 (m, 1H), 5.39 (br. s., 0.5H), 4.28-4.86 (m, 3.5H), 3.70-3.97 (m, 1H), 3.44 (d, J=14.3 Hz, 1H), 3.23-3.39 (m, 1H), 1.68-1.91 (m, 1H), 1.53 (td, J=7.8, 3.5 Hz, 1H), 1.08-1.23 (m, 3H), 0.77-1.07 (m, 5H). LC-MS: m/z 492.2 $(M+H)^+$

6-cyclopropyl-5-(isoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-(trifluoromethyl)piperazin-1-yl)nicotinonitrile (Compound 398; General procedure 4, Step R and S)

[0734] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (br. s., 1H), 8.55 (t, J=6.0 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.60-7.80 (m, 3H), 7.42 (dd, J=19.3, 5.5 Hz, 1H), 5.29-5.48 (m, 0.5H), 4.71-4.92 (m, 1.5H), 4.44-4.62 (m, 1H), 4.02 (d, J=13.3 Hz, 0.5H), 3.63-3.86 (m, 2.5H), 3.33-3.51 (m, 3.5H), 3.19-3.32 (m, 2H), 2.75-2.94 (m, 1H), 2.52-2.75 (m, 1H), 2.06 (br. s., 1H), 1.52 (tq, J=8.0, 4.1 Hz, 1H), 1.10-1.22 (m, 2H), 0.76-0.93 (m, 2H). LC-MS: m/z 510.4 $(M+H)^+$

6-cyclopropyl-5-(isoquinolin-5-yl)-2-(3-(trifluoromethyl)-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl) nicotinonitrile (Compound 399; General procedure 4, Step R and S)

[0735] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (s, 1H), 8.54 (t, J=6.5 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.55-7.80 (m, 3H), 7.32-7.45 (m, 1H), 5.26-5.49 (m, 0.5H), 4.45-5.03 (m, 2.5H), 3.72-3.95 (m, 2H), 3.22-3.52 (m, 5H), 1.54 (tq, J=8.0, 4.2 Hz, 1H), 1.10-1.22 (m, 2H), 0.78-0.94 (m, 3H). LC-MS: m/z 534.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 402; General procedure 1, Step H)

[0736] ^{1}H NMR (CHLOROFORM-d) δ 9.36 (br. s., 1H), 8.55 (d, J=5.8 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 7.52-7.77 (m, 3H), 7.44 (t, J=6.0 Hz, 1H), 4.93 (br. s., 0.5H), 4.25-4.48 (m, 2.5H), 4.21 (br. s., 0.5H), 3.95 (br. s., 2H), 3.66-3.86 (m, 1.5H), 3.56-3.66 (m, 1H), 3.28-3.47 (m, 1H), 2.99-3.28 (m, 2H), 2.49-2.77 (m, 1H), 1.40-1.57 (m, 3H), 1.11-1.40 (m, 2H), 0.75-1.04 (m, 2H); LC-MS: m/z 442.2 (M+H).

(R)-6-cyclopropyl-5-(3-(dimethylamino)phenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile (Compound 413; General procedure 1, Step H)

[0737] ^{1}H NMR (CHLOROFORM-d) δ 7.61-7.69 (m, 1H), 7.29-7.34 (m, 1H), 6.65-6.83 (m, 3H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.14-4.34 (m, 2.5H), 3.70-3.87 (m, 2.5H), 3.56 (t, J=11.2 Hz, 0.5H), 3.34-3.46 (m, 3H), 3.00-3.28 (m, 8.5H), 2.54-2.83 (m, 2H), 2.14-2.23 (m, 1H), 1.29-1.43 (m, 3H), 1.07-1.20 (m, 2H), 0.84-1.01 (m, 2H). LC-MS: m/z 448.4 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-(methylamino)phenyl) nicotinonitrile (Compound 414; General procedure 1, Step H)

[0738] ^{1}H NMR (CHLOROFORM-d) δ 7.63 (s, 1H), 7.23-7.27 (m, 1H), 6.72 (d, J=7.8 Hz, 1H), 6.62-6.68 (m, 1H), 6.56-6.62 (m, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.6 Hz, 0.5H), 4.15-4.33 (m, 2.5H), 3.70-3.88 (m, 2.5H), 3.52-3.62 (m, 0.5H), 3.39 (s, 3H), 3.00-3.28 (m, 2.5H), 2.89 (s, 3H), 2.65-2.83 (m, 1H), 2.51-2.65 (m, 1H), 2.14-2.21 (m, 1H), 1.30-1.47 (m, 3H), 1.10-1.19 (m, 2H), 0.89-0.98 (m, 2H). LC-MS: m/z 434.5 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 409; General procedure 1, Step H)

[0739] ^{1}H NMR (CHLOROFORM-d) δ 9.36 (br. s., 1H), 8.54 (d, J=4.5 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.60-7.84 (m, 3H), 7.44 (dd, J=12.3, 6.0 Hz, 1H), 4.71-4.73 (m, 0.5H), 4.56 (d, J=11.8 Hz, 1H), 4.38-4.50 (m, 1H), 4.07-4.19 (m, 0.5H), 3.91 (d, J=11.0 Hz, 0.5H), 3.69-3.83 (m, 3H), 3.51 (s, 3H), 3.20-3.29 (m, 1.5H), 3.13 (br. s., 1H), 2.61-2.70 (m, 2H), 1.52 (ddd, J=12.0, 7.9, 4.6 Hz, 1H), 1.40 (br. s., 1H), 1.12-1.20 (m, 2H), 0.80-0.90 (m, 2H), 0.48-0.77 (m, 4H). LC-MS: m/z 482.6 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 419; General procedure 1, Step H)

[0740] ^{1}H NMR (CHLOROFORM-d) δ 9.40 (br. s., 1H), 8.48-8.69 (m, 1H), 8.11 (d, J=8.0 Hz, 1H), 7.63-7.86 (m, 3H), 7.44-7.55 (m, 1H), 4.70-4.73 (m, 0.5H), 4.57 (dd, J=13.1, 2.0 Hz, 1H), 4.41-4.52 (m, 1H), 4.13 (d, J=7.8 Hz, 0.5H), 3.94 (br. s., 2H), 3.69-3.82 (m, 1H), 3.13-3.26 (m, 3H), 2.50-2.71 (m, 2H), 1.48-1.57 (m, 1H), 1.39-1.48 (m, 1H), 1.12-1.21 (m, 2H), 0.86-0.91 (m, 2H), 0.42-0.69 (m, 4H). LC-MS: m/z 468.5 $(M+H)^+$

(R)-5-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)isoquinoline 2-oxide (Compound 420)

[0741] ^{1}H NMR (CHLOROFORM-d) δ 8.88 (br. s., 1H), 8.15 (d, J=6.5 Hz, 1H), 7.81 (d, J=8.3 Hz, 1H), 7.73 (t, J=7.7 Hz, 1H), 7.63 (s, 1H), 7.52-7.58 (m, 1H), 7.44-7.52 (m, 1H), 4.94 (br. s., 0.5H), 4.55-4.59 (m, 0.5H), 4.21-4.44 (m, 2.5H), 3.57-3.86 (m, 3H), 3.34-3.40 (m, 4H), 3.19-3.22 (m, 1.5H), 2.58-2.86 (m, 2H), 1.47-1.55 (m, 1H), 1.30-1.38 (m, 3H), 1.09-1.21 (m, 2H), 0.78-0.95 (m, 2H). LC-MS: m/z 472.4 $(M+H)^+$

6-cyclopropyl-5-(isoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (Compound 421; General procedure 1, Step H)

[0742] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (br. s., 1H), 8.53 (d, J=5.0 Hz, 1H), 8.06 (d, J=8.3 Hz, 1H), 7.68-7.75 (m, 1H), 7.60-7.67 (m, 2H), 7.42 (d, J=5.8 Hz, 1H), 3.39-3.85 (m, 10H), 3.38 (s, 3H), 2.63-2.75 (m, 2H), 1.46-1.55 (m, 1H), 1.08-1.18 (m, 2H), 0.75-0.85 (m, 2H). LC-MS: m/z 442.5 $(M+H)^+$

2-(4-(cyclopropanecarbonyl)-3-(difluoromethyl) piperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl) nicotinonitrile (Compound 422; General procedure 4, Step R and S)

[0743] ^{1}H NMR (CHLOROFORM-d) δ 9.37 (br. s., 1H), 8.56 (br. s., 1H), 8.09 (d, J=8.0 Hz, 1H), 7.60-7.79 (m, 3H), 7.43 (d, J=10.3 Hz, 1H), 6.09 (br. s., 1H), 4.97-5.45 (m, 4H), 3.12-3.89 (m, 3H), 1.98-2.08 (m, 1H), 1.80-1.87 (m, 1H), 1.00-1.21 (m, 4H), 0.83-0.92 (m, 4H). LC-MS: m/z 474.5 $(M+H)^+$

2-(4-(cyclopropanecarbonyl)-3-(2,2,2-trifluoroethyl) piperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl) nicotinonitrile (Compound 423; General procedure 4, Step R and S)

[0744] ^{1}H NMR (CHLOROFORM-d) δ 9.36 (s, 1H), 8.55 (dd, J=5.8, 3.5 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 7.59-7.81 (m, 3H), 7.33-7.50 (m, 1H), 5.24 (br. s., 0.5H), 4.34 (d, J=13.1 Hz, 1H), 4.26-4.50 (m, 2.5H), 3.69 (br. s., 0.5H), 3.20-3.45 (m, 2H), 3.13 (br. s., 0.51H), 2.58-2.75 (m, 2H), 1.77 (br. s., 1H), 1.47-1.61 (m, 1H), 1.09-1.24 (m, 4H), 0.77-0.93 (m, 4H). LC-MS: m/z 506.5 $(M+H)^+$

(R)-2-cyclopropyl-2'-ethyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4-bipyridine-5-carbonitrile (Compound 426)

[0745] Compound 390 (18 mg) in EtOH was treated with Pd/C and hydrogenated at room temperature and normal pressure to give the title compound as a white solid. 1H NMR (CHLOROFORM-d) δ 8.63 (d, J=4.8 Hz, 1H), 7.63 (s, 1H), 7.23 (d, J=4.5 Hz, 2H), 4.92 (br. s., 1H), 4.55 (d, J=12.8 Hz, 1H), 4.14-4.43 (m, 3H), 3.64-3.89 (m, 3H), 3.57 (br. s., 1H), 3.40 (s, 3H), 3.32 (d, J=11.8 Hz, 1H), 3.14 (d, J=14.3 Hz, 1H), 2.94 (q, J=7.4 Hz, 2H), 2.65-2.83 (m, 1H), 2.39-2.65 (m, 1H), 2.03 (td, J=8.0, 3.9 Hz, 2H), 1.25-1.42 (m, 8H), 1.11-1.25 (m, 3H), 1.01 (dd, J=7.8, 3.0 Hz, 2H). LC-MS: m/z 434.2 $(M+H)^+$

Compound 430 (General Procedure 1, Step I)

[0746] ^{1}H NMR (CHLOROFORM-d) δ 8.41 (dd, J=7.9, 1.4 Hz, 1H), 8.14 (s, 1H), 7.72-7.84 (m, 1H), 7.57-7.71 (m, 2H), 4.93 (d, J=13.3 Hz, 0.5H), 4.55 (d, J=13.3 Hz, 0.5H), 4.14-4.43 (m, 3H), 3.69-3.90 (m, 3H), 3.53-3.68 (m, 1H), 3.34-3.46 (m, 3H), 3.27 (t, J=11.2 Hz, 1H), 2.97-3.22 (m, 2H), 2.54-2.84 (m, 2H), 1.55-1.80 (m, 2H), 1.43 (d, J=6.5 Hz, 2H), 1.18-1.38 (m, 3H), 1.09 (br. s., 1H), 0.70-0.99 (m, 2H).

[0747] LC-MS: m/z 473.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-methylisoquinolin-5-yl) nicotinonitrile (Compound 433)

[0748] ^{1}H NMR (CHLOROFORM-d) δ 9.23 (s, 1H), 7.93-8.03 (m, 1H), 7.50-7.66 (m, 3H), 7.21 (d, J=6.0 Hz, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.19-4.42 (m, 2.5H), 3.83 (d, J=12.3 Hz, 0.5H), 3.65-3.78 (m, 2H), 3.56 (d, J=16.8 Hz, 0.5H), 3.37 (s, 3H), 3.31 (d, J=13.1 Hz, 1H), 2.98-3.25 (m, 1.5H), 2.68-2.84 (m, 1H), 2.53-2.68 (m, 5H), 1.47-1.57 (m, 1H), 1.43 (d, J=6.3 Hz, 1.5H), 1.29-1.36 (m, 1.5H), 1.13 (dd, J=6.5, 4.0 Hz, 2H), 0.76-0.84 (m, 2H). LC-MS: m/z 470.2 $(M+H)^+$

(R)-6-cyclopropyl-5-(1-methoxyisoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile (Compound 434)

[0749] ^{1}H NMR (CHLOROFORM-d) δ 8.32 (dd, J=7.5, 1.3 Hz, 1H), 7.98 (d, J=6.0 Hz, 1H), 7.52-7.65 (m, 3H), 6.94 (t, J=5.9 Hz, 1H), 4.85 (br. s., 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.20-4.40 (m, 2.5H), 4.15 (s, 3H), 3.66-3.89 (m, 3H), 3.38 (s, 3H), 3.31 (d, J=8.3 Hz, 1H), 3.17 (d, J=13.3 Hz, 1.5H), 2.65-2.84 (m, 1H), 2.51-2.65 (m, 1H), 1.48-1.60 (m, 1H), 1.42 (m, 1.5H), 1.29-1.36 (m, 1.5H), 1.03-1.19 (m, 2H), 0.81 (dd, J=8.0, 3.0 Hz, 2H). LC-MS: m/z 486.2 $(M+H)^+$

(1R,2R)-ethyl 2-((R)-4-(3-cyano-6-cyclopropyl-5-(isoquinolin-5-yl)pyridin-2-yl)-2-methyl piperazine-1-carbonyl)cyclopropanecarboxylate (Compound 435)

[0750] ^{1}H NMR (CHLOROFORM-d) δ 9.34 (s, 1H), 8.53 (d, J=5.8 Hz, 1H), 8.06 (d, J=8.0 Hz, 1H), 7.62-7.80 (m, 3H), 7.42 (t, J=5.9 Hz, 1H), 4.87 (br. s., 0.5H), 4.38-4.65 (m, 1.5H), 4.33 (d, J=12.0 Hz, 2H), 4.19 (q, J=7.0 Hz, 2H), 3.62-3.85 (m, 0.5H), 3.46 (d, J=13.1 Hz, 0.5H), 3.10-3.40 (m, 2H), 2.36 (br. s., 1H), 2.17-2.31 (m, 1H), 2.09 (br. s., 1H), 1.38-1.45 (m, 2H), 1.22-1.37 (m, 6H), 1.03-1.22 (m, 2H), 0.69-0.94 (m, 2H). LC-MS: m/z 461.2 $(M+H)^+$

(R)-5-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl) isoquinoline 2-oxide (Compound 439)

[0751] ^{1}H NMR (CHLOROFORM-d) δ 8.87 (br. s., 1H), 8.06-8.26 (m, 1H), 7.70-7.83 (m, 2H), 7.61-7.69 (m, 1H), 7.54 (br. s., 2H), 4.59 (d, J=7.0 Hz, 1H), 4.47 (d, J=12.5 Hz, 1H), 3.51-4.30 (m, 3H), 3.32 (br. s., 1H), 3.17 (br. s., 1H), 1.96-2.10 (m, 1H), 1.75 (br. s., 1H), 1.43-1.54 (m, 1H), 1.14-1.23 (m, 2H), 1.00-1.12 (m, 2H), 0.81-0.94 (m, 4H), 0.38-0.73 (m, 4H). LC-MS: m/z 480.2 $(M+H)^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl) phenyl)-N-(vinylsulfonyl)ethenesulfonamide (Compound 440; General procedure 3, Step N, method 1)

[0752] ^{1}H NMR (CHLOROFORM-d) δ 7.60-7.64 (m, 1H), 7.50-7.56 (m, 2H), 7.29-7.37 (m, 3H), 7.01-7.16 (m, 2H), 6.26-6.40 (m, 2H), 6.11-6.25 (m, 2H), 4.92 (s, 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.19-4.37 (m, 2.5H), 3.73-3.79 (m, 3H), 3.52-3.61 (m, 0.5H), 3.39 (s, 3H), 3.28 (t, J=10.4 Hz, 1H), 3.02-3.14 (m, 1H), 2.65-2.80 (m, 1H), 2.55-2.64 (m, 1H), 1.98-2.07 (m, 1H), 1.27 (s, 3H), 1.14-1.19 (m, 2H), 0.95-1.01 (m, 2H). LC-MS: m/z 600.2 $(M+H)^+$

(R,E)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl) phenyl)-4-(dimethylamino)but-2-enamide (Compound 441; General procedure 3, Step N, method 2)

[0753] ^{1}H NMR (CHLOROFORM-d) δ 9.22 (s, 1H), 7.68 (s, 1H), 7.53-7.60 (m, 1H), 7.41-7.53 (m, 1H), 7.31 (s, 1H), 7.08 (d, J=7.3 Hz, 1H), 6.86 (s, 1H), 6.61 (d, J=15.3 Hz, 1H), 4.83 (s, 0.5H), 4.46 (d, J=11.0 Hz, 0.5H), 4.22 (d, J=9.8 Hz, 2.5H), 3.90 (s, 1.5H), 3.67-3.81 (m, 2.5H), 3.52 (s, 0.5H), 3.28-3.41 (m, 3H), 3.24 (s, 1H), 3.04-3.15 (m, 1H), 2.94-3.04 (m, 1H), 2.88 (s, 2H), 2.82 (s, 6H), 2.57 (d, J=15.8 Hz, 1H), 1.97-2.08 (m, 1H), 1.33-1.40 (m, 2H), 1.18-1.30 (m, 2H), 1.02-1.15 (m, 2H), 0.89 (s, 2H). LC-MS: m/z 531.3 $(M+H)^+$

(R)-6-cyclopropyl-5-(2-hydroxyquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 442)

[0754] 1H NMR (CHLOROFORM-d) δ 7.88 (d, J=9.5 Hz, 1H), 7.63-7.70 (m, 1H), 7.43-7.63 (m, 3H), 6.80 (d, J=9.5 Hz, 1H), 4.92 (br. s., 0.5H), 4.57 (d, J=13.1 Hz, 0.5H), 4.15-4.45 (m, 3H), 3.66-3.87 (m, 2H), 3.40 (s, 2H), 3.29 (t, J=9.7 Hz, 1H), 3.11-3.22 (m, 1H), 2.66-2.88 (m, 1H), 2.48-2.66 (m, 1H), 1.96-2.10 (m, 1H), 1.36-1.56 (m, 1.5H), 1.08-1.36 (m, 3.5H), 0.97 (dd, J=7.8, 3.0 Hz, 2H). LC-MS: m/z 472.3 $(M+H)^+$

(R)-6-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 443; General procedure 5, Step W):

[0755] 1H NMR (CHLOROFORM-d) δ 8.66 (d, J=4.3 Hz, 1H), 7.59-7.67 (m, 1H), 7.35-7.45 (m, 1H), 7.24 (d, J=4.3 Hz, 1H), 6.89 (dd, J=17.3, 10.8 Hz, 1H), 6.29 (d, J=17.3 Hz, 1H), 5.58 (d, J=10.8 Hz, 1H), 4.87 (br. s., 1H), 4.56 (br. s., 1H), 4.30 (d, J=13.3 Hz, 1H), 4.13 (br. s., 1H), 3.58-3.88 (m, 1H), 3.33 (d, J=10.0 Hz, 1H), 3.20 (br. s., 2H), 1.91-2.09 (m, 1H), 1.38-1.51 (m, 1.5H), 1.11-1.38 (m, 2.5H), 0.87-1.08 (m, 6H), 0.79-0.87 (m, 2H). LC-MS: m/z 414.4 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-methyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 444; General procedure 5, Step W)

[0756] 1H NMR (CHLOROFORM-d) δ 7.59-7.69 (m, 1H), 7.34-7.43 (m, 1H), 7.15-7.27 (m, 1H), 6.89 (dd, J=17.6, 10.8 Hz, 1H), 6.23-6.37 (m, 1H), 5.58 (d, J=11.5 Hz, 1H), 4.94 (br. s., 1H), 4.20-4.48 (m, 2H), 3.51-3.79 (m, 1H), 3.37 (d, J=5.5 Hz, 1H), 3.05-3.34 (m, 4H), 1.87-2.07 (m, 1H), 1.42-1.51 (m, 2H), 1.13-1.42 (m, 3H), 0.95-1.08 (m, 2H). LC-MS: m/z 456.8 $(M+H)^+$

(R)-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 485; General procedure 5, Step W)

[0757] ^{1}H NMR (CHLOROFORM-d) δ 8.77 (br. s., 1H), 7.96 (br. s., 1H), 7.80-7.92 (m, 2H), 7.12-7.27 (m, 1H), 6.82 (d, J=17.6 Hz, 1H), 6.06 (d, J=10.8 Hz, 1H), 4.67 (d, J=12.3 Hz, 1H), 4.54 (d, J=11.5 Hz, 2H), 4.24 (br. s., 1H), 3.67 (br. s., 1H), 3.33 (br. s., 1H), 3.18 (br. s., 1H), 1.93 (br. s., 1H), 1.67 (br. s., 1H), 1.25 (br. s., 2H), 1.04-1.23 (m, 3H), 0.89-1.04 (m, 3H), 0.47 (d, J=4.8 Hz, 2H), 0.39 (br. s., 2H). LC-MS: m/z 440.2 $(M+H)^+$

Compound 527 (General Procedure 5, Step W)

[0758] ^{1}H NMR (CHLOROFORM-d) δ 8.65 (d, J=4.7 Hz, 1H), 7.65 (s, 1H), 7.38 (s, 1H), 7.23 (d, J=4.1 Hz, 1H), 6.87 (dd, J=17.5, 10.7 Hz, 1H), 6.28 (d, J=17.6 Hz, 1H), 5.56 (d, J=10.9 Hz, 1H), 4.55 (d, J=13.2 Hz, 1H), 4.43 (d, J=12.6 Hz, 1H), 4.03-4.16 (m, 1H), 3.91 (br. s., 2H), 3.65-3.82 (m, 1H), 3.40-3.53 (m, 1H), 3.02-3.32 (m, 3H), 2.49-2.69 (m, 2H), 1.98-2.10 (m, 1H), 1.13-1.38 (m, 3H), 1.01 (dd, J=7.5, 3.4 Hz, 2H), 0.63 (br. s., 1H), 0.55 (br. s., 1H), 0.32-0.51 (m, 2H). LC-MS: m/z 444.3 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 498; General procedure 5, Step W)

[0759] ^{1}H NMR (CHLOROFORM-d) δ 8.54-8.72 (m, 1H), 7.57-7.74 (m, 1H), 7.38 (d, J=1.0 Hz, 1H), 7.23 (dd, J=5.1, 1.6 Hz, 1H), 6.88 (dd, J=17.3, 10.8 Hz, 1H), 6.28 (dd, J=17.4, 1.1 Hz, 1H), 5.48-5.63 (m, 1H), 4.56 (dd, J=13.2, 1.9 Hz, 1H), 4.45 (d, J=13.1 Hz, 1H), 4.11 (br. s., 1H), 3.65-3.88 (m, 2H), 3.32 (q, J=9.6 Hz, 2H), 3.20 (d, J=12.0 Hz, 1H), 2.98-3.15 (m, 1H), 2.04 (tt, J=8.0, 4.7 Hz, 1H), 1.30-1.39 (m, 1H), 1.14-1.25 (m, 2H), 0.96-1.07 (m, 2H), 0.65 (br. s., 1H), 0.56 (br. s., 1H), 0.41-0.54 (m, 2H). LC-MS: m/z 482.5 $(M+H)^+$

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 500; General procedure 5, Step W)

[0760] 1H NMR (CHLOROFORM-d) δ 8.66 (d, J=5.0 Hz, 1H), 7.60-7.71 (m, 1H), 7.41 (s, 1H), 7.26 (dd, J=5.0, 1.3 Hz, 1H), 6.90 (dd, J=17.4, 10.9 Hz, 1H), 6.31 (d, J=17.1 Hz, 1H), 5.60 (d, J=11.0 Hz, 1H), 4.72-4.99 (m, 0.5H), 4.54 (d, J=13.1 Hz, 0.5H), 4.22-4.49 (m, 2H), 3.74 (d, J=13.6 Hz, 1H), 3.56 (br. s., 1H), 3.40 (br. s., 1H), 3.32 (td, J=8.6, 3.9 Hz, 1H), 2.95-3.25 (m, 2H), 2.68 (br. s., 1H), 2.44-2.65 (m, 2H), 2.00-2.19 (m, 1H), 1.16-1.45 (m, 3H), 0.95-1.12 (m, 3H), 0.90 (t, J=6.8 Hz, 1H). LC-MS: m/z 418.6 $(M+H)^+$

(R)-2-cyclopropyl-6-(4-(4,4-dimethoxybutanoyl)-3-methylpiperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile (Compound 606; General procedure 5, Step W)

[0761] ^{1}H NMR (CHLOROFORM-d) δ 8.64 (d, J=5.0 Hz, 1H), 7.63 (s, 1H), 7.38 (s, 1H), 7.23 (dd, J=5.0, 1.5 Hz, 1H), 6.81-6.93 (m, 1H), 6.28 (d, J=11.0 Hz, 1H), 5.56 (d, J=11.0 Hz, 1H), 4.88 (s, 0.5H), 4.24-4.53 (m, 1.5H), 4.24-4.36 (m, 2.5H), 3.78 (d, 0.5H), 3.54 (t, 0.5H), 3.27-3.37 (m, 4H), 3.02-3.18 (m, 1.5H), 2.35-2.56 (m, 2H), 1.92-2.06 (m, 4H), 1.38 (d, 1.5H), 1.28 (d, 1.5H), 1.18-1.21 (m, 2H), 0.99-1.02 (m, 2H). LC-MS: m/z 476.2 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-methyl-4-(4-oxobutanoyl) piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile (Compound 607), which was obtained as the by-product of Compound 606

[0762] ^{1}H NMR (CHLOROFORM-d) δ 9.90 (s, 1H), 8.65 (d, J=5.0 Hz, 1H), 7.64 (s, 1H), 7.38 (s, 1H), 7.24 (d, J=5.0 Hz, 1H), 6.88 (q, 1H), 6.28 (d, 1H), 5.56 (d, 1H), 4.85 (br. s., 0.5H), 4.48 (d, J=12.8 Hz, 0.5H), 4.25-4.37 (m, 2.5H), 3.80 (br. s., 0.5H), 3.60 (br. s., 0.5H), 3.03-3.38 (m, 3H), 2.62-2.89 (m, 4.5H), 2.03 (m, 1H), 1.42 (d, 1.5H), 1.28 (d, 1.5H), 1.18-1.21 (m, 2H), 0.99-1.10 (m, 2H). LC-MS: m/z 430.2 $(M+H)^+$

(S)-2-cyclopropyl-6-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile (Compound 587; General procedure 5, Step W)

[0763] ^{1}H NMR (CHLOROFORM-d) δ 8.66 (d, J=5.0 Hz, 1H), 7.62-7.73 (m, 1H), 7.39 (s, 1H), 7.24 (dd, J=5.0, 1.5 Hz, 1H), 6.88 (dd, J=17.6, 10.8 Hz, 1H), 6.29 (d, J=17.3 Hz, 1H), 5.57 (d, J=10.8 Hz, 1H), 4.56 (d, J=13.1 Hz, 1H), 4.43 (d, J=11.3 Hz, 1.5H), 4.09 (d, J=8.8 Hz, 0.5H), 3.93 (d, J=5.0 Hz, 2H), 3.75-3.82 (m, 1.5H), 3.43 (br. s., 1H), 3.16-3.32 (m, 1.5H), 3.02-3.16 (m, 1H), 2.43-2.71 (m, 2H), 2.00-2.09 (m, 1H), 1.67 (s, 1H), 1.16-1.25 (m, 2H), 0.95-1.08 (m, 2H), 0.40-0.80 (m, 4H). LC-MS: m/z 444.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinoxalin-6-yl)nicotinonitrile (Compound 445; General procedure 1, Step H)

[0764] ^{1}H NMR (CHLOROFORM-d) δ 8.90 (d, J=3.0 Hz, 2H), 8.05-8.34 (m, 2H), 7.85 (d, J=8.5 Hz, 1H), 7.74 (s, 1H), 4.92 (br. s., 0.5H), 4.26-4.56 (m, 3H), 3.57-3.84 (m, 3H), 3.31-3.38 (m, 4H), 3.13-3.16 (m, 1.5H), 2.27-2.78 (m, 2H), 2.04-2.16 (m, 1H), 1.41 (d, J=5.8 Hz, 1.5H), 1.30 (d, J=6.0 Hz, 1.5H), 1.22 (br. s., 2H), 0.94-1.06 (m, 2H). LC-MS: m/z 457.2 $(M+H)^+$

Compound 446 (General Procedure 3, Step N, method 1)

[0765] 1H NMR (CHLOROFORM-d) δ 7.58-7.67 (m, 1H), 7.38-7.50 (m, 2H), 7.32 (dd, J=7.7, 1.6 Hz, 2H), 6.49 (dd, J=16.6, 10.0 Hz, 1H), 6.25 (d, J=16.6 Hz, 1H), 6.06 (d, J=10.0 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.1 Hz, 0.5H), 4.13-4.41 (m, 3H), 3.71-3.87 (m, 2H), 3.49-3.63 (m, 1H), 3.39 (s, 3H), 3.21-3.34 (m, 4H), 2.95-3.21 (m, 2H), 2.51-2.81 (m, 2H), 1.91-2.17 (m, 1H), 1.73 (br. s., 2H), 1.23-1.50 (m, 5H), 0.94-1.23 (m, 4H). LC-MS: m/z 524.2 $(M+H)^+$

(S)-2-chloro-N-(3-(5-cyano-2-cyclopropyl-6-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propanamide (Compound 447; General procedure 3, Step N, method 2)

[0766] ^{1}H NMR (CHLOROFORM-d) δ 8.57 (s, 1H), 7.70 (s, 1H), 7.57-7.64 (m, 1H), 7.47-7.56 (m, 1H), 7.42 (t, J=7.8 Hz, 1H), 7.18 (d, J=7.5 Hz, 1H), 4.90 (br. s., 0.5H), 4.47-4.65 (m, 1.5H), 4.18-4.30 (m, 2.5H), 3.73-3.81 (m, 2.5H), 3.48-3.64 (m, 0.5H), 3.37 (s, 3H), 3.21-3.31 (m, 1H), 2.95-3.18 (m, 1.5H), 2.53-2.79 (m, 2H), 2.04-2.12 (m, 1H), 1.83 (d, J=7.0 Hz, 3H), 1.38 (d, J=6.3 Hz, 1.5H), 1.28 (d, J=6.5 Hz, 1.5H), 1.11-1.18 (m, 2H), 0.89-1.03 (m, 2H). LC-MS: m/z 510.1 $(M+H)^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl) phenyl)ethanesulfonamide (Compound 448; General procedure 3, Step N, method 1)

[0767] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.38-7.49 (m, 2H), 7.30-7.34 (m, 1H), 7.26 (dd, J=8.0, 1.3 Hz, 1H), 7.18 (d, J=7.8 Hz, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.3 Hz, 0.5H), 4.13-4.40 (m, 2.5H), 3.67-3.93 (m, 2.5H), 3.51-3.66 (m, 0.5H), 3.38 (s, 3H), 3.02-3.32 (m, 4.5H), 2.55-2.84 (m, 2H), 2.00-2.11 (m, 1H), 1.38-1.44 (m, 4H), 1.24-1.31 (m, 2H), 1.12-1.21 (m, 2H), 0.90-1.03 (m, 2H). LC-MS: m/z 512.1 $(M+H)^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)methacrylamide (Compound 449; General procedure 3, Step N, method 1)

[0768] ^{1}H NMR (CHLOROFORM-d) δ 7.83 (s, 1H), 7.72 (s, 1H), 7.60 (s, 1H), 7.51-7.57 (m, 1H), 7.40 (t, J=7.9 Hz, 1H), 7.15 (d, J=7.8 Hz, 1H), 5.83 (s, 1H), 5.43-5.54 (m, 1H), 4.89 (br. s., 0.5H), 4.52 (d, J=13.3 Hz, 0.5H), 4.13-4.36 (m, 2.5H), 3.68-3.87 (m, 2.5H), 3.55 (t, J=11.3 Hz, 0.5H), 3.35-3.46 (m, 3H), 3.20-3.31 (m, 1H), 2.96-3.17 (m, 1.5H), 2.81 (s, 2H), 2.51-2.77 (m, 2H), 2.03-2.19 (m, 4H), 1.38 (d, J=6.3 Hz, 1.5H), 1.28 (d, J=6.5 Hz, 1.5H), 1.10-1.18 (m, 2H), 0.88-1.02 (m, 2H). LC-MS: m/z 488.1 $(M+H)^+$

(R)—N-(3-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)phenyl)propiolamide (Compound 451; General procedure 3, Step N, method 1)

[0769] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.35-7.47 (m, 1H), 7.28 (s, 1H), 7.23-7.27 (m, 1H), 7.15-7.22 (m, 2H), 6.63 (dd, J=16.6, 9.8 Hz, 1H), 6.26-6.39 (m, 1H), 6.01 (d, J=9.8 Hz, 1H), 4.52 (d, J=12.5 Hz, 1H), 4.40 (d, J=12.3 Hz, 1H), 4.07-4.24 (m, 1H), 3.65-3.90 (m, 1H), 3.22-3.52 (m, 1.5H), 3.10 (s, 1.5H), 2.03-2.10 (m, 1H), 1.29-1.36 (m, 1H), 1.14-1.21 (m, 2H), 0.93-1.12 (m, 4H), 0.85-0.92 (m, 1H), 0.76-0.85 (m, 2H), 0.60-0.71 (m, 1H), 0.38-0.60 (m, 3H). LC-MS: m/z 518.2 $(M+H)^+$

(R)—N-(3-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)phenyl)-N-(vinylsulfonyl)ethenesulfonamide (Compound 452; General procedure 3, Step N, method 1)

[0770] ^{1}H NMR (CHLOROFORM-d) δ 7.63 (s, 1H), 7.49-7.58 (m, 2H), 7.33-7.36 (m, 1H), 7.31 (dt, J=6.7, 2.3 Hz, 1H), 7.07 (d, J=9.8 Hz, 1H), 7.10-7.13 (m, 1H), 6.28-6.38 (m, 2H), 6.14-6.22 (m, 2H), 4.41-4.62 (m, 2.5H), 3.98-4.18 (m, 1H), 3.75-3.90 (m, 1H), 3.09-3.33 (2.5, 1H), 2.00-2.07 (m, 1H), 1.15-1.25 (m, 3H), 0.97-1.11 (m, 4H), 0.86-0.92 (m, 1H), 0.82 (dd, J=7.8, 2.3 Hz, 2H), 0.39-0.67 (m, 4H). LC-MS: m/z 608.2 $(M+H)^+$

(R)—N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-2-fluoro-N-methylacrylamide (Compound 453; General procedure 3, Step N, method 2)

[0771] ^{1}H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.43-7.54 (m, 1H), 7.34 (d, J=7.8 Hz, 1H), 7.17-7.26 (m, 2H), 5.44 (d, J=3.3 Hz, 1H), 5.18-5.38 (m, 1H), 4.82-5.11 (m, 2H), 4.54 (d, J=12.3 Hz, 1H), 4.10-4.40 (m, 3H), 3.75 (br. s., 2H), 3.57 (d, J=7.8 Hz, 1H), 3.35-3.48 (m, 6H), 3.28 (br. s., 1H), 3.14 (d, J=10.5 Hz, 1H), 2.94-3.10 (m, 1H), 2.73 (br. s., 1H), 2.60 (br. s., 1H), 2.19 (s, 1H), 1.90-2.10 (m, 1H), 1.78 (br. s., 1H), 1.23-1.51 (m, 8H), 1.06-1.23 (m, 2H), 0.78-1.06 (m, 3H). LC-MS: m/z 506.2 $(M+H)^+$

(R)—N-(3-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)phenyl)acrylamide (Compound 454; General procedure 3, Step N, method 1)

[0772] ^{1}H NMR (CHLOROFORM-d) δ 7.73-7.80 (m, 2H), 7.63 (s, 1H), 7.51-7.59 (m, 1H), 7.42 (t, J=7.8 Hz, 1H), 7.17 (d, J=7.5 Hz, 1H), 6.40-6.54 (m, 1H), 6.31 (dd, J=16.8, 10.3 Hz, 1H), 5.81 (d, J=10.3 Hz, 1H), 4.51 (d, J=12.3 Hz, 1H), 4.39 (d, J=12.3 Hz, 1H), 3.92-4.27 (m, 1H), 3.51-3.94 (m, 1H), 3.25 (m, 1H), 2.85-3.42 (m, 3H), 2.08-2.15 (m, 1H), 1.29-1.36 (m, 1H), 1.13-1.20 (m, 2H), 0.94-1.11 (m, 4H), 0.86-0.93 (m, 1H), 0.75-0.85 (m, 2H), 6.68 (d, J=12.5 Hz, 1H), 0.40-0.54 (m, 3H). LC-MS: m/z 482.2 $(M+H)^+$

Compound 455 (General Procedure 3, Step N, Method 2)

[0773] ^{1}H NMR (CHLOROFORM-d) 7.61 (s, 1H), 7.47 (d, J=7.5 Hz, 1H), 7.31-7.36 (m, 1H), 5.87 (s, 1H), 4.83-5.04 (m, 1H), 4.19-4.42 (m, 3H), 3.76 (br. s., 2H), 3.56 (br. s., 1H), 3.36-3.49 (m, 6H), 3.30 (br. s., 1H), 2.91-3.20 (m, 4H), 2.74 (br. s., 1H), 2.68 (br. s., 1H), 2.61 (br. s., 1H), 1.93-2.02 (m, 1H), 1.15-1.45 (m, 16H), 0.99 (dd, J=7.8, 2.8 Hz, 2H), 0.76-0.94 (m, 2H). LC-MS: m/z 512.2 $(M+H)^+$

Compound 456 (General Procedure 3, Step N, Method 2)

[0774] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.52 (t, J=7.7 Hz, 1H), 7.40 (d, J=7.8 Hz, 1H), 7.29-7.37 (m, 2H), 4.10-4.39 (m, 3H), 3.70-3.90 (m, 2H), 3.66 (s, 1H), 3.49 (s, 1H), 3.38 (s, 5H), 3.30 (d, J=14.8 Hz, 1H), 3.14 (br. s., 2H), 2.71-2.91 (m, 2H), 2.48-2.71 (m, 2H), 2.05 (dt, J=7.8, 4.0 Hz, 2H), 1.13-1.42 (m, 8H), 0.91-1.08 (m, 2H). LC-MS: m/z 486.2 $(M+H)^+$

(R)-6-cyclopropyl-5-(1-hydroxyisoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 457; General procedure 1, Step I)

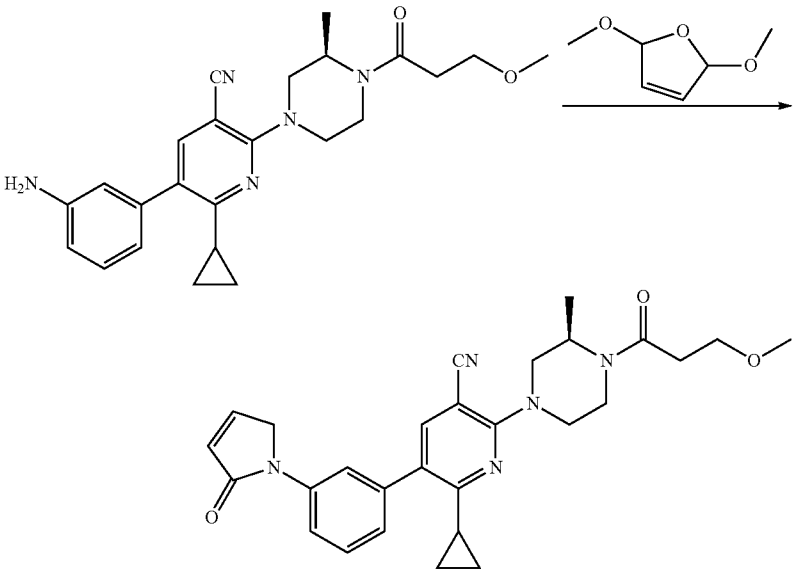
[0775] ^{1}H NMR (CHLOROFORM-d) δ 10.93 (s, 1H), 8.51 (dd, J=6.8, 2.3 Hz, 1H), 7.51-7.67 (m, 3H), 6.32 (s, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.18-4.41 (m, 2.5H), 3.53-3.92 (m, 3.5H), 3.40 (s, 1H), 3.16-3.38 (m, 2.5H), 2.51-2.83 (m, 2H), 1.61 (br. s., 1H), 1.39-1.49 (m, 1.5H), 1.31-1.39 (m, 1.5H), 1.14 (dd, J=8.3, 4.8 Hz, 2H), 0.79-0.93 (m, 2H). LC-MS: m/z 472.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(3-methylisoquinolin-5-yl)nicotinonitrile (Compound 458; General procedure 1, Step I)

[0776] ^{1}H NMR (CHLOROFORM-d) δ 9.25 (s, 1H), 8.00 (dd, J=7.2, 1.6 Hz, 1H), 7.54-7.67 (m, 3H), 7.16-7.27 (m, 1H), 4.57 (d, J=12.5 Hz, 1H), 4.46 (d, J=12.5 Hz, 1H), 3.62-4.63 (m, 2H), 3.10-3.40 (m, 2.5H), 2.67 (d, J=4.5 Hz, 3H), 2.25-2.49 (m, 0.5H), 1.74 (br. s., 1H), 1.54 (dtd, J=12.7, 3.9, 1.9 Hz, 2H), 1.13-1.23 (m, 2H), 0.95-1.13 (m, 2H), 0.77-0.91 (m, 4H), 0.70 (br. s., 1H), 0.39-0.60 (m, 3H). LC-MS: m/z 478.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-(2-oxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl)nicotinonitrile (Compound 459)

[0777]



[0778] A mixture of (R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile (300 mg), pentane-2,4-dione (100 mg) and TFA (1 drop) in cyclohexane was refluxed for 3 h. After evaporation, the residue was dissolved in CH_3CN and some Na_2SO4 was added followed by select-F-TEDA-BF_4 (800 mg). The mixture was refluxed for overnight. After evaporation, the residue was purified by pre-TLC to give the title compound (75 mg). ^1H NMR (CHLOROFORM-d) δ 7.86 (s, 1H), 7.58-7.75 (m, 2H), 7.47 (t, J=8.0 Hz, 1H), 7.10-7.26 (m, 2H), 6.33 (dt, J=6.0, 1.8 Hz, 1H), 4.91 (br. s., 0.5H), 4.42-4.63 (m, 2.5H), 4.13-4.40 (m, 2.5H), 3.65-3.95 (m, 2.5H), 3.39 (s, 3H), 3.21-3.32 (m, 1H), 2.99-3.20 (m, 2H), 2.52-2.81 (m, 2H), 2.00-2.29 (m, 1H), 1.35-1.53 (m, 1.5H), 1.23-1.35 (m, 1.5H), 1.07-1.23 (m, 2H), 0.92-1.07 (m, 2H). LC-MS: m/z 486.2 $(M+H)^+$

(R)-6-Cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-methyl-1-oxoisoindolin-4-yl)nicotinonitrile (Compound 460; General procedure 1, Step I)

[0779] ^1H NMR (CHLOROFORM-d) δ 7.93-7.88 (m, 1H), 7.61-7.55 (m, 2H), 7.45 (dd, J=7.5, 0.9 Hz, 1H), 4.97 (ddd, J=13.1, 10.1, 1.5 Hz, 1H), 4.42-4.15 (m, 5H), 3.90-3.49 (m, 3H), 3.39 (d, J=5.2 Hz, 3H), 3.32 (dd, J=13.1, 3.6 Hz, 1H), 3.26-3.09 (m, 4H), 2.85-2.53 (m, 2H), 2.12-1.88 (m, 1H), 1.17 (dd, J=7.5, 3.1 Hz, 3H), 0.96 (dd, J=7.9, 3.2 Hz, 2H), 0.90 (t, J=6.8 Hz, 3H).

[0780] LC-MS: m/z 474.6 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(2-methyl-1-oxoisoindolin-4-yl)nicotinonitrile (Compound 461; General procedure 1, Step I)

[0781] ^1H NMR (400 MHz, $CDCl_3$) δ=7.93 (d, J=7.5 Hz, 1H), 7.64-7.57 (m, 2H), 7.53-7.47 (m, 1H), 7.44 (s, 1H), 4.93-4.21 (m, 6H), 4.21-2.84 (m, 6H), 1.82-1.65 (m, 2H), 1.55-1.29 (m, 4H), 1.17 (dd, J=7.0, 3.8 Hz, 2H), 1.10-0.97 (m, 2H), 0.95 (dd, J=7.8, 3.2 Hz, 2H), 0.84-0.75 (m, 2H).

[0782] LC-MS: m/z 458.6.3 $(M+H)^+$

(R)-2-(4-(Cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-oxoisoindolin-4-yl) nicotinonitrile (Compound 464; General procedure 1, Step I)

[0783] ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J=7.6, 0.8 Hz, 1H), 7.64-7.59 (m, 2H), 7.51 (dd, J=5.4, 2.1 Hz, 1H), 6.76 (s, 1H), 5.07-4.24 (m, 6H), 3.22 (d, J=59.5 Hz, 2H), 2.05 (dt, J=15.3, 7.7 Hz, 1H), 1.31 (s, 2H), 1.19 (dd, J=4.4, 3.2 Hz, 2H), 0.96 (dd, J=7.9, 3.2 Hz, 2H), 0.90 (t, J=6.8 Hz, 3H), 0.82 (dd, J=7.9, 2.4 Hz, 2H), 0.49 (ddd, J=18.9, 9.9, 4.8 Hz, 3H). LC-MS: m/z 468.6 $(M+H)^+$

[0784] (R)-2-(4-(Cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(2-methyl-1-oxoisoindolin-4-yl) nicotinonitrile (Compound 465; General procedure 1, Step I)

[0785] ^1H NMR (400 MHz, $CDCl_3$) δ=7.90 (d, J=7.6 Hz, 1H), 7.61-7.54 (m, 2H), 7.45 (d, J=7.5 Hz, 1H), 5.04-3.99 (m, 6H), 3.78-3.06 (m, 6H), 2.13-1.83 (m, 1H), 1.31 (d, J=5.5 Hz, 4H), 1.20-1.14 (m, 2H), 1.09-0.99 (m, 2H), 0.95 (dd, J=7.9, 3.2 Hz, 2H), 0.83 (dd, J=7.9, 1.3 Hz, 2H). LC-MS: m/z 466.6 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2,3-dioxoindolin-7-yl) nicotinonitrile (Compound 513; General procedure 1, Step I)

[0786] A mixture of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (103.9 mg, 0.25 mol), 7-bromoisatin (67.8 mg, 0.30 mmol), $Pd(PPh_3)_4$

(29 mg, 0.03 mmol), and K_2CO_3 (86.3 mg, 0.63 mmol) suspended in 5 mL of 1,4-dioxane was subjected to microwave reaction at 120° C. for 1 h. After the reaction, the reaction mixture was concentrated in vacuo, residue was purified by column chromatography to afford the title compound. Yield: 14.1 mg (11.7%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.65 (m, 2H), 7.64 (s, 1H), 7.53 (dd, J=7.8, 1.2 Hz, 1H), 7.25 (d, J=7.7 Hz, 1H), 4.62 (d, J=13.4 Hz, 1H), 4.49 (d, J=12.2 Hz, 1H), 4.24 (m, 1H), 3.77 (m, 1H), 3.26 (m, 2H), 1.88-1.77 (m, 1H), 1.73 (s, 2H), 1.30-1.16 (m, 3H), 1.16-0.96 (m, 4H), 0.83 (dd, J=7.9, 2.5 Hz, 2H), 0.52 (dd, J=17.5, 12.8 Hz, 3H). LC-MS: m/z 482.3 $(M+H)^+$

(R)-5-(benzo[d]oxazol-6-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 466; General procedure 1, Step I)

[0787] ^{1}H NMR (CHLOROFORM-d) δ: 8.18 (s, 1H), 7.88 (d, J=8.3 Hz, 1H), 7.68 (s, 1H), 7.65 (d, J=1.0 Hz, 1H), 7.43 (dd, J=8.2, 1.6 Hz, 1H), 4.55 (d, J=12.5 Hz, 1H), 4.43 (d, J=12.5 Hz, 1H), 4.18-4.34 (m, 1H), 3.91-4.18 (m, 1H), 3.73 (br. s., 1H), 3.28 (br. s., 1H), 3.12 (br. s., 1H), 2.00-2.12 (m, 1H), 1.73 (br. s., 1H), 1.44 (br. s., 1H), 1.18-1.24 (m, 2H), 0.94-1.12 (m, 4H), 0.77-0.87 (m, 2H), 0.68 (br. s., 1H), 0.40-0.61 (m, 3H). LC-MS: m/z 454.5 $(M+H)^+$

(R)-5-(benzo[d]oxazol-6-yl)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 467; General procedure 1, Step I)

[0788] ^{1}H NMR (CHLOROFORM-d) δ: 8.15-8.21 (m, 1H), 7.84-7.90 (m, 1H), 7.67 (s, 1H), 7.61-7.66 (m, 1H), 7.39-7.47 (m, 1H), 4.59 (br. s., 1H), 4.21-4.46 (m, 3H), 3.43-3.61 (m, 1H), 3.39 (br. s., 1H), 3.18 (br. s., 1H), 2.00-2.10 (m, 1H), 1.78 (br. s., 1H), 1.25-1.32 (m, 3H), 1.16-1.24 (m, 2H), 1.00-1.11 (m, 2H), 0.93-1.00 (m, 2H), 0.83 (dd, J=7.8, 1.8 Hz, 2H). LC-MS: m/z 428.5 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(3-methylisoquinolin-5-yl)nicotinonitrile (Compound 471; General procedure 2, Step M)

[0789] ^{1}H NMR (CHLOROFORM-d) δ 9.26 (s, 1H), 7.96-8.06 (m, 1H), 7.55-7.69 (m, 3H), 7.21 (d, J=15.1 Hz, 1H), 4.57 (dt, J=13.1, 2.3 Hz, 1H), 4.46 (d, J=12.3 Hz, 1H), 4.15 (br. s., 0.5H), 3.69-3.95 (m, 1.5H), 3.21-3.45 (m, 3H), 3.04-3.21 (m, 2H), 2.67 (d, J=4.5 Hz, 3H), 1.40-1.61 (m, 2H), 1.24-1.31 (m, 1H), 1.07-1.21 (m, 2H), 0.77-0.91 (m, 2H), 0.70 (br. s., 1H), 0.43-0.56 (m, 2H). LC-MS: m/z 520.2 $(M+H)^+$

(R)—N-(3-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)phenyl)ethenesulfonamide (Compound 472; General procedure 3, Step N, method 2)

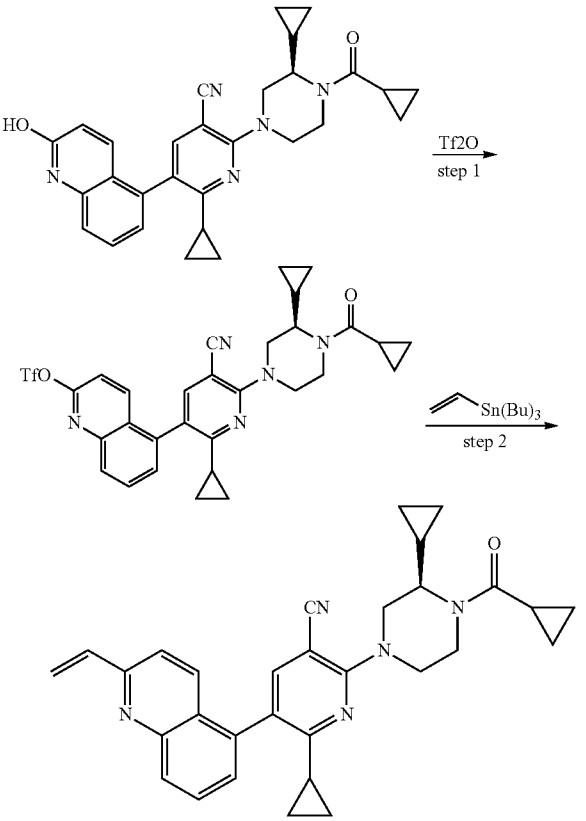
[0790] To a solution of (R)-5-(3-aminophenyl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (30 mg, 0.07 mmol) in DCM was added propiolic acid (5 mg, 0.07 mmol) and DCC (18 mg, 0.084 mmol). The mixture was stirred at 25° C. for 16 hours. TLC and LC-MS showed product and the mixture was purified by prep-TLC to give 15 mg of the compound. ^{1}H NMR (CHLOROFORM-d) δ 8.19 (s, 1H), 7.66-7.77 (m, 1H), 7.62 (s, 1H), 7.47-7.56 (m, 1H), 7.36-7.47 (m, 1H), 7.19 (d, J=7.8 Hz, 1H), 4.51 (d, J=12.0 Hz, 1.5H), 4.29-4.45 (m, 1.5H), 4.08-4.29 (m, 1H), 3.42-3.87 (m, 1H), 3.13-3.42 (m, 1H), 2.99-3.13 (m, 1H), 2.98 (s, 1H), 2.05-2.14 (m, 1H), 1.68-1.77 (m, 1H), 1.11-1.21 (m, 3H), 1.04-1.11 (m, 1H), 0.93-1.04 (m, 3H), 0.76-0.86 (m, 2H), 0.66 (s, 1H), 0.38-0.60 (m, 3H). LC-MS: m/z 480.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-hydroxyquinolin-5-yl)nicotinonitrile (Compound 476; General procedure, Step I)

[0791] ^{1}H NMR (CHLOROFORM-d) δ 7.89 (d, J=9.5 Hz, 1H), 7.67 (s, 1H), 7.52-7.64 (m, 3H), 6.81 (d, J=9.5 Hz, 1H), 4.53 (d, J=12.5 Hz, 2H), 4.41 (d, J=12.3 Hz, 2H), 3.28 (br. s., 2H), 3.11 (br. s., 1H), 1.96-2.07 (m, 2H), 1.14-1.32 (m, 2H), 0.93-1.11 (m, 4H), 0.76-0.92 (m, 2H), 0.67 (br. s., 1H), 0.31-0.60 (m, 3H). LC-MS: m/z 490.2 (M+H)

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-vinylquinolin-5-yl) nicotinonitrile (Compound 475)

[0792]



Step 1

[0793] To a solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-hydroxyquinolin-5-yl)nicotinonitrile (50 mg, 0.104 mmol), Et3N (12 mg, 0.12 mmol) in DCM (2 mL) was added dropwise

Tf2O (30.3 mg, 0.107 mmol) at 0° C. and stirred at r.t. for 3 h. Water was added and the organic layer was combined, dried, concentrated to give 50 mg product after prep-TLC.

Step 2

[0794] To a solution of (R)-5-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)quinolin-2-yl trifluoromethanesulfonate (50 mg, 0.082 mmol), tributyl(vinyl)stannane (27 mg, 0.086 mmol), LiCl (5.2 mg, 0.123 mmol) in THF (2 mL) was added $Pd(PPh_3)_4$(4.7 mg, 0.0041 mmol) under N2 and the reaction mixture was heated to 85° C. for 2 h. The mixture was cooled and the solvent was removed. Product (9 mg) was obtained by prep-TLC. ^{1}H NMR (CHLOROFORM-d) δ 8.16 (t, J=9.3 Hz, 2H), 7.72-7.86 (m, 3H), 7.68 (d, J=8.5 Hz, 1H), 7.04-7.14 (m, 2H), 6.34 (d, J=17.6 Hz, 1H), 5.73 (d, J=11.0 Hz, 1H), 4.53 (d, J=12.5 Hz, 2H), 4.41 (d, J=12.3 Hz, 2H), 3.28 (br. s., 2H), 3.11 (br. s., 1H), 1.67 (br. s., 2H), 0.95-1.16 (m, 6H), 0.77-0.95 (m, 6H). LC-MS: m/z 490.2 (M+H).

2-(4-(cyclopropanecarbonyl)-6-fluoro-1,4-diazepan-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 477; General procedure 4, Step R and S)

[0795] ^{1}H NMR (CHLOROFORM-d) δ 9.36 (s, 1H), 8.48-8.65 (m, 1H), 8.08 (d, J=8.0 Hz, 1H), 7.69-7.77 (m, 1H), 7.62-7.69 (m, 2H), 7.42 (d, J=6.0 Hz, 1H), 4.99 (br. s., 0.5H), 4.84 (br. s., 0.5H), 4.72 (br. s., 1.5H), 4.60 (br. s., 1H), 4.49 (d, J=13.8 Hz, 1H), 4.17-4.39 (m, 2H), 3.76 (br. s., 0.5H), 3.32-3.57 (m, 2H), 3.22 (br. s., 1H), 1.70 (br. s., 1H), 1.54 (br. s., 1H), 1.14-1.20 (m, 2H), 1.04-1.12 (m, 2H), 0.83-0.90 (m, 4H). LC-MS: m/z 456.1 (M+H)

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1H-pyrazol-4-yl)nicotinonitrile (Compound 479; General procedure 1, Step H)

[0796] ^{1}H NMR (CHLOROFORM-d) δ 7.70-7.81 (m, 2H), 7.65 (S, 1H), 4.49 (d, J=13.1 Hz, 1H), 4.37 (d, J=12.3 Hz, 1H), 4.13 (d, J=14.8 Hz, 1H), 3.79 (s, 1H), 3.25 (s, 1.5H), 3.08 (s, 1.5H), 2.19-2.28 (m, 1H), 1.64-1.80 (m, 1H), 1.15-1.22 (m, 2H), 0.95-1.11 (m, 4H), 0.86-0.93 (m, 1H), 0.81 (dd, J=7.8, 2.3 Hz, 2H), 0.66 (s, 1H), 0.38-0.59 (m, 3H). LC-MS: m/z 442.2 $(M+H)^+$

6-cyclopropyl-2-((R)-3-cyclopropyl-4-((1S,2R)-2-(methoxymethyl)cyclopropanecarbonyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 480)

[0797] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (s, 1H), 8.54 (dd, J=6.0, 1.5 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.65-7.74 (m, 3H), 7.43 (dd, J=6.0 Hz, 1H), 4.58 (br. s., 0.5H), 4.46 (d, J=11.8 Hz, 1H), 4.26 (br. s., 0.5H), 4.09 (br. s., 0.5H), 3.83 (br. s., 0.5H), 3.68 (br. s., 0.5H), 3.52 (dd, J=10.3, 5.3 Hz, 1H), 3.29-3.41 (m, 4H), 3.23 (br. s., 2H), 1.67-1.75 (m, 2H), 1.39-1.59 (m, 2H), 1.26-1.36 (m, 3H), 1.16-1.19 (m, 2H), 0.82-0.85 (m, 3H), 0.55 (br. s., 2H), 0.48 (br. s., 2H). LC-MS: m/z 508.1 $(M+H)^+$

Compound 481

[0798] ^{1}H NMR (CHLOROFORM-d) δ 9.38 (br. s., 1H), 8.55 (d, J=5.3 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 7.66-7.75 (m, 3H), 7.44-7.47 (m, 1H), 4.45-4.59 (m, 2.5H), 4.09-4.19 (m, 1H), 3.86 (s, 0.5H), 3.57-3.68 (m, 3.5H), 3.05-3.45 (m, 2.5H), 1.93 (br. s., 1H), 1.51-1.54 (m, 1H), 1.18-1.25 (m, 6H), 0.83-0.91 (m, 4H), 0.49-0.68 (m, 4H). LC-MS: m/z 508.3 $(M+H)^+$

(R)-5-(benzo[d]oxazol-7-yl)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 482; General procedure 1, Step H)

[0799] ^{1}H NMR (CHLOROFORM-d) δ 8.16 (s, 1H), 7.85 (dd, J=7.8, 1.0 Hz, 1H), 7.49 (t, J=7.7 Hz, 1H), 7.42 (dd, J=7.5, 1.0 Hz, 1H), 4.58 (br. s., 1H), 4.32 (d, J=13.1 Hz, 2H), 3.49-3.62 (m, 1H), 3.46 (br. s., 1H), 3.21 (br. s., 2H), 1.85-1.93 (m, 1H), 1.78 (br. s., 1H), 1.31-1.45 (m, 3H), 1.18-1.25 (m, 2H), 1.00-1.11 (m, 2H), 0.89-0.99 (m, 2H), 0.84 (d, J=6.8 Hz, 2H). LC-MS: m/z 428.5 $(M+H)^+$

(R)-5-(benzo[d]oxazol-7-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 483; General procedure 1, Step H)

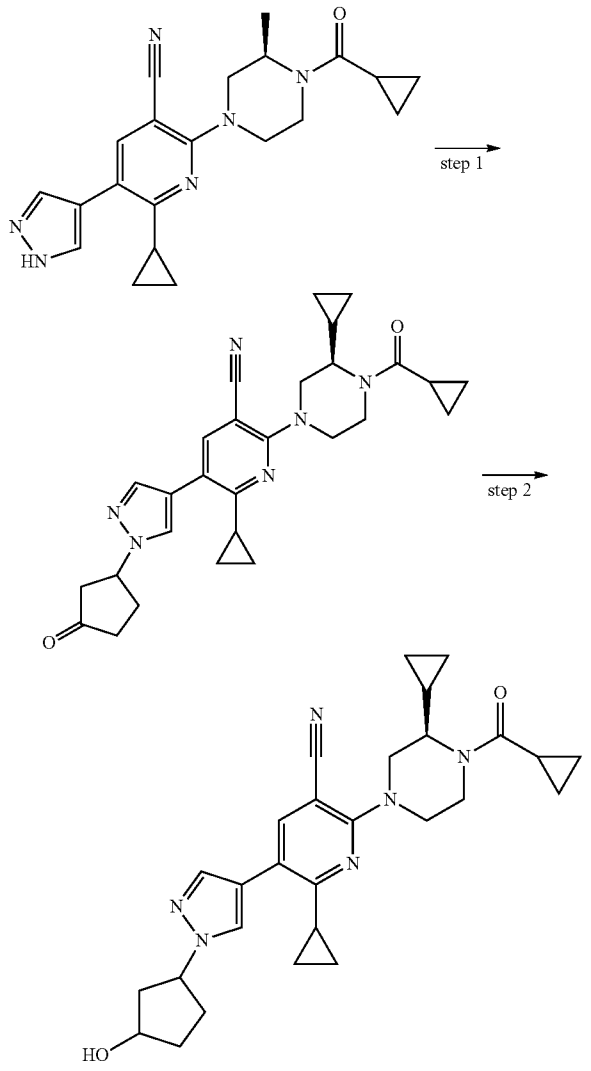
[0800] ^{1}H NMR (CHLOROFORM-d) δ 8.16 (s, 1H), 7.82-7.87 (m, 1H), 7.79 (s, 1H), 7.49 (t, J=7.8 Hz, 1H), 7.42 (dd, J=7.5, 1.0 Hz, 1H), 4.59 (d, J=12.8 Hz, 1H), 4.47 (d, J=12.0 Hz, 1H), 3.95-4.20 (m, 2H), 3.79 (br. s., 1H), 3.30 (br. s., 1H), 3.15 (br. s., 1H), 1.85-1.97 (m, 1H), 1.61 (br. s., 2H), 1.19-1.25 (m, 2H), 1.06 (d, J=16.8 Hz, 2H), 0.91-0.98 (m, 2H), 0.82 (d, J=6.5 Hz, 2H), 0.68 (br. s., 1H), 0.40-0.61 (m, 3H). LC-MS: m/z 454.5 $(M+H)^+$2-(4-(cyclopropanecarbonyl)-6-fluoro-3-methyl-1,4-diazepan-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 484; General procedure 4, Step R and S): ^{1}H NMR (CHLOROFORM-d) δ 9.40 (br. s., 1H), 8.56 (br. s., 1H), 8.12 (d, J=8.0 Hz, 1H), 7.69-7.81 (m, 2H), 7.68 (d, J=1.0 Hz, 1H), 7.47-7.54 (m, 1H), 4.54-4.98 (m, 6H), 3.25-3.44 (m, 1H), 3.17 (br. s., 1H), 1.77-1.89 (m, 1H), 1.49-1.54 (m, 1H), 1.25-1.30 (m, 3H), 1.19-1.23 (m, 2H), 1.10 (br. s., 2H), 0.84-0.91 (m, 4H). LC-MS: m/z 470.2 (M+H)

(R)-5-(1-(cyanomethyl)-1H-pyrazol-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 486)

[0801] To a solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1H-pyrazol-4-yl)nicotinonitrile (60 mg, 0.149 mmol) in DMF was added K_2CO_3 (42 mg, 0.298 mmol) and 2-bromoacetonitrile (27 mg, 0.224 mmol). The resulting mixture was stirred for 16 hours. Then the mixture was partitioned between EtOAc and water, the organic layer was washed with water, brine and dried over Na_2SO_4, concentrated to give the crude which was purified by prep-TLC to give 25 mg of the product. ^{1}H NMR (CHLOROFORM-d) δ 7.72 (s, 1H), 7.69 (s, 1H), 7.61 (s, 1H), 5.17 (s, 2H), 4.32-4.52 (m, 2.5H), 3.65-3.89 (m, 1H), 4.01-4.22 (m, 1H), 3.55-4.92 (m, 1H), 2.89-3.33 (m, 2.5H), 2.10-2.23 (m, 1H), 1.72 (s, 1H), 1.31-1.47 (m, 1H), 1.14-1.22 (m, 2H), 0.92-1.09 (m, 4H), 0.75-0.86 (m, 2H), 0.39-0.63 (m, 4H). LC-MS: m/z 442.2 $(M+H)^+$

2-((R)-4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-(3-hydroxycyclopentyl)-1H-pyrazol-4-yl)nicotinonitrile (Compound 493)

[0802]



Step 1

[0803] To a solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1H-pyrazol-4-yl)nicotinonitrile (100 mg, 0.248 mmol) in CH_2Cl_2 was added cyclopent-2-enone (51 mg, 0.621 mmol) and $ScCl_3$ (338 mg, 2.24 mmol). The mixture was stirred for 16 hours at room temperature. The mixture was partitioned between EtOAc and water. The organic layer was washed with water, brine and dried over Na_2SO_4, concentrated to give the crude which was purified by prep-TLC to give 50 mg of the product. LC-MS: m/z 485.3 $(M+H)^+$

Step 2

[0804] a solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1H-pyrazol-4-yl)nicotinonitrile (40 mg, 0.0825 mmol) in MeOH was added $NaBH_4$, the mixture was stirred for 2 hours at room temperature. The mixture was partitioned between EtOAc and water. The organic layer was washed with water, brine and dried over Na_2SO_4, concentrated to give the crude which was purified by prep-TLC to give 15 mg of the product. ^1H NMR (CHLOROFORM-d) δ 7.56-7.70 (m, 3H), 4.85 (br. s., 1H), 4.25-4.70 (m, 4H), 4.00-4.25 (m, 1H), 3.50-3.90 (m, 1H), 2.95-3.41 (m, 3H), 2.12-2.41 (m, 6H), 1.90-2.03 (m, 1H), 1.37-1.54 (m, 1H), 1.23-1.37 (m, 1H), 1.17-1.28 (m, 2H), 0.94-1.09 (m, 4H), 0.76-0.85 (m, 2H), 0.39-0.64 (m, 4H). LC-MS: m/z 487.3 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-(methylsulfonyl)-1H-pyrazol-4-yl)nicotinonitrile (Compound 502)

[0805] To a solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1H-pyrazol-4-yl)nicotinonitrile (30 mg, 0.074 mmol) in DCM was added TEA (15 mg, 0.149 mmol) and methanesulfonyl chloride (9.4 mg, 0.082 mmol) and the mixture was stirred at r.t. for 2 h. The mixture was partitioned between EtOAc and water. The organic layer was washed with H_2O, brine and dried over Na_2SO_4, concentrated to give the crude which was purified by prep-TLC to give 15 mg of the product. ^1H NMR (CHLOROFORM-d) δ 8.16 (s, 1H), 7.97 (s, 1H), 7.65 (s, 1H), 4.40-4.60 (m, 2.5H), 4.09-4.25 (m, 1H), 3.53-3.90 (m, 1H), 3.45 (s, 3H), 3.05-3.41 (m, 2.5H), 2.06-2.19 (m, 1H), 1.12-1.26 (m, 3H), 0.95-1.12 (m, 4H), 0.89 (t, J=6.8 Hz, 1H), 0.75-0.85 (m, 2H), 0.36-0.64 (m, 4H). LC-MS: m/z 481.2 $(M+H)^+$

(R)-2-(4-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)-1H-pyrazol-1-yl)acetamide (Compound 501)

[0806] To a solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1H-pyrazol-4-yl)nicotinonitrile (30 mg, 0.0745 mmol) in DMF was added K_2CO_3 (21 mg, 0.149 mmol) and 2-bromoacetamide (12 mg, 0.082 mmol). The mixture was stirred for 16 hours at room temperature, then the mixture was partitioned between EtOAc and water. The organic layer was partitioned between EtOAc and water, the organic layer was washed with water, brine and dried over Na_2SO_4 concentrated to give 25 mg of the product. ^1H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.57-7.69 (m, 2H), 6.43 (br. s., 1H), 6.04 (br. s., 1H), 4.88 (s, 2H), 4.30-4.60 (m, 2.5H), 3.84-4.23 (m, 1H), 3.50-3.80 (m, 1H), 3.00-3.45 (m, 2.5H), 2.13-2.25 (m, 1H), 1.92 (s, 1H), 1.71 (s, 1H), 1.12-1.21 (m, 2H), 0.94-1.10 (m, 4H), 0.72-0.84 (m, 2H), 0.35-0.63 (m, 4H). LC-MS: m/z 460.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-((methylthio)methyl)-1H-pyrazol-4-yl)nicotinonitrile (Compound 510)

[0807] To a solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1H-pyrazol-4-yl)nicotinonitrile (50 mg, 0.124 mmol) in DMF was added NaH (10 mg, 0.248 mmol) and (chloromethyl)(methyl)sulfane (24 mg, 0.248 mmol). The mixture was stirred for 2 hours at room temperature. The mixture was partitioned between EtOAc and water, the organic layer was washed with water, brine and dried over Na_2SO_4, concentrated to give the crude which was purified by prep-TLC to give 15 mg of the

product. ^{1}H NMR (CHLOROFORM-d) δ 7.73 (s, 1H), 7.59-7.68 (m, 2H), 5.20 (s, 2H), 4.28-4.48 (m, 2.5H), 4.26-4.30 (m, 1H), 3.50-3.80 (m, 1H), 2.99-3.40 (m, 2.5H), 2.22-2.28 (m, 1H), 2.21 (s, 3H), 1.73 (s, 1H), 1.30-1.48 (m, 1H), 1.14-1.23 (m, 2H), 0.94-1.10 (m, 4H), 0.75-0.85 (m, 2H), 0.39-0.64 (m, 4H). LC-MS: m/z 463.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)nicotinonitrile (Compound 490):

[0808] ^{1}H NMR (CHLOROFORM-d) δ 7.66 (s, 1H), 7.58-7.64 (m, 2H), 4.47 (d, J=12.3 Hz, 1H), 4.25-4.41 (m, 3H), 3.97-4.18 (m, 3H), 3.77 (s, 1H), 3.23 (s, 2H), 3.07 (s, 1H), 2.16-2.30 (m, 1H), 1.23-1.35 (m, 2H), 1.12-1.21 (m, 2H), 0.95-1.09 (m, 4H), 0.74-0.87 (m, 2H), 0.38-0.64 (m, 4H). LC-MS: m/z 446.2M+H)$^+$

(R)-5-(benzo[d]thiazol-6-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 487; General procedure 1, Step I)

[0809] 1H NMR (CHLOROFORM-d) δ 9.07 (s, 1H), 8.22 (d, J=8.3 Hz, 1H), 8.00 (d, J=1.5 Hz, 1H), 7.68-7.73 (m, 1H), 7.58 (dd, J=8.4, 1.6 Hz, 1H), 4.55 (d, J=12.3 Hz, 1H), 4.43 (d, J=12.3 Hz, 1H), 3.50 (d, J=9.0 Hz, 2H), 3.29 (br. s., 2H), 3.13 (br. s., 1H), 2.04-2.12 (m, 1H), 1.29-1.40 (m, 2H), 1.18-1.25 (m, 2H), 0.94-1.12 (m, 4H), 0.77-0.86 (m, 2H), 0.68 (br. s., 1H), 0.40-0.61 (m, 3H); LC-MS: m/z 470.2 (M+H).

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(furan-3-carbonyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 488; General procedure 4, Step R and S)

[0810] 1H NMR (CHLOROFORM-d) δ 9.36 (s, 1H), 8.55 (dd, J=5.8, 2.0 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 7.64-7.79 (m, 4H), 7.41-7.50 (m, 2H), 6.59 (s, 1H), 4.61 (dd, J=13.1, 2.0 Hz, 1H), 4.43 (br. s., 2H), 3.98 (br. s., 1H), 3.73 (br. s., 1H), 3.22-3.36 (m, 1H), 3.07-3.22 (m, 1H), 1.50-1.57 (m, 2H), 1.12-1.21 (m, 2H), 0.81-0.89 (m, 2H), 0.65-0.78 (m, 1H), 0.53-0.62 (m, 1H), 0.47 (br. s., 2H). LC-MS: m/z 490.6 $(M+H)^+$

(R)-methyl 4-(3-cyano-6-cyclopropyl-5-(isoquinolin-5-yl)pyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (Compound 489; General procedure 4, Step R and S)

[0811] 1H NMR (CHLOROFORM-d) δ 9.37 (br. s., 1H), 8.55 (br. s., 1H), 8.08 (d, J=8.0 Hz, 1H), 7.70-7.77 (m, 1H), 7.60-7.70 (m, 2H), 7.46 (dd, J=12.0, 5.8 Hz, 1H), 4.50-4.60 (m, 1H), 4.37-4.47 (m, 1H), 4.17 (d, J=12.5 Hz, 1H), 3.76 (s, 3H), 3.45-3.59 (m, 2H), 3.29 (ddd, J=12.9, 6.4, 3.8 Hz, 1H), 3.13 (tdd, J=12.5, 7.2, 3.5 Hz, 1H), 1.47-1.57 (m, 1H), 1.34-1.47 (m, 1H), 1.18 (dd, J=7.3, 4.0 Hz, 2H), 0.85-0.93 (m, 2H), 0.60-0.72 (m, 1H), 0.48-0.60 (m, 2H), 0.36-0.48 (m, 1H). LC-MS: m/z 454.5 $(M+H)^+$

(R)-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-[3,3'-bipyridine]-5,5'-dicarbonitrile (Compound 494; General procedure 1, Step H)

[0812] ^{1}H NMR (CHLOROFORM-d) δ 8.92 (br. s., 2H), 7.99-8.07 (m, 1H), 7.63 (s, 1H), 4.63 (d, J=12.8 Hz, 1H), 4.50 (d, J=12.3 Hz, 1H), 3.33 (br. s., 1H), 3.17 (m, 2H), 1.80-1.90 (m, 2H), 1.73 (m., 1H), 1.19-1.31 (m, 4H), 0.94-1.12 (m, 4H), 0.76-0.88 (m, 2H), 0.36-0.60 (m, 4H). LC-MS: m/z 439.5 $(M+H)^+$

(R)-5-(cinnolin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 495; General procedure 1, Step H)

[0813] ^{1}H NMR (CHLOROFORM-d) δ: 9.28 (d, J=2.0 Hz, 1H), 8.66 (d, J=8.5 Hz, 1H), 7.88-7.97 (m, 1H), 7.72-7.85 (m, 2H), 7.66-7.72 (m, 2H), 4.60-4.74 (m, 1.5H), 4.43-4.60 (m, 1.5H), 3.60-3.89 (m, 1H), 3.35 (br. s., 1H), 3.22 (br. s., 1H), 1.49-1.58 (m, 1H), 1.16-1.36 (m, 4H), 0.99-1.16 (m, 2H), 0.78-0.99 (m, 4H), 0.63-0.78 (m, 1H), 0.42-0.63 (m, 3H). LC-MS: m/z 465.6 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-vinylpyrimidin-4-yl) nicotinonitrile (Compound 496)

[0814] The procedure was similar to the synthesis of Compound 390. ^{1}H NMR (CHLOROFORM-d) δ 8.67-8.84 (m, 1H), 8.07 (s, 1H), 7.43 (d, J=5.0 Hz, 1H), 6.87-7.03 (m, 1H), 6.74 (dd, J=17.4, 1.6 Hz, 1H), 5.76-5.88 (m, 1H), 4.68 (d, J=13.1 Hz, 1H), 4.55 (d, J=13.3 Hz, 1H), 4.07 (br. s., 1H), 3.88 (s, 1H), 3.66 (br. s., 1H), 3.33 (br. s., 1H), 3.17 (br. s., 1H), 2.34-2.47 (m, 1H), 1.96-2.08 (m, 2H), 1.30-1.42 (m, 2H), 1.00-1.11 (m, 3H), 0.85-0.93 (m, 1H), 0.82 (dd, J=8.0, 2.5 Hz, 2H), 0.65 (br. s., 1H), 0.39-0.59 (m, 3H). LC-MS: m/z 441.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-methylisoquinolin-5-yl)nicotinonitrile (Compound 497; General procedure 1, Step I)

[0815] ^{1}H NMR (CHLOROFORM-d) δ 8.40 (dd, J=6.0, 2.0 Hz, 1H), 8.24 (d, J=8.3 Hz, 1H), 7.68-7.76 (m, 1H), 7.31 (d, J=6.5 Hz, 2H), 4.58 (d, J=10.5 Hz, 1H), 4.46 (d, J=12.5 Hz, 1H), 4.23 (br. s., 1H), 3.82 (br. s., 1H), 3.67 (br. s., 1H), 3.32 (br. s., 1H), 3.17 (br. s., 1H), 2.93-3.12 (m, 3H), 1.74 (br. s., 1H), 1.47-1.57 (m, 2H), 1.14-1.22 (m, 2H), 1.00-1.12 (m, 2H), 0.83 (dd, J=6.7, 4.6 Hz, 4H), 0.70 (br. s., 1H), 0.41-0.63 (m, 3H). LC-MS: m/z 478.3 $(M+H)^+$

(R)-6'-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2'-cyclopropyl-6-vinyl-2,3'-bipyridine-5'-carbonitrile (Compound 499; General procedure 1, Step H)

[0816] The procedure was similar to the synthesis of Compound 390. ^{1}H NMR (CHLOROFORM-d) δ 7.95 (s, 1H), 7.75 (t, J=7.8 Hz, 1H), 7.39-7.45 (m, 1H), 7.32-7.37 (m, 1H), 6.82-6.96 (m, 1H), 6.31 (dd, J=17.6, 1.3 Hz, 1H), 5.49-5.59 (m, 1H), 4.58 (d, J=12.8 Hz, 1H), 4.45 (d, J=12.5 Hz, 1H), 4.19 (br. s., 0.5H), 4.06 (br. s., 0.5H), 3.78 (br. s., 0.5H), 3.60 (br. s., 0.5H), 3.28 (br. s., 2H), 3.11 (br. s., 1H), 2.29-2.39 (m, 1H), 1.67-1.79 (m, 1H), 1.32-1.45 (m, 1H), 1.18-1.25 (m, 2H), 0.96-1.12 (m, 4H), 0.74-0.87 (m, 2H), 0.65 (br. s., 1H), 0.35-0.58 (m, 3H). LC-MS: m/z 440.6 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(imidazo[1,2-a]pyrazin-3-yl)nicotinonitrile (Compound 503; General procedure 1, Step I)

[0817] ^{1}H NMR (400 MHz, $CDCl_3$) δ=9.20 (s, 1H), 7.89 (dd, J=25.5, 17.4 Hz, 3H), 7.73 (s, 1H), 4.66 (d, J=12.8 Hz,

1H), 4.53 (d, J=12.8 Hz, 1H), 3.49 (s, 4H), 3.36-3.10 (m, 2H), 2.15-1.83 (m, 3H), 1.53 (m, 1H), 1.08-0.95 (m, 4H), 0.84 (m, 3H), 0.61-0.40 (m, 3H). LC-MS: m/z 454.1 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2,3-dioxoindolin-5-yl) nicotinonitrile (Compound 504; General procedure 1, Step I)

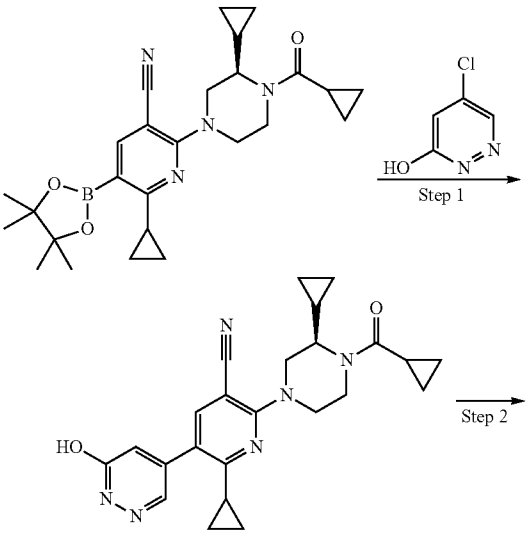
[0818] ^1H NMR (400 MHz, $CDCl_3$) δ=8.38 (s, 1H), 7.68 (d, J=1.8 Hz, 1H), 7.64-7.57 (m, 2H), 7.04 (d, J=8.4 Hz, 1H), 5.48-5.23 (m, 1H), 4.98 (m, 1H), 3.38-3.05 (m, 2H), 2.14-1.88 (m, 4H), 1.01 (dd, J=7.9, 3.4 Hz, 3H), 0.90 (dd, J=9.0, 4.7 Hz, 5H), 0.86-0.77 (m, 3H), 0.57-0.40 (m, 3H). LC-MS: m/z 482.2 $(M+H)^+$

5-(4-acryloylmorpholin-2-yl)-2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 600)

[0819] A mixture of 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(morpholin-2-yl) nicotinonitrile (13 mg, 0.03 mmol), acryloyl chloride (1 drop) and TEA (1 drop) in 10 mL of DCM was stirred at r.t. for 10 mins. After the mixture was quenched and worked up, the filtrate was concentrated and the residue was purified by column chromatography (50% PE/EA) to afford 11 mg of title compound. ^1H NMR (CHLOROFORM-d) δ 7.86 (s, 1H), 6.48-6.69 (m, 1H), 6.31-6.48 (m, 1H), 5.80 (d, J=9.3 Hz, 1H), 4.91 (d, J=13.1 Hz, 1H), 4.71 (d, J=8.8 Hz, 1H), 4.44-4.63 (m, 1.5H), 4.05-4.34 (m, 4H), 3.92 (d, J=12.5 Hz, 0.5H), 3.74 (d, J=9.8 Hz, 1.5H), 3.35-3.52 (m, 1.5H), 3.04-3.29 (m, 3H), 2.62 (t, J=11.3 Hz, 0.5H), 2.10 (br. s., 1H), 1.75 (br. s., 1H), 1.40 (br. s., 1.5H), 1.27 (br. s., 1.5H), 1.13 (br. s., 2H), 1.03 (br. s., 4H), 0.81 (d, J=7.0 Hz, 2H). LC-MS: m/z 450.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(6-vinylpyridazin-4-yl) nicotinonitrile (Compound 613)

[0820]



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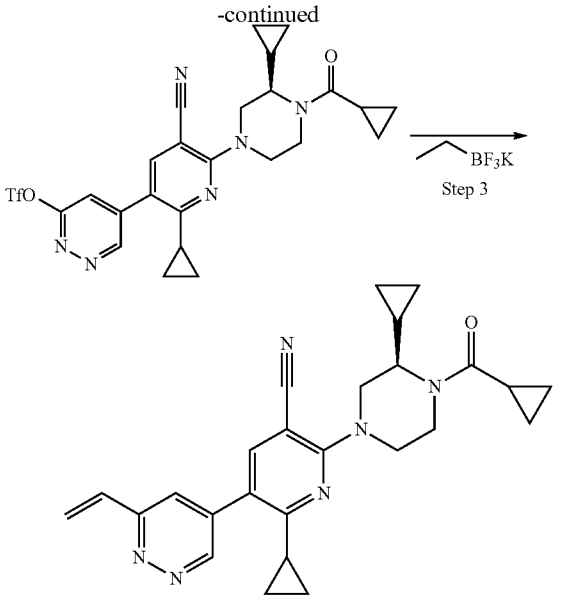


Step 1

[0821] A mixture of 8-4 (50 mg, 0.11 mmol), 5-chloropyridazin-3-ol (21 mg, 0.16 mmol), CsF (33 mg, 0.22 mmol) and $Pd(dppf)Cl_2$(5 mg) in dioxane and water was heated at 100° C. for 1 hr. The reaction mixture was concentrated and the residue was purified by pre-TLC to afford 35 mg of title compound. ^1H NMR (CHLOROFORM-d) δ 12.68 (br. s., 1H), 7.97 (s, 1H), 7.65 (s, 1H), 7.02 (br. s., 1H), 4.51-4.64 (m, 2.5H), 4.21 (br. s., 1H), 3.56-3.84 (m, 1H), 3.17-3.32 (m, 2.5H), 1.99 (br. s., 1H), 1.71 (br. s., 1H), 1.24 (br. s., 3H), 1.01-1.08 (m, 4H), 0.72-0.92 (m, 2H), 0.32-0.64 (m, 4H). LC-MS: m/z 431.1 $(M+H)^+$

Step 2

[0822] A solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(6-hydroxypyridazin-4-yl)nicotinonitrile, Tf_2O and TEA in DCM was stirred for 1 hr. The reaction mixture was washed with water, dried and concentrated. The residue was purified by pre-TLC to afford 150 mg of title compound. ^1H NMR (CHLOROFORM-d, 400 MHz) δ 9.42 (br. s., 1H), 7.72 (s, 1H), 7.52 (s, 1H), 4.58-4.75 (m, 2.5H), 4.32 (br. s., 0.5H), 4.00 (br. s., 0.5H), 3.73 (br. s., 1H), 3.25-3.39 (m, 2.5H), 1.89-1.94 (m, 1H), 1.72 (br. s., 1H), 1.31 (br. s., 3H), 1.00-1.18 (m, 4H), 0.84 (d, J=6.3 Hz, 2H), 0.45-0.66 (m, 4H).

Step 3

[0823] A mixture of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(6-vinylpyridazin-4-yl)nicotinonitrile (50 mg, 0.09 mmol), potassium vinyltrifluoroborate (24 mg, 0.18 mmol), TEA(27 mg, 0.27 mmol) and $Pd(dppf)Cl_2$(5 mg) in i-PrOH and water was heated at 100° C. for 1 hr. The reaction mixture was concentrated and the residue was purified by pre-TLC to afford 11 mg of title compound. ^1H NMR (CHLOROFORM-d) δ 9.20 (br. s., 1H), 7.68 (br. s., 1H), 7.61 (br. s., 1H), 7.04-7.22 (m, 1H), 6.36 (d, J=17.6 Hz, 1H), 5.78 (d, J=10.8 Hz, 1H), 4.53-4.58 (m, 2.5H), 4.17 (br. s., 1H), 3.72 (br. s., 1H), 3.19-3.34

(m, 1H), 1.94 (br. s., 1H), 1.80 (br. s., 1H), 1.26 (br. s., 3H), 1.07 (br. s., 4H), 0.82 (br. s., 2H), 0.46-0.65 (m, 4H). LC-MS: m/z 441.2 $(M+H)^+$

(R)-5-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)pyridazin-3-yl trifluoromethanesulfonate (Compound 614):

[0824] ^{1}H NMR (CHLOROFORM-d) δ 9.41 (s, 1H), 7.71 (s, 1H), 7.50 (d, J=1.3 Hz, 1H), 4.93 (br. s., 0.5H), 4.56 (d, J=7.8 Hz, 0.5H), 4.47 (d, J=7.3 Hz, 1.5H), 4.25-4.40 (m, 1H), 3.86 (d, J=12.5 Hz, 0.5H), 3.76 (br. s., 2H), 3.57 (br. s., 0.5H), 3.36-3.48 (m, 4H), 3.30 (br. s., 0.5H), 3.11-3.24 (m, 1H), 2.71 (br. s., 1H), 2.61 (br. s., 1H), 1.89-1.93 (m, 1H), 1.37 (d, J=5.5 Hz, 1.5H), 1.22-1.32 (m, 3.5H), 1.08-1.22 (m, 2H). LC-MS: m/z 555.1 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(6-vinylpyridazin-4-yl)nicotinonitrile (Compound 615)

[0825] The procedure is similar to Compound 613. ^{1}H NMR (CHLOROFORM-d) δ 9.20 (br. s., 1H), 7.67 (s, 1H), 7.58-7.65 (m, 1H), 7.13 (dd, J=17.8, 11.0 Hz, 1H), 6.37 (d, J=17.8 Hz, 1H), 5.79 (d, J=11.0 Hz, 1H), 4.92 (br. s., 0.5H), 4.48-4.62 (m, 0.5H), 4.35-4.48 (m, 1.5H), 4.31 (d, J=14.1 Hz, 1H), 3.83 (d, J=13.3 Hz, 0.5H), 3.67-3.80 (m, 2H), 3.51-3.63 (m, 0.5H), 3.30-3.45 (m, 4H), 3.13-3.28 (m, 1.5H), 2.65-2.82 (m, 1H), 2.51-2.65 (m, 1H), 1.92-1.96 (m, 1H), 1.38 (d, J=5.5 Hz, 1.5H), 1.24-1.27 (m, 3.5H), 1.07 (d, J=4.8 Hz, 2H). LC-MS: m/z 433.1 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(6-hydroxypyridazin-4-yl)nicotinonitrile (Compound 616)

[0826] ^{1}H NMR (CHLOROFORM-d) δ 12.68 (br. s., 1H), 7.97 (s, 1H), 7.65 (s, 1H), 7.02 (br. s., 1H), 4.51-4.64 (m, 2.5H), 4.21 (br. s., 1H), 3.56-3.84 (m, 1H), 3.17-3.32 (m, 2.5H), 1.99 (br. s., 1H), 1.71 (br. s., 1H), 1.24 (br. s., 3H), 1.01-1.08 (m, 4H), 0.72-0.92 (m, 2H), 0.32-0.64 (m, 4H). LC-MS: m/z 431.1 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-methyl-6-oxo-1,6-dihydropyridazin-4-yl)nicotinonitrile (Compound 640)

[0827] ^{1}H NMR (CHLOROFORM-d) δ 7.85 (br. s., 1H), 7.60 (br. s., 1H), 6.95 (br. s., 1H), 4.50-4.63 (m, 2.5H), 4.21 (br. s., 1H), 3.84 (br. s., 3H), 3.69 (br. s., 1H), 3.17-3.30 (m, 2.5H), 1.99 (br. s., 1H), 1.76 (br. s., 1H), 1.22 (br. s., 3H), 1.07 (br. s., 4H), 0.81 (br. s., 2H), 0.51 (br. s., 4H). LC-MS: m/z 445.2 $(M+H)^+$

(R)-5-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl) pyridazine-3-carbonitrile (Compound 641)

[0828] ^{1}H NMR (CHLOROFORM-d) δ 9.51 (d, J=2.3 Hz, 1H), 7.93 (d, J=2.3 Hz, 1H), 7.70 (s, 1H), 4.59-4.72 (m, 2.5H), 4.09-4.26 (m, 1H), 3.75 (br. s., 1H), 3.23-3.39 (m, 2.5H), 1.82-1.95 (m, 1H), 1.65 (br. s., 1H), 1.26-1.34 (m, 3H), 0.96-1.20 (m, 4H), 0.76-0.91 (m, 2H), 0.38-0.75 (m, 4H). LC-MS: m/z 440.2 $(M+H)^+$

(R)-2-(4-acetyl-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 516; General procedure 4, Step R and S)

[0829] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (s, 1H), 8.54 (d, J=5.8 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.64-7.74 (m, 3H), 7.43 (t, J=5.9 Hz, 1H), 4.91 (br. s., 0.5H), 4.57-4.53 (d, 0.5H), 4.18-4.39 (m, 2.5H), 3.6-3.77 (m, 1H), 3.34 (br. s., 1H), 3.05-3.25 (m, 1.5H), 1.91 (br. s., 3H), 1.33-1.54 (m, 4H), 1.14-1.17 (m, 2H), 0.82-0.85 (m, 2H). LC-MS: m/z 412.2 $(M+H)^+$

6-cyclopropyl-2((R)-4((1S,2R)-2-ethoxycyclopropanecarbonyl)-3-methylpiperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 517; General procedure 4, Step R and S)

[0830] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (s, 1H), 8.54 (d, J=5.8 Hz, 1H), 8.06 (d, J=8.0 Hz, 1H), 7.59-7.76 (m, 3H), 7.44 (t, J=6.8 Hz, 1H), 4.87-5.02 (m, 0.5H), 4.61-4.64 (m, 0.5H), 4.12-4.43 (m, 2.5), 3.05-3.70 (m, 5.5H), 2.0 (s, 1H), 1.76-1.86 (m, 1H), 1.40-1.62 (m, 3H), 1.27-1.35 (m, 2H), 1.16-1.21 (m, 4H), 0.92-0.99 (m, 1H), 0.81-0.84 (m, 2H). LC-MS: m/z 482.2 $(M+H)^+$

6-cyclopropyl-2-((R)-3-cyclopropyl-4-((1S,2S)-2-ethoxycyclopropanecarbonyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 518; General procedure 4, Step R and S)

[0831] 1H NMR (CHLOROFORM-d) δ 9.37 (s, 1H), 8.54 (dd, J=6.0, 2.0 Hz, 1H), 8.08 (d, J=8.0 Hz, 1H), 7.73 (t, 1H), 7.64-7.69 (m, 2H), 7.46 (q, 1H), 4.73 (m, 0.5H), 4.43-4.62 (m, 2.5H), 4.13-4.26 (m, 2H), 3.68-3.87 (m, 1.5H), 3.50-3.60 (m, 3.5H), 3.19-3.30 (s, 2H), 1.97-2.19 (m, 2H), 1.50-1.54 (m, 1H), 1.16-1.23 (m, 6H), 0.82-0.91 (m, 5H), 0.64-0.68 (m, 2H), 0.43-0.51 (m, 2H). LC-MS: m/z 508.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(4-oxobutanoyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 519; General procedure 4, Step R and S)

[0832] ^{1}H NMR (CHLOROFORM-d) δ 9.91 (s, 1H), 9.38 (s, 1H), 8.55 (br. s., 1H), 8.09 (d, J=8.0 Hz, 1H), 7.74 (t, 1H), 7.66-7.70 (m, 2H), 7.47 (q, 1H), 4.55-4.58 (d, 1H), 4.44-4.47 (d, 1H), 4.09 (br. s., 1H), 3.90 (br. s., 1H), 3.07-3.40 (m, 2.5H), 2.69-2.91 (m, 3.5H), 2.05 (m, 2H), 14.53 (m, 1H), 0.83-0.92 (m, 6H), 0.44-0.71 (br. s., 4H). LC-MS: m/z 480.2 $(M+H)^+$

6-cyclopropyl-2-((R)-3-cyclopropyl-4-((1S,2R)-2-ethoxycyclopropanecarbonyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 526; General procedure 4, Step R and S)

[0833] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (br. s., 1H), 8.53 (br. s., 1H), 8.07 (d, J=8.0 Hz, 1H), 7.68-7.74 (t, 1H), 7.64-7.67 (m, 2H), 7.45 (dd, J=5.8 Hz, 1H), 4.58 (d, J=12.8 Hz, 1H), 4.49 (d, J=11.3 Hz, 1H), 4.13-4.27 (m, 1.5H), 3.80 (br. s., 0.5H), 3.52-3.59 (m, 3H), 3.22 (br. s., 2H), 1.82 (d, J=7.5 Hz, 1H), 1.47-1.57 (m, 2H), 1.17-1.20 (m, 6H), 0.82-0.99 (m, 5H), 0.45-0.65 (m, 4H). LC-MS: m/z 508.3 $(M+H)^+$

6-cyclopropyl-2-((R)-4-((1R,2R)-2-(hydroxymethyl) cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 505; General procedure 4, Step R and S)

[0834] ^{1}H NMR (CHLOROFORM-d) δ 9.39 (br. s., 1H), 8.56 (br. s., 1H), 8.08 (d, J=8.0 Hz, 1H), 7.71-7.76 (m, 1H), 7.66-7.70 (m, 1H), 7.64 (s, 1H), 7.47 (br. s., 1H), 4.18-4.89 (m, 4H), 3.25-3.80 (m, 5H), 2.01-2.08 (m, 1H), 1.46-1.57 (m, 2H), 1.24-1.39 (m, 4H), 1.10-1.20 (m, 2H), 0.79-0.91 (m, 3H). LC-MS: m/z 468.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(quinoxalin-5-yl)nicotinonitrile (Compound 531; General procedure 1, Step I)

[0835] ^{1}H NMR (CHLOROFORM-d) δ 8.88 (d, J=1.8 Hz, 1H), 8.91 (d, J=1.5 Hz, 1H), 8.21 (dd, J=8.4, 1.4 Hz, 1H), 7.88 (t, J=8.4, 7.2 Hz, 1H), 7.79 (dd, J=7.2, 1.4 Hz, 1H), 7.73 (s, 1H), 4.53 (d, 1H), 4.56 (d, 1H), 4.53-4.27 (m, 2.5H), 3.05-3.45 (m, 2.5H), 1.74 (br. s., 1H), 1.56-1.65 (m, 1H), 0.97-1.26 (m, 6H), 0.42-0.87 (m, 8H). LC-MS: m/z 465.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(quinoxalin-5-yl)nicotinonitrile (Compound 532; General procedure 1, Step I)

[0836] ^{1}H NMR (CHLOROFORM-d) δ 8.89-8.92 (m, 2H), 8.22 (dd, J=8.4, 1.4 Hz, 1H), 7.89 (t, J=8.3, 7.3 Hz, 1H), 7.79-7.81 (dd, J=8.3, 7.3 Hz, 1H), 7.75 (s, 1H), 4.53 (d, J=13.1 Hz, 1H), 4.44 (d, J=12.0 Hz, 1H), 4.14 (br. s., 0.5H), 3.75-3.89 (m, 1.5H), 3.07-3.37 (m, 5H), 1.62 (m, 1H), 1.19 (br. s., 2H), 0.48-0.84 (m, 6H). LC-MS: m/z 507.3 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinoxalin-5-yl) nicotinonitrile (Compound 579; General procedure 1, Step I)

[0837] ^{1}H NMR (CHLOROFORM-d) δ 9.00 (s, 1H), 8.13 (dd, J=8.5, 1.3 Hz, 1H), 7.84 (dd, J=8.3, 7.3 Hz, 1H), 7.67-7.74 (m, 1H), 7.01-7.12 (m, 1H), 6.50 (d, J=11.3 Hz, 1H), 5.84 (d, J=11.3 Hz, 1H), 4.92 (br. s., 0.5H), 4.57 (br. s., 0.5H), 4.19-4.40 (m, 2.5H), 3.68-3.78 (m, 2.5H), 3.58 (br. s., 0.5H), 3.39 (s, 3H), 3.02-3.31 (m, 2.5H), 2.58-2.75 (m, 2H), 1.86 (br. s., 1H), 1.62 (m, 1H), 1.43 (d, J=6.3 Hz, 1.5H), 1.33 (d, J=6.3 Hz, 1.5H), 1.16 (br. s., 2H), 0.81 (br. s., 2H). LC-MS: m/z 485.2 $(M+H)^+$

(R,E)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-(2-(2-vinylquinoxalin-5-yl)vinyl)quinoxalin-5-yl)nicotinonitrile (Compound 604)

[0838] It was obtained as the by-product of Compound 579. ^{1}H NMR (CHLOROFORM-d) δ 9.23 (s, 1H), 9.09 (s, 1H), 8.17-8.20 (m, 2H), 8.08 (d, J=8.5 Hz, 1H), 7.70-7.87 (m, 5H), 7.04-7.11 (q, 1H), 6.53 (d, J=11.3 Hz, 1H), 5.85 (d, J=11.3 Hz, 1H), 4.94 (br. s., 0.5H), 4.56 (d, J=12.8 Hz, 0.5H), 4.26-4.37 (m, 2.5H), 3.75-3.84 (m, 2.5H), 3.59 (t, 0.5H), 3.40 (s, 3H), 3.06-3.32 (m, 2.5H), 2.59-2.81 (m, 2H), 1.61-1.73 (m, 1H), 1.45 (d, J=6.3 Hz, 1.5H), 1.32 (d, J=6.3 Hz, 1.5H), 1.25-1.29 (m, 2H), 0.83-0.86 (m, 2H). LC-MS: m/z 637.3 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinylquinoxalin-5-yl) nicotinonitrile (Compound 605; General procedure 1, Step I)

[0839] ^{1}H NMR (CHLOROFORM-d) δ 9.00 (s, 1H), 8.13 (d, J=8.5 Hz, 1H), 7.83 (t, J=7.8 Hz, 1H), 7.62-7.77 (m, 2H), 6.97-7.13 (q, 1H), 6.50 (d, J=11.0 Hz, 1H), 5.84 (d, J=11.0 Hz, 1H), 4.58-4.73 (m, 1.5H), 4.39-4.48 (m, 1.5H), 3.87 (d, J=13.3 Hz, 0.5H), 3.74 (m, 2H), 3.42-3.60 (m, 1H), 3.39 (d, J=3.3 Hz, 3H), 2.93-3.17 (m, 2.5H), 2.53-2.83 (m, 2H), 2.16-2.33 (m, 1H), 1.62 (br. s., 1H), 1.07-1.10 (m, 4H), 0.82-0.93 (m, 6H). LC-MS: m/z 511.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinoxalin-5-yl) nicotinonitrile (Compound 618; General procedure 1, Step I)

[0840] ^{1}H NMR (CHLOROFORM-d) δ 9.00 (s, 1H), 8.13 (dd, J=8.5, 1.3 Hz, 1H), 7.84 (dd, J=8.3, 7.3 Hz, 1H), 7.67-7.74 (m, 2H), 7.02-7.07 (m, 1H), 6.50 (d, J=11.3 Hz, 1H), 5.82 (d, J=11.3 Hz, 1H), 4.92 (br. s., 0.5H), 4.57 (br. s., 0.5H), 4.19-4.33 (m, 3H), 3.93 (s, 2.5H), 3.58 (br. s., 0.5H), 3.01-3.48 (m, 4H), 2.48-2.75 (m, 3H), 1.63 (m, 1H), 1.43 (d, J=6.3 Hz, 1.5H), 1.35 (d, J=6.3 Hz, 1.5H), 1.16 (br. s., 2H), 0.82 (br. s., 2H). LC-MS: m/z 469.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinylquinoxalin-5-yl)nicotinonitrile (Compound 644; General procedure 1, Step I)

[0841] ^{1}H NMR (CHLOROFORM-d) δ 9.00 (s, 1H), 8.13 (dd, J=8.5, 1.3 Hz, 1H), 7.70-7.72 (m, 2H), 7.01-7.12 (q, 1H), 6.50 (d, J=11.3 Hz, 1H), 5.84 (d, J=11.3 Hz, 1H), 4.71 (br. s., 0.5H), 4.52 (d, 1H), 4.41 (d, 1H), 4.12 (br. s., 0.5H), 3.89 (br. s., 0.5H), 3.74 (m, 2H), 3.39 (s, 3H), 3.01-3.31 (m, 3H), 2.59-2.83 (m, 2H), 1.58-1.68 (m, 1H), 0.97-1.32 (m, 4H), 0.46-0.89 (m, 7H). LC-MS: m/z 509.1 $(M+H)^+$

(R)-2'-bromo-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-3,4'-bipyridine-5-carbonitrile (Compound 508; General procedure 1, Step H)

[0842] ^{1}H NMR CHLOROFORM-d) δ 8.46 (d, J=5.0 Hz, 1H), 7.63 (s, 1H), 7.57-7.61 (m, 1H), 7.34 (dd, J=5.0, 1.5 Hz, 1H), 4.61 (d, J=12.8 Hz, 1H), 4.49 (d, J=13.6 Hz, 1H), 4.18-4.38 (m, 1H), 3.76 (br. s., 2H), 3.31 (br. s., 1H), 3.15 (br. s., 1H), 1.93-2.08 (m, 1H), 1.72 (br. s., 1H), 1.33 (br. s., 1H), 1.17-1.26 (m, 2H), 0.95-1.12 (m, 4H), 0.76-0.91 (m, 2H), 0.66 (br. s., 1H), 0.35-0.60 (m, 3H). LC-MS: m/z 493.4 $(M+H)^+$

(R)-2'-chloro-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-3'-fluoro-3,4'-bipyridine-5-carbonitrile (Compound 509; General procedure 1, Step H)

[0843] ^{1}H NMR (CHLOROFORM-d) δ 8.29 (d, J=5.0 Hz, 1H), 7.59-7.75 (s, 1H), 7.11-7.41 (d, J=5.0 Hz, 1H), 4.63 (d, J=13.1 Hz, 1H), 4.50 (d, J=12.5 Hz, 1H), 4.06 (br. s., 1H), 3.75 (br. s., 1H), 3.65 (br. s., 1H), 3.31 (br. s., 1H), 3.16 (br. s., 1H), 1.70-1.81 (m, 1H), 1.30-1.42 (m, 1H), 1.13-1.25 (m, 2H), 0.94-1.13 (m, 4H), 0.75-0.87 (m, 2H), 0.66 (br. s., 1H), 0.35-0.60 (m, 3H). LC-MS: m/z 466.9 $(M+H)^+$

(R)-5-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl) isoquinoline-1-carbonitrile (Compound 511)

[0844] ^{1}H NMR (CHLOROFORM-d) δ 8.66 (dd, J=5.8, 1.8 Hz, 1H), 8.45 (d, J=8.3 Hz, 1H), 7.87-7.97 (m, 1H), 7.80 (ddd, J=7.2, 2.1, 1.0 Hz, 1H), 7.70 (ddd, J=11.1, 5.8, 0.9 Hz, 1H), 7.64 (d, J=0.8 Hz, 1H), 4.61 (d, J=12.0 Hz, 1H), 4.49 (d, J=12.8 Hz, 1H), 3.42-4.43 (m, 2H), 3.10-3.40 (m, 3H), 1.75 (br. s., 1H), 1.38-1.47 (m, 2H), 0.95-1.12 (m, 2H), 0.75-0.93 (m, 6H), 0.70 (br. s., 1H), 0.38-0.61 (m, 3H). LC-MS: m/z 489.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(1-hydroxyisoquinolin-5-yl)nicotinonitrile (Compound 547; General procedure 2, Step M)

[0845] ^{1}H NMR (CHLOROFORM-d) δ 10.95 (s, 1H), 8.53 (dd, J=6.4, 3.1 Hz, 1H), 7.57-7.72 (m, 3H), 7.17 (br. s., 1H), 6.31 (dd, J=12.9, 7.4 Hz, 1H), 4.38-4.61 (m, 2H), 4.15 (br. s., 0.5H), 3.69-3.95 (m, 1.5H), 3.03-3.41 (m, 5H), 1.53-1.77 (m, 3H), 1.16 (dd, J=8.3, 4.5 Hz, 2H), 0.81-0.98 (m, 2H), 0.47-0.64 (m, 3H). LC-MS: m/z 522.2 $(M+H)^+$

(R)-5-(3-chloroisoquinolin-5-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 555; General procedure 1, Step H)

[0846] ^{1}H NMR (CHLOROFORM-d) δ 9.17 (s, 1H), 8.06 (d, J=7.5 Hz, 1H), 7.66-7.73 (m, 2H), 7.64 (d, J=1.0 Hz, 1H), 7.49 (d, J=14.8 Hz, 1H), 4.61 (d, J=12.0 Hz, 1H), 4.49 (d, J=12.8 Hz, 1H), 3.42-4.43 (m, 2H), 3.10-3.40 (m, 3H), 1.69 (br. s., 1H), 1.39-1.57 (m, 2H), 1.15-1.23 (m, 2H), 1.08 (br. s., 2H), 0.79-0.93 (m, 4H), 0.70 (br. s., 1H), 0.38-0.63 (m, 3H). LC-MS: m/z 498.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-hydroxyisoquinolin-5-yl)nicotinonitrile (Compound 566; General procedure 1, Step H)

[0847] ^{1}H NMR (CHLOROFORM-d) δ 11.20 (br. s., 1H), 8.52 (dd, J=7.0, 2.3 Hz, 1H), 7.51-7.76 (m, 3H), 7.12-7.24 (m, 1H), 6.33 (dd, J=12.7, 7.4 Hz, 1H), 4.56 (d, J=12.5 Hz, 1H), 4.44 (d, J=12.3 Hz, 1H), 3.52-4.35 (m, 2H), 3.05-3.45 (m, 3H), 1.63 (td, J=7.8, 4.0 Hz, 1H), 1.27-1.45 (m, 2H), 0.96-1.23 (m, 4H), 0.77-0.96 (m, 4H), 0.70 (br. s., 1H), 0.36-0.62 (m, 3H). LC-MS: m/z 480.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(3-vinylisoquinolin-5-yl)nicotinonitrile (Compound 565; General procedure 1, Step H)

[0848] ^{1}H NMR (CHLOROFORM-d) δ 9.29 (s, 1H), 8.03 (d, J=7.5 Hz, 1H), 7.55-7.77 (m, 3H), 7.31 (d, J=12.5 Hz, 1H), 6.88 (ddd, J=17.3, 10.6, 6.8 Hz, 1H), 6.38 (ddd, J=17.2, 5.6, 1.3 Hz, 1H), 5.44-5.59 (m, 1H), 4.59 (d, J=11.8 Hz, 1H), 4.47 (d, J=12.5 Hz, 1H), 3.55-4.35 (m, 2H), 3.05-3.45 (m, 3H), 1.68-1.80 (m, 1H), 1.42-1.61 (m, 2H), 1.22-1.34 (m, 2H), 1.00-1.14 (m, 2H), 0.76-0.92 (m, 4H), 0.71 (br. s., 1H), 0.39-0.63 (m, 3H). LC-MS: m/z 490.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-methylisoquinolin-5-yl) nicotinonitrile (Compound 588; General procedure 1, Step H)

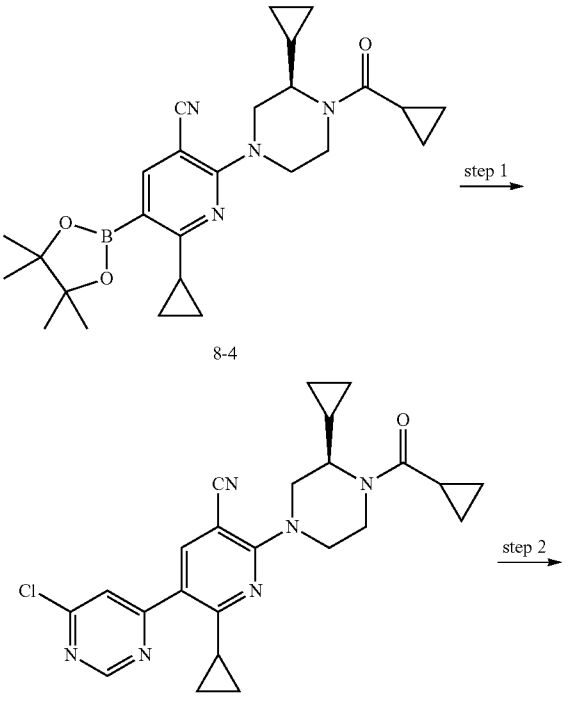
[0849] ^{1}H NMR (CHLOROFORM-d) δ 9.23 (s, 1H), 7.99 (d, J=7.3 Hz, 1H), 7.53-7.67 (m, 3H), 7.21 (d, J=6.5 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.1 Hz, 0.5H), 4.15-4.43 (m, 2.5H), 3.86-4.02 (m, 2H), 3.68-3.83 (m, 0.5H), 3.51-3.68 (m, 0.5H), 3.26-3.42 (m, 1H), 2.97-3.24 (m, 1.5H), 2.49-2.78 (m, 5H), 1.49-1.58 (m, 1H), 1.41-1.49 (m, 1.5H), 1.30-1.40 (m, 1.5H), 1.06-1.20 (m, 2H), 0.72-0.91 (m, 2H). LC-MS: m/z 456.2 $(M+H)^+$

(R)-5-(5-chloro-2-vinylpyrimidin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 533; General procedure 1, Step H)

[0850] 1H NMR (CHLOROFORM-d) δ 8.69-8.87 (m, 1H), 7.70-7.91 (m, 1H), 6.91 (dd, J=17.3, 10.5 Hz, 1H), 6.59-6.78 (m, 1H), 5.71-5.98 (m, 1H), 4.66 (d, J=12.8 Hz, 1H), 4.53 (d, J=12.5 Hz, 1H), 3.09-4.42 (m, 5H), 1.76-1.85 (m, 1H), 1.39-1.46 (m, 1H), 1.21-1.25 (m, 2H), 0.99-1.10 (m, 4H), 0.90 (t, J=6.9 Hz, 1H), 0.78-0.85 (m, 2H), 0.66 (br. s., 1H), 0.41-0.60 (m, 3H). LC-MS: m/z 475.2 $(M+H)^+$

Compound 541

[0851]



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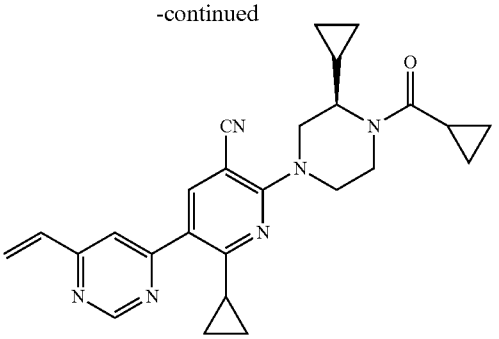
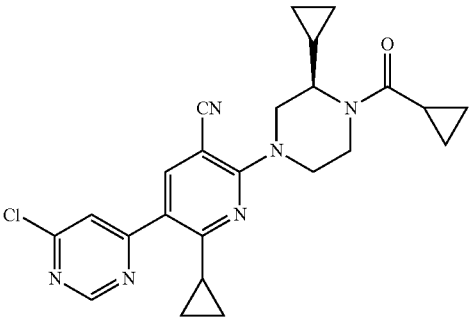


Step 1: (R)-5-(6-chloropyrimidin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile

[0852]



[0853] To a solution of 4,6-dichloropyrimidine (50 mg, 0.32 mmol) in a mixture of dimethoxyethane (3 mL) and a 2M aqueous sodium carbonate solution (0.6 mL) were added 8-4 (100 mg, 0.22 mmol) and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.1 eq) under nitrogen atmosphere, and the mixture was heated for 2 hours at 100° C. After cooling to ambient temperature, the separated organic layer was evaporated under reduced pressure. The residue was taken up into ethyl acetate, washed in turn with a 10% aqueous potassium carbonate solution and brine, and dried over sodium sulfate. After evaporation, the residue was purified on silica gel eluding with 5%-20% ethyl acetate in petroleum ether to give 4-chloro-6-phenylpyrimidine (75 mg), 69% yield. ^{1}H NMR (CHLOROFORM-d) δ 8.67-8.84 (m, 1H), 8.07 (s, 1H), 7.43 (d, J=5.0 Hz, 1H), 4.68 (d, J=13.1 Hz, 1H), 4.53 (d, J=13.3 Hz, 1H), 4.07 (br. s., 1H), 3.88 (s, 1H), 3.68 (br. s., 1H), 3.33 (br. s., 1H), 3.17 (br. s., 1H), 2.34-2.47 (m, 1H), 1.96-2.08 (m, 2H), 1.30-1.42 (m, 2H), 1.00-1.11 (m, 3H), 0.85-0.93 (m, 1H), 0.82 (dd, J=8.0, 2.5 Hz, 2H), 0.65 (br. s., 1H), 0.39-0.59 (m, 3H). LC-MS: m/z 449.2 (M+H)$^+$

Step 2: (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(6-vinylpyrimidin-4-yl)nicotinonitrile (Compound 541)

[0854] A mixture of above (R)-5-(6-chloropyrimidin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (60 mg, 0.06 mmol) (60 mg, 0.13 mmol), vinyl potassium-trifluoroborate (25 mg, 0.2 mmol), Pd(PPh3)4 (3 mg, 0.1 eq), and CsF (40 mg, 0.26 mmol) were suspended in 5 mL of dioxane and 1 mL of water, the resulting mixture was refluxed for 1 h. After the reaction was complete, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography to afford 35 mg of title compound as yellow solid. 75% yield. ^{1}H NMR (CHLOROFORM-d) δ 9.16-9.30 (m, 1H), 7.93-8.07 (m, 1H), 7.49-7.56 (m, 1H), 6.82 (dd, J=17.3, 10.5 Hz, 1H), 6.57 (dd, J=17.3, 1.0 Hz, 1H), 5.72-5.83 (m, 1H), 4.68 (d, J=13.1 Hz, 1H), 4.55 (d, J=12.3 Hz, 1H), 4.39-3.11 (br. s., 5H), 2.34-2.43 (m, 1H), 1.70 (br. s., 1H), 1.31-1.40 (m, 2H), 0.99-1.11 (m, 4H), 0.89-0.94 (m, 1H), 0.82 (dd, J=7.9, 2.4 Hz, 2H), 0.64 (br. s., 1H), 0.41-0.58 (m, 3H). LC-MS: m/z 441.2 (M+H)$^+$

(S)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(6-vinylpyrimidin-4-yl) nicotinonitrile (Compound 578)

[0855] ^{1}H NMR (CHLOROFORM-d) δ9.24 (d, J=1.3 Hz, 1H), 7.94-8.05 (m, 1H), 7.46-7.58 (m, 1H), 6.82 (dd, J=17.3, 10.8 Hz, 1H), 6.57 (dd, J=17.3, 1.0 Hz, 1H), 5.73-5.84 (m, 1H), 4.68 (d, J=12.5 Hz, 1H), 4.55 (d, J=12.3 Hz, 1H), 4.08 (br. s., 1H), 3.76 (s, 1H), 3.66 (t, J=6.7 Hz, 1H), 3.40-3.58 (m, 1H), 3.33 (br. s., 1H), 3.17 (br. s., 1H), 2.34-2.45 (m, 1H), 1.29-1.35 (m, 2H), 1.00-1.11 (m, 4H), 0.89-0.92 (m, 1H), 0.82 (dd, J=7.9, 2.4 Hz, 2H), 0.64 (br. s., 1H), 0.43-0.58 (m, 3H). LC-MS: m/z 441.2 (M+H)$^+$

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(6-vinylpyrimidin-4-yl) nicotinonitrile (Compound 621)

[0856] ^{1}H NMR (CHLOROFORM-d) δ 9.24 (d, J=1.3 Hz, 1H), 7.82-8.04 (m, 1H), 7.47-7.61 (m, 1H), 6.68-6.93 (m, 1H), 6.42-6.62 (m, 1H), 5.64-5.88 (m, 1H), 4.88 (br. s., 1H), 4.29-4.57 (m, 3H), 4.17 (br. s., 1H), 3.93 (br. s., 2H), 3.74 (d, J=13.3 Hz, 1H), 3.47-3.63 (m, 1H), 3.29-3.41 (m, 1H), 3.05-3.25 (m, 2H), 2.51-2.72 (m, 2H), 2.33-2.42 (m, 1H), 1.32-1.44 (m, 2H), 1.22-1.28 (m, 3H), 1.02-1.11 (m, 2H). LC-MS: m/z 419.2 (M+H)$^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(6-vinylpyrimidin-4-yl)nicotinonitrile (Compound 638)

[0857] ^{1}H NMR (CHLOROFORM-d) δ 9.24 (s, 1H), 7.95-8.11 (m, 1H), 7.50-7.56 (m, 1H), 6.74-6.87 (m, 1H), 6.48-6.65 (m, 1H), 5.74-5.89 (m, 1H), 4.67 (d, J=12.8 Hz, 1H), 4.53 (d, J=11.0 Hz, 1H), 4.10 (br. s., 0.5H), 3.83-3.93 (m, 0.5H), 3.61-3.81 (m, 3H), 3.39 (s, 3H), 3.21-3.35 (m, 2H), 3.08-3.21 (m, 1H), 2.72 (br. s., 1H), 2.65 (br. s., 1H), 2.33-2.43 (m, 1H), 1.21-1.36 (m, 3H), 1.03-1.13 (m, 2H), 0.60 (br. s., 2H), 0.45 (br. s., 2H). LC-MS: m/z 459.2 (M+H)$^+$

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(6-vinylpyrimidin-4-yl) nicotinonitrile (Compound 639)

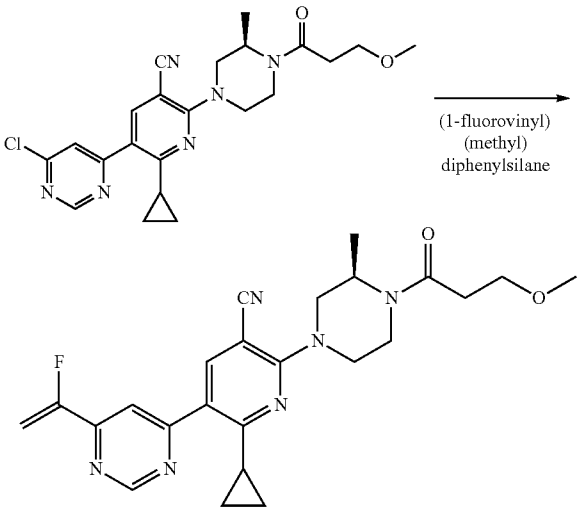
[0858] 1H NMR (CHLOROFORM-d) δ 9.09-9.32 (m, 1H), 7.99 (s, 1H), 7.51 (s, 1H), 6.81 (dd, J=17.3, 10.5 Hz, 1H), 6.56 (d, J=17.3 Hz, 1H), 5.78 (d, J=11.3 Hz, 1H), 4.67-4.76 (m, 1H), 4.50 (d, J=14.6 Hz, 1H), 3.88 (d, J=13.6 Hz, 1H), 3.68-3.79 (m, 2H), 3.60 (d, J=10.5 Hz, 1H), 3.39-3.55 (m, 1H), 3.02-3.24 (m, 2H), 2.85-3.02 (m, 1H), 2.52-2.82 (m, 2H), 2.33-2.43 (m, 1H), 1.92-2.05 (m, 1H), 1.23-1.31 (m, 2H), 1.00-1.10 (m, 5H), 0.83-0.92 (m, 3H). LC-MS: m/z 461.3 (M+H)$^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(6-vinylpyrimidin-4-yl) nicotinonitrile (Compound 597)

[0859] 1H NMR (CHLOROFORM-d) δ 9.22 (s, 1H), 7.98 (s, 1H), 7.50 (s, 1H), 6.80 (dd, J=17.3, 10.8 Hz, 1H), 6.44-6.69 (m, 1H), 5.64-5.92 (m, 1H), 4.89 (br. s., 0.5H), 4.52 (d, J=9.5 Hz, 0.5H), 4.28-4.46 (m, 2H), 3.65-3.95 (m, 3H), 3.44-3.65 (m, 1H), 3.27-3.44 (m, 4H), 3.00-3.27 (m, 2H), 2.51-2.81 (m, 2H), 2.25-2.47 (m, 1H), 1.14-1.44 (m, 5H), 0.93-1.14 (m, 2H). LC-MS: m/z 433.2 $(M+H)^+$

(R)-6-cyclopropyl-5-(6-(1-fluorovinyl)pyrimidin-4-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 602)

[0860]



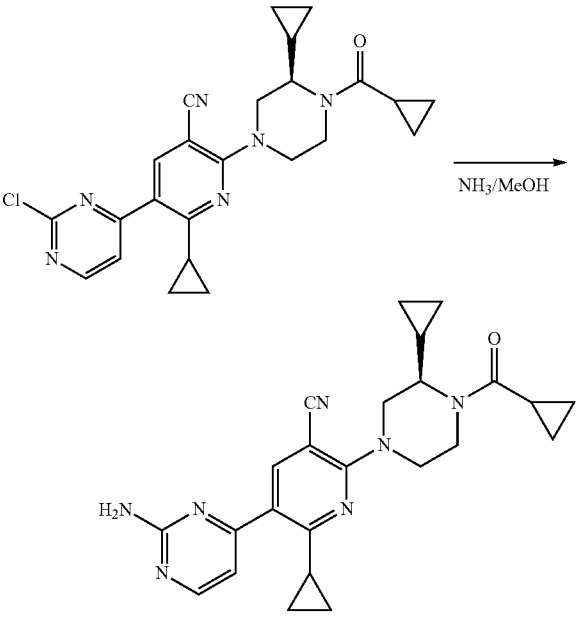
[0861] To a solution of (R)-5-(6-chloropyrimidin-4-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (80 mg 0.21 mmol), CuI (10 mg, 10%), and Pd(PPh3)2Cl2 (15 mg) in 5 ml of DMF was added (1-fluorovinyl)(methyl)diphenylsilane (7.6 mg, 0.41 mmol). The mixture was stirred at room temperature for 2 h under nitrogen atmosphere. After removal of the solvent under reduced pressure, the residue was purified by prep-TLC (20% ethyl acetate in petroleum ether) to afford 20 mg of pure product, 30% yield. ^{1}H NMR (CHLOROFORM-d) δ 9.25 (s, 1H), 8.04 (s, 1H), 7.76 (s, 1H), 6.11 (d, J=3.0 Hz, 1H), 5.99 (d, J=3.0 Hz, 1H), 5.27 (dd, J=15.8, 3.0 Hz, 1H), 4.91 (br. s., 1H), 4.54 (d, J=10.3 Hz, 1H), 4.31-4.49 (m, 1H), 3.71-3.78 (m, 1H), 3.49-3.63 (m, 1H), 3.31-3.44 (m, 4H), 3.16-3.28 (m, 1H), 3.13 (br. s., 1H), 2.51-2.81 (m, 2H), 2.30-2.44 (m, 1H), 1.35 (d, J=6.5 Hz, 2H), 1.25 (dd, J=4.3, 2.8 Hz, 3H), 1.04-1.13 (m, 2H). LC-MS: m/z 451.2 $(M+H)^+$

(R)-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-2% (prop-1-en-2-yl)-3, 4% bipyridine-5-carbonitrile (Compound 544)

[0862] Synthesized according to the procedure described for Compound 602 except using trimethyl(prop-1-en-2-yl) silane instead of (1-fluorovinyl)(methyl)diphenylsilane. ^{1}H NMR (CHLOROFORM-d) δ8.67 (d, J=5.0 Hz, 1H), 7.65 (s, 1H), 7.53 (s, 1H), 7.16-7.27 (m, 1H), 5.92 (s, 1H), 5.38 (s, 1H), 4.57 (d, J=12.3 Hz, 1H), 4.45 (d, J=12.3 Hz, 1H), 4.07 (br. s., 1H), 3.78 (br. s., 1H), 3.56-3.74 (m, 1H), 3.50 (s, 1H), 3.29 (br. s., 1H), 3.14 (br. s., 1H), 2.26 (s, 3H), 1.98-2.10 (m, 1H), 1.72 (br. s., 1H), 1.17-1.27 (m, 2H), 0.97-1.09 (m, 4H), 0.86-0.95 (m, 1H), 0.76-0.84 (m, 2H), 0.66 (br. s., 1H), 0.40-0.59 (m, 3H). LC-MS: m/z 453.2 $(M+H)^+$

(R)-5-(2-aminopyrimidin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 507)

[0863]



[0864] To a solution NH_3/MeOH (10 mL, 7 M) was added (R)-5-(2-chloropyrimidin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (40 mg, 0.09 mmol), the mixture was stirred at 50 C overnight. After removal of the solvent under reduced pressure, the residue was purified by prep-TLC (30% ethyl acetate in petroleum ether) to afford 21 mg of pure product, 51% yield. ^{1}H NMR (CHLOROFORM-d) δ 8.36 (d, J=5.3 Hz, 1H), 7.97 (s, 1H), 6.90 (d, J=5.0 Hz, 1H), 5.25 (br. s., 2H), 4.64 (d, J=12.5 Hz, 1H), 4.51 (d, J=12.3 Hz, 1H), 3.69 (br. s., 1H), 3.32 (br. s., 1H), 3.26 (br. s., 1H), 3.15 (br. s., 2H), 2.32-2.45 (m, 1H), 2.03-2.08 (m, 1H), 1.02-1.10 (m, 4H), 0.77-0.89 (m, 4H), 0.63 (br. s., 2H), 0.43-0.58 (m, 3H). LC-MS: m/z 430.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-(dimethylamino) pyrimidin-4-yl)nicotinonitrile (Compound 506)

[0865] Synthesized according to the procedure described for Compound 507 except using dimethylamine instead of NH_3.EtOH. ^{1}H NMR (CHLOROFORM-d) δ 8.38 (d, J=5.0 Hz, 1H), 7.90-8.06 (m, 1H), 6.72 (d, J=5.0 Hz, 1H), 4.61 (d, J=12.8 Hz, 1H), 4.49 (d, J=12.5 Hz, 1H), 4.09-4.26 (m, 1H), 3.30-3.58 (m, 2H), 3.26 (s, 6H), 3.16-3.24 (m, 1H), 3.11 (d, J=18.3 Hz, 1H), 2.48-2.56 (m, 1H), 1.19-1.24 (m, 3H), 0.98-

1.08 (m, 4H), 0.86-0.92 (m, 1H), 0.76-0.84 (m, 2H), 0.64 (br. s., 1H), 0.40-0.58 (m, 3H). LC-MS: m/z 458.3 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(2-(dimethylamino) pyrimidin-4-yl)nicotinonitrile (Compound 534)

[0866] 1H NMR (CHLOROFORM-d) δ8.37 (d, J=5.3 Hz, 1H), 7.97 (s, 1H), 6.89 (d, J=5.0 Hz, 1H), 4.63 (d, J=13.1 Hz, 1H), 4.51 (d, J=12.8 Hz, 1H), 4.00-4.17 (m, 1H), 3.68-3.87 (m, 1H), 3.17-3.38 (m, 3H), 3.12 (d, J=11.8 Hz, 1H), 2.82 (s, 2H), 2.33-2.45 (m, 1H), 1.35 (br. s., 1H), 1.18-1.25 (m, 2H), 0.98-1.10 (m, 2H), 0.64 (br. s., 1H), 0.57 (br. s., 1H), 0.38-0.54 (m, 2H). LC-MS: m/z 472.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-(2-hydroxyethylamino)pyrimidin-4-yl)nicotinonitrile (Compound 512)

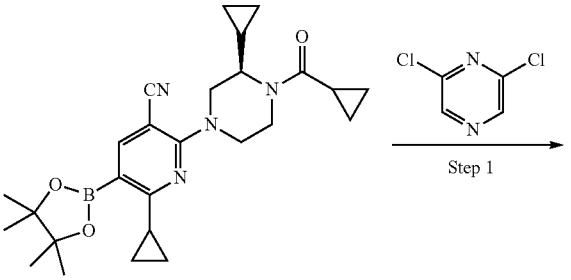
[0867] Synthesized according to the procedure described in Compound 507 except using 2-(methylamino)ethanol instead of NH_3.EtOH. ^{1}H NMR (CHLOROFORM-d) δ 8.32 (d, J=5.0 Hz, 1H), 7.94 (s, 1H), 6.83 (d, J=5.3 Hz, 1H), 5.91 (br. s., 1H), 4.63 (d, J=12.8 Hz, 1H), 4.50 (d, J=12.5 Hz, 1H), 3.96-4.33 (m, 1H), 3.82-3.92 (m, 2H), 3.63-3.72 (m, 2H), 3.29 (br. s., 1H), 3.14 (br. s., 1H), 2.68-2.78 (m, 1H), 2.66 (br. s., 1H), 2.34-2.44 (m, 1H), 1.20-1.35 (m, 4H), 1.04 (dd, J=7.7, 3.4 Hz, 4H), 0.77-0.90 (m, 3H), 0.64 (br. s., 1H), 0.49-0.55 (m, 1H), 0.44 (dt, J=9.3, 4.4 Hz, 1H). LC-MS: m/z 474.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(2-(dimethylamino) pyrimidin-4-yl)nicotinonitrile (Compound 521)

[0868] 1H NMR (CHLOROFORM-d) δ 8.42 (d, J=5.3 Hz, 1H), 8.00 (s, 1H), 6.75 (d, J=5.3 Hz, 1H), 4.62 (d, J=13.1 Hz, 1H), 4.50 (d, J=12.8 Hz, 1H), 3.96-4.20 (m, 1H), 3.68-3.96 (m, 1H), 3.28-3.42 (m, 2H), 3.09-3.15 (m, 1H), 2.42-2.54 (m, 1H), 1.39-1.56 (m, 1H), 1.14-1.25 (m, 2H), 0.98-1.08 (m, 2H), 0.65 (br. s., 1H), 0.56 (br. s., 1H), 0.43-0.53 (m, 2H). LC-MS: m/z 500.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(6-vinylpyrazin-2-yl) nicotinonitrile (Compound 515)

[0869]



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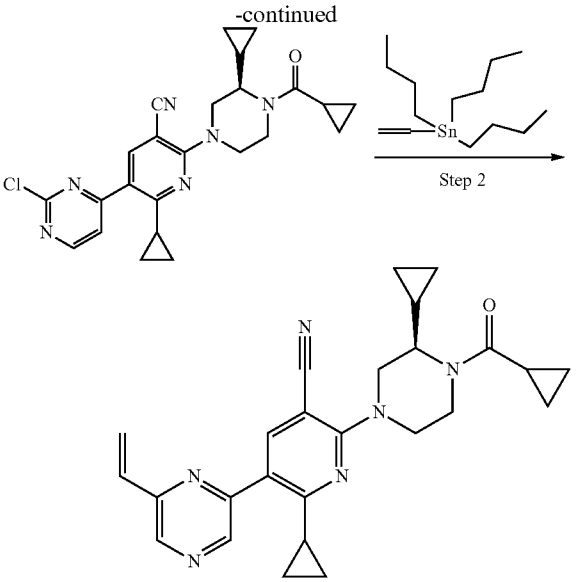


Step 1

[0870] To a flask was added with (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (70 mg, 0.151 mmol), 2,6-dichloropyrazine (30 mg, 0.197 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), K_2CO_3 (63 mg, 0.453 mmol), and 1.5 mL DMF. The mixture was stirred at 120° C. for 2 h. After washing with Satd. NaHCO3, brine, the combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Prep-TLC purification (20% EtOAc/petroleum ether) afforded 25 mg of(R)-5-(6-chloropyrazin-2-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile.

Step 2

[0871] To a flask was added with (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(6-vinylpyrazin-2-yl)nicotinonitrile (18 mg 0.04 mmol), tributyl(vinyl)stannane (17 mg, 0.052 mmol), $Pd(PPh_3)_4$(5 mg, 0.004 mmol), K_2CO_3 (14 mg, 0.052 mmol), and 1.5 mL DMF. The mixture was stirred at 120° C. for 2 h. After washing with Satd. $NaHCO_3$, brine, the combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Prep-TLC purification (20% EtOAc/petroleum ether) afforded 10 mg of title compound. ^{1}H NMR (CHLOROFORM-d) δ 8.72 (s, 1H), 8.56 (s, 1H), 8.00 (s, 1H), 6.90 (dd, J=17.3, 10.8 Hz, 1H), 6.47 (dd, J=17.6, 1.0 Hz, 1H), 5.70 (dd, J=10.8, 1.0 Hz, 1H), 4.65 (d, J=13.1 Hz, 1H), 4.52 (d, J=12.8 Hz, 1H), 3.99-4.29 (m, 1H), 3.52-3.91 (m, 1H), 3.32 (br. s., 1H), 3.16 (br. s., 1H), 2.22-2.35 (m, 1H), 1.23-1.38 (m, 5H), 0.97-1.14 (m, 4H), 0.81 (dd, J=7.8, 2.3 Hz, 2H), 0.65 (br. s., 1H), 0.48-0.55 (m, 1H), 0.45 (dt, J=9.6, 4.6 Hz, 1H).

[0872] LC-MS: m/z 441.2 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 530; General procedure 5, Step W)

[0873] 1H NMR (CHLOROFORM-d) δ 8.61 (d, J=5.0 Hz, 1H), 7.55-7.68 (m, 1H), 7.36 (s, 1H), 7.21 (dd, J=10, 1.5 Hz,

1H), 6.84 (dd, J=17.6, 10.8 Hz, 1H), 6.17-6.35 (m, 1H), 5.53 (dd, J=10.8, 0.8 Hz, 1H), 4.53 (d, J=12.5 Hz, 1H), 4.32-4.47 (m, 1H), 4.01-4.16 (m, 0.5H), 3.86 (d, J=12.5 Hz, 0.5H), 3.70 (t, J=5.5 Hz, 3H), 3.35 (s, 3H), 3.18 (d, J=11.3 Hz, 2H), 2.94-3.14 (m, 1H), 2.56-2.73 (m, 2H), 1.90-2.10 (m, 1H), 1.22-1.34 (m, 1H), 1.14-1.32 (m, 2H), 0.83-1.06 (m, 2H), 0.58 (br. s., 1H), 0.52 (br. s., 1H), 0.28-0.48 (m, 2H). LC-MS: m/z 458.2 $(M+H)^+$

(R)-6-(4-acetyl-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 562; General procedure 5, Step W)

[0874] 1H NMR (CHLOROFORM-d) δ 8.66 (d, J=4.5 Hz, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 7.24 (d, J=4.0 Hz, 1H), 6.88 (dd, J=17.3, 10.8 Hz, 1H), 6.28 (d, J=17.3 Hz, 1H), 5.57 (d, J=10.8 Hz, 1H), 4.65 (br. s., 0.5H), 4.55 (d, J=12.5 Hz, 1H), 4.43 (d, J=12.0 Hz, 1H), 4.08 (br. s., 0.5H), 3.77 (br. s., 1H), 3.21 (br. s., 2H), 3.11 (br. s., 1H), 2.17 (br. s., 2H), 2.11 (br. s., 1H), 2.03 (br. s., 1H), 1.28 (d, J=12.0 Hz, 2H), 1.24-1.50 (br. s., 3H), 0.60 (br. s., 2H), 0.45 (br. s., 2H). LC-MS: m/z 414.3 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3-hydroxy-3-methylbutanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 561; General procedure 5, Step W)

[0875] 1H NMR (CHLOROFORM-d) δ 8.66 (d, J=5.0 Hz, 1H), 7.66 (s, 1H), 7.39 (s, 1H), 7.24 (d, J=4.0 Hz, 1H), 6.88 (dd, J=17.6, 10.8 Hz, 1H), 6.28 (d, J=17.6 Hz, 1H), 5.57 (d, J=10.8 Hz, 1H), 5.16 (br. s., 1H), 4.56 (d, J=13.1 Hz, 1H), 4.43 (d, J=12.5 Hz, 1H), 4.14 (d, J=8.8 Hz, 0.5H), 3.65-3.78 (m, 1H), 3.17-3.91 (m, 1.5H), 3.04-3.14 (m, 1H), 2.43-2.57 (m, 2H), 2.02-2.07 (m, 1H), 1.33 (s, 6H), 1.25-1.30 (m, 2H), 1.21 (br. s., 2H), 1.02 (dd, J=7.5, 3.3 Hz, 2H), 0.65 (d, J=6.5 Hz, 1H), 0.42-0.53 (m, 2H). LC-MS: m/z 472.3 $(M+H)^+$

(R)-2-cyclopropyl-6-(4-(2-ethoxyacetyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 573; General procedure 5, Step W)

[0876] 1H NMR (CHLOROFORM-d) δ 8.65 (d, J=5.0 Hz, 1H), 7.64 (s, 1H), 7.36-7.41 (m, 1H), 7.23 (dd, J=5.0, 1.8 Hz, 1H), 6.88 (dd, J=17.6, 10.8 Hz, 1H), 6.21-6.35 (m, 1H), 5.57 (dd, J=10.9, 0.9 Hz, 1H), 4.84 (br. s., 0.5H), 4.35 (br. s., 2H), 4.27 (br. s., 1H), 4.20 (br. s., 2H), 3.89 (br. s., 0.5H), 3.53-3.65 (m, 2.5H), 3.24-3.35 (m, 1H), 3.17 (br. s., 1.5H), 1.98-2.08 (m, 1H), 1.29-1.41 (m, 3H), 1.23-1.28 (m, 3H), 1.15-1.23 (m, 2H), 0.95-1.07 (m, 2H). LC-MS: m/z 432.2 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(2-methoxyacetyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 590; General procedure 5, Step W)

[0877] 1H NMR (CHLOROFORM-d) δ 8.63 (d, J=5.0 Hz, 1H), 7.53-7.75 (m, 2H), 7.37 (s, 1H), 7.22 (dd, J=4.8, 1.5 Hz, 1H), 6.86 (dd, J=17.6, 10.8 Hz, 1H), 6.19-6.37 (m, 1H), 5.54 (d, J=11.5 Hz, 1H), 4.55 (d, J=13.1 Hz, 1H), 4.42 (d, J=12.8 Hz, 1H), 4.11-4.17 (m, 2H), 3.44 (s, 4H), 3.19-3.25 (m, 1H), 3.04-3.11 (m, 1H), 2.80 (s, 1H), 1.89-2.07 (m, 2H), 1.17-1.27 (m, 4H), 0.95-1.02 (m, 2H), 0.41-0.54 (m, 3H). LC-MS: m/z 444.2 $(M+H)^+$

2-cyclopropyl-6-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 572; General procedure 5, Step W)

[0878] 1H NMR (CHLOROFORM-d) δ 8.66 (d, J=5.0 Hz, 1H), 7.61-7.69 (m, 1H), 7.36-7.44 (m, 1H), 7.24 (dd, J=5.0, 1.8 Hz, 1H), 6.89 (dd, J=17.3, 10.8 Hz, 1H), 6.29 (dd, J=17.6, 1.0 Hz, 1H), 5.58 (dd, J=10.8, 0.8 Hz, 1H), 4.90 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.26-4.40 (m, 2H), 4.12-4.23 (m, 1H), 3.93 (br. s., 2H), 3.74 (d, J=13.1 Hz, 1H), 3.29-3.34 (m, 1H), 3.06-3.18 (m, 1H), 2.50-2.63 (m, 1H), 2.17-2.25 (m, 1H), 2.02-2.07 (m, 1H), 1.41 (d, J=6.8 Hz, 1H), 1.29-1.33 (m, 2H), 1.28 (d, J=2.8 Hz, 1H), 1.19-1.22 (m, 1.5H), 1.02 (dd, J=7.9, 3.1 Hz, 1.5H). LC-MS: m/z 418.2 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(furan-3-carbonyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 546; General procedure 5, Step W)

[0879] 1H NMR (CHLOROFORM-d) δ 8.66 (d, J=4.5 Hz, 1H), 7.73 (s, 1H), 7.65 (s, 1H), 7.46 (s, 1H), 7.36-7.44 (m, 1H), 7.25 (d, J=4.3 Hz, 1H), 6.88 (dd, J=17.4, 10.9 Hz, 1H), 6.56 (s, 1H), 6.26 (d, J=17.6 Hz, 1H), 5.56 (d, J=10.8 Hz, 1H), 4.60 (d, J=13.1 Hz, 1H), 4.44 (d, J=12.8 Hz, 1H), 4.27 (br. s., 1H), 3.93 (br. s., 1H), 3.66 (br. s., 1H), 3.19-3.38 (m, 1H), 3.09 (t, J=11.3 Hz, 1H), 2.03 (dd, J=7.4, 3.1 Hz, 1H), 1.35-1.50 (m, 1H), 1.13-1.35 (m, 2H), 0.90-1.08 (m, 2H), 0.59-0.76 (m, 1H), 0.52 (t, J=8.0 Hz, 1H), 0.42 (br. s., 2H). LC-MS: m/z 466.2 $(M+H)^+$

2-cyclopropyl-6-((R)-3-cyclopropyl-4-((S)-3-hydroxybutanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 595; General procedure 5, Step W)

[0880] 1H NMR (CHLOROFORM-d) δ 8.65 (d, J=4.8 Hz, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 7.24 (d, J=4.3 Hz, 1H), 6.88 (dd, J=17.4, 10.9 Hz, 1H), 6.28 (d, J=17.3 Hz, 1H), 5.57 (d, J=10.8 Hz, 1H), 4.49-4.79 (m, 2H), 4.43 (d, J=12.5 Hz, 1H), 4.17-4.33 (m, 2H), 3.96-4.17 (m, 1H), 3.79 (br. s., 1H), 3.71 (d, J=11.8 Hz, 1H), 3.02-3.31 (m, 2H), 2.53 (d, J=9.8 Hz, 1H), 2.48 (m, 1H), 2.04 (m, 1H), 1.32 (br. s., 3H), 0.82-1.12 (m, 3H), 0.72 (br. s., 1H), 0.63 (br. s., 1H), 0.55 (br. s., 1H), 0.22-0.51 (m, 2H). LC-MS: m/z 458.2 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 631; General procedure 5, Step W)

[0881] 1H NMR (CHLOROFORM-d) δ ^{1}H NMR (CHLOROFORM-d) v 8.61 (d, J=5.0 Hz, 1H), 7.60 (d, J=2.5 Hz, 1H), 7.20 (dd, J=5.0, 1.5 Hz, 1H), 6.84 (dd, J=17.3, 10.8 Hz, 1H), 6.25 (d, J=17.6 Hz, 1H), 5.52 (d, J=11.0 Hz, 1H), 4.50-4.79 (m, 2H), 4.28-4.50 (m, 2H), 3.85 (d, J=13.6 Hz, 1H), 3.63-3.79 (m, 2H), 3.57 (d, J=10.0 Hz, 1H), 3.30-3.49 (m, 3H), 2.99-3.27 (m, 2H), 2.83-2.98 (m, 1H), 2.49-2.79 (m, 1H), 2.17 (dt, J=10.5, 6.7 Hz, 1H), 1.08-1.30 (m, 3H), 0.78-1.08 (m, 7H). LC-MS: m/z 460.1 $(M+H)^+$

(R)-2-cyclopropyl-6-(4-(2-hydroxyacetyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 632; General procedure 5, Step W)

[0882] 1H NMR (CHLOROFORM-d) δ 8.64 (d, J=5.0 Hz, 1H), 7.64 (s, 1H), 7.31-7.50 (m, 1H), 7.23 (dd, J=5.1, 1.6 Hz,

1H), 6.87 (dd, J=17.4, 10.9 Hz, 1H), 6.27 (dd, J=17.4, 0.9 Hz, 1H), 5.42-5.72 (m, 1H), 4.84 (br. s., 1H), 4.20-4.40 (m, 3H), 4.00-4.20 (m, 1H), 3.36-3.65 (m, 2H), 3.20-3.36 (m, 2H), 2.97-3.20 (m, 1H), 2.70-2.96 (m, 4H), 1.86-2.06 (m, 1H), 1.40 (d, J=6.3 Hz, 1H), 1.09-1.36 (m, 4H), 0.79-1.09 (m, 2H). LC-MS: m/z 404.0 $(M+H)^+$

2-cyclopropyl-6-((R)-3-cyclopropyl-4-((R)-3-hydroxybutanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 585; General procedure 5, Step W)

[0883] 1H NMR (CHLOROFORM-d) δ 8.65 (d, J=4.8 Hz, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 7.24 (d, J=4.3 Hz, 1H), 6.88 (dd, J=17.4, 10.9 Hz, 1H), 6.28 (d, J=17.3 Hz, 1H), 5.57 (d, J=10.8 Hz, 1H), 4.49-4.79 (m, 2H), 4.43 (d, J=12.5 Hz, 1H), 4.17-4.33 (m, 2H), 3.96-4.17 (m, 1H), 3.79 (br. s., 1H), 3.71 (d, J=11.8 Hz, 1H), 3.02-3.31 (m, 2H), 2.53 (d, J=9.8 Hz, 1H), 2.48 (m, 1H), 2.04 (m, 1H), 1.32 (br. s., 3H), 0.82-1.12 (m, 3H), 0.72 (br. s., 1H), 0.63 (br. s., 1H), 0.55 (br. s., 1H), 0.22-0.51 (m, 2H). LC-MS: m/z 458.2 $(M+H)^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(1H-pyrrolo[2,3-b]pyridin-5-yl)nicotinonitrile (Compound 539; General procedure 2, Step M)

[0884] 1H NMR (CHLOROFORM-d) δ 10.76 (br. s., 1H), 8.37 (br. s., 1H), 8.00 (s, 1H), 7.65-7.77 (m, 1H), 7.48 (d, J=3.3 Hz, 1H), 6.59 (d, J=3.3 Hz, 1H), 4.71 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 1H), 4.41 (d, J=12.5 Hz, 1H), 4.14 (d, J=7.3 Hz, 0.5H), 3.66-3.95 (m, 1.5H), 3.15-3.44 (m, 4.5H), 2.40 (br. s., 1H), 2.05-2.15 (m, 1H), 1.39-1.48 (m, 1H), 1.17-1.25 (m, 2H), 0.94-1.04 (m, 2H), 0.44-0.81 (m, 4H). LC-MS: m/z 495.3 $(M+H)^+$

6-cyclopropyl-2-((R)-3-cyclopropyl-4-((1S,2S)-2-ethoxycyclopropanecarbonyl)piperazin-1-yl)-5-(4-fluorophenyl)nicotinonitrile (Compound 548; General procedure 3, Step R and S)

[0885] 1H NMR (CHLOROFORM-d) δ 7.58-7.63 (m, 1H), 7.33-7.43 (m, 2H), 7.09-7.21 (m, 2H), 4.39-4.50 (m, 2.5H), 4.05-4.13 (m, 1H), 3.82 (br. s., 0.5H), 3.50-3.72 (m, 4H), 2.97-3.29 (m, 3H), 1.99-2.06 (m, 1H), 1.84-1.96 (m, 1H), 1.14-1.27 (m, 7H), 0.93-1.00 (m, 2H), 0.38-0.72 (m, 4H). LC-MS: m/z 475.3 $(M+H)^+$

(R)-5-(2-chloroquinolin-5-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 549)

[0886] 1H NMR (400 MHz, CHLOROFORM-d) δ 8.09 (d, J=8.5 Hz, 1H), 7.91 (dd, J=11.4, 8.9 Hz, 1H), 7.82 (t, J=7.9 Hz, 1H), 7.64 (s, 1H), 7.46-7.57 (m, 1H), 7.39 (d, J=8.8 Hz, 1H), 4.78 (dq, J=13.5, 6.8 Hz, 0.5H), 4.57 (d, J=11.8 Hz, 1.5H), 4.45 (d, J=11.0 Hz, 1H), 3.92-4.07 (m, 0.5H), 3.57-3.76 (m, 0.5H), 3.40 (q, J=7.0 Hz, 1H), 3.18-3.35 (m, 2H), 1.65-1.82 (m, 1H), 1.20-1.31 (m, 4H), 1.07-1.20 (m, 2H), 0.64-0.91 (m, 4H), 0.38-0.60 (m, 4H). LC-MS: m/z 498.2 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(4-fluorophenyl)nicotinonitrile (Compound 550)

[0887] 1H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.33-7.43 (m, 2H), 7.09-7.20 (m, 2H), 4.55 (br. s., 1H), 4.47 (br. s., 1H), 4.25 (d, J=13.1 Hz, 3H), 3.40 (br. s., 1H), 3.31 (br. s., 1H), 3.15 (br. s., 1H), 1.95-2.10 (m, 1H), 1.77 (br. s., 2H), 1.64 (br. s., 2H), 1.39-1.53 (m, 2H), 1.34 (br. s., 2H), 0.90-1.12 (m, 5H), 0.69-0.90 (m, 2H). LC-MS: m/z 405.2 $(M+H)^+$

6-cyclopropyl-2-((R)-3-cyclopropyl-4-((1R,2S)-2-ethoxycyclopropanecarbonyl)piperazin-1-yl)-5-(4-fluorophenyllnicotinonitrile (Compound 564)

[0888] 1H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.33-7.41 (m, 2H), 7.15 (t, J=8.7 Hz, 2H), 4.69-4.72 (m, 0.5H), 4.31-4.58 (m, 2H), 4.20 (d, J=13.8 Hz, 1H), 3.16-3.82 (m, 7.5H), 1.98-2.09 (m, 1H), 1.77-1.90 (m, 1H), 1.08-1.32 (m, 7H), 0.86-1.08 (m, 2H), 0.31-0.62 (m, 4H). LC-MS: m/z 475.3 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 556; General procedure 2, Step M)

[0889] 1H NMR (CHLOROFORM-d) δ 9.36 (br. s., 1H), 8.52 (br. s., 1H), 8.07 (d, J=8.0 Hz, 1H), 7.70-7.75 (m, 1H), 7.65-7.69 (m, 1H), 7.63 (s, 1H), 7.47 (t, J=5.6 Hz, 1H), 4.89-5.55 (m, 3H), 4.15-4.58 (m, 4H), 1.56-1.68 (m, 1H), 1.42-1.56 (m, 1H), 1.12-1.21 (m, 2H), 0.97-1.09 (m, 4H), 0.75-0.96 (m, 6H). LC-MS: m/z 438.3 $(M+H)^+$

(R)-5-(1-acryloyl-1,2,5,6-tetrahydropyridin-3-yl)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 575; General procedure 1, Step I)

[0890] 1H NMR (CHLOROFORM-d) δ 7.49 (s, 1H), 6.47-6.77 (m, 1H), 6.22-6.44 (m, 1H), 5.88 (br. s., 1H), 5.76 (d, J=10.0 Hz, 1H), 3.01-4.86 (m, 11H), 2.40 (br. s., 2H), 1.95-2.16 (m, 1H), 1.76 (br. s., 1H), 1.29-1.38 (m, 3H), 1.08-1.19 (m, 2H), 0.92-1.08 (m, 4H), 0.71-0.86 (m, 2H). LC-MS: m/z 448.0 $(M+H)^+$

5-(1-acryloylpiperidin-3-yl)-2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (Compound 576; General procedure 1, Step I)

[0891] 1H NMR (CHLOROFORM-d) δ 7.51-7.57 (m, 1H), 6.53-6.73 (m, 1H), 6.25-6.41 (m, 1H), 5.65-5.80 (m, 1H), 4.02-5.02 (m, 6H), 2.94-4.00 (m, 5H), 2.37-2.49 (m, 1H), 2.28-2.37 (m, 1H), 1.92-2.13 (m, 1H), 1.57-1.80 (m, 6H), 0.96-1.22 (m, 6H), 0.69-0.88 (m, 2H). LC-MS: m/z 448.2 $(M+H)^+$

(R)-6-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropyl-3,3'-bipyridine-5,6'-dicarbonitrile (Compound 583; General procedure 1, Step H)

[0892] 1H NMR (CHLOROFORM-d) δ 8.80 (d, J=1.8 Hz, 1H), 7.91 (dd, J=8.0, 2.3 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.62 (s, 1H), 4.09-4.85 (m, 4H), 3.22-3.64 (m, 3H), 1.82-1.93 (m, 1H), 1.75 (br. s., 1H), 1.19-1.27 (m, 2H), 0.96-1.12 (m, 4H), 0.73-0.92 (m, 2H). LC-MS: m/z 413.2 $(M+H)^+$

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,3'-bipyridine-5,6'-dicarbonitrile (Compound 584; General procedure 1, Step I)

[0893] 1H NMR (CHLOROFORM-d) 8.79 (d, J=1.5 Hz, 1H), 7.90 (dd, J=8.0, 2.3 Hz, 1H), 7.81 (d, J=8.0 Hz, 1H), 7.62 (s, 1H), 4.89 (br. s., 0.5H), 4.52 (d, J=9.8 Hz, 0.5H), 4.19-4.44

(m, 2.5H), 3.65-3.78 (m, 2.5H), 3.54 (t, J=11.0 Hz, 0.5H), 3.28-3.43 (m, 4H), 3.03-3.27 (m, 1.5H), 2.50-2.80 (m, 2H), 1.82-1.92 (m, 1H), 1.36 (d, J=6.5 Hz, 1.5H), 1.23-1.28 (m, 1.5H), 1.17-1.23 (m, 2H), 0.94-1.06 (m, 2H); LC-MS: m/z 431.2 (M+H)

(R)-6-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropyl-2'-ethynyl-3,4'-bipyridine-5-carbonitrile (Compound 593; General procedure 1, Step H)

[0894] 1H NMR (CHLOROFORM-d) δ 8.67 (d, J=5.3 Hz, 1H), 7.62 (s, 1H), 7.46-7.59 (m, 1H), 7.35 (dd, J=5.1, 1.6 Hz, 1H), 4.15-4.90 (m, 4H), 3.13-3.75 (m, 4H), 1.94-2.04 (m, 1H), 1.76 (br. s., 1H), 1.28-1.39 (m, 3H), 1.21 (dt, J=7.0, 3.5 Hz, 2H), 0.95-1.09 (m, 4H), 0.76-0.88 (m, 2H). LC-MS: m/z 413.9 $(M+H)^+$

(R)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(1-propioloyl-1,2,5,6-tetrahydropyridin-3-yl)nicotinonitrile (Compound 594; General procedure 1, Step H)

[0895] 1H NMR (CHLOROFORM-d) δ 7.48 (d, J=5.5 Hz, 1H), 5.90 (d, J=11.3 Hz, 1H), 4.01-4.85 (m, 7), 3.96 (t, J=5.9 Hz, 1H), 3.82 (t, J=5.9 Hz, 1H), 3.03-3.80 (m, 4H), 2.82 (s, 1H), 2.44 (d, J=3.5 Hz, 1H), 2.38 (d, J=3.5 Hz, 1H), 2.06-2.12 (m, 1H), 1.31-1.37 (m, 3H), 0.97-1.17 (m, 6H), 0.81 (d, J=7.8 Hz, 2H). LC-MS: m/z 444.1 $(M+H)^+$

(R)-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-3'-fluoro-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 520; General procedure 1, Step I)

[0896] ^{1}H NMR (CHLOROFORM-d) δ 8.46 (d, J=4.8 Hz, 1H), 7.64 (s, 1H), 7.19 (t, J=5.1 Hz, 1H), 7.08 (ddd, J=17.4, 11.0, 1.3 Hz, 1H), 6.51 (dd, J=17.3, 1.8 Hz, 1H), 5.66 (dd, J=10.9, 1.6 Hz, 1H), 4.59 (d, J=12.8 Hz, 1H), 4.47 (d, J=12.5 Hz, 1H), 4.22 (br. s., 0.5H), 4.05 (br. s., 0.5H), 3.76 (dt, J=8.2, 4.0 Hz, 1H), 3.47-3.70 (m, 1H), 3.29 (br. s., 1H), 3.14 (br. s., 1H), 1.77-1.85 (m, 1H), 1.57-1.70 (m, 1H), 1.32-1.41 (m, 1H), 1.14-1.24 (m, 2H), 0.88-1.11 (m, 4H), 0.73-0.86 (m, 2H), 0.59-0.73 (m, 1H), 0.36-0.59 (m, 3H). LC-MS: m/z 458.5 $(M+H)^+$

6-cyclopropyl-2-((R)-3-cyclopropyl-4-((1S,2S)-2-ethoxycyclopropanecarbonyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 514; General procedure 2, Step M)

[0897] ^{1}H NMR (CHLOROFORM-d) δ 9.35 (s, 1H), 8.54 (dd, J=5.9, 1.9 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.69-7.75 (m, 1H), 7.64-7.68 (m, 2H), 7.44 (dd, J=12.5, 6.0 Hz, 1H), 4.46-4.59 (m, 2.5H), 4.08-4.18 (m, 1H), 3.86 (br. s., 0.5H), 3.53-3.74 (m, 3H), 3.21-3.32 (m, 2H), 1.87-2.06 (m, 2H), 1.49-1.58 (m, 1H), 1.33 (d, J=5.8 Hz, 1H), 1.14-1.28 (m, 7H), 0.81-0.90 (m, 2H), 0.65 (br. s., 1H), 0.36-0.59 (m, 3H). LC-MS: m/z 508.2 $(M+H)^+$

(R)-6-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropyl-3,4'-bipyridine-2',5-dicarbonitrile (Compound 522; General procedure 1, Step H)

[0898] ^{1}H NMR (CHLOROFORM-d) δ 8.81 (d, J=5.0 Hz, 1H), 7.80 (s, 1H), 7.63 (s, 1H), 7.59 (dd, J=5.1, 1.6 Hz, 1H), 4.86 (br. s., 1H), 4.48 (br. s., 1H), 4.35 (d, J=13.6 Hz, 2H), 3.63 (br. s., 0.5H), 3.53 (br. s., 1H), 3.25 (br. s., 1.5H), 1.85-1.99 (m, 1H), 1.76 (br. s., 1H), 1.60 (br. s., 3H), 1.17-1.34 (m, 4H), 1.07 (dd, J=7.8, 3.0 Hz, 4H). LC-MS: m/z 413.5 $(M+H)^+$

(R)-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-2'-methyl-3,4'-bipyridine-5-carbonitrile (Compound 523; General procedure 1, Step H)

[0899] ^{1}H NMR (CHLOROFORM-d) 8.56 (d, J=5.0 Hz, 1H), 7.62 (s, 1H), 7.21 (s, 1H), 7.17 (d, J=5.3 Hz, 1H), 4.56 (d, J=12.5 Hz, 1H), 4.44 (d, J=12.3 Hz, 1H), 4.04 (br. s., 1H), 3.75 (br. s., 1.5H), 3.28 (br. s., 1.5H), 3.12 (br. s., 1H), 2.58-2.68 (m, 3H), 1.97-2.07 (m, 1H), 1.72 (br. s., 1H), 1.37 (br. s., 1H), 1.14-1.23 (m, 2H), 0.93-1.10 (m, 4H), 0.74-0.85 (m, 2H), 0.65 (br. s., 1H), 0.36-0.58 (m, 3H). LC-MS: m/z 428.5 $(M+H)^+$

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-[3,3'-bipyridine]-5,5'-dicarbonitrile (Compound 525; General procedure 2, Step M)

[0900] ^{1}H NMR (CHLOROFORM-d) δ8.90 (d, 2H), 8.04 (s, 1H), 7.64 (s, 1H), 4.63 (d, J=13.1 Hz, 1H), 4.51 (d, J=12.3 Hz, 1H), 4.13 (br. s., 1H), 3.78 (br. s., 1H), 3.51 (s, 1H), 3.33 (d, J=9.0 Hz, 2H), 3.24 (d, J=12.5 Hz, 1H), 3.15 (d, J=12.3 Hz, 1H), 2.03 (dt, J=15.3, 7.4 Hz, 1H), 1.01-1.12 (m, 3H), 0.82-0.95 (m, 4H), 0.66 (br. s., 1H), 0.45-0.53 (m, 1H)

[0901] LC-MS: m/z 481.4 $(M+H)^+$

Compound 540 (General Procedure 2, Step M)

(R)-5'-cyano-2'-cyclopropyl-6'-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-[3,3'-bipyridine]-5-carboxamide

[0902] ^{1}H NMR (METHANOL-d) δ9.05 (br. s., 1H), 8.81 (br. s., 1H), 8.26 (t, J=2.1 Hz, 1H), 7.60-7.77 (m, 1H), 6.81 (br. s., 1H), 6.25 (br. s., 1H), 4.57 (d, J=13.1 Hz, 1H), 4.46 (d, J=12.3 Hz, 1H), 4.01-4.25 (m, 1H), 3.65-3.88 (m, 2H), 3.12-3.38 (m, 4H), 2.03-2.24 (m, 1H), 1.86-1.96 (m, 1H), 1.15-1.28 (m, 4H), 0.97-1.06 (m, 2H), 0.28-0.58 (m, 4H)

[0903] LC-MS: m/z 499.5 $(M+H)^+$

Compound 554 (General Procedure, Step I)

(R)-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-5'-(1H-tetrazol-5-yl)-[3,3'-bipyridine]-5-carbonitrile

[0904] ^{1}H NMR (CHLOROFORM-d) δ9.47 (br. s., 1H), 8.86 (s, 1H), 8.62 (s, 1H), 7.73 (s, 1H), 4.59-4.47 (m., 7H), 1.19-1.30 (m, 1H), 1.14-1.05 (m, 3H), 0.84-0.98 (m, 10H), 0.42-0.57 (m, 4H)

[0905] LC-MS: m/z 482.5 $(M+H)^+$

Compound 601 (General Procedure, Step I)

(R)-6-cyclopropyl-5-(5-fluoro-4-vinylpyrimidin-2-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[0906] ^{1}H NMR (CHLOROFORM-d) δ8.62 (d, J=1.8 Hz, 1H), 8.35-8.44 (m, 1H), 7.03 (dd, J=17.3, 10.8 Hz, 1H), 6.70-6.82 (m, 1H), 5.81-5.92 (m, 1H), 4.90 (br. s., 0.5H), 4.52 (m, 3.5H), 4.28-4.47 (m, 3H), 3.68-3.86 (m, 3H), 3.54 (br. s.,

1H), 3.01-3.21 (m, 3H), 2.63-2.79 (m, 1H), 2.51-2.63 (m, 1H), 1.23-1.26 (m, 4H), 1.18-1.23 (m, 2H), 1.04 (m, 2H)

[0907] LC-MS: m/z 451.5 $(M+H)^+$

Compound 538 (General Procedure 1, Step I)

(R)-5-(2-aminoquinazolin-5-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile

[0908] ^{1}H NMR (CHLOROFORM-d) δ 8.82 (d, J=9.5 Hz, 1H), 7.70-7.84 (m, 1H), 7.55-7.70 (m, 2H), 7.11-7.23 (m, 1H), 5.52 (br. s., 2H), 4.39-4.67 (m, 2.5H), 4.16-4.32 (m, 1H), 3.60-3.85 (m, 1H), 3.10-3.41 (m, 2.5H), 1.73 (s, 1H), 1.53-1.65 (m, 1H), 1.27-1.33 (m, 1H), 1.18-1.24 (m, 1H), 1.11-1.18 (m, 1H), 0.98-1.10 (m, 2H), 0.79-0.90 (m, 4H), 0.61-0.74 (m, 1H), 0.40-0.61 (m, 3H)

[0909] LC-MS: m/z 480.2 $(M+H)^+$

Compound 567 (General Procedure 1, Step H)

(R)-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-6'-(trifluoromethyl)-[3,3'-bipyridine]-5-carbonitrile

[0910] ^{1}H NMR (CHLOROFORM-d) δ 8.83 (d, J=1.8 Hz, 1H), 7.94 (dd, J=8.0, 2.0 Hz, 1H), 7.77-7.87 (m, 1H), 7.65 (s, 1H), 4.40-4.72 (m, 2.5H), 3.97-4.20 (m, 1H), 3.51-3.78 (m, 1H), 3.08-3.62 (m, 2.5H), 1.86-1.98 (m, 1H), 1.72 (s, 1H), 1.34-1.45 (m, 1H), 1.20-1.28 (m, 2H), 0.97-1.10 (m, 4H), 0.76-0.87 (m, 2H), 0.40-0.67 (m, 3H)

[0911] LC-MS: m/z 482.2 $(M+H)^+$

Compound 586 (General Procedure 1, Step H)

(R)-2,6'-dichloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile

[0912] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.34 (s, 2H), 4.91 (s, 0.5H), 4.50-4.56 (m, 0.5H), 4.22-4.50 (m, 2.5H), 3.68-3.89 (m, 2.5H), 3.49-3.62 (m, 0.5H), 3.28-3.43 (m, 4H), 3.06-3.27 (m, 1.5H), 2.64-2.83 (m, 1H), 2.55-2.64 (m, 1H), 1.92-2.01 (m, 1H), 1.37 (d, J=6.5 Hz, 2H), 1.21-1.31 (m, 3H), 1.01-1.12 (m, 2H)

[0913] LC-MS: m/z 474.1 $(M+H)^+$

Compounnd 622

(R)-2-cyclopropyl-2'-methoxy-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-6'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[0914] The mixture of (R)-2'-chloro-2-cyclopropyl-6'-methoxy-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile (40 mg, 0.085 mmol), Potassium vinyltrifluoroborate (18 mg, 0.128 mmol), $Pd(dppf)Cl_2$ (4 mg, 0.0043 mmol), CsF (39 mg, 0.255 mmol) in dioxane/H_2O was stirred at 100° C. for 16 hours, the mixture was partitioned between EtOAc and water, the organic was washed with water, brine and concentrated to give the crude which was purified by column to give 15 mg of the product.

[0915] ^{1}H NMR (CHLOROFORM-d) 7.60 (s, 1H), 6.86 (d, J=1.0 Hz, 1H), 6.75 (dd, J=17.1, 10.5 Hz, 1H), 6.66 (d, J=1.0 Hz, 1H), 6.36 (dd, J=17.2, 1.6 Hz, 1H), 5.49 (dd, J=10.5, 1.8 Hz, 1H), 4.90 (s, 0.5H), 4.53 (d, J=13.3 Hz, 0.5H), 4.22-4.38 (m, 2.5H), 4.02 (s, 3H), 3.78-3.84 (m, 0.5H), 3.75 (t, J=6.1 Hz, 2H), 3.51-3.58 (m, 0.5H), 3.38 (s, 3H), 3.28 (t, J=9.9 Hz, 1H), 3.00-3.19 (m, 1.5H), 2.65-2.79 (m, 1H), 2.54-2.64 (m, 1H) 2.03-2.10 (m, 1H), 1.38 (d, J=6.3 Hz, 1H), 1.28 (d, J=6.8 Hz, 2H), 1.13-1.21 (m, 2H), 0.94-1.03 (m, 2H)

[0916] LC-MS: m/z 461.2 $(M+H)^+$

Compound 623

(R)-2'-chloro-2-cyclopropyl-6'-methoxy-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile

[0917] To a solution of (R)-2',6'-dichloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile (300 mg, 0.623 mmol) MeOH was added NaOMe (69 mg, 1.26 mmol), the mixture was refluxed for 16 hours. After cooling, the mixture was partitioned between EtOAc and water, the organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated to give the crude which was purified by prep-HPLC to obtained 150 mg of the product.

[0918] ^{1}H NMR (CHLOROFORM-d) 7.54-7.63 (m, 1H), 6.97 (d, J=1.3 Hz, 1H), 6.70 (d, J=1.0 Hz, 1H), 4.91 (s, 0.5H), 4.54 (d, J=12.8 Hz, 0.5H), 4.23-4.39 (m, 2.5H), 3.96 (s, 3H), 3.79-3.85 (m, 0.5H), 3.68-3.78 (m, 2H), 3.49-3.60 (m, 0.5H), 3.39 (s, 3H), 3.26-3.36 (m, 1H), 3.04-3.20 (m, 1.5H), 2.64-2.82 (m, 1H), 2.50-2.63 (m, 1H), 2.00-2.04 (m, 1), 1.38 (d, J=6.5 Hz, 1H), 1.28 (d, J=5.5 Hz, 2H), 1.13-1.21 (m, 2H), 0.97-1.06 (m, 2H)

[0919] LC-MS: m/z 470.2 $(M+H)^+$

Compound 624

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-2',6'-divinyl-[3,4'-bipyridine]-5-carbonitrile

[0920] The mixture of (R)-2',6'-dichloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile (50 mg, 0.105 mmol), Potassium vinyltrifluoroborate (50 mg, 0.316 mmol), $Pd(dppf)Cl_2$ (4 mg, 0.0043 mmol), CsF (50 mg, 0.316 mmol) in dioxane/H_2O was stirred at 100° C. for 16 hours, the mixture was partitioned between EtOAc and water, the organic was washed with water, brine and concentrated to give the crude which was purified by column to give 25 mg of the product.

[0921] ^{1}H NMR (CHLOROFORM-d) 7.63 (s, 1H), 7.24 (s, 1H), 7.28 (s, 1H), 6.77-6.98 (m, 2H), 6.30 (s, 1H), 6.34 (s, 1H), 5.55 (d, J=10.8 Hz, 2H), 4.09 (s, 0.5H), 4.53 (d, J=12.3 Hz, 0.5H), 4.21-4.36 (m, 2.5H), 3.68-3.85 (m, 3H), 3.50-3.61 (m, 0.5H), 3.38 (s, 4H), 3.03-3.15 (m, 1H), 2.70 (dd, J=15.7, 6.4 Hz, 1H), 2.51-2.59 (m, 1H), 1.90-2.12 (m, 1H), 1.36-1.42 (m, 1H), 1.22-1.30 (m, 2H), 1.18 (s, 2H), 0.94-1.05 (m, 2H)

[0922] LC-MS: m/z 458.2 $(M+H)^+$

Compound 634 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinylquinazolin-5-yl) nicotinonitrile

[0923] ^{1}H NMR (CHLOROFORM-d) δ 9.15 (d, J=11.3 Hz, 1H), 8.03 (d, J=8.3 Hz, 1H), 7.93 (t, J=7.8 Hz, 1H), 7.64 (d, J=3.3 Hz, 1H), 7.50 (dd, J=10.3, 7.3 Hz, 1H), 7.04 (dd, J=17.2, 10.7 Hz, 1H), 6.78 (d, J=17.1 Hz, 1H), 5.85 (d, J=10.5 Hz, 1H), 4.64-4.76 (m, 1H), 4.42-4.49 (m, 1H), 3.88 (d,

J=13.6 Hz, 0.5H), 3.73 (d, J=5.8 Hz, 2H), 3.61 (d, J=9.8 Hz, 0.5H), 3.39-3.50 (m, 0.5H), 3.37 (s, 3H), 3.05-3.25 (m, 2H), 2.85-3.10 (m, 0.5H), 2.50-2.85 (m, 2H), 2.18-2.33 (m, 1H), 1.99-2.15 (m, 1H), 0.99-1.22 (m, 6H), 0.82-0.94 (m, 5H)

[0924] LC-MS: m/z 511.3 $(M+H)^+$

Compound 635 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinylquinazolin-5-yl)nicotinonitrile

[0925] ^{1}H NMR (CHLOROFORM-d) δ 9.15 (d, J=7.8 Hz, 1H), 8.04 (d, J=8.5 Hz, 1H), 7.94 (t, J=7.8 Hz, 1H), 7.66 (d, J=1.5 Hz, 1H), 7.43-7.56 (m, 1H), 7.04 (dd, J=17.3, 10.5 Hz, 1H), 6.78 (d, J=17.1 Hz, 1H), 5.85 (d, J=10.5 Hz, 1H), 4.33-4.80 (m, 2.5H), 4.07-4.22 (m, 0.5H), 3.85-4.02 (m, 1H), 3.60-3.81 (m, 3H), 3.37 (s, 3H), 2.98-3.26 (m, 2H), 2.37-2.76 (m, 2H), 1.98-2.28 (m, 1H), 1.51-1.61 (m, 1H), 1.11-1.26 (m, 2H), 0.86 (d, J=7.8 Hz, 2H), 0.40-0.55 (m, 4H)

[0926] LC-MS: m/z 509.3 $(M+H)^+$

Compound 636 (General Procedure 1, Step I)

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-vinylquinazolin-5-yl)nicotinonitrile

[0927] ^{1}H NMR (CHLOROFORM-d) δ 9.16 (d, J=8.0 Hz, 1H), 8.04 (d, J=8.5 Hz, 1H), 7.94 (t, J=7.8 Hz, 1H), 7.62-7.72 (m, 1H), 7.44-7.56 (m, 1H), 7.05 (dd, J=17.3, 10.5 Hz, 1H), 6.78 (d, J=17.1 Hz, 1H), 5.75-5.95 (m, 1H), 4.49-4.66 (m, 2.5H), 4.05-4.25 (m, 1H), 3.75-3.88 (m, 1H), 3.06-3.32 (m, 2.5H), 2.29 (s, 1H), 1.50-1.57 (m, 1H), 1.34-1.47 (m, 1H), 1.14-1.22 (m, 2H), 0.98-1.09 (m, 2H), 0.77-0.91 (m, 4H), 0.39-0.67 (m, 4H)

[0928] LC-MS: m/z 491.2 $(M+H)^+$

Compound 645 (General procedure 1, Step I)

[0929] (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinyl-1,8-naphthyridin-4-yl)nicotinonitrile (Core synthesis method 1 using 4-chloro-2-vinyl-1,8-naphthyridine as starting material)

[0930] In a sealed tube was added 120 mg of 4-chloro-2-vinyl-1,8-naphthyridine, 242 mg of 8-3 (0.5 mmol), 230 mg of CsF (1.5 mmol), 41 mg of $Pd(dppf)_2Cl_2$ (0.05 mmol) and 10 mL of Dioxane, then the mixture was heated in a microwave reactor (100° C., 30 minutes), when LC-MS indicated the product formation. Then the resulting mixture was filtered, the filtrated was concentrated, purified by Prep-TLC (Petroleum ether:Ethyl acetate=2:1) to give 45 mg of title compound. ^{1}H NMR (CHLOROFORM-d) δ 9.17 (dd, J=4.3, 1.8 Hz, 1H), 8.03 (td, J=8.7, 1.8 Hz, 1H), 7.68 (d, J=1.3 Hz, 1H), 7.61 (d, J=3.5 Hz, 1H), 7.48 (dd, J=8.3, 4.3 Hz, 1H), 7.15 (dd, J=17.7, 10.9 Hz, 1H), 6.57 (dd, J=17.6, 1.8 Hz, 1H), 5.83 (d, J=11.0 Hz, 1H), 4.60 (d, J=12.3 Hz, 2H), 4.49 (d, J=12.8 Hz, 1H), 4.15 (br. s., 0.5H), 3.91 (br. s., 0.5H), 3.65-3.85 (m, 3H), 3.40 (s, 4H), 3.27 (d, J=12.0 Hz, 2H), 2.67 (br. s., 2H), 1.20 (d, J=4.5 Hz, 2H), 0.82-0.98 (m, 2H), 0.66 (br. s., 1H), 0.59 (br. s., 1H), 0.49 (d, J=5.0 Hz, 2H)

[0931] LC-MS: m/z 509.1 $(M+H)^+$

Compound 629 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-5-(2-vinyl-1,8-naphthyridin-4-yl)nicotinonitrile

[0932] ^{1}H NMR (CHLOROFORM-d) δ 8.99-9.21 (m, 1H), 7.99 (dd, J=12.4, 8.4 Hz, 1H), 7.50-7.72 (m, 2H), 7.45 (dt, J=7.8, 3.7 Hz, 1H), 7.11 (dd, J=17.4, 10.9 Hz, 1H), 6.53 (d, J=17.6 Hz, 1H), 5.79 (d, J=10.8 Hz, 1H), 4.56-4.78 (m, 1.5H), 4.35-4.56 (m, 2H), 3.74-3.99 (m, 2.5H), 3.37-3.60 (m, 1H), 3.06-3.28 (m, 2H), 2.92-3.06 (m, 1H), 2.53-2.83 (m, 3H), 2.12 (dt, J=10.0, 6.5 Hz, 1H), 1.43-1.55 (m, 1H), 0.98-1.15 (m, 4H), 0.72-0.97 (m, 5H)

[0933] LC-MS: m/z 497.3 $(M+H)^+$

Compound 625 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinyl-1,8-naphthyridin-4-yl)nicotinonitrile

[0934] ^{1}H NMR (CHLOROFORM-d) δ 9.05-9.19 (m, 1H), 7.98 (ddd, J=6.1, 4.3, 2.1 Hz, 1H), 7.63-7.68 (m, 1H), 7.55-7.61 (m, 1H), 7.41-7.47 (m, 1H), 7.03-7.17 (m, 1H), 6.52 (d, J=17.6 Hz, 1H), 5.72-5.84 (m, 1H), 4.89 (br. s., 0.5H), 4.54 (d, J=12.5 Hz, 1H), 4.39 (d, J=13.8 Hz, 1H), 4.29 (d, J=19.8 Hz, 2H), 4.20 (br. s., 1H), 3.82-4.00 (m, 2.5H), 3.01-3.24 (m, 2H), 2.46-2.76 (m, 3H), 1.06-1.19 (m, 2H), 0.75-0.94 (m, 3H)

[0935] LC-MS: m/z 469.2 $(M+H)^+$

Compound 626 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinyl-1,8-naphthyridin-4-yl)nicotinonitrile

[0936] ^{1}H NMR (CHLOROFORM-d) δ 9.12 (S, 1h), 7.99 (br. s., 1H), 7.52-7.69 (m, 2H), 7.36-7.50 (m, 1H), 7.00-7.19 (m, 1H), 6.53 (d, J=17.6 Hz, 1H), 5.78 (d, J=10.8 Hz, 1H), 4.71 (br. s., 1.5H), 4.35-4.52 (m, 2H), 3.58-3.81 (m, 3.5H), 3.37 (d, J=3.0 Hz, 4H), 3.18 (dd, J=13.6, 3.5 Hz, 2H), 2.52-2.82 (m, 2H), 1.08 (dt, J=12.0, 5.7 Hz, 4H), 0.87 (d, J=6.8 Hz, 6H)

[0937] LC-MS: m/z 511.2 $(M+H)^+$

Compound 599 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinyl-1,8-naphthyridin-4-yl)nicotinonitrile

[0938] ^{1}H NMR (CHLOROFORM-d) δ 9.14 (dd, J=4.1, 1.9 Hz, 1H), 7.98 (br. s., 1H), 7.65 (s, 1H), 7.59 (s, 1H), 7.45 (dd, J=8.3, 4.3 Hz, 1H), 7.11 (d, J=10.8 Hz, 1H), 6.44-6.62 (m, 1H), 5.80 (d, J=10.8 Hz, 1H), 4.94 (br. S., 0.5H), 4.55 (br. s., 0.5H), 4.42 (br. s., 3H), 3.75 (d, J=6.3 Hz, 3H), 3.39 (s, 4H), 3.15 (br. s., 2H), 2.63 (br. s., 2H), 1.10-1.22 (m, 3H), 0.72-0.97 (m, 4H)

[0939] LC-MS: m/z 483.1 $(M+H)^+$

Compound 596 (General Procedure 1, Step I)

(R)-2'-cyclopropyl-6'-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-vinyl-2,3'-bipyridine-5'-carbonitrile

[0940] ^{1}H NMR (CHLOROFORM-d) δ: 8.67 (d, J=5.3 Hz, 1H), 7.89 (s, 1H), 7.50 (s, 3H), 6.63-6.82 (m, 1H), 6.04 (d, J=17.6 Hz, 1H), 5.57 (d, J=11.0 Hz, 1H), 4.91 (br. s., 0.5H), 4.51 (br. s., 1H), 4.34 (br. s., 3H), 3.65-3.83 (m, 2.5H), 3.33-3.44 (m, 4H), 3.29 (br. s., 1H), 2.71 (br. s., 1H), 2.62 (br. s., 2H), 1.33-1.43 (m, 3H), 1.15-1.25 (m, 4H)

[0941] LC-MS: m/z 431.2 $(M+H)^+$

Compound 612 (General Procedure 1, Step I)

(R)-5-(1-acryloyl-2,5-dihydro-1H-pyrrol-3-yl)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropylnicotinonitrile

[0942] 1H NMR (CHLOROFORM-d) δ 7.48-7.56 (m, 1H), 6.31-6.57 (m, 2H), 5.97 (d, J=2.0 Hz, 1H), 5.65-5.88 (m, 1H), 4.01-4.90 (m, 8H), 3.02-3.81 (m, 3H), 2.09-2.34 (m, 1H), 1.75 (br. s., 2H), 1.25-1.37 (m, 3H), 1.09-1.22 (m, 2H), 0.95-1.09 (m, 4H), 0.67-0.94 (m, 2H)

[0943] LC-MS: m/z 432.2 $(M+H)^+$

Compound 620 (General Procedure 1, Step I)

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-6'-vinyl-3,3'-bipyridine-5-carbonitrile

[0944] ^{1}H NMR (CHLOROFORM-d) δ 8.63 (d, J=2.0 Hz, 1H), 7.66-7.74 (m, 1H), 7.58-7.65 (m, 1H), 7.40-7.50 (m, 1H), 6.87 (dd, J=17.6, 10.8 Hz, 1H), 6.27 (dd, J=17.6, 1.0 Hz, 1H), 5.54 (dd, J=10.8, 1.0 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 4.17-4.41 (m, 2.5H), 3.66-3.88 (m, 2.5H), 3.54 (t, J=11.2 Hz, 0.5H), 3.37 (s, 3H), 3.28 (t, J=9.8 Hz, 1H), 2.99-3.20 (m, 1.5H), 2.52-2.81 (m, 2H), 1.94-2.06 (m, 1H), 1.33-1.41 (m, 1.5H), 1.24-1.29 (m, 1.5H), 1.14-1.23 (m, 2H), 0.91-1.04 (m, 2H)

[0945] LC-MS: m/z 432.1 $(M+H)^+$

Compound 619 (General Procedure 1, Step I)

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,3'-bipyridine-5-carbonitrile

[0946] ^{1}H NMR (CHLOROFORM-d) δ 8.54-8.72 (m, 1H), 7.45-7.58 (m, 2H), 7.18-7.34 (m, 1H), 6.53-6.69 (m, 1H), 6.38-6.47 (m, 1H), 5.43 (d, J=10.8 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 4.14-4.39 (m, 2.5H), 3.68-3.88 (m, 2.5H), 3.54 (d, J=4.8 Hz, 0.5H), 3.37 (s, 3H), 3.23-3.33 (m, 1H), 2.99-3.21 (m, 1.5H), 2.51-2.80 (m, 2H), 1.55-1.69 (m, 1H), 1.39 (br. s., 1.5H), 1.29 (br. s., 1.5H), 1.04-1.19 (m, 2H), 0.79-1.00 (m, 2H)

[0947] LC-MS: m/z 432.2 $(M+H)^+$

Compound 630 (General Procedure 1, Step I)

(R)-5-(1-acryloyl-1,2,3,6-tetrahydropyridin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropylnicotinonitrile

[0948] 1H NMR (CHLOROFORM-d) δ 7.45 (s, 1H), 6.64 (td, J=16.1, 10.7 Hz, 1H), 6.29-6.42 (m, 1H), 5.67-5.86 (m, 2H), 4.00-5.00 (m, 6H), 3.85-3.93 (m, 1H), 3.79 (t, J=5.3 Hz, 1H), 3.00-3.63 (m, 3H), 2.39-2.52 (m, 2H), 1.96-2.12 (m, 1H), 1.75 (br. s., 1H), 1.28-1.51 (m, 3H), 1.08-1.17 (m, 2H), 0.94-1.08 (m, 4H), 0.76-0.86 (m, 2H)

[0949] LC-MS: m/z 446.0 $(M+H)^+$

Compound 557 (General Procedure 1, Step I)

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-methyl-1,8-naphthyridin-4-yl)nicotinonitrile

[0950] ^{1}H NMR (CHLOROFORM-d) δ 0.39-0.53 (m, 1H) 0.56 (d, J=4.52 Hz, 3H) 0.79-0.94 (m, 4H) 0.94-1.14 (m, 3H) 1.22 (br. s., 2H) 1.27 (br. s., 2H) 1.33 (br. s., 2H) 3.01 (s, 3H) 4.53 (d, J=12.55 Hz, 2.5H) 7.46 (s, 1H) 7.58 (br. s., 1H) 7.67 (s, 1H) 8.14 (br. s., 1H) 9.22 (br. s., 1H)

[0951] LC-MS: m/z 479.3 $(M+H)^+$

Compound 552 (General Procedure 2, Step M)

(R)-tert-butyl 5-(5-cyano-2-cyclopropyl-6-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)pyridin-3-yl)-1H-indazole-1-carboxylate

[0952] 70 mg of (R)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)-5-(1H-indazol-5-yl)nicotinonitrile (NB247-78) (0.18 mmol), 83 mg of HATU (0.22 mmol), 37 mg of TEA in 10 mL of DCM was added 23 mg of 3,3,3-trifluoropropanoic acid (0.18 mmol), then the mixture was stirred at room temperature for 2 hours, concentrated, purified by Prep-TLC (Petroleum ether:Ethyl acetate=1:1) to give 31.5 mg of title compound. ^{1}H NMR (CHLOROFORM-d) 7.98 (br. s., 1H), 7.77 (s, 1H), 7.42-7.62 (m, 2H), 7.15 (d, J=7.0 Hz, 1H), 4.56 (d, J=13.1 Hz, 2H), 4.13 (br. s., 0.5H), 3.84 (br. s., 1.5H), 3.35 (d, J=10.0 Hz, 2H), 3.23 (br. s., 2H), 3.12 (br. s., 1H), 1.94 (s, 1H), 1.15-1.32 (m, 5H), 0.94 (dd, J=7.8, 3.3 Hz, 2H), 0.52 (d, J=5.3 Hz, 2H)

[0953] LC-MS: m/z 495.2 $(M+H)^+$

Compound 537 (General Procedure 2, Step M)

(R)-5-(benzo[d]thiazol-6-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)nicotinonitrile

[0954] ^{1}H NMR (CHLOROFORM-d) δ 9.07 (s, 1H), 8.22 (d, J=8.5 Hz, 1H), 7.99 (d, J=1.5 Hz, 1H), 7.71 (s, 1H), 7.57 (dd, J=8.4, 1.6 Hz, 1H), 4.53 (d, J=13.3 Hz, 1H), 4.42 (d, J=12.8 Hz, 1H), 3.98-4.21 (m, 0.5H), 3.67-3.95 (m, 1.5H), 3.26-3.38 (m, 2H), 3.15-3.26 (m, 2H), 3.09 (t, J=11.3 Hz, 1H), 2.04-2.12 (m, 1H), 1.42 (d, J=14.3 Hz, 1H), 1.17-1.24 (m, 2H), 0.95-1.03 (m, 2H), 0.67 (br. s., 1H), 0.57 (br. s., 1H), 0.45-0.53 (m, 2H)

[0955] LC-MS: m/z 512.1 $(M+H)^+$

Compound 536 (General Procedure 2, Step M)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(2-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)nicotinonitrile

[0956] ^{1}H NMR (CHLOROFORM-d) δ: 8.45-8.58 (m, 1H), 7.59-7.69 (m, 2H), 7.47-7.59 (m, 1H), 7.23 (d, J=8.0 Hz,

1H), 7.07 (d, J=1.8 Hz, 1H), 4.53 (d, J=13.1 Hz, 1H), 4.43 (d, J=12.0 Hz, 1H), 4.12 (br. s., 0.5H), 3.78 (br. s., 1H), 3.67 (s, 3H), 3.33 (q, J=9.8 Hz, 2H), 3.16-3.26 (m, 1H), 3.03-3.16 (m, 0.5H), 1.92 (br. s., 1H), 1.69-1.80 (m, 1H), 1.20-1.28 (m, 2H), 1.07-1.19 (m, 2H), 0.81-0.95 (m, 2H), 0.67 (br. s., 1H), 0.57 (br. s., 1H), 0.43-0.54 (m, 2H)

[0957] LC-MS: m/z 536.2 $(M+H)^+$

Compound 580 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[0958] 1H NMR (CHLOROFORM-d) d: 9.56 (s, 1H), 8.59 (d, J=5.8 Hz, 1H), 7.74 (s, 1H), 7.64-7.70 (m, 1H), 7.44-7.52 (m, 1H), 7.11 (dd, J=17.7, 10.9 Hz, 1H), 6.44 (dd, J=17.7, 1.6 Hz, 1H), 5.83 (d, J=11.0 Hz, 1H), 4.95 (br. s., 0.5H), 4.58 (d, J=11.3 Hz, 0.5H), 4.42 (d, J=11.3 Hz, 1.5H), 4.31 (br. s., 1H), 3.86 (d, J=13.1 Hz, 0.5H), 3.72-3.81 (m, 2H), 3.55-3.68 (m, 0.5H), 3.4 (s, 3H) 3.34-3.39 (m, 0.5H), 3.04-3.30 (m, 2H), 2.53-2.83 (m, 2H), 1.47-1.55 (m, 1H), 1.37-1.46 (m, 1.5H), 1.29-1.37 (m, 1.5H), 1.20 (t, J=4.9 Hz, 2H), 0.84-0.96 (m, 2H)

[0959] LC-MS: m/z 483.2 $(M+H)^+$

Compound 609 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[0960] ^{1}H NMR (CHLOROFORM-d) δ 9.50-9.65 (m, 1H), 8.60 (d, J=6.0 Hz, 1H), 7.74-7.82 (m, 1H), 7.62-7.72 (m, 1H), 7.48-7.57 (m, 1H), 7.11 (dd, J=17.7, 10.9 Hz, 1H), 6.45 (dd, J=17.6, 1.8 Hz, 1H), 5.85 (d, J=11.0 Hz, 1H), 4.93 (br. s., 0.5H), 4.50-4.64 (m, 0.5H), 4.40-4.49 (m, 1H), 4.31-4.40 (m, 1H), 4.22 (br. s., 0.5H), 3.91-4.01 (m, 2H), 3.78 (d, J=11.3 Hz, 0.5H), 3.61 (d, J=11.8 Hz, 0.5H), 3.39 (d, J=13.6 Hz, 1H), 3.10-3.31 (m, 1.5H), 2.65-2.80 (m, 1H), 2.52-2.65 (m, 1H), 1.43-1.54 (m, 3H), 1.35 (t, J=5.6 Hz, 2H), 1.21 (dd, J=6.9, 3.6 Hz, 2H), 0.87-0.98 (m, 2H)

[0961] LC-MS: m/z 469.2 $(M+H)^+$

Compound 611 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

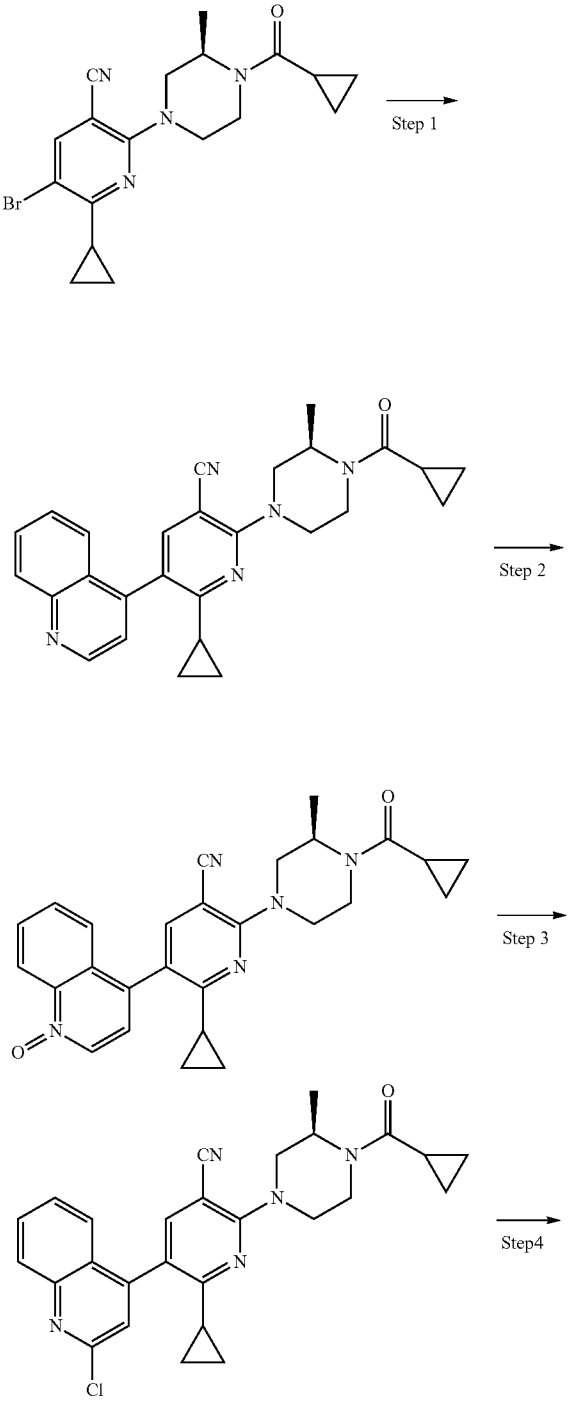
[0962] ^{1}H NMR (CHLOROFORM-d) d: 9.57 (s, 1H), 8.60 (dd, J=5.6, 3.1 Hz, 1H), 7.75 (d, J=12.0 Hz, 1H), 7.66 (dd, J=4.8, 3.3 Hz, 1H), 7.45-7.55 (m, 1H), 7.04-7.17 (m, 1H), 6.44 (d, J=17.6 Hz, 1H), 5.84 (d, J=10.8 Hz, 1H), 4.61-4.81 (m, 1.5H), 4.42-4.56 (m, 1.5H), 3.92 (d, J=13.6 Hz, 0.5H), 3.70-3.83 (m, 2H), 3.44-3.56 (m, 0.5H), 3.37-3.43 (m, 3H), 3.08-3.31 (m, 2H), 2.90-3.05 (m, 0.5H), 2.55-2.85 (m, 2H), 1.49 (dd, J=7.4, 4.4 Hz, 1H), 1.14-1.32 (m, 2H), 1.11 (ddd, J=15.2, 6.5, 4.1 Hz, 4H), 0.83-0.98 (m, 5H)

[0963] LC-MS: m/z 511.3 $(M+H)^+$

Compound 542

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-vinylquinolin-4-yl)nicotinonitrile

[0964]



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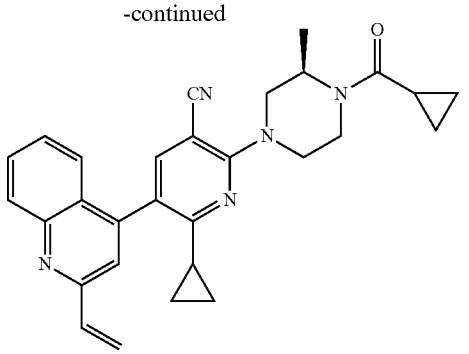


Step 1

[0965] To 10 mg PdCl2(dppf).CH_2Cl_2 in a reaction tube under nitrogen were added 5 mL dioxane, 3 mL water, 150 mg (0.98 mmol) CsF, 75 mg (0.43 mmol) quinolin-4-ylboronic acid and 150 mg (0.36 mmol) (R)-5-bromo-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile. The reaction solution was heated to 100° C. for half hour under microwave irradiation. The reaction was extracted with ethyl acetate, washed several times with water and purified by TLC preparation (petroleum ether:ethyl acetate=1:1) to give desired compound 50 mg (32%, yield). LC-MS: m/z 438.22 $(M+H)^+$

Step 2

[0966] To a stirred solution of (R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(quinolin-4-yl)nicotinonitrile (50 mg, 0.108 mmol) in 10 mL of anhydrous CH_2Cl_2 was added 3-chlorobenzoperoxoic acid (37 mg, 0.216 mmol) portionwise over 1 min. The resulting mixture was stirred at room temperature for 3 hours. Then saturated aqueous Na2SO3 (10 mL) was added to the reaction. The reaction was extracted with ethyl acetate to give desired compound (R)-4-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl) quinoline 1-oxide 48 mg (93%). LC-MS: m/z 453.22 $(M+H)^+$

Step 3

[0967] To a solution of (R)-4-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)quinoline 1-oxide (35 mg, 0.07 mmol) in 20 mL of CHCl3 was added $POCl_3$ (32 mg, 0.209) dropwise at room temperature. The reaction mixture was then heated at reflux for 3 hours. After LC-MS showed completion of reaction, the mixture was cooled to room temperature and poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo to give the title compound as a brown solid 30 mg (83.3%). LC-MS: m/z 472.18 $(M+H)^+$

Step 4 is Similar to Compound 390 Step 2: Compound 542

[0968] ^{1}H NMR (CHLOROFORM-d) d: 8.21 (d, J=8.3 Hz, 1H), 7.77 (t, J=7.5 Hz, 1H), 7.68 (d, J=1.0 Hz, 1H), 7.48-7.66 (m, 3H), 7.13 (dd, J=17.4, 10.9 Hz, 1H), 6.35 (d, J=17.6 Hz, 1H), 5.76 (d, J=11.0 Hz, 1H), 4.61 (d, J=12.5 Hz, 1.5H), 4.49 (d, J=12.3 Hz, 1.5H), 4.12 (br. s., 1H), 3.67-3.82 (m, 1H), 3.34 (br. s., 1.5H), 3.19 (br. s., 1.5H), 1.58 (ddd, J=12.0, 7.8, 4.5 Hz, 1H), 1.14-1.35 (m, 4H), 1.00-1.13 (m, 2H), 0.76-0.93 (m, 4H), 0.71 (br. s., 1H), 0.38-0.63 (m, 3H)

[0969] LC-MS: m/z 490.6 $(M+H)^+$

Compound 543

(R)-5-(2-chloroquinolin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile

[0970] The synthesis was similar to Compound 542.

[0971] ^{1}H NMR (CHLOROFORM-d) d: 8.12 (d, J=8.3 Hz, 1H), 7.76-7.84 (m, 1H), 7.61-7.68 (m, 2H), 7.53-7.61 (m, 1H), 7.38 (d, J=1:8 Hz, 1H), 4.63 (d, J=12.5 Hz, 1H), 4.51 (d, J=12.5 Hz, 1H), 3.97-4.20 (m, 1H), 3.82 (br. s., 1H), 3.59-3.78 (m, 1H), 3.34 (br. s., 1H), 3.20 (br. s., 1H), 1.74 (br. s., 2H), 1.50-1.59 (m, 1H), 1.14-1.26 (m, 2H), 0.97-1.14 (m, 2H), 0.79-0.97 (m, 4H), 0.70 (br. s., 1H), 0.42-0.63 (m, 3H)

[0972] LC-MS: m/z 499.0 $(M+H)^+$

Compound 571

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylquinolin-4-yl) nicotinonitrile

[0973] The synthesis was similar to Compound 542.

[0974] 1H NMR (CHLOROFORM-d) d: 8.18 (d, J=8.5 Hz, 1H), 7.76 (t, J=7.7 Hz, 1H), 7.69 (d, J=1.0 Hz, 1H), 7.46-7.64 (m, 3H), 7.11 (dd, J=17.7, 10.9 Hz, 1H), 6.28-6.39 (m, 1H), 5.75 (d, J=11.0 Hz, 1H), 4.59 (d, J=13.1 Hz, 1H), 4.47 (d, J=13.1 Hz, 1H), 4.13 (d, J=8.3 Hz, 0.5H), 3.94 (br. s., 2H), 3.82 (br. s., 1H), 3.76 (br. s., 1H), 3.43 (br. s., 1H), 3.21-3.37 (m, 1.5H), 3.15 (d, J=11.5 Hz, 1H), 2.55-2.70 (m, 2H), 1.67 (br. s., 1H), 1.59 (tt, J=8.1, 4.3 Hz, 1H), 1.10-1.24 (m, 2H), 0.80-0.94 (m, 2H), 0.69 (br. s., 1H), 0.58 (br. s., 1H), 0.51 (br. s., 2H)

[0975] LC-MS: m/z 494.2 $(M+H)^+$

Compound 574

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinylquinolin-4-yl) nicotinonitrile

[0976] The synthesis was similar to Compound 542.

[0977] ^{1}H NMR (CHLOROFORM-d) δ 8.15 (d, J=8.5 Hz, 1H), 7.71-7.78 (m, 1H), 7.67 (d, J=1.0 Hz, 1H), 7.56-7.64 (m, 1H), 7.54 (d, J=4.5 Hz, 1H), 7.46-7.53 (m, 1H), 7.02-7.14 (m, 1H), 6.32 (dd, J=17.6, 1.3 Hz, 1H), 5.73 (d, J=11.3 Hz, 1H), 4.71-4.74 (m, 0.5H), 4.53-4.66 (m, 1H), 4.45 (d, J=13.1 Hz, 1H), 4.06-4.24 (m, 0.5H), 3.91 (d, J=11.5 Hz, 0.5H), 3.68-3.84 (m, 3H), 3.39 (s, 3H), 3.26 (br. s., 1.5H), 3.07-3.21 (m, 1H), 2.61-2.85 (m, 2H), 1.53-1.64 (m, 1H), 1.32-1.44 (m, 1H), 1.11-1.24 (m, 2H), 0.80-0.94 (m, 2H), 0.48-0.78 (m, 1H)

[0978] LC-MS: m/z 508.1 $(M+H)^+$

Compound 591

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinolin-4-yl)nicotinonitrile

[0979] The synthesis was similar to Compound 542.

[0980] ^{1}H NMR (CHLOROFORM-d) δ 8.18 (d, J=8.3 Hz, 1H), 7.76 (ddd, J=8.3, 6.8, 1.4 Hz, 1H), 7.68 (s, 1H), 7.57-7.63 (m, 1H), 7.48-7.57 (m, 2H), 7.10 (dd, J=17.7, 10.9 Hz,

1H), 6.34 (dd, J=17.6, 1.8 Hz, 1H), 5.74 (d, J=11.0 Hz, 1H), 4.93 (br. s., 0.5H), 4.48-4.68 (m, 0.5H), 4.26-4.45 (m, 2H), 3.87-3.98 (m, 2H), 3.74-3.87 (m, 0.5H), 3.61 (t, J=12.3 Hz, 0.5H), 3.31-3.48 (m, 2H), 3.05-3.29 (m, 1H), 2.49-2.79 (m, 2H), 1.53-1.63 (m, 1H), 1.46 (dd, J=6.5, 2.5 Hz, 1.5H), 1.32-1.40 (m, 1.5H), 1.15-1.23 (m, 2H), 0.80-0.93 (m, 2H)

[0981] LC-MS: m/z 468.2 $(M+H)^+$

Compound 592

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinolin-4-yl)nicotinonitrile

[0982] The synthesis was similar to Compound 542.

[0983] ^{1}H NMR (CHLOROFORM-d) δ 8.19 (d, J=8.3 Hz, 1H), 7.76 (t, J=7.5 Hz, 1H), 7.65-7.68 (m, 1H), 7.58-7.64 (m, 1H), 7.48-7.57 (m, 2H), 7.11 (dd, J=17.7, 10.9 Hz, 1H), 6.34 (d, J=17.8 Hz, 1H), 5.75 (d, J=10.8 Hz, 1H), 4.95 (br. s., 0.5H), 4.50-4.70 (m, 0.5H), 4.24-4.47 (m, 2.5H), 3.71-3.89 (m, 2.5H), 3.59 (d, J=9.8 Hz, 0.5H), 3.31-3.45 (m, 4H), 3.07-3.28 (m, 1.5H), 2.67-2.85 (m, 1H), 2.54-2.67 (m, 1H), 1.52-1.62 (m, 1H), 1.33-1.49 (m, 3H), 1.11-1.21 (m, 2H), 0.78-0.93 (m, 2H)

[0984] LC-MS: m/z 482.2 $(M+H)^+$

Compound 553 (General Procedure 1, Step I)

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-methyl-1,7-naphthyridin-4-yl)nicotinonitrile

[0985] 1H NMR (CHLOROFORM-d) d: 9.53 (s, 1H), 8.59 (d, J=5.5 Hz, 1H), 7.65 (s, 1H), 7.42-7.50 (m, 2H), 4.63 (d, J=9.3 Hz, 1H), 4.51 (d, J=11.0 Hz, 2.5H), 3.08-3.48 (m, 4.5H), 2.87 (s, 3H), 1.59-1.68 (m, 1H), 1.46-1.53 (m, 1H), 1.22 (d, J=3.0 Hz, 1H), 1.05-1.11 (m, 2H), 0.92-0.98 (m, 2H), 0.87-0.92 (m, 2H), 0.84 (dd, J=7.9, 2.6 Hz, 2H), 0.70 (br. s., 1H), 0.42-0.63 (m, 3H)

[0986] LC-MS: m/z 479.6 $(M+H)^+$

Compound 551

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(2-vinylquinolin-5-yl)nicotinonitrile

[0987] The synthesis was similar to Compound 542.

[0988] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.18 (d, J=8.2 Hz, 1H), 7.91 (dd, J=12.5, 8.8 Hz, 1H), 7.79 (t, J=7.8 Hz, 1H), 7.64-7.71 (m, 1H), 7.57-7.64 (m, 1H), 7.46 (dd, J=6.9, 2.3 Hz, 1H), 6.97-7.17 (m, 1H), 6.34 (d, J=17.8 Hz, 1H), 5.75 (d, J=10.7 Hz, 1H), 4.56 (dd, J=13.0, 1.7 Hz, 1H), 4.45 (d, J=11.8 Hz, 1H), 4.15 (m, 0.5H), 3.87 (m, 1.5H), 3.26-3.44 (m, 2.5H), 3.01-3.20 (m, 2.5H), 1.42-1.52 (m, 1H), 1.07-1.21 (m, 2H), 0.79-0.92 (m, 3H), 0.66-0.76 (m, 2H), 0.46-0.56 (m, 2H)

[0989] LC-MS: m/z 532.2 $(M+H)^+$

Compound 570

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinylquinolin-5-yl)nicotinonitrile

[0990] The synthesis was similar to Compound 542.

[0991] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.11-8.17 (m, 1H), 7.85-7.95 (m, 1H), 7.78 (t, J=7.3 Hz, 1H), 7.64-7.68 (m, 1H), 7.60 (dd, J=8.8, 1.5 Hz, 1H), 7.42-7.47 (m, 1H), 7.00-7.13 (m, 1H), 6.32 (d, J=17.6 Hz, 1H), 5.72 (d, J=11.0 Hz, 1H), 4.72 (m, 0.5H), 4.54 (d, J=12.5 Hz, 1H), 4.43 (d, J=12.8 Hz, 1H), 4.14 (d, J=7.8 Hz, 0.5H), 3.91 (d, J=11.8 Hz, 0.5H), 3.75 (t, J=5.6 Hz, 2.5H), 3.40 (s, 3H), 3.23 (d, J=8.0 Hz, 1H), 3.01-3.17 (m, 1H), 2.70-2.81 (m, 1H), 2.67 (m, 1H), 2.03 (d, J=5.5 Hz, 1H), 1.56 (td, J=7.8, 4.0 Hz, 1H), 1.11-1.20 (m, 3H), 0.78-0.86 (m, 2H), 0.58-0.66 (m, 2H), 0.42-0.52 (m, 2H)

[0992] LC-MS: m/z 508.2 $(M+H)^+$

Compound 569

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylquinolin-5-yl)nicotinonitrile

[0993] The synthesis was similar to Compound 542.

[0994] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ8.10-8.19 (m, 1H), 7.90 (dd, J=12.3, 8.8 Hz, 1H), 7.74-7.82 (m, 1H), 7.67 (s, 1H), 7.58-7.63 (m, 1H), 7.45 (ddd, J=7.0, 3.0, 1.0 Hz, 1H), 7.07 (dd, J=17.6, 10.9 Hz, 1H), 6.33 (d, J=17.5 Hz, 1H), 5.73 (d, J=11.0 Hz, 1H), 4.72 (d, J=9.5 Hz, 0.5H), 4.55 (d, J=13.0 Hz, 1H), 4.43 (d, J=12.5 Hz, 1H), 4.12 (d, J=7.2 Hz, 0.5H), 3.87-3.99 (m, 2H), 3.73-3.84 (m, 1H), 3.46 (m, 1H), 3.26 (m, 1.5H), 3.13 (d, J=10.5 Hz, 1H), 2.59-2.68 (m, 1.5H), 2.03 (d, J=6.0 Hz, 1H), 1.54-1.59 (m, 1H), 1.11-1.19 (m, 3H), 0.86-0.94 (m, 2H), 0.80-0.86 (m, 2H), 0.51-0.57 (m, 2H)

[0995] LC-MS: m/z 493.3 $(M+H)^+$

Compound 608 (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinolin-5-yl)nicotinonitrile

[0996] The synthesis was similar to Compound 542.

[0997] 1H NMR (400 MHz, CHLOROFORM-d) δ8.16-8.24 (m, 1H), 7.90-7.97 (m, 1H), 7.76-7.83 (m, 1H), 7.59-7.66 (m, 2H), 7.46 (d, J=7.0 Hz, 1H), 7.12 (dd, J=17.6, 10.9 Hz, 1H), 6.35 (d, J=17.5 Hz, 1H), 5.76 (d, J=11.0 Hz, 1H), 4.95 (m, 0.5H), 4.58 (d, J=12.5 Hz, 0.5H), 4.19-4.44 (m, 2.5H), 3.67-3.91 (m, 1.5H), 3.40 (s, 3H), 3.15-3.26 (m, 1.5H), 2.67-2.82 (m, 1.5H), 2.03 (d, J=5.7 Hz, 1H), 1.55 (td, J=8.0, 4.1 Hz, 1H), 1.31-1.37 (m, 3H), 1.11-1.18 (m, 2H) 0.77-0.86 (m, 2H)

[0998] LC-MS: m/z 482.2 $(M+H)^+$

Compound 633 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinolin-5-yl)nicotinonitrile

[0999] The synthesis was similar to Compound 542.

[1000] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.21 (d, J=8.2 Hz, 1H), 7.87-7.99 (m, 1H), 7.75-7.85 (m, 1H), 7.58-7.69 (m, 2H), 7.41-7.50 (m, 1H), 7.12 (dd, J=17.0, 11.0 Hz, 1H), 6.35 (d, J=17.5 Hz, 1H), 5.76 (d, J=11.0 Hz, 1H), 4.93 (m, 0.5H), 4.51-4.61 (m, 0.5H), 4.37 (d, J=12.8 Hz, 1H), 4.21-4.29 (m, 1H), 3.88-3.99 (m, 2H), 3.77 (d, J=12.0 Hz, 0.5H), 3.60 (t, J=12.3 Hz, 0.5H), 3.27-3.44 (m, 2H), 3.02-3.26 (m, 1H), 2.49-2.79 (m, 2H), 1.96-2.07 (m, 1H), 1.51-1.60 (m, 1H), 1.27 (s, 3H), 1.08-1.17 (m, 2H), 0.77-0.87 (m, 2H)

[1001] LC-MS: m/z 468.2 $(M+H)^+$

Compound 637

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinazolin-4-yl) nicotinonitrile

[1002] The synthesis was similar to Compound 542.

[1003] ^{1}H NMR (CHLOROFORM-d) δ 8.07 (d, J=8.3 Hz, 1H), 7.85-7.96 (m, 2H), 7.81 (d, J=8.0 Hz, 1H), 7.57 (td, J=7.7, 1.0 Hz, 1H), 7.08 (dd, J=17.3, 10.5 Hz, 1H), 6.81 (dd, J=17.3, 1.8 Hz, 1H), 5.79-5.94 (m, 1H), 4.82-4.98 (m, 0.5H), 4.54 (d, J=12 Hz, 0.5H), 4.29-4.48 (m, 2H), 3.93 (br. s., 2H), 3.69-3.82 (m, 0.5H), 3.52-3.66 (m, 0.5H), 3.43-3.52 (m, 1H), 3.31-3.43 (m, 1H), 3.01-3.30 (m, 1.5H), 2.47-2.77 (m, 2H), 1.64-1.79 (m, 1H), 1.42 (d, J=6.5 Hz, 1.5H), 1.32 (d, J=6.5 Hz, 1.5H), 1.11-1.24 (m, 2H), 0.90 (d, J=5.8 Hz, 2H)

[1004] LC-MS: m/z 469.2 $(M+H)^+$

Compound 334 (General Procedure 1, Step H)

(R)-6-cyclopropyl-5-(2-ethyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1005] ^{1}H NMR (METHANOL-d) δ 7.59 (s, 1H), 7.33-7.36 (d, J=4.4 Hz, 2H), 7.24-7.27 (m, 1H), 7.12-7.13 (d, J=7.6 Hz, 1H), 4.40-4.46 (m, 1H), 4.14-4.23 (m, 2H), 3.92-3.96 (d, J=14.4 Hz, 0.5H), 3.34 (s, 3H), 3.14-3.19 (m, 2H), 3.34 (s, 4H), 2.99-3.14 (m, 0.5H), 2.60-2.81 (m, 2H), 2.46-2.50 (m, 2H), 1.64-1.69 (m, 1H), 1.37-1.41 (q, J=7.2 Hz, 1.3H), 1.26-1.30 (t, J=6.4 Hz, 1.7H), 1.02-1.11 (m, 5H), 0.82-0.91 (m, 2H); LC-MS: m/z 433.6 (M+H)

Compound 357 (General Procedure 1, Step H)

(R)-6-cyclopropyl-5-(2,6-dimethyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1006] ^{1}H NMR (METHANOL-d) δ 7.48 (s, 1H), 7.11-7.18 (m, 3H), 4.79 (s, 1H), 4.39-4.45 (m, 1H), 4.21-4.24 (d, J=12.8 Hz, 1.5H), 4.13-4.17 (d, J=13.2 Hz, 0.5H), 3.91-3.95 (d, J=13.6 Hz, 0.5H), 3.66-3.69 (t, J=5.2 Hz, 2H), 3.55-3.61 (t, J=7.2 Hz, 0.5H), 3.34 (s, 4H), 3.10-3.21 (m, 1H), 2.96-3.01 (m, 0.5H), 2.69-2.80 (m, 1H), 2.60-2.65 (m, 1H), 2.01-2.02 (d, J=2.8 Hz, 6H), 1.51-1.57 (m, 1H), 1.38-1.39 (d, J=6.4 Hz, 1.3H), 1.26-1.28 (d, J=6.8 Hz, 1.7H), 1.08-1.11 (m, 1H), 0.75-0.91 (m, 2H) LC-MS: m/z 433.2 (M+H)

Compound 344 (General Procedure 1, Step H)

(R)-6-cyclopropyl-5-(2-hydroxymethyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1007] 1H NMR (METHANOL-d) δ 7.63 (s, 1H), 7.58-7.60 (d, J=7.6 Hz, 1H), 7.40-7.44 (t, J=7.6 Hz, 1H), 7.33-7.36 (t, J=7.6 Hz, 1H), 7.16-7.18 (d, J=7.6 Hz, 1H), 4.78 (s, 1H), 4.36-4.49 (m, 3H), 4.13-4.24 (m, 2H), 3.91-3.95 (d, J=13.2 Hz, 0.5H), 3.66-6.69 (m, 2H), 3.54-3.61 (m, 0.5H), 3.33-3.34 (m, 4H), 3.25-3.28 (m, 0.5H), 3.13-3.15 (m, 1H), 2.96-3.02 (m, 0.5H), 2.69-2.81 (m, 1H), 2.60-2.65 (m, 1H), 1.62-1.68 (m, 1H), 1.37-1.39 (m, 1.5H), 1.25-1.28 (m, 1.5H), 1.11-1.12 (m, 2H), 0.83-0.92 (m, 2H); LC-MS: m/z 435.2 (M+H)

Compound 328 (General Procedure 1, Step H)

(R)-2-cyclopropyl-2'-methoxy-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-[3,3']bipyridinyl-5-carbonitrile

[1008] ^{1}H NMR (METHANOL-d) δ 8.17-8.18 (dd, J=4.8 Hz, 1H), 7.65 (s, 1H), 7.61-7.63 (dd, J=7.2 Hz, 1H), 7.04-7.07 (dd, J=7.2 Hz, 1H), 4.76-4.78 (m, 0.5H), 4.38-4.44 (m, 1H), 4.13-4.25 (m, 2H), 3.90 (s, 3H), 3.66-3.69 (t, J=5.6 Hz, 2H), 3.54-6.60 (m, 0.5H), 3.33 (s, 3H), 3.15-3.19 (m, 0.5H), 3.12-3.13 (m, 1H), 2.97-3.03 (m, 0.5H), 2.69-2.80 (m, 1H), 2.59-2.65 (m, 1H), 1.67-1.73 (m, 1H), 1.37-1.38 (d, J=6.4 Hz, 1H), 1.25-1.27 (d, J=6.8 Hz, 2H), 1.10-1.11 (m, 2H), 0.85-0.92 (m, 2H)

[1009] LC-MS: m/z 436.2 (M+H)

Compound 338 (General Procedure 1, Step H)

(R)-6-cyclopropyl-5-[2-(2-methoxy-ethyl)-phenyl]-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1010] 1H NMR (METHANOL-d) δ 7.63 (s, 1H), 7.51-7.53 (d, J=6.4 Hz, 1H), 7.39-7.42 (m, 2H), 7.22-7.23 (dd, J=6.8 Hz, 1H), 4.15-4.45 (m, 4H), 3.93-3.96 (m, 0.5H), 3.66-3.69 (m, 2H), 3.34 (s, 4H), 3.16-3.17 (d, J=4.0 Hz, 3H), 3.13-3.14 (m, 0.5H), 3.00-3.04 (m, 0.5H), 2.70-2.81 (m, 1H), 2.61-2.64 (m, 1H), 1.63-1.67 (m, 1H), 1.38-1.40 (m, 1H), 1.26-1.29 (m, 2H), 1.12-1.25 (m, 2H), 0.83-0.94 (m, 2H) LC-MS: m/z 449.2 (M+H)

Compound 360 (General Procedure 1, Step H)

(R)-5-(2-chloro-quinolin-3-yl)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1011] 1H NMR (METHANOL-d) δ 8.38 (S, 1H), 8.00-8.02 (m, 2H), 7.85 (t, J=7.2 Hz, 2H), 7.81 (S, 1H), 7.68 (t, J=8.0 Hz, 1H), 4.8 (m, 1H), 4.4-4.5 (m, 1H), 4.2-4.4 (m, 1H), 3.95 (d, J=14.0 Hz, 0.5H), 3.67 (t, J=18.0 Hz, 2h), 3.54-3.60 (m, 0.5H), 3.32-3.45 (m, 4.5H), 3.22-3.25 (m, 1H), 3.09-3.22 (m, 0.5H), 2.71-2.79 (m, 1H), 2.60-2.65 (m, 1H), 1.63-1.69 (m, 1H), 1.39-1.41 (m, 1H), 1.30 (t, J=6.8 Hz, 2H), 1.18-1.24 (m, 1H), 1.12-1.17 (m, 1H), 0.95-1.15 (m, 1H), 0.85-0.95 (m, 1H).

[1012] LC-MS: m/z 490.1 (M+H)+.

Compound 371 (General Procedure 1, Step H)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-(2-methyl-2H-pyrazol-3-yl)-nicotinonitrile

[1013] 1H NMR (METHANOL-d) δ 7.77 (s, 1H), 7.55 (d, J=2.0 Hz, 1H), 6.36 (d, J=2.0 Hz, 1H), 4.78 (m, 0.5H), 4.21-4.44 (m, 3H), 3.94 (d, J=12.6 Hz, 0.5H), 3.66-3.69 (m, 4.5H), 3.54-3.62 (m, 0.5H), 3.33 (m, 3.5H), 2.70-2.82 (m, 1H), 2.59-2.65 (m, 1H), 1.68-1.74 (m, 1H), 1.36 (d, J=6.8 Hz, 1H), 1.27 (d, J=11.2 Hz, 2H), 1.14-1.24 (m, 2H), 0.97-1.02 (m, 2H). LC-MS: m/z 409.2 $(M+H)^+$.

Compound 345 (General Procedure 1, Step H)

(R)-6-cyclopropyl-5-(3,5-dimethyl-isoxazol-4-yl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1014] 1H NMR (METHANOL-d) δ 7.70 (s, 1H), 4.77-4.80 (m, 0.5H), 4.42 (d, J=13.2 Hz, 1H), 4.17-4.28 (m, 2H), 3.94 (d, J=13.2 Hz, 0.5H), 3.68 (t, J=5.2 Hz, 2H), 3.51-3.62 (m, 1H), 3.31-3.33 (m, 3H), 3.14-3.24 (m, 1H), 3.01-3.08 (m, 0.5H), 2.71-2.80 (m, 1H), 2.59-2.70 (m, 1H), 2.30 (s, 3H), 2.14 (s, 3H), 1.75-1.82 (m, 1H), 1.38 (d, J=6.8 Hz, 1H), 1.25 (d, J=11.2 Hz, 2H), 1.15-1.20 (m, 2H), 0.98-1.02 (m, 2H). LC-MS: m/z 424.2 (M+H)+.

Compound 394 (General Procedure 1, Step H)

(R)-6-cyclopropyl-5-(1H-indol-2-yl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1015] ^{1}H NMR (CHLOROFORM-d) δ 8.27 (s, 1H), 7.79 (s, 1H0, 7.64 (d, J=8.0 Hz, 1H), 7.23 (t, J=8.0 Hz, 1H), 7.16 (t, J=7.6 Hz, 1H), 6.65 (t, J=1.2 Hz, 1H), 4.89 (s, 0.5H), 4.52 (d, J=13.2 Hz, 0.5H), 4.23-4.35 (m, 2.5H), 3.72-3.77 (m, 2.5H), 3.54-3.60 (m, 0.5H), 3.37 (s, 3H), 3.26-3.32 (m, 1H), 3.04-3.17 (m, 1H), 2.55-2.72 (m, 2H), 2.36-2.43 (m, 1H), 1.37 (d, J=5.6 Hz, 1H), 1.26 (d, J=6.8 Hz, 2H), 1.18-1.20 (m, 2H), 1.03-1.04 (m, 2H). LC-MS: m/z 444.2 $(M+H)^+$.

Compound 361 (General Procedure 1, Step I)

(R)-5-(1H-benzoimidazol-5-yl)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1016] ^{1}H NMR (METHANOL-d) 8.226 (s, 1H), 7.764 (s, 1H), 7.697-7.614 (m, 2H), 7.333-7.313 (d, J=8 Hz, 2H), 4.775-4.856 (m, 0.5H), 4.459-4.389 (m, 1H), 4.268-4.147 (m, 2H), 3.968-3.929 (m, 0.5H), 3.688-3.567 (m, 3H), 3.342 (s, 3H), 3.193-3.022 (m, 2H), 2.814-2.626 (m, 2H), 2.125-2.076 (m, 1H), 1.402-1.274 (m, 3H), 1.175 (s, 2H), 1.54-0.928 (m, 2H). LC-MS: m/z 445.1 $(M+H)^+$.

Compound 352 (General Procedure 1, Step I)

(R)-5-benzothiazol-5-yl-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1017] 1H NMR (METHANOL-d) 9.301 (s, 1H), 8.163-8.142 (d, J=8.4 Hz, 1H), 8.102-8.099 (d, J=1.2, 1H), 7.807 (s, 1H), 7.559-7.535 (dd, J1=9.6 Hz, J2=1.6 Hz, 1H), 4.792 (m, 0.5H), 4.453-4.418 (m, 1H), 4.282-4.170 (m, 2H), 3.959-3.926 (m, 0.5H), 3.682-3.667 (m, 2H), 3.616-3.561 (m, 0.5H), 3.338 (s, 3H), 3.212-3.004 (m, 2H), 2.806-2.594 (m, 2H), 2.085-2.022 (m, 1H), 1.392-1.262 (m, 3H), 1.211-1.176 (m, 2H), 1.000-0.900 (m, 2H). LC-MS: m/z 462.1 (M+H)+.

Compound 364 (General Procedure 1, Step I)

(R)-5-benzothiazol-6-yl-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1018] 1H NMR (METHANOL-d) 9.292 (s, 1H), 8.131 (s, 2H), 7.806 (s, 1H), 7.624-7.606 (d, J=7.2 Hz, 1H), 4.775-4.856 (m, 0.5H), 4.412-4.172 (m, 3H), 3.960-3.931 (m, 0.5H), 3.555-3.688 (m, 3H), 3.345 (s, 3H), 3.188-3.038 (m, 2H), 2.762-2.640 (m, 2H), 2.047-2.035 (m, 1H), 1.379-1.266 (m, 3H), 1.192 (s, 2H), 0.965 (s, 2H). LC-MS: m/z 462.0 (M+H)+.

Compound 417 (General Procedure 1, Step I)

(R)-5-(2-amino-benzothiazol-6-yl)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1019] 1H NMR (CHLOROFORM-d) 7.844 (s, 1H), 7.719-7.715 (d, J=1.6 Hz, 1H), 7.547 (s, 2H), 7.402-7.381 (d, J=8.4 Hz, 1H), 7.266-7.242 (d, J=9.6, 1H), 4.631-4.664 (m, 0.5H), 4.297-4.017 (m, 3H), 3.869-3.838 (m, 0.5H), 3.564-3.453 (m, 3H), 3.349-3.228 (m, 3H), 3.109-2.929 (m, 2H), 2.669-2.500 (m, 2H), 2.081-2.058 (m, 1H), 1.236 (s, 1H), 1.135-1.079 (m, 4H), 0.964-0.936 (m, 2H). LC-MS: m/z 477.1 (M+H)+.

Compound 370 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-tetrazolo[1,5-a]pyridin-6-yl-nicotinonitrile

[1020] 1H NMR (METHANOL-d) 9.213-9.215 (d, J=0.8 Hz, 1H), 8.131-8.154 (d, J=9.2 Hz, 1H), 7.917-7.947 (m, 2H), 4.784 (s, 0.5H), 4.220-4.782 (m, 3H), 3.973-3.939 (d, J=13.6 Hz, 0.5H), 3.680 (s, 0.5H), 3.051-3.40 (m, 6H), 2.595-2.821 (m, 2H), 1.973-2.033 (m, 1H), 1.231-1.369 (m, 5H), 0.90-1.120 (s, 2H). LC-MS: m/z 447.1 (M+H)+.

Compound 367 (General Procedure 1, Step I)

(R)-6-cyclopropyl-5-isoquinolin-8-yl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1021] 1H NMR (METHANOL-d) 9.342-9.356 (d, J=5.6 Hz, 1H), 8.626-8.642 (d, J=6.4 Hz, 1H), 8.530-8.546 (d, J=6.4 Hz 1H), 8.347-8.368 (d, J=8.4 Hz 1H), 8.263-8.284 (d, J=8.4 Hz 1H), 7.976-7.994 (d, J=7.2 Hz, 1H), 7.912 (s, 1H), 4.814 (s, 0.5H), 4.265-4.808 (m, 3H), 3.968-4.002 (m, 2.5H), 3.151-3.441 (m, 5H), 2.622-2.804 (m, 2H), 1.182-1.496 (m, 5H), 0.801-0.981 (m, 2H). LC-MS: m/z 456.1 $(M+H)^+$.

Compound 373 (General Procedure 1, Step I)

(R)-6-cyclopropyl-5-(1H-indol-7-yl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1022] 1H NMR (METHANOL-d) 7.759 (s, 1H), 7.579-7.599 (d, J=8 Hz, 1H), 7.218 (s, 1H), 7.080-7.099 (d, J=7.6 Hz 1H), 7.000-7.018 (d, J=7.2 Hz 1H), 6.506-6.513 (d, J=7.2 Hz, 1H), 4.417-4.466 (dd, J=8 Hz, 1H), 4.191-4.261 (m, 3H), 3.940-3.976 (d, J=1.44 Hz, 0.5H), 3.603-3.642 (m, 3H), 2.617-3.346 (m, 7H), 1.717-1.828 (m, 1H), 1.155-1.421 (m, 5H), 0.832-0.851 (dd, J=4.4 HZ, 2H). LC-MS: m/z 444.2 (M+H)+.

Compound 353 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-quinolin-6-yl-nicotinonitrile

[1023] ^{1}H NMR (METHANOL-d) 9.170-9.183 (d, J=5.2 Hz, 1H), 9.076-9.097 (d, J=8.4 Hz, 1H), 8.304-8.333 (t, 2H),

8.194-8.216 (d, J=8.8 Hz 1H), 8017-8.050 (m, 1H), 7.918 (s, 1H), 4.787 (s, 0.5H), 4.214-4.447 (m, 3H), 3.974-4.214 (d, J=96 Hz, 0.5H), 3.336-3.397 (m, 3H), 3.076-3.3.250 (m, 5H), 2.599-2.811 (m, 2H), 2.023-2.043 (m, 1H), 1.363-1.379 (d, J=6.4 Hz 1H), 1.244-1.263 (d, J=7.6 Hz 4H), 0.99-1.026 (m, 2H). LC-MS: m/z 456.1 (M+H)+.

Compound 374 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-(1H-pyrrolo[2,3-b]pyridin-5-yl)-nicotinonitrile

[1024] ^{1}H NMR (METHANOL-d) 8.313 (s, 1H), 8.280 (s, 1H), 7.831 (s, 1H), 7.563-7.572 (d, J=3.6 Hz 1H), 6.682-6.690 (d, J=3.2 Hz 1H), 4.795 (s, 0.5H), 4.183-4.455 (m, 3H), 3.929-3.969 (m, 0.5H), 3.568-3.687 (m, 3H), 3.179-3.342 (m, 4H), 3.046-3.078 (m, 1H), 2.609-2.810 (m, 2H), 2.020 (s, 1H), 1.194-1.392 (m, 5H), 0.964-0.991 (m, 2H). LC-MS: m/z 445.2 (M+H)+.

Compound 395 (General Procedure 1, Step I)

(R)-(4-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-pyridin-3-yl}-thiazol-2-yl)-carbamic acid tert-butyl ester

[1025] ^{1}H NMR (CHLOROFORM-d) 8.282 (s, 1H), 7.884-7.889 (d, J=2 Hz, 1H), 6.947-6.951 (d, J=1.6 Hz, 1H), 4.888 (s, 0.5H), 4.493-4.524 (d, J=12.4 Hz, 0.5H), 4.205-4.371 (m, J=44.8 Hz, 2.5H), 3.719-3.790 (m, J=28.4 Hz, 2.5H), 3.499-3.550 (m, J=20.4, 0.5H), 3.367-3.372 (d, J=2 Hz, 3H), 3.218-3.246 (t, J=11.2 Hz, 1H), 3.006-3.118 (m, J=44.8 Hz, 1.5H), 2.544-2.745 (m, J=80.4 Hz, 2H), 2.404-2.465 (m, J=24.4 Hz, 1H), 1.532 (s, 9H), 1.243-1.355 (q, J=44.8 Hz, 3H), 1.153-1.158 (d, J=2 Hz, 2H), 0.969-0.985 (t, J=6.4 Hz, 2H). LC-MS: m/z 527.2 (M+H)+.

Compound 418 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-(2-methyl-1-oxo-1,2-dihydro-isoquinolin-4-yl)-nicotinonitrile

[1026] 1H NMR (CHLOROFORM-d) 8.506-8.526 (d, J=8.0 Hz, 1H), 7.617-7.658 (t, J=16.4 Hz, 1H), 7.596 (s, 1H), 7.529-7.569 (t, J=16 Hz, 1H), 7.209-7.240 (t, J=12.4 Hz, 1H), 7.036 (s, 1H), 4.916 (s, 0.5H), 4.534-4.642 (m, J=43.2 Hz, 3H), 4.208-4.351 (m, J=57.2 Hz, 3H), 3.836-3.869 (m, J=13.2 Jz, 0.5H), 3.681-3.739 (t, J=23.2 Hz, 2H), 3.589 (s, 3H), 3.287-3.371 (m, J=33.6 Hz, 1H), 3.155-3.192 (m, 1.5H), 2.594-2.773 (m, 2H), 1.678-1.740 (m, J=24.8 Hz, 1H), 1.301-1.423 (d, J=48.8 Hz, 3H), 1.089-1.143 (m, 2H), 0.809-0.909 (m, 2H). LC-MS: m/z 486.2 (M+H)+.

Compound 354 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-(4-morpholin-4-yl-phenyl)-nicotinonitrile

[1027] 1H NMR (CHLOROFORM-d) 7.665 (s, 1H), 7.348-7.327 (d, J=8.4 Hz, 2H), 7.129-7.107 (d, J=8.8 Hz, 2H), 4.824-4.780 (m, 1H), 4.440-4.408 (m, 1H), 4.220-4.109 (m, 2H), 3.884-3.860 (m, 4H), 3.693-3.520 (m, 3H), 3.361-3.4 (s, 3H), 3.230-3.298 (m, 4.5H), 3.183-2.988 (m, 1.5H), 2.798-2.600 (m, 2H), 2.115-2.076 (m, 1H), 1.382-1.253 (m, 3H), 1.162-1.128 (m, 2H), 0.986-0.957 (m, 2H). LC-MS: m/z 490.2 (M+H)+.

Compound 396 (General Procedure 1, Step I)

(R)-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-6'-piperazin-1-yl-[3,3']bipyridinyl-5-carbonitrile

[1028] 1H NMR (CHLOROFORM-d) 8.201-8.207 (d, J=2.4 Hz, 1H), 7.531 (s, 2H), 6.718-6.739 (d, J=8.4 Hz, 1H), 4.867 (m, 1H), 4.477-4.507 (m, 4H), 4.149-4.302 (m, 3H), 4.17-4.39 (m, 3H), 3.601-3.807 (m, 6H), 3.494-3.549 (m, 1H), 3.349 (s, 3H), 2.992-3.213 (m, 6H), 2.531-2.734 (m, 2H), 1.974-2.030 (m, 1H), 1.352-1.367 (d, J=6 Hz, 1H), 1.235-1.265 (t, 2H), 0.967-0.992 (m, 2H). LC-MS: m/z 490.2 (M+H)+.

Compound 406 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-[3-(1H-pyrazol-4-yl)-phenyl]-nicotinonitrile

[1029] 1H NMR (CHLOROFORM-d) 8.030 (s, 2H), 7.735 (s, 1H), 7.589-7.613 (m, 2H), 7.423-7.462 (m, 1H), 7.242-7.269 (m, 1H), 4.781 (m, 0.5H), 4.376-4.441 (m, 1H), 4.131-4.243 (m, 2H), 3.908-3.940 (d, J=12.8 Hz, 1H), 3.660-3.675 (m, 2H), 3.540-3.602 (m, 0.5H), 3.334 (s, 3H), 3.253-3.262 (d, J=3.6 Hz, 0.5H), 3.122-3.183 (t, 1H), 2.966-3.022 (t, 0.5H), 2.631-2.810 (m, 1H), 2.586-2.615 (m, 1H), 2.061-2.124 (m, 1H), 1.362-1.379 (d, J=6.8 Hz, 1H), 1.249-1.266 (d, J=6.8 Hz, 2H), 1.165-1.182 (m, 2H), 0.900-0.970 (m, 2H) 137. LC-MS: m/z 471.2 (M+H)+.

Compound 363 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-[3-(1H-pyrazol-3-yl)-phenyl]-nicotinonitrile

[1030] ^{1}H NMR (CHLOROFORM-d) 7.820-7.824 (d, J=1.6 Hz, 1H), 7.767-7.795 (t, 2H), 7.686-7.692 (d, J=2.4 Hz, 1H), 7.490-7.528 (t, 1H), 7.374-7.393 (d, J=7.6 Hz, 1H), 6.720-6.725 (d, J=2 Hz, 1H), 4.790 (m, 0.5H), 4.396-4.452 (m, 1H), 4.153-4.264 (m, 2H), 3.920-3.953 (d, J=13.2 Hz, 0.5H), 3.608-3.680 (m, 2H), 3.554-3.582 (t, 0.5H), 3.337 (s, 3H), 3.220 (m, 0.5H), 3.140-3.197 (t, 1H), 2.986-3.043 (t, 0.5H), 2.751-2.803 (m, 1H), 2.591-2.729 (m, 1H), 2.069-2.120 (m, 1H), 1.372-1.388 (d, J=6.4 Hz, 1H), 1.259-1.276 (d, J=6.8 Hz, 2H), 1.156-1.191 (m, 2H), 0.982 (m, 2H). LC-MS: m/z 471.4 (M+H)+.

Compound 436 (General Procedure 1, Step I)

(R)-6-cyclopropyl-5-imidazo[1,2-a]pyridin-6-yl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1031] ^{1}H NMR (CHLOROFORM-d) 8.126 (s, 1H), 7.952 (bs, 1H), 7.681-7.684 (d, J=1.2 Hz, 1H), 7.621 (s, 1H), 7.547 (s, 1H), 7.257-7.280 (d, J=13.6 Hz, 1H), 4.823 (br, 0.5H), 4.436-4.467 (d, J=12.4 Hz, 0.5H), 4.149-4.278 (m, 3H)), 3.649-3.717 (m, 2.5H), 3.446-3.501 (m, 0.5H), 3.299 (s, 3H), 3.219-3.254 (m, 1H), 3.019-3.121 (m, 2H), 2.628-2.646 (m, 1H), 2.501-2.531 (m, 1H), 1.842-1.897 (m, 1H), 1.293-1.308

(d, J=6 Hz, 1.5H), 1.183-1.204 (d, J=8.4 Hz, 1.5H), 1.097-1.115 (m, 2H), 0.902-0.933 (m, 2H). LC-MS: m/z 445.1 (M+H)+.

Compound 437 (General Procedure 1, Step I)

(R)-5-benzo[1,2,5]oxadiazol-4-yl-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1032] 1H NMR (CHLOROFORM-d) 7.785-7.808 (d, J=9.2 Hz, 1H), 7.646 (s, 1H), 7.433-7.473 (d, J=16 Hz, 1H), 7.335-7.353 (dd, J=7.2 Hz, 1H), 4.835 (m, 0.5H), 4.441 (m, 0.5H), 4.201-4.320 (m, 3H)), 3.669-3.725 (m, 2.5H), 3.478-3.487 (m, 0.5H), 3.312 (s, 3H), 3.103-3.106 (m, 1H), 3.402-3.705 (m, 2H), 2.596-2.654 (m, 1H), 2.484-2.537 (m, 1H), 1.769-1.800 (m, 1H), 1.308 (m, 1.5H), 1.204-1.219 (d, J=6 Hz, 1.5H), 1.127-1.145 (m, 2H), 0.870-0.889 (m, 2H). LC-MS: m/z 447.1 (M+H)+.

Compound 438 (General Procedure 1, Step I)

(R)-6-cyclopropyl-5-(1H-indazol-4-yl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1033] ^{1}H NMR (CHLOROFORM-d) 7.887 (bs, 1H), 7.646 (s, 1H), 7.462-7.483 (d, J=8.4 Hz, 1H), 7.391-7.429 (t, J=15.2 Hz, 1H), 7.055-7.071 (d, J=6.4 Hz, 1H), 4.859 (m, 0.5H), 4.465-4.500 (d, J=14 Hz, 0.5H), 4.166-4.281 (m, 3H)), 3.671-3.733 (m, 2.5H), 3.486-3.510 (m, 0.5H), 3.312 (s, 3H), 3.200-3.252 (m, 1H), 2.992-3.103 (m, 2H), 2.614-2.670 (m, 1H), 2.527-2.557 (m, 1H), 1.819-1.840 (m, 1H), 1.340-1.355 (d, J=6 Hz, 1.5H), 1.238-1.253 (d, J=6 Hz, 1.5H), 1.101-1.117 (m, 2H), 0.819-0.846 (m, 2H). LC-MS: m/z 445.1 (M+H)$^+$.

Compound 473 (General Procedure 1, Step I)

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-5-(2-oxo-2,3-dihydro-benzooxazol-5-yl)-nicotinonitrile

[1034] 1H NMR (CHLOROFORM-d) 8.492 (s, 1H), 7.568-7.569 (d, J=0.4 Hz, 1H), 7.277 (s, 1H), 7.121-7.125 (t, 1H), 7.064-7.068 (d, J=1.6 Hz, 1H), 6.720-6.725 (d, J=2 Hz, 1H), 4.897 (m, 0.5H), 4.510-4.549 (m, 0.5H), 4.175 (m, 2.5H), 3.780 (m, 2.5H), 3.543 (t, 0.5H), 3.369 (s, 3H), 3.246-3.273 (m, 1H), 3.113-3.119 (m, 1H), 3.019-3.048 (t, 0.5H), 2.649-2.759 (m, 1H), 2.556-2.609 (m, 1H), 1.998-2.006 (m, 1H), 1.268-1.387 (m, 3H), 1.129-1.155 (m, 2H), 0.928-0.955 (m, 2H). LC-MS: m/z 462.1 (M+H)+.

Compound 474 (General Procedure 1, Step I)

(R)-6-cyclopropyl-5-(1-methoxy-isoquinolin-4-yl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1035] ^{1}H NMR (CHLOROFORM-d) 8.350-8.325 (d, J=10 Hz, 1H), 7.913 (s, 1H), 7.660-7.415 (m, 4H), 4.915 (s, 0.5H), 4.562-4.530 (m, 0.5H), 4.278-4.228 (m, 2.5H), 4.261 (s, 3H), 3.797-3.553 (m, 3H), 3.797 (s, 3H), 3.577-3.044 (m, 2.5H), 2.750-2.568 (m, 2H), 1.633-1.625 (m, 1H), 1.429-1.322 (m, 3H), 1.137-1.093 (m, 2H), 0.842-0.765 (m, 2H). LC-MS: m/z 486.1 (M+H)$^+$.

Compound 299

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(4-fluorophenyl)-4-methylnicotinonitrile

[1036] ^{1}H NMR (CHLOROFORM-d) δ 7.10-7.16 (m, 4H), 4.62-4.65 (m, 0.5H), 4.23 (d, J=12.8 Hz, 1H), 4.15 (d, J=12.5 Hz, 1H), 4.04 (d, J=8.3 Hz, 0.5H), 3.61-3.88 (m, 3.5H), 3.31-3.38 (m, 3H), 3.25 (br. s., 0.5H), 3.02-3.17 (m, 1H), 2.89-3.02 (m, 1H), 2.51-2.73 (m, 2H), 2.09-2.18 (m, 3H), 1.53-1.59 (m, 1H), 1.33-1.44 (m, 1H), 0.99-1.08 (m, 2H), 0.75-0.86 (m, 2H), 0.29-0.63 (m, 4H)

[1037] LC-MS: m/z 463.4 (M+H)$^+$

Compound 300

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(4-fluorophenyl)-4-methylnicotinonitrile

[1038] ^{1}H NMR (CHLOROFORM-d) δ 7.19 (d, J=7.3 Hz, 4H), 4.70 (br. s., 0.5H), 4.30 (d, J=13.1 Hz, 1H), 4.18-4.27 (m, 1H), 4.12 (d, J=8.3 Hz, 0.5H), 3.81-3.94 (m, 1H), 3.66-3.78 (m, 1H), 3.32 (q, J=9.8 Hz, 2H), 3.08-3.21 (m, 1H), 2.97-3.08 (m, 1H), 2.14-2.25 (m, 3H), 1.58-1.67 (m, 1H), 1.50 (br. s., 1H), 1.04-1.14 (m, 2H), 0.81-0.89 (m, 2H), 0.65 (br. s., 1H), 0.56 (br. s., 1H), 0.37-0.52 (m, 2H)

[1039] LC-MS: m/z 487.2 (M+H)$^+$

Compound 627 (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(6-vinylpyrimidin-4-yl)nicotinonitrile

[1040] 1H NMR (CHLOROFORM-d) δ 9.30 (d, J=1.1 Hz, 1H), 9.30 (d, J=1.1 Hz, 1H), 7.32 (t, J=4.5 Hz, 1H), 6.82 (dd, J=17.4, 10.7 Hz, 1H), 6.64-6.49 (m, 1H), 5.81 (dd, J=14.9, 4.1 Hz, 1H), 4.93 (d, J=17.7 Hz, 1H), 4.53 (d, J=13.3 Hz, 1H), 4.20 (dd, J=33.1, 13.9 Hz, 2H), 3.77 (dd, J=18.0, 11.5 Hz, 2H), 3.57 (dd, J=12.8, 9.6 Hz, 1H), 3.39 (s, 3H), 3.34-2.95 (m, 3H), 2.82-2.49 (m, 2H), 2.26 (s, 3H), 2.88-1.49 (m, 8H), 1.57 (ddd, J=12.5, 8.0, 4.5 Hz, 1H), 1.45-1.37 (m, 2H), 1.33-1.28 (m, 2H), 1.14 (dt, J=7.4, 3.5 Hz, 2H), 0.96-0.81 (m, 3H).

[1041] LC-MS: m/z 447.2 (M+H)$^+$

Compound 628 (R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1042] 1H NMR (CHLOROFORM-d) δ 8.70 (d, J=4.9 Hz, 1H), 7.23 (s, 1H), 7.08 (d, J=4.1 Hz, 1H), 6.88 (dd, J=17.4, 10.8 Hz, 1H), 6.30 (d, J=17.4 Hz, 1H), 5.58 (d, J=10.9 Hz, 1H), 4.92 (s, 1H), 4.53 (t, J=14.2 Hz, 1H), 4.29-4.08 (m, 3H), 3.76 (t, J=6.3 Hz, 2H), 3.57 (dd, J=23.8, 17.1 Hz, 1H), 3.40 (s, 3H), 3.31-2.95 (m, 3H), 2.68 (ddd, J=33.7, 17.4, 11.1 Hz, 2H), 2.20 (d, J=8.0 Hz, 3H), 1.57 (ddd, J=12.5, 8.1, 4.6 Hz, 1H), 1.41 (d, J=6.3 Hz, 2H), 1.36-1.25 (m, 4H), 1.10 (s, 2H), 0.94-0.74 (m, 3H).

[1043] LC-MS: m/z 446.2 (M+H)$^+$

Compound 411 (R)-5-(4-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1044] 1H NMR (CHLOROFORM-d) d: 6.97-7.10 (m, 2H), 6.87-6.97 (m, J=8.0 Hz, 2H), 4.92 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.23 (br. s., 0.5H), 3.95-4.18 (m, 2H),

3.71-3.83 (m, 2.5H), 3.58 (m, 0.5H) 3.40 (s, 3H), 3.11-3.27 (m, 1.5H), 2.88-3.10 (m, 1H), 2.53-2.82 (m, 2H), 2.16-2.28 (m, 3H), 1.68-1.78 (m, 1H), 1.38-1.47 (m, 1.5H), 1.33 (d, J=6.5 Hz, 1.5H), 0.98-1.13 (m, 2H), 0.75-0.93 (m, 2H)

[1045] LC-MS: m/z 433.5 $(M+H)^+$

Compound 278 (R)-6-cyclopropyl-5-(6-methoxynaphthalen-2-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1046] ^{1}H NMR (CHLOROFORM-d) δ 7.83 (d, J=8.3 Hz, 1H), 7.71-7.78 (m, 1H), 7.60 (s, 1H), 7.25-7.32 (m, 1H), 7.17-7.24 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=13.3 Hz, 0.5H), 4.05-4.21 (m, 2.5H), 3.91-4.00 (m, 3H), 3.69-3.87 (m, 2.5H), 3.52-3.69 (m, 0.5H), 3.33-3.46 (m, 3H), 3.13-3.29 (m, 1.5H), 2.97-3.11 (m, 1H), 2.65-2.83 (m, 1H), 2.60 (dd, J=13.1, 6.5 Hz, 1H), 2.17-2.28 (m, 3H), 1.61-1.74 (m, 1H), 1.39-1.49 (m, 1.5H), 1.33 (d, J=6.5 Hz, 1.5H), 0.99-1.17 (m, 2H), 0.69-0.84 (m, 2H)

[1047] LC-MS: m/z 499.1 $(M+H)^+$

Compound 282 (R)-6-cyclopropyl-5-(2-fluorobiphenyl-4-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1048] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (d, J=8.0 Hz, 2H), 7.44-7.57 (m, 3H), 7.37-7.44 (m, 1H), 7.00-7.10 (m, 2H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.1 Hz, 0.5H), 4.04-4.32 (m, 2.5H), 3.69-3.89 (m, 2.5H), 3.58 (t, J=10.8 Hz, 0.5H), 3.34-3.42 (m, 3H), 3.12-3.30 (m, 1.5H), 2.93-3.12 (m, 1H), 2.64-2.82 (m, 1H), 2.59 (dd, J=13.3, 6.5 Hz, 1H), 2.25 (s, 3H), 1.66-1.76 (m, 1H), 1.41 (d, J=6.3 Hz, 1.5H), 1.32 (d, J=6.8 Hz, 1.5H), 1.04-1.15 (m, 2H), 0.87 (dt, J=7.5, 3.7 Hz, 2H)

[1049] LC-MS: m/z 513.1 $(M+H)^+$

Compound 318 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(3-methyl-pyridyl-5-yl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-nicotinonitrile

[1050] 1H NMR (METHANOL-d) δ 8.79 (s, 1H), 8.70 (s, 1H), 8.40 (d, J=0.4 Hz, 1H), 4.77-4.79 (m, 0.5H), 4.42 (d, J=14.4 Hz, 1H), 4.22-4.24 (m, 1.5H), 4.14 (d, J=13.2 Hz, 0.5H), 3.94 (d, J=13.2 Hz, 0.5H), 3.68 (t, J=6.0 Hz, 2H), 3.55-3.62 (m, 0.5H), 3.31-3.33 (m, 3H), 3.13-3.22 (m, 1H), 3.00-3.06 (m, 0.5H), 2.68-2.82 (m, 1H), 2.58-2.63 (m, 4H), 2.22 (s, 3H), 1.47-1.54 (m, 1H), 1.37 (d, J=6.8 Hz, 1H), 1.26 (d, J=11.2 Hz, 2H), 1.13-1.17 (m, 2H), 0.91-0.94 (m, 2H)

[1051] LC-MS: m/z 434.2 (M+H)+.

Compound 319 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(4-methanesulfonyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1052] ^{1}H NMR (METHANOL-d) d 8.07 (d, J=8.4 Hz, 2H), 7.52 (d, J=8.4 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 3H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.43 (s, 3H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H)

[1053] LC-MS: m/z 497.2 $(M+H)^+$

Compound 320 (General Procedure 6, Step G')

(R)-2-cyclopropyl-2'-methoxy-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-[3,3'] bipyridinyl-5-carbonitrile

[1054] 1H NMR (METHANOL-d) δ 8.22 (dd, J1=2.0 Hz, J2=4.8 Hz, 1H), 7.54 (dd, J1=2.0 Hz, J2=7.2 Hz, 1H), 7.07-7.10 (m, 1H), 4.78 (s, 0.5H), 4.38-4.45 (m, 1H), 4.01-4.13 (m, 2H), 3.88-3.94 (m, 3.5H), 3.66-3.69 (m, 2H), 3.55-3.61 (m, 0.5H), 3.33 (s, 3H), 3.09-3.25 (m, 2H), 2.91-2.97 (m, 0.5H), 2.69-2.78 (m, 1H), 2.60-2.64 (m, 1H), 2.12 (s, 3H), 1.49-1.52 (m, 1H), 1.40 (d, J=6.4 Hz, 1.3H), 1.28 (dd, J1=2.4 Hz, J2=6.4 Hz, 1.7H), 0.99-1.10 (m, 2H), 0.80-0.83 (m, 2H)

[1055] LC-MS: m/z 450.2 $(M+H)^+$

Compound 321 (General Procedure 6, Step G')

(R)-5-(3-cyano-4-fluoro-phenyl)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1056] 1H NMR (METHANOL-d) δ 7.71 (dd, J1=2.0 Hz, J2=6.4 Hz, 1H), 7.60-7.64 (m, 1H), 7.50 (t, J=9.2 Hz, 1H), 4.77-4.79 (m, 0.5H), 4.38-4.44 (m, 1H), 4.05-4.16 (m, 2H), 3.93 (d, J=13.6 Hz, 0.5H), 3.67-369 (m, 2H), 3.57-3.58 (m, 0.5H), 3.33 (s, 3H), 3.21-3.28 (m, 1H), 3.11-3.15 (m, 1H), 2.96-2.97 (m, 0.5H), 2.69-2.77 (m, 1H), 2.59-2.65 (m, 1H), 2.17 (s, 3H), 1.50-1.54 (m, 1H), 1.38 (d, J=6.4 Hz, 1.3H), 1.26 (d, J=6.8 Hz, 1.7H), 1.09-1.10 (m, 2H), 0.84-0.89 (m, 2H)

[1057] LC-MS: m/z 462.1 $(M+H)^+$

Compound 322 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(3-methoxymethyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1058] 1H NMR (METHANOL-d) δ 7.47 (t, J=7.6 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.20 (s, 1H), 7.15 (d, J=7.6 Hz, 1H), 4.79 (s, 0.5H), 4.50 (s, 2H), 4.37-4.45 (m, 1H), 4.01-4.12 (m, 2H), 3.93 (d, J=13.6 Hz, 0.5H), 3.66-3.69 (m, 2H), 3.55-3.62 (m, 0.6H), 3.39 (s, 3H), 3.33 (s, 3H), 3.04-3.29 (m, 2H), 2.90-2.97 (m, 0.5H), 2.59-2.81 (m, 2H), 2.15 (s, 3H), 1.62-1.66 (m, 1H), 1.42 (d, J=6.4 Hz, 1.4H), 1.31 (d, J=6.4 Hz, 1.6H), 1.02-1.09 (m, 2H), 0.77-0.84 (m, 2H)

[1059] LC-MS: m/z 463.2 $(M+H)^+$

Compound 323 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(3-fluoro-4-methoxy-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1060] 1H NMR (METHANOL-d) δ 7.19 (t, J=8.4 Hz, 1H), 6.95-6.99 (m, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 3.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H)

[1061] LC-MS: m/z 467.2 $(M+H)^+$

Compound 324 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(2-fluoro-3-methoxy-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1062] 1H NMR (METHANOL-d) δ 7.25-7.34 (m, 2H), 6.75-6.79 (m, 1H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 3.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H)

[1063] LC-MS: m/z 467.2 (M+H)+.

Compound 325 (General Procedure 6, Step G')

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-5-(1-methyl-1H-indol-5-yl)-nicotinonitrile

[1064] 1H NMR (METHANOL-d) δ 7.45 (d, J=8.4 Hz, 1H), 7.35 (s, 1H), 7.21 (s, 1H), 6.96 (d, J=8.4 Hz, 1H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 3.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H).

[1065] LC-MS: m/z 472.2 (M+H)+.

Compound 326 (General Procedure 6, Step G')

(R)—N-(4-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-phenyl)-acetamide

[1066] 1H NMR (METHANOL-d) δ 7.66 (d, J=8.8 Hz, 2H), 7.16 (d, J=8.8 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 2.15 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H).

[1067] LC-MS: m/z 476.2 (M+H)+.

Compound 327 (General Procedure 6, Step G')

(R)-3-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-N-methyl-benzamide

[1068] 1H NMR (METHANOL-d) δ 7.87 (d, J=8.0 Hz, 1H), 7.69 (s, 1H), 7.56-7.62 (m, 1H), 7.41 (d, J=8.0 Hz, 1H) 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 3.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.16 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H).

[1069] LC-MS: m/z 476.2 (M+H)+.

Compound 329 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(3-methanesulfonyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1070] 1H NMR (METHANOL-d) δ 8.02 (d, J=7.6 Hz, 1H), 7.85 (s, 1H), 7.75-7.79 (m, 1H), 7.61 (d, J=7.6 Hz, 1H) 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 5H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.16 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H).

[1071] LC-MS: m/z 497.1 (M+H)+.

Compound 330 (General Procedure 6, Step G')

(R)—N-(4-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-benzyl)-methanesulfonamide

[1072] 1H NMR (METHANOL-d) δ 7.51 (d, J=8.0 Hz, 2H), 7.22 (d, J=8.0 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 3H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 3.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H).

[1073] LC-MS: m/z 526.2 (M+H)+.

Compound 331 (General Procedure 6, Step G')

(R)-4-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-N-methyl-benzenesulfonamide

[1074] 1H NMR (METHANOL-d) δ 7.95 (d, J=8.4 Hz, 2H), 7.47 (d, J=8.4 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.43 (s, 3H), 3.16-3.25 (m, 1.5H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 4H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H).

[1075] LC-MS: m/z 512.2 $(M+H)^+$.

Compound 332 (General Procedure 6, Step G')

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-5-[3-(pyrrolidine-1-carbonyl)-phenyl]-nicotinonitrile

[1076] 1H NMR (METHANOL-d) δ 7.57-7.59 (m, 2H), 7.40 (s, 1H), 7.34-7.37 (m, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.45-3.62 (m, 4.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.88-1.99 (m, 4H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H). LC-MS: m/z 516.2 $(M+H)^+$.

Compound 333 (General Procedure 6, Step G')

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-5-[4-(pyrrolidine-1-carbonyl)-phenyl]-nicotinonitrile

[1077] 1H NMR (METHANOL-d) δ 7.65 (d, J=8.4 Hz, 2H), 7.33 (d, J=8.4 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48

(m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 4.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.88-1.99 (m, 4H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H).

[1078] LC-MS: m/z 516.2 (M+H)+.

Compound 335 (General Procedure 6, Step G')

(R)—N-(3-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-benzyl)-methanesulfonamide

[1079] ^{1}H NMR (METHANOL-d) δ 7.42-7.50 (m, 2H), 7.26 (s, 1H), 7.22 (d, J=7.2 Hz, 1H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.31 (s, 2H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.87 (s, 3H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H). LC-MS: m/z 526.2 $(M+H)^+$.

Compound 336 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(4-cyclopropylmethoxy-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1080] ^{1}H NMR (METHANOL-d) δ 7.11 (d, J=8.4 Hz, 2H), 7.01 (d, J=8.4 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 3.88-4.12 (m, 5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.21-1.41 (m, 4H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H), 0.61-0.69 (m, 2H), 0.35-0.41 (m, 2H).

[1081] LC-MS: m/z 489.2 (M+H)+.

Compound 337 (General Procedure 6, Step G')

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-5-(4-propoxy-phenyl)-nicotinonitrile

[1082] 1H NMR (METHANOL-d) δ 7.10 (d, J=8.8 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 3.98-4.12 (m, 4H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.78-1.89 (m, 2H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 5H), 0.78-0.85 (m, 2H).

[1083] LC-MS: m/z 477.2 (M+H)+.

Compound 340 (General Procedure 6, Step G')

(R)—N-(4-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-benzyl)-acetamide

[1084] 1H NMR (METHANOL-d) δ 7.41 (d, J=8.0 Hz, 2H), 7.19 (d, J=8.0 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 3H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 2.01 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H).

[1085] LC-MS: m/z 490.1 (M+H)+.

Compound 346 (General Procedure 6, Step G')

(R)-5-(4-fluoro-pyridyl-3-yl)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1086] 1H NMR (METHANOL-d) δ 8.10-8.09 (d, J=2.4 Hz, 1H), 7.89-7.85 (m, 1H), 7.23-7.20 (m, 1H), 4.79-4.78 (d, J=1.2 Hz, 0.5H), 4.44-4.41 (d, J=14 Hz, 1H), 4.18-4.01 (m, 2H), 3.95-3.92 (d, J=13.6 Hz, 0.5H), 3.68-3.67 (d, J=5.6 Hz, 2H), 3.62-3.56 (t, J=11.6 Hz, 0.5H), 3.33 (s, 3H), 3.26-3.24 (m, 1H), 3.20-3.11 (m, 1H), 3.01-2.98 (m, 0.5H), 2.80-2.69 (m, 1H), 2.64-2.59 (m, 1H), 2.19 (s, 3H), 1.56-1.54 (m, 1H), 1.39-1.37 (d, J=6.4 Hz, 1H), 1.27-1.26 (d, J=6.8 Hz, 1H), 1.11-1.09 (t, J=3.6 Hz, 2H), 0.89-0.87 (m, 2H). LC-MS: m/z 438.1 (M+H)+.

Compound 347 (General Procedure 6, Step G')

(R)-5-(4-cyano-phenyl)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1087] 1H NMR (METHANOL-d) δ 7.87-7.85 (d, J=8.4 Hz, 2H), 7.47-7.45 (d, J=8 Hz, 2H), 4.79 (s, 1H), 4.45-4.39 (m, 1H), 4.16-4.05 (m, 2H), 3.95-3.92 (d, J=13.2 Hz, 0.5H), 3.69-3.66 (t, J=11.6 Hz, 2H), 3.62-3.55 (m, 0.5H), 3.33 (s, 3H), 3.27-3.08 (m, 2H), 2.99-2.94 (m, 0.5H), 2.81-2.69 (m, 1H), 2.64-2.59 (m, 1H), 2.16 (s, 3H), 1.55-1.49 (m, 1H), 1.39-1.28 (m, 3H), 1.12-1.09 (m, 1H), 0.89-0.86 (m, 2H). LC-MS: m/z 444.1 (M+H)+.

Compound 348 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(2-methoxymethyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1088] 1H NMR (METHANOL-d) δ 7.53-7.55 (m, 1H), 7.40-7.45 (m, 2H), 7.11-7.14 (m, 1H), 4.79 (s, 0.5H), 4.42 (t, J=14.4 Hz, 1H), 4.04-4.15 (m, 4H), 3.93 (d, J=12.8 Hz, 0.5H), 3.59-3.69 (m, 2.5H), 3.33 (s, 3H), 3.20 (d, J=4.8 Hz, 4H), 2.95-3.18 (m, 1H), 2.71-2.76 (m, 1H), 2.60-2.65 (m, 1H), 2.08 (s, 3H), 1.40-1.5 (m, 2.3H), 1.27-1.38 (m, 1.7H), 1.02-1.09 (m, 2H), 0.75-0.82 (m, 2H).

[1089] LC-MS: m/z 463.2 (M+H)+.

Compound 349 (General Procedure 6, Step G')

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-5-(2-methyl-2H-pyrazol-3-yl)-nicotinonitrile

[1090] 1H NMR (METHANOL-d) d 7.60 (s, 1H), 6.33 (s, 1H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.21-4.38 (m, 2H), 3.88-3.95 (m, 0.5H), 3.65-3.72 (m, 2H), 3.63 (s, 3H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 1H), 2.97-3.08 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.19 (m, 2H), 0.78-0.95 (m, 2H). LC-MS: m/z 423.2 $(M+H)^+$.

Compound 350 (General Procedure 6, Step G')

(R)—N-(3-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-phenyl)-methanesulfonamide

[1091] 1H NMR (METHANOL-d) d 7.45-7.48 (m, 1H), 7.30 (d, J=7.6 Hz, 1H), 7.11 (s, 1H), 7.02 (d, J=7.6 Hz, 1H),

4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.98 (s, 3H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.16 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H). LC-MS: m/z 512.1 $(M+H)^+$.

Compound 351 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(3,5-dimethyl-isoxazol-4-yl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1092] 1H NMR (METHANOL-d) d 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.24 (s, 3H), 2.21 (s, 3H), 2.08 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.12 (m, 2H), 0.85-0.95 (m, 2H).

[1093] LC-MS: m/z 438.2 $(M+H)^+$.

Compound 358 (General Procedure 6, Step G')

(R)-5-(1-benzyl-1H-pyrazol-4-yl)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1094] 1H NMR (METHANOL-d) 7.742 (s, 1H), 7.499 (s, 1H), 4.365-7.255 (m, 5H), 5.410 (s, 2H), 4.773 (s, 0.5H), 4.429-4.359 (m, 1H), 4.109-4.004 (m, 2H), 3.924-3.891 (m, 0.5H), 3.683-3.655 (m, 2H), 3.592-3.535 (m, 0.5H), 3.328 (s, 3H), 3.255-3.041 (m, 2H), 2.954-2.898 (m, 0.5H), 2.801-2.588 (m, 2H), 2.260 (s, 3H), 1.909-1.869 (m, 1H), 1.375-1.246 (m, 3H), 1.071 (s, 2H), 0.90-0.80 (m, 2H). LC-MS: m/z 499.2 $(M+H)^+$.

[1095] Compound 359 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(2-ethyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1096] 1H NMR (METHANOL-d) δ 7.40-7.37 (m, 2H), 7.35-7.27 (m, 1H), 7.07-7.04 (m, 1H), 4.80-4.79 (d, J=2.4 Hz, 0.5H), 4.46-4.38 (m, 1H), 4.14-4.04 (m, 2H), 3.95-3.92 (d, J=12.8 Hz, 0.5H), 3.68-3.63 (m, 2H), 3.60 (m, 0.5H), 3.34 (s, 3H), 3.26-3.06 (m, 2H), 2.97-2.94 (d, J=12 Hz, 0.5H), 2.80-2.60 (m, 2H), 2.42-2.30 (m, 2H), 2.09 (s, 3H), 1.55-1.50 (m, 1H), 1.43-1.39 (m, 1H), 1.32-1.27 (m, 1H), 1.08-1.03 (m, 5.5H) 0.82-0.80 (m, 2H). LC-MS: m/z 447.2 (M+H)+.

Compound 362 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(3-dimethylamino-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1097] 1H NMR (METHANOL-d) δ 7.53 (t, J=8.0 Hz, 1H), 7.27 (d, J=8.4 Hz, 1H), 7.09 (s, 1H), 7.02 (d, J=7.2 Hz, 1H), 4.78 (s, 1H), 4.38-4.45 (m, 1H), 4.03-4.14 (m, 2H), 3.91-3.95 (m, 0.5H), 3.65-3.70 (m, 2H), 3.53-3.62 (m, 0.5H), 3.34 (s, 4H), 3.21-3.31 (m, 1.5H), 3.16 (s, 7H), 2.96-2.98 (m, 0.5H), 2.71-2.79 (m, 1H), 2.62-2.65 (m, 1H), 2.19 (s, 3H), 1.61-1.67 (m, 1H), 1.38-1.40 (d, J=6.4 Hz, 1.3H), 1.27-1.28 (d, J=6.4 Hz, 1.7H), 1.07-1.09 (m, 2H), 0.81-0.84 (m, 2H). LC-MS: m/z 462.1 (M+H)+.

Compound 365 (General Procedure 6, Step G')

(R)-6-cyclopropyl-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-5-(1-methyl-1H-pyrazol-4-yl)-nicotinonitrile

[1098] 1H NMR (METHANOL-d) d 7.64 (s, 1H), 7.44 (s, 1H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 3.88-4.12 (m, 5.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H). LC-MS: m/z 423.1 (M+H)+.

Compound 366 (General Procedure 6, Step G')

(R)-3-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-benzoic acid methyl ester

[1099] 1H NMR (METHANOL-d) d 8.06 (d, J=8.0 Hz, 1H), 7.87 (s, 1H), 7.58-7.63 (m, 1H), 7.48 (d, J=8.0 Hz, 1H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 3.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.16 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H). LC-MS: m/z 477.1 (M+H)+.

Compound 369 (General Procedure 6, Step G')

(R)-2-cyclopropyl-2'-fluoro-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-[3,3']bipyridinyl-5-carbonitrile

[1100] 1H NMR (METHANOL-d) δ 8.31-8.30 (d, J=4.4 Hz, 1H), 7.90-7.86 (t, J=8.4 Hz, 1H), 7.48-7.45 (m, 1H), 4.82-4.79 (m, 0.5H), 4.45-4.37 (m, 0.5H), 4.20-4.10 (m, 2H), 3.95-3.92 (d, J=12.8 Hz, 0.5H), 3.68-3.67 (m, 2H), 3.62-3.56 (t, J=12 Hz, 0.5H), 3.34-3.33 (m, 3.5H), 3.18-3.16 (d, J=10.8 Hz, 1H), 3.01 (m, 1H), 2.80-2.71 (m, 1H), 2.65-2.61 (m, 1H), 2.2 (s, 3H), 1.52-1.49 (m, 1H), 1.39-1.38 (d, J=2.8 Hz, 1H), 1.28-1.27 (d, J=6.4 Hz, 1H), 1.13-0.90 (m, 1H), 0.90-0.88 (m, 1H). LC-MS: m/z 438.2 $(M+H)^+$.

Compound 372 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(2-hydroxymethyl-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1101] 1H NMR (CHLOROFORM-d) δ 7.61-7.59 (d, J=7.6 Hz, 1H), 7.46-7.37 (m, 2H), 7.10-7.08 (d, J=7.2 Hz, 1H), 4.90 (s, 0.5H), 4.53-4.34 (M, 2.5H), 4.22-4.05 (m, 2.5H), 3.79-3.71 (m, 2.5H), 3.60-3.54 (M, 0.5H), 3.48 (S, 1H), 3.37 (S, 3H), 3.19-3.14 (M, 1.5H), 3.03-2.98 (m, 1H), 2.75-2.66 (M, 1H), 2.60-2.55 (m, 1H), 2.11 (s, 3H), 1.48-1.44 (m, 2H), 1.31-1.30 (d, J=4.8 Hz, 1.5H), 1.10-1.07 (m, 2H). LC-MS: m/z 449.1 $(M+H)^+$.

Compound 380 (General Procedure 6, Step G')

(R)—N-(4-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-phenyl)-methanesulfonamide

[1102] 1H NMR (METHANOL-d) d 7.36 (d, J=8.4 Hz, 2H), 7.21 (d, J=8.4 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 1H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.43 (s, 3H), 3.16-3.25 (m, 1.5H), 3.03 (s, 3H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H). LC-MS: m/z 512.2 (M+H)+.

Compound 393 (General Procedure 6, Step G')

(R)-4-{5-cyano-2-cyclopropyl-6-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-pyridin-3-yl}-benzenesulfonamide

[1103] 1H NMR (METHANOL-d) d 8.02 (d, J=8.4 Hz, 2H), 7.43 (d, J=8.4 Hz, 2H), 4.75-4.85 (m, 0.5H), 4.35-4.48 (m, 3H), 4.05-4.12 (m, 2H), 3.88-3.97 (m, 0.5H), 3.65-3.72 (m, 2H), 3.52-3.62 (m, 0.5H), 3.34 (s, 3H), 3.03-3.25 (m, 2H), 2.87-2.98 (m, 0.5H), 2.68-2.85 (m, 1H), 2.57-2.63 (m, 1H), 2.18 (s, 3H), 1.62-1.69 (m, 1H), 1.34-1.41 (m, 3H), 1.05-1.09 (m, 2H), 0.78-0.85 (m, 2H). LC-MS: m/z 498.1 $(M+H)^+$.

Compound 405 (General Procedure 6, Step G')

(R)-6-cyclopropyl-5-(2,3-difluoro-phenyl)-2-[4-(3-methoxy-propionyl)-3-methyl-piperazin-1-yl]-4-methyl-nicotinonitrile

[1104] 1H NMR (METHANOL-d) δ 7.26-7.39 (m, 2H), 7.07 (t, J=6.8 Hz, 1H), 4.72 (s, 0.5H), 4.41-4.45 (m, 1H), 4.07-4.19 (m, 2H), 3.93 (d, J=13.6 Hz, 0.5H), 3.66-3.69 (m, 2H), 3.56-3.62 (m, 0.5H), 3.33 (s, 3H), 3.20-3.28 (m, 1H), 3.14-3.17 (m, 1H), 2.96-3.02 (m, 0.5H), 2.60-2.81 (m, 2H), 2.18 (s, 3H), 1.55-1.61 (m, 1H), 1.38 (d, J=6.4 Hz, 1.3H), 1.27 (d, J=6.8 Hz, 1.7H), 1.06-1.1 (m, 2H), 0.82-0.89 (m, 2H). LC-MS: m/z 455.1 $(M+H)^+$.

Compound 589

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1105] It was obtained by the same procedure of Compound 527.

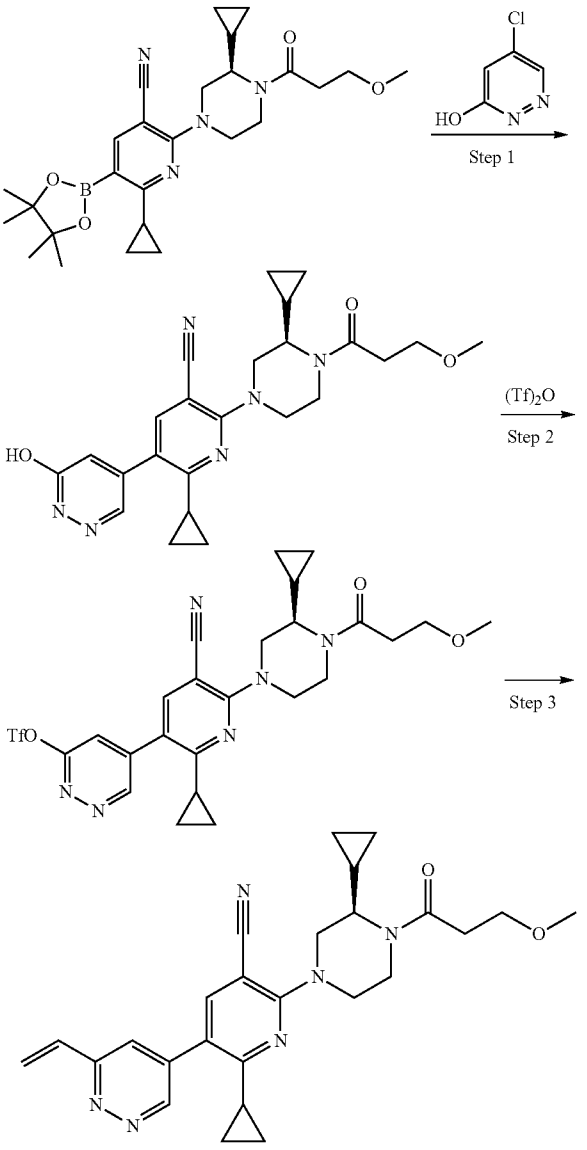
[1106] ^{1}H NMR (CHLOROFORM-d) δ 8.70 (d, J=5.0 Hz, 1H), 7.26 (s, 1H), 7.10 (d, J=3.8 Hz, 1H), 6.90 (dd, J=17.4, 10.9 Hz, 1H), 6.32 (d, J=17.3 Hz, 1H), 5.61 (d, J=11.3 Hz, 1H), 4.60-4.76 (m, 0.5H), 4.34 (d, J=12.8 Hz, 1H), 4.26 (d, J=12.8 Hz, 1H), 4.08 (d, J=9.0 Hz, 0.5H), 3.92 (br. s., 2H), 3.78 (br. s., 1H), 3.39-3.56 (m, 1H), 3.23 (br. s., 1H), 3.15 (d, J=11.8 Hz, 1H), 3.05 (br. s., 1H), 2.61 (br. s., 2H), 2.17-2.29 (m, 3H), 1.55-1.60 (m, 1H), 1.38-1.47 (m, 1H), 1.27-1.33 (br. s., 1H), 1.12 (br. s., 2H), 0.64 (br. s., 2H), 0.33-0.54 (m, 2H)

[1107] LC-MS: m/z 458.3 $(M+H)^+$

Compound 674

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(6-vinylpyridazin-4-yl) nicotinonitrile

[1108]



Step 1(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(6-hydroxypyridazin-4-yl)nicotinonitrile

[1109] A mixture of (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (200 mg, 0.42 mmol), 5-chloropyridazin-3-ol (109 mg, 0.625 mmol), CsF (127 mg, 0.84 mmol) and $Pd(dppf)Cl_2$ (17 mg) in dioxane and water was heated at 100° C. for 2 hrs. The reaction mixture

was concentrated and the residue was purified by pre-TLC to afford 120 mg of title compound.

[1110] LC-MS: m/z 449.2 $(M+H)^+$

Step 2 (R)-5-(5-cyano-2-cyclopropyl-6-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)pyridin-3-yl)pyridazin-3-yl trifluoromethanesulfonate

[1111] A solution of (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(6-hydroxypyridazin-4-yl)nicotinonitrile (120 mg, 0.27 mmol), Tf_2O (100 mg, 0.48 mmol) and TEA (0.1 mL) in DCM was stirred for 1 hr. The reaction mixture was washed with water, dried and concentrated. The residue was purified by pre-TLC to afford 60 mg of title compound.

[1112] ^1H NMR (CHLOROFORM-d) δ: 9.41 (d, J=1.5 Hz, 1H), 7.71 (s, 1H), 7.51 (d, J=1.8 Hz, 1H), 4.71 (d, J=12.8 Hz, 1.5H), 4.58 (d, J=11.5 Hz, 1H), 4.14 (brs, 0.5H), 3.93 (br. s., 0.5H), 3.75 (br. s., 2.5H), 3.39 (s, 3H), 3.21-3.36 (m, 3H), 2.54-2.83 (m, 2H), 1.86-1.96 (m, 1H), 1.08-1.28 (m, 5H), 0.48-0.63 (m, 4H).

[1113] LC-MS: m/z 580.7 $(M+H)^+$

Step 3 (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(6-vinylpyridazin-4-yl)nicotinonitrile (Compound 674)

[1114] A mixture of (R)-5-(5-cyano-2-cyclopropyl-6-(3-cyclopropyl-4-(3-methoxypropanoyppiperazin-1-yl)pyridin-3-yl)pyridazin-3-yl trifluoromethanesulfonate (25 mg, 0.043 mmol), Potassium vinyltrifluoroborate (12 mg, 0.083 mmol), TEA (20 mg, 0.215 mmol) and $Pd(dppf)Cl_2$(3.5 mg) in i-PrOH and water was heated at 100° C. for 2 hrs. The reaction mixture was concentrated and the residue was purified by pre-TLC to afford 11 mg of title compound.

[1115] ^1H NMR (CHLOROFORM-d) δ9.21 (br. s., 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.13 (dd, J=17.6, 11.0 Hz, 1H), 6.37 (d, J=17.6 Hz, 1H), 5.79 (d, J=11.0 Hz, 1H), 4.63 (d, J=12.8 Hz, 1.5H), 4.50 (d, J=12.3 Hz, 1H), 4.05-4.18 (m, 0.5H), 3.90 (d, J=11.0 Hz, 0.5H), 3.63-3.83 (m, 2.5H), 3.38 (s, 3H), 3.18-3.33 (m, 2H), 3.15 (br. s., 1H), 2.71-2.64 (m, 2H), 1.89-1.99 (m, 1H), 1.29-1.40 (m, 3H), 1.07 (dd, J=7.4, 2.9 Hz, 2H), 0.61-0.44 (m, 4H).

[1116] LC-MS: m/z 459.0 $(M+H)^+$

Compound 675

(R)-5-(5-cyano-2-cyclopropyl-6-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)pyridin-3-yl)pyridazin-3-yl trifluoromethanesulfonate

[1117] ^1H NMR (CHLOROFORM-d) δ: 9.41 (d, J=1.5 Hz, 1H), 7.71 (s, 1H), 7.51 (d, J=1.8 Hz, 1H), 4.71 (d, J=12.8 Hz, 1.5H), 4.58 (d, J=11.5 Hz, 1H), 4.14 (brs, 0.5H), 3.93 (br. s., 0.5H), 3.75 (br. s., 2.5H), 3.39 (s, 3H), 3.21-3.36 (m, 3H), 2.54-2.83 (m, 2H), 1.86-1.96 (m, 1H), 1.08-1.28 (m, 5H), 0.48-0.63 (m, 4H).

[1118] LC-MS: m/z 580.7 $(M+H)^+$

Compound 687

(R)-5-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)pyridazin-3-yl trifluoromethanesulfonate

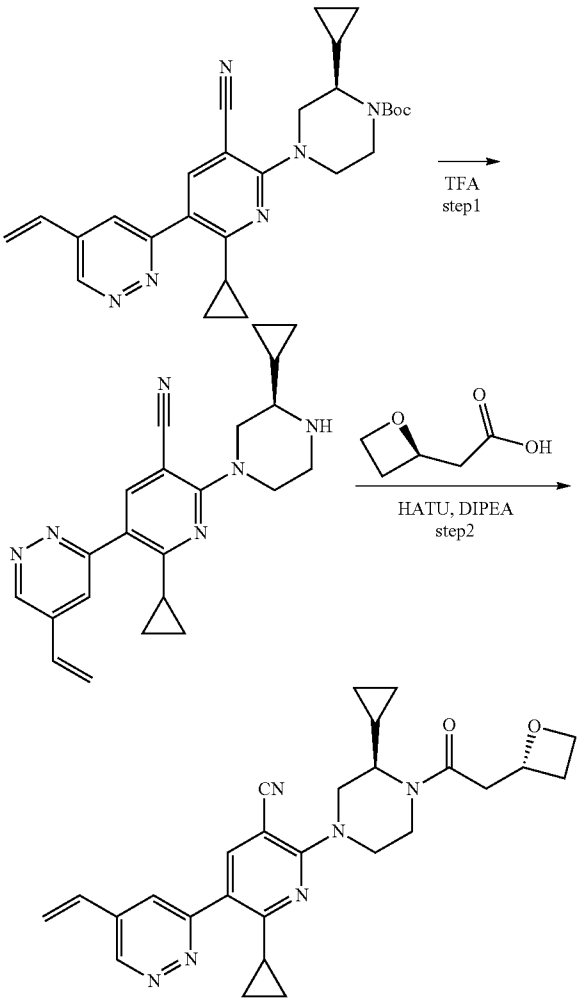
[1119] ^1H NMR (CHLOROFORM-d) δ: 9.42 (br. s., 1H), 7.72 (s, 1H), 7.52 (s, 1H), 4.73 (d, J=12.8 Hz, 1.5H), 4.60 (d, J=12.0 Hz, 1H), 4.33 (brs, 0.5H), 4.05 (brs, 0.5H), 3.76 (br. s., 1H), 3.24-3.40 (m, 2.5H), 1.89-1.97 (m, 1H), 1.72 (br. s., 1H), 1.29-1.34 (m, 3H), 0.99-1.20 (m, 4H), 0.78-0.90 (m, 2H), 0.41-0.66 (m, 4H).

[1120] LC-MS: m/z 563.0 $(M+H)^+$

Compound 766

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1121]



Step 1(R)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1122] A stirred solution of (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-(5-vinylpyridazin-3-yl)pyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (100 mg, 0.2 mmol) in TFA (2 mL) was stirred at room temperature overnight. When LC-MS showed completion of the reaction, the mixture was evaporated under reduced pressure and the residue was dissolved in DCM, washed with Sat. NaHCO3, and brine. The

organic layer was evaporated under reduced pressure to give crude product which was used without further purification (70 mg)

Step 2. Compound 766

[1123] To a stirred 2-(oxetan-2-yl)acetic acid (20 mg) in CH_2Cl_2 was added HATU (72 mg, 0.19 mmol) followed by DIPEA, the mixture was stirred at room temperature for 1 hr, then (R)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)-5-(5-vinylpyridazin-3-yl)nicotinonitrile (70 mg) was added. The mixture was stirred at room temperature overnight. It was quenched with water, extracted with CH_2Cl_2. The organic layer was washed with Sat. NaHCO3, brine and dried over Na2SO4, evaporated and purified by prepTLC to give product.

[1124] ^{1}H NMR (CHLOROFORM-d) δ: 9.23 (br. s., 1H), 7.97 (s, 1H), 7.61 (d, J=1.8 Hz, 1H), 6.74 (dd, J=17.8, 11.0 Hz, 1H), 6.20 (d, J=17.6 Hz, 1H), 5.76 (d, J=10.9 Hz, 1H), 5.11-5.36 (m, 1H), 4.48-4.77 (m, 4H), 4.08 (d, J=8.5 Hz, 0.5H), 3.95 (d, J=13.2 Hz, 0.5H), 3.75 (d, J=11.2 Hz, 0.5H), 3.32 (br. s., 1H), 3.05-3.27 (m, 2H), 2.98 (dd, J=14.8, 6.0 Hz, 1.5H), 2.79-2.90 (m, 2H), 2.54 (d, J=7.9 Hz, 1H), 2.12-2.26 (m, 1H), 1.25 (dd, J=6.6, 3.7 Hz, 3H), 0.94-1.12 (m, 2H), 0.51-0.72 (m, 2H), 0.35-0.49 (m, 2H)

[1125] LC-MS: m/z 471.6 $(M+H)^+$

Compound 769

(R,E)-6-cyclopropyl-2-(3-cyclopropyl-4-(5-hydroxypent-2-enoyl)piperazin-1-yl)-4-methyl-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1126] ^{1}H NMR (CHLOROFORM-d) δ: 9.27 (d, J=2.1 Hz, 1H), 7.43 (d, J=2.1 Hz, 1H), 6.87 (dt, J=14.8, 7.3 Hz, 1H), 6.73 (dd, J=17.8, 11.0 Hz, 1H), 6.26-6.48 (m, 1H), 6.21 (d, J=17.6 Hz, 1H), 5.77 (d, J=10.9 Hz, 1H), 4.42 (d, J=12.9 Hz, 1H), 4.33 (d, J=12.6 Hz, 1H), 3.89-4.21 (m, 1H), 3.79 (t, J=6.0 Hz, 2H), 3.38 (br. s., 1H), 3.23 (d, J=10.0 Hz, 1H), 3.08 (td, J=12.5, 2.9 Hz, 1H), 2.50 (q, J=6.2 Hz, 2H), 2.18-2.29 (m, 3H), 1.36-1.50 (m, 2H), 1.15 (br. s., 2H), 0.88 (dd, J=7.6, 3.2 Hz, 2H), 0.65 (br. s., 1H), 0.51 (br. s., 1H), 0.44 (br. s., 2H)

[1127] LC-MS: m/z 485.6 $(M+H)^+$

Compound 768

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methyl-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1128] ^{1}H NMR (CHLOROFORM-d) δ:9.28 (d, J=2.1 Hz, 1H), 7.43 (d, J=2.1 Hz, 1H), 6.74 (dd, J=17.6, 10.9 Hz, 1H), 6.21 (d, J=17.9 Hz, 1H), 5.71-5.86 (m, 1H), 5.27 (quin, J=6.7 Hz, 1H), 4.64-4.76 (m, 1H), 4.49-4.63 (m, 1H), 4.41 (d, J=12.6 Hz, 1H), 4.23-4.37 (m, 1H), 4.07 (d, J=8.2 Hz, 1H), 3.92 (d, J=12.6 Hz, 1H), 3.69-3.86 (m, 1H), 3.20-3.36 (m, 1H), 2.93-3.20 (m, 3H), 2.74-2.93 (m, 2H), 2.46-2.66 (m, 1H), 2.18-2.30 (m, 3H), 1.78 (br. s., 1H), 1.41-1.51 (m, 2H), 1.33-1.41 (m, 1H), 1.10-1.20 (m, 2H), 0.89 (dd, J=7.8, 3.1 Hz, 2H), 0.58-0.72 (m, 1H), 0.53 (br. s., 1H), 0.45 (d, J=5.6 Hz, 2H)

[1129] LC-MS: m/z 485.6 $(M+H)^+$

[1130] Compound 767

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-4-methyl-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1131] ^{1}H NMR (CHLOROFORM-d) δ:9.28 (s, 1H), 7.44 (d, J=2.1 Hz, 1H), 7.28 (s, 1H), 6.74 (dd, J=17.6, 10.9 Hz, 1H), 6.21 (d, J=17.6 Hz, 1H), 5.78 (d, J=10.9 Hz, 1H), 4.37-4.47 (m, 1H), 4.26-4.36 (m, 1H), 4.01-4.13 (m, 1H), 3.83-3.98 (m, 2H), 3.65-3.83 (m, 1H), 3.13-3.29 (m, 2H), 2.98-3.13 (m, 1H), 2.46-2.68 (m, 2H), 2.19-2.29 (m, 3H), 1.84-2.10 (m, 1H), 1.42-1.55 (m, 1H), 1.15 (br. s., 1H), 0.81-0.95 (m, 3H), 0.63 (br. s., 1H), 0.53 (br. s., 1H), 0.32-0.48 (m, 2H)

[1132] LC-MS: m/z 459.6 $(M+H)^+$

Compound 749

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-4-methyl-5-(6-vinylpyridazin-4-yl)nicotinonitrile

[1133] ^{1}H NMR (CHLOROFORM-d) δ: 9.21 (d, J=2.1 Hz, 1H), 7.70 (s, 1H), 7.64 (d, J=2.1 Hz, 1H), 7.15 (dd, J=17.8, 11.0 Hz, 1H), 6.39 (d, J=17.9 Hz, 1H), 5.81 (d, J=10.9 Hz, 1H), 4.64 (d, J=13.2 Hz, 1H), 4.52 (d, J=12.9 Hz, 1H), 4.10 (d, J=9.7 Hz, 1H), 3.85-3.99 (m, 2H), 3.71-3.83 (m, 1H), 3.07-3.36 (m, 3H), 2.42-2.71 (m, 2H), 1.88-2.02 (m, 1H), 1.20-1.40 (m, 3H), 1.01-1.12 (m, 2H), 0.45-0.78 (m, 4H)

[1134] LC-MS: m/z 473.3 $(M+H)^+$

Compound 724

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-methoxyacetyl)piperazin-1-yl)-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1135] ^{1}H NMR (CHLOROFORM-d) δ: 9.22 (s, 1H), 7.93-8.03 (m, 1H), 7.61 (d, J=1.8 Hz, 1H), 6.74 (dd, J=17.8, 11.0 Hz, 1H), 6.20 (d, J=17.6 Hz, 1H), 5.76 (d, J=10.9 Hz, 1H), 4.65 (d, J=13.2 Hz, 1H), 4.52 (d, J=12.6 Hz, 1H), 4.16 (m, 1H), 3.80-4.02 (m, 2H), 3.58-3.74 (m, 1H), 3.45 (s, 3H), 3.26 (d, J=10.3 Hz, 2H), 3.12 (t, J=10.6 Hz, 1H), 2.11-2.32 (m, 1H), 1.23-1.30 (m, 3H), 0.98-1.08 (m, 2H), 0.41-0.72 (m, 4H)

[1136] LC-MS: m/z 445.2 $(M+H)^+$

Compound 723

(R)-tert-butyl(6-(5-cyano-2-cyclopropyl-6-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)pyridin-3-yl)pyridazin-4-yl)carbamate

[1137] The mixture of ((R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (67 mg, 0.157 mmol), tert-butyl (6-chloropyridazin-4-yl)carbamate (30 mg, 0.131 mmol), $Pd(dppf)Cl_2$ (5 mg, 0.007 mmol) and CsF (40 mg, 0.216 mmol) in dioxane/H_2O was stirred at 100° C. for 16 hours. The mixture was diluted with EtOAc (30 mL) and filtered. The filtrated was partitioned between EtOAc (30 mL) and water (10 mL), the organic layer was washed with water (10 mL), brine and dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 20 mg of the product.

[1138] ^{1}H NMR (CHLOROFORM-d) δ: 9.08 (s, 1H), 8.29 (s, 1H), 7.98 (s, 1H), 7.60 (br. s., 1H), 4.64 (d, J=12.9 Hz, 1H), 4.52 (d, J=12.3 Hz, 1H), 4.08 (d, J=8.5 Hz, 1H), 3.93 (s, 2H), 3.66-3.84 (m, 1H), 3.25 (m, 3H), 2.50-2.61 (m, 2H), 1.56 (s, 9H), 1.21-1.28 (m, 3H), 1.07 (s, 2H), 0.41-0.80 (m, 4H)

[1139] LC-MS: m/z 534.3 $(M+H)^+$

Compound 716

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(5-vinylpyridazin-3-yl) nicotinonitrile

[1140] ^{1}H NMR (CHLOROFORM-d) δ9.23 (s, 1H), 7.98 (s, 1H), 7.61 (d, J=2.1 Hz, 1H), 6.74 (dd, J=17.8, 11.0 Hz, 1H), 6.20 (d, J=17.6 Hz, 1H), 5.71-5.84 (m, 1H), 4.64 (d, J=12.9 Hz, 1H), 4.51 (d, J=12.6 Hz, 1H), 4.01-4.16 (m, 1H), 3.92 (s, 2H), 3.65-3.83 (m, 1H), 3.05-3.25 (d, J=11.2 Hz, 2H), 2.50-2.68 (m, 2H), 2.12-2.30 (m, 1H), 1.19-1.27 (m, 3H), 1.00-1.11 (m, 2H), 0.39-0.62 (m, 1H)

[1141] LC-MS: m/z 445.2 $(M+H)^+$

Compound 715

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-methoxyacetyl)piperazin-1-yl)-5-(6-vinylpyridazin-4-yl)nicotinonitrile

[1142] ^{1}H NMR (CHLOROFORM-d) δ9.20 (s, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.11 (dd, J=17.8, 11.0 Hz, 1H), 6.36 (d, J=17.9 Hz, 1H), 5.77 (d, J=11.2 Hz, 1H), 4.64 (d, J=12.9 Hz, 1H), 4.50 (d, J=12.6 Hz, 1H), 4.15 (s, 2H), 3.80-4.12 (m, 1H), 3.60-3.66 (m, 1H), 3.44 (s, 3H), 3.26 (dd, J=13.2, 3.5 Hz, 1H), 3.07-3.18 (m, 1H), 1.87-2.04 (m, 1H), 1.19-1.29 (m, 3H), 1.06 (dd, J=7.9, 2.9 Hz, 2H), 0.47-0.65 (m, 4H)

[1143] LC-MS: m/z 445.2 $(M+H)^+$

Compound 696

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(5-vinylpyridazin-3-yl) nicotinonitrile

[1144] ^{1}H NMR (CHLOROFORM-d) δ: 9.23 (d, J=2.1 Hz, 1H), 7.98 (s, 1H), 7.63 (d, J=2.1 Hz, 1H), 6.75 (dd, J=17.6, 10.9 Hz, 1H), 6.21 (d, J=17.6 Hz, 1H), 5.78 (d, J=10.9 Hz, 1H), 4.66 (d, J=12.9 Hz, 2.5H), 3.98-4.54 (m, 1H), 3.51-3.88 (m, 1H), 3.00-3.45 (m, 1H), 2.16-2.28 (m, 1H), 1.72 (s, 1H), 1.17-1.30 (m, 3H), 0.95-1.11 (m, 4H), 0.77-0.87 (m, 2H), 0.39-0.64 (m, 1H)

[1145] LC-MS: m/z 441.2 $(M+H)^+$

Compound 686

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(6-vinylpyridazin-4-yl) nicotinonitrile

[1146] The mixture of (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (100 mg, 0.235 mmol), 5-chloro-3-vinylpyridazine (30 mg, 0.213 mmol), Pd(dppf)Cl_2 (8 mg, 0.011 mmol) and CsF (98 mg, 0.640 mmol) in dioxane/H_2O was stirred at 100° C. for 16 hours. The mixture was diluted with EtOAc (30 mL) and filtered. The filtrate was partitioned between EtOAc (30 mL) and water (10 mL), the organic layer was washed with water (10 mL), brine, dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 25 mg of the product.

[1147] ^{1}H NMR (CHLOROFORM-d) δ: 9.21 (d, J=2.1 Hz, 1H), 7.70 (s, 1H), 7.64 (d, J=2.1 Hz, 1H), 7.15 (dd, J=17.8, 11.0 Hz, 1H), 6.39 (d, J=17.9 Hz, 1H), 5.81 (d, J=10.9 Hz, 1H), 4.64 (d, J=13.2 Hz, 1H), 4.52 (d, J=12.9 Hz, 1H), 4.10 (d, J=9.7 Hz, 1H), 3.87-4.01 (m, 2H), 3.71-3.87 (m, 1H), 3.07-3.36 (m, 3H), 2.46-2.70 (m, 2H), 1.81-2.03 (m, 1H), 1.20-1.34 (m, 3H), 1.03-1.13 (m, 2H), 0.60-0.69 (m, 1H), 0.46-0.57 (m, 4H)

[1148] LC-MS: m/z 445.2 $(M+H)^+$

Compound 671

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(6-hydroxypyridazin-4-yl)nicotinonitrile

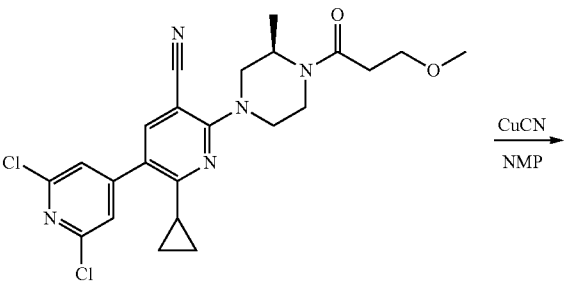
[1149] ^{1}H NMR (CHLOROFORM-d) δ: 12.36 (br. s., 1H), 7.95 (d, J=2.0 Hz, 1H), 7.65 (s, 1H), 7.00 (d, J=2.0 Hz, 1H), 4.63 (d, J=13.1 Hz, 1H), 4.50 (d, J=12.8 Hz, 1H), 4.01-4.19 (m, 1H), 3.89-3.98 (m, 2H), 3.60-3.85 (m, 1H), 3.01-3.29 (m, 3H), 2.60 (dd, J=11.8, 6.0 Hz, 2H), 1.87-2.05 (m, 1H), 1.14-1.26 (m, 3H), 0.31-1.14 (m, 4H).

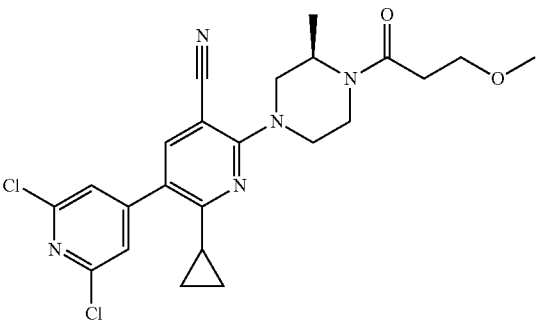
[1150] LC-MS: m/z 435.2 $(M+H)^+$

Compound 673

(R)-6'-chloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-2', 5-dicarbonitrile

[1151]





[1152] The mixture of (R)-2',6'-dichloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile (40 mg, 0.084 mmol), CuCN (15 mg, 0.169 mmol), CuI (1 mg) in NMP (2 mL) was stirred at 230° C. for 2 hours. After cooling to room temperature, the mixture was partitioned between EtOAc (30 mL) and water (10 mL), the organic layer was washed with water (10 mL), brine and

dried over Na2SO4, concentrated to give the crude which was purified by prep-TLC to give 20 mg of the product.

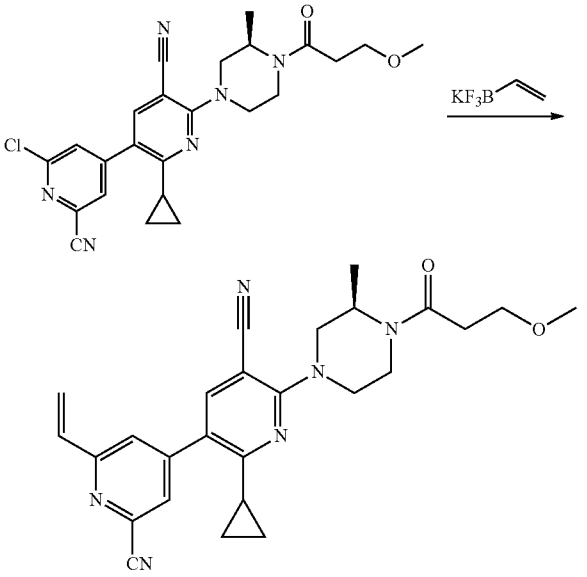
[1153] ^{1}H NMR (CHLOROFORM-d) δ: 7.72 (d, J=1.0 Hz, 1H), 7.59-7.66 (m, 2H), 4.91 (s, 0.5H), 4.54 (d, J=10.3 Hz, 0.5H), 4.24-4.48 (m, 2.5H), 3.69-3.79 (m, 2H), 3.51-3.62 (m, 0.5H), 3.33-3.44 (m, 4H), 3.18-3.29 (m, 1.5H), 3.10-3.25 (m, 1.5H), 2.63-2.82 (m, 1H), 2.52-2.63 (m, 1H), 1.82-1.95 (m, 1H), 1.36 (d, J=6.5 Hz, 1H), 1.23-1.28 (m, 4H), 1.04-1.15 (m, 2H)

[1154] LC-MS: m/z 465.2 $(M+H)^+$

Compound 672

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-6'-vinyl-[3,4'-bipyridine]-2',5-dicarbonitrile

[1155]



[1156] The mixture of (R)-6'-chloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-2',5-dicarbonitrile (10 mg, 0.0215 mmol), Potassium vinyltrifluoroborate (5 mg, 0.032 mmol), $Pd(dppf)Cl_2$ (1 mg, 0.001 mmol) and CsF (10 mg, 0.064 mmol) in dioxane/H_2O was stirred at 100° C. for 16 hours. The mixture was diluted with EtOAc (30 mL) and filtered. The filtrated was partitioned between EtOAc (30 mL) and water (10 mL), the organic layer was washed with water (10 mL), brine and dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 5 mg of the product.

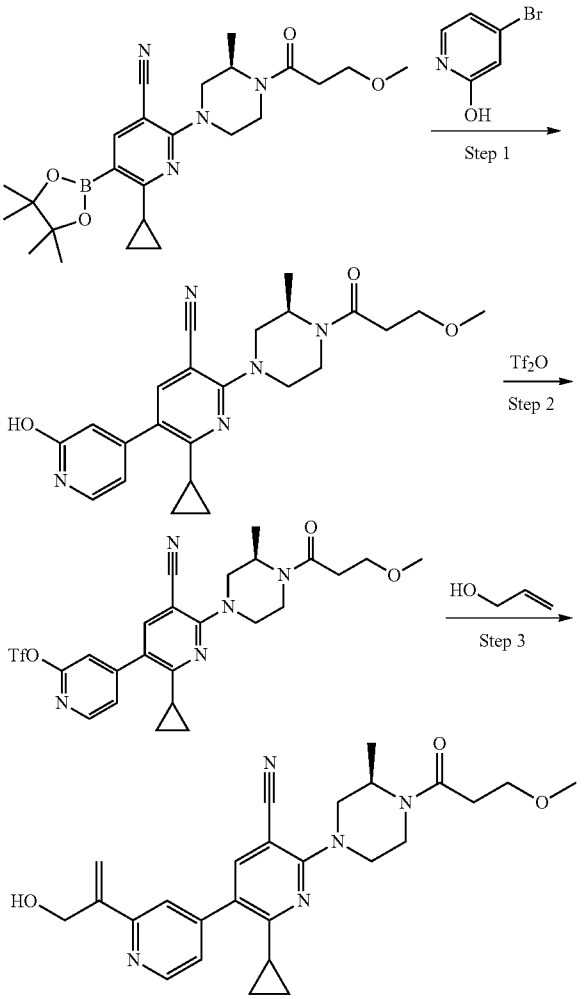
[1157] ^{1}H NMR (CHLOROFORM-d) δ: 7.63 (s, 2H), 7.52-7.59 (m, 1H), 6.86 (dd, J=17.4, 10.7 Hz, 1H), 6.42 (d, J=17.6 Hz, 1H), 5.71 (d, J=10.8 Hz, 1H), 4.92 (s, 0.5H), 4.54 (d, J=9.5 Hz, 0.5H), 4.25-4.46 (m, 2.5H), 3.71-3.86 (m, 3.5H), 3.35-3.42 (m, 3.5H), 3.03-3.29 (m, 1.5H), 2.63-2.82 (m, 1H), 2.53-2.62 (m, 1H), 1.83-1.96 (m, 1H), 1.34-1.40 (m, 2H), 1.20-1.26 (m, 3H), 1.00-1.11 (m, 2H).

[1158] LC-MS: m/z 457.2 $(M+H)^+$

Compound 653

(R)-2-cyclopropyl-2'-(3-hydroxyprop-1-en-2-yl)-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile

[1159]



Step 1(R)-2-cyclopropyl-2'-hydroxy-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile

[1160] A mixture of (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (100 mg, 0.22 mmol), 4-bromopyridin-2-ol (38 mg, 0.22 mmol), CsF (66 mg, 0.44 mmol) and $Pd(dppf)Cl_2$ (5 mg) in dioxane and water was heated at 100° C. for 0.5 hr. The reaction mixture was concentrated and the residue was purified by pre-TLC to afford 52 mg of title compound.

[1161] LC-MS: m/z 422.1 $(M+H)^+$

Step 2 (R)-5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridin]-2'-yl trifluoromethanesulfonate

[1162] A solution of (R)-2-cyclopropyl-2'-hydroxy-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipy-

ridine]-5-carbonitrile (100 mg, 0.24 mmol), Tf_2O (40 mg) and TEA (1 drop) in DCM (5 ml) was stirred for 1 hr. The reaction mixture was washed with water, dried and concentrated. The residue was purified by pre-TLC to afford 60 mg of title compound.

[1163] LC-MS: m/z 554.1 $(M+H)^+$

Step 3 (R)-2-cyclopropyl-2'-(3-hydroxyprop-1-en-2-yl)-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridine]-5-carbonitrile Compound 653

[1164] A mixture of (R)-5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridin]-2'-yl trifluoromethanesulfonate (150 mg, 0.27 mmol), prop-2-en-1-ol (31 mg, 0.54 mmol), TEA (30 mg, 0.30 mmol), $Pd(OAc)_2$(15 mg, 0.0675 mmol), and Dppf (72 mg, 0.13 mmol) in DMF (10 mL) was heated at 100° C. for 2 hrs. The reaction mixture was diluted with DCM and washed with water and brine, dried and concentrated and the residue was purified by prep-TLC and prep-HPLC to afford 16 mg of title compound.

[1165] ^{1}H NMR (CHLOROFORM-d) δ8.62 (d, J=5.3 Hz, 1H), 7.69 (s, 1H), 7.65 (s, 1H), 7.31 (dd, J=5.0, 1.3 Hz, 1H), 5.87 (s, 1H), 5.60 (s, 1H), 4.92 (brs, 0.5H), 4.65 (s, 2H), 4.54 (d, J=12.5 Hz, 0.5H), 4.20-4.46 (m, 2.5H), 3.68-3.88 (m, 2.5H), 3.49-3.65 (m, 0.5H), 3.39 (s, 3H), 3.33 (d, J=13.3 Hz, 1H), 3.01-3.27 (m, 1.5H), 2.64-2.85 (m, 1H), 2.51-2.64 (m, 1H), 1.96-2.08 (m, 1H), 1.39 (d, J=6.5 Hz, 1.5H), 1.25-1.36 (m, 1.5H), 1.17-1.25 (m, 2H), 0.95-1.09 (m, 2H).

[1166] LC-MS: m/z 462.1 $(M+H)^+$

Compound 765

6-cyclopropyl-2-((R)-3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-4-methyl-5-(2-vinylquinoxalin-5-yl)nicotinonitrile

[1167] ^{1}H NMR (CHLOROFORM-d) δ: 9.00 (s, 1H), 8.09-8.21 (m, 1H), 7.80-7.91 (m, 1H), 7.53-7.66 (m, 1H), 7.00-7.13 (m, 1H), 6.51 (d, J=17.6 Hz, 1H), 5.85 (d, J=11.2 Hz, 1H), 4.71 (d, J=10.0 Hz, 0.5H), 4.47 (d, J=10.3 Hz, 0.5H), 4.40 (d, J=13.5 Hz, 1H), 4.23-4.35 (m, 1H), 3.85 (d, J=13.5 Hz, 0.5H), 3.71-3.81 (m, 2H), 3.59 (d, J=10.3 Hz, 0.5H), 3.46-3.55 (m, 0.5H), 3.40 (d, J=5.0 Hz, 3H), 3.05-3.14 (m, 2H), 3.02 (d, J=9.7 Hz, 1H), 2.55-2.83 (m, 3H), 2.28-2.44 (m, 1H), 2.15-2.28 (m, 1H), 2.04-2.10 (m, 3H), 1.02-1.12 (m, 6H), 0.84-0.95 (m, 2H), 0.72-0.81 (m, 1H), 0.59-0.70 (m, 1H)

[1168] LC-MS: m/z 525.6 $(M+H)^+$

Compound 760

2-cyclopropyl-6-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1169] ^{1}H NMR (CHLOROFORM-d) δ: 8.70 (d, J=4.4 Hz, 1H), 7.25 (s, 1H), 7.09 (d, J=3.5 Hz, 1H), 6.90 (dd, J=17.5, 10.7 Hz, 1H), 6.32 (d, J=17.3 Hz, 1H), 5.60 (d, J=10.9 Hz, 1H), 5.22-5.34 (m, 1H), 4.65-4.77 (m, 1H), 4.52-4.63 (m, 1H), 4.22-4.41 (m, 2H), 4.09 (d, J=8.2 Hz, 1H), 3.91 (br. s., 1H), 3.38 (s, 1H), 3.14 (br. s., 1H), 2.94-3.09 (m, 2H), 2.68-2.94 (m, 3H), 2.49-2.63 (m, 1H), 2.14-2.28 (m, 3H), 1.27 (s, 1H), 1.12 (br. s., 2H), 0.88 (dd, J=7.6, 2.9 Hz, 2H), 0.62 (br. s., 1H), 0.55 (br. s., 1H), 0.34-0.51 (m, 2H)

[1170] LC-MS: m/z 484.7 $(M+H)^+$

Compound 761

2-cyclopropyl-6-((R)-3-cyclopropyl-4-(2-((S)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1171] ^{1}H NMR (CHLOROFORM-d) δ: 8.70 (d, J=4.4 Hz, 1H), 7.25 (s, 1H), 7.09 (d, J=3.5 Hz, 1H), 6.90 (dd, J=17.5, 10.7 Hz, 1H), 6.32 (d, J=17.3 Hz, 1H), 5.60 (d, J=10.9 Hz, 1H), 5.22-5.34 (m, 1H), 4.65-4.77 (m, 1H), 4.52-4.63 (m, 1H), 4.22-4.41 (m, 2H), 4.09 (d, J=8.2 Hz, 1H), 3.91 (br. s., 1H), 3.38 (s, 1H), 3.14 (br. s., 1H), 2.94-3.09 (m, 2H), 2.68-2.94 (m, 3H), 2.49-2.63 (m, 1H), 2.14-2.28 (m, 3H), 1.27 (s, 1H), 1.12 (br. s., 2H), 0.88 (dd, J=7.6, 2.9 Hz, 2H), 0.62 (br. s., 1H), 0.55 (br. s., 1H), 0.34-0.51 (m, 2H)

[1172] LC-MS: m/z 484.7 $(M+H)^+$

Compound 664

(R)-2-cyclopropyl-6-(4-(1-hydroxycyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1173] ^{1}H NMR (CHLOROFORM-d) δ:8.64 (d, J=5.0 Hz, 1H), 7.64 (s, 1H), 7.40 (s, 1H), 7.24 (dd, J=5.0, 1.5 Hz, 1H), 6.88 (dd, J=17.6, 10.8 Hz, 1H), 6.27 (d, J=17.6 Hz, 1H), 5.57 (d, J=11.3 Hz, 1H), 4.87 (br. s., 1H), 4.50 (d, J=11.8 Hz, 1H), 4.39 (d, J=12.8 Hz, 1H), 4.32 (d, J=11.5 Hz, 1H), 3.32 (dd, J=13.1, 2.8 Hz, 1H), 3.21-3.66 (m, 2H), 1.99-2.07 (m, 1H), 1.30-1.50 (m, 3H), 1.21 (dt, J=7.2, 3.5 Hz, 2H), 1.11-1.17 (m, 1H), 0.91-1.09 (m, 5H).

[1174] LC-MS: m/z 430.2 $(M+H)^+$

Compound 739

(R)-methyl 4-(4-(2'-chloro-5-cyano-2-cyclopropyl-3,4'-bipyridin-6-yl)-2-cyclopropylpiperazin-1-yl)-4-oxobutanoate

[1175] ^{1}H NMR (CHLOROFORM-d) δ:8.48 (d, J=5.0 Hz, 1H), 7.63 (s, 1H), 7.41 (s, 1H), 7.30 (d, J=4.4 Hz, 1H), 4.59 (d, J=12.3 Hz, 1H), 4.46 (d, J=12.0 Hz, 1H), 4.06 (br. s., 1H), 3.81-3.94 (m, 1H), 3.72 (s, 3H), 3.06-3.36 (m, 1.5H), 2.84 (br. s., 1.5H), 2.71 (d, J=7.9 Hz, 3H), 2.50-2.66 (m, 1H), 1.91-2.07 (m, 1H), 1.33 (br. s., 1H), 1.27 (br. s., 1H), 1.14-1.25 (m, 2H), 1.05 (dd, J=7.5, 3.4 Hz, 2H), 0.61 (br. s., 1H), 0.54 (br. s., 1H), 0.45 (d, J=4.1 Hz, 2H).

[1176] LC-MS: m/z 494.2 $(M+H)^+$

Compound 738

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(2-hydroxyacetyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1177] ^{1}H NMR (CHLOROFORM-d) δ:8.55-8.78 (m, 1H), 7.66 (s, 1H), 7.39 (br. s., 1H), 7.17-7.26 (m, 1H), 6.88 (dd, J=17.3, 10.9 Hz, 1H), 6.29 (d, J=17.3 Hz, 1H), 5.57 (d, J=10.9 Hz, 1H), 4.56 (d, J=12.9 Hz, 1H), 4.43 (d, J=12.9 Hz, 1H), 4.22 (br. s., 1H), 4.18 (br. s., 1H), 4.01 (br. s., 0.5H), 3.68 (br. s., 1.5H), 3.34-3.53 (m, 1H), 3.24 (d, J=10.9 Hz, 1H), 3.09 (t, J=11.3 Hz, 1H), 2.00-2.07 (m, 1H), 1.32 (br. s., 1H), 1.27 (br. s., 1H), 1.21 (br. s., 2H), 1.02 (br. s., 2H), 0.66 (br. s., 1H), 0.57 (br. s., 1H), 0.48 (br. s., 1H).

[1178] LC-MS: m/z 430.2 $(M+H)^+$

Compound 747

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(4-methoxybutanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1179] ^{1}H NMR (CHLOROFORM-d) δ: 8.67 (d, J=4.7 Hz, 1H), 7.66 (s, 1H), 7.46 (br. s., 1H), 7.31 (br. s., 1H), 6.95 (dd, J=17.3, 10.9 Hz, 1H), 6.38 (d, J=17.3 Hz, 1H), 5.66 (d, J=10.6 Hz, 1H), 4.58 (d, J=12.9 Hz, 1H), 4.46 (d, J=12.3 Hz, 1H), 3.70-4.12 (br. s., 2H), 3.46 (br. s., 2H), 3.36 (s, 3H), 3.23 (br. s., 1H), 3.11 (br. s., 1H), 2.49 (br. s., 2H), 1.89-2.14 (m, 4H), 1.27-1.31 (m, 1H), 1.18-1.25 (m, 2H), 1.00-1.08 (m, 2H), 0.59 (d, J=15.6 Hz, 2H), 0.47 (d, J=5.0 Hz, 2H).

[1180] LC-MS: m/z 472.5 $(M+H)^+$

Compound 753

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(4-hydroxybutanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1181] ^{1}H NMR (CHLOROFORM-d) δ: 8.64 (d, J=5.0 Hz, 1H), 7.64 (s, 1H), 7.39 (s, 1H), 7.18-7.27 (m, 1H), 6.87 (dd, J=17.3, 10.9 Hz, 1H), 6.28 (d, J=17.6 Hz, 1H), 5.57 (d, J=10.9 Hz, 1H), 4.55 (d, J=12.9 Hz, 1H), 4.42 (d, J=12.6 Hz, 1H), 4.09 (d, J=7.9 Hz, 0.5H), 3.86 (d, J=13.2 Hz, 0.5H), 3.73 (br. s., 2H), 3.05-3.32 (m, 2H), 2.97 (s, 1H), 2.89 (s, 1H), 2.57 (br. s., 3H), 2.00-2.08 (m, 1H), 1.91-1.98 (m, 2H), 1.28 (d, J=17.3 Hz, 1H), 1.21 (br. s., 2H), 1.01 (dd, J=7.6, 3.2 Hz, 2H), 0.61 (br. s., 1H), 0.54 (br. s., 1H), 0.30-0.50 (m, 2H).

[1182] LC-MS: m/z 458.6 $(M+H)^+$

Compound 726

(R)-2-cyclopropyl-6-(3-isopropyl-4-(2-methoxyacetyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1183] ^{1}H NMR (CHLOROFORM-d) δ: 8.64 (d, J=5.0 Hz, 1H), 7.58-7.66 (m, 1H), 7.37 (s, 1H), 7.22 (dd, J=5.0, 1.5 Hz, 1H), 6.87 (dd, J=17.5, 10.7 Hz, 1H), 6.21-6.33 (m, 1H), 5.50-5.60 (m, 1H), 4.54-4.71 (m, 1H), 4.33-4.49 (m, 1.5H), 4.02-4.22 (m, 2H), 3.87 (d, J=13.8 Hz, 0.5H), 3.33-3.50 (m, 4H), 3.03-3.23 (m, 2.5H), 2.21 (d, J=7.6 Hz, 0.5H), 1.96-2.16 (m, 2H), 1.11-1.24 (m, 2H), 0.94-1.11 (m, 5H), 0.84-0.92 (m, 3H).

[1184] LC-MS: m/z 446.1 $(M+H)^+$

Compound 721

(R)-2-cyclopropyl-6-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

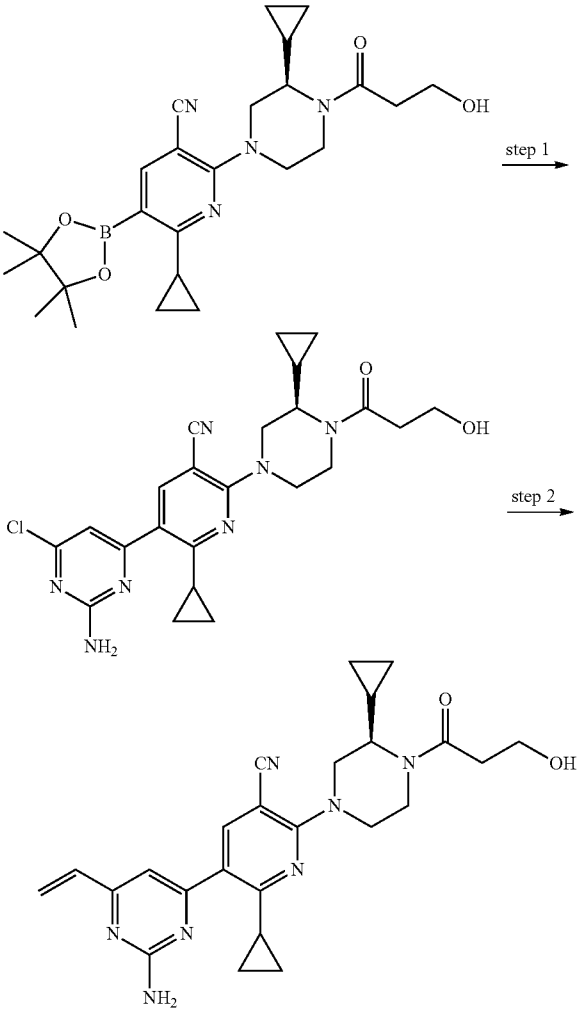
[1185] ^{1}H NMR (CHLOROFORM-d) δ: 8.66 (d, J=5.0 Hz, 1H), 7.64 (d, J=2.3 Hz, 1H), 7.40 (s, 1H), 7.25 (dd, J=5.1, 1.6 Hz, 1H), 6.89 (dd, J=17.5, 10.7 Hz, 1H), 6.23-6.35 (m, 1H), 5.55-5.63 (m, 1H), 4.58-4.74 (m, 1.5H), 4.38-4.50 (m, 1.5H), 3.87-4.00 (m, 2H), 3.78 (d, J=13.8 Hz, 1H), 3.39-3.55 (m, 1H), 3.05-3.24 (m, 2H), 2.56-2.66 (m, 2H), 2.20-2.30 (m, 1H), 1.98-2.06 (m, 2H), 1.25-1.33 (m, 6H), 0.84-0.95 (m, 4H)

[1186] LC-MS: m/z 446.1 $(M+H)^+$

Compound 719

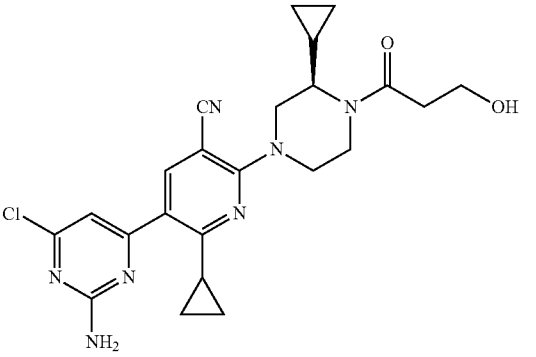
(R)-5-(2-amino-6-vinylpyrimidin-4-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

[1187]



Step 1(R)-5-(2-amino-6-chloropyrimidin-4-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

[1188]



[1189] To a solution of 4,6-dichloropyrimidin-2-amine (270 mg, 0.58 mmol) in a mixture of dimethoxyethane (5 mL) and a 2M aqueous sodium carbonate solution (0.8 mL) were added (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (100 mg, 0.22 mmol) and tetrakis(triphenylphosphine)palladium(0) (20 mg, 0.1 eq) under nitrogen atmosphere, and the mixture was heated for 2 hours at 100° C. After cooling to ambient temperature, the separated organic layer was evaporated under reduced pressure. The residue was taken up into ethyl acetate, washed in turn with a 10% aqueous potassium carbonate solution and brine, and dried over sodium sulfate. After evaporation, the residue was chromatographed on silica gel eluding with 5%-20% ethyl acetate in petroleum ether to give (R)-5-(2-amino-6-chloropyrimidin-4-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile (140 mg crude).

[1190] LC-MS: m/z 468.2 $(M+H)^+$

Step 2: Compound 719

(R)-5-(2-amino-6-vinylpyrimidin-4-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

[1191] A mixture of above (R)-5-(2-amino-6-chloropyrimidin-4-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile (60 mg, 0.13 mmol), potassium vinylfluoborate (25 mg, 0.2 mmol), $Pd(PPh_3)_4$ (3 mg, 0.1 eq), and CsF (40 mg, 0.26 mmol) were suspended in 5 mL of dioxane and 1 mL of water, the resulting mixture was refluxed for 1 h. After the reaction was complete, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography to afford 40 mg of title compound as yellow solid. (70% yield)

[1192] LC-MS: m/z 460.2 $(M+H)^+$

[1193] ^{1}H NMR (CHLOROFORM-d) δ: 7.92 (s, 1H), 6.87 (s, 1H), 6.65 (dd, J=17.3, 10.6 Hz, 1H), 6.39 (d, J=17.5 Hz, 1H), 5.69 (d, J=10.7 Hz, 1H), 5.44 (br. s., 2H), 4.61 (d, J=13.2 Hz, 1H), 4.48 (d, J=12.1 Hz, 1H), 4.07 (d, J=7.5 Hz, 1H), 3.87-3.98 (m, 2H), 3.63-3.84 (m, 2H), 3.17-3.31 (m, 2H), 3.00-3.17 (m, 1H), 2.50-2.66 (m, 2H), 2.30-2.45 (m, 1H), 1.17-1.28 (m, 3H), 0.97-1.13 (m, 2H), 0.61 (br. s., 1H), 0.54 (br. s., 1H), 0.46 (br. s., 2H).

[1194] LC-MS: m/z 460.2 $(M+H)^+$

Compound 663

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(6-vinylpyrimidin-4-yl)nicotinonitrile

[1195] ^{1}H NMR (CHLOROFORM-d) δ:9.19-9.32 (m, 1H), 8.01 (s, 1H), 7.46-7.59 (m, 1H), 6.82 (dd, J=17.3, 10.8 Hz, 1H), 6.51-6.63 (m, 1H), 5.80 (d, J=11.3 Hz, 1H), 5.32 (s, 1H), 4.66 (d, J=13.1 Hz, 1H), 4.53 (d, J=12.8 Hz, 1H), 4.08 (d, J=9.8 Hz, 1H), 3.88-3.97 (m, 2H), 3.67-3.82 (m, 2H), 3.32 (br. s., 1H), 3.20-3.29 (m, 2H), 3.02-3.20 (m, 2H), 2.49-2.66 (m, 2H), 2.34-2.45 (m, 1H), 1.22-1.29 (m, 3H), 1.02-1.10 (m, 2H), 0.63 (d, J=7.8 Hz, 1H), 0.55 (br. s., 1H), 0.47 (br. s., 2H).

[1196] LC-MS: m/z 445.2 $(M+H)^+$

Compound 701

(R)-5-(2-amino-6-(2-aminoethyl)pyrimidin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile

[1197] ^{1}H NMR (CHLOROFORM-d) δ 7.97-8.12 (m, 1H), 7.51 (br. s., 1H), 6.21 (br. s., 2H), 4.71 (d, J=12.8 Hz, 1H), 4.57 (d, J=11.0 Hz, 1H), 4.06 (s, 1H), 3.52 (br. s., 3H), 3.31 (br. s., 3H), 3.22 (br. s., 2H), 2.38 (br. s., 1H), 1.71 (br. s., 1H), 1.19-1.28 (m, 3H), 0.96-1.14 (m, 4H), 0.75-0.87 (m, 2H), 0.62 (br. s., 1H), 0.51 (br. s., 2H), 0.38-0.48 (m, 1H).

[1198] LC-MS: m/z 473.3 $(M+H)^+$

Compound 759

(R)-5-(2-amino-6-vinylpyrimidin-4-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-methoxyacetyl)piperazin-1-yl)nicotinonitrile

[1199] ^{1}H NMR (CHLOROFORM-d) δ: 7.95 (s, 1H), 6.88 (s, 1H), 6.66 (dd, J=17.5, 10.7 Hz, 1H), 6.47 (d, J=17.6 Hz, 1H), 5.71 (d, J=11.2 Hz, 1H), 5.27 (br. s., 2H), 4.64 (d, J=13.2 Hz, 2H), 4.50 (d, J=12.6 Hz, 2H), 4.16 (br. s., 3H), 4.01 (br. s., 1H), 3.90 (br. s., 1H), 3.65 (d, J=17.0 Hz, 1H), 3.46 (s, 3H), 3.18-3.32 (m, 2H), 3.02-3.18 (m, 1H), 2.32-2.47 (m, 1H), 1.18-1.32 (m, 3H), 1.00-1.11 (m, 2H), 0.63 (br. s., 2H), 0.46 (br. s., 2H)

[1200] LC-MS: m/z 460.2 $(M+H)^+$

Compound 727

(R)-5-(1-acryloyl-1,2,5,6-tetrahydropyridin-3-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

[1201] ^{1}H NMR (CHLOROFORM-d) δ: 7.51 (br. s., 1H), 6.66 (dd, J=16.7, 10.6 Hz, 1H), 6.35 (d, J=16.7 Hz, 1H), 5.88 (br. s., 1H), 5.66-5.83 (m, 1H), 4.44 (d, J=12.6 Hz, 1H), 4.25-4.38 (m, 2H), 4.19 (br. s., 1H), 3.98-4.10 (m, 1H), 3.91 (br. s., 2H), 3.84 (br. s., 1H), 3.60-3.79 (m, 3H), 3.08-3.25 (m, 2H), 2.89-3.08 (m, 1H), 2.47-2.65 (m, 2H), 2.40 (br. s., 2H), 2.01-2.08 (m, 1H), 1.27 (br. s., 1H), 1.14 (br. s., 2H), 0.98-1.10 (m, 2H), 0.62 (br. s., 1H), 0.53 (br. s., 1H), 6.34-0.50 (m, 2H).

[1202] LC-MS: m/z 476.6 $(M+H)^+$

Compound 728

(R)-5-(1-acryloyl-1,2,5,6-tetrahydropyridin-3-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-methoxyacetyl)piperazin-1-yl)nicotinonitrile

[1203] ^{1}H NMR (CHLOROFORM-d) δ: 7.44-7.56 (m, 1H), 6.49-6.74 (m, 1H), 6.35 (d, J=16.7 Hz, 1H), 5.88 (br. s., 1H), 5.67-5.82 (m, 1H), 4.46 (d, J=12.9 Hz, 1H), 4.25-4.39 (m, 2H), 4.07-4.23 (m, 3H), 3.98 (d, J=8.5 Hz, 1H), 3.84 (t, J=5.1 Hz, 1H), 3.73 (t, J=5.4 Hz, 1H), 3.45 (s, 3H), 3.10-3.21 (m, 1H), 3.02 (t, J=11.9 Hz, 1H), 2.39 (br. s., 2H), 2.00-2.16 (m, 1H), 1.69 (br. s., 1H), 1.30-1.37 (m, 1H), 1.14 (br. s., 2H), 0.97-1.09 (m, 2H), 0.64 (br. s., 1H), 0.51 (br. s., 1H), 0.45 (br. s., 1H).

[1204] LC-MS: m/z 476.6 $(M+H)^+$

Compound 680

(R)-5-(1-acryloyl-1,2,5,6-tetrahydropyridin-3-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1205] ^{1}H NMR (CHLOROFORM-d) δ: 6.65 (d, J=10.0 Hz, 1H), 6.36 (d, J=16.8 Hz, 1H), 5.65-5.84 (m, 2H), 4.90 (br. s., 0.5H), 4.52 (d, J=13.1 Hz, 0.5H), 4.25-4.38 (m, 0.5H), 4.01-4.25 (m, 4H), 3.87-4.01 (m, 1H), 3.67-3.86 (m, 4H), 3.39 (s, 3H), 3.09-3.22 (m, 1H), 2.95-3.09 (m, 1H), 2.54-2.71 (m, 2H), 2.36-2.48 (m, 5H), 2.03 (br. s., 1H), 1.20-1.35 (m, 4H), 0.84-1.08 (m, 4H).

[1206] LC-MS: m/z 478.6 (M+H)$^+$

Compound 745

(R)-5-(1-acryloyl-1,2,5,6-tetrahydropyridin-3-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-4-methylnicotinonitrile

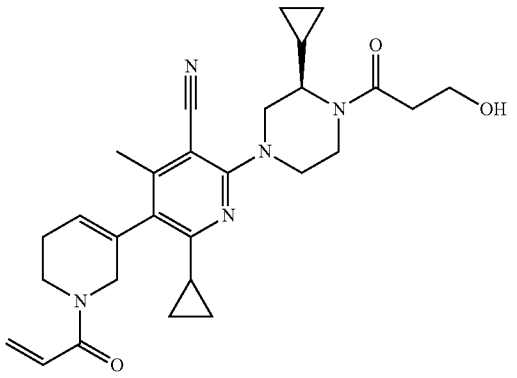
[1207] ^{1}H NMR (CHLOROFORM-d) δ: 6.67 (dd, J=16.3, 10.4 Hz, 1H), 6.36 (d, J=16.1 Hz, 1H), 5.65-5.85 (m, 2H), 4.13-4.34 (m, 3H), 4.03-4.11 (m, 1H), 3.95 (d, J=18.8 Hz, 1H), 3.78-3.89 (m, 1H), 3.62-3.78 (m, 4H), 3.38 (s, 3H), 3.27 (br. s., 1H), 3.10 (br. s., 1H), 2.98 (br. s., 1H), 2.36-2.47 (m, 5H), 1.96-2.08 (m, 1H), 1.23-1.39 (m, 3H), 0.81-1.07 (m, 4H), 0.60 (br. s., 1H), 0.52 (br. s., 1H), 0.43 (br. s., 2H).

[1208] LC-MS: m/z 504.6 (M+H)$^+$

Compound 755

(R)-5-(1-acryloyl-1,2,5,6-tetrahydropyridin-3-yl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-4-methylnicotinonitrile

[1209]



[1210] ^{1}H NMR (CHLOROFORM-d) δ: 6.67 (dd, J=16.7, 10.9 Hz, 1H), 6.36 (d, J=16.7 Hz, 1H), 5.64-5.85 (m, 1H), 4.10-4.38 (m, 3H), 4.04 (br. s., 1H), 3.98 (br. s., 1H), 3.91 (br. s., 2H), 3.61-3.83 (m, 3H), 3.04-3.34 (m, 2H), 2.59 (br. s., 1H), 2.52 (d, J=10.3 Hz, 1H), 2.37-2.48 (m, 5H), 2.06 (br. s., 1H), 1.34-1.50 (m, 1H), 1.16 (br. s., 1H), 0.93-1.10 (m, 3H), 0.62 (br. s., 1H), 0.27-0.56 (m, 3H)

[1211] LC-MS: m/z 490.6 (M+H)$^+$

Compound 762

(R)-1'-acryloyl-2-cyclopropyl-6-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-4-methyl-1',2',5',6'-tetrahydro-[3,3'-bipyridine]-5-carbonitrile

[1212] ^{1}H NMR (CHLOROFORM-d) δ: 6.36 (d, J=16.7 Hz, 1H), 5.68-5.98 (m, 2H), 4.33 (d, J=11.7 Hz, 1H), 4.22 (d, J=13.2 Hz, 2H), 4.04 (br. s., 1H), 3.92 (t, J=5.0 Hz, 3H), 3.64-3.78 (m, 2H), 3.47 (d, J=7.9 Hz, 1H), 2.96-3.09 (m, 2H), 2.52-2.65 (m, 2H), 2.38-2.48 (m, 5H), 2.04 (br. s., 2H), 0.95-1.07 (m, 6H), 0.83-0.95 (m, 4H)

[1213] LC-MS: m/z 492.6 (M+H)$^+$

Compound 649

2-cyclopropyl-6-((3R)-3-methyl-4-(2-(oxetan-2-yl)acetyl)piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1214] ^{1}H NMR (CHLOROFORM-d) δ: 8.60 (m, 1H), 7.64 (s, 1H), 7.37 (s, 1H), 7.19-7.27 (m, 1H), 6.88 (dd, J=17.4, 10.9 Hz, 1H), 6.28 (d, J=17.6 Hz, 1H), 5.57 (d, J=11.0 Hz, 1H), 5.17-5.42 (m, 1H), 4.89 (m, 0.5H), 4.73 (q, J=7.0 Hz, 1H), 4.46-4.62 (m, 1.5H), 4.34 (m, 2H), 4.28 (d, J=13.3 Hz, 0.5H), 3.85 (t, J=13.3 Hz, 0.5H), 3.50-3.67 (m, 0.5H), 3.21-3.32 (m, 1H), 2.99-3.20 (m, 1.5H), 2.76-2.94 (m, 3H), 2.46-2.60 (m, 1H), 1.87-2.09 (m, 1H), 1.24-1.32 (m, 3H), 1.14-1.23 (m, 2H), 0.93-1.10 (m, 3H).

[1215] LC-MS: m/z 444.0 (M+H)$^+$

Compound 648

2-cyclopropyl-6-((R)-3-methyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1216] ^{1}H NMR (CHLOROFORM-d) δ: 8.65 (d, J=5.0 Hz, 1H), 7.63 (s, 1H), 7.38 (s, 1H), 7.13-7.27 (m, 1H), 6.88 (dd, J=17.4, 10.9 Hz, 1H), 6.13-6.40 (m, 1H), 5.56 (d, J=11.5 Hz, 1H), 5.18-5.34 (m, 1H), 4.81-5.03 (m, 0.5H), 4.65-4.79 (m, 1H), 4.48-4.65 (m, 1.5H), 4.30-4.42 (m, 2H), 4.26 (d, J=12.8 Hz, 0.5H), 3.86 (d, J=13.3 Hz, 0.5H), 3.49-3.66 (m, 0.5H), 3.23-3.40 (m, 1H), 3.01-3.20 (m, 1.5H), 2.71-3.01 (m, 3H), 2.37-2.64 (m, 1H), 1.90-2.10 (m, 1H), 1.24-1.34 (m, 3H), 1.13-1.24 (m, 2H), 0.93-1.09 (m, 2H)

[1217] LC-MS: m/z 444.0 (M+H)$^+$

Compound 654

(R)-2-cyclopropyl-6-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1218] ^{1}H NMR (CHLOROFORM-d) δ: 8.70 (d, J=4.8 Hz, 1H), 7.23 (s, 1H), 7.07 (d, J=4.8 Hz, 1H), 6.88 (dd, J=17.4, 10.9 Hz, 1H), 6.30 (d, J=17.3 Hz, 1H), 5.58 (d, J=11.3 Hz, 1H), 4.90 (br. s., 0.5H), 4.54 (d, J=13.6 Hz, 0.5H), 4.07-4.26 (m, 2.5H), 3.93 (br. s., 2H), 3.66-3.79 (m, 0.5H), 3.58 (t, J=11.0 Hz, 0.5H), 3.46 (br. s., 1H), 3.13-3.29 (m, 1.5H), 2.95-3.13 (m, 1H), 2.47-2.75 (m, 2H), 2.22 (s, 3H), 1.74 (br. s., 1H), 1.50-1.63 (m, 1H), 1.37-1.46 (m, 1.5H), 1.33 (d, J=6.8 Hz, 1.5H), 1.01-1.14 (m, 2H), 0.79-0.95 (m, 2H).

[1219] LC-MS: m/z 431.5 (M+H)$^+$

Compound 655

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinyl-1,8-naphthyridin-4-yl)nicotinonitrile

[1220] ^{1}H NMR (CHLOROFORM-d) δ: 7.94-8.05 (m, 1H), 7.69 (d, J=1.3 Hz, 1H), 7.60 (d, J=3.5 Hz, 1H), 7.43-7.48 (m, 1H), 7.14 (dd, J=17.6, 10.8 Hz, 1H), 6.55 (dd, J=17.6, 1.8 Hz, 1H), 5.81 (d, J=11.0 Hz, 1H), 4.60 (d, J=13.1 Hz, 1.5H), 4.48 (d, J=13.1 Hz, 1H), 4.13 (d, J=6.0 Hz, 0.5H), 3.86-3.99 (m, 2H), 3.82 (br. s., 1.5H), 3.28 (br. s., 1.5H), 3.15 (dd, J=15.7, 8.2 Hz, 2H), 2.56-2.68 (m, 2H), 1.13-1.23 (m, 2H), 0.80-0.97 (m, 3H), 0.68 (br. s., 1H), 0.59 (br. s., 1H), 0.51 (br. s., 2H).

[1221] LC-MS: m/z 495.1 $(M+H)^+$

Compound 650

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-5-(2-vinylquinazolin-5-yl)nicotinonitrile

[1222] ^{1}H NMR (CHLOROFORM-d) δ9.20 (d, J=11.0 Hz, 1H), 8.14 (d, J=8.5 Hz, 1H), 7.96-8.04 (m, 1H), 7.68 (dd, J=4.4, 2.9 Hz, 1H), 7.49-7.59 (m, 1H), 7.06-7.23 (m, 1H), 6.86 (d, J=17.1 Hz, 1H), 5.94 (d, J=10.5 Hz, 1H), 4.62-4.80 (m, 1.5H), 4.43-4.54 (m, 1.5H), 3.87-4.03 (m, 2H), 3.73-3.86 (m, 1H), 2.91-3.31 (m, 3H), 2.54-2.67 (m, 2H), 2.09-2.25 (m, 1H), 1.54 (td, J=8.0, 4.1 Hz, 1H), 1.11 (dd, J=13.7, 6.4 Hz, 4H), 0.79-0.94 (m, 6H).

[1223] LC-MS: m/z 497.3 $(M+H)^+$

Compound 652

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinazolin-5-yl)nicotinonitrile

[1224] ^{1}H NMR (CHLOROFORM-d) δ9.17 (d, J=3.3 Hz, 1H), 8.08 (d, J=8.5 Hz, 1H), 7.97 (dd, J=8.4, 7.2 Hz, 1H), 7.68 (s, 1H), 7.52 (d, J=7.0 Hz, 1H), 7.08 (dd, J=17.3, 10.5 Hz, 1H), 6.74-6.90 (m, 1H), 5.89 (dd, J=10.5, 1.5 Hz, 1H), 4.93 (br. s., 0.5H), 4.57 (d, J=12.5 Hz, 0.5H), 4.28-4.47 (m, 2H), 4.21 (br. s., 0.5H), 3.94 (s, 2H), 3.71-3.84 (m, 0.5H), 3.50-3.68 (m, 0.5H), 3.29-3.44 (m, 1H), 3.06-3.26 (m, 2H), 2.49-2.78 (m, 2H), 1.50-1.62 (m, 1H), 1.45 (t, J=7.2 Hz, 1H), 1.35 (t, J=6.4 Hz, 2H), 1.14-1.22 (m, 2H), 0.83-0.98 (m, 2H)

[1225] LC-MS: m/z 469.2 $(M+H)^+$

Compound 651

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylquinazolin-5-yl)nicotinonitrile

[1226] ^{1}H NMR (CHLOROFORM-d) δ: 8.08 (d, J=8.3 Hz, 1H), 7.97 (td, J=7.8, 1.3 Hz, 1H), 7.69 (d, J=1.5 Hz, 1H), 7.47-7.56 (m, 1H), 7.09 (dd, J=17.1, 10.5 Hz, 1H), 6.82 (d, J=17.1 Hz, 1H), 5.90 (dd, J=10.7, 1.6 Hz, 1H), 4.61 (dd, J=13.1, 7.3 Hz, 1H), 4.41-4.55 (m, 1H), 4.12 (d, J=6.5 Hz, 1H), 3.94 (s, 2H), 3.67-3.82 (m, 1H), 3.10-3.40 (m, 3H), 2.49-2.68 (m, 2H), 1.56 (td, J=8.1, 4.1 Hz, 1H), 1.32-1.41 (m, 1H), 1.14-1.24 (m, 2H), 0.84-0.95 (m, 2H), 0.51-0.69 (m, 4H)

[1227] LC-MS: m/z 495.2 $(M+H)^+$

Compound 657

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylquinoxalin-5-yl)nicotinonitrile

[1228] ^{1}H NMR (CHLOROFORM-d) δ: 9.00 (s, 1H), 8.08-8.18 (m, 1H), 7.79-7.90 (m, 1H), 7.65-7.76 (m, 2H), 7.07 (dd, J=17.8, 11.0 Hz, 1H), 6.51 (d, J=17.6 Hz, 1H), 5.84 (d, J=11.0 Hz, 1H), 4.51 (d, J=13.1 Hz, 1H), 4.40 (d, J=12.8 Hz, 1H), 4.13 (q, J=7.0 Hz, 1.5H), 3.86-3.99 (m, 2.5H), 3.76 (d, J=19.8 Hz, 2H), 3.37 (d, J=7.8 Hz, 1H), 3.22-3.33 (m, 1H), 3.17 (d, J=12.3 Hz, 1H), 3.09 (br. s., 1H), 2.55-2.69 (m, 2H), 1.58-1.69 (m, 1H), 1.17-1.37 (m, 3H), 1.08 (br. s., 2H), 0.83 (br. s., 2H), 0.66 (br. s., 1H), 0.55 (br. s., 1H), 0.48 (d, J=5.8 Hz, 3H).

[1229] LC-MS: m/z 495.1 $(M+H)^+$

Compound 740

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(6-vinyl-1H-pyrrolo[2,3-b]pyridin-4-yl)nicotinonitrile

[1230] ^{1}H NMR (CHLOROFORM-d) δ: 10.15 (br. s., 1H), 7.69-7.87 (m, 1H), 7.36-7.45 (m, 1H), 7.23 (s, 1H), 6.97 (dd, J=17.3, 11.2 Hz, 1H), 6.43 (d, J=3.2 Hz, 1H), 6.28 (d, J=17.3 Hz, 1H), 5.56 (d, J=10.9 Hz, 1H), 4.58 (d, J=12.9 Hz, 1H), 4.45 (d, J=12.6 Hz, 1H), 4.12 (d, J=8.5 Hz, 1H), 3.94 (br. s., 2H), 3.63-3.87 (m, 2H), 3.13-3.27 (m, 2H), 2.54-2.69 (m, 2H), 1.95-2.02 (m, 1H), 1.54-1.74 (m, 1H), 1.22 (br. s., 2H), 0.97 (dd, J=7.6, 3.5 Hz, 2H), 0.67 (br. s., 1H), 0.57 (br. s., 1H), 0.50 (br. s., 2H)

[1231] LC-MS: m/z 483.6 $(M+H)^+$

Compound 735

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-5-yl)nicotinonitrile

[1232] ^{1}H NMR (CHLOROFORM-d) δ9.53 (s, 1H), 8.54 (d, J=3.2 Hz, 1H), 7.88-8.00 (m, 1H), 7.79 (d, J=8.8 Hz, 1H), 7.69 (s, 1H), 7.09 (dd, J=17.8, 11.0 Hz, 1H), 6.41 (d, J=17.6 Hz, 1H), 5.81 (d, J=11.2 Hz, 1H), 4.59 (d, J=13.2 Hz, 1H), 4.47 (d, J=12.6 Hz, 1H), 4.1-4.2 (m, 0.5H), 3.93 (br. s., 2H), 3.82 (m, 1.5H), 3.44 (m, 1H), 3.05-3.35 (m, 3H), 2.54-2.70 (m, 2H), 1.47-1.64 (m, 2H), 1.13-1.23 (m, 2H), 0.90-0.96 (m, 2H), 0.68 (br. s., 1H), 0.58 (br. s., 1H), 0.51 (br. s., 2H)

[1233] LC-MS: m/z 495.2 $(M+H)^+$

Compound 744

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(1-methyl-6-vinyl-1H-pyrazolo[3,4-b]pyridin-4-yl)nicotinonitrile

[1234] ^{1}H NMR (CHLOROFORM-d) δ7.90 (s, 1H), 7.77 (s, 1H), 7.21 (s, 1H), 6.99 (dd, J=17.5, 10.7 Hz, 1H), 6.41 (d, J=17.3 Hz, 1H), 5.58-5.73 (m, 1H), 4.60 (d, J=13.2 Hz, 1H), 4.48 (d, J=12.6 Hz, 1H), 4.20 (s, 3H), 4.11 (d, J=8.8 Hz, 1H), 3.93 (br. s., 2H), 3.65-3.85 (m, 1H), 3.44 (br. s., 1H), 3.18-3.36 (m, 2H), 3.13 (d, J=10.0 Hz, 1H), 2.46-2.70 (m, 2H), 1.88-2.01 (m, 1H), 1.31-1.42 (m, 1H), 1.24 (dt, J=7.0, 3.5 Hz, 2H), 0.93-1.04 (m, 2H), 0.66 (br. s., 1H), 0.57 (br. s., 1H), 0.32-0.53 (m, 2H)

[1235] LC-MS: m/z 498.2 $(M+H)^+$

Compound 670

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylquinazolin-4-yl)nicotinonitrile

[1236] ^{1}H NMR (CHLOROFORM-d) δ 8.09 (d, J=8.3 Hz, 1H), 7.86-7.97 (m, 2H), 7.82 (d, J=8.0 Hz, 1H), 7.58 (td, J=7.7, 1.0 Hz, 1H), 7.09 (dd, J=17.2, 10.4 Hz, 1H), 6.82 (dd, J=17.3, 1.8 Hz, 1H), 5.76-5.93 (m, 1H), 4.65 (d, J=13.1 Hz, 1H), 4.52 (d, J=12.8 Hz, 1H), 4.11 (d, J=9.3 Hz, 0.5H), 3.93 (br. s., 2H), 3.7-3.85 (m, 1.5H), 3.48 (br. s., 1H), 3.26 (d, J=13.1 Hz, 2H), 3.17 (m, 1H), 2.52-2.68 (m, 2H), 1.88 (br. s., 1H), 1.66-1.80 (m, 1H), 0.81-0.99 (m, 4H), 0.62-0.79 (m, 1H), 0.57 (br. s., 1H), 0.50 (d, J=5.8 Hz, 2H)

[1237] LC-MS: m/z 495.2 $(M+H)^+$

Compound 669

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-vinylquinazolin-4-yl)nicotinonitrile

[1238] ^{1}H NMR (CHLOROFORM-d) δ8.08 (d, J=8.5 Hz, 1H), 7.87-7.97 (m, 2H), 7.83 (d, J=8.3 Hz, 1H), 7.54-7.66 (m, 1H), 7.08 (dd, J=17.2, 10.4 Hz, 1H), 6.74-6.90 (m, 1H), 5.78-5.94 (m, 1H), 4.66 (d, J=11.3 Hz, 1H), 4.46-4.62 (m, 1H), 4.15-4.35 (m, 1H), 3.53-3.77 (m, 1H), 3.48 (d, J=4.5 Hz, 1H), 3.30 (m, 1H), 3.19 (m, 1H), 1.60-1.83 (m, 2H), 1.43 (br. s., 1H), 1.16-1.29 (m, 2H), 1.04 (d, J=18.8 Hz, 2H), 0.77-0.97 (m, 4H), 0.59-0.77 (m, 1H), 0.37-0.59 (m, 3H)

[1239] LC-MS: m/z 491.2 $(M+H)^+$

Compound 720

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylquinolin-7-yl)nicotinonitrile

[1240] ^{1}H NMR (CHLOROFORM-d) δ: 8.15-8.23 (m, 1H), 8.08-8.15 (m, 1H), 7.88 (d, J=8.3 Hz, 1H), 7.72-7.79 (m, 1H), 7.66 (d, J=8.6 Hz, 1H), 7.56 (dd, J=8.1, 1.6 Hz, 1H), 7.07 (dd, J=17.6, 10.9 Hz, 1H), 6.34 (d, J=17.7 Hz, 1H), 5.73 (d, J=11.0 Hz, 1H), 4.69 (d, J=9.4 Hz, 0.5H), 4.54 (d, J=13.2 Hz, 1H), 4.42 (d, J=12.6 Hz, 1H), 4.10 (d, J=8.3 Hz, 0.5H), 3.93 (br. s., 2H), 3.69-3.86 (m, 1H), 3.16-3.36 (m, 2H), 2.99-3.16 (m, 1H), 2.48-2.69 (m, 2H), 2.11-2.20 (m, 1H), 1.16-1.31 (m, 3H), 0.93-1.05 (m, 2H), 0.66 (br. s., 1H), 0.56 (br. s., 1H), 0.39-0.52 (m, 2H)

[1241] LC-MS: m/z 494.9 $(M+H)^+$

Compound 709

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-vinylquinolin-7-yl)nicotinonitrile (Exemplified by procedure COMPOUND 720)

[1242] ^{1}H NMR (CHLOROFORM-d) δ: 8.17 (d, J=8.5 Hz, 1H), 8.11 (s, 1H), 7.86 (d, J=8.3 Hz, 1H), 7.74 (s, 1H), 7.65 (d, J=8.5 Hz, 1H), 7.56 (dd, J=8.3, 1.5 Hz, 1H), 7.06 (dd, J=17.7, 10.9 Hz, 1H), 6.33 (d, J=17.8 Hz, 1H), 5.71 (d, J=10.8 Hz, 1H), 4.56 (d, J=12.8 Hz, 1H), 4.43 (d, J=12.3 Hz, 1H), 4.09 (m, 1H), 3.72 (m, 1H), 3.29 (br. s., 2H), 3.12 (br. s., 1H), 2.10-2.20 (m, 1H), 1.73 (br. s., 1H), 1.44 (br. s., 1H), 1.18-1.25 (m, 2H), 1.06 (t, J=4.4 Hz, 1H), 0.94-1.04 (m, 3H), 0.81 (dd, J=7.8, 2.3 Hz, 2H), 0.67 (br. s., 1H), 0.41-0.58 (m, 3H).

[1243] LC-MS: m/z 490.9 $(M+H)^+$

Compound 746

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-4-methyl-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[1244] ^{1}H NMR (CHLOROFORM-d) δ: 9.58 (br. s., 1H), 8.57 (br. s., 1H), 7.67 (d, J=7.3 Hz, 1H), 7.21-7.34 (m, 2H), 7.10 (dd, J=17.6, 10.9 Hz, 1H), 6.42 (dd, J=17.6, 2.6 Hz, 1H), 5.82 (d, J=10.9 Hz, 1H), 4.38-4.49 (m, 1H), 4.34 (d, J=12.6 Hz, 1H), 4.14 (d, J=7.0 Hz, 1H), 3.89 (br. s., 1H), 3.69-3.82 (m, 2H), 3.40 (s, 3H), 3.23 (d, J=13.8 Hz, 2H), 3.02-3.17 (m, 1H), 2.72 (br. s., 1H), 2.67 (br. s., 1H), 2.11 (d, J=1.8 Hz, 3H), 1.45 (br. s., 1H), 1.06-1.18 (m, 2H), 0.79-0.90 (m, 1H), 0.69-0.79 (m, 2H), 0.64 (br. s., 1H), 0.57 (br. s., 1H), 0.41-0.55 (m, 2H).

[1245] LC-MS: m/z 522.3 $(M+H)^+$

Compound 741

(R)-6-cyclopropyl-2-(3-isopropyl-4-(2-methoxyacetyl)piperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[1246] ^{1}H NMR (CHLOROFORM-d) δ: 9.58 (s, 1H), 8.60 (br. s., 1H), 7.79 (d, J=10.9 Hz, 1H), 7.63-7.71 (m, 1H), 7.50-7.63 (m, 1H), 7.12 (dd, J=17.6, 10.9 Hz, 1H), 6.47 (d, J=17.6 Hz, 1H), 5.83-5.94 (m, 1H), 4.63-4.80 (m, 1.5H), 4.37-4.58 (m, 2H), 4.04-4.26 (m, 2H), 3.93 (d, J=13.5 Hz, 1H), 3.10-3.33 (m, 2H), 2.09-2.30 (m, 0.5H), 1.92-2.08 (m, 1H), 1.11 (dd, J=16.3, 6.6 Hz, 4H), 0.85-0.98 (m, 6H).

[1247] LC-MS: m/z 496.3 $(M+H)^+$

Compound 717

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-methoxyacetyl)piperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[1248] ^{1}H NMR (CHLOROFORM-d) δ: 9.56 (s, 1H), 8.59 (d, J=5.6 Hz, 1H), 7.72 (d, J=3.2 Hz, 1H), 7.68 (s, 1H), 7.45 (dd, J=9.5, 5.7 Hz, 1H), 7.10 (dd, J=17.8, 11.0 Hz, 1H), 6.42 (dd, J=17.6, 2.1 Hz, 1H), 5.72-5.90 (m, 1H), 4.63 (d, J=13.2 Hz, 1H), 4.45-4.55 (m, 1H), 4.18 (br. s., 2H), 4.06 (br. s., 1H), 3.96 (br. s., 1H), 3.60-3.85 (m, 1H), 3.44-3.49 (m, 3H), 3.23-3.34 (m, 1H), 3.16 (br. s., 1H), 1.97 (br. s., 1H), 1.48-1.56 (m, 1H), 1.22 (dd, J=7.9, 3.8 Hz, 2H), 0.86-0.94 (m, 2H), 0.70 (br. s., 1H), 0.57 (br. s., 1.5H), 0.51 (br. s., 1.5H).

[1249] LC-MS: m/z 494.6 $(M+H)^+$

Compound 689

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[1250] ^{1}H NMR (CHLOROFORM-d) δ: 9.58 (br. s., 1H), 8.61 (br. s., 1H), 7.77 (d, J=3.0 Hz, 1H), 7.64-7.73 (m, 1H), 7.54 (br. s., 1H), 7.12 (dd, J=17.6, 10.8 Hz, 1H), 6.45 (dd, J=17.7, 2.1 Hz, 1H), 5.85 (d, J=11.0 Hz, 1H), 4.64 (d, J=10.0 Hz, 1H), 4.52 (d, J=12.0 Hz, 1H), 4.25 (br. s., 1H), 3.69-3.81 (br. s., 1H), 3.38 (d, J=15.3 Hz, 1.5H), 3.21 (br. s., 1.5H), 1.75 (br. s., 1H), 1.50 (br. s., 1H), 1.26-1.37 (m, 1H), 1.23 (br. s.,

2H), 0.99-1.14 (m, 2H), 0.87-0.96 (m, 2H), 0.84 (dd, J=7.8, 2.3 Hz, 2H), 0.71 (br. s., 1H), 0.52-0.62 (m, 2H), 0.43-0.52 (m, 1H).

[1251] LC-MS: m/z 490.6 $(M+H)^+$

Compound 688

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[1252] ^{1}H NMR (CHLOROFORM-d) δ: 9.59 (s, 1H), 8.60 (d, J=5.5 Hz, 1H), 7.80 (d, J=2.8 Hz, 1H), 7.69 (d, J=1.3 Hz, 1H), 7.54-7.63 (m, 1H), 7.12 (dd, J=17.6, 10.8 Hz, 1H), 6.48 (dd, J=17.7, 2.1 Hz, 1H), 5.88 (d, J=11.0 Hz, 1H), 4.63 (d, J=12.5 Hz, 1H), 4.52 (d, J=7.5 Hz, 1H), 4.13 (d, J=9.3 Hz, 1H), 3.87-3.99 (m, 2H), 3.67-3.87 (m, 1H), 3.30 (br. s., 2H), 3.18 (br. s., 1H), 2.57-2.68 (m, 2H), 1.43-1.54 (m, 1H), 1.32-1.41 (m, 1H), 1.19-1.26 (m, 2H), 0.87-0.97 (m, 2H), 0.67 (br. s., 1H), 0.60 (br. s., 1H), 0.40-0.55 (m, 2H).

[1253] LC-MS: m/z 494.6 $(M+H)^+$

Compound 658

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[1254] ^{1}H NMR (CHLOROFORM-d) δ: 9.57 (s, 1H), 8.59 (d, J=5.5 Hz, 1H), 7.76 (d, J=3.5 Hz, 1H), 7.68 (d, J=1.3 Hz, 1H), 7.49-7.60 (m, 1H), 7.11 (dd, J=17.6, 11.0 Hz, 1H), 6.45 (dd, J=17.6, 1.8 Hz, 1H), 5.85 (d, J=11.3 Hz, 1H), 4.55-4.68 (m, 1H), 4.50 (dd, J=12.8, 2.3 Hz, 1H), 4.15 (br. s., 0.5H), 3.92 (br. s., 0.5H), 3.66-3.84 (m, 3H), 3.40 (s, 3H), 3.30 (br. s., 1H), 3.22 (br. s., 1H), 3.15 (d, J=7.5 Hz, 1H), 2.66 (br. s., 1H), 2.56 (br. s., 1H), 1.46-1.54 (m, 1H), 1.32 (d, J=16.1 Hz, 1H), 1.19-1.24 (m, 2H), 0.84-0.99 (m, 2H), 0.66 (br. s., 1H), 0.60 (br. s., 1H), 0.49 (br. s., 2H).

[1255] LC-MS: m/z 508.6 $(M+H)^+$

Compound 681

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-5-(2-vinyl-1,7-naphthyridin-4-yl)nicotinonitrile

[1256] ^{1}H NMR (CHLOROFORM-d) δ: 9.55 (s, 1H), 8.59 (dd, J=5.3, 3.0 Hz, 1H), 7.73 (d, J=11.5 Hz, 1H), 7.67 (dd, J=4.5, 2.8 Hz, 1H), 7.45 (dd, J=12.5, 5.5 Hz, 1H), 7.10 (ddd, J=17.6, 10.9, 1.1 Hz, 1H), 6.42 (d, J=17.6 Hz, 1H), 5.82 (d, J=10.8 Hz, 1H), 4.61-4.79 (m, 1H), 4.41-4.60 (m, 2H), 3.86-4.01 (m, 2H), 3.82 (d, J=13.6 Hz, 0.5H), 3.53-3.60 (m, 0.5H), 3.10-3.30 (m, 2H), 3.01 (d, J=12.8 Hz, 0.5H), 2.73-2.84 (m, 0.5H), 2.56-2.68 (m, 2H), 2.09-2.37 (m, 1H), 1.47-1.55 (m, 1H), 1.05-1.17 (m, 4H), 0.80-1.01 (m, 6H).

[1257] LC-MS: m/z 496.6 $(M+H)^+$

Compound 710

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(1-vinylisoquinolin-7-yl)nicotinonitrile

[1258] 1H NMR (CHLOROFORM-d) δ 8.61 (d, J=5.8 Hz, 1H), 8.30 (s, 1H), 7.95 (d, J=8.3 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H), 7.74 (s, 1H), 7.65-7.72 (m, 1H), 7.58-7.65 (m, 1H), 6.64 (d, J=16.1 Hz, 1H), 5.84 (d, J=10.3 Hz, 1H), 4.58 (d, J=11.5 Hz, 1H), 4.46 (d, J=11.8 Hz, 1H), 4.01-4.31 (m, 1H), 3.61-3.89 (m, 1H), 3.33 (d, J=17.3 Hz, 1.5H), 3.15 (br. s., 1.5H), 2.02-2.09 (m, 1H), 1.42-1.47 (m, 1H), 1.34 (d, J=8.5 Hz, 1H), 1.25-1.30 (m, 3H), 1.06-1.11 (m, 1H), 0.98-1.02 (m, 2H), 0.90 (t, J=6.7 Hz, 1H), 0.80-0.84 (m, 2H), 0.68 (br. s., 1H), 0.52-0.56 (m, 1H), 0.46-0.49 (m, 1H)

[1259] LC-MS: m/z 492.0 $(M+H)^+$

Compound 685

(R)-5-((2-chloropyridin-4-yl)methyl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile

[1260] ^{1}H NMR (CHLOROFORM-d) δ: 8.33 (d, J=5.0 Hz, 1H), 7.49 (s, 1H), 7.12 (s, 1H), 6.98-7.06 (m, 1H), 4.47 (d, J=12.5 Hz, 1H), 4.30-4.50 (m, 2.5H), 4.20-4.30 (m, 1H), 4.04 (s, 1H), 3.60-3.90 (s, 1H), 2.90-3.45 (m, 1H), 2.01 (s, 1H), 1.80-1.91 (m, 1H), 1.72 (s, 1H), 1.09-1.17 (m, 2H), 0.93-1.09 (m, 4H), 0.74-0.86 (m, 2H), 0.37-0.65 (m, 4H)

[1261] LC-MS: m/z 462.2 $(M+H)^+$

Compound 684

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-((2-vinylpyridin-4-yl)methyl)nicotinonitrile

[1262] ^{1}H NMR (CHLOROFORM-d): 8.50 (d, J=5.0 Hz, 1H), 7.47 (s, 1H), 7.12 (s, 1H), 6.89-6.99 (m, 1H), 6.80 (dd, J=17.6, 10.8 Hz, 1H), 6.16-6.29 (m, 1H), 5.44-5.57 (m, 1H), 4.25-4.60 (m, 2.5H), 4.12-4.20 (m, 1H), 4.03 (s, 2H), 3.49-3.90 (m, 1H), 2.95-3.29 (m, 2.5H), 1.85-1.98 (m, 1H), 1.71 (s, 1H), 1.35-1.45 (m, 1H), 1.07-1.17 (m, 2H), 0.92-1.07 (m, 4H), 0.76-0.82 (m, 2H), 0.30-0.63 (m, 4H)

[1263] LC-MS: m/z 454.2 $(M+H)^+$

Compound 708

(R)-5-((2-chloropyridin-4-yl)methyl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

[1264] ^{1}H NMR (CHLOROFORM-d) δ: 8.34 (d, J=5.3 Hz, 1H), 7.49 (s, 1H), 7.11 (s, 1H), 7.03 (d, J=5.0 Hz, 1H), 4.39-4.52 (m, 2H), 4.33 (d, J=12.3 Hz, 1H), 4.04 (s, 2H), 3.85-3.97 (m, 2H), 3.66-3.81 (m, 1H), 3.01-3.22 (m, 3H), 2.51-2.65 (m, 2H), 1.79-1.92 (m, 1H), 1.31-1.39 (m, 1H), 1.08-1.15 (m, 2H), 0.93-1.03 (m, 2H), 0.46-0.63 (m, 4H)

[1265] LC-MS: m/z 466.2 $(M+H)^+$

Compound 697

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-((2-vinylpyridin-4-yl)methyl)nicotinonitrile

[1266] A mixture of (R)-5-((2-chloropyridin-4-yl)methyl)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile (80 mg, 0.172 mmol), potassium vinyltrifluoroborate (46 mg, 0.343 mmol), $Pd(dppf)Cl_2$ (7 mg, 0.009 mmol) and CsF (79 mg, 0.515 mmol) in dioxane/H_2O was stirred at 100° C. for 16 hours. The mixture was diluted with EtOAc (30 mL) and filtered. The filtrated was partitioned between EtOAc (30 mL) and water (10 mL), the organic layer was washed with water (10 mL), brine and dried

over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 25 mg of the product.

[1267] ^{1}H NMR (CHLOROFORM-d): 8.47 (d, J=5.0 Hz, 1H), 7.46 (s, 1H), 7.10 (s, 1H), 6.87-6.97 (m, 1H), 6.76 (dd, J=17.3, 10.8 Hz, 1H), 6.18 (dd, J=17.6, 1.0 Hz, 1H), 5.41-5.53 (m, 1H), 4.39 (d, J=12.8 Hz, 1H), 4.27 (d, J=12.5 Hz, 1H), 4.01 (m, 2H), 3.80-3.92 (m, 2H), 3.51-3.79 (m, 2H), 2.99-3.18 (m, 3H), 2.42-2.66 (m, 2H), 1.85-1.97 (m, 1H), 1.30-1.40 (m, 1H), 1.03-1.12 (m, 2H), 0.88-1.00 (m, 2H), 0.30-0.59 (m, 4H)

[1268] LC-MS: m/z 458.3 $(M+H)^+$

Compound 698 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-((2-vinyl-1,7-naphthyridin-4-yl)amino)nicotinonitrile

[1269] ^{1}H NMR (CHLOROFORM-d) δ: 9.48 (s, 1H), 8.59 (d, J=5.8 Hz, 1H), 7.90 (br. s., 1H), 7.68-7.77 (m, 1H), 7.35-7.48 (m, 1H), 6.91 (dd, J=17.4, 10.9 Hz, 1H), 6.56 (s, 1H), 6.26 (d, J=17.6 Hz, 1H), 5.67 (d, J=11.0 Hz, 1H), 4.86-4.98 (m, 0.5H), 4.51-4.62 (d, 0.5H) 4.14-4.38 (m, 3H), 3.94 (br. s., 2H), 3.70-3.81 (m, 0.5H), 3.59 (t, J=10.8 Hz, 0.5H), 3.27-3.41 (m, 1H), 3.01-3.24 (m, 2H), 2.48-2.78 (m, 2H), 1.97-2.09 (m, 1H), 1.44 (d, J=6.5 Hz, 1.5H), 1.34 (d, J=6.8 Hz, 1.5H), 1.10-1.20 (m, 2H), 0.94-1.06 (m, 2H).

[1270] LC-MS: m/z 483.2 $(M+H)^+$

Compound 679 (General Procedure 7)

(R)-5-((2-chloropyridin-4-yl)amino)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile

[1271] ^{1}H NMR (CHLOROFORM-d) δ: 8.06 (d, J=5.4 Hz, 1H), 7.60 (s, 1H), 6.57-6.47 (m, 2H), 6.08 (s, 1H), 4.75-4.64 (m, 0.5H), 4.49 (t, J=11.8 Hz, 1H), 4.37 (t, J=10.9 Hz, 1H), 4.14-4.09 (m, 0.5H), 3.89 (ddd, J=7.5, 3.5, 2.5 Hz, 0.5H), 3.81-3.64 (m, 2.5H), 3.39 (s, 3H), 3.31-3.17 (m, 1.5H), 3.10 (td, J=12.8, 3.4 Hz, 1H), 2.69 (ddd, J=22.8, 14.8, 9.9 Hz, 2H), 2.52 (dd, J=20.7, 9.1 Hz, 0.5H), 2.06 (ddd, J=7.5, 4.5, 1.6 Hz, 1H), 1.28 (m, J=4.7 Hz, 1H), 1.15 (m, 2H), 1.08-0.99 (m, 2H), 0.72-0.52 (m, 2H), 0.52-0.39 (m, 2H).

[1272] LC-MS: m/z NB250-076-2 481.1 $(M+H)^+$

Compound 678 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-((2-vinylpyridin-4-yl)amino)nicotinonitrile

[1273] ^{1}H NMR (CHLOROFORM-d) δ: 8.26 (d, J=5.7 Hz, 1H), 7.62 (s, 1H), 6.72 (dd, J=17.4, 10.8 Hz, 1H), 6.58 (s, 1H), 6.46 (d, J=4.1 Hz, 1H), 6.20 (d, J=17.4 Hz, 1H), 5.94 (s, 1H), 5.49 (d, J=10.8 Hz, 1H), 4.70 (dd, J=14.5, 4.5 Hz, 0.5H), 4.46 (t, J=11.4 Hz, 1H), 4.33 (d, J=10.6 Hz, 1H), 4.13-4.07 (m, 0.5H), 3.92-3.85 (m, 0.5H), 3.83-3.62 (m, 2.5H), 3.39 (s, 3H), 3.31-3.16 (m, 1.5H), 3.09 (td, J=13.2, 3.7 Hz, 1H), 2.82-2.58 (m, 2H), 2.58-2.45 (m, 0.5H), 2.10 (dt, J=4.5, 3.0 Hz, 1H), 1.28 (s, 1H), 1.18-1.10 (m, 2H), 1.02 (ddd, J=9.9, 6.4, 3.2 Hz, 2H), 0.73-0.53 (m, 2H), 0.53-0.39 (m, 2H).

[1274] LC-MS: m/z 473.2 $(M+H)^+$

Compound 661 (General Procedure 7)

(R)-5-((2-chloropyridin-4-yl)amino)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1275] ^{1}H NMR (CHLOROFORM-d) δ: 8.06 (d, J=5.8 Hz, 1H), 7.60 (s, 1H), 6.54 (s, 1H), 6.51 (dd, J=5.8, 2.0 Hz, 1H), 6.15 (s, 1H), 4.90 (s, 0.5H), 4.54 (d, J=13.4 Hz, 0.5H), 4.35-4.16 (m, 2.5H), 3.93 (s, 2H), 3.74 (d, J=13.4 Hz, 0.5H), 3.58 (d, J=11.0 Hz, 0.5H), 3.30 (dd, J=10.8, 6.4 Hz, 1H), 3.15 (t, J=12.2 Hz, 1H), 3.08-3.01 (m, 0.5H), 2.74-2.51 (m, 2H), 2.07 (ddd, J=12.6, 8.0, 4.7 Hz, 1H), 1.42 (d, J=6.6 Hz, 1.5H), 1.32 (d, J=6.7 Hz, 1.5H), 1.13 (dt, J=7.2, 3.6 Hz, 2H), 1.05 (ddd, J=10.3, 6.6, 3.5 Hz, 2H).

[1276] LC-MS: m/z 441.0 $(M+H)^+$

Compound 677 (General Procedure 7)

(R)-5-((2-chloropyridin-4-yl)amino)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

[1277] ^{1}H NMR (CHLOROFORM-d) δ: 8.01 (d, J=5.7 Hz, 1H), 7.59 (s, 1H), 6.49 (d, J=1.8 Hz, 1H), 6.46 (dd, J=5.7, 2.0 Hz, 1H), 6.41 (s, 1H), 4.66 (d, J=13.6 Hz, 0.5H), 4.45 (d, J=12.9 Hz, 1H), 4.33 (d, J=12.7 Hz, 1H), 4.06 (d, J=9.3 Hz, 0.5H), 3.91 (s, 2H), 3.80 (d, J=13.2 Hz, 0.5H), 3.72 (d, J=11.6 Hz, 0.5H), 3.56 (m, 0.5H), 3.27-3.01 (m, 2.5H), 2.59 (dd, J=17.2, 5.2 Hz, 1.5H), 2.11-2.04 (m, 1H), 1.98 (m, 0.5H), 1.43-1.27 (m, 1H), 1.18-1.09 (m, 2H), 1.07-0.98 (m, 2H), 0.63 (m, J=7.2, 4.7 Hz, 1H), 0.58-0.28 (m, 3H).

[1278] LC-MS: m/z 467.0 $(M+H)^+$

Compound 676 (General Procedure 6)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-((2-vinylpyridin-4-yl)amino)nicotinonitrile

[1279] ^{1}H NMR (CHLOROFORM-d) δ: 8.20 (d, J=6.1 Hz, 1H), 7.63 (s, 1H), 6.73 (dd, J=17.5, 10.9 Hz, 1H), 6.69 (d, J=3.2 Hz, 1H), 6.63 (d, J=3.1 Hz, 1H), 6.29 (d, J=17.5 Hz, 1H), 5.57 (d, J=10.9 Hz, 1H), 4.69 (d, J=11.0 Hz, 0.5H), 4.46 (d, J=13.0 Hz, 1H), 4.35 (d, J=13.1 Hz, 1H), 4.10 (d, J=7.7 Hz, 0.5H), 3.92 (d, J=3.9 Hz, 2H), 3.74 (ddd, J=21.2, 17.7, 8.0 Hz, 1.5H), 3.30-3.17 (m, 1.5H), 3.13-3.03 (m, 1H), 2.69-2.48 (m, 2H), 2.15-2.06 (m, 1H), 1.28 (d, J=5.0 Hz, 1H), 1.14 (dt, J=7.3, 3.6 Hz, 2H), 1.08-0.98 (m, 2H), 0.76-0.62 (m, 1H), 0.62-0.32 (m, 3H).

[1280] LC-MS: m/z 459.0 $(M+H)^+$

Compound 718 (General Procedure 7)

(R)-5-((2-chloropyridin-4-yl)amino)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-methoxyacetyl)piperazin-1-yl)nicotinonitrile

[1281] ^{1}H NMR (CHLOROFORM-d) δ: 8.06 (d, J=5.7 Hz, 1H), 7.60 (s, 1H), 6.50 (d, J=2.1 Hz, 1H), 6.46 (dd, J=5.7, 2.2 Hz, 1H), 5.79 (s, 1H), 4.43 (dd, J=52.6, 11.8 Hz, 2.5H), 4.16 (s, 2H), 4.00 (s, 1.5H), 3.67 (d, J=24.8 Hz, 1H), 3.46 (s, 3H), 3.21 (dd, J=13.0, 3.4 Hz, 1H), 3.09 (t, J=11.3 Hz, 1H), 2.07 (ddd, J=12.7, 8.0, 4.7 Hz, 1H), 1.38 (s, 1H), 1.15 (dt, J=7.5, 3.7 Hz, 2H), 1.08-1.00 (m, 2H), 0.67 (s, 1H), 0.63-0.39 (m, 3H).

[1282] LC-MS: m/z 467.2 $(M+H)^+$

Compound 711 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-methoxy-acetyl)piperazin-1-yl)-5-((2-vinylpyridin-4-yl) amino)nicotinonitrile

[1283] ^{1}H NMR (CHLOROFORM-d) δ: 8.26 (d, J=5.7 Hz, 1H), 7.62 (s, 1H), 6.71 (dd, J=17.4, 10.8 Hz, 1H), 6.59 (d, J=2.2 Hz, 1H), 6.45 (dd, J=5.7, 2.3 Hz, 1H), 6.18 (dd, J=17.4, 1.0 Hz, 1H), 6.01 (s, 1H), 5.47 (dd, J=10.8, 0.9 Hz, 1H), 4.81-4.26 (m, 2.6H), 4.16 (s, 2H), 3.95 (d, J=43.6 Hz, 1.5H), 3.70 (s, 1H), 3.46 (s, 3H), 3.20 (dd, J=13.0, 3.4 Hz, 1H), 3.07 (t, J=11.4 Hz, 1H), 2.15-2.07 (m, 1H), 1.41 (s, 1H), 1.19-1.10 (m, 2H), 1.02 (ddd, J=10.2, 6.6, 3.4 Hz, 2H), 0.67 (s, 1H), 0.61-0.37 (m, 3H).

[1284] LC-MS: m/z NB295-002-01 459.1 $(M+H)^+$

Compound 743

(R)-6-cyclopropyl-2-(3-isopropyl-4-(2-methoxy-acetyl)piperazin-1-yl)-5-((2-vinylpyridin-4-yl) amino)nicotinonitrile

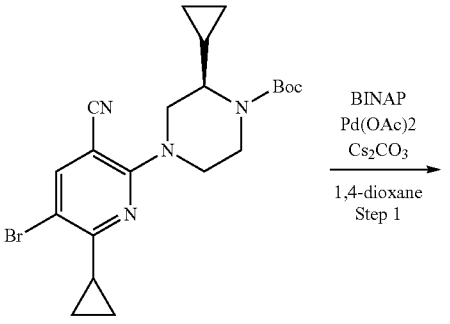
[1285] ^{1}H NMR (CHLOROFORM-d) δ: 8.24 (d, J=5.8 Hz, 1H), 7.60 (d, J=3.1 Hz, 1H), 6.72 (dd, J=17.4, 10.8 Hz, 1H), 6.61 (s, 1H), 6.51 (d, J=4.3 Hz, 1H), 6.37 (s, 1H), 6.23 (d, J=17.5 Hz, 1H), 5.52 (d, J=10.9 Hz, 1H), 4.68-4.47 (m, 1.5H), 4.37 (t, J=12.7 Hz, 1.5H), 4.28 (d, J=13.4 Hz, 0.5H), 4.22-4.13 (m, 1H), 4.08 (d, J=13.5 Hz, 0.5H), 3.88 (d, J=13.6 Hz, 0.5H), 3.56 (d, J=10.6 Hz, 0.5H), 3.47 (d, J=2.5 Hz, 3H), 3.42 (dd, J=13.3, 2.9 Hz, 0.5H), 3.24-2.95 (m, 2.5H), 2.19-2.04 (m, 2H), 1.28 (d, J=4.7 Hz, 1H), 1.19-1.11 (m, 1H), 1.07 (d, J=6.5 Hz, 3H), 1.05-0.97 (m, 2H), 0.91 (dd, J=15.7, 6.8 Hz, 3H).

[1286] LC-MS: m/z NB295-018-01 461.4 $(M+H)^+$

Compound 731

(R)-5-((2-chloropyridin-4-yl)(methyl)amino)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl) piperazin-1-yl)nicotinonitrile

[1287]



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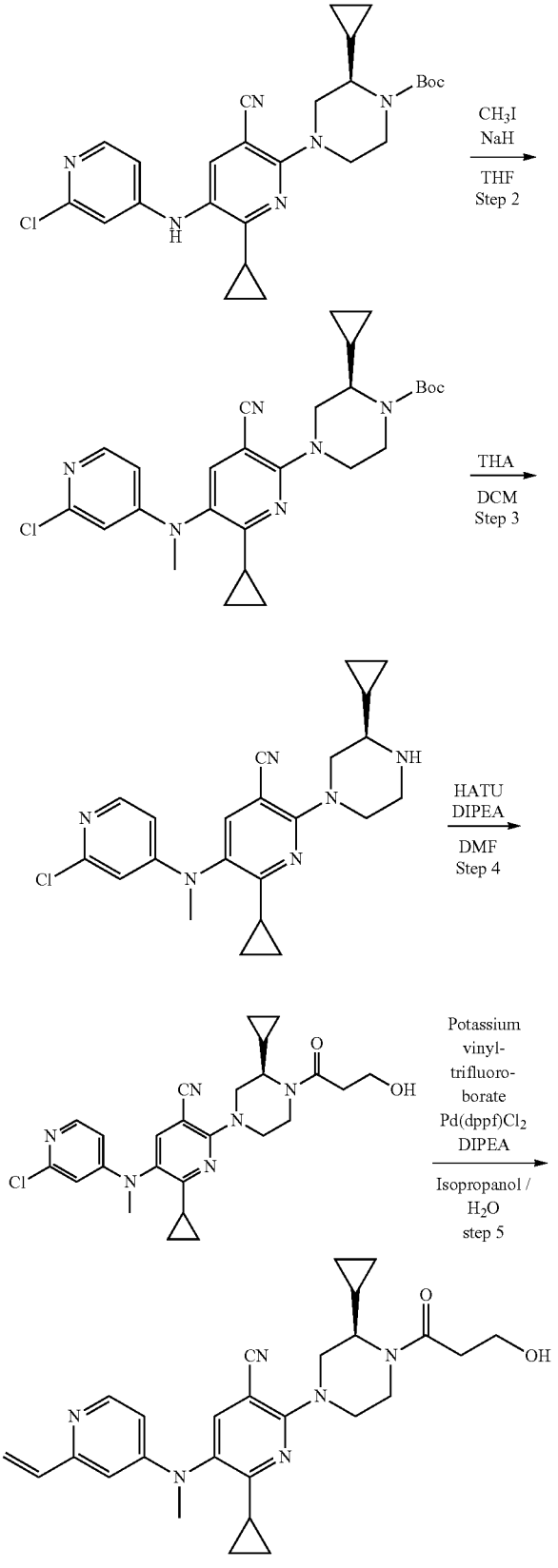


Step 1: (R)-tert-butyl-4-(5-(2-chloropyridin-4-ylamino)-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate

[1288] To a solution of (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (1.5 g, 3.363 mmol) and 2-chloropyridin-4-amine (518.6 mg, 4.036 mmol) in 1,4-dioxane (20 mL) was added $Pd(OAc)_2$ (76 mg, 0.34 mmol), BINAP (314.3 mg, 0.505 mmol) and Cs_2CO_3 (2.2 g, 6.726 mmol) at r.t. under N_2. The resulting mixture was heated and stirred at 155° C. under N_2 in microwave for 1 h. The solvent was removed in vacuum and the residue was purified via column chromatography (petroleum ether: EtOAc) to afford the title compound (1.1 g, 66.2%) as a yellow solid.

[1289] LC-MS: m/z 495.0 $(M+H)^+$

Step 2: (R)-tert-butyl 4-(5-((2-chloropyridin-4-yl)(methyl)amino)-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate

[1290] To a solution of (R)-tert-butyl 4-(5-(2-chloropyridin-4-ylamino)-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (550 mg, 1.1 mmol) in anhydrous THF (10 mL) was added NaH (89 mg, 2.22 mmol) and iodomethane (2 drops) at r.t. The reaction mixture was stirred at r.t. for 3 hrs. The reaction mixture was quenched by water at 0° C. The mixture was extracted with EtOAc (15 mL×2). The combined organic layer was washed with brine, dried over Na_2SO_4. The organic phase was filtered and the filtrate was concentrated in vacuum to give out the title compound (crude, 567 mg) as a yellow solid.

[1291] LC-MS: m/z 509.1 $(M+H)^+$

Step 3: (R)-5-((2-chloropyridin-4-yl)(methyl)amino)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile

[1292] To a solution of (R)-tert-butyl 4-(5-((2-chloropyridin-4-yl)(methyl)amino)-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (567 mg, 1.1 mmol) in anhydrous DCM (5 mL) was added TFA (5 mL) at r.t. The reaction mixture was stirred at r.t. for 2 hrs. The solvent was removed in vacuum and the residue was adjusted to pH>7.0. The residue mixture was extracted with EtOAc (15 mL×2). The combined organic layer was washed with brine, dried over Na_2SO_4. The organic phase was filtered and the filtrate was concentrated in vacuum to give out the title compound (crude, 432 mg) as a yellow solid.

[1293] LC-MS: m/z 409.1 $(M+H)^+$

Step 4: (R)-5-((2-chloropyridin-4-yl)(methyl)amino)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

[1294] To a solution of (R)-5-((2-chloropyridin-4-yl)(methyl)amino)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile (410 mg, 1.0 mmol) in DMF (8 mL) was added sodium 3-hydroxypropanoate (203.5 mg, 1.5 mmol), HATU (572.3 mg, 1.5 mmol) and DIPEA (194 mg, 1.5 mmol) at r.t. The reaction mixture was stirred at r.t. for 3 hrs. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM: MeOH) to afford the title compound (270 mg, 56.3%) as a pale yellow solid.

[1295] ^1H NMR (CHLOROFORM-d) δ: 8.03 (d, J=5.8 Hz, 1H), 7.56 (s, 1H), 6.45 (s, 1H), 6.35 (d, J=3.5 Hz, 1H), 4.70 (d, J=11.2 Hz, 0.5H), 4.51 (d, J=13.0 Hz, 1H), 4.39 (d, J=13.4 Hz, 1H), 4.10 (d, J=9.2 Hz, 0.5H), 3.93 (d, J=4.5 Hz, 2H), 3.86-3.65 (m, 1.5H), 3.40 (s, 1H), 3.30 (s, 3H), 3.28-3.15 (m, 1.5H), 3.15-3.01 (m, 1H), 2.69-2.44 (m, 2H), 1.89-1.78 (m, 1H), 1.28 (d, J=5.0 Hz, 1H), 1.13 (s, 2H), 1.01 (d, J=11.8 Hz, 2H), 0.82-0.65 (m, 1H), 0.64-0.32 (m, 3H)

[1296] LC-MS: m/z 481.0 $(M+H)^+$

Step 5: Compound 731

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(methyl(2-vinylpyridin-4-yl)amino)nicotinonitrile

[1297] To a solution of (R)-5-((2-chloropyridin-4-yl)(methyl)amino)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile (270 mg, 0.563 mmol) in isopropanol (10 mL) and H_2O (3 mL) was added Vinyltrifluoroboric acid potassium salt (113.1 mg, 0.844 mmol), $Pd(dppf)Cl_2$ (49.0 mg, 0.06 mmol) and DIPEA (145.3 mg, 1.126 mmol) at r.t. under N_2. The reaction mixture was heated and stirred at reflux under N_2 overnight. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM: MeOH) to afford the title compound (121 mg, 45.5%) as a pale yellow solid.

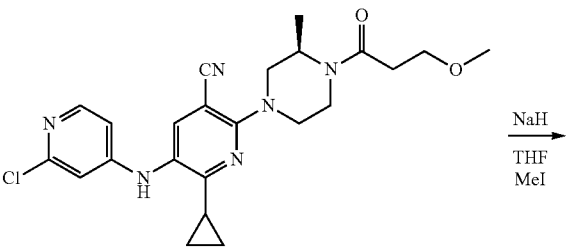
[1298] ^1H NMR (CHLOROFORM-d) δ: 8.25 (d, J=5.9 Hz, 1H), 7.58 (s, 1H), 6.71 (dd, J=17.4, 10.7 Hz, 1H), 6.46 (s, 1H), 6.33 (s, 1H), 6.20 (d, J=17.3 Hz, 1H), 5.45 (d, J=11.2 Hz, 1H), 4.69 (d, J=13.4 Hz, 0.4H), 4.49 (d, J=13.0 Hz, 1H), 4.37 (d, J=12.7 Hz, 1H), 4.10 (d, J=8.6 Hz, 0.6H), 3.92 (s, 2H), 3.86-3.65 (m, 1.5H), 3.42 (s, 1H), 3.31 (s, 3H), 3.22 (m, 1.5H), 3.15-3.00 (m, 1H), 2.69-2.45 (m, 2H), 1.88 (ddd, J=12.7, 8.1, 4.7 Hz, 1H), 1.40-1.31 (m, 1H), 1.12 (s, 2H), 0.99 (s, 2H), 0.81-0.34 (m, 4H).

[1299] LC-MS: m/z 473.4 $(M+H)^+$

Compound 699

(R)-5-((2-chloropyridin-4-yl)(methyl)amino)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1300]



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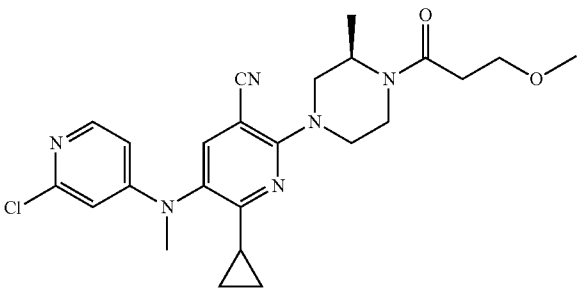


[1301] To a solution of (R)-5-(2-chloropyridin-4-ylamino)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (675 mg, 1.487 mmol) in anhydrous THF (15 mL) was added iodomethane (0.5 mL) and NaH (119 mg, 2.974 mmol) at r.t. The reaction mixture was stirred at r.t. for 3 hrs. The reaction mixture was quenched by water at 0° C. The mixture was extracted with EtOAc (15 mL×2). The combined organic layer was washed with brine, dried over Na_2SO_4. The organic phase was filtered and the filtrate was concentrated in vacuum. The residue was purified via silica gel column chromatography (DCM: MeOH) to afford the title compound (350 mg, 50.3%) as a white solid.

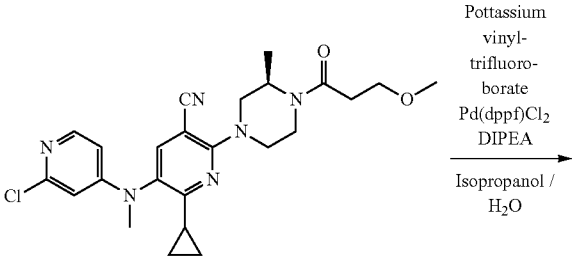
[1302] ^{1}H NMR (CHLOROFORM-d) δ: 8.04 (d, J=5.7 Hz, 1H), 7.54 (s, 1H), 6.42 (d, J=44.6 Hz, 2H), 4.92 (s, 0.5H), 4.55 (d, J=13.0 Hz, 0.5H), 4.40-4.25 (m, 2H), 4.22 (d, J=13.9 Hz, 0.5H), 3.83 (d, J=13.7 Hz, 0.5H), 3.76 (t, J=6.3 Hz, 2H), 3.57 (t, J=11.5 Hz, 0.5H), 3.39 (s, 3H), 3.37-3.33 (m, 0.5H), 3.31 (s, 3H), 3.28-2.97 (m, 2H), 2.85-2.65 (m, 1H), 2.64-2.51 (m, 1H), 1.80 (ddd, J=12.5, 8.0, 4.6 Hz, 1H), 1.36 (dd, J=41.2, 6.2 Hz, 3H), 1.12 (s, 2H), 1.07-0.93 (m, 2H).

[1303] LC-MS: m/z 469.2 $(M+H)^+$

Compound 690 (General Procedure 6)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(methyl(2-vinylpyridin-4-yl)amino)nicotinonitrile

[1304]



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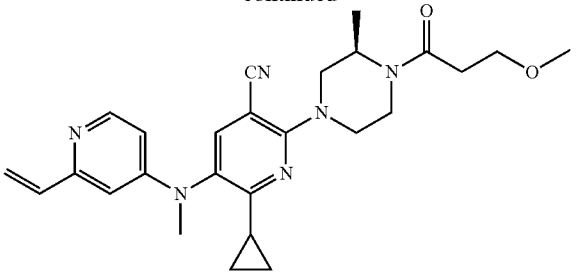


[1305] To a solution of (R)-5-((2-chloropyridin-4-yl)(methyl)amino)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (330 mg, 0.71 mmol) in isopropanol (30 mL) and H_2O (3 mL) was added Vinyltrifluoroboric acid potassium salt (142.1 mg, 1.06 mmol), Pd(dppf)Cl_2 (58.0 mg, 0.071 mmol) and DIPEA (182 mg, 1.41 mmol) at r.t. under N_2. The reaction mixture was heated and stirred at reflux under N_2 overnight. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM: MeOH) to afford the title compound (89 mg, 27.5%) as a white solid.

[1306] ^{1}H NMR (CHLOROFORM-d) δ: 8.24 (d, J=5.9 Hz, 1H), 7.55 (s, 1H), 6.71 (dd, J=17.4, 10.8 Hz, 1H), 6.46 (s, 1H), 6.33 (s, 1H), 6.20 (d, J=17.3 Hz, 1H), 5.46 (d, J=11.0 Hz, 1H), 4.91 (s, 0.5H), 4.54 (d, J=13.1 Hz, 0.5H), 4.34-4.16 (m, 2.5H), 3.89-3.68 (m, 2.5H), 3.56 (t, J=11.5 Hz, 0.5H), 3.39 (s, 3H), 3.31 (s, 3H), 3.29 (s, 1H), 3.10 (m, 1.5H), 2.80-2.52 (m, 2H), 1.88-1.83 (m, 1H), 1.41 (d, J=6.3 Hz, 1.5H), 1.30 (d, J=6.6 Hz, 1.5H), 1.10 (m, 2H), 0.97 (m, 2H).

[1307] LC-MS: m/z 461.2 $(M+H)^+$

Compound 660 (General Procedure 6)

(R)-4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-ylamino) picolinonitrile

[1308] ^{1}H NMR (CHLOROFORM-d) δ: 8.32 (d, J=5.8 Hz, 1H), 7.59 (s, 1H), 7.01 (s, 1H), 6.72 (d, J=3.8 Hz, 1H), 6.62 (s, 1H), 4.92 (s, 0.5H), 4.55 (d, J=12.7 Hz, 0.5H), 4.30 (t, J=11.2 Hz, 2H), 4.22 (d, J=12.7 Hz, 0.5H), 3.83 (d, J=13.8 Hz, 0.5H), 3.76 (t, J=6.3 Hz, 2H), 3.57 (t, J=11.5 Hz, 0.5H), 3.39 (s, 3H), 3.33 (d, J=12.5 Hz, 1H), 3.21-3.04 (m, 1.5H), 2.73 (ddd, J=22.1, 14.2, 6.5 Hz, 1H), 2.64-2.53 (m, 1H), 2.05-1.99 (m, 1H), 1.40 (d, J=6.3 Hz, 1.5H), 1.30 (d, J=6.7 Hz, 1.5H), 1.18-1.10 (m, 2H), 1.09-0.98 (m, 2H).

[1309] LC-MS: m/z 446.0 $(M+H)^+$

Compound 659 (General Procedure 6)

(R)-4,4'-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-ylazanediyl)dipicolinonitrile

[1310] ^{1}H NMR (CHLOROFORM-d) δ: 8.62 (d, J=5.5 Hz, 2H), 7.53 (s, 1H), 7.28-7.20 (m, 4H), 4.95 (s, 0.5H), 4.58 (d, J=10.0 Hz, 0.5H), 4.37 (dd, J=42.6, 13.4 Hz, 2.5H), 3.89 (d, J=13.8 Hz, 0.5H), 3.77 (t, J=6.3 Hz, 2H), 3.66-3.57 (m, 0.5H), 3.44 (s, 0.5H), 3.40 (s, 3H), 3.35-3.13 (m, 1.5H), 2.87-2.67 (m, 1H), 2.62 (dd, J=13.7, 7.4 Hz, 1H), 1.68 (d, J=4.3 Hz, 1H), 1.44 (d, J=6.6 Hz, 1.5H), 1.34 (d, J=6.3 Hz, 1.5H), 1.11 (dt, J=6.9, 3.5 Hz, 2H), 0.97-0.88 (m, 2H).

[1311] LC-MS: m/z 548.1 $(M+H)^+$

Compound 729 (General Procedure 6)

(R)-4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-ylamino) picolinamide

[1312] ^{1}H NMR (CHLOROFORM-d) δ: 8.24 (d, J=5.7 Hz, 1H), 7.98 (s, 1H), 7.61 (s, 1H), 7.53 (s, 1H), 6.62 (dd, J=5.6, 2.3 Hz, 1H), 6.03 (s, 1H), 5.65 (s, 1H), 4.92 (s, 0.5H), 4.55 (d, J=13.9 Hz, 0.5H), 4.27 (t, J=11.1 Hz, 2H), 4.19 (d, J=13.0 Hz, 0.5H), 3.82 (d, J=13.0 Hz, 0.5H), 3.76 (t, J=6.2 Hz, 2H), 3.57 (t, J=11.5 Hz, 0.5H), 3.40 (s, 3H), 3.34-3.23 (m, 1H), 3.15 (t, J=12.1 Hz, 1H), 3.10-3.00 (m, 0.5H), 2.84-2.65 (m, 1H), 2.60 (m, 1H), 2.07 (ddd, J=12.6, 8.0, 4.6 Hz, 1H), 1.41 (d, J=6.2 Hz, 1.5H), 1.31 (d, J=6.7 Hz, 1.5H), 1.13 (dt, J=7.4, 3.6 Hz, 2H), 1.00 (td, J=6.6, 3.4 Hz, 2H).

[1313] LC-MS: m/z 464.1 $(M+H)^+$

Compound 742 (General Procedure 6)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-4-methyl-5-(2-vinylpyridin-4-ylamino)nicotinonitrile

[1314] ^{1}H NMR (CHLOROFORM-d) δ: 8.24 (d, J=5.7 Hz, 1H), 6.70 (dd, J=17.4, 10.8 Hz, 1H), 6.49 (s, 1H), 6.35 (s, 1H), 6.19 (d, J=17.4 Hz, 1H), 5.79 (s, 1H), 5.48 (d, J=10.9 Hz, 1H), 4.68 (d, J=12.8 Hz, 0.5H), 4.51-4.38 (m, 0.5H), 4.34 (d, J=12.9 Hz, 1H), 4.26 (d, J=12.6 Hz, 1H), 4.08 (d, J=9.0 Hz, 0.5H), 3.93 (s, 2H), 3.82-3.70 (m, 1H), 3.31 (dd, J=19.9, 7.5 Hz, 0.5H), 3.24-3.12 (m, 1H), 3.11-2.97 (m, 1H), 2.56 (m, 2H), 2.39 (s, 3H), 2.11 (ddd, J=12.6, 8.0, 4.7 Hz, 1H), 1.35-1.25 (m, 1H), 1.10 (s, 2H), 0.97 (dd, J=7.9, 3.2 Hz, 2H), 0.78-0.34 (m, 4H).

[1315] LC-MS: m/z 473.4 $(M+H)^+$

Compound 748 (General Procedure 6)

5-(2-chloropyridin-4-ylamino)-6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)nicotinonitrile

[1316] To a solution of (R)-5-(2-chloropyridin-4-ylamino)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile (300 mg, 0.761 mmol) in DMF (3 mL) was added (R)-2-(oxetan-2-yl)acetic acid (115 mg, 0.99 mmol), HATU (436.0 mg, 1.142 mmol) and DIPEA (196.4 mg, 1.53 mmol) at r.t. The reaction mixture was stirred at r.t. for 3 hs. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM: MeOH) to afford the title compound (182 mg, 48.5%) as a pale yellow solid.

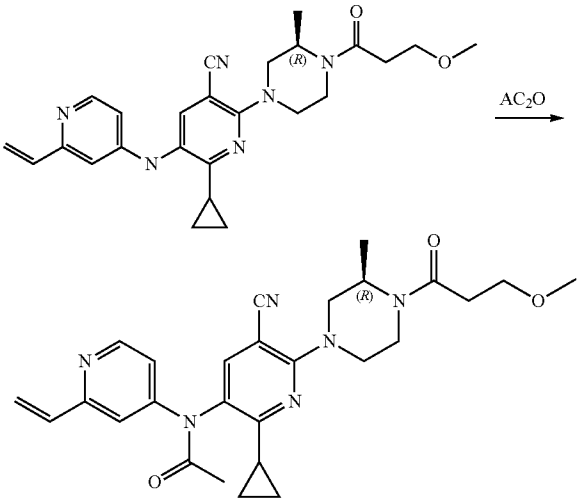
[1317] ^{1}H NMR (CHLOROFORM-d) δ: 8.06 (d, J=5.7 Hz, 1H), 7.60 (s, 1H), 6.50 (d, J=1.8 Hz, 1H), 6.47 (dd, J=5.7, 2.0 Hz, 1H), 5.80 (s, 1H), 5.27 (dt, J=13.0, 6.5 Hz, 1H), 4.72 (dd, J=14.0, 8.0 Hz, 1H), 4.65-4.43 (m, 2H), 4.37 (d, J=13.2 Hz, 1H), 4.09 (d, J=7.2 Hz, 0.5H), 3.95 (d, J=15.5 Hz, 0.5H), 3.80-3.67 (m, 1H), 3.28 (ddd, J=9.8, 9.1, 5.3 Hz, 1H), 3.16 (d, J=11.2 Hz, 6.5H), 3.13-3.03 (m, 1H), 2.98 (dd, J=15.2, 6.8 Hz, 1H), 2.93-2.78 (m, 2H), 2.78-2.66 (m, 0.5H), 2.66-2.47 (m, 1H), 2.10-2.02 (m, 1H), 1.28 (d, J=4.9 Hz, 1H), 1.15 (dt, J=7.3, 3.5 Hz, 2H), 1.04 (dt, J=7.0, 3.2 Hz, 2H), 0.77-0.38 (m, 4H).

[1318] LC-MS: m/z 494.0 $(M+H)^+$

Compound 662

(R)—N-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)—N-(2-vinylpyridin-4-yl)acetamide

[1319]



[1320] A solution of (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylpyridin-4-ylamino)nicotinonitrile (200 mg, 0.448 mmol) in acetic anhydride (5 mL) was heated and stirred at 135° C. overnight. The solvent was removed in vacuum and the residue was purified via reverse phase silica gel column chromatography (MeOH: H_2O) to afford the title compound (16 mg, 7.3%) as a pale yellow solid.

[1321] ^{1}H NMR (CHLOROFORM-d) δ: 8.52 (d, J=5.5 Hz, 1H), 7.57 (s, 1H), 7.36 (d, J=5.3 Hz, 1H), 7.03 (d, J=5.2 Hz, 1H), 6.78 (dd, J=17.4, 10.8 Hz, 1H), 6.23 (d, J=17.3 Hz, 1H), 5.52 (d, J=10.9 Hz, 1H), 4.92 (s, 1H), 4.55 (d, J=11.4 Hz, 1H), 4.40-4.23 (m, 3H), 3.84 (d, J=12.8 Hz, 1H), 3.76 (t, J=6.3 Hz, 2H), 3.57 (t, J=11.0 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 1H), 3.17 (dt, J=24.0, 11.2 Hz, 2H), 2.73 (ddd, J=23.2, 13.8, 6.3 Hz, 1H), 2.59 (dd, J=13.3, 7.2 Hz, 1H), 2.20-2.06 (m, 3H), 2.01 (dt, J=12.8, 6.2 Hz, 1H), 1.40 (d, J=5.9 Hz, 2H), 1.29 (d, J=6.7 Hz, 2H), 1.16 (d, J=4.3 Hz, 3H), 1.03 (d, J=7.5 Hz, 1H).

[1322] LC-MS: m/z 489.3 $(M+H)^+$

Compound 758 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[1323] ^{1}H NMR (CHLOROFORM-d) δ: 8.12 (d, J=5.4 Hz, 1H), 7.82 (d, J=5.7 Hz, 1H), 6.83 (d, J=5.4 Hz, 1H), 6.59 (dd, J=17.6, 10.8 Hz, 1H), 6.40 (s, 2H), 5.90 (d, J=17.5 Hz, 1H), 5.47 (d, J=10.9 Hz, 1H), 4.71 (d, J=12.5 Hz, 0.5H), 4.45 (dd, J=16.5, 9.9 Hz, 1.5H), 4.33-4.22 (m, 1H), 3.85 (d, J=13.3 Hz, 0.5H), 3.82-3.70 (m, 2H), 3.57 (d, J=10.5 Hz, 0.5H), 3.49-3.41 (m, 0.5H), 3.39 (d, J=3.3 Hz, 3H), 3.05 (dddd, J=21.0, 19.1, 13.7, 2.9 Hz, 2H), 2.82-2.54 (m, 2H), 2.27 (dd, J=16.7,

6.8 Hz, 0.5H), 2.18 (ddd, J=12.8, 8.2, 4.8 Hz, 1H), 1.35-1.27 (m, 1H), 1.18-0.97 (m, 7H), 0.91 (d, J=6.8 Hz, 1.5H), 0.86 (d, J=6.8 Hz, 1.5H).

[1324] LC-MS: m/z 475.6 $(M+H)^+$

Compound 764 (General Procedure 7)

6-cyclopropyl-2-((R)-3-isopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl) amino)nicotinonitrile

[1325] ^{1}H NMR (CHLOROFORM-d) δ: 8.10 (d, J=5.3 Hz, 1H), 7.81 (d, J=8.1 Hz, 1H), 6.82 (d, J=5.4 Hz, 1H), 6.69 (s, 1H), 6.58 (dd, J=17.6, 10.8 Hz, 1H), 6.39 (s, 1H), 5.89 (d, J=17.5 Hz, 1H), 5.46 (d, J=10.9 Hz, 1H), 5.32-5.24 (m, 1H), 4.83-4.61 (m, 1.5H), 4.56 (dtd, J=7.7, 5.8, 1.8 Hz, 1H), 4.48 (d, J=13.5 Hz, 0.5H), 4.46-4.39 (m, 1H), 4.27 (d, J=11.9 Hz, 1H), 3.88 (d, J=13.4 Hz, 0.5H), 3.56 (d, J=10.0 Hz, 0.5H), 3.45 (dd, J=13.4, 3.2 Hz, 0.5H), 3.13-2.92 (m, 3H), 2.92-2.75 (m, 2H), 2.65-2.44 (m, 1H), 2.31-2.24 (m, 0.5H), 2.21-2.10 (m, 2H), 1.16-1.07 (m, 2H), 1.05 (dd, J=6.5, 3.0 Hz, 3H), 1.04-0.98 (m, 2H), 0.92 (d, J=6.8 Hz, 1H), 0.86 (d, J=6.8 Hz, 2H).

[1326] LC-MS: m/z 487.6 $(M+H)^+$

Compound 763 (General Procedure 7)

[1327] ^{1}H NMR (CHLOROFORM-d) δ: 8.08 (d, J=5.6 Hz, 1H), 7.81 (s, 1H), 6.87 (d, J=5.6 Hz, 1H), 6.59 (dd, J=17.5, 10.9 Hz, 1H), 6.43 (s, 1H), 5.94 (d, J=17.6 Hz, 1H), 5.53 (d, J=10.9 Hz, 1H), 5.31-5.22 (m, 1H), 4.77-4.68 (m, 1H), 4.59-4.51 (m, 1H), 4.41 (s, 1H), 4.29-4.31 (m, 1 H), 4.10-4.03 (m, 1H), 3.96-3.89 (m, 0.5H), 3.74-3.76 (m, 1H), 3.10-3.41 (m, 3H), 2.83-2.90 (m, 2.5H), 2.54-2.55 (m, 1H), 2.18-2.20 (m, 1H), 1.35-1.36 (m, 1H), 1.14-1.16 (m, 2H), 1.04-1.06 (m, 2H), 0.38-0.49 (m, 4H).

[1328] LC-MS: m/z 485.6 $(M+H)^+$

Compound 756 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl) amino)nicotinonitrile

[1329] To a solution of (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile (180 mg, 0.46 mmol) in 10 mL DMF was added sodium 3-hydroxypropanoate (104 mg, 0.92 mmol), and triethylamine (1 mL), HATU (350 mg, 0.92 mmol). The resulting reaction mixture was stirred at r.t. for overnight. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by Prep-HPLC (50% EtOAc/petroleum ether) to get 100 mg title compound.

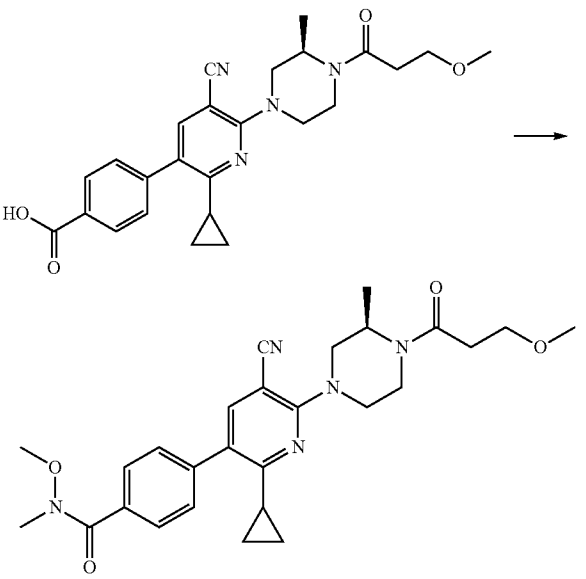
[1330] ^{1}H NMR (CHLOROFORM-d) δ8.11 (d, 1H), 7.86 (s, 1H), 7.65 (s, 1H), 6.82 (dd, 1H), 6.53-6.62 (m, 1H), 6.40 (s, 1H), 5.89 (d., 1H), 5.45 (s, 1H), 4.75 (m, 0.5H), 4.37-4.32 (dd, 2H), 3.92 (m, 0.5H), 3.39-3.05 (m, 3H), 2.61-2.60 (m, 2H), 2.20-1.69 (m, 1H), 1.28-1.26 (m, 1H), 1.40-1.00 (m, 4H), 0.47-0.45 (m, 4H).

[1331] LC-MS: m/z 4 459 $(M+H)^+$

Compound 656

(R)-4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)-N-methoxy-N-methylbenzamide

[1332]



[1333] To a solution of (R)-4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)benzoic acid (450 mg, 1 mmol) and N,O-dimethylhydroxylammonium chloride (146 mg, 1.5 mmol) in DCM (10 mL) was added HATU(570 mg, 1.5 mmol) and DIPEA (516 mg, 4 mmol). The resulting mixture was stirred at r.t. for 2 h. The organic phase was washed with 1N HCl (10 mL×3), sat. $NaHCO_3$ (20 mL×1) and brine, dried over Na_2SO_4 and concentrated under vacuum to give 390 mg of the title compound as a white solid.

[1334] ^{1}H NMR (CHLOROFORM-d) δ: 7.71-7.85 (m, J=8.3 Hz, 2H), 7.64 (s, 1H), 7.39-7.50 (m, J=8.3 Hz, 2H), 4.92 (br. s., 0.5H), 4.54 (d, J=12.3 Hz, 0.5H), 4.13-4.39 (m, 2.5H), 3.78-3.87 (m, 0.5H), 3.76 (br. s., 2H), 3.63 (s, 3H), 3.58 (d, J=10.3 Hz, 0.5H), 3.35-3.46 (m, 6H), 3.23-3.34 (m, 1H), 3.13 (br. s., 1H), 3.06 (d, J=12.5 Hz, 0.5H), 2.73 (br. s., 1H), 2.61 (br. s., 1H), 2.00-2.12 (m, 1H), 1.35-1.47 (m, 1.5H), 1.24-1.35 (m, 1.5H), 1.12-1.24 (m, 2H), 0.87-1.02 (m, 2H)

[1335] LC-MS: m/z 492.6 $(M+H)^+$

Compound 714 (General Procedure 7)

(R)-5-(bis(4-ethynylpyridin-2-yl)amino)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1336] ^{1}H NMR (CHLOROFORM-d) δ: 8.29 (d, J=5.1 Hz, 2H), 7.59 (s, 1H), 7.12 (br. s., 2H), 7.03 (dd, J=5.1, 1.1 Hz, 2H), 4.92 (br. s., 0.5H), 4.54 (d, J=13.2 Hz, 0.5H), 4.14-4.36 (m, 2.5H), 3.76 (t, J=6.2 Hz, 2.5H), 3.49-3.66 (m, 0.5H), 3.39 (s, 3H), 3.20-3.35 (m, 3H), 3.14 (d, J=11.3 Hz, 1H), 3.06 (d,

J=11.3 Hz, 0.5H), 2.65-2.84 (m, 1H), 2.52-2.65 (m, 1H), 1.86-1.99 (m, 1H), 1.22-1.38 (m, 3H), 0.95-1.08 (m, 2H), 0.68-0.82 (m, 2H)

[1337] LC-MS: m/z 546.6 $(M+H)^+$

Compound 713 (General Procedure 7)

(R)-6-cyclopropyl-5-(4-ethynylpyridin-2-ylamino)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile

[1338] ^{1}H NMR (CHLOROFORM-d) δ: 8.12 (d, J=5.4 Hz, 1H), 7.78 (s, 1H), 6.82 (dd, J=5.4, 1.1 Hz, 1H), 6.61 (br. s., 1H), 6.52 (s, 1H), 4.92 (br. s., 0.5H), 4.54 (d, J=13.4 Hz, 0.5H), 4.07-4.32 (m, 2.5H), 3.68-3.87 (m, 2.5H), 3.49-3.65 (m, 0.5H), 3.39 (s, 3H), 3.18-3.33 (m, 2H), 2.92-3.17 (m, 1.5H), 2.64-2.83 (m, 1H), 2.53-2.64 (m, 1H), 2.08-2.22 (m, 1H), 1.41 (d, J=6.2 Hz, 1.5H), 1.31 (d, J=6.4 Hz, 1.5H), 1.07-1.18 (m, 2H), 0.96-1.07 (m, 2H)

[1339] LC-MS: m/z 445.5 $(M+H)^+$

Compound 750 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-methoxyacetyl)piperazin-1-yl)-5-(4-ethynylpyridin-2-ylamino)nicotinonitrile

[1340] ^{1}H NMR (CHLOROFORM-d) δ: 8.00 (d, J=5.9 Hz, 1H), 7.71 (s, 1H), 6.88 (dd, J=5.9, 1.2 Hz, 1H), 6.64 (s, 1H), 4.51 (d, J=13.2 Hz, 1H), 4.37 (d, J=12.9 Hz, 1H), 4.17 (br. s., 2H), 4.01 (br. s., 0.5H), 3.89 (br. s., 0.5H), 3.71 (br. s., 0.5H), 3.40-3.52 (m, 4.5H), 3.22 (d, J=9.7 Hz, 1H), 3.02-3.16 (m, 1H), 2.09-2.20 (m, 1H), 1.03-1.22 (m, 4H), 0.67 (br. s., 2H), 0.47 (br. s., 4H)

[1341] LC-MS: m/z 457.5 $(M+H)^+$

Compound 647 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl) amino)nicotinonitrile

[1342] To a solution of (R)-5-amino-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (140 mg, 0.41 mmol) and 2-chloro-4-vinylpyridine (57 mg, 0.41 mmol) in 1,4-dioxane (15 mL) was added Pd2(dba)3 (56 mg, 0.061 mmol) and Xantphos (59 mg, 0.1 mmol) and Cs2CO3 (267 mg, 0.82 mmol) and the mixture was heated at 110° C. under N2. for 16 h. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (DCM:MeOH=20:1) to afford 25 mg of title compound COMPOUND 647 and 20 mg compound COMPOUND 646.

[1343] ^{1}H NMR (CHLOROFORM-d) δ: 7.94-7.93 (d, 1H), 7.68 (s, 1H), 6.84-6.82 (d, 1H), 6.58-6.51 (q, 1H), 6.38 (s, 1H), 5.95-5.90 (d, 1H), 5.55-5.52 (d, 1H), 4.87 (s, 0.5H), 4.54-4.51 (d, 0.5H); 4.48-4.13 (m, 3H) 3.79-3.70 (m, 2H) 3.44-3.35 (m, 1H) 3.25 (s, 3H), 3.11-2.98 (m, 3H), 2.77-2.56 (m, 2H), 2.17-2.12 (m, 1H), 1.38-1.13 (m, 3H), 1.09-1.00 (m, 2H), 0.99-0.98 (m, 2H).

[1344] LC-MS: m/z 447 $(M+H)^+$

Compound 646 (General Procedure 7)

(R)-5-(bis(4-vinylpyridin-2-yl)amino)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1345] ^{1}H NMR (CHLOROFORM-d) δ: 8.15-8.14 (d, 1H), 7.58 (s, 1H), 7.26-7.23 (d, 1H), 6.97-6.94 (dd, 1H), 6.79-6.72 (q, 1H), 6.03-5.98 (dd, 1H), 5.58 (s, 1H), 5.36-5.33 (dd, 1H), 4.88 (s, 0.5H), 4.54-4.51 (d, 0.5H); 4.20-4.09 (dd, 2H) 3.93 (s, 2H) 3.75-3.52 (m, 2H) 3.25-2.98 (m, 3H), 2.71-2.50 (m, 2H), 2.18-2.10 (m, 1H), 1.41-1.26 (m, 3H), 1.43-1.30 (m, 2H), 1.13-1.11 (m, 2H), 1.03-1.09 (m, 2H).

[1346] LC-MS: m/z 433 $(M+H)^+$

Compound 706 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl) amino)nicotinonitrile

[1347] ^{1}H NMR (CHLOROFORM-d) δ: 8.13 (d, 1H), 7.85 (s, 1H), 6.83 (dd, 1.2 Hz, 1H), 6.58 (dd, 10.7 Hz, 1H), 6.41 (s, 1H), 6.33 (br. s., 1H), 5.90 (d, 1H), 5.46 (d, 0.5H), 4.36 (d, 1H), 4.26 (d, Hz, 1H), 4.00-4.15 (m, 0.5H), 3.87 (d, 0.5H), 3.74 (t, 3H), 3.39 (s, 3H), 3.74-3.04 (m, 3H), 2.48-2.77 (m, 2H), 2.14-2.25 (m, 1H), 1.39 (br. s., 1H), 1.14 (t, 2H), 0.98-1.06 (m, 2H), 0.62-0.46 (d, 4H).

[1348] LC-MS: m/z 473 $(M+H)^+$

Compound 754 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-5-(2-vinylpyridin-4-ylamino)nicotinonitrile

[1349] ^{1}H NMR (DMSO-d_6) δ: 8.08-8.20 (m, 1H), 7.92 (d, J=5.3 Hz, 1H), 6.67-6.84 (m, 2H), 6.64 (br. s., 1H), 6.25 (d, J=16.7 Hz, 1H), 5.63 (br. s., 1H), 4.56 (t, J=5.3 Hz, 1.5H), 4.08-4.52 (m, 4.5H), 3.94 (d, J=13.5 Hz, 1H), 3.59-3.72 (m, 3.5H), 3.07-3.20 (m, 2H), 1.91-2.11 (m, 3H), 0.91-1.06 (m, 8H), 0.74 (d, J=6.7 Hz, 3H)

[1350] LC-MS: m/z 461.6 $(M+H)^+$

Compound 707 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl) amino)nicotinonitrile

[1351] ^{1}H NMR (CHLOROFORM-d) δ: 8.11 (d, 1H), 7.84 (s, 1H), 7.28 (s, 1H), 6.74-6.92 (m, 1H), 6.67 (br. s., 1H), 6.58 (dd, 10.8 Hz, 1H), 6.41 (s, 1H), 5.90 (d, 1H), 5.47 (d, 1H), 4.89 (br. s., 0.5H), 4.53 (d, 0.5H), 4.07-4.36 (m, 2H), 3.93 (br. s., 2H), 3.72-3.65 (m, 1H), 2.98-3.27 (m, 2.5H), 2.44-2.74 (m, 2.5H), 2.14-2.44 (m, 1H), 1.83-2.11 (m, 1.5H), 1.21-1.50 (m, 1.5H), 0.96-1.20 (m, 2H), 0.90 (t, 2H).

[1352] LC-MS: m/z 433 $(M+H)^+$

Compound 725 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-4-methyl-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[1353] ^{1}H NMR (CHLOROFORM-d) δ: 8.07 (d, J=5.3 Hz, 1H), 6.88 (br. s., 1H), 6.79 (dd, J=5.3, 1.2 Hz, 1H), 6.41-6.57 (m, 1H), 6.10 (s, 1H), 5.86 (d, J=17.6 Hz, 1H), 5.43 (d, J=10.9

Hz, 1H), 4.71-4.62 (m, 2-0.5H), 4.16-4.34 (m, 2H), 4.07 (d, J=8.8 Hz, 0.5H), 3.92 (br. s., 3H), 3.77 (br. s., 1H), 3.21-3.12 (d, 2H), 2.54-2.68 (m, 2H), 2.41 (s, 3H), 2.14-2.31 (m, 1H), 1.03-1.13 (m, 2H), 0.89-1.01 (m, 2H), 0.32-0.57 (m, 4H).

[1354] LC-MS: m/z 473 $(M+H)^+$

Compound 682 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-((2-methoxypyridin-4-yl) amino)nicotinonitrile

[1355] ^{1}H NMR (CHLOROFORM-d) δ: 8.33 (s, 1H), 7.82 (s, 1H), 7.57 (s, 1H), 6.41-6.41 (d, 1H), 6.06 (s, 1H), 5.05 (m, 0.5H), 4.51-4.58 (m, 0.5H), 4.14 (s, 3H), 4.12 (m, 0.5H), 3.85 (m, 2H), 3.54-3.52 (m, 0.5H); 3.28 (s, 3H) 3.12-3.03 (m, 2H), 2.72-2.70 (m, 2H), 2.57-2.55 (m, 1H), 1.38-1.36 (m, 1.5H), 1.32 (m, 1.5H), 1.26-1.25 (m, 2H), 1.09-1.05 (m, 2H).

[1356] LC-MS: m/z 451 $(M+H)^+$

Compound 683 (General Procedure 7)

(R)-methyl 4-((5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl) amino)picolinate

[1357] ^{1}H NMR (CHLOROFORM-d) δ: 8.35 (s, 1H), 7.60 (s, 1H), 7.44 (s, 1H), 6.82 (s, 1H), 5.32-5.31 (m, 0.5H), 4.28-4.26 (m, 0.5H), 4.25-4.22 (m, 3H), 3.96 (s, 3H), 4.12 (m, 3H), 3.37 (s, 3H), 3.03-3.28 (m, 2H), 2.61-2.58 (m, 2H) 2.05-2.03 (m, 1H), 1.40-1.38 (m, 1.5H), 1.33-1.29 (m, 1.5H), 1.27-1.25 (m, 2H), 1.11-0.99 (m, 2H).

[1358] LC-MS: m/z 479 $(M+H)^+$

Compound 736 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-((4-vinylpyrimidin-2-yl) amino)nicotinonitrile

[1359] ^{1}H NMR (CHLOROFORM-d) δ: 8.36 (d, 1H), 8.30 (s, 1H), 7.02-7.13 (m, 1H), 6.75 (d, 1H), 6.63 (dd, 10.6 Hz, 1H), 6.40 (d, 1H), 5.67 (d, 1H), 4.91 (br. s., 0.5H), 4.54 (d, 0.5H), 4.23 (br. s., 0.5H), 4.00-4.17 (m, 2H), 3.66-3.82 (m, 2H), 3.37-3.42 (m, 4H), 2.93-3.23 (m, 2H), 2.53-2.79 (m, 2H), 2.08-2.20 (m, 1H), 1.38-1.45 (m, 1.5H), 1.31 (d, 1.5H), 1.09-1.17 (m, 2H), 1.03 (dd, 2H).

[1360] LC-MS: m/z 448 $(M+H)^+$

Compound 705 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinyl-1,8-naphthyridin-4-ylamino)nicotinonitrile

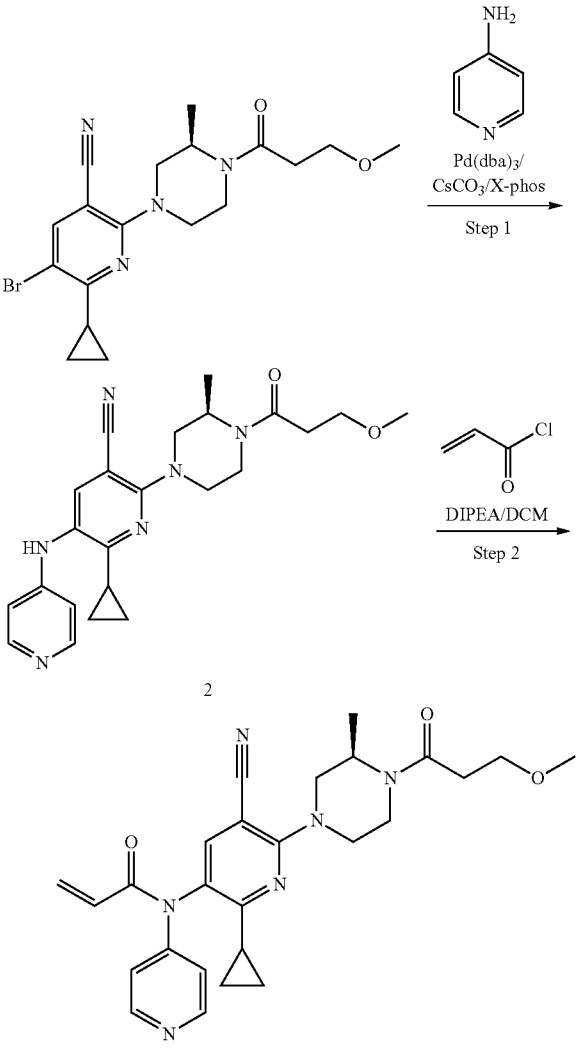
[1361] ^{1}H NMR (CHLOROFORM-d) δ: 8.99 (br. s., 1H), 8.55 (d, J=7.8 Hz, 1H), 7.64 (s, 1H), 7.39 (dd, J=8.3, 4.3 Hz, 1H), 6.82 (dd, J=17.1, 10.8 Hz, 1H), 6.38 (br. s., 1H), 6.30 (d, J=17.6 Hz, 1H), 5.59 (d, J=10.8 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.6 Hz, 0.5H), 4.26 (d, J=11.3 Hz, 2H), 4.16 (d, J=13.3 Hz, 1H), 3.70-3.89 (m, 3H), 3.50-3.09 (m, 7H), 3.04 (d, J=12.3 Hz, 1H), 2.52-2.82 (m, 2.5H), 1.98-2.13 (m, 1.5H), 1.28-1.44 (m, 5H), 0.93-1.02 (m, 2H)

[1362] LC-MS: m/z 498.1 $(M+H)^+$

Compound 702

(R)—N-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)-N-(pyridin-4-yl)acryl amide

[1363]



2

Step 1: (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(pyridin-4-ylamino)nicotinonitrile

[1364] To a solution of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (406 mg, 1 mmol) and pyridin-4-amine (94 mg, 1 mmol) in 1,4-dioxane (5 mL) was added $Pd(dba)_3$ (136 mg, 0.15 mmol) and X-phos (72 mg, 0.15 mmol) and Cs_2CO_3 (752 mg, 2 mmol) at room temperature under N_2. The resulting mixture was heated and stirred at 120° C. under N_2 in microwave for 1.5 h. The solvent was removed in vacuum and the residue was purified by column chromatography (MeOH/DCM=1/15) afforded 168 mg of title compound as a yellow solid.

[1365] LC-MS: m/z 471.4 $(M+H)^+$

Step 2: Compound 702

(R)—N-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)-N-(pyridin-4-yl)acryl amide

[1366] To a solution of (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(pyridin-4-ylamino) nicotinonitrile (41 mg, 0.1 mmol) and N,N-Diisopropylethylamine (26 mg, 0.2 mmol) in 5 mL of DCM was added Acryloyl chloride (10 mg, 0.1 mmol) at room temperature. The reaction mixture was then stirred at room temperature for 3 h. After LC-MS showed the completion of reaction, the mixture was poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated in vacuo. Column chromatography (MeOH/DCM=1/15) afforded 12.6 mg of title compound as a colorless oil.

[1367] ^{1}H NMR (CHLOROFORM-d) δ: 8.60 (d, J=4.8 Hz, 2H), 7.53 (s, 1H), 7.28 (s, 2H), 6.58 (d, J=16.7 Hz, 1H), 6.16 (d, J=5.1 Hz, 1H), 5.82 (d, J=10.5 Hz, 1H), 4.92 (m, 0.5H), 4.56 (m, 0.5H), 4.20-4.42 (m, 2H), 3.69-3.91 (m, 2H), 3.58 (m, 1H), 3.37-3.41 (m, 3H), 3.36 (br. s., 1H), 3.14 (br. s., 2H), 2.59 (d, J=5.9 Hz, 2H), 1.82-1.94 (m, 1H), 1.37-1.44 (m, 2H), 1.20-1.36 (m, 5H).

[1368] LC-MS: m/z 475.5 $(M+H)^+$

Compound 712

(R)—N-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)-N-(quinolin-4-yl)acryl amide

[1369] ^{1}H NMR (CHLOROFORM-d) δ: 8.96 (d, J=4.5 Hz, 1H), 8.26 (d, J=8.5 Hz, 1H), 7.93-8.03 (m, 1H), 7.84 (t, J=7.5 Hz, 1H), 7.70 (d, J=7.3 Hz, 1H), 7.44 (br. s., 1H), 7.30 (br. s., 1H), 6.61 (d, J=16.8 Hz, 1H), 6.16 (d, J=5.10 Hz, 1H), 5.82 (d, J=10.48 Hz, 1H), 4.88 (m, J=10.48 Hz, 0.5H), 4.52 (m, J=6.48 Hz, 0.5H), 4.27 (t, J=12.9 Hz, 2H), 3.74 (t, J=6.1 Hz, 2H), 3.52 (m, J=9.1 Hz, 1H), 3.37 (s, 3H), 3.29 (d, J=10.8 Hz, 1H), 3.12 (br. s., 2H), 2.72 (t, J=9.8 Hz, 1H), 2.58 (t, J=5.8 Hz, 1H), 2.23 (t, J=7.7 Hz, 1H), 1.31-1.40 (m, 2H), 1.21-1.31 (m, 3H), 1.14 (br. s., 2H).

[1370] LC-MS: m/z 525.5 $(M+H)^+$

Compound 732 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinolin-7-ylamino) nicotinonitrile

[1371] To a solution of (R)-5-amino-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (34 mg, 0.1 mmol) and 7-bromo-2-vinylquinoline (23 mg, 0.1 mmol) in 1,4-dioxane (1 mL) was added $Pd(dba)_3$ (13.6 mg, 0.015 mmol) and X-phos (7.2 mg, 0.15 mmol) and Cs_2CO_3 (75.2 mg, 0.2 mmol) at room temperature under N_2. The resulting mixture was heated and stirred at 120° C. under N_2 in microwave for 1.5 h. The solvent was removed in vacuum and the residue was purified by column chromatography (MeOH/DCM=1/15) afforded 17.2 mg of title compound as a colorless oil.

[1372] ^{1}H NMR (CHLOROFORM-d) δ: 8.08 (d, J=8.2 Hz, 1H), 7.68 (d, J=8.8 Hz, 1H), 7.64 (s, 1H), 7.44 (d, J=8.5 Hz, 1H), 7.31 (br. s., 1H), 7.03-7.18 (m, 2H), 6.32 (d, J=17.6 Hz, 1H), 6.18 (br. s., 1H), 5.74 (d, J=10.9 Hz, 1H), 4.92 (m, 0.5H), 4.54 (m, 0.5H), 4.09-4.33 (m, 2H), 3.71-3.86 (m, 2H), 3.57 (br. s., 1H), 3.40 (s, 3H), 3.25 (t, J=11.4 Hz, 1H), 3.13 (br. s., 2H), 2.75 (br. s., 1H), 2.53-2.64 (m, 1H), 2.14-2.27 (m, 1H), 1.40-1.47 (m, 1H), 1.24-1.35 (m, 2H), 1.12 (t, J=3.7 Hz, 2H), 0.97 (dd, J=7.9, 3.5 Hz, 2H).

[1373] LC-MS: m/z 497.4 $(M+H)^+$

Compound 665

(R)-methyl-4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl) benzoate

[1374] 1H NMR (CHLOROFORM-d) δ 8.12 (d, J=7.5 Hz, 2H), 7.63 (br. s., 1H), 7.48 (d, J=7.5 Hz, 2H), 4.47-4.61 (d, J=12.5 Hz, 0.5H), 4.19-4.37 (m, 2.5H), 3.96 (br. s., 3H), 3.75 (br. s., 2H), 3.47-3.61 (m, 1H), 3.38 (br. s., 3H), 3.28 (br. s., 1H), 3.01-3.18 (m, 1H), 2.65-2.79 (m, 1H), 2.60 (br. s., 1H), 1.96-2.10 (m, 1H), 1.72-1.91 (m, 1H), 1.38 (br. s., 1H), 1.28 (br. s., 2H), 1.18 (br. s., 2H), 0.97 (br. s., 2H)

[1375] LC-MS: m/z 463.2 $(M+H)^+$

Compound 704 (General Procedure 8)

(R)-5-((2-chloropyridin-4-yl)oxy)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile

[1376] ^{1}H NMR (CHLOROFORM-d) δ: 8.29 (d, J=5.7 Hz, 1H), 7.47 (s, 1H), 6.83-6.77 (m, 2H), 4.90-4.91 (m, 1H), 4.53-4.55 (m, 1H), 4.20 (t, J=12.8 Hz, 3H), 3.92 (s, 2H), 3.79-3.70 (m, 1H), 3.55 (d, J=10.9 Hz, 1H), 3.31-3.20 (m, 1H), 3.14-2.99 (m, 1H), 2.55 (s, 2H), 2.01 (t, J=4.6 Hz, 1H), 1.87 (d, J=3.4 Hz, 1H), 1.43 (d, J=6.4 Hz, 1H), 1.32 (d, J=6.4 Hz, 2H), 1.12 (dd, J=7.9, 3.1 Hz, 2H), 1.03 (dt, J=7.9, 3.1 Hz, 2H).

[1377] LC-MS: m/z 442.1 $(M+H)^+$

Compound 695 (General Procedure 8)

(R)-5-((2-chloropyridin-4-yl)oxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile

[1378] ^{1}H NMR (CHLOROFORM-d) δ: 8.29 (d, J=5.6 Hz, 1H), 7.46 (s, 1H), 6.83-6.76 (m, 2H), 4.69-4.72 (m, 0.5H), 4.40 (d, J=12.6 Hz, 1H), 4.28 (d, J=12.7 Hz, 1H), 4.13 (dd, J=14.3, 7.2 Hz, 1H), 3.88 (d, J=12.0 Hz, 1H), 3.78-3.64 (m, 3H), 3.38 (s, 3H), 3.18 (d, J=13.1 Hz, 1H), 3.04 (d, J=26.4 Hz, 1H), 2.74-2.57 (m, 2H), 2.48-2.50 (m, 0.5H), 1.98-2.04 (m, 1H), 1.35 (t, J=10.7 Hz, 1H), 1.13 (dd, J=7.4, 3.1 Hz, 2H), 1.02 (dt, J=7.9, 3.1 Hz, 2H), 0.59 (d, J=30.2 Hz, 2H), 0.45-0.48 (m, 2H).

[1379] LC-MS: m/z 482.1 $(M+H)^+$

Compound 694 (General Procedure 8)

(R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl) nicotinonitrile

[1380] A mixture of (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile (3, general procedure 8 scheme) (0.35 g, 0.88 mol), sodium 3-hydroxypropanoate (0.10 g, 0.88 mol), HATU (0.5 g, 1.32 mmol) and 0.23 g DIEA (1.76 mmol) was stirred in 8 mL DMF for 4 hrs. Then the mixture was quenched by adding 6

mL water and extracted with EtOAc (15 mL×2), the organic phase was combined and concentrated to give a yellow oil, which was further purified by silica gel chromatography (DCM:MeOH=20:1) to give 0.10 g of product as yellow solid (52% yield).

[1381] ^{1}H NMR (CHLOROFORM-d) δ: 8.30 (d, J=5.6 Hz, 1H), 7.48-7.49 (m, 0.5H), 6.81 (dt, J=5.6, 2.0 Hz, 2H), 4.70 (s, 1H), 4.41 (d, J=13.0 Hz, 1H), 4.29 (d, J=13.0 Hz, 1H), 4.12 (dd, J=18.6, 7.4 Hz, 1H), 3.93 (s, 2H), 3.84-3.67 (m, 1H), 3.18 (d, J=12.8 Hz, 1H), 3.13-2.99 (m, 1H), 2.61 (s, 2H), 2.32-2.22 (m, 0.5H), 2.02 (t, J=4.6 Hz, 1H), 1.35 (s, 1H), 1.29 (d, J=9.4 Hz, 3H), 1.14 (dd, J=7.4, 3.0 Hz, 2H), 1.04 (dt, J=7.9, 3.1 Hz, 2H), 0.66-0.67 (m, 2H), 0.46-0.51 (m, 2H).

[1382] LC-MS: m/z 468.1 $(M+H)^+$

Compound 692 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylpyridin-4-yloxy)nicotinonitrile

[1383] A mixture of (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxy propanoyl)piperazin-1-yl)nicotinonitrile (4) 0.35 g, (0.75 mmol), potassium trifluoro(vinyl)borate (0.15 g, 1.1 mmol), $PdCl_2$dppf (80 mg, 0.075 mmol) and DIEA (0.24 mL, 1.5 mmol) was heated in isopropanol at reflux at 85° C. under nitrogen for 5 hrs. The mixture was then concentrated under reduced pressure to give a yellow solid which was further purified by silica chromatography (PE/EA/MeOH=150/120/8) to give 0.19 g of product as a white solid (55% yield).

[1384] ^{1}H NMR (CHLOROFORM-d) δ:8.47 (d, J=5.6 Hz, 1H), 7.48-7.49 (m, 0.5H), 6.86 (d, J=2.3 Hz, 1H), 6.77 (dd, J=17.4, 10.8 Hz, 1H), 6.66 (dd, J=5.6, 2.4 Hz, 1H), 6.22 (dd, J=17.4, 0.9 Hz, 1H), 5.53 (dd, J=10.8, 0.8 Hz, 1H), 4.68 (d, J=11.7 Hz, 1H), 4.38 (d, J=12.9 Hz, 1H), 4.30-4.22 (m, 1H), 4.15-4.04 (m, 1H), 3.92 (s, 2H), 3.75 (d, J=20.7 Hz, 1H), 3.47 (d, J=21.7 Hz, 1H), 3.25-3.12 (m, 1H), 3.09-2.95 (m, 1H), 2.60 (s, 2H), 2.32-2.22 (m, 0.5H), 2.11-2.05 (m, 1H), 1.37 (d, J=20.5 Hz, 1H), 1.27 (d, J=2.0 Hz, 1H), 1.16-1.10 (m, 2H), 1.01 (ddd, J=10.1, 6.7, 3.3 Hz, 2H), 0.65 (t, J=33.7 Hz, 2H), 0.45-0.48 (m, 2H).

[1385] LC-MS: m/z 460.1 $(M+H)^+$

Compound 693 (General Procedure 8)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-vinylpyridin-4-yloxy)nicotinonitrile

[1386] ^{1}H NMR (CHLOROFORM-d) δ: 8.46 (d, J=5.6 Hz, 1H), 7.46 (s, 1H), 6.86 (d, J=2.3 Hz, 1H), 6.77 (dd, J=17.4, 10.8 Hz, 1H), 6.66 (dd, J=5.6, 2.4 Hz, 1H), 6.22 (d, J=17.4 Hz, 1H), 5.53 (d, J=10.9 Hz, 1H), 4.54-4.71 (m, 0.5H), 4.37 (d, J=12.4 Hz, 1H), 4.26 (d, J=12.6 Hz, 1H), 4.11 (s, 1H), 3.88 (d, J=11.9 Hz, 1H), 3.80-3.68 (m, 3H), 3.38 (s, 3H), 3.20 (t, J=23.2 Hz, 1H), 3.05 (s, 1H), 2.68 (dd, J=15.1, 12.2 Hz, 2H), 2.47-2.53 (m, 0.5H), 2.06 (dd, J=8.6, 3.9 Hz, 1H), 1.38-1.28 (m, 1H), 1.13 (dd, J=7.4, 3.1 Hz, 2H), 1.01 (dt, J=7.9, 3.2 Hz, 2H), 0.73-0.51 (m, 2H), 0.43-0.46 (m, 2H).

[1387] LC-MS: m/z 476.1 $(M+H)^+$

Compound 668 (General Procedure 8)

(R)-5-((2-chloropyridin-4-yl)oxy)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile

[1388] ^{1}H NMR (CHLOROFORM-d) δ: 8.33 (s, 1H), 7.47 (s, 1H), 6.85 (s, 2H), 4.93-5.05 (m, 0.5H), 4.56-4.58 (m, 0.5H), 4.33-4.09 (m, 3H), 3.88-3.68 (m, 3H), 3.57 (s, 1H), 3.40 (s, 3H), 3.30 (s, 1H), 3.10 (dd, J=36.0, 11.2 Hz, 1H), 2.82-2.48 (m, 1H), 1.42 (d, J=6.5 Hz, 2H), 1.36-1.29 (m, 2H), 1.14 (s, 2H), 1.03-1.05 (m, 2H).

[1389] LC-MS: m/z 456.0 $(M+H)^+$

Compound 666 (General Procedure 8)

(R)-5-((6-chloropyrimidin-4-yl)oxy)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile

[1390] ^{1}H NMR (CHLOROFORM-d) δ: 8.33 (s, 1H), 7.47 (s, 1H), 6.85 (s, 2H), 4.92-4.96 (m, 0.5H), 4.55-4.58 (m, 0.5H), 4.33-4.09 (m, 3H), 3.88-3.68 (m, 2H), 3.57 (s, 1H), 3.40 (s, 3H), 3.30 (s, 1H), 3.10 (dd, J=36.0, 11.2 Hz, 1H), 2.82-2.48 (m, 1H), 1.42 (d, J=6.5 Hz, 2H), 1.36-1.29 (m, 2H), 1.14 (s, 2H), 1.03 (d, J=4.1 Hz, 2H).

[1391] LC-MS: m/z 449.0 $(M+H)^+$

Compound 734 (General Procedure 8)

(R)-5-((4-chloropyridin-2-yl)oxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

[1392] ^{1}H NMR (CHLOROFORM-d) δ: 8.07 (d, J=6.0 Hz, 1H), 7.54 (s, 1H), 7.09-7.05 (m, 2H), 4.60-4.68 (m, 1H), 4.31-4.35 (m, 1H), 4.21 (d, J=13.0 Hz, 1H), 4.07 (d, J=9.8 Hz, 1H), 3.92 (s, 2H), 3.74 (d, J=11.5 Hz, 1H), 3.48 (d, J=24.4 Hz, 1H), 3.21-3.07 (m, 1H), 3.03 (d, J=10.9 Hz, 1H), 2.58 (d, J=17.5 Hz, 2H), 2.15-2.00 (m, 1H), 1.44 (s, 1H), 1.13 (dd, J=7.3, 3.6 Hz, 2H), 0.98 (dt, J=6.8, 2.7 Hz, 2H), 0.65 (s, 2H), 0.45-0.48 (m, 2H).

[1393] LC-MS: m/z 469.2 $(M+H)^+$

Compound 733 (General Procedure 8)

(R)-5-((4-chloropyridin-2-yl)oxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile

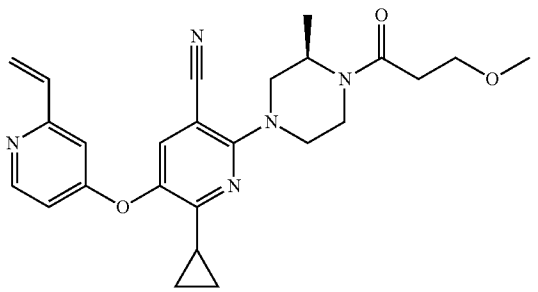
[1394] ^{1}H NMR (CHLOROFORM-d) δ: 8.10 (d, J=5.3 Hz, 1H), 7.53 (s, 1H), 7.07 (dd, J=5.3, 1.1 Hz, 1H), 6.97 (s, 1H), 6.70 (dd, J=17.6, 10.9 Hz, 1H), 6.01 (d, J=17.6 Hz, 1H), 5.56 (d, J=10.9 Hz, 1H), 4.69-4.71 (m, 0.5H), 4.28 (d, J=12.4 Hz, 1H), 4.18 (d, J=12.5 Hz, 1H), 4.09 (d, J=8.0 Hz, 1H), 3.80-3.90 (m, 0.5H), 3.72 (dd, J=13.7, 7.8 Hz, 3H), 3.39 (d, J=5.9 Hz, 3H), 3.27 (s, 1H), 3.09 (d, J=12.5 Hz, 1H), 2.97 (s, 1H), 2.73-2.59 (m, 2H), 2.18-2.10 (m, 1H), 1.12 (d, J=4.0 Hz, 2H), 0.96 (ddd, J=9.2, 8.5, 5.1 Hz, 3H), 0.89 (dd, J=13.9, 6.8 Hz, 2H), 0.62 (s, 2H), 0.45-0.47 (m, 2H).

[1395] LC-MS: m/z 474.2 $(M+H)^+$

Compound 832 (General Procedure 8)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-((2-vinylpyridin-4-yl)oxy) nicotinonitrile

[1396]



[1397] ^{1}H NMR (CHLOROFORM-d) δ: 8.47 (d, J=5.6 Hz, 1H), 7.44 (d, J=3.5 Hz, 1H), 6.88 (s, 1H), 6.84-6.74 (m, 1H), 6.69 (d, J=3.5 Hz, 1H), 6.28 (d, J=17.4 Hz, 1H), 5.58 (d, J=10.7 Hz, 1H), 4.89-4.91 (m, 0.5H), 4.50-4.54 (m, 0.5H), 4.23-4.06 (m, 2H), 3.82-3.68 (m, 2H), 3.50-3.53 (m, 0.5H), 3.37 (s, 3H), 3.26 (d, J=12.7 Hz, 1H), 3.05-3.10 (m, 1.5H), 2.78-2.52 (m, 2H), 2.05-1.93 (m, 1H), 1.39 (d, J=6.0 Hz, 1H), 1.32-1.25 (m, 3H), 1.14-1.08 (m, 2H), 0.99 (dt, J=11.5, 3.3 Hz, 2H).

[1398] LC-MS: m/z 448.0 $(M+H)^+$

Compound 703 (General Procedure 8)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-((2-vinylpyridin-4-yl)methoxy)nicotinonitrile

[1399] ^{1}H NMR (CHLOROFORM-d) δ: 8.61 (d, J=5.0 Hz, 1H), 7.39 (s, 1H), 7.21-7.26 (m, 1H), 7.18 (s, 1H), 6.85 (dd, J=17.4, 10.9 Hz, 1H), 6.26 (dd, J=17.4, 1.1 Hz, 1H), 5.47-5.61 (m, 1H), 5.06 (s, 2H), 4.88 (br. s., 0.5H), 4.52 (d, J=13.6 Hz, 0.5H), 4.21 (d, J=6.8 Hz, 0.5H), 3.85-4.05 (m, 2H), 3.67-3.81 (m, 2.5H), 3.54 (d, J=6.8 Hz, 0.5H), 3.37 (s, 3H), 3.04-3.18 (m, 1.5H), 2.84-3.04 (m, 1H), 2.63-2.80 (m, 1H), 2.44-2.63 (m, 2H), 1.22-1.36 (m, 3H), 1.03-1.17 (m, 4H)

[1400] LC-MS: m/z 461.6 $(M+H)^+$

Compound 789

5-(1-acryloyl-1,2,5,6-tetrahydropyridin-3-yl)-6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methylnicotinonitrile

[1401] 1H NMR (CHLOROFORM-d) 6.67 (dd, J=16.7, 10.6 Hz, 1H), 6.35 (dd, J=16.7, 7.0 Hz, 1H), 5.64-5.85 (m, 2H), 5.26 (m, 6.6 Hz, 1H), 4.66-4.79 (m, 1H), 4.56 (br. s., 1H), 4.23-4.39 (m, 2H), 4.18 (d, J=12.6 Hz, 1H), 3.95-4.11 (m, 2H), 3.90 (d, J=17.9 Hz, 1H), 3.63-3.83 (m, 2H), 3.27 (br. s., 1H), 3.08 (br. s., 1H), 2.96 (d, J=10.3 Hz, 2H), 2.79-2.92 (m, 2H), 2.53 (d, J=7.9 Hz, 1H), 2.31-2.48 (m, 5H), 2.04 (dd, J=13.4, 6.0 Hz, 1H), 1.44 (d, J=8.2 Hz, 1H), 1.15 (br. s., 1H), 0.85-1.07 (m, 3H), 0.60 (br. s., 1H), 0.52 (br. s., 1H), 0.44 (br. s., 2H)

[1402] LC-MS: m/z 516.6 (M+H)

Compound 778

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-5-(1-methyl-6-vinyl-1H-pyrazolo[3,4-b]pyridin-4-yl)nicotinonitrile

[1403] ^{1}H NMR (CHLOROFORM-d) 7.86-7.94 (s, 1H), 7.71-7.81 (s, 1H), 7.22 (s, 1H), 6.99 (dd, J=17.6, 10.9 Hz, 1H), 6.28-6.48 (m, 1H), 5.66 (dd, J=10.9, 0.9 Hz, 1H), 5.28 (t, J=6.7 Hz, 1H), 4.68-4.78 (m, 1H), 4.54-4.68 (m, 2H), 4.48 (d, J=14.1 Hz, 1H), 4.21 (s, 3H), 3.75-4.17 (m, 2H), 2.77-3.35 (m, 6H), 2.45-2.65 (m, 1H), 1.85-2.01 (m, 2H), 1.18-1.25 (m, 2H), 0.95-1.05 (m, 2H), 0.61-0.81 (m, 1H), 0.57 (br. s., 1H), 0.48 (br. s., 2H)

[1404] LC-MS: m/z 524.2 $(M+H)^+$

Compound 777

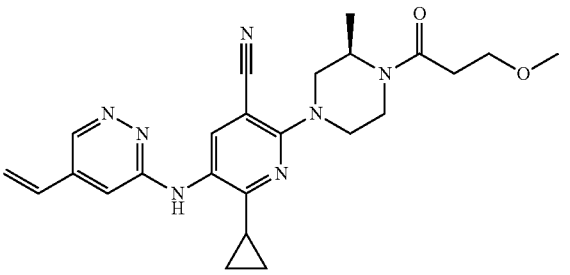
(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-4-methyl-5-((2-vinylpyridin-4-yl)oxy)nicotinonitrile

[1405] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J=5.7 Hz, 1H), 6.93-6.75 (m, 2H), 6.65 (d, J=3.7 Hz, 1H), 6.30 (d, J=17.4 Hz, 1H), 5.60 (d, J=10.7 Hz, 1H), 4.60-4.71 (m, 0.5H), 4.27-4.28 (m, 1H), 4.23-4.14 (m, 1H), 4.10-4.15 (m, 0.5H), 3.92-3.93 (m, 2H), 3.78-3.79 (m, 1H), 3.44-3.45 (m, 1H), 3.26-3.10 (m, 1H), 3.04-3.05 (m, 1H), 2.61-2.62 (m, 2H), 2.31 (s, 3H), 2.01-1.94 (m, 1H), 1.44-1.45 (m, 1H), 1.13-1.07 (m, 2H), 1.01-0.94 (m, 2H), 0.91-0.86 (m, 1H), 0.65-0.66 (m, 1H), 0.46-0.52 (m, 2H). MS (ES) M+H expected 474.0, found 474.6

Compound 833

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-((5-vinylpyridazin-3-yl)amino)nicotinonitrile

[1406]



[1407] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.76 (s, 1H), 6.58 (dd, J=17.6, 11.0 Hz, 2H), 6.05 (d, J=17.6 Hz, 1H), 5.66 (d, J=11.0 Hz, 1H), 4.65-4.70 (m, 0.5H), 4.43-4.46 (m, 1H), 4.33 (d, J=12.4 Hz, 1H), 4.16-4.07 (m, 1H), 3.87-3.88 (m, 0.5H), 3.71-3.74 (m, 3H), 3.39 (s, 3H), 3.20 (s, 1H), 3.07-3.09 (m, 1H), 2.65-2.66 (m, 2H), 2.55-2.47 (m, 1H), 2.18 (d, J=10.1 Hz, 1H), 1.30-1.25 (m, 1H), 1.15 (s, 2H), 1.07-0.98 (m, 2H), 0.50-0.60 (m, 2H), 0.45-0.47 (m, 2H). MS (ES) M+H expected 474.0, found 474.6

Compound 792

(R)-5-(4-cyanopyridin-2-ylamino)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile

[1408] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 8.31 (d, J=5.0 Hz, 1H), 7.80-7.69 (m, 1H), 6.94 (dd, J=1.3, 5.1 Hz, 1H), 6.59 (s, 1H), 6.51 (s, 1H), 4.34 (d, J=12.6 Hz, 2H), 4.14-3.65 (m, 4H), 3.39 (s, 3H), 2.61-3.23 (m, 5H), 2.15-2.05 (m, 1H), 1.20-1.11 (m, 2H), 1.04 (td, J=3.0, 7.8 Hz, 2H), 0.45 (d, J=5.3 Hz, 5H) LC_MS (M+1)$^+$472.5

Compound 783

4-(5-cyano-2-cyclopropyl-6-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)pyridin-3-ylamino)picolinonitrile

[1409] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 8.30 (d, J=5.9 Hz, 1H), 7.59 (s, 1H), 6.92 (d, J=2.3 Hz, 1H), 6.77-6.62 (m, 2H), 5.27 (t, J=6.7 Hz, 1H), 4.75-4.65 (m, 1H), 4.62-4.51 (m, 1H), 4.47 (d, J=12.6 Hz, 1H), 4.37 (d, J=12.6 Hz, 1H), 4.07 (d, J=7.9 Hz, 1H), 3.65-3.75 (m, 1H), 3.30-3.04 (m, 2H), 2.98 (s, 1H), 2.92-2.72 (m, 3H), 2.62-2.44 (m, 1H), 2.05-1.98 (m, 1H), 1.08-0.99 (m, 2H), 0.93-0.80 (m, 4H), 0.63 (br. s., 1H), 0.52 (br. s., 1H), 0.48-0.36 (m, 1H)

[1410] LC_MS (M+1)$^+$484.6

Compound 774

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((S)-oxetan-2-yl)acetyl)piperazin-1-yl)-5-((2-vinylpyridin-4-yl)amino)nicotinonitrile

[1411] ^{1}H NMR (CHLOROFORM-d) δ 8.23 (d, J=5.9 Hz, 1H), 7.62 (s, 1H), 6.72 (dd, J=17.4, 10.9 Hz, 1H), 6.63 (s, 1H), 6.55 (s, 1H), 6.26 (d, J=17.6 Hz, 1H), 5.54 (d, J=10.7 Hz, 1H), 5.34-5.22 (m, 1H), 4.73 (dd, J=14.6, 8.2 Hz, 1H), 4.56 (dt, J=9.1, 5.8 Hz, 1H), 4.47 (d, J=12.9 Hz, 1H), 4.34 (d, J=13.2 Hz, 1H), 4.09 (d, J=10.0 Hz, 0.5H), 3.89 (d, J=13.3 Hz, 0.5H), 3.80-0.64 (m, 1H), 3.42-3.15 (m, 2H), 3.15-2.78 (m, 3H), 2.75-2.34 (m, 2H), 2.10 (ddd, J=12.7, 8.1, 4.7 Hz, 1H), 1.29 (dd, J=6.7, 4.8 Hz, 1H), 1.18-1.10 (m, 2H), 1.03 (dd, J=7.7, 3.2 Hz, 2H), 0.81-0.53 (m, 2H), 0.52-0.38 (m, 2H).

[1412] LC-MS: m/z NB295-063-01 485.1 (M+H)$^+$

Compound 791

(R,E)-6-cyclopropyl-2-(4-(5-hydroxypent-2-enoyl)-3-isopropylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[1413] ^{1}H NMR (CHLOROFORM-d) δ 8.10 (d, J=5.3 Hz, 1H), 7.81 (s, 1H), 6.90 (tt, J=14.6, 7.3 Hz, 1H), 6.82 (d, J=5.3 Hz, 1H), 6.79-6.63 (m, 1H), 6.58 (dd, J=17.6, 10.8 Hz, 1H), 6.41 (d, J=14.1 Hz, 2H), 5.89 (d, J=17.5 Hz, 1H), 5.46 (d, J=10.8 Hz, 1H), 4.76-4.64 (m, 0.5H), 4.55-4.37 (m, 1.5H), 4.26 (t, J=11.6 Hz, 1H), 4.18 (d, J=5.2 Hz, 0.5H), 3.95 (d, J=13.7 Hz, 0.5H), 3.81 (t, J=6.0 Hz, 2H), 3.67 (d, J=9.3 Hz, 0.5H), 3.54-3.42 (m, 0.5H), 3.29-3.16 (m, 0.5H), 3.16-2.96 (m, 2.5H), 2.52 (dd, J=13.0, 6.4 Hz, 2H), 2.36-2.24 (m, 0.5H), 2.24-2.11 (m, 1.5H), 1.18-1.08 (m, 2H), 1.07 (d, J=6.5 Hz, 3H), 1.04-0.98 (m, 2H), 0.93-0.84 (m, 3H).

[1414] LC-MS: m/z NB295-055-02 487.7 (M+H)$^+$

Compound 790

(R)-6-cyclopropyl-2-(4-(5-hydroxypent-2-enoyl)-3-isopropylpiperazin-1-yl)-5-(2-vinylquinoxalin-5-yl)nicotinonitrile

[1415] ^{1}H NMR (400 MHz, CHLOROFORM-d) δ: 9.02 (s, 1H), 8.19-8.09 (m, 1H), 7.91-7.80 (m, 1 H), 7.76-7.67 (m, 2H), 7.08 (dd, J=11.2, 17.6 Hz, 1H), 6.98-6.82 (m, 0.5H), 6.57-6.37 (m, 1.5H), 5.97-5.73 (m, 2H), 4.70-4.35 (m, 3.5H), 4.23-4.16 (m, 1H), 3.86-3.75 (m, 1.5H), 3.60-3.42 (m, 1H), 3.32-3.05 (m, 4H), 2.58-2.48 (m, 1H), 2.37-2.18 (m, 1H), 1.32-1.23 (m, 2H), 1.16-1.05 (m, 3H), 0.98-0.72 (m, 6H)

[1416] LC_MS (M+1)$^+$523.7

Compound 794

2-cyclopropyl-6-((R)-3-cyclopropyl-4-(3-((R)-oxetan-2-yl)propanoyl)piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1417] ^{1}H NMR (CHLOROFORM-d) δ 8.63 (d, J=5.3 Hz, 1H), 7.63 (s, 1H), 7.38 (s, 1H), 7.22 (dd, J=5.0, 1.5 Hz, 1H), 6.86 (dd, J=17.3, 10.9 Hz, 1H), 6.26 (d, J=17.3 Hz, 1H), 5.55 (d, J=10.9 Hz, 1H), 4.86 (s, 1H), 4.60-4.74 (m, 1H), 4.46-4.60 (m, 2H), 4.40 (d, J=12.9 Hz, 1H), 4.07 (s, 1H), 3.82 (s, 1H), 3.69 (s, 1H), 3.12-3.42 (m, 2H), 2.99-3.10 (m, 1H), 2.48-2.63 (m, 3H), 1.96-2.24 (m, 3H), 1.19 (m, 2H), 0.93-1.02 (m, 2H), 0.33-0.54 (m, 4H)

[1418] LC-MS: m/z 484.3 (M+H)$^+$

Compound 785

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methyl-5-(6-vinylpyridazin-4-yl)nicotinonitrile

[1419] ^{1}H NMR (CHLOROFORM-d) δ 9.01 (d, J=1.8 Hz, 1H), 7.50 (d, J=2.1 Hz, 1H), 7.13 (dd, J=17.8, 11.0 Hz, 1H), 6.36 (d, J=17.9 Hz, 1H), 5.79 (d, J=11.2 Hz, 1H), 5.27 (t, J=6.7 Hz, 1H), 4.66-4.79 (m, 1H), 4.51-4.63 (m, 1H), 4.41 (d, J=12.6 Hz, 1H), 4.09 (d, J=7.6 Hz, 1H), 3.95 (d, J=12.6 Hz, 1H), 3.79 (d, J=10.9 Hz, 1H), 2.92-3.32 (m, 4H), 2.84-2.92 (m, 1H), 2.46-2.61 (m, 1H), 2.24 (s, 3H), 2.04 (dd, J=15.1, 7.5 Hz, 1H), 1.43-1.50 (m, 1H), 1.09-1.19 (m, 2H), 0.83-0.91 (m, 2H), 0.35-0.62 (m, 4H)

[1420] LC-MS: m/z 485.3 (M+H)$^+$

Compound 786

6-cyclopropyl-2-((R)-3-isopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methyl-5-(6-vinylpyridazin-4-yl)nicotinonitrile

[1421] ^{1}H NMR (CHLOROFORM-d) δ 9.01 (s, 1H), 7.50 (s, 1H), 7.12 (dd, J=17.9, 11.2 Hz, 1H), 6.36 (d, J=17.9 Hz, 1H), 5.78 (d, J=11.2 Hz, 1H), 5.23-5.31 (m, 1H), 4.64-4.78 (m, 1H), 4.39-4.63 (m, 3H), 4.34 (d, J=12.6 Hz, 1H), 3.91 (d, J=13.5 Hz, 1H), 3.43-3.65 (m, 1H), 2.92-3.17 (m, 4H), 2.82-2.91 (m, 1H), 2.44-2.66 (m, 1H), 2.22 (s, 3H), 2.07-2.17 (m, 1H), 1.91-2.04 (m, 1H), 1.38-1.58 (m, 1H), 1.00-1.15 (m, 3H), 0.85-0.94 (m, 6H)

[1422] LC-MS: m/z 487.3 (M+H)$^+$

Compound 776

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-4-methyl-5-(6-vinylpyridazin-4-yl)nicotinonitrile

[1423] ^{1}H NMR (CHLOROFORM-d) δ 9.01 (d, J=1.8 Hz, 1H), 7.50 (d, J=1.8 Hz, 1H), 7.13 (dd, J=17.8, 11.0 Hz, 1H), 6.37 (d, J=17.6 Hz, 1H), 5.80 (d, J=11.2 Hz, 1H), 4.41 (d, J=13.2 Hz, 1H), 4.32 (d, J=12.9 Hz, 1H), 4.09 (d, J=7.0 Hz, 1H), 3.93 (s, 2H), 3.68-3.84 (m, 2H), 3.13-3.37 (m, 2H), 3.09 (d, J=8.5 Hz, 1H), 2.54-2.67 (m, 2H), 2.24 (s, 3H), 1.45-1.49 (m, 1H), 1.07-1.19 (m, 2H), 0.92 (dd, J=12.5, 6.3 Hz, 2H), 0.47-0.67 (m, 4H)

[1424] LC-MS: m/z 459.2 $(M+H)^+$

Compound 793

6-cyclopropyl-2-((R)-3-isopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methyl-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1425] ^{1}H NMR (CHLOROFORM-d) δ 9.27 (br. s., 1H), 7.43 (br. s., 1H), 6.73 (dd, J=17.6, 11.2 Hz, 1 H), 6.20 (d, J=17.6 Hz, 1H), 5.77 (d, J=10.9 Hz, 1H), 5.28 (m, 1H), 4.63-4.78 (m, 1H), 4.30-4.60 (m, 3.5H), 3.87 (d, J=13.2 Hz, 0.5H), 3.41-3.61 (m, 1H), 2.88-3.18 (m, 4H), 2.72-2.88 (m, 2H), 2.41-2.65 (m, 1H), 2.22 (s, 3H), 2.01-2.16 (m, 1H), 1.38-1.51 (m, 1H), 1.12 (d, J=16.4 Hz, 2H), 0.98-1.05 (m, 3H), 0.75-0.98 (m, 6H)

[1426] LC-MS: m/z 487.1 (M+H)

Compound 784

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-4-methyl-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1427] ^{1}H NMR (CHLOROFORM-d) δ 9.28 (d, J=2.1 Hz, 1H), 7.44 (d, J=2.1 Hz, 1H), 6.75 (dd, J=17.6, 10.9 Hz, 1H), 6.21 (d, J=17.6 Hz, 1H), 5.79 (d, J=11.2 Hz, 1H), 4.40-4.55 (m, 1.5H), 4.35 (d, J=11.2 Hz, 1H), 3.94 (t, J=4.8 Hz, 2H), 3.67-3.81 (m, 0.5H), 3.41-3.57 (m, 1H), 3.01-3.21 (m, 3H), 2.57-2.66 (m, 2H), 2.28 (s, 3H), 1.63-1.67 (m, 1H), 1.12-1.16 (m, 2H), 1.01-1.09 (m, 3H), 0.79-0.98 (m, 6H)

[1428] LC-MS: m/z 461.1 (M+H)

Compound 780

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((S)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methyl-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1429] ^{1}H NMR (CHLOROFORM-d) δ 9.27 (d, J=2.1 Hz, 1H), 7.43 (d, J=2.3 Hz, 1H), 6.74 (dd, J=17.8, 11.0 Hz, 1H), 6.20 (d, J=17.6 Hz, 1H), 5.77 (d, J=10.9 Hz, 1H), 5.20-5.29 (m, 1H), 4.68-4.78 (m, 1H), 4.51-4.68 (m, 1H), 4.43 (d, J=12.9 Hz, 1H), 4.33 (d, J=12.0 Hz, 1H), 4.07 (d, J=9.1 Hz, 0.5H), 3.81-3.93 (m, 0.5H), 3.69-3.81 (m, 0.5H), 3.09-3.28 (m, 3.5H), 2.81-3.01 (m, 3H), 2.55 (m, 1H), 2.30 (s, 3H), 1.82 (br. s., 1H), 1.41-1.54 (m, 1H), 1.15 (br. s., 2H), 0.88 (m, 2H), 0.43-0.72 (m, 4H)

[1430] LC-MS: m/z 485.1 (M+H)

Compound 779

(R)-5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-[3,4'-bipyridin]-2'-yl trifluoromethanesulfonate

[1431] ^{1}H NMR (CHLOROFORM-d) δ 8.49 (d, J=5.0 Hz, 1H), 7.65 (s, 1H), 7.46 (dd, J=5.1, 1.3 Hz, 1H), 7.23-7.28 (m, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J=10.3 Hz, 0.5H), 4.23-4.47 (m, 2.5H), 3.68-3.88 (m, 2.5H), 3.49-3.65 (m, 0.5H), 3.31-3.45 (m, 4H), 3.05-3.29 (m, 1.5H), 2.64-2.80 (m, 1H), 2.53-2.64 (m, 1H), 1.90-2.03 (m, 1H), 1.38 (d, J=6.2 Hz, 1.5H), 1.18-1.33 (m, 3.5H), 1.02-1.13 (m, 2H)

[1432] LC-MS: m/z 554.1 (M+H)

Compound 773

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-4-methyl-5-(6-vinylpyridazin-4-yl)nicotinonitrile

[1433] ^{1}H NMR (CHLOROFORM-d) δ 9.02 (s, 1H), 7.52 (s, 1H), 7.14 (dd, J=17.6, 11.2 Hz, 1H), 6.37 (d, J=17.9 Hz, 1H), 5.80 (d, J=11.2 Hz, 1H), 4.65-4.76 (m, 0.5H), 4.40-4.55 (m, 1.5H), 4.34 (t, J=10.4 Hz, 1H), 3.86-4.01 (m, 2H), 3.77 (d, J=13.5 Hz, 0.5H), 3.42-3.57 (m, 1H), 2.96-3.21 (m, 3H), 2.53-2.69 (m, 2H), 2.20 (s, 3H), 1.42-1.50 (m, 1H), 1.10-1.16 (m, 2H), 1.00-1.08 (m, 3H), 0.83-1.00 (m, 6H)

[1434] LC-MS: m/z 461.1 (M+H)

Compound 771

(R)-tert-butyl 4-(3-cyano-6-cyclopropyl-4-methyl-5-(5-vinylpyridazin-3-yl)pyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate

[1435] ^{1}H NMR (CHLOROFORM-d) δ 9.28 (d, J=2.1 Hz, 1H), 7.44 (d, J=2.1 Hz, 1H), 6.75 (dd, J=17.8, 11.0 Hz, 1H), 6.15-6.26 (m, 1H), 5.79 (d, J=10.9 Hz, 1H), 4.41 (d, J=12.9 Hz, 1H), 4.31 (d, J=12.6 Hz, 1H), 4.08 (d, J=14.4 Hz, 1H), 3.36-3.55 (m, 2H), 3.24 (dd, J=12.9, 3.5 Hz, 1H), 3.07 (td, J=12.5, 3.5 Hz, 1H), 2.24 (s, 3H), 1.54 (s, 9H), 1.41-1.47 (m, 1H), 1.31-1.39 (m, 1H), 1.16 (br. s., 2H), 0.79-0.96 (m, 2H), 0.42-0.66 (m, 3H), 0.28-0.42 (m, 1H)

[1436] LC-MS: m/z 487.1 (M+H)

Compound 772

(R)-tert-butyl 4-(3-cyano-6-cyclopropyl-4-methyl-5-(6-vinylpyridazin-4-yl)pyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate

[1437] ^{1}H NMR (CHLOROFORM-d) δ ^{1}H NMR (CHLOROFORM-d): 9.27 (d, J=2.1 Hz, 1H), 7.44 (d, J=2.1 Hz, 1H), 6.74 (dd, J=17.8, 11.0 Hz, 1H), 6.21 (d, J=17.6 Hz, 1H), 5.77 (d, J=10.9 Hz, 1H), 4.41 (d, J=12.9 Hz, 1H), 4.30 (d, J=12.6 Hz, 1H), 4.02-4.22 (m, 1H), 3.36-3.53 (m, 2H), 3.18-3.30 (m, 1H), 3.07 (td, J=12.4, 3.4 Hz, 1H), 2.23 (s, 3H), 1.49 (s, 9H), 1.42-1.48 (m, 1H), 1.31-1.38 (m, 1H), 1.09-1.21 (m, 2H), 0.87 (dd, J=7.8, 3.1 Hz, 2H), 0.42-0.65 (m, 3H), 0.30-0.42 (m, 1H)

[1438] LC-MS: m/z 487.1 (M+H)

Compound 769

(R,E)-6-cyclopropyl-2-(3-cyclopropyl-4-(5-hydroxypent-2-enoyl)piperazin-1-yl)-4-methyl-5-(5-vinylpyridazin-3-yl)nicotinonitrile

[1439] ^{1}H NMR (CHLOROFORM-d) δ 9.27 (d, J=2.1 Hz, 1H), 7.43 (d, J=2.1 Hz, 1H), 6.87 (dt, J=14.8, 7.3 Hz, 1H), 6.73 (dd, J=17.8, 11.0 Hz, 1H), 6.26-6.49 (m, 1H), 6.21 (d, J=17.6 Hz, 1H), 5.77 (d, J=10.9 Hz, 1H), 4.42 (d, J=12.9 Hz, 1H), 4.33 (d, J=12.6 Hz, 1H), 4.04-4.21 (m, 1H), 3.79 (t, J=6.0 Hz, 3H), 3.38 (br. s., 1H), 3.23 (d, J=10.0 Hz, 1H), 3.08 (td, J=12.5, 2.9 Hz, 1H), 2.50 (q, J=6.2 Hz, 2H), 2.27 (s, 3H), 1.35-1.52 (m, 2H), 1.15 (br. s., 2H), 0.88 (dd, J=7.6, 3.2 Hz, 2H), 0.65 (br. s., 1H), 0.51 (br. s., 1H), 0.44 (br. s., 2H)

[1440] LC-MS: m/z 485.1 (M+H)

Compound 770

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(4-hydroxybutanoyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1441] ^{1}H NMR (CHLOROFORM-d) 8.69 (d, J=5.0 Hz, 1H), 7.23 (s, 1H), 7.07 (d, J=5.0 Hz, 1H), 6.87 (dd, J=17.5, 10.7 Hz, 1H), 6.29 (d, J=17.3 Hz, 1H), 5.57 (dd, J=10.7, 1.0 Hz, 1H), 4.33 (d, J=12.9 Hz, 1H), 4.25 (d, J=12.6 Hz, 1H), 4.09 (d, J=7.6 Hz, 0.5H), 3.79-3.92 (m, 1H), 3.65-3.79 (m, 2.5H), 3.31 (br. s., 0.5H), 3.14 (d, J=12.0 Hz, 1H), 2.99-3.11 (m, 1.5H), 2.58 (br. s., 2H), 2.17-2.26 (m, 3H), 1.90-2.00 (m, 2H), 1.51-1.62 (m, 1H), 1.43 (d, J=10.3 Hz, 1H), 1.02-1.16 (m, 2H), 0.87 (dd, J=7.9, 2.9 Hz, 2H), 0.62 (br. s., 1H), 0.54 (br. s., 1H), 0.31-0.50 (m, 2H)

[1442] LC-MS: m/z 472.5 $(M+H)^+$

Compound 781

2-cyclopropyl-6-((R)-3-isopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1443] 1H NMR (CHLOROFORM-d) 8.70 (d, J=5.0 Hz, 1H), 7.21-7.28 (m, 1H), 7.09 (br. s., 1H), 6.89 (dd, J=17.3, 10.9 Hz, 1H), 6.30 (d, J=17.3 Hz, 1H), 5.59 (d, J=10.9 Hz, 1H), 5.26-5.33 (m, 1H), 4.67-4.78 (m, 1.5H), 4.56 (dt, J=9.1, 5.9 Hz, 1H), 4.38-4.48 (m, 1.5H), 4.29 (d, J=12.3 Hz, 1H), 3.89 (d, J=13.5 Hz, 0.5H), 3.45-3.61 (m, 1H), 2.92-3.15 (m, 3.5H), 2.78-2.91 (m, 2H), 2.44-2.65 (m, 1H), 2.26 (br. s., 0.5H), 2.19-2.23 (m, 3H), 2.11-2.18 (m, 0.5H), 1.56 (td, J=8.0, 4.5 Hz, 1H), 1.12 (br. s., 1H), 1.04 (d, J=6.5 Hz, 4H), 0.93 (d, J=6.7 Hz, 1H), 0.83-0.90 (m, 4H)

[1444] LC-MS: m/z 486.6 $(M+H)^+$

Compound 795

(R,E)-2-cyclopropyl-6-(4-(5-hydroxypent-2-enoyl)-3-isopropylpiperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1445] ^{1}H NMR (CHLOROFORM-d) 8.68 (d, J=5.0 Hz, 1H), 7.23 (d, J=9.7 Hz, 1H), 7.07 (br. s., 1H), 6.81-6.94 (m, 2H), 6.40 (d, J=15.3 Hz, 1H), 6.28 (d, J=17.6 Hz, 1H), 5.57 (d, J=10.9 Hz, 1H), 4.35-4.52 (m, 1.5H), 4.28 (d, J=9.4 Hz, 1H), 3.94 (d, J=12.9 Hz, 0.5H), 3.80 (t, J=5.9 Hz, 2H), 3.68 (d, J=9.7 Hz, 0.5H), 3.52 (t, J=11.9 Hz, 0.5H), 3.05-3.18 (m, 2H), 2.51 (q, J=6.4 Hz, 2H), 2.25-2.32 (m, 1H), 2.20 (s, 3H), 2.05 (d, J=7.3 Hz, 1H), 1.51-1.61 (m, 1H), 1.10 (br. s., 1H), 1.04 (d, J=6.5 Hz, 4H), 0.93 (d, J=6.7 Hz, 1H), 0.76-0.95 (m, 4H)

[1446] LC-MS: m/z 486.6 $(M+H)^+$

Compound 782

(R)-6-(4-(2-cyclopentylacetyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1447] 1H NMR (CHLOROFORM-d) 8.69 (d, J=5.0 Hz, 1H), 7.24 (s, 1H), 7.08 (d, J=4.4 Hz, 1H), 6.88 (dd, J=17.3, 10.9 Hz, 1H), 6.29 (d, J=17.6 Hz, 1H), 5.57 (d, J=10.9 Hz, 1H), 4.34 (d, J=12.9 Hz, 1H), 4.26 (d, J=12.0 Hz, 1H), 4.13 (q, J=7.2 Hz, 1H), 3.70-3.91 (br. s., 1.5H), 3.23-3.39 (m, 0.5H), 3.09-3.21 (m, 1H), 3.03 (t, J=10.7 Hz, 1H), 2.33-2.51 (m, 2H), 2.24-2.32 (m, 1H), 2.17-2.24 (m, 3H), 1.80-1.95 (m, 2H), 1.61-1.72 (m, 2H), 1.50-1.61 (m, 3H), 1.43 (d, J=12.6 Hz, 1H), 1.14-1.24 (m, 2H), 1.11 (br. s., 2H), 0.82-0.91 (m, 2H), 0.51-0.75 (m, 2H), 0.44 (d, J=5.0 Hz, 2H)

[1448] LC-MS: m/z 496.7 $(M+H)^+$

COMPOUND 788

(R)-2-cyclopropyl-6-(3-isopropyl-4-(4-methoxybutanoyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1449] 1H NMR (CHLOROFORM-d) 8.68 (d, J=5.0 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 7.07 (br. s., 1H), 6.87 (dd, J=17.3, 10.9 Hz, 1H), 6.23-6.33 (m, 1H), 5.48-5.66 (m, 1H), 4.69 (d, J=10.9 Hz, 0.5H), 4.37-4.48 (m, 1.5H), 4.23-4.31 (m, 1H), 3.82 (d, J=13.8 Hz, 0.5H), 3.41-3.53 (m, 3H), 3.22-3.38 (m, 3H), 2.92-3.15 (m, 3H), 2.39-2.56 (m, 2H), 2.25-2.33 (m, 0.5H), 2.17-2.24 (m, 3H), 2.09-2.17 (m, 0.5H), 1.90-2.00 (m, 2H), 1.52-1.60 (m, 1H), 1.09-1.15 (m, 1H), 1.03 (dd, J=6.5, 2.6 Hz, 4H), 0.91 (d, J=6.7 Hz, 1H), 0.80-0.89 (m, 4H)

[1450] LC-MS: m/z 488.7 $(M+H)^+$

Compound 787

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(2-cyclopropylacetyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1451] 1H NMR (CHLOROFORM-d) 8.71 (d, J=5.0 Hz, 1H), 7.26 (br. s., 1H), 7.09 (d, J=4.7 Hz, 1H), 6.88 (dd, J=17.6, 10.9 Hz, 1H), 6.25 (d, J=17.6 Hz, 1H), 5.57 (d, J=11.2 Hz, 1H), 4.34 (d, J=12.9 Hz, 1H), 4.25 (d, J=12.6 Hz, 1H), 4.04-4.16 (m, 0.5H), 3.68-3.86 (m, 1.5H), 3.16 (br. s., 1.5H), 3.03 (br. s., 1H), 2.36 (br. s., 1.5H), 2.26 (d, J=7.3 Hz, 2H), 2.20 (s, 3H), 1.50-1.59 (m, 1H), 1.05-1.11 (m, 3H), 0.86 (dd, J=7.9, 3.2 Hz, 2H), 0.55-0.61 (m, 4H), 0.44 (br. s., 1H), 0.16-0.23 (m, 3H)

[1452] LC-MS: m/z 468.6 $(M+H)^+$

Compound 408

6-cyclopropyl-5-(isoquinolin-4-yl)-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1453] ^{1}H NMR (CHLOROFORM-d) δ 9.36 (s, 1H), 8.41 (br. s., 1H), 8.07-8.19 (m, 1H), 7.65-7.76 (m, 2H), 7.46 (t, J=9.0 Hz, 1H), 4.96 (br. s., 0.5H), 4.58 (br. s., 0.5H), 4.11-4.38 (m, 2.5H), 3.73-3.89 (m, 2.5H), 3.58-3.64 (m, 0.5H), 3.41

(s, 3H), 3.04-3.32 (m, 2.5H), 2.56-2.84 (m, 2H), 2.10 (s, 3H), 1.42-1.51 (m, 1H), 1.31-1.41 (m, 3H), 1.03-1.14 (m, 2H), 0.63-0.83 (m, 2H)

[1454] LC-MS: m/z 470.4 $(M+H)^+$

Compound 410

6-cyclopropyl-5-(isoquinolin-5-yl)-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1455] ^{1}H NMR (CHLOROFORM-d) δ 9.48 (br. s., 1H), 8.58 (br. s., 1H), 8.13 (d, J=8.3 Hz, 1H), 7.78 (t, J=7.7 Hz, 1H), 7.64 (d, J=7.0 Hz, 1H), 7.32 (d, J=10.3 Hz, 1H), 4.96 (br. s., 0.5H), 4.58 (d, J=12.3 Hz, 0.5H), 4.08-4.36 (m, 2.5H), 3.71-3.93 (m, 2.5H), 3.56-3.70 (m, 0.5H), 3.41 (s, 3H), 3.19-3.36 (m, 1.5H), 3.01-3.14 (m, 1H), 2.56-2.78 (m, 2H), 2.02-2.10 (m, 3H), 1.81 (br. s., 1H), 1.42-1.50 (m, 3H), 1.05-1.15 (m, 2H), 0.61-0.81 (m, 2H)

[1456] LC-MS: m/z 470.6 $(M+H)^+$

Compound 470

(R)—N-(3-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-4-methylpyridin-3-yl)phenyl)ethenesulfonamide

[1457] ^{1}H NMR (CHLOROFORM-d) δ 7.44 (t, J=7.8 Hz, 1H), 7.13-7.23 (m, 1H), 6.96-7.12 (m, 2H), 6.48-6.67 (m, 2H), 6.32 (d, J=16.3 Hz, 1H), 6.02 (d, J=10.0 Hz, 1H), 4.58 (br. s., H), 4.34 (d, J=12.5 Hz, 1H), 4.26 (d, J=12.3 Hz, 1H), 3.76 (br. s., 2H), 3.23 (br. s., 1H), 3.07 (br. s., 1H), 2.19 (s, 3H), 1.73 (br. s., 1H), 1.32 (d, J=11.5 Hz, 2H), 0.96-1.15 (m, 4H), 0.74-0.88 (m, 4H), 0.67 (br. s., 1H), 0.37-0.60 (m, 3H)

[1458] LC-MS: m/z 532.7 $(M+H)^+$

Compound 271

(R)-5-(3-chloro-4-fluorophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1459] ^{1}H NMR (CHLOROFORM-d) δ 7.22-7.30 (m, 2H), 7.08 (ddd, J=8.2, 4.6, 2.0 Hz, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=13.6 Hz, 0.5H), 4.00-4.29 (m, 2.5H), 3.66-3.85 (m, 2.5H), 3.49-3.65 (m, 0.5H), 3.38 (s, 3H), 3.01-3.25 (m, 2.5H), 2.63-2.84 (m, 1H), 2.48-2.63 (m, 1H), 2.18 (s, 3H), 1.51-1.61 (m, 1H), 1.31-1.40 (m, 2H), 1.01-1.14 (m, 2H), 0.80-0.90 (m, 2H)

[1460] LC-MS: m/z 471.2 $(M+H)^+$

Compound 568

2-cyclopropyl-6-((3R)-3-cyclopropyl-4-(3-hydroxybutanoyl)piperazin-1-yl)-2'-vinyl-3,4'bipyridine-5-carbonitrile

[1461] 1H NMR (CHLOROFORM-d) δ 8.65 (d, J=4.8 Hz, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 7.24 (d, J=4.3 Hz, 1H), 6.88 (dd, J=17.4, 10.9 Hz, 1H), 6.28 (d, J=17.3 Hz, 1H), 5.57 (d, J=10.8 Hz, 1H), 4.49-4.79 (m, 2H), 4.43 (d, J=12.5 Hz, 1H), 4.17-4.33 (m, 2H), 3.96-4.17 (m, 1H), 3.79 (br. s., 1H), 3.71 (d, J=11.8 Hz, 1H), 3.02-3.31 (m, 2H), 2.53 (d, J=9.8 Hz, 1H), 2.48 (m, 1H), 2.04 (m, 1H), 1.32 (br. s., 3H), 0.82-1.12 (m, 3H), 0.72 (br. s., 1H), 0.63 (br. s., 1H), 0.55 (br. s., 1H), 0.22-0.51 (m, 2H)

[1462] LC-MS: m/z 458.2 $(M+H)^+$

Compound 558

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1463] 1H NMR (CHLOROFORM-d) δ 8.59 (d, J=4.8 Hz, 1H), 7.16 (s, 1H), 7.00 (d, J=4.8 Hz, 1H), 6.78 (dd, J=17.3, 10.8 Hz, 1H), 6.19 (d, J=17.6 Hz, 1H), 5.46 (dd, J=10.8, 1.0 Hz, 1H), 4.60 (d, J=10.5 Hz, 0.5H), 4.26 (d, J=12.8 Hz, 1H), 4.17 (d, J=12.5 Hz, 1H), 3.96-4.06 (m, 0.5H), 3.80 (d, J=12.3 Hz, 1H), 3.59-3.74 (m, 3H), 3.18-3.37 (m, 4H), 3.04-3.14 (m, 1H), 2.90-3.01 (m, 1H), 2.37-2.67 (m, 2H), 2.08-2.18 (m, 3H), 1.39-1.56 (m, 1H), 0.98-1.10 (m, 2H), 0.78 (dd, J=7.9, 3.1 Hz, 2H), 0.51 (br. s., 1H), 0.44 (br. s., 1H), 0.29-0.40 (m, 2H)

[1464] LC-MS: m/z 472.4 $(M+H)^+$

Compound 598

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(6-(prop-1-en-2-yl)pyrimidin-4-yl)nicotinonitrile

[1465] 1H NMR (CHLOROFORM-d) δ 9.22 (s, 1H), 7.98 (s, 1H), 7.61-7.76 (m, 1H), 6.18 (s, 1H), 5.54 (s, 1H), 4.88 (br. s., 1H), 4.51 (d, J=9.8 Hz, 1H), 4.18-4.47 (m, 3H), 3.63-3.93 (m, 3H), 3.41-3.63 (m, 1H), 3.36 (s, 4H), 2.97-3.24 (m, 2H), 2.49-2.79 (m, 2H), 2.28-2.47 (m, 1H), 2.22 (s, 3H), 1.34 (d, J=6.3 Hz, 2H), 1.14-1.30 (m, 4H), 1.04 (dd, J=7.9, 2.9 Hz, 2H)

[1466] LC-MS: m/z 447.2 $(M+H)^+$

Compound 478

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-4-methyl-5-(1H-pyrazol-4-yl)nicotinonitrile

[1467] ^{1}H NMR (CHLOROFORM-d) δ 7.61 (s, 2H), 4.59 (s, 1H), 4.33 (d, J=12.5 Hz, 1H), 4.24 (d, J=12.5 Hz, 1H), 3.98-4.15 (m, 1H), 3.84 (s, 1H), 3.22 (d, J=15.1 Hz, 1H), 3.05 (s, 1H), 2.31 (s, 3H), 1.83-1.98 (m, 1H), 1.73 (s, 1H), 1.37-1.60 (m, 1H), 0.98-1.15 (m, 4H), 0.74-0.92 (m, 4H), 0.34-0.65 (m, 4H).

[1468] LC-MS: m/z 416.2 $(M+H)^+$

Compound 463

(R)—N-(3-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-4-methylpyridin-3-yl)phenyl)-N-(vinylsulfonyl)ethenesulfonamide

[1469] ^{1}H NMR (CHLOROFORM-d) δ 7.47-7.60 (m, 1H), 7.31-7.40 (m, 2H), 7.00-7.14 (m, 2H), 6.28 (s, 1H), 6.32 (s, 1H), 6.17 (d, J=9.8 Hz, 2H), 4.34 (d, J=12.8 Hz, 1H), 4.26 (d, J=12.5 Hz, 2H), 3.85 (s, 1H), 3.06 (br. s., 2H), 1.85 (br. s., 1H), 1.72 (br. s., 1H), 1.58 (td, J=8.2, 4.1 Hz, 2H), 0.95-1.18 (m, 4H), 0.72-0.95 (m, 5H), 0.65 (br. s., 1H), 0.32-0.59 (m, 3H)

[1470] LC-MS: m/z 622.2 $(M+H)^+$

Compound 535

(R)-5-(5-cyano-2-cyclopropyl-6-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)pyridin-3-yl) quinoline-2-carbonitrile

[1471] ^{1}H NMR (CHLOROFORM-d) δ 8.27 (d, J=8.5 Hz, 1H), 8.11 (dd, J=11.5, 8.8 Hz, 1H), 7.94 (t, J=7.8 Hz, 1H), 7.53-7.78 (m, 3H), 4.59 (dt, J=13.1, 2.3 Hz, 1H), 4.48 (d, J=11.8 Hz, 1H), 4.04-4.34 (m, 1H), 3.81 (br. s., 1H), 3.21-3.51 (m, 3H), 3.15 (d, J=11.5 Hz, 2H), 1.68 (br. s., 2H), 1.37-1.48 (m, 3H), 1.14-1.36 (m, 13H), 0.77-1.04 (m, 4H), 0.71 (br. s., 1H), 0.60 (br. s., 1H), 0.31-0.57 (m, 2H)

[1472] LC-MS: m/z 513.2 $(M+H)^+$

Compound 563

(R)-5-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl) quinoline-2-carbonitrile

[1473] ^{1}H NMR (CHLOROFORM-d) δ 8.25 (d, J=8.8 Hz, 1H), 8.13 (dd, J=10.3, 9.0 Hz, 1H), 7.85-8.04 (m, 1H), 7.56-7.76 (m, 3H), 4.59 (d, J=12.0 Hz, 1H), 4.47 (d, J=12.5 Hz, 2H), 4.13 (q, J=7.0 Hz, 1H), 3.72 (br. s., 1H), 3.42 (d, J=10.0 Hz, 1H), 3.09-3.36 (m, 2H), 1.66-1.86 (m, 1H), 1.52-1.66 (m, 1H), 1.36-1.52 (m, 2H), 1.00-1.30 (m, 8H), 0.75-1.00 (m, 6H), 0.71 (d, J=7.8 Hz, 1H), 0.34-0.63 (m, 4H)

[1474] LC-MS: m/z 489.2 $(M+H)^+$

Compound 610

(R)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(1-propioloyl-2,5-dihydro-1H-pyrrol-3-yl)nicotinonitrile

[1475] ^{1}H NMR (CHLOROFORM-d) d: 7.53 (d, J=1.0 Hz, 1H), 6.00 (dt, J=19.1, 2.0 Hz, 1H), 4.61-4.91 (m, 2H), 4.52-4.61 (m, 1H), 4.40-4.52 (m, 2H), 4.19-4.40 (m, 2H), 3.50 (s, 1H), 3.43 (d, J=6.0 Hz, 1H), 3.02-3.32 (m, 3H), 2.09-2.31 (m, 2H), 1.75 (br. s., 2H), 1.37-1.48 (m, 1H), 1.11-1.37 (m, 7H), 0.95-1.11 (m, 2H), 0.66-0.95 (m, 2H).

[1476] LC-MS: m/z 430.2 $(M+H)^+$

Compound 450 (R)—N-(3-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)phenyl)propionamide

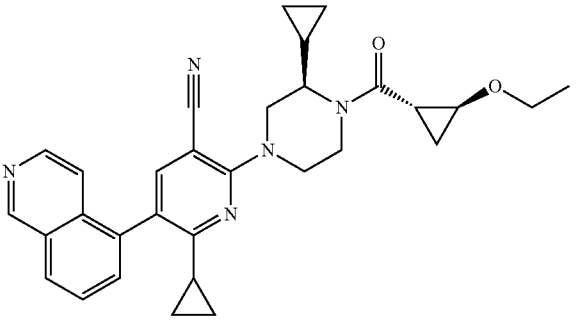
[1477] ^{1}H NMR (CHLOROFORM-d) d: 7.70 (d, J=6.0 Hz, 2H), 7.61 (s, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.38 (t, J=7.8 Hz, 1H), 7.13 (d, J=7.5 Hz, 1H), 4.50 (d, J=11.8 Hz, 1H), 4.38 (d, J=12.3 Hz, 1H), 3.73 (d, J=7.0 Hz, 1H), 3.25 (br. s., 1H), 3.07 (br. s., 1H), 2.38-2.51 (m, 2H), 1.98-2.22 (m, 1H), 1.73 (br. s., 1H), 1.21-1.45 (m, 6H), 1.16 (dt, J=7.8, 3.6 Hz, 3H), 0.87-1.11 (m, 5H), 0.76-0.86 (m, 2H), 0.65 (br. s., 1H), 0.29-0.59 (m, 3H).

[1478] LC-MS: m/z 484.3 $(M+H)^+$

Compound 834 (General Procedure 2, Step M)

6-cyclopropyl-2-((R)-3-cyclopropyl-4-((1S,2S)-2-ethoxycyclopropanecarbonyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile

[1479]



[1480] ^{1}H NMR (DEUTERIUM OXIDE) 9.35 (s, 1H), 8.54 (dd, J=5.9, 1.9 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.69-7.75 (m, 1H), 7.64-7.68 (m, 2H), 7.44 (dd, J=12.5, 6.0 Hz, 1H), 4.46-4.59 (m, 2.5H), 4.08-4.18 (m, 1H), 3.86 (br. s., 0.5H), 3.53-3.74 (m, 3H), 3.21-3.32 (m, 2H), 1.87-2.06 (m, 2H), 1.49-1.58 (m, 1H), 1.33 (d, J=5.8 Hz, 1H), 1.14-1.28 (m, 7H), 0.81-0.90 (m, 2H), 0.65 (br. s., 1H), 0.36-0.59 (m, 3H).

[1481] LC-MS: m/z 508.2 $(M+H)^+$

COMPOUND 730 (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(methyl(2-vinylpyridin-4-yl)amino)nicotinonitrile

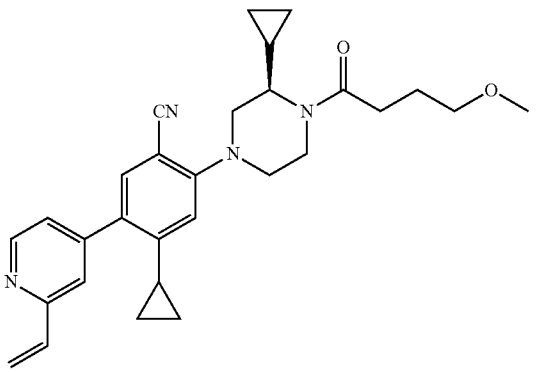
[1482] ^{1}H NMR (CHLOROFORM-d) δ 8.25 (d, J=5.9 Hz, 1H), 7.58 (s, 1H), 6.71 (dd, J=17.4, 10.7 Hz, 1H), 6.46 (s, 1H), 6.33 (s, 1H), 6.20 (d, J=17.3 Hz, 1H), 5.45 (d, J=11.2 Hz, 1H), 4.69 (d, J=13.4 Hz, 0.4H), 4.49 (d, J=13.0 Hz, 1H), 4.37 (d, J=12.7 Hz, 1H), 4.10 (d, J=8.6 Hz, 0.6H), 3.92 (s, 2H), 3.86-3.65 (m, 1.5H), 3.42 (s, 1H), 3.31 (s, 3H), 3.22 (m, 1.5H), 3.15-3.00 (m, 1H), 2.69-2.45 (m, 2H), 1.88 (ddd, J=12.7, 8.1, 4.7 Hz, 1H), 1.40-1.31 (m, 1H), 1.12 (s, 2H), 0.99 (s, 2H), 0.81-0.34 (m, 4H).

[1483] LC-MS: m/z 473.4 $(M+H)^+$

Compound 835

(R)-4-cyclopropyl-2-(3-cyclopropyl-4-(4-methoxybutanoyl)piperazin-1-yl)-5-(2-vinylpyridin-4-yl) benzonitrile

[1484]



[1485] ^{1}H NMR (CHLOROFORM-d) 8.64 (d, J=5.0 Hz, 1H), 7.46 (s, 1H), 7.34-7.42 (m, 1H), 7.21 (dd, J=5.0, 1.5 Hz, 1H), 6.87 (dd, J=17.6, 10.9 Hz, 1H), 6.54 (s, 1H), 6.21-6.33 (m, 1H), 5.55 (dd, J=10.9, 0.9 Hz, 1H), 4.63-4.77 (m, 0.3H), 4.01-4.18 (m, 0.7H), 3.80-3.94 (m, 1H), 3.41-3.82 (m, 4H), 3.35 (s, 3H), 3.18-3.35 (m, 1H), 2.97-3.05 (m, 1H), 2.79-2.93 (m, 1H), 2.46 (d, J=7.3 Hz, 2H), 1.81-1.99 (m, 4H), 0.94-1.07 (m, 2H), 0.72-0.83 (m, 2H), 0.36-0.56 (m, 4H).

[1486] LC-MS: m/z 471.2 $(M+H)^+$

Compound 775

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-((5-vinylpyridazin-3-yl)amino)nicotinonitrile

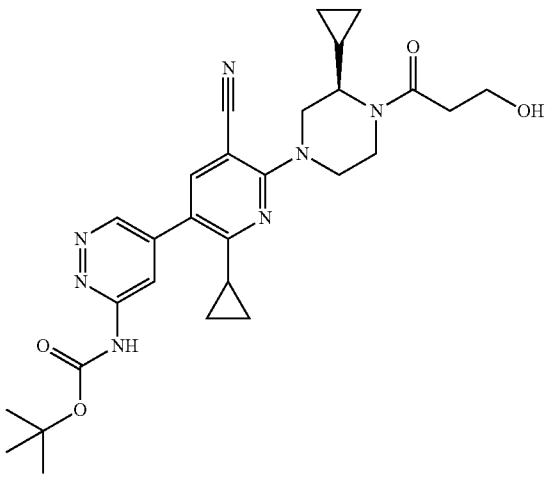
[1487] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.76 (s, 1H), 6.58 (dd, J=17.6, 11.0 Hz, 2H), 6.05 (d, J=17.6 Hz, 1H), 5.66 (d, J=11.0 Hz, 1H), 4.65-4.70 (m, 0.5H), 4.43-4.46 (m, 1H), 4.33 (d, J=12.4 Hz, 1H), 4.16-4.07 (m, 1H), 3.87-3.88 (m, 0.5H), 3.71-3.74 (m, 3H), 3.39 (s, 3H), 3.20 (s, 1H), 3.07-3.09 (m, 1H), 2.65-2.66 (m, 2H), 2.55-2.47 (m, 1H), 2.18 (d, J=10.1 Hz, 1H), 1.30-1.25 (m, 1H), 1.15 (s, 2H), 1.07-0.98 (m, 2H), 0.50-0.60 (m, 2H), 0.45-0.47 (m, 2H).

[1488] LC-MS: m/z 474.6 $(M+H)^+$

Compound 836

(R)-tert-butyl(5-(5-cyano-2-cyclopropyl-6-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)pyridin-3-yl)pyridazin-3-yl)carbamate

[1489]



[1490] The mixture of (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (268 mg, 0.627 mmol), tert-butyl (5-chloropyridazin-3-yl)carbamate (120 mg, 0.523 mmol), Pd(dppf)Cl_2 (20 mg, 0.026 mmol) and CsF (159 mg, 1.045 mmol) in dioxane/H_2O (8 mL/2 mL) was stirred at 100° C. for 16 hours. The mixture was diluted with EtOAc (50 mL) and filtered. The filtrated was partitioned between EtOAc (50 mL) and water (30 mL), the organic layer was washed with water (30 mL), brine and dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 150 mg of the product.

[1491] ^{1}H NMR (CHLOROFORM-d): 8.97 (d, J=2.1 Hz, 1H), 8.33 (d, J=1.8 Hz, 1H), 8.24 (br. s., 1H), 7.70 (s, 1H), 4.62 (d, J=13.2 Hz, 1H), 4.49 (d, J=12.9 Hz, 1H), 4.08 (d, J=8.8 Hz, 1H), 3.92 (t, J=4.5 Hz, 2H), 3.63-3.85 (m, 1H), 3.02-3.23 (m, 3H), 2.41-2.67 (m, 2H), 1.91-2.06 (m, 1H), 1.48-1.63 (m, 9H), 1.15-1.25 (m, 3H), 1.02-1.13 (m, 2H), 0.46-0.72 (m, 4H)

[1492] LC-MS: m/z 534.3 $(M+H)^+$

Compound 339 (General Procedure 9)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinolin-3-ylamino)nicotinonitrile

[1493] ^{1}H NMR (MeOD): δ 8.797-8.790 (d, J=2.8 Hz, 1H), 8.059-8.037 (d, J=8.8 Hz, 1H), 7.985-7.962 (d, J=9.2 Hz, 1H), 7.926-7.920 (d, J=2.4 Hz, 1H), 7.861 (s, 1H), 7.795-7.710 (m, 2H), 4.797-4.783 (m, 0.5H), 4.451-4.416 (m, 1H), 4.227-4.112 (m, 2H), 3.972-3.932 (m, 0.5H), 3.694-3.613 (m, 2H), 3.608-3.577 (m, 0.5H), 3.334 (s, 3H), 3.284 (m, 0.5H), 3.211-3.137 (m, 1H), 3.045-3.007 (m, 0.5H), 2.852-2.704 (m, 1H), 2.700-2.578 (m, 1.5H), 2.240-2.177 (m, 1H), 1.401-1.384 (d, J=6.8 Hz, 1.5H), 1.284-1.267 (d, J=6.8 Hz, 1.5H), 1.188-1.170 (m, 2H), 0.992-0.965 (m, 2H);

[1494] LC-MS: m/z 471.5 $(M+H)^+$

Compound 355 (General Procedure 9)

(R)-6-cyclopropyl-5-((4-fluorophenyl)amino)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1495] 1H NMR (MeOD): δ 7.543 (s, 1H), 6.936-6.893 (t, J=8.6 Hz, 2H), 6.723-6.690 (q, J=4.4 Hz, 2H), 4.798-4.781 (m, 0.5H), 4.443-4.361 (m, 1H), 4.050-3.898 (m, 2.5H), 3.675-3.509 (m, 2.5H), 3.336 (s, 3H), 3.254-2.877 (m, 2.5H), 2.792-2.588 (m, 2H), 2.260-2.196 (m, 1H), 1.402-1.255 (m, 3H), 1.115-1.097 (m, 2H), 0.992-0.968 (m, 2H);

[1496] LC-MS: m/z 438.5 $(M+H)^+$

Compound 356 (General Procedure 9)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinolin-4-ylamino)nicotinonitrile

[1497] ^{1}H NMR (MeOD): δ 8.593-8.572 (d, J=8.4 Hz, 1H), 8.440-8.422 (d, J=7.2 Hz, 1H), 8.065-8.026 (m, 1H), 7.983-7.962 (d, J=8.4 Hz, 1H), 7.931 (s, 1H), 7.854-7.813 (m, 2H), 6.552-6.535 (d, J=6.8 Hz, 1H), 4.792-4.783 (m, 0.5H), 4.451-4.420 (m, 1H), 4.329-4.207 (m, 2H), 3.982-3.948 (m, 0.5H), 3.414-3.338 (m, 4H), 3.257-3.068 (m, 1.5H), 2.829-2.610 (m, 2H), 2.091-2.026 (m, 1H), 1.389-1.256 (m, 3H), 1.199-1.181 (m, 2H), 1.050-0.988 (m, 2H);

[1498] LC-MS: m/z 471.5 $(M+H)^+$

Compound 368 (General Procedure 9)

(R)-5-(4-acetylpiperazin-1-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1499] 1H NMR (MeOD): δ 7.558 (s, 1H), 4.763-4.752 (m, 0.5H), 4.429-4.346 (m, 1H), 4.052-3.883 (m, 3H), 3.747-3.

668 (m, 6H), 3.328 (s, 3H), 3.182-3.119 (m, 2H), 3.061-2.886 (m, 4.5H), 2.781-2.677 (m, 1H), 2.623-2.562 (m, 2H), 2.142 (s, 3H), 1.375-1.358 (m, 1.5H), 1.261-1.244 (m, 1.5H), 1.109-1.036 (m, 4H);

[1500] LC-MS: m/z 455.5 $(M+H)^+$

Compound 375 (General Procedure 9)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-morpholinonicotinonitrile

[1501] ^{1}H NMR (MeOD): δ 7.551 (s, 1H), 4.762-4.748 (m, 0.5H), 4.428-4.352 (m, 1H), 4.039-3.975 (m, 2H), 3.941-3.827 (m, 5H), 3.681-3.667 (m, 2H), 3.574-3.501 (m, 1H), 3.327 (s, 3H), 3.173-3.116 (m, 2H), 3.046-2.991 (m, 1H), 2.940-2.882 (m, 4H), 2.744-2.522 (m, 2.5H), 1.378-1.361 (m, 1.5H), 1.264-1.247 (m, 1.5H), 1.097-1.012 (m, 4H);

[1502] LC-MS: m/z 414.5 $(M+H)^+$

Compound 376 (General Procedure 9)

(R)-ethyl 4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl) piperazine-1-carboxylate

[1503] 1H NMR (MeOD): δ 7.549 (s, 1H), 4.763-4.747 (m, 0.5H), 4.426-4.343 (m, 1H), 4.171-4.118 (m, 2H), 4.044-3.882 (m, 1.5H), 3.666-3.639 (m, 6H), 3.573-3.501 (m, 1H), 3.327 (s, 3H), 3.176-2.988 (m, 2H), 2.911-2.886 (m, 4.5H), 2.781-2.546 (m, 3H), 1.374-1.358 (m, 1.5H), 1.289-1.253 (m, 4.5H), 1.101-1.026 (m, 4H);

[1504] LC-MS: m/z 485.6 $(M+H)^+$

Compound 377 (General Procedure 9)

(R)-6-cyclopropyl-5-(4-(ethylsulfonyl)piperazin-1-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1505] 1H NMR (MeOD): δ 7.587 (s, 1H), 4.765-4.749 (m, 0.5H), 4.426-4.348 (m, 1H), 4.055-3.882 (m, 1.5H), 3.669-3.457 (m, 7H), 3.329 (s, 3H), 3.152-3.066 (m, 4H), 3.004-2.888 (m, 4.5H), 2.742-2.538 (m, 3H), 1.373-1.335 (m, 4.5H), 1.261-1.245 (m, 1.5H), 1.094-1.036 (m, 4H);

[1506] LC-MS: m/z 505.6 $(M+H)^+$

Compound 378 (General Procedure 9)

(R)-6-cyclopropyl-5-(4-(cyclopropylmethyl)piperazin-1-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1507] 1H NMR (MeOD): δ 7.598 (s, 1H), 4.768-4.752 (m, 0.5H), 4.431-4.355 (m, 1H), 4.068-3.892 (m, 2.5H), 3.688-3.660 (m, 2H), 3.572-3.507 (m, 1H), 3.333 (s, 3H), 3.101-2.930 (m, 9H), 2.903-2.871 (m, 1H), 2.787-2.586 (m, 4H), 2.544-2.493 (m, 1H), 1.378-1.362 (m, 1.5H), 1.264-1.248 (m, 1.5H), 1.124-1.044 (m, 5H), 0.698-0.652 (m, 2H), 0.357-0.268 (m, 2H);

[1508] LC-MS: m/z 467.6 $(M+H)^+$

Compound 379 (General Procedure 9)

(R)-5-(4-benzoylpiperazin-1-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1509] 1H NMR (MeOD): δ 7.588 (s, 1H), 7.492-7.451 (m, 5H), 4.780-4.768 (m, 0.5H), 4.430-4.346 (m, 1H), 4.053-3.881 (m, 4.5H), 3.667-3.630 (m, 2.5H), 3.536-3.477 (m, 2H), 3.326 (m, 4H), 3.180-3.085 (m, 1.5H), 3.023-2.923 (m, 5H), 2.756-2.709 (m, 1H), 2.619-2.567 (m, 2H), 1.373-1.357 (m, 1.5H), 1.259-1.243 (m, 1.5H), 1.113-1.033 (m, 4H);

[1510] LC-MS: m/z 517.6 $(M+H)^+$

Compound 265 (General Procedure 6)

(R)-6-cyclopropyl-5-(3-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1511] ^{1}H NMR (CHLOROFORM-d) δ 7.41-7.51 (m, 1H), 7.12 (td, J=8.5, 2.5 Hz, 1H), 7.01 (d, J=7.5 Hz, 1H), 6.95 (d, J=9.0 Hz, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J=12.8 Hz, 0.5H), 4.02-4.22 (m, 2.5H), 3.70-3.92 (m, 2.5H), 3.53-3.67 (m, 0.5H), 3.40 (s, 3H), 2.92-3.31 (m, 2.5H), 2.61-2.84 (m, 21H), 2.16-2.25 (m, 3H), 1.57-1.65 (m, 1H), 1.43 (d, J=6.5 Hz, 1.5H), 1.33 (d, J=6.8 Hz, 1.5H), 1.08 (t, J=4.6 Hz, 2H), 0.79-0.90 (m, 2H)

[1512] LC-MS: m/z 437.4 $(M+H)^+$

Compound 264 (General Procedure 6)

6-cyclopropyl-5-(2,4-difluorophenyl)-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1513] ^{1}H NMR (CHLOROFORM-d) δ 7.15-7.25 (m, 1H), 6.94-7.06 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=13.3 Hz, 0.5H), 4.05-4.34 (m, 2.5H), 3.70-3.85 (m, 2.5H), 3.52-3.67 (m, 0.5H), 3.40 (s, 3H), 2.93-3.31 (m, 2.5H), 2.73 (td, J=15.3, 7.3 Hz, 1H), 2.54-2.64 (m, 1H), 2.21 (s, 3H), 1.54-1.61 (m, 1H), 1.39-1.45 (m, 1.5H), 1.32 (t, J=5.8 Hz, 1.5H), 1.01-1.18 (m, 2H), 0.83-0.93 (m, 2H)

[1514] LC-MS: m/z 455.4 $(M+H)^+$

Compound 263 (General Procedure 6)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(4-(trifluoromethoxy)phenyl)nicotinonitrile

[1515] ^{1}H NMR (CHLOROFORM-d) δ 7.31-7.36 (m, J=8.0 Hz, 2H), 7.23-7.28 (m, J=8.3 Hz, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=13.8 Hz, 0.5H), 4.00-4.22 (m, 2.5H), 3.68-3.87 (m, 2.5H), 3.53-3.67 (m, 0.5H), 3.36-3.44 (m, 3H), 3.12-3.31 (m, 1.5H), 2.94-3.12 (m, 1H), 2.64-2.83 (m, 1H), 2.61 (br. s., 1H), 2.16-2.22 (m, 3H), 1.52-1.63 (m, 1H), 1.39-1.47 (m, 1.5H), 1.32 (d, J=6.3 Hz, 1.5H), 1.03-1.15 (m, 2H), 0.78-0.90 (m, 2H)

[1516] LC-MS: m/z 503.3 $(M+H)^+$

Compound 272 (General Procedure 8)

(R)-benzyl 2-(5-cyano-2-isopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yloxy)ethylcarbamate

[1517] ^{1}H NMR (CHLOROFORM-d) δ 7.32-7.40 (m, 5H), 7.18 (s, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J=12.5 Hz, 0.5H), 4.21 (br. s., 0.5H), 4.06 (d, J=14.1 Hz, 1H), 3.95-4.01 (m, 2.5H), 3.68-3.79 (m, 3H), 3.53-3.67 (m, 2.5H), 3.30-3.44 (m, 5H), 3.07-3.25 (m, 2H), 2.89-3.07 (m, 1H), 2.51-2.79 (m, 2.5H), 1.40 (d, J=6.5 Hz, 1.5H), 1.30 (d, J=6.8 Hz, 1.5H), 1.11-1.20 (m, 7H)

[1518] LC-MS: m/z 524.3 $(M+H)^+$

Compound 270 (General Procedure 6)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(thiophen-3-yl)nicotinonitrile

[1519] ^{1}H NMR (CHLOROFORM-d) δ 7.47 (dd, J=5.0, 3.0 Hz, 1H), 7.17 (dd, J=2.8, 1.3 Hz, 1H), 7.00 (dd, J=5.0, 1.3 Hz, 1H), 4.91 (br. s., 0.5H), 4.55 (d, J=10.8 Hz, 0.5H), 3.98-4.28 (m, 2.5H), 3.75 (q, J=6.0 Hz, 2.5H), 3.50-3.67 (m, 0.5H), 3.36-3.46 (m, 3H), 3.10-3.30 (m, 1.5H), 2.89-3.10 (m, 1H), 2.65-2.81 (m, 2H), 2.25 (s, 3H), 1.71-1.79 (m, 1H), 1.42 (d, J=6.5 Hz, 1.5H), 1.32 (d, J=6.8 Hz, 1.5H), 1.05-1.12 (m, 2H), 0.81-0.90 (m, 2H)

[1520] LC-MS: m/z 425.3 $(M+H)^+$

Compound 269 (General Procedure 6)

(R)-5-(benzo[d][1,3]dioxol-5-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1521] ^{1}H NMR (CHLOROFORM-d) δ 6.91 (d, J=8.0 Hz, 1H), 6.60-6.74 (m, 2H), 6.01-6.11 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J=13.6 Hz, 0.5H), 4.24 (br. s., 0.5H), 4.02-4.20 (m, 2H), 3.70-3.85 (m, 2.5H), 3.59 (t, J=11.7 Hz, 0.5H), 3.39 (s, 3H), 3.19 (t, J=13.7 Hz, 1.5H), 2.92-3.08 (m, 1H), 2.65-2.83 (m, 1H), 2.55-2.64 (m, 1H), 2.19-2.27 (m, 3H), 1.67-1.76 (m, 1H), 1.42 (d, J=6.5 Hz, 1.5H), 1.31-1.38 (m, 1.5H), 1.06 (t, J=5.3 Hz, 2H), 0.79-0.91 (m, 2H)

[1522] LC-MS: m/z 463.3 $(M+H)^+$

Compound 268 (General Procedure 6)

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-3,4'-bipyridine-5-carbonitrile

[1523] ^{1}H NMR (CHLOROFORM-d) δ 8.87 (br. s., 2H), 7.86 (br. s., 2H), 4.90-5.00 (m, 0.5H), 4.57 (br. s., 0.5H), 4.33 (d, J=12.5 Hz, 2.5H), 3.71-3.82 (m, 2.5H), 3.58 (br. s., 0.5H), 3.40 (s, 3H), 3.09-3.28 (m, 2.5H), 2.68 (br. s., 1H), 2.61 (br. s., 1H), 2.23-2.28 (m, 3H), 1.62-1.66 (m, 1H), 1.32-1.38 (m, 3H), 1.20 (br. s., 2H), 0.98 (br. s., 2H)

[1524] LC-MS: m/z 420.5 $(M+H)^+$

Compound 267 (General Procedure 6)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(naphthalen-2-yl)nicotinonitrile

[1525] ^{1}H NMR (CHLOROFORM-d) δ 7.84-8.00 (m, 3H), 7.71 (s, 1H), 7.53-7.60 (m, 2H), 7.34 (dd, J=8.4, 1.4 Hz, 1H), 4.94 (br. s., 0.5H), 4.57 (d, J=13.3 Hz, 0.5H), 4.06-4.34 (m, 2.5H), 3.71-3.85 (m, 2.5H), 3.52-3.69 (m, 0.5H), 3.37-3.45 (m, 3H), 3.14-3.30 (m, 1.5H), 2.94-3.12 (m, 1H), 2.67-2.85 (m, 1H), 2.54-2.66 (m, 1H), 2.19-2.28 (m, 3H), 1.62-1.70 (m, 1H), 1.45 (d, J=5.8 Hz, 1.5H), 1.35 (d, J=5.5 Hz, 1.5H), 1.03-1.16 (m, 2H), 0.74-0.84 (m, 2H)

[1526] LC-MS: m/z 469.4 $(M+H)^+$

Compound 559 (General Procedure 9)

(R)-6-cyclopropyl-5-(4-(ethylsulfonyl)piperazin-1-yl)-2-(3-methyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)nicotinonitrile

[1527] ^{1}H NMR (CHLOROFORM-d) δ 7.38 (s, 1H), 4.29 (d, J=12.8 Hz, 1H), 4.18 (d, J=12.5 Hz, 1H), 4.09 (d, J=7.5 Hz, 0.5H), 3.70-3.81 (m, 1.5H), 3.46-3.55 (m, 4.5H), 3.30 (q, J=9.8 Hz, 2H), 2.92-3.14 (m, 8.5H), 2.38-2.53 (m, 1H), 1.38-1.49 (m, 3H), 1.29-1.36 (m, 1H), 1.02-1.17 (m, 4H), 0.42-0.67 (m, 4H)

[1528] LC-MS: m/z 555.2 $(M+H)^+$

Compound 529 (General Procedure 9)

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(4-(ethyl sulfonyl)piperazin-1-yl)nicotinonitrile

[1529] ^{1}H NMR (CHLOROFORM-d) δ 7.37 (s, 1H), 3.42-4.57 (m, 9H), 2.90-3.22 (m, 8H), 2.40-2.52 (m, 1H), 1.73 (br. s., 1H), 1.39-1.50 (m, 4H), 1.10-1.17 (m, 2H), 0.95-1.09 (m, 4H), 0.76-0.85 (m, 2H), 0.35-0.58 (m, 4H)

[1530] LC-MS: m/z 513.2 $(M+H)^+$

Compound 528 (General Procedure 9)

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(quinolin-4-ylamino)nicotinonitrile

[1531] ^{1}H NMR (CHLOROFORM-d) δ 8.55 (d, J=5.5 Hz, 1H), 8.05 (d, J=8.0 Hz, 1H), 8.10 (d, J=8.3 Hz, 1H), 7.67-7.78 (m, 2H), 7.51-7.63 (m, 1H), 6.32 (d, J=5.3 Hz, 1H), 4.50 (d, J=12.3 Hz, 1H), 4.38 (d, J=12.3 Hz, 1H), 3.12-4.18 (m, 5H), 2.05-2.13 (m, 1H), 1.03-1.22 (m, 5H), 0.95-1.01 (m, 3H), 0.83 (dd, J=7.9, 2.4 Hz, 2H), 0.39-0.62 (m, 4H)

[1532] LC-MS: m/z 479.3 $(M+H)^+$

Compound 722 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-((2-vinyl-1,7-naphthyridin-4-yl)amino)nicotinonitrile

[1533] ^{1}H NMR (CHLOROFORM-d) δ 9.48 (s, 1H), 8.58 (d, J=5.9 Hz, 1H), 7.87 (br. s., 1H), 7.74 (s, 1H), 6.91 (dd, J=17.6, 10.9 Hz, 1H), 6.57 (s, 1H), 6.27 (d, J=17.6 Hz, 1H), 5.69 (d, J=10.9 Hz, 1H), 4.52 (d, J=12.9 Hz, 1H), 4.40 (d, J=12.3 Hz, 1H), 4.11 (d, J=7.9 Hz, 1H), 3.94 (br. s., 2H), 3.64-3.88 (m, 1H), 3.33 (br. s., 1H), 3.24 (d, J=13.5 Hz, 1H),

3.03-3.19 (m, 1H), 2.48-2.69 (m, 2H), 1.98-2.09 (m, 1H), 1.37 (d, J=16.1 Hz, 1H), 1.10-1.22 (m, 2H), 0.95-1.08 (m, 2H), 0.66 (br. s., 1H), 0.57 (br. s., 1H), 0.49 (br. s., 2H)

[1534] LC-MS: m/z 430.2 $(M+H)^+$

Compound 819 (General Procedure 6)

(R)-6-(4-(2-cyclobutylacetyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1535] 1H NMR (CHLOROFORM-d) δ 8.69 (d, J=4.7 Hz, 1H), 7.23 (br. s., 1H), 7.07 (d, J=4.4 Hz, 1H), 6.87 (dd, J=17.3, 10.9 Hz, 1H), 6.29 (d, J=17.3 Hz, 1H), 5.57 (d, J=11.7 Hz, 1H), 4.34 (d, J=12.9 Hz, 1H), 4.25 (d, J=12.0 Hz, 1H), 4.09 (br. s., 1H), 3.80 (br. s., 1H), 3.13 (br. s., 2H), 3.02 (br. s., 1H), 2.73 (dt, J=15.6, 7.8 Hz, 1H), 2.51 (br. s., 2H), 2.21 (s, 3H), 2.10-2.20 (m, 2H), 1.67-1.97 (m, 5H), 1.50-1.66 (m, 1H), 1.43 (d, J=15.8 Hz, 1H), 1.11 (br. s., 2H), 0.83-0.93 (m, 2H), 0.61 (br. s., 1H), 0.52 (br. s., 1H), 0.31-0.48 (m, 2H)

[1536] LC-MS: m/z 482.6 $(M+H)^+$

Compound 820 (General Procedure 6)

(R)-6-(4-(2-cyclobutylideneacetyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1537] 1H NMR (CHLOROFORM-d) δ 8.70 (d, J=5.0 Hz, 1H), 7.25 (s, 1H), 7.09 (d, J=3.8 Hz, 1H), 6.89 (dd, J=17.6, 10.9 Hz, 1H), 6.31 (d, J=17.3 Hz, 1H), 5.92 (br. s., 1H), 5.59 (d, J=11.2 Hz, 1H), 4.35 (d, J=12.9 Hz, 1H), 4.27 (d, J=12.6 Hz, 1H), 3.91-4.19 (m, 1H), 3.78 (br. s., 1H), 3.10-3.31 (m, 3H), 3.04 (td, J=12.4, 3.4 Hz, 1H), 2.84 (t, J=8.4 Hz, 2H), 2.43-2.55 (m, 1H), 2.22 (s, 3H), 1.98-2.17 (m, 2H), 1.53-1.63 (m, 1H), 1.45 (br. s., 1H), 1.04-1.18 (m, 2H), 0.82-0.96 (m, 2H), 0.64 (br. s., 1H), 0.50 (br. s., 1H), 0.31-0.48 (m, 2H)

[1538] LC-MS: m/z 480.6 $(M+H)^+$

Compound 266 (General Procedure 6)

(R)-6-cyclopropyl-5-(3-fluoro-4-methylphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile

[1539] ^{1}H NMR (CHLOROFORM-d) δ 7.25-7.31 (m, 1H), 6.85-6.92 (m, 2H), 4.91 (br. s., 0.5H), 4.54 (d, J=13.3 Hz, 0.5H), 4.00-4.23 (m, 2.5H), 3.68-3.87 (m, 2.5H), 3.51-3.63 (m, 0.5H), 3.39 (s, 3H), 3.10-3.27 (m, 1.5H), 2.94-3.09 (m, 1H), 2.64-2.82 (m, 1H), 2.55-2.64 (m, 1H), 2.32-2.39 (m, 3H), 2.20 (s, 3H), 1.60-1.70 (m, 1H), 1.39-1.47 (m, 1.5H), 1.30-1.35 (m, 1.5H), 1.07 (t, J=4.6 Hz, 2H), 0.83 (dt, J=7.5, 3.5 Hz, 2H)

[1540] LC-MS: m/z 451.4 $(M+H)^+$

Compound 277 (General Procedure 8)

6-cyclopropyl-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(1-phenylethoxy)nicotinonitrile

[1541] ^{1}H NMR (CHLOROFORM-d) δ 7.28-7.42 (m, 5H), 6.97 (d, J=3.3 Hz, 1H), 5.15 (q, J=6.3 Hz, 1H), 4.85 (br. s., 0.5H), 4.48 (d, J=13.1 Hz, 0.5H), 4.15 (br. s., 0.5H), 3.76-3.94 (m, 2H), 3.64-3.76 (m, 2.5H), 3.41-3.57 (m, 0.5H), 3.36 (s, 3H), 2.96-3.13 (m, 1.5H), 2.77-2.96 (m, 1H), 2.61-2.77 (m, 1H), 2.48-2.61 (m, 2H), 1.67 (d, J=6.3 Hz, 3H), 1.26 (d, J=5.3 Hz, 3H), 0.97-1.15 (m, 4H)

[1542] LC-MS: m/z 449.2 $(M+H)^+$

Compound 279 (General Procedure 8)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(pyridin-2-ylmethoxy)nicotinonitrile

[1543] ^{1}H NMR (CHLOROFORM-d) δ 8.64 (d, J=4.5 Hz, 1H), 7.82 (t, J=7.3 Hz, 1H), 7.51-7.62 (m, 1H), 7.29-7.39 (m, 1H), 7.23 (s, 1H), 5.22 (s, 2H), 4.88 (br. s., 0.5H), 4.51 (d, J=12.8 Hz, 0.5H), 4.18 (br. s., 0.5H), 3.82-4.03 (m, 2H), 3.63-3.81 (m, 2.5H), 3.44-3.61 (m, 0.5H), 3.37 (s, 3H), 3.09 (t, J=13.2 Hz, 1.5H), 2.82-3.01 (m, 1H), 2.62-2.79 (m, 1H), 2.45-2.61 (m, 2H), 1.26 (d, J=5.3 Hz, 3H), 0.99-1.16 (m, 4H)

[1544] LC-MS: m/z 436.2 $(M+H)^+$

Compound 280 (General Procedure 8)

(R)-6-cyclopropyl-5-(3-methoxybenzyloxy)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1545] ^{1}H NMR (CHLOROFORM-d) δ 7.32 (t, J=7.9 Hz, 1H), 7.18 (s, 1H), 6.93-7.05 (m, 2H), 6.89 (dd, J=8.0, 2.3 Hz, 1H), 5.02 (s, 2H), 4.87 (br. s., 0.5H), 4.51 (d, J=13.3 Hz, 0.5H), 4.18 (br. s., 0.5H), 3.92 (t, J=12.7 Hz, 2H), 3.83 (s, 3H), 3.73 (t, J=6.1 Hz, 2.5H), 3.53 (d, J=8.0 Hz, 0.5H), 3.37 (s, 3H), 3.01-3.18 (m, 1.5H), 2.81-3.00 (m, 1H), 2.62-2.78 (m, 1H), 2.45-2.62 (m, 2H), 1.27-1.44 (m, 3H), 0.97-1.15 (m, 4H)

[1546] LC-MS: m/z 465.2 $(M+H)^+$

Compound 281 (General Procedure 8)

(R)-6-cyclopropyl-5-(4-methoxybenzyloxy)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1547] ^{1}H NMR (CHLOROFORM-d) δ 7.28-7.39 (m, J=8.8 Hz, 2H), 7.20 (s, 1H), 6.88-6.97 (m, J=8.8 Hz, 2H), 4.96 (s, 2H), 4.88 (d, J=7.8 Hz, 0.5H), 4.51 (d, J=13.3 Hz, 0.5H), 4.18 (br. s., 1H), 3.92 (t, J=12.5 Hz, 2H), 3.83 (s, 3H), 3.67-3.78 (m, 2.5H), 3.46-3.60 (m, 0.5H), 3.37 (s, 3H), 3.00-3.16 (m, 1.5H), 2.80-2.99 (m, 1H), 2.61-2.80 (m, 1H), 2.42-2.61 (m, 2H), 1.39 (d, J=6.5 Hz, 1.5H), 1.29 (d, J=6.8 Hz, 1.5H), 0.92-1.14 (m, 4H)

[1548] LC-MS: m/z 465.2 $(M+H)^+$

Compound 292 (General Procedure 8)

(R)-methyl 3-((5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yloxy)methyl)benzoate

[1549] ^{1}H NMR (CHLOROFORM-d) δ 8.11 (s, 1H), 8.04 (d, J=7.8 Hz, 1H), 7.63 (d, J=7.5 Hz, 1H), 7.50 (t, J=7.7 Hz, 1H), 7.19 (s, 1H), 5.07 (s, 2H), 4.88 (br. s., 0.5H), 4.51 (d, J=13.6 Hz, 0.5H), 4.18 (br. s., 0.5H), 3.94 (s, 3H), 3.83-4.02 (m, 2H), 3.64-3.80 (m, 2.5H), 3.52 (br. s., 0.5H), 3.37 (s, 3H), 3.09 (t, J=13.6 Hz, 1.5H), 2.82-3.01 (m, 1H), 2.62-2.80 (m, 1H), 2.41-2.62 (m, 2H), 1.39 (d, J=6.5 Hz, 1.5H), 1.29 (d, J=6.8 Hz, 1.5H), 0.98-1.15 (m, 4H)

[1550] LC-MS: m/z 493.2 $(M+H)^+$

Compound 293 (General Procedure 8)

(R)-methyl 4-((5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yloxy)methyl)benzoate

[1551] ^{1}H NMR (CHLOROFORM-d) δ 8.01-8.14 (m, 2H), 7.44-7.56 (m, J=8.5 Hz, 2H), 7.18 (s, 1H), 5.10 (s, 2H), 4.88 (br. s., 0.5H), 4.51 (d, J=13.6 Hz, 0.5H), 4.19 (br. s., 0.5H), 3.93 (s, 3H), 3.82-4.02 (m, 2H), 3.66-3.81 (m, 2.5H), 3.46-3.60 (m, 0.5H), 3.37 (s, 3H), 3.10 (t, J=13.7 Hz, 1.5H), 2.82-3.01 (m, 1H), 2.62-2.79 (m, 1H), 2.43-2.62 (m, 2H), 1.39 (d, J=6.5 Hz, 1.5H), 1.27-1.34 (m, 1.5H), 0.96-1.17 (m, 4H)

[1552] LC-MS: m/z 493.2 $(M+H)^+$

Compound 294 (General Procedure 8)

(R)-5-(3-cyanobenzyloxy)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1553] ^{1}H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.61-7.71 (m, 2H), 7.54 (t, J=7.9 Hz, 1H), 7.17 (s, 1H), 5.06 (s, 2H), 4.88 (br. s., 0.5H), 4.52 (d, J=13.6 Hz, 0.5H), 4.21 (br. s., 0.5H), 3.85-4.06 (m, 2H), 3.74 (br. s., 2.5H), 3.54 (br. s., 0.5H), 3.37 (s, 3H), 3.04-3.21 (m, 1.5H), 2.84-3.04 (m, 1H), 2.55-2.81 (m, 2H), 2.40-2.51 (m, 1H), 1.39 (d, J=5.5 Hz, 1.5H), 1.30 (d, J=6.3 Hz, 1.5H), 0.98-1.16 (m, 4H)

[1554] LC-MS: m/z 460.2 $(M+H)^+$

Compound 301 (General Procedure 8)

(R)-6-cyclopropyl-5-(4-(hydroxymethyl)benzyloxy)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1555] ^{1}H NMR (CHLOROFORM-d) δ 7.35-7.49 (m, 4H), 7.18 (s, 5.04 (s, 2H), 4.81-4.91 (m, 0.5H), 4.73 (s, 2H), 4.50 (d, J=13.3 Hz, 0.5H), 4.18 (br. s., 0.5H), 3.81-4.00 (m, 2H), 3.64-3.81 (m, 2.5H), 3.45-3.60 (m, 0.5H), 3.37 (s, 3H), 3.00-3.17 (m, 1.5H), 2.81-2.99 (m, 1H), 2.61-2.79 (m, 1H), 2.43-2.61 (m, 2H), 1.92-2.08 (m, 1H), 1.31-1.41 (m, 3H), 0.97-1.14 (m, 4H)

[1556] LC-MS: m/z 465.2 $(M+H)^+$

Compound 302 (General Procedure 8)

6-cyclopropyl-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-methyl-1-phenylpropoxy)nicotinonitrile

[1557] ^{1}H NMR (CHLOROFORM-d) δ 7.27-7.39 (m, 5H), 6.87 (d, J=1.5 Hz, 1H), 4.84 (br. s., 0.5H), 4.66-4.74 (m, 1H), 4.47 (d, J=13.3 Hz, 0.5H), 4.14 (br. s., 0.5H), 3.63-3.90 (m, 4.5H), 3.40-3.57 (m, 0.5H), 3.35 (s, 3H), 2.93-3.12 (m, 1.5H), 2.76-2.93 (m, 1H), 2.47-2.75 (m, 3H), 2.18 (dq, J=13.3, 6.6 Hz, 1H), 1.19-1.39 (m, 3H), 1.00-1.11 (m, 7H), 0.87-0.97 (m, 3H)

[1558] LC-MS: m/z 477.2 $(M+H)^+$

Compound 303 (General Procedure 8)

6-cyclopropyl-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-((S)-1-phenylethoxy)nicotinonitrile

[1559] ^{1}H NMR (CHLOROFORM-d) δ 7.27-7.42 (m, 5H), 6.91-7.00 (m, 1H), 5.15 (q, J=6.5 Hz, 1H), 4.85 (br. s., 0.5H), 4.48 (d, J=13.6 Hz, 0.5H), 4.15 (br. s., 0.5H), 3.78-3.95 (m, 2H), 3.61-3.77 (m, 2.5H), 3.43-3.57 (m, 0.5H), 3.36 (s, 3H), 2.96-3.13 (m, 1.5H), 2.85 (td, J=12.4, 2.8 Hz, 1H), 2.48-2.76 (m, 3H), 1.67 (d, J=6.5 Hz, 3H), 1.36 (d, J=6.5 Hz, 1.5H), 1.21-1.28 (m, 1.5H), 0.97-1.13 (m, 4H)

[1560] LC-MS: m/z 449.2 $(M+H)^+$

Compound 304 (General Procedure 8)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(pyridin-3-ylmethoxy)nicotinonitrile

[1561] ^{1}H NMR (CHLOROFORM-d) δ 8.70 (s, 1H), 8.63 (d, J=3.8 Hz, 1H), 7.79 (dt, J=7.8, 1.9 Hz, 1H), 7.37 (dd, J=7.8, 4.8 Hz, 1H), 7.24 (s, 1H), 5.06 (s, 2H), 4.88 (br. s., 0.5H), 4.51 (d, J=12.5 Hz, 0.5H), 4.20 (br. s., 0.5H), 3.83-4.04 (m, 2H), 3.63-3.83 (m, 2.5H), 3.53 (br. s., 0.5H), 3.37 (s, 3H), 3.03-3.17 (m, 1.5H), 2.84-3.02 (m, 1H), 2.62-2.78 (m, 1H), 2.51-2.62 (m, 1H), 2.39-2.51 (m, 1H), 1.36-1.43 (m, 2H), 1.27-1.34 (m, 2H), 0.91-1.15 (m, 4H)

[1562] LC-MS: m/z 436.2 $(M+H)^+$

Compound 307 (General Procedure 8)

6-cyclopropyl-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-((R)-1-phenylethoxy)nicotinonitrile

[1563] ^{1}H NMR (CHLOROFORM-d) δ 7.27-7.42 (m, 5H), 6.92-6.98 (m, 1H), 5.15 (q, J=6.4 Hz, 1H), 4.84 (br. s., 0.5H), 4.49 (d, J=13.6 Hz, 0.5H), 4.15 (br. s., 0.5H), 3.77-3.95 (m, 2H), 3.72 (t, J=6.3 Hz, 2.5H), 3.43-3.56 (m, 0.5H), 3.36 (s, 3H), 2.97-3.13 (m, 1.5H), 2.78-2.95 (m, 1H), 2.48-2.78 (m, 3H), 1.67 (d, J=6.3 Hz, 3H), 1.36 (d, J=6.8 Hz, 1.5H), 1.26 (d, J=5.5 Hz, 1.5H), 0.97-1.14 (m, 4H)

[1564] LC-MS: m/z 449.2 $(M+H)^+$

Compound 308 (General Procedure 8)

6-cyclopropyl-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(1-phenylpropoxy)nicotinonitrile

[1565] ^{1}H NMR (CHLOROFORM-d) δ 7.28-7.42 (m, 5H), 6.92 (d, J=2.3 Hz, 1H), 4.78-4.95 (m, 1.5H), 4.48 (d, J=13.3 Hz, 0.5H), 4.14 (br. s., 0.5H), 3.77-3.93 (m, 2H), 3.65-3.77 (m, 2.5H), 3.48 (br. s., 0.5H), 3.36 (s, 3H), 2.95-3.12 (m, 1.5H), 2.76-2.95 (m, 1H), 2.46-2.76 (m, 3H), 2.00-2.13 (m, 1H), 1.84-1.98 (m, 1H), 1.36 (d, J=6.8 Hz, 1.5H), 1.25-1.29 (m, 1.5H), 0.92-1.12 (m, 7H)

[1566] LC-MS: m/z 463.2 $(M+H)^+$

Compound 309 (General Procedure 8)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(pyridin-4-ylmethoxy)nicotinonitrile

[1567] ^{1}H NMR (CHLOROFORM-d) δ 8.67 (d, J=5.8 Hz, 2H), 7.39 (d, J=5.8 Hz, 2H), 7.17 (s, 1H), 5.07 (s, 2H), 4.79-4.95 (m, 0.5H), 4.51 (d, J=13.6 Hz, 0.5H), 4.19 (br. s., 0.5H), 3.86-4.04 (m, 2H), 3.62-3.81 (m, 2.5H), 3.45-3.59 (m, 0.5H), 3.37 (s, 3H), 3.03-3.18 (m, 1.5H), 2.83-3.02 (m, 1H), 2.62-2.79 (m, 1H), 2.43-2.61 (m, 2H), 1.39 (d, J=6.8 Hz, 1.5H), 1.27-1.31 (m, 1.5H), 0.99-1.15 (m, 4H)

[1568] LC-MS: m/z 436.2 $(M+H)^+$

Compound 310 (General Procedure 8)

5-(1-(3-chlorophenyl)ethoxy)-6-cyclopropyl-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile

[1569] ^{1}H NMR (CHLOROFORM-d) δ 7.33-7.38 (m, 1H), 7.27-7.33 (m, 3H), 7.19-7.25 (m, 1H), 6.96 (d, J=4.5 Hz, 1H), 5.11 (q, J=6.3 Hz, 1H), 4.85 (br. s., 0.5H), 4.49 (d, J=13.6 Hz, 0.5H), 4.16 (br. s., 0.5H), 3.78-3.97 (m, 2H), 3.63-3.78 (m, 2.5H), 3.49 (br. s., 0.5H), 3.36 (s, 3H), 2.98-3.14 (m, 1.5H), 2.79-2.97 (m, 1H), 2.60-2.77 (m, 1H), 2.46-2.60 (m, 2H), 1.65 (d, J=6.3 Hz, 3H), 1.36 (d, J=6.5 Hz, 1.5H), 1.26 (d, J=7.8 Hz, 1.5H), 0.98-1.15 (m, 4H)

[1570] LC-MS: m/z 483.2 $(M+H)^+$

Compound 311 (General Procedure 8)

5-(1-(4-chlorophenyl)ethoxy)-6-cyclopropyl-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile

[1571] ^{1}H NMR (CHLOROFORM-d) δ 7.23-7.40 (m, 4H), 6.95 (d, J=3.8 Hz, 1H), 5.13 (q, J=6.1 Hz, 1H), 4.85 (br. s., 0.5H), 4.49 (d, J=13.1 Hz, 0.5H), 4.16 (br. s., 0.5H), 3.79-3.98 (m, 2H), 3.63-3.78 (m, 2.5H), 3.42-3.57 (m, 0.5H), 3.36 (s, 3H), 2.98-3.13 (m, 1.5H), 2.77-2.97 (m, 1H), 2.60-2.76 (m, 1H), 2.43-2.60 (m, 2H), 1.65 (d, J=6.3 Hz, 3H), 1.33-1.39 (m, 1.5H), 1.22-1.29 (m, 1.5H), 0.97-1.13 (m, 4H)

[1572] LC-MS: m/z 483.2 $(M+H)^+$

Compound 312 (General Procedure 8)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-nitrobenzyloxy)nicotinonitrile

[1573] ^{1}H NMR (CHLOROFORM-d) δ 8.33 (s, 1H), 8.24 (dd, J=8.2, 1.2 Hz, 1H), 7.72-7.84 (m, 1H), 7.54-7.67 (m, 1H), 7.21 (s, 1H), 5.13 (s, 2H), 4.88 (br. s., 0.5H), 4.51 (d, J=13.7 Hz, 0.5H), 4.19 (br. s., 0.5H), 3.86-4.03 (m, 2H), 3.63-3.84 (m, 2.5H), 3.53 (br. s., 0.5H), 3.37 (s, 3H), 3.04-3.18 (m, 1.5H), 2.84-3.04 (m, 1H), 2.62-2.78 (m, 1H), 2.42-2.61 (m, 2H), 1.39 (d, J=6.7 Hz, 1.5H), 1.29 (d, J=6.7 Hz, 1.5H), 0.97-1.19 (m, 4H)

[1574] LC-MS: m/z 480.2 $(M+H)^+$

Compound 341 (General Procedure 8)

(R)-5-(3-aminobenzyloxy)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1575] ^{1}H NMR (CHLOROFORM-d) δ 7.13-7.24 (m, 2H), 6.79 (d, J=7.8 Hz, 1H), 6.74 (s, 1H), 6.67 (dd, J=8.0, 1.5 Hz, 1H), 4.95 (s, 2H), 4.87 (br. s., 0.5H), 4.50 (d, J=13.6 Hz, 0.5H), 4.17 (br. s., 0.5H), 3.81-3.98 (m, 2H), 3.73 (t, J=6.1 Hz, 2.5H), 3.53 (d, J=8.8 Hz, 0.5H), 3.37 (s, 3H), 3.01-3.16 (m, 1.5H), 2.81-3.00 (m, 1H), 2.61-2.79 (m, 1H), 2.46-2.61 (m, 2H), 1.39 (d, J=6.5 Hz, 1.5H), 1.29 (d, J=6.5 Hz, 1.5H), 0.95-1.14 (m, 4H)

[1576] LC-MS: m/z 450.2 $(M+H)^+$

Compound 381 (General Procedure 8)

(R)—N-(3-((5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yloxy)methyl)phenyl)acrylamide

[1577] ^{1}H NMR (CHLOROFORM-d) δ 8.11 (br. s., 1H), 7.82 (br. s., 1H), 7.52 (d, J=8.3 Hz, 1H), 7.35 (t, J=7.8 Hz, 1H), 7.13-7.23 (m, 2H), 6.45 (dd, J=16.8, 1.3 Hz, 1H), 6.31 (dd, J=16.8, 10.0 Hz, 1H), 5.76 (dd, J=10.2, 1.4 Hz, 1H), 4.99 (s, 2H), 4.86 (br. s., 0.5H), 4.50 (d, J=13.6 Hz, 0.5H), 4.18 (br. s., 0.5H), 3.81-3.99 (m, 2H), 3.72 (t, J=6.0 Hz, 2.5H), 3.45-3.59 (m, 0.5H), 3.35 (s, 3H), 3.00-3.16 (m, 1.5H), 2.81-2.99 (m, 1H), 2.62-2.79 (m, 1H), 2.41-2.62 (m, 2H), 1.39 (d, J=6.8 Hz, 1.5H), 1.25-1.32 (m, 1.5H), 0.94-1.15 (m, 4H)

[1578] LC-MS: m/z 504.2 $(M+H)^+$

Compound 382 (General Procedure 8)

(R)-2-bromo-N-(3-((5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yloxy)methyl)phenyl)acetamide

[1579] ^{1}H NMR (CHLOROFORM-d) δ 8.52 (s, 1H), 7.73 (s, 1H), 7.48 (d, J=8.0 Hz, 1H), 7.38 (t, J=7.8 Hz, 1H), 7.12-7.26 (m, 2H), 5.02 (s, 2H), 4.87 (br. s., 0.5H), 4.50 (d, J=13.3 Hz, 0.5H), 4.19 (d, J=8.5 Hz, 0.5H), 4.03 (s, 2H), 3.81-3.99 (m, 2H), 3.64-3.81 (m, 2.5H), 3.45-3.61 (m, 0.5H), 3.36 (s, 3H), 3.02-3.18 (m, 1.5H), 2.82-3.02 (m, 1H), 2.62-2.80 (m, 1H), 2.42-2.62 (m, 2H), 1.39 (d, J=6.5 Hz, 1.5H), 1.22-1.33 (m, 1.5H), 0.95-1.14 (m, 4H)

[1580] LC-MS: m/z 570.1 $(M+H)^+$

Compound 388 (General Procedure 8)

6-cyclopropyl-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(1-(pyridin-4-yl)ethoxy) nicotinonitrile

[1581] ^{1}H NMR (CHLOROFORM-d) δ 8.57-8.70 (m, 2H), 7.33 (d, J=6.0 Hz, 2H), 6.96 (d, J=3.3 Hz, 1H), 5.17 (q, J=6.4 Hz, 1H), 4.86 (br. s., 0.5H), 4.49 (d, J=12.8 Hz, 0.5H), 4.17 (br. s., 0.5H), 3.81-4.05 (m, 2H), 3.63-3.81 (m, 2.5H), 3.51 (d, J=15.3 Hz, 0.5H), 3.36 (s, 3H), 3.07 (t, J=12.9 Hz, 1.5H), 2.81-3.00 (m, 1H), 2.60-2.78 (m, 1H), 2.46-2.60 (m, 2H), 1.67 (d, J=6.5 Hz, 3H), 1.36 (d, J=5.0 Hz, 1.5H), 1.24-1.28 (m, 1.5H), 0.99-1.16 (m, 4H)

[1582] LC-MS: m/z 450.2 $(M+H)^+$

Compound 389 (General Procedure 8)

N-(4-(1-(5-cyano-2-cyclopropyl-6-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yloxy)ethyl)phenyl)acrylamide

[1583] ^{1}H NMR (CHLOROFORM-d) δ 8.03 (br. s., 1H), 7.56-7.64 (m, 2H), 7.30 (d, J=8.3 Hz, 2H), 6.90-7.05 (m, 1H), 6.43 (dd, J=16.8, 1.3 Hz, 1H), 6.29 (dd, J=16.8, 10.0 Hz, 1H), 5.74 (dd, J=10.0, 1.3 Hz, 1H), 5.05-5.19 (m, 1H), 4.85 (br. s., 0.5H), 4.48 (d, J=12.5 Hz, 0.5H), 4.16 (br. s., 0.5H), 3.65-3.95 (m, 5.5H), 3.50 (d, J=11.3 Hz, 0.5H), 3.34 (s, 3H), 2.97-3.14 (m, 1.5H), 2.77-2.95 (m, 1H), 2.61-2.77 (m, 1H), 2.47-2.61 (m, 2H), 1.65 (d, J=6.3 Hz, 3H), 1.36 (d, J=6.5 Hz, 1.5H), 1.26 (d, J=5.0 Hz, 1.5H), 0.97-1.15 (m, 4H)

[1584] LC-MS: m/z 518.2 $(M+H)^+$

Compound 400 (General Procedure 8)

(R,E)-N-(3-((5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yloxy)methyl)phenyl)but-2-enamide

[1585] ^{1}H NMR (CHLOROFORM-d) δ 7.75 (br. s., 1H), 7.47 (d, J=8.0 Hz, 1H), 7.30-7.40 (m, 2H), 7.10-7.23 (m, 2H), 6.88-7.09 (m, 1H), 5.96 (dd, J=15.1, 1.5 Hz, 1H), 5.01 (s, 2H), 4.87 (br. s., 0.5H), 4.50 (d, J=13.6 Hz, 0.5H), 4.18 (br. s., 0.5H), 3.82-4.00 (m, 2H), 3.64-3.80 (m, 2.5H), 3.46-3.62 (m, 0.5H), 3.36 (s, 3H), 3.01-3.16 (m, 1.5H), 2.83-3.01 (m, 1H), 2.62-2.77 (m, 1H), 2.44-2.61 (m, 2H), 1.93 (dd, J=6.9, 1.6 Hz, 3H), 1.39 (d, J=6.5 Hz, 1.5H), 1.29 (d, J=7.0 Hz, 1.5H), 0.95-1.13 (m, 4H)

[1586] LC-MS: m/z 518.2 $(M+H)^+$

Compound 407 (General Procedure 8)

N-(3-(1-(5-cyano-2-cyclopropyl-6-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yloxy)ethyl)phenyl)acrylamide

[1587] ^{1}H NMR (CHLOROFORM-d) δ 7.75 (br. s., 1H), 7.63 (br. s., 1H), 7.46 (br. s., 1H), 7.34 (t, J=7.8 Hz, 1H), 7.13 (d, J=7.5 Hz, 1H), 6.94-7.01 (m, 1H), 6.46 (dd, J=16.8, 1.3 Hz, 1H), 6.28 (dd, J=16.9, 10.2 Hz, 1H), 5.79 (dd, J=10.3, 1.0 Hz, 1H), 5.13 (q, J=6.1 Hz, 1H), 4.86 (br. s., 0.5H), 4.49 (d, J=13.3 Hz, 0.5H), 4.17 (br. s., 0.5H), 3.78-3.95 (m, 2H), 3.63-3.78 (m, 2.5H), 3.52 (d, J=14.6 Hz, 0.5H), 3.37 (s, 3H), 2.98-3.14 (m, 1.5H), 2.79-2.97 (m, 1H), 2.63-2.78 (m, 1H), 2.48-2.63 (m, 2H), 1.68 (d, J=6.3 Hz, 3H), 1.38 (d, J=6.3 Hz, 1.5H), 1.24-1.30 (m, 1.5H), 1.00-1.14 (m, 4H)

[1588] LC-MS: m/z 518.2 $(M+H)^+$

Compound 827 (General Procedure 6)

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-hexanoylpiperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1589] ^{1}H NMR (CHLOROFORM-d) δ 8.69 (d, J=4.7 Hz, 1H), 7.23 (s, 1H), 7.07 (d, J=4.7 Hz, 1H), 6.87 (dd, J=17.6, 10.9 Hz, 1H), 6.19-6.36 (m, 1H), 5.47-5.63 (m, 1H), 4.34 (d, J=12.9 Hz, 1H), 4.26 (d, J=12.6 Hz, 1H), 4.10 (br. s., 0.65H), 3.64-3.91 (m, 1.35H), 2.88-3.38 (m, 2H), 2.37 (br. s., 2H), 2.21 (s, 3H), 1.61-1.73 (m, 2H), 1.51-1.61 (m, 1H), 1.44 (br. s., 1H), 1.35 (br. s., 4H), 1.04-1.17 (m, 2H), 0.90-0.98 (m, 3H), 0.87 (dd, J=8.1, 3.1 Hz, 2H), 0.60 (br. s., 1H), 0.55 (br. s., 1H), 0.23-0.50 (m, 2H)

[1590] LC-MS: m/z 484.3 $(M+H)^+$

Compound 826 (General Procedure 6)

(R)-6-(4-(3-cyclobutylpropanoyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1591] ^{1}H NMR (CHLOROFORM-d) δ 8.70 (d, J=5.0 Hz, 1H), 7.25 (s, 1H), 7.09 (d, J=4.7 Hz, 1H), 6.88 (dd, J=17.6, 10.9 Hz, 1H), 6.28 (d, J=17.6 Hz, 1H), 5.51-5.64 (m, 1H), 4.34 (d, J=12.9 Hz, 1H), 4.26 (d, J=12.0 Hz, 1H), 4.09 (br. s., 0.6H), 3.63-3.92 (m, 1.4H), 3.01-3.13 (m, 2H), 2.25-2.38 (m, 2H), 2.22 (s, 3H), 2.00-2.13 (m, 4H), 1.82-1.90 (m, 2H), 1.75 (q, J=7.4 Hz, 2H), 1.61-1.69 (m, 2H), 1.56 (td, J=8.3, 4.0 Hz, 1H), 1.12 (br. s., 2H), 0.80-0.94 (m, 2H), 0.61 (br. s., 1H), 0.55 (br. s., 1H), 0.44 (br. s., 2H)

[1592] LC-MS: m/z 496.3 $(M+H)^+$

Compound 825 (General Procedure 6)

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3-cyclopropylpropanoyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1593] ^{1}H NMR (CHLOROFORM-d) δ 8.72 (d, J=5.0 Hz, 1H), 7.26 (s, 1H), 7.09 (d, J=4.7 Hz, 1H), 6.89 (dd, J=17.6, 10.9 Hz, 1H), 6.27 (d, J=17.6 Hz, 1H), 5.52-5.65 (m, 1H), 4.34 (d, J=12.6 Hz, 1H), 4.26 (d, J=12.6 Hz, 1H), 4.02-4.17 (m, 0.6H), 3.71-3.95 (m, 1.4H), 2.95-3.4 (m, 2H), 2.45-2.56 (m, 1H), 2.36 (t, J=7.5 Hz, 3H), 2.22 (s, 3H), 1.63-1.70 (m, 2H), 1.11 (br. s., 2H), 0.75-0.89 (m, 3H), 0.51-0.74 (m, 3H), 0.34-0.50 (m, 4H), 0.10 (d, J=4.1 Hz, 2H)

[1594] LC-MS: m/z 482.2 $(M+H)^+$

Compound 582 (General Procedure 7)

(R)-5-((5-cyano-2-cyclopropyl-6-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)amino)picolinonitrile

[1595] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.17 (d, 1H), 7.61 (s, 1H), 7.51-7.49 (d, 1H), 6.89-6.86 (dd, 1H), 6.38 (s, 1H), 4.87 (s, 0.5H), 4.53-4.50 (d, 0.5H); 4.27-4.16 (dd, 2H) 3.92 (s, 2H) 3.75-3.10 (m, 4H) 2.69-2.51 (m, 2H), 2.07-2.02 (m, 1H), 1.41-1.26 (m, 3H), 1.43-1.10 (m, 2H), 1.04-1.01 (m, 2H).

[1596] LC-MS: m/z 432.2 $(M+H)^+$

Compound 577 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-((6-vinylpyridin-3-yl)amino)nicotinonitrile

[1597] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.14 (d, 1H), 7.58 (s, 1H), 7.26-7.23 (d, 1H), 6.97-6.94 (dd, 1H), 6.79-6.72 (q, 1H), 6.03-5.98 (dd, 1H), 5.58 (s, 1H), 5.36-5.33 (dd, 1H), 4.88 (s, 0.5H), 4.54-4.51 (d, 0.5H); 4.20-4.09 (dd, 2H) 3.93 (s, 2H) 3.75-3.52 (m, 2H) 3.25-2.98 (m, 3H), 2.71-2.50 (m, 2H), 2.18-2.10 (m, 1H), 1.41-1.26 (m, 3H), 1.43-1.30 (m, 2H), 1.13-1.11 (m, 2H), 1.03-1.09 (m, 2H).

[1598] LC-MS: m/z 433.2 $(M+H)^+$

Compound 298 (General Procedure 6)

(R)-6-cyclopropyl-5-(4-fluorophenyl)-4-(methoxymethyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile

[1599] ^{1}H NMR (CHLOROFORM-d) δ t: 7.21-7.27 (m, 2H), 7.11-7.19 (m, 2H), 4.85-4.95 (s, 0.5H), 4.45-4.57 (m, 0.5H), 4.05-4.27 (m, 4H), 3.74 (t, J=6.4 Hz, 2.5H), 3.57-3.63 (m, 0.5H), 3.35-3.40 (m, 3H), 3.29 (s, 3H), 3.09-3.26 (m, 2H), 2.59 (br. s., 1H), 1.60-1.70 (m, 1H), 1.38-1.44 (m, 1H), 1.30 (d, J=6.8 Hz, 2H), 1.25 (s, 1H), 1.04-1.10 (m, 2H), 0.81-0.88 (m, 2H).

[1600] LC-MS: m/z 487.2 $(M+H)^+$

Compound 823 (General Procedure 6)

2-Cyclopropyl-6-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-4-ethyl-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1601] ^{1}H NMR (CHLOROFORM-d) δ 8.57-8.87 (m, 1H), 7.25 (s, 1H), 7.02-7.16 (m, 1H), 6.89 (dd, J=17.5, 10.7 Hz, 1H), 6.30 (d, J=17.3 Hz, 1H), 5.59 (d, J=10.9 Hz, 1H), 5.27 (t, J=6.6 Hz, 1H), 4.51-4.78 (m, 2H), 4.30-4.42 (m, 1H), 4.26 (d, J=11.4 Hz, 1H), 4.09 (d, J=9.1 Hz, 1H), 3.84-3.98 (m, 1H), 3.56-3.84 (m, 1H), 2.95-3.45 (m, 3H), 2.68-2.92 (m, 2H), 2.41-2.63 (m, 3H), 1.49-1.55 (m, 1H), 1.34 (d, J=8.2 Hz, 1H), 1.10 (t, J=7.6 Hz, 5H), 0.80-0.94 (m, 3H), 0.35-0.75 (m, 4H)

[1602] LC-MS: m/z 498.3 $(M+H)^+$

Compound 805 (General Procedure 6)

2-cyclopropyl-6-((3R)-3-cyclopropyl-4-(2-(tetrahydrofuran-2-yl)acetyl)piperazin-1-yl)-4-methyl-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1603] ^{1}H NMR (CHLOROFORM-d) δ 8.69 (d, J=5.0 Hz, 1H), 7.23 (s, 1H), 7.07 (d, J=5.0 Hz, 1H), 6.87 (dd, J=17.3, 10.9 Hz, 1H), 6.22-6.40 (m, 1H), 5.57 (dd, J=10.9, 0.9 Hz, 1H), 4.60-4.70 (m, 0.5H), 4.18-4.41 (m, 3H), 4.02-4.15 (m, 0.5H), 3.89 (d, J=7.3 Hz, 1.5H), 3.63-3.82 (m, 1.5H), 2.90-3.45 (m, 3H), 2.64-2.85 (m, 1H), 2.53 (dd, J=14.8, 6.0 Hz, 1H), 2.08-2.32 (m, 4H), 1.88-2.00 (m, 2H), 1.51-1.69 (m, 2H), 1.43 (d, J=13.8 Hz, 1H), 1.11 (s, 2H), 0.87 (dd, J=7.9, 2.9 Hz, 2H), 0.35-0.66 (m, 4H)

[1604] LC-MS: m/z 498.3 $(M+H)^+$

Compound 806 (General Procedure 6)

2-cyclopropyl-6-((3R)-3-cyclopropyl-4-(2-(5-oxotetrahydrofuran-2-yl)acetyl)piperazin-1-yl)-4-methyl-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1605] ^{1}H NMR (CHLOROFORM-d) δ 8.71 (d, J=4.7 Hz, 1H), 7.25 (s, 1H), 7.09 (d, J=4.7 Hz, 1H), 6.90 (dd, J=17.3, 10.9 Hz, 1H), 6.31 (d, J=17.3 Hz, 1H), 5.60 (d, J=11.2 Hz, 1H), 4.94-5.08 (m, 1H), 4.17-4.45 (m, 2H), 4.08 (s, 1H), 3.79 (s, 2H), 2.80-3.45 (m, 4H), 2.51-2.73 (m, 4H), 2.19-2.28 (m, 3H), 1.57 (td, J=8.1, 4.0 Hz, 1H), 1.12 (s, 3H), 0.88 (dd, J=7.9, 3.2 Hz, 3H), 0.25-0.74 (m, 4H)

[1606] LC-MS: m/z 512.3 $(M+H)^+$

Compound 808 (General Procedure 7)

2-(5-cyano-2-cyclopropyl-6-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)pyridin-3-ylamino)pyrimidine-4-carbonitrile

[1607] ^{1}H NMR (CHLOROFORM-d) δ: 8.59 (d, J=4.7 Hz, 1H), 7.87-8.13 (m, 1H), 7.00-7.17 (m, 2H), 5.10-5.32 (m, 2H), 4.67-4.83 (m, 1H), 4.47-4.63 (m, 1H), 4.39 (d, J=11.7 Hz, 1H), 4.30 (d, J=12.3 Hz, 1H), 4.08 (d, J=7.3 Hz, 1H), 3.92 (d, J=12.9 Hz, 1H), 3.64-3.84 (m, 1H), 3.18-3.45 (m, 1H), 2.93-3.18 (m, 3H), 2.54 (d, J=6.7 Hz, 1H), 1.94-2.14 (m, 2H), 1.86 (br. s., 2H), 1.46 (d, J=8.2 Hz, 1H), 1.39 (br. s., 1H), 1.33 (br. s., 1H), 1.27 (s, 1H), 0.97-1.23 (m, 4H), 0.63 (br. s., 1H), 0.54 (br. s., 1H), 0.27-0.50 (m, 2H).

[1608] LC-MS: m/z 485.2 $(M+H)^+$

Compound 809 (General Procedure 7)

5-(4-cyanopyridin-2-ylamino)-6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)nicotinonitrile

[1609] ^{1}H NMR (CHLOROFORM-d) δ: 8.65 (d, J=5.3 Hz, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 7.24 (dd, J=5.0, 1.5 Hz, 1H), 6.88 (dd, J=17.3, 10.9 Hz, 1H), 6.20-6.35 (m, 1H), 5.51-5.65 (m, 1H), 4.55 (d, J=12.9 Hz, 1H), 4.29-4.48 (m, 1H), 4.05-4.29 (m, 2H), 4.00 (br. s., 1H), 3.80 (br. s., 1H), 3.62-3.77 (m, 1H), 3.54 (br. s., 2H), 3.22 (d, J=12.6 Hz, 2H), 3.09 (t, J=10.9 Hz, 1H), 2.40-2.54 (m, 3H), 2.01-2.17 (m, 4H), 1.15-1.45 (m, 11H), 0.94-1.10 (m, 3H), 0.74-0.94 (m, 2H), 0.65 (br. s., 2H), 0.47 (br. s., 3H).

[1610] LC-MS: m/z 484.2 $(M+H)^+$

Compound 803 (General Procedure 6)

2-cyclopropyl-6-((3R)-3-cyclopropyl-4-(3-(oxetan-2-yl)propanoyl)piperazin-1-yl)-4-methyl-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1611] ^{1}H NMR (CHLOROFORM-d) δ 8.69 (d, J=5.0 Hz, 1H), 7.23 (s, 1H), 7.07 (d, J=3.8 Hz, 1H), 6.87 (dd, J=17.3, 10.9 Hz, 1H), 6.29 (d, J=17.3 Hz, 1H), 5.45-5.62 (m, 1H), 4.88 (s, 1H), 4.64-4.74 (m, 1H), 4.54 (dt, J=8.8, 5.9 Hz, 1H), 4.33 (d, J=12.6 Hz, 1H), 4.18-4.29 (m, 1H), 4.03-4.15 (m, 1H), 3.60-3.90 (m, 1H), 3.09-3.39 (m, 2H), 2.94-3.09 (m, 1H), 2.66-2.78 (m, 1H), 2.25-2.60 (m, 3H), 2.21 (s, 3H), 2.01-2.14 (m, 2H), 1.51-1.68 (m, 1H), 1.43 (d, J=12.9 Hz, 1H), 1.00-1.16 (m, 2H), 0.87 (dd, J=7.9, 2.9 Hz, 2H), 0.25-0.65 (m, 4H)

[1612] LC-MS: m/z 498.3 $(M+H)^+$

Compound 802 (General Procedure 5)

2-cyclopropyl-6-((3R)-3-cyclopropyl-4-(2-(5-oxotetrahydrofuran-2-yl)acetyl)piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1613] ^{1}H NMR (CHLOROFORM-d) δ 8.67 (d, J=5.0 Hz, 1H), 7.60-7.71 (m, 1H), 7.40 (s, 1H), 7.21-7.27 (m, 1H), 6.89 (dd, J=17.5, 10.7 Hz, 1H), 6.29 (d, J=17.3 Hz, 1H), 5.58 (d, J=10.9 Hz, 1H), 4.94-5.06 (m, 1H), 4.35-4.75 (m, 2.5H), 4.01-4.09 (m, 0.5H), 3.70-3.81 (m, 1.5H), 2.90-3.40 (m, 3.5H), 2.50-2.79 (m, 4H), 1.98-2.04 (m, 1H), 1.29-1.37 (m, 2H), 1.22 (dt, J=7.0, 3.5 Hz, 2H), 0.97-1.06 (m, 2H), 0.26-0.70 (m, 4H)

[1614] LC-MS: m/z 498.2 $(M+H)^+$

Compound 801 (General Procedure 5)

2-cyclopropyl-6-((3R)-3-cyclopropyl-4-(2-(tetrahydrofuran-2-yl)acetyl)piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile

[1615] ^{1}H NMR (CHLOROFORM-d) δ 8.65 (d, J=5.0 Hz, 1H), 7.64 (s, 1H), 7.39 (s, 1H), 7.23 (d, J=4.7 Hz, 1H), 6.88 (dd, J=17.6, 10.9 Hz, 1H), 6.28 (d, J=17.6 Hz, 1H), 5.56 (d, J=10.9 Hz, 1H), 4.50-4.62 (m, 1H), 4.43 (d, J=12.9 Hz, 1H), 4.21-4.35 (m, 1H), 4.05-4.11 (m, 1H), 3.80-3.92 (m, 1.5H), 3.62-3.80 (m, 1.5H), 3.07-3.41 (m, 3H), 2.45-2.97 (m, 2H), 2.15-2.20 (m, 1H), 1.98-2.05 (m, 2H), 1.92 (dt, J=14.2, 6.9 Hz, 2H), 1.62 (d, J=7.3 Hz, 1H), 1.16-1.24 (m, 2H), 1.00 (dd, J=7.5, 3.4 Hz, 2H), 0.34-0.71 (m, 4H)

[1616] LC-MS: m/z 484.3 $(M+H)^+$

Compound 824 (General Procedure 7)

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-5-((2-(hydroxymethyl)pyridin-4-yl)amino)nicotinonitrile

[1617] ^{1}H NMR (400 MHz, MeOD) δ 8.08 (d, J=6.5 Hz, 1H), 7.80 (d, J=2.2 Hz, 1H), 6.81 (d, J=2.0 Hz, 1H), 6.71 (dd, J=6.4, 2.3 Hz, 1H), 6.18-6.11 (m, 1H), 5.62 (dd, J=6.8, 5.5 Hz, 1H), 5.24 (s, 1H), 4.66 (d, J=7.0 Hz, 3H), 4.51 (d, J=13.1 Hz, 1H), 4.37 (s, 1H), 4.14-3.97 (m, 1H), 3.71 (dd, J=10.8, 4.4 Hz, 2H), 3.62 (s, 1H), 3.18-3.04 (m, 1H), 2.84 (s, 1H), 2.49 (d, J=6.5 Hz, 1H), 2.17-2.09 (m, 1H), 1.96 (s, 1H), 1.53-1.25 (m, 3H), 1.21-1.13 (m, 2H), 1.04 (dd, J=7.7, 3.4 Hz, 2H), 0.71-0.36 (m, 4H).

[1618] LC-MS: m/z 489.2 $(M+H)^+$

Compound 810 (General Procedure 5)

Sodium (R)-3-(4-(5-cyano-2-cyclopropyl-2'-vinyl-[3,4'-bipyridin]-6-yl)-2-cyclopropylpiperazin-1-yl)-3-oxopropyl phosphate

[1619] ^{1}H NMR (400 MHz, D_2O) δ 8.37 (d, J=5.0 Hz, 1H), 7.61 (s, 1H), 7.40 (s, 1H), 7.26 (s, 1H), 6.74 (dd, J=17.5, 11.3 Hz, 1H), 6.04 (d, J=17.8 Hz, 1H), 5.51 (d, J=11.2 Hz, 1H), 4.47 (s, 1H), 4.35 (s, 2H), 3.91 (d, J=6.7 Hz, 3H), 3.82 (s, 1H), 3.56 (q, J=7.1 Hz, 2H), 3.20 (s, 1H), 2.78 (s, 1H), 2.71-2.63 (m, 1H), 1.92 (s, 1H), 1.55 (s, 4H), 1.18 (s, 2H), 0.89 (s, 1H), 0.45-0.46 (m, 2H), 0.37-0.22 (m, 2H).

[1620] LC-MS: m/z 568.2 $(M+H)^+$

Compound 828 (General Procedure 7)

[1621] 1H NMR (CHLOROFORM-d) δ 8.07 (d, J=5.3 Hz, 1H), 7.81 (s, 1H), 7.02 (br. s., 1H), 6.71-6.84 (m, 1H), 6.55 (dd, J=17.6, 10.9 Hz, 1H), 6.38 (s, 1H), 5.86 (d, J=17.6 Hz, 1H), 5.42 (d, J=11.2 Hz, 1H), 4.18-4.44 (m, 3H), 4.11 (q, J=7.0 Hz, 1H), 3.81-3.99 (m, 2H), 3.62-3.81 (m, 2H), 3.11 (d, J=12.9 Hz, 2H), 3.04 (m, 1H), 2.73 (d, J=6.5 Hz, 1H), 2.08-2.28 (m, 2H), 1.82-1.97 (m, 2H), 1.59 (dd, J=12.0, 7.9 Hz, 1H), 1.25 (t, J=7.0 Hz, 1H), 1.04-1.18 (m, 2H), 0.88-1.02 (m, 2H), 0.51-0.59 (m, 2H), 0.42-0.49 (m, 2H)

[1622] LC-MS: m/z 499.2 $(M+H)^+$

Compound 829 (General Procedure 7)

[1623] 1H NMR (CHLOROFORM-d) δ 7.56 (s, 1H), 7.14 (d, J=7.3 Hz, 1H), 6.11 (br, s, 1H), 5.79 (dd, J=7.3, 2.3 Hz, 1H), 5.58 (br. s., 1H), 5.26 (t, J=6.6 Hz, 1H), 4.71 (td, J=7.9, 6.2 Hz, 1H), 4.56 (m, 1H), 4.43 (d, J=12.3 Hz, 1H), 4.32 (d, J=12.6 Hz, 1H), 4.06 (d, J=9.1 Hz, 0.5H), 3.92 (d, J=12.3 Hz, 0.5H), 3.69-3.82 (m, 1H), 3.47 (s, 3H), 3.08-3.34 (m, 2H), 2.92-3.08 (m, 2.5H), 2.78-2.90 (m, 1.5H), 2.54 (d, J=7.3 Hz, 1H), 2.06-2.17 (m, 1H), 1.27 (s, 1H), 1.06-1.16 (m, 2H), 0.98-1.05 (m, 2H), 0.53-0.63 (m, 2H), 0.30-0.49 (m, 2H)

[1624] LC-MS: m/z 489.2 $(M+H)^+$

Compound 830 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-hexanoylpiperazin-1-yl)-5-(4-vinylpyridin-2-ylamino)nicotinonitrile

[1625] ^{1}H NMR (CHLOROFORM-d) δ 8.02 (d, J=4.4 Hz, 1H), 7.72 (s, 1H), 6.82 (d, J=5.3 Hz, 1H), 6.56 (dd, J=17.3, 10.9 Hz, 1H), 6.34 (s, 1H), 5.90 (d, J=17.6 Hz, 1H), 5.49 (d, J=10.9 Hz, 1H), 4.40 (d, J=12.9 Hz, 1H), 4.29 (d, J=12.0 Hz, 1H), 4.11 (br. s., 1H), 3.80 (br. s., 2H), 3.16 (br. s., 2H), 2.90-3.11 (m, 1H), 2.25-2.45 (m, 5H), 1.56-1.73 (m, 4H), 1.20-1.48 (m, 4H), 1.07-1.20 (m, 2H), 0.82-1.07 (m, 2H).

[1626] LC-MS: m/z 485.2 $(M+H)^+$

Compound 818 (General Procedure 5)

[1627] ^{1}H NMR (CHLOROFORM-d) δ 8.66 (d, J=4.7 Hz, 1H), 7.66 (s, 1H), 7.41 (s, 1H), 7.22-7.28 (m, 1H), 6.90 (dd, J=17.3, 10.9 Hz, 1H), 6.31 (d, J=17.3 Hz, 1H), 5.60 (d, J=10.9 Hz, 1H), 4.55 (d, J=12.9 Hz, 1H), 4.43 (dd, J=12.9, 2.1 Hz, 1H), 4.14 (m, 2H), 3.72 (m, 1H), 3.43-3.63 (m, 2H), 3.22 (d, J=11.4 Hz, 2H), 3.01-3.16 (m, 2H), 2.06-2.11 (m, 1H), 1.79-2.09 (m, 1H), 1.65 (br. s., 1H), 1.40-1.53 (m, 1H), 1.17-1.25 (m, 2H), 0.96-1.08 (m, 2H), 0.66-0.75 (m, 2H), 0.39-0.61 (m, 2H)

[1628] LC-MS: m/z 483.7 $(M+H)^+$

Compound 821 (General Procedure 5)

[1629] 1H NMR (CHLOROFORM-d) δ 8.66 (d, J=5.3 Hz, 1H), 7.65 (s, 1H), 7.33-7.46 (m, 1H), 7.24 (dd, J=5.0, 1.5 Hz, 1H), 6.88 (dd, J=17.5, 10.7 Hz, 1H), 6.24-6.39 (m, 1H), 5.57 (dd, J=10.9, 1.2 Hz, 1H), 5.01 (t, J=6.3 Hz, 1H), 4.56 (m, 1.5H), 4.44 (d, J=14.1 Hz, 1H), 3.79 (m, 1H), 3.22 (m, 1.5H), 2.70 (d, J=6.7 Hz, 1H), 2.49-2.65 (m, 3H), 1.90-2.14 (m, 4H), 1.35 (m, 1H), 1.21 (m, 3H), 0.92-1.08 (m, 2H), 0.48 (m, 4H)

[1630] LC-MS: m/z 498.7 $(M+H)^+$

Compound 822 (General Procedure 5)

[1631] ^{1}H NMR (CHLOROFORM-d) δ 8.64 (d, J=4.7 Hz, 1H), 7.53 (s, 1H), 7.38 (s, 1H), 7.22 (dd, J=5.0, 1.5 Hz, 1H), 6.87 (dd, J=17.6, 10.9 Hz, 1H), 6.18-6.36 (m, 1H), 5.49-5.62 (m, 1H), 4.67-4.71 (m, 0.5H), 4.54 (d, J=12.6 Hz, 1H), 4.36-4.46 (m, 1H), 4.28 (quin, J=6.5 Hz, 1H), 4.11 (d, J=7.9 Hz, 0.5H), 3.81-4.00 (m, 1.5H), 3.63-3.79 (m, 1.5H), 3.08-3.20 (m, 1H), 2.64-2.85 (m, 2H), 2.46-2.60 (m, 1H), 2.08-2.24 (m, 1H), 1.97-2.08 (m, 1H), 1.82-1.97 (m, 2H), 1.52-1.70 (m, 1H), 1.26-1.30 (m, 2H), 1.12-1.24 (m, 2H), 0.92-1.05 (m, 2H), 0.49-0.73 (m, 2H), 0.45 (m, 2H)

[1632] LC-MS: m/z 484.7 $(M+H)^+$

Compound 811 (General Procedure 6)

[1633] ^{1}H NMR (CHLOROFORM-d) δ 7.23 (s, 1H), 7.07 (dd, J=5.0, 1.2 Hz, 1H), 6.87 (dd, J=17.5, 10.7 Hz, 1H), 6.29 (d, J=17.3 Hz, 1H), 5.57 (dd, J=10.9, 1.2 Hz, 1H), 4.32 (d, J=12.9 Hz, 1H), 4.23 (dd, J=12.6, 2.1 Hz, 1H), 4.14 (m, 1H), 3.99 (br. s., 1H), 3.72 (br. s., 1.5H), 3.42-3.57 (m, 2.5H), 3.10-3.25 (m, 2H), 2.98-3.10 (m, 3H), 2.10-2.38 (m, 4H), 1.51-1.62 (m, 1H), 1.45 (dq, J=14.7, 7.3 Hz, 1H), 1.07-1.17 (m, 2H), 0.88 (dd, J=7.9, 3.2 Hz, 2H), 0.66 (br. s., 1H), 0.30-0.59 (m, 3H)

[1634] LC-MS: m/z 497.7 $(M+H)^+$

Compound 814 (General Procedure 5)

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(2-(2-oxopyrrolidin-1-yl)acetyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1635] ^{1}H NMR (CHLOROFORM-d) δ 8.65 (d, J=5.3 Hz, 1H), 7.65 (s, 1H), 7.39 (s, 1H), 7.24 (dd, J=5.0, 1.5 Hz, 1H), 6.88 (dd, J=17.3, 10.9 Hz, 1H), 6.20-6.35 (m, 1H), 5.51-5.65 (m, 1H), 4.55 (d, J=12.9 Hz, 1H), 4.29-4.48 (m, 1H), 4.05-4.

29 (m, 2H), 4.00 (br. s., 1H), 3.80 (br. s., 1H), 3.62-3.77 (m, 1H), 3.54 (br. s., 2H), 3.22 (d, J=12.6 Hz, 2H), 3.09 (t, J=10.9 Hz, 1H), 2.40-2.54 (m, 3H), 2.01-2.17 (m, 4H), 1.15-1.45 (m, 4H), 0.94-1.10 (m, 3H), 0.74-0.94 (m, 2H), 0.65 (br. s., 2H), 0.47 (br. s., 3H).

[1636] LC-MS: m/z 497.2 $(M+H)^+$

Compound 815 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(4-hydroxybutanoyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[1637] ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J=5.5 Hz, 1H), 7.84 (s, 1H), 6.86 (dd, J=5.5, 1.1 Hz, 1H), 6.80 (s, 1H), 6.59 (dd, J=17.6, 10.9 Hz, 1H), 6.44 (s, 1H), 5.93 (d, J=17.5 Hz, 1H), 5.51 (d, J=10.9 Hz, 1H), 4.75-4.61 (m, 0.5H), 4.37 (d, J=12.8 Hz, 1H), 4.27 (d, J=12.6 Hz, 1H), 4.10 (d, J=7.2 Hz, 0.5H), 3.85 (d, J=10.0 Hz, 0.5H), 3.81-3.65 (m, 2.5H), 3.30 (dd, J=9.3, 5.7 Hz, 1H), 3.22-3.12 (m, 1H), 3.12-2.97 (m, 1H), 2.66-2.43 (m, 2H), 2.21-2.14 (m, 1H), 1.97 (dd, J=12.0, 6.2 Hz, 2H), 1.46 (dd, J=8.5, 6.8 Hz, 1H), 1.14 (dd, J=7.1, 4.0 Hz, 2H), 1.04 (ddd, J=9.5, 6.4, 3.0 Hz, 2H), 0.77-0.38 (m, 4H).

[1638] LC-MS: m/z 473.2 $(M+H)^+$

Compound 816 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(2-(2-oxopyrrolidin-1-yl)acetyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[1639] ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J=5.6 Hz, 1H), 7.83 (s, 1H), 7.19 (s, 1H), 6.87 (dd, J=5.7, 1.3 Hz, 1H), 6.60 (dd, J=17.5, 10.9 Hz, 1H), 6.44 (s, 1H), 5.95 (d, J=17.5 Hz, 1H), 5.54 (d, J=10.9 Hz, 1H), 4.55 (s, 0.5H), 4.39 (d, J=12.9 Hz, 1H), 4.28 (dd, J=12.7, 2.1 Hz, 1H), 4.19 (s, 1H), 4.00 (s, 0.5H), 3.75 (dd, J=30.5, 3.9 Hz, 2H), 3.55 (s, 2H), 3.33 (s, 1H), 3.18 (d, J=11.9 Hz, 1H), 3.05 (t, J=13.2 Hz, 1H), 2.47 (t, J=8.0 Hz, 2H), 2.21-2.16 (m, 1H), 2.12 (dt, J=15.4, 7.6 Hz, 2H), 1.28 (d, J=5.1 Hz, 1H), 1.19-1.10 (m, 2H), 1.05 (ddd, J=9.0, 6.6, 2.5 Hz, 2H), 0.78-0.41 (m, 4H).

[1640] LC-MS: m/z 513.6 $(M+H)^+$

Compound 817 (General Procedure 7)

(R)-2-(4-(2-cyclobutylacetyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[1641] ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J=5.6 Hz, 1H), 7.80 (s, 1H), 6.87 (dd, J=5.7, 1.2 Hz, 1H), 6.59 (dd, J=17.6, 10.8 Hz, 1H), 6.43 (s, 1H), 5.95 (d, J=17.5 Hz, 1H), 5.54 (d, J=10.8 Hz, 1H), 4.65 (d, J=11.7 Hz, 0.4H), 4.41 (d, J=12.6 Hz, 1H), 4.30 (d, J=12.3 Hz, 1H), 4.09 (d, J=5.2 Hz, 0.6H), 3.91-3.59 (m, 1.5H), 3.34-3.10 (m, 1.5H), 3.09-2.94 (m, 1H), 2.74 (dt, J=15.5, 7.8 Hz, 1H), 2.52 (s, 2H), 2.25-2.12 (m, 3H), 1.98-1.82 (m, 2H), 1.82-1.63 (m, 2H), 1.28 (s, 1H), 1.19-1.09 (m, 2H), 1.04 (dt, J=6.9, 3.0 Hz, 2H), 0.78-0.34 (m, 4H).

[1642] LC-MS: m/z 483.6 $(M+H)^+$

Compound 812 (General Procedure 7)

6-cyclopropyl-2-((3R)-3-cyclopropyl-4-(3-(oxetan-2-yl)propanoyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[1643] ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J=5.4 Hz, 1H), 7.85 (s, 1H), 6.83 (dd, J=5.4, 1.3 Hz, 1H), 6.59 (dd, J=17.6, 10.8 Hz, 1H), 6.41 (s, 1H), 6.39 (s, 1H), 5.90 (d, J=17.6 Hz, 1H), 5.47 (d, J=11.0 Hz, 1H), 4.89 (s, 1H), 4.70 (dd, J=14.1, 7.8 Hz, 1H), 4.55 (dd, J=14.7, 5.8 Hz, 1H), 4.36 (d, J=12.8 Hz, 1H), 4.25 (dd, J=12.5, 1.8 Hz, 1H), 4.09 (dd, J=7.2, 2.6 Hz, 1H), 3.78 (ddd, J=23.5, 14.1, 6.1 Hz, 1.5H), 3.28 (s, 0.5H), 3.13 (d, J=12.4 Hz, 1H), 3.02 (dd, J=21.5, 9.8 Hz, 1H), 2.74 (ddd, J=14.2, 11.1, 8.0 Hz, 1H), 2.62-2.47 (m, 1H), 2.46-2.32 (m, 2H), 2.23-1.98 (m, 3H), 1.28 (d, J=4.8 Hz, 1H), 1.19-1.09 (m, 2H), 1.02 (ddd, J=9.4, 6.4, 3.0 Hz, 2H), 0.75-0.35 (m, 4H).

[1644] LC-MS: m/z 499.6 $(M+H)^+$

Compound 813 (General Procedure 7)

6-cyclopropyl-2-((3R)-3-cyclopropyl-4-(2-(tetrahydrofuran-2-yl)acetyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile

[1645] ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J=5.4 Hz, 1H), 7.84 (s, 1H), 6.84 (dd, J=5.4, 1.2 Hz, 1H), 6.59 (dd, J=17.5, 10.8 Hz, 1H), 6.46 (s, 1H), 6.41 (s, 1H), 5.91 (d, J=17.6 Hz, 1H), 5.47 (d, J=10.9 Hz, 1H), 4.69 (d, J=13.9 Hz, 0.5H), 4.46-4.33 (m, 1H), 4.28 (dd, J=15.4, 9.1 Hz, 2H), 4.11 (d, J=5.3 Hz, 0.5H), 3.98-3.83 (m, 1.5H), 3.75 (dt, J=22.2, 11.1 Hz, 1.5H), 3.40-3.09 (m, 2H), 3.09-2.93 (m, 1H), 2.83-2.47 (m, 2H), 2.47-2.29 (m, 0.5H), 2.26-2.12 (m, 2H), 2.11-1.99 (m, 0.5H), 1.93 (dt, J=13.7, 7.0 Hz, 2H), 1.28 (d, J=5.3 Hz, 1H), 1.19-1.09 (m, 2H), 1.02 (ddd, J=9.8, 6.6, 2.9 Hz, 2H), 0.77-0.32 (m, 4H).

[1646] LC-MS: m/z 499.3 $(M+H)^{+COMPOUND}$ 807 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-4-methyl-5-((2-vinylpyridin-4-yl)amino)nicotinonitrile

[1647] ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J=6.1 Hz, 1H), 6.69 (dd, J=17.4, 10.9 Hz, 1H), 6.57 (s, 1H), 6.45 (s, 1H), 6.21 (d, J=17.6 Hz, 1H), 6.18-6.10 (m, 1H), 5.60 (d, J=11.1 Hz, 1H), 4.71 (d, J=13.2 Hz, 0.5H), 4.50-4.37 (m, 1.5H), 4.33-4.25 (m, 1H), 3.87 (d, J=13.1 Hz, 0.5H), 3.82-3.67 (m, 2H), 3.60 (d, J=10.2 Hz, 0.5H), 3.47 (dd, J=18.2, 7.7 Hz, 0.5H), 3.38 (d, J=4.2 Hz, 3H), 3.14 (ddd, J=13.3, 9.5, 5.2 Hz, 1.5H), 3.09-2.94 (m, 1H), 2.81-2.56 (m, 2H), 2.38 (s, 3H), 2.25 (dd, J=13.6, 6.4 Hz, 0.5H), 2.07 (ddd, J=15.8, 11.1, 6.8 Hz, 1.5H), 1.15-1.09 (m, 1H), 1.04 (dd, J=6.5, 2.9 Hz, 4H), 0.97 (dd, J=7.5, 5.0 Hz, 2H), 0.93 (d, J=6.8 Hz, 1.5H), 0.86 (d, J=6.8 Hz, 1.5H).

[1648] LC-MS: m/z 489.6 $(M+H)^+$

Compound 799 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-4-methyl-5-((2-vinylpyridin-4-yl)amino)nicotinonitrile

[1649] ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J=5.7 Hz, 1H), 6.70 (dd, J=17.4, 10.8 Hz, 1H), 6.50 (s, 1H), 6.33 (s, 1H), 6.16 (d, J=17.4 Hz, 1H), 5.74 (s, 1H), 5.48 (dd, J=10.8, 0.9

Hz, 1H), 4.69 (d, J=9.7 Hz, 0.5H), 4.41 (ddd, J=6.7, 6.1, 4.4 Hz, 1.5H), 4.27 (t, J=10.2 Hz, 1H), 4.00-3.86 (m, 2H), 3.76 (d, J=13.5 Hz, 0.5H), 3.60-3.52 (m, 1H), 3.50-3.44 (m, 1H), 3.17-3.05 (m, 2H), 3.01 (dd, J=11.6, 9.4 Hz, 0.5H), 2.61 (pd, J=11.7, 5.1 Hz, 2H), 2.38 (s, 3H), 2.33-2.22 (m, 0.5H), 2.11 (ddd, J=12.7, 9.3, 5.2 Hz, 1.5H), 1.11 (ddd, J=8.9, 6.6, 4.7 Hz, 1H), 1.05 (d, J=6.5 Hz, 4H), 0.97 (dt, J=7.8, 6.6 Hz, 2H), 0.93 (d, J=6.9 Hz, 1.5H), 0.86 (d, J=6.8 Hz, 1.5H).

[1650] LC-MS: m/z 475.2 $(M+H)^+$

Compound 798 (General Procedure 7)

(R,E)-6-cyclopropyl-2-(3-cyclopropyl-4-(5-hydroxy-pent-2-enoyl)piperazin-1-yl)-5-((4-vinylpyridin-2-yl) amino)nicotinonitrile

[1651] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J=5.3 Hz, 1H), 7.83 (s, 1H), 6.89-6.77 (m, 2H), 6.57 (dd, J=17.6, 10.8 Hz, 1H), 6.53-6.43 (m, 1H), 6.40 (s, 1H), 6.39-6.26 (m, 1H), 5.88 (d, J=17.5 Hz, 1H), 5.44 (d, J=10.9 Hz, 1H), 4.74-4.43 (m, 0.3H), 4.35 (t, J=11.7 Hz, 1H), 4.26 (d, J=12.5 Hz, 1H), 4.11-3.87 (m, 0.8H), 3.78 (dd, J=11.6, 5.5 Hz, 2H), 3.75-3.68 (m, 1H), 3.53 (m, 0.5H), 3.45 (m, 0.5H), 3.42-3.28 (m, 0.5H), 3.24-3.11 (m, 1.5H), 3.03 (td, J=12.6, 3.3 Hz, 1H), 2.49 (dd, J=12.5, 6.2 Hz, 2H), 2.22-2.15 (m, 1H), 1.45 (d, J=6.5 Hz, 1H), 1.17-1.08 (m, 2H), 1.00 (ddd, J=9.4, 6.5, 3.0 Hz, 2H), 0.73-0.32 (m, 4H).

[1652] LC-MS: m/z 485.6 $(M+H)^+$

Compound 581 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-((2-vinylpyridin-4-yl) amino)nicotinonitrile

[1653] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J=5.7 Hz, 1H), 7.62 (s, 1H), 6.71 (dd, J=17.4, 10.8 Hz, 1H), 6.58 (d, J=2.0 Hz, 1H), 6.45 (dd, J=5.7, 2.2 Hz, 1H), 6.19 (d, J=17.2 Hz, 1H), 5.90 (s, 1H), 5.48 (d, J=11.2 Hz, 1H), 4.90 (s, 0.5H), 4.54 (d, J=13.6 Hz, 0.5H), 4.23 (dd, J=31.3, 14.0 Hz, 2.5H), 3.94 (s, 2H), 3.74 (d, J=13.6 Hz, 0.5H), 3.57 (t, J=11.0 Hz, 0.5H), 3.29 (dd, J=10.5, 6.5 Hz, 1H), 3.15 (dd, J=23.7, 11.6 Hz, 1H), 3.09-2.99 (m, 0.5H), 2.62 (m, J=34.8, 15.8 Hz, 2H), 2.12 (td, J=8.1, 4.1 Hz, 1H), 1.43 (d, J=6.4 Hz, 1.5H), 1.32 (d, J=6.8 Hz, 1.5H), 1.13 (dd, J=7.2, 4.2 Hz, 2H), 1.03 (ddd, J=10.0, 6.4, 3.3 Hz, 2H).

[1654] LC-MS: m/z 447.6 $(M+H)^+$

Compound 642 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-((2-vinylpyridin-4-yl) amino)nicotinonitrile

[1655] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J=5.9 Hz, 1H), 7.61 (s, 1H), 6.72 (dd, J=17.5, 10.9 Hz, 1H), 6.62 (s, 1H), 6.53 (d, J=4.4 Hz, 1H), 6.24 (d, J=17.4 Hz, 1H), 5.53 (d, J=10.9 Hz, 1H), 4.92 (s, 1H), 4.55 (d, J=16.6 Hz, 1H), 4.25 (t, J=11.9 Hz, 2H), 4.17 (d, J=13.8 Hz, 1H), 3.82 (d, J=8.4 Hz, 1H), 3.76 (t, J=6.2 Hz, 2H), 3.58 (d, J=12.3 Hz, 1H), 3.39 (s, 3H), 3.30 (d, J=13.0 Hz, 1H), 3.15 (t, J=11.7 Hz, 1H), 3.06 (d, J=12.2 Hz, 1H), 2.73 (ddd, J=22.9, 14.3, 6.7 Hz, 1H), 2.64-2.53 (m, 1H), 2.09 (td, J=7.9, 4.1 Hz, 1H), 1.40 (d, J=5.7 Hz, 2H), 1.30 (d, J=7.1 Hz, 2H), 1.13 (dd, J=6.8, 4.1 Hz, 2H), 1.02 (dd, J=7.6, 3.3 Hz, 2H).

[1656] LC-MS: m/z 447.2 $(M+H)^+$

Compound 643 (General Procedure 7)

(R)-5-((2-chloropyridin-4-yl)-amino)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile

[1657] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J=4.9 Hz, 1H), 7.59 (s, 1H), 6.53 (s, 1H), 6.50 (s, 1H), 6.00 (s, 1H), 4.91 (s, 1H), 4.55 (d, J=10.6 Hz, 1H), 4.29 (d, J=11.2 Hz, 2H), 4.20 (d, J=12.9 Hz, 1H), 3.82 (d, J=13.8 Hz, 1H), 3.73 (dt, J=9.5, 5.8 Hz, 2H), 3.57 (t, J=11.0 Hz, 1H), 3.39 (s, 3H), 3.30 (d, J=12.0 Hz, 1H), 3.15 (t, J=11.8 Hz, 1H), 3.07 (d, J=12.0 Hz, 1H), 2.83-2.65 (m, 1H), 2.60 (dd, J=13.4, 7.5 Hz, 1H), 2.07 (ddd, J=12.6, 7.0, 4.8 Hz, 1H), 1.40 (d, J=6.4 Hz, 2H), 1.34-1.27 (m, 1H), 1.13 (s, 2H), 1.09-0.99 (m, 2H).

[1658] LC-MS: m/z 455.3 $(M+H)^+$

Compound 796 (General Procedure 6)

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3-(furan-2-yl)propanoyl)piperazin-1-yl)-4-methyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1659] ^{1}H NMR (CHLOROFORM-d) δ 8.69 (d, J=5.0 Hz, 1H), 7.31-7.38 (m, 1H), 7.23 (s, 1H), 7.07 (d, J=4.1 Hz, 1H), 6.88 (dd, J=17.6, 10.9 Hz, 1H), 6.21-6.40 (m, 2H), 6.06 (d, J=2.9 Hz, 1H), 5.57 (d, J=11.4 Hz, 1H), 4.22 (d, J=12.6 Hz, 2H), 2.93-3.18 (m, 4H), 2.72 (br. s., 2H), 2.21 (s, 3H), 1.33-1.62 (m, 2H), 1.03-1.33 (m, 3H), 0.87 (dd, J=7.9, 3.2 Hz, 2H), 0.44 (br. s., 4H).

[1660] LC-MS: m/z 508.6 $(M+H)^+$

Compound 797 (General Procedure 6)

(R)-6-(4-(3-cyclopentylpropanoyl)-3-cyclopropy-lpiperazin-1-yl)-2-cyclopropyl-4-methyl-2'-vinyl-3, 4'-bipyridine-5-carbonitrile

[1661] ^{1}H NMR (CHLOROFORM-d) δ 8.69 (d, J=4.7 Hz, 1H), 7.23 (s, 1H), 7.07 (d, J=4.4 Hz, 1H), 6.87 (dd, J=17.5, 10.7 Hz, 1H), 6.12-6.41 (m, 1H), 5.41-5.69 (m, 1H), 4.19-4.48 (m, 2H), 3.96-4.19 (m, 1H), 3.80 (br. s., 1H), 3.15 (br. s., 2H), 3.04 (br. s., 1H), 2.28-2.49 (m, 2H), 2.21 (s, 3H), 1.86 (br. s., 1H), 1.80 (br. s., 3H), 1.47-1.72 (m, 8H), 1.11 (br. s., 4H), 0.73-1.00 (m, 3H), 0.60 (br. s., 1H), 0.55 (br. s., 1H), 0.23-0.50 (m, 2H).

[1662] LC-MS: m/z 510.7 $(M+H)^+$

Compound 804 (General Procedure 5)

(R)-di-tert-butyl 4-(4-(5-cyano-2-cyclopropyl-2'-vinyl-3,4'-bipyridin-6-yl)-2-cyclopropylpiperazin-1-yl)-4-oxobutyl phosphate

[1663] ^{1}H NMR (CHLOROFORM-d) δ 8.66 (d, J=5.0 Hz, 1H), 7.65 (s, 1H), 7.40 (s, 1H), 7.25 (dd, J=5.1, 1.6 Hz, 1H), 6.89 (dd, J=17.6, 10.9 Hz, 1H), 6.30 (d, J=16.7 Hz, 1H), 5.58 (d, J=11.2 Hz, 1H), 4.56 (d, J=12.9 Hz, 1H), 4.35-4.49 (m, 1H), 3.99-4.20 (m, 3H), 3.71-3.84 (m, 1H), 2.99-3.22 (m, 2H), 2.53 (d, J=5.9 Hz, 1H), 2.00-2.07 (m, 3H), 1.66 (d, J=12.3 Hz, 3H), 1.52 (s, 18H), 1.18-1.25 (m, 2H), 0.98-1.06 (m, 2H), 0.62 (br. s., 1H), 0.56 (br. s., 1H), 0.47 (d, J=5.0 Hz, 2H)

[1664] LC-MS: m/z 650.3 $(M+H)^+$

Compound 560 (General Procedure 7)

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(quinolin-4-ylamino) nicotinonitrile

[1665] ^{1}H NMR (CHLOROFORM-d) δ 8.55 (d, J=5.5 Hz, 1H), 8.11 (d, J=8.3 Hz, 1H), 8.03 (d, J=8.3 Hz, 1H), 7.80 (t, J=7.3 Hz, 1H), 7.71 (s, 1H), 7.63 (t, J=7.7 Hz, 1H), 6.36 (d, J=5.5 Hz, 1H), 4.52 (d, J=13.3 Hz, 1H), 4.41 (d, J=13.8 Hz, 1H), 4.15 (br. s., 1H), 3.69-3.86 (m, 2H), 3.12-3.35 (m, 4H), 2.01-2.13 (m, 1H), 1.33-1.35 (m, 1H), 1.12-1.21 (m, 2H), 0.95-1.07 (m, 2H), 0.45-0.73 (m, 4H)

[1666] LC-MS: m/z 521.2 $(M+H)^+$

Compound 617 (General Procedure 7)

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(6-vinylpyrimidin-4-ylamino)nicotinonitrile

[1667] ^{1}H NMR (CHLOROFORM-d) δ 8.58-8.68 (m, 1H), 7.72-7.80 (m, 1H), 6.90-7.01 (m, 1H), 6.53-6.66 (m, 1H), 6.35-6.48 (m, 1H), 6.27 (s, 1H), 5.62 (dd, J=10.5, 1.3 Hz, 1H), 4.90 (br. s., 0.5H), 4.54 (d, J=13.6 Hz, 0.5H), 4.11-4.34 (m, 2.5H), 3.93 (br. s., 2H), 3.74 (d, J=13.6 Hz, 0.5H), 3.50-3.65 (m, 0.5H), 3.45 (br. s., 0.5H), 3.23-3.32 (m, 1H), 3.10-3.20 (m, 0.5H), 2.98-3.09 (m, 0.5H), 2.48-2.76 (m, 2H), 2.08-2.16 (m, 1H), 1.42 (d, J=6.5 Hz, 1.5H), 1.32 (d, J=6.8 Hz, 1.5H), 1.10-1.20 (m, 2H), 0.97-1.09 (m, 2H)

[1668] LC-MS: m/z 434.3 $(M+H)^+$

Compound 700 (General Procedure 5)

(R)-5-(2-amino-6-vinylpyrimidin-4-yl)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile

[1669] ^{1}H NMR (CHLOROFORM-d) δ 7.97 (s, 1H), 6.89 (s, 1H), 6.66 (dd, J=17.3, 10.5 Hz, 1H), 6.52 (d, J=17.8 Hz, 1H), 5.74 (d, J=10.5 Hz, 1H), 5.41 (br. s., 2H), 4.66 (d, J=12.5 Hz, 1H), 4.52 (d, J=12.5 Hz, 1H), 3.16-4.28 (m, 5H), 2.33-2.49 (m, 1H), 1.72 (br. s., 2H), 1.21-1.26 (m, 2H), 0.98-1.15 (m, 4H), 0.82 (dd, J=7.8, 2.3 Hz, 2H), 0.63 (br. s., 1H), 0.36-0.58 (m, 3H)

[1670] LC-MS: m/z 456.4 $(M+H)^+$

Compound 751 (General Procedure 7)

6-cyclopropyl-2-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-5-(2-vinylpyridin-4-ylamino)nicotinonitrile

[1671] ^{1}H NMR (CHLOROFORM-d) δ 8.24 (d, J=5.9 Hz, 1H), 7.62 (s, 1H), 6.70 (dd, J=17.3, 10.9 Hz, 1H), 6.61 (d, J=2.1 Hz, 1H), 6.49 (d, J=5.9 Hz, 1H), 6.19 (d, J=17.6 Hz, 1H), 6.04 (br. s., 1H), 5.53 (d, J=10.9 Hz, 1H), 5.27 (quin, J=6.7 Hz, 1H), 4.69-4.79 (m, 1H), 4.42-4.58 (m, 2H), 4.35 (d, J=12.9 Hz, 1H), 4.09 (d, J=8.8 Hz, 1H), 3.95 (d, J=13.8 Hz, 1H), 3.67-3.82 (m, 1H), 2.75-3.34 (m, 5H), 2.55 (d, J=9.1 Hz, 1H), 2.08 (td, J=8.1, 4.0 Hz, 1H), 1.33 (br. s., 1H), 1.10-1.18 (m, 2H), 1.03 (dd, J=7.8, 3.4 Hz, 2H), 0.63 (br. s., 1H), 0.55 (br. s., 1H), 0.47 (d, J=5.9 Hz, 2H)

[1672] LC-MS: m/z 485.6 $(M+H)^+$

Compound 752 (General Procedure 5)

2-cyclopropyl-6-((R)-3-cyclopropyl-4-(2-((R)-oxetan-2-yl)acetyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

[1673] ^{1}H NMR (CHLOROFORM-d) δ 8.66 (d, J=5.0 Hz, 1H), 7.65 (s, 1H), 7.35-7.46 (m, 1H), 7.23 (dd, J=5.1, 1.6 Hz, 1H), 6.88 (dd, J=17.5, 10.7 Hz, 1H), 6.21-6.36 (m, 1H), 5.49-5.61 (m, 1H), 5.27 (quin, J=6.6 Hz, 1H), 4.72 (td, J=7.9, 6.2 Hz, 1H), 4.50-4.65 (m, 2H), 4.44 (d, J=12.9 Hz, 1H), 4.09 (d, J=8.2 Hz, 0.6H), 3.84-4.02 (m, 0.7H), 3.74 (t, J=12.0 Hz, 0.7H), 3.25 (br. s., 1H), 2.91-3.23 (m, 3.5H), 2.55-2.9 (m, 2.5H), 2.55 (d, J=8.8 Hz, 1H), 1.97-2.11 (m, 1H), 1.33 (br. s., 1H), 1.18-1.26 (m, 2H), 0.94-1.07 (m, 2H), 0.63 (br. s., 1H), 0.56 (br. s., 1H), 0.47 (br. s., 2H)

[1674] LC-MS: m/z 470.2 $(M+H)^+$

Compound 800 (General Procedure 5)

2-cyclopropyl-6-((3R)-3-cyclopropyl-4-(3-(tetrahydrofuran-2-yl)propanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile

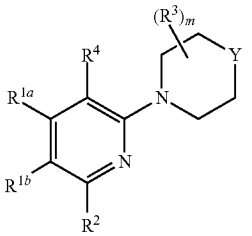
[1675] ^{1}H NMR (CHLOROFORM-d) δ: 8.63 (d, J=5.3 Hz, 1H), 7.62 (s, 1H), 7.37 (s, 1H), 7.21 (dd, J=5.0, 1.5 Hz, 1H), 6.86 (dd, J=17.5, 10.7 Hz, 1H), 6.26 (d, J=17.6 Hz, 1H), 5.54 (d, J=10.9 Hz, 1H), 4.53 (d, J=12.9 Hz, 1H), 4.41 (d, J=12.6 Hz, 1H), 4.00-4.22 (m, 1H), 3.85 (d, J=6.5 Hz, 3H), 3.62-3.77 (m, 2H), 3.08-3.29 (m, 3H), 2.31-2.60 (m, 2H), 1.83-2.11 (m, 5H), 1.68-1.83 (m, 1H), 1.46-1.58 (m, 1H), 1.20 (dt, J=7.3, 3.6 Hz, 2H), 0.93-1.07 (m, 2H), 0.49-0.76 (m, 2H), 0.43 (br. s., 2H)

[1676] LC-MS: m/z 498.7 $(M+H)^+$

[1677] Having thus described several aspects of several embodiments, it is to be appreciated various alterations, modifications, and improvements will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and are intended to be within the spirit and scope of the invention. Accordingly, the foregoing description and drawings are by way of example only.

1. A compound of Structural Formula (I):

(I)



or a pharmaceutically acceptable salt thereof, wherein:

Y is —N(R^5)—, —N(R_5)—CH_2—, —CH_2—N(R^5)— or —CH(R^5)—;

each R^{1a} and R^{1b} is independently hydrogen, —C_1-C_4 alkyl, —N(R^7)(C_1-C_4 alkylene)-N(R^7)(C_1-C_4 alkyl), aryl, heteroaryl, heterocyclyl, —C(O)N(R^7)-aryl, —N(R^7)C(O)-aryl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, —O—(C_0-C_4 alkylene)-heteroaryl, —O—(C_0-C_4 alky-

lene)-heterocyclyl, —O—(C_0-C_4 alkylene)-carbocyclyl, —N(R^7)-aryl, or —N(R^7)-heteroaryl, —N(R^9)-aryl, —N(R^9)-heteroaryl, —O—(C_1-C_4 alkeylene)-N(R^7)C(O)O—(C_1-C_4 alkylene)-aryl, —N(R^9)—C(O)—(C_2-C_4 alkenyl) wherein:

at least one of R^{1a} and R^{1b} is not hydrogen or methyl;

any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;

each R^7 is independently selected from hydrogen and C_1-C_4 alkyl; and

any aryl, heteroaryl, or heterocyclyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from -G-L-M, halo, —NO_2, C_1-C_6 alkyl, —C≡N, =O, —CF_3 and —OCF_3;

G is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by —NR^8—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR^8)—, —N=N—, or —C(=N_2)—;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —N(R^8)C(O)—, —C(O)N(R^8)—, —N(R^8)SO_2—, SO_2N(R^8)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR^8)—, —N=N—, or —C(=N_2)—;

M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -D-E, oxo, NO_2, halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

D is a covalent bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by —NR^8—, —S—, —O—, —C(O)—, —SO—, or —SO_2—;

E is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

each R^8 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, —C_1-C_6 alkoxy, —S(O)$_2$—C_2-C_4 alkenyl, or an optionally substituted group selected from phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is selected from phenyl, a 3-7 membered cycloalkyl, C_2-C_4 alkyl, or CF_3, wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

each R^3 is independently selected from halo, —(C_1-C_4 alkylene)-O—(C_1-C_4 alkyl), —C_1-C_4 fluoroalkyl, —C(O)—O—(C_1-C_4 alkyl), -phenyl, -heteroaryl, C_3-C_7 cycloalkyl, —CH_2—N(C_1-C_4 alkyl)$_2$, C(O)—N—(C_1-C_4 alkyl)$_2$, —C(O)—NH—(C_1-C_4 alkyl), —C_1-C_4 alkyl optionally substituted with one or more halo or —OH, or two R^3s are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or a fused phenyl is optionally substituted with 1 to 2 methyl;

R^4 is selected from hydrogen, —CN, halo, C_1-C_4 alkoxy, —CH_2NH(C_1-C_4 alkyl), C_2-C_4 alkenyl, C_2-C_4 alkynyl, —(C_1-C_4 alkyl)-O—(C_1-C_4 alkyl), C_1-C_4 fluoroalkyl, C(O)—N—(C_1-C_4 alkyl)$_2$, —C(O)—NH—(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkyl), —C(O)—OH, —S(O)$_2$—(C_1-C_4 alkyl), and a 5-membered heteroaryl;

R^5 is selected from: —C(O)—(C_1-C_5 alkyl), —C(O)—(C_2-C_6 alkenyl), —C(O)—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_4 alkenylene)-Q, —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_0-C_2 alkylene)-Q, —C(O)—O—(C_0-C_2 alkylene)-Q, —C(O)—(C_1-C_2 alkylene)-O—(C_0-C_2 alkylene)-Q, —C(O)—C(O)-Q, —S(O)$_2$-Q, —C(O)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_1-C_6 alkyl), —C(O)—(C_0-C_2 alkylene)N(R^6)—(C_2-C_6 alkynyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_2-C_6 alkenyl), —C(O)—(C_0-C_2 alkylene)-N(R^6)—(C_0-C_2 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-C(O)C(O)N(R)(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkylene)-O—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —(C_0-C_4 alkylene)-O—(C_1-C_4 alkyl), —C(O)—(C_1-C_2 alkylene)-S(O)$_{0-2}$-(C_1-C_4 alkyl), —S(O)$_2$—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)C(O)N(R^6)(C_1-C_6 alkyl), —C(O)—(C_1-C_4 alkylene)-N(R^6)S(O)$_2$—(C_1-C_6 alkyl), or —C(O)—(C_1-C_4 alkylene)-N(R^6)S(O)$_2$Q, wherein:

any alkylene moiety present in R^5 is optionally substituted with OCH_3, OH or F;

any terminal methyl moiety present in R^5 is optionally replaced with —CH_2OH, CF_3, CH_2F, —CH_2Cl, C(O)CH_3, C(O)CF_3, CN, —OCH_3, —C(O)H, —OP(O)(OH)$_2$, —OP(O)(C_1-C_4 alkoxy)$_2$ or CO_2H;

each R^6 is independently selected from hydrogen and methyl;

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3 substituents independently selected from C_1-C_4 alkyl optionally substituted with OH, C_1-C_4 alkoxy, —C(O)O—(C_1-C_4 alkyl), —(C_1-C_4 alkylene)-(C_1-C_4 alkoxy), —CN, —OH, fluoro, chloro, and bromo;

R^9 is selected from aryl and heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one or more substituents selected from -G-L-M, halo, C_1-C_6 alkyl, —C≡N, =O, —CF_3 and —OCF_3; and

m is 0, 1, 2 or 3.

2. The compound of claim **1**, wherein:

Y is —N(R^5)— or —CH(R^5)—;

each R^{1a} and R^{1b} is independently hydrogen, —C_1-C_4 alkyl, —N(R^7)(C_1-C_4 alkylene)-N(R^7)(C_1-C_4 alkyl), aryl, heteroaryl, heterocyclyl, —C(O)N(R^7)-aryl, —N(R^7)C(O)-aryl, —(C_1-C_4 alkylene)-aryl, —(C_1-C_4 alkylene)-heteroaryl, —O—(C_1-C_4 alkylene)-aryl, —O—(C_1-C_4 alkylene)-heteroaryl, —O—(C_1-C_4 alkylene)-heterocyclyl, —N(R^7)-aryl, or —N(R^7)-heteroaryl, wherein:

at least one of R^{1a} and R^{1b} is not hydrogen or methyl;

any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;

each R^7 is independently selected from hydrogen and C_1-C_4 alkyl; and

any aryl, heteroaryl, or hetercylyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from -G-L-M, halo, C_1-C_6 alkyl, —C≡N, =O, —CF_3 and —OCF_3;

G is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by —NR^8—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR^8)—, —N=N—, or —C(=N_2)—;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, —$N(R^8)C(O)$—, —$C(O)N(R^8)$—, —$N(R^8)SO_2$—, $SO_2N(R^8)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO—, —SO_2—, —C(=S)—, —C(=NR^8)—, —N=N—, or —C(=N_2)—;

M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -D-E, oxo, NO_2, halogen, CN, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

D is a covalent bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by —NR^8—, —S—, —O—, —C(O)—, —SO—, or —SO_2—;

E is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

each R^8 is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or an optionally substituted group selected from phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is selected from phenyl, a 3-7 membered cycloalkyl, and C_2-C_4 alkyl, wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

each R^3 is independently selected from —C_1-C_4 alkyl, —(C_1-C_4 alkyl)-O—(C_1-C_4 fluoroalkyl, —C(O)—O—(C_1-C_4 alkyl), -phenyl, -heteroaryl, C_3-C_7 cycloalkyl, —CH_2—$N(C_1$-C_4 alkyl$)_2$, C(O)—N—(C_1-C_4 alkyl$)_2$, and —C(O)—NH—(C_1-C_4 alkyl), or

or two R^3s are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl groups;

R^4 is selected from hydrogen, —CN, halo, C_1-C_4 alkoxy, —$CH_2NH(C_1$-C_4 alkyl), C_2-C_4 alkenyl, C_2-C_4 alkynyl, —(C_1-C_4 alkyl)-O—(C_1-C_4 alkyl), C_1-C_4 fluoroalkyl, C(O)—N—(C_1-C_4 alkyl$)_2$, —C(O)—NH—(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkyl), —C(O)—OH, —$S(O)_2$—(C_1-C_4 alkyl), and a 5-membered heteroaryl;

R^5 is selected from: —C(O)—(C_1-C_4alkyl), —C(O)—$(CH_2)_{0-2}$-Q, —C(O)—$(CH_2)_{0-2}$—$N(R^6)$—$(CH_2)_{0-2}$-Q, —C(O)—O—$(CH_2)_{1-2}$-Q, —C(O)—$(CH_2)_{1-2}$—O—$(CH_2)_{0-2}$-Q, —C(O)—C(O)-Q, —$S(O)_2$-Q, —C(O)—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—$N(R^6)$—(C_1-C_4 alkylene)-O—C(O)—(C_1-C_4 alkyl), —C(O)—N(R^6)—(C_1-C_4alkylene)-C(O)—O—(C_1-C_4 alkyl), —C(O)—$(CH_2)_{0-2}$—$N(R^6)$—(C_1-C_6 alkyl), —C(O)—$(CH_2)_{0-2}$—$N(R^6)$—(C_2-C_6 alkynyl), —C(O)—$(CH_2)_{0-2}$—$N(R^6)$—(C_2-C_6 alkenyl), —C(O)—$(CH_2)_{0-2}$—$N(R^6)$—$(CH_2)_{0-2}$—O—(C_1-C_4 alkyl), —C(O)—$(CH_2)_{1-2}$—O—(C_1-C_4 alkyl), —C(O)—O—(C_1-C_4 alkylene)-O—(C_1-C_4 alkyl), —$(CH_2)_{0-4}$—O—C(O)—(C_1-C_4 alkyl), —$(CH_2)_{0-4}$—C(O)—O—(C_1-C_4 alkyl), —$(CH_2)_{0-4}$—O—(C_1-C_4 alkyl), —C(O)—$(CH_2)_{1-2}$—S—(C_1-C_4 alkyl), —$S(O)_2$—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkylene)-C(O)C(O)$N(R^6)$(C_1-C_6 alkyl), —C(O)—(C_1-C_4 alkylene)-$N(R^6)S(O)_2$—(C_1-C_6 alkyl), and —C(O)—(C_1-C_4 alkylene)-$N(R^6)S(O)_2$Q, wherein:

any alkylene moiety present in R^5 is optionally substituted with OH or F;

any terminal methyl moiety present in R^5 is optionally replaced with —CH_2OH, CF_3, —CH_2F, —CH_2Cl, $C(O)CH_3$, or $C(O)CF_3$;

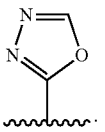
each R^6 is independently selected from hydrogen and methyl;

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3 substituents independently selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, —CN, fluoro, chloro, and bromo; and

m is 0, 1, 2 or 3.

3. The compound of claim **1**, wherein R^4 is selected from —CN or C(O)—O—C_1-C_4 alkyl.

4. The compound of claim **1**, wherein R^4 is



5. The compound of claim **1**, wherein Y is —$N(R^5)$—.

6. The compound of claim **6**, wherein R^5 is —C(O)—(C_1-C_3 alkyl)-O—(C_1-C_2 alkyl), —C(O)-Q, —C(O)—(C_1-C_5 alkyl), —C(O)—(C_1-C_2 alkylene)-Q, —C(O)—(C_2-C_4 alkenyl), —C(O)O—(C_1-C_4 alkyl), or —C(O)—(C_1-C_4 alkenylene)-Q; wherein: any alkylene moiety present in R^5 is optionally substituted with OH; any terminal methyl moiety present in R^5 is optionally replaced with —OH, CF_3, OCH_3, —C(O)H, $OP(O)(C_1$-C_4 alkoxy$)_2$, or —$OP(O)(OH)_2$ (or a salt of —$OP(O)(OH)_2$).

7. The compound of claim **6**, wherein Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with one substituent independently selected from C_1-C_4 alkyl optionally substituted with OH, C_1-C_4 alkoxy, alkylene)-(C_1-C_4 alkoxy), and —OH.

8. The compound of claim **1**, wherein R^{1a} is H and R^{1b} is aryl, heteroaryl, heterocyclyl, alkylene)-aryl, alkylene)-heteroaryl, —O—(C_0-C_4 alkylene)-aryl, —O—(C_0-C_4 alky-

lene)-heteroaryl, —N(R^7)-aryl, —N(R^7)heteroaryl, —N(R^9)-aryl, or —N(R^9)-heteroaryl; wherein said aryl or heteroaryl is substituted with -G-L-M, CH_3, or CN.

9. The compound of claim **8**, wherein aryl associated with R^{1b} is phenyl.

10. The compound of claim **8**, wherein heteroaryl is associated with R^{1b} pyridyl, pyrimidinyl, naphthyridinyl, quinolyl, isoquinolyl, isoxazolyl, benzoxazolyl, imidazopyrazinyl, benzothiazolyl, benzimidazolyl, pyrollopyridinyl, pyrazolopyridinyl, indolyl, indazolyl, imidazopyridinyl, quinoxalinyl, quinazolinyl, pyridazinyl or pyrazolyl.

11. The compound of claim **8**, wherein heterocyclyl is associated with R^{1b} benzodioxole, pyridazinone, benzoxazolone, indolinone, N-methylindolinone, piperazinyl, N-methylisoquinolinone, tetrahydropyridinyl, dihydropyrrolyl and said phenyl, pyridyl, pyrimidinyl, naphthyridinyl, quinolyl, isoquinolyl, isoxazolyl, benzoxazolyl, imidazopyrazinyl, benzothiazolyl, benzimidazolyl, pyrollopyridinyl, pyrazolopyridinyl, indolyl, indazolyl, imidazopyridinyl, quinoxalinyl, quinazolinyl, pyridazinyl, pyrazolyl, benzodioxole, pyridazinone, benzoxazolone, indolinone, N-methylindolinone, piperazinyl, N-methylisoquinolinone, tetrahydropyridinyl, or dihydropyrrolyl

12. The compound of claim **9**, wherein aryl, heteroaryl or heterocyclyl associated with R^{1b} is substituted with -G-L-M, —CF_3, —OCF_3, halo (e.g., fluoro, chloro or bromo), CH_3, or CN.

13. The compound of claim **1**, wherein R^{1a} is methyl and R^{1b} is aryl, heteroaryl, heterocyclyl, —O—(C_0-C_4 alkylene)-aryl, or —O—(C_0-C_4 alkylene)-heteroaryl.

14. The compound of claim **13**, wherein R^{1a} is methyl and R^{1b} is aryl, heteroaryl, heterocyclyl, —O—(CH_2)-aryl, —O—CH(CH_3)-aryl, —O—(CH_2)-heteroaryl or —O—CH(CH_3)-heteroaryl.

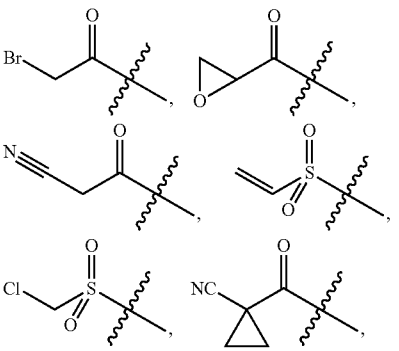
15. The compound of claim **13**, wherein aryl associated with R^{1b} is phenyl or naphthyl.

16. The compound of claim **13**, wherein heteroaryl associated with R^{1b} is quinolinyl, pyrazolyl, isoquinolinyl, pyridyl, pyrimidinyl, indolyl, or pyrazolyl.

17. The compound of claim **13**, wherein heterocyclyl associated with R^{1b} is tetrahydropyridinyl and said phenyl, pyridyl, pyrimidinyl, indolyl, or pyrazolyl.

18. The compound of claim **13**, wherein aryl, heteroaryl or heterocyclyl associated with R^{1b} is substituted with -G-L-M, halo, CH_3, or CN.

19. The compound of claim **8**, wherein -G-L-M:



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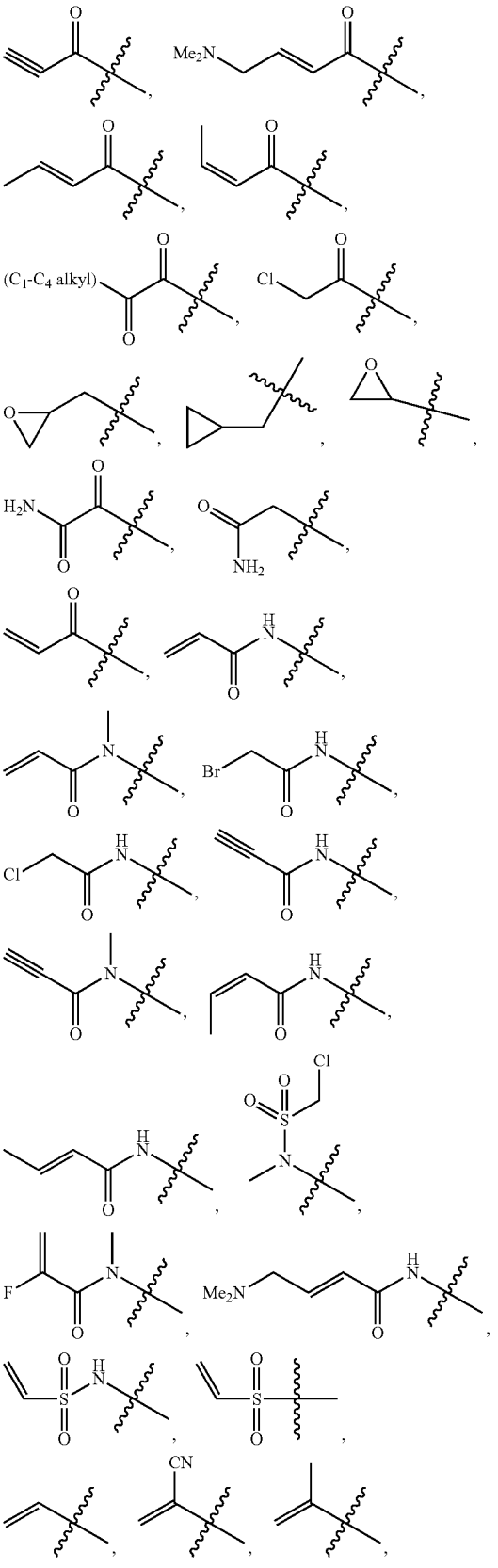

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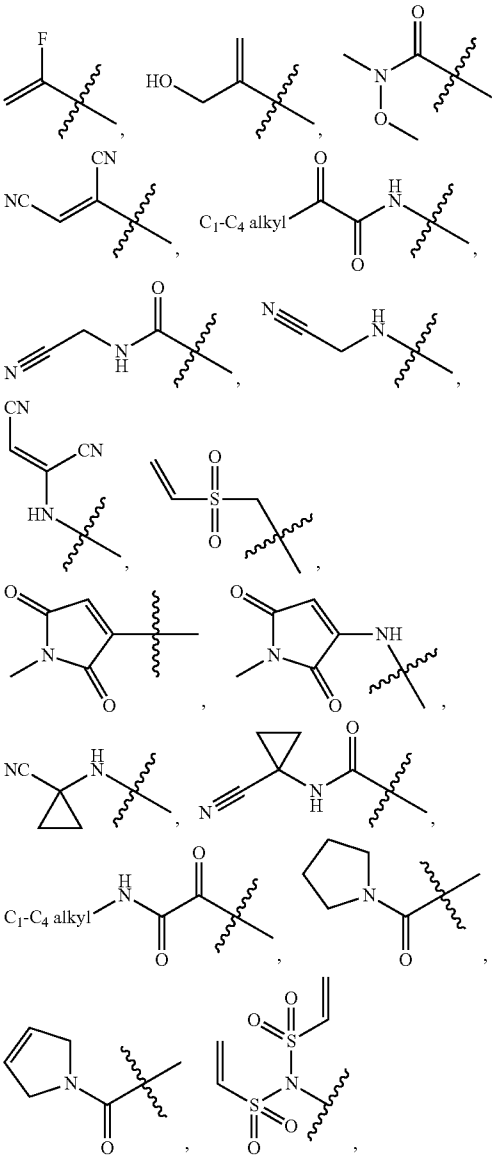

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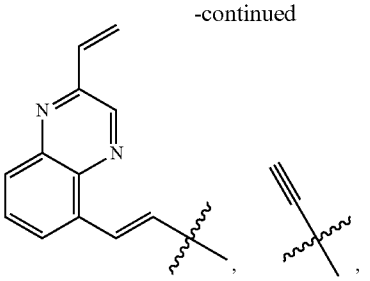

C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkoxy, tetrazolyl, morpholino, piperazinyl, pyrrolidinone, pyrazolyl, benzyl, —$(CH_2)_{1-4}$—SH, —$(CH_2)_{1-4}$—NH_2, —NH_2, —$(CH_2)_{1-4}$—OH, —N(H)C(O)$OCH(CH_3)_3$, —$(CH_2)_{1-4}$—OCH_3, —NH—$(CH_2)_{1-4}$—OH, —C(O)—(C_1-C_4 alkyl), —C(O)—(C_1-C_4 alkenyl), —O—$(CH_2)_{1-4}$—C(O)—O—(C_1-C_4 alkyl), —$C(O)NH_2$, —$(CH_2)_{1-4}C(O)CH_3$, —$N(CH_3)(CH_3)$, —NHC(O)(C_2-C_4 alkenyl), —NHC(O)(C_2-C_4 alkyl), —$SO_2(CH_2)_{1-4}$, —$(CH_2)_{1-4}$—$NHSO_2Me$, —$NHSO_2(CH_2)_{1-4}$, —O—SO_2CF_3, —SO_2NH—(C_1-C_4 alkyl), —SO_2NH—(C_2-C_4 alkenyl), SO_2—NH_2 or —$NHSO_2Me$

20. A pharmaceutical composition comprising a compound of claim **1**, and a pharmaceutically acceptable carrier.

21. The composition of claim **20**, further comprising a second therapeutic agent.

22. A method of treating a cancer characterized by the presence of an IDH1 mutation, wherein the IDH1 mutation result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of a-ketoglutarate to R(−)-2-hydroxyglutarate in a patient, comprising the step of administering to the patient in need thereof a composition of claim **20**.

23. The method of claim **22**, wherein the IDH1 mutation is an IDH1 R132H or IDH1 R132C mutation.

24. The method of claim **23**, wherein the cancer is selected from glioma (glioblastoma), acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer and cholangiocarcinomas, cholangiocarcinomas, chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), or colon cancer.

25. The method of claim **22**, further comprising administering to the patient in need thereof a second therapeutic agent.

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