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(54) **SUBSTITUTED HETEROARYL ALDEHYDE COMPOUNDS AND METHODS FOR THEIR USE IN INCREASING TISSUE OXYGENATION**

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(57) **ABSTRACT**

Provided are substituted heteroaryl aldehydes and derivatives thereof that act as allosteric modulators of hemoglobin, methods and intermediates for their preparation, pharmaceutical compositions comprising the modulators, and methods for their use in treating disorders mediate by hemoglobin and disorders that would benefit from increased tissue oxygenation.

SUBSTITUTED HETEROARYL ALDEHYDE COMPOUNDS AND METHODS FOR THEIR USE IN INCREASING TISSUE OXYGENATION

REFERENCES TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 13/730,730 filed Dec. 28, 2012, which claims the benefit under 35 U.S.C. 119(e) to U.S. Provisional Patent Application Nos. 61/661,327 filed Jun. 18, 2012 and 61/581,063 filed Dec. 28, 2011, the disclosures of which are hereby incorporated by reference in their entireties for all purpose.

FIELD OF THE INVENTION

[0002] The present invention generally relates to substituted heteroaryl aldehydes and derivatives thereof that act as allosteric modulators of hemoglobin, methods and intermediates for their preparation, pharmaceutical compositions comprising the modulators, and methods for their use in treating disorders mediate by hemoglobin and disorders that would benefit from increased tissue oxygenation.

BACKGROUND OF THE INVENTION

[0003] Hemoglobin (Hb) is a tetrameric protein in red blood cells that transports up to four oxygen molecules from the lungs to various tissues and organs throughout the body. Hemoglobin binds and releases oxygen through conformational changes, and is in the tense (T) state when it is unbound to oxygen and in the relaxed (R) state when it is bound to oxygen. The equilibrium between the two conformational states is under allosteric regulation. Natural compounds such as 2,3-bisphosphoglycerate (2,3-BPG), protons, and carbon dioxide stabilize hemoglobin in its de-oxygenated T state, while oxygen stabilizes hemoglobin in its oxygenated R state. Other relaxed R states have also been found, however their role in allosteric regulation has not been fully elucidated.

[0004] Sickle cell disease is a prevalent disease particularly among those of African and Mediterranean descent. Sickle hemoglobin (HbS) contains a point mutation where glutamic acid is replaced with valine, allowing the T state to become susceptible to polymerization to give the HbS containing red blood cells their characteristic sickle shape. The sickled cells are also more rigid than normal red blood cells, and their lack of flexibility can lead to blockage of blood vessels. Certain synthetic aldehydes have been found to shift the equilibrium from the polymer forming T state to the non-polymer forming R state (Nnamani et al. Chemistry & Biodiversity Vol. 5, 2001 pp. 1762-1769) by acting as allosteric modulators to stabilize the R state through formation of a Schiff base with an amino group on hemoglobin.

[0005] U.S. Pat. No. 7,160,910 discloses 2-furfuraldehydes and related compounds that are also allostric modulators of hemoglobin. One particular compound 5-hydroxymethyl-2-furfuraldehyde (5HMF) was found to be a potent hemoglobin modulator both in vivo and in vivo. Transgenic mice producing human HbS that were treated with 5HMF were found to have significantly improved survival times when exposed to extreme hypoxia (5% oxygen). Under these hypoxic conditions, the 5HMF treated mice were also found to have reduced amounts of hypoxia-induced sickled red blood cells as compared to the non-treated mice.

[0006] A need exists for therapeutics that can shift the equilibrium between the deoxygenated and oxygenated states of Hb to treat disorders that are mediated by Hb or by abnormal Hb such as HbS. A need also exists for therapeutics to treat disorders that would benefit from having Hb in the R state with an increased affinity for oxygen. Such therapeutics would have applications ranging, for example, from sensitizing hypoxic tumor cells that are resistant to standard radiotherapy or chemotherapy due to the low levels of oxygen in the cell, to treating pulmonary and hypertensive disorders, and to promoting wound healing.

BRIEF SUMMARY OF THE INVENTION

[0007] The present invention provides, in one aspect, allosteric modulators of hemoglobin. In another aspect, provided are pharmaceutical compositions comprising the allosteric modulators disclosed herein. In other aspects, provided are methods for treating disorders mediated by hemoglobin and methods for increasing tissue oxygenation for treating disorders that would benefit from increased oxygenation, such methods comprising administering the allosteric modulators disclosed herein to a subject in need thereof. In still other aspects, provided are methods for preparing the allosteric modulators disclosed herein. These and other embodiments of the invention are more fully described in the description that follows.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0008] As used herein, the below terms have the following meanings unless specified otherwise.

[0009] The abbreviations used herein are conventional, unless otherwise defined: aq=aqueous; Boc=t-butylcarboxy, $(Boc)_2O$=di-tert-butyl dicarbonate, ° C.=degrees celcius, mCPBA=m-chloroperoxybenzoic acid, DCM=dichloromethane (CH_2Cl_2), DIBAL=diisobutylaluminum hydride, DIEA=diisopropylethyl amine; DMF=dimethyl formamide, EtOAc=ethyl acetate, EtOH=ethanol, g=gram, H_2=hydrogen H_2O water; HBr=hydrogen bromide; HCl=hydrogen chloride, HPLC=high pressure liquid chromatography, h=hour, LAH=lithium aluminum hydride ($LiAlH_4$); MeCN=acetonitrile; LRMS=Low Resolution Mass Spectrum MS=Mass Spectrum, m/z=mass to charge ratio, MHz=Mega Hertz MeOH=methanol, μM=micromolar, μL=microliter, mg=milligram, mM=millimolar, mmol=millimole, mL=milliliter, min=minute, M=molar, Na_2CO_3=sodium carbonate, ng=nanogram, N=Normal, NMR=nuclear magnetic resonance, Pd/C=palladium on carbon, rp=reverse phase, sat=saturated, rt=room temperature SEM=(2-(trimethylsilyl)ethoxy)methyl, TEA=triethylamine, THF=tetrahydrofuran, TFA=trifluroacetic acid, TLC=thin layer chromatography, and TMS=trimethylsilyl.

[0010] It is noted hue that as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

[0011] "Alkoxy" refers to —O(alkyl) where alkyl as defined herein. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy, and the like.

[0012] "Alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, fully saturated aliphatic hydrocarbon radical having the number of carbon atoms designated. For example, "C_{1-8}alkyl" refers to a hydrocarbon radical straight or branched, containing from 1 to 8 carbon atoms that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Alkyl includes branched chain isomers of straight chain alkyl groups such as isopropyl, t-butyl, isobutyl, sec-butyl, and the like. Representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. Further representative alkyl groups include straight and branched chain alkyl groups having, 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms.

[0013] "Alkenyl" refers to a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix and containing at least one double bond, but no more than three double bonds. For example, C_{2-8}alkenyl is meant to include, ethenyl, propenyl, 1,3-butadienyl and the like.

[0014] "Alkynyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical containing at least one triple bond and having the number of carbon atoms indicated in the prefix. The term "alkynyl" is also meant to include those alkyl groups having one triple bond and one double bond. For example, C_{2-8}alkynyl is meant to include ethynyl, propynyl and the like.

[0015] The term "allosteric modulators" refers to compounds that bind to hemoglobin to modulate its affinity for oxygen. In one group of embodiments, the allosteric modulators act to stabilize or destabilize a particular hemoglobin conformation. In one group of embodiments, the modulators stabilize the relaxed R state. In other embodiments, the modulators destabilize the tense T state. In one group of embodiments, the allosteric modulators can destabilize one conformation while stabilizing another. In some such embodiments, the modulators stabilize a relaxed R state and destabilize the tense T state. The modulators, in addition to modulating the affinity of hemoglobin for oxygen, may also confer additional properties to hemoglobin such as increasing its solubility. The present disclosure is not intended to be limited to the mechanism by which the allosteric modulators interact with and regulate hemoglobin. In one group of embodiments, the allosteric modulators inhibit the polymerization of HbS and the sickling of red blood cells. In one group of embodiments, the binding of the allosteric modulators provided herein to hemoglobin can occur through covalent or non-covalent interactions. In one embodiment, the allosteric modulators react through its aldehyde substituent with an amine group on a hemoglobin amino acid side chain to form a Schiff base.

[0016] "Amino" refers to a monovalent radical —NH_2.

[0017] "Aryl" by itself or as pert of another substituent refers to a polyunsaturated, aromatic, hydrocarbon group containing from 6 to 14 carbon atoms, which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. Thus the phrase includes, but is not limited to, groups such as phenyl, biphenyl, anthracenyl, naphthyl by way of example. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl and 4-biphenyl.

[0018] "Bond" when used as an element in a Markush group means that the corresponding group does not exist, and the groups of both side are directly linked.

[0019] "Cycloalkyl" refers to a saturated or partially saturated cyclic group of from 3 to 14 carbon atoms and no ring heteroatoms and having a single ring or multiple rings including fused, bridged, and spiro ring systems. The term "cycloalkyl" includes cycloalkenyl groups, a partially saturated cycloalkyl ring having at least one site of >C═C< ring unsaturation. Examples of cycloalkyl groups include, for instance, adamantyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and cyclohexenyl. "$C_{u'-v'}$cycloalkyl" refers to cycloalkyl groups having u' to v' carbon atoms ring members. "$C_{u'-v'}$cycloalkenyl" refers to cycloalkenyl groups having u' to v' carbon atoms as ring members.

[0020] The term "hemoglobin" as used herein refers to any hemoglobin protein, including normal hemoglobin (Hb) and sickle hemoglobin (HbS).

[0021] "Heteroaryl" refers to a cyclic or polycyclic radical having at least one aromatic ring and from one to five ring heteroatom selected from N, O, and S, and optionally one or more oxo (═O) substituents attached to one or more carbon ring atoms, and wherein the nitrogen and sulfur ring atoms are optionally oxidized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom or through a carbon atom and can contain 5 to 10 carbon atoms. Heteroaryl groups include polycyclic aromatic ring(s) fused to non-aromatic cycloalkyl or heterocycloalkyl groups, and where the point of attachment to the remainder of the molecule can be through any suitable ring atom of any ring. In a polycyclic heteroaryl group, the ring heteroatom(s) can be in either an aromatic or non-aromatic ring or both. The term "aromatic ring" include any ring having at least one planar resonance structure where 2n+2 pi electrons are delocalized about the ring. Examples of heteroaryl groups include, but are not limited to, imidazopyridinyl groups, pyrrolopyridinyl groups, pyrazolopyridinyl groups, triazolopyridinyl groups, pyrazolopyrazinyl groups, pyridinyl groups, pyrazinyl groups, oxazolyl groups, imidazolyl groups, triazolyl groups, tetrazolyl groups, pyrazolyl groups, quinolinyl groups, isoquinolinyl groups, indazolyl groups, benzooxazolyl groups, naphthyridinyl groups, and quinoxalinyl groups. Other non-limiting examples of heteroaryl groups include xanthine, hypoxanthine, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, benzopyrazolyl, 5-indolyl, azaindole, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, 6-quinolyl 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl 3-pyrazolyl 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl and 4-pyrimidyl. "Bicyclic heteroaryl" refers to a heteroaryl radical that contains two rings.

[0022] The term "heterocycloalkyl" refers to a cycloalkyl group containing at least one ring heteroatom and optionally one or more oxo substituents. As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S), wherein the heteroatoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Each heterocycle can be attached at any available ring

carbon or heteroatom. Each heterocycle may have one or more rings. When multiple rings are present, they can be fused together. Each heterocycle typically contains 1, 2, 3, 4 or 5, independently selected heteroatoms. Preferably, these groups contain 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, 0, 1, 2, 3, 4 or 5 nitrogen atoms, 0, 1 or 2 sulfur atoms and 0, 1 or 2 oxygen atoms. More preferably, these groups contain 1, 2 or 3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Non-limiting examples of heterocycle groups include morpholin-3-one, piperazin-2-one, piperazin-1-oxide, piperidine, morpholine, piperazine, isoxazoline, pyrazoline, imidazoline, pyrrolidine, and the like.

[0023] "Halo" or "halogen" by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl", are meant to include alkyl in which one or more hydrogen is substituted with halogen atoms which can be the same or different, in a number ranging from one up to the maximum number of halogens permitted e.g. for alkyl, (2m'+1), where m' is the total number of carbon atoms in the alkyl group. For example, the term "haloC_{1-8}alkyl" is meant to include difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. The term "haloalkenyl", and "haloalkynyl" refers to alkenyl and alkynyl radicals having one or more halogen atoms. Additionally, term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms. In one group of embodiments, the haloalkyl, haloalkenyl, haloalkynyl, and haloalkoxy groups have from one to 5 or from one to 3 halo atoms. Examples of haloalkoxy groups include difluoromethoxy and trifluoromethoxy. In one group of embodiments, the halo atoms of the haloalkenyl and haloalkynyl groups are attached to the aliphatic portions of these groups.

[0024] The terms "optional" or "optionally" as used throughout the specification means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "heteroaryl group optionally substituted with an alkyl group means that the alkyl may but need not be present, and the description includes situation where the heteroaryl group is substituted with an alkyl group and situations where the heteroaryl group is not substituted with the alkyl group.

[0025] "Oxo" refers to the divalent atom =O.

[0026] In each of the above embodiments designating a number of atoms e.g. "C_{1-8}" is meant to include all possible embodiments that have one fewer atom. Non-limiting examples include C_{1-4}, C_{1-5}, C_{1-6}, C_{1-7}, C_{2-8}, C_{2-7}, C_{3-8}, C_{3-7} and the like.

[0027] The term "pharmaceutically acceptable alts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholin, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginase and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see e.g., Berge, S. M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19, 1977). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

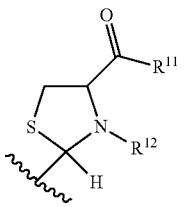
[0028] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0029] The term "pharmaceutically acceptable carrier or excipient" means a carrier or excipient that is useful in preparing a pharmaceutical composition that is generally safe, nontoxic and neither biologically nor otherwise undesirable, and includes a carrier or excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable carrier or excipient" as used in the specification and claims includes both one and more than one such carrier or excipient.

[0030] The terms "pharmaceutically effective amount", "therapeutically effective amount" or "therapeutically effective dose" refers to the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. The term "therapeutically effective amount" includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective amount will vary depending on the compound, the disorder or condition and its severity and the age, weight, etc., of the mammal to be treated.

[0031] "Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, Protective Groups in Organic Chemistry, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., Compendium of Synthetic Organic Methods, Vols. 14, 1971-1996, John Wiley & Sons, NY. Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), tert-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethenesulfonyl ("TES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxy protecting groups include, but are not limited to, those where the hydroxy group is either acylated or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPPS groups) and allyl ethers.

[0032] The term "aldehyde protecting group" refers to any known protecting group used to mask the aldehyde functionality. Aldehyde protecting groups include acetals and hemiacetals. The acetals and hemiacetals can be prepared from C_{1-8} alcohols or C_{2-8} diols. In one group of embodiments, the aldehyde protecting group is a five or six membered cyclic acetal formed from condensation of the aldehyde with ethylene or propylene glycol. In another group of embodiments the aldehyde protecting group is an imine or hydroxylimine. The aldehyde protecting groups of the present disclosure also include prodrug groups that convert the aldehyde to a prodrug, where the aldehyde is formed in vivo as the active agent under physiological conditions upon administration of the prodrug. The prodrug group can also serve to increase the bioavailability of the aldehyde. In one group of embodiments, the prodrug group is hydrolyzed in vivo to the aldehyde. In one group of embodiments, the aldehyde protecting group is a thiazolidine or N-acetylthiazolidine prodrug group. In one group of embodiments, the aldehyde protecting group is a thiazolidine prodrug group disclosed in U.S. Pat. No. 6,355,661. In one group of embodiments the modulators provided herein are condensed with L-cysteine or a L-cysteine derivative to form the corresponding thiazolidine protected aldehyde prodrug. In one group of embodiments, the thiazolidine has the formula



wherein R^{11} is selected from the group consisting of OH, alkoxy, substituted alkoxy, cycloalkoxy, substituted cycloalkoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, $N(R^{13})_2$ where R^{13} is independently H, alkyl, substituted alkyl, alkenyl, substituted alkenyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; R^{12} is H or -L-R^{14}, where L is carbonyl or sulfonyl; R^{14} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; the wavy line signifies the point of attachment to the phenyl ring of the allosteric modulators disclosed herein; and the term "substituted" refers to substitution by one or more substituents selected from the group consisting of COOH, CHO, oxyacyl, acyloxy, cycloalkoxy, phenol, phenoxy, pyridinyl, pyrrolidinyl, amino, amido, hydroxy, alkoxy, cycloalkoxy, F, Cl, Br, NO_2, cyano, sulfuryl, and the like. In one group of embodiments, provided are modulators having a thiazolidine protecting group where R^{11} is alkoxy and R^{12} is H, or where R^{11} is OH and R^{12} is —C(O)alkyl, or where R^{11} is NH(heteroaryl) and R^{12} is —C(O)alkyl.

[0033] The term "sickle cell disease" refers to diseases mediated by sickle hemoglobin (HbS) that results from a single point mutation in the hemoglobin (Hb). Sickle cell diseases includes sickle cell anemia, sickle-hemoglobin C disease (HbSC), sickle beta-plus-thalassaemia (HbS/β^+) and sickle beta-zero-thalassaemia (HbS/β^0).

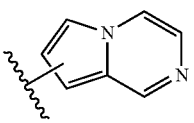
[0034] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[0035] "Tautomer" refers to alternate forms of a molecule that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a —N—C(H)—NH— ring atom arrangement, such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles. A person of ordinary skill in the art would recognize that other tautomeric ring atom arrangements are possible.

[0036] The terms "treat", "treating", "treatment" and grammatical variations thereof as used herein, includes partially or completely delaying, alleviating, mitigating or reducing the intensity, progression, or worsening of one or more attendant symptoms of a disorder or condition and/or alleviating, mitigating or impeding one or more causes of a disorder or condition. Treatments according to the invention may be applied preventively, prophylactically, pallatively or remedially.

[0037] The symbol > when used in connection with a substituent signifies that the substituent is a divalent substituent attached to two different atoms through a single atom on the substituent.

[0038] The term "wavy line" signifies the point of attachment of the substituent to the remainder of the molecule. When the wavy line is not depicted as being specifically appended to a specific ring atom, the point of attachment can be to my suitable atom of the substituent. For example, the wavy line in the following structure:



is intended to include, as the point of attachment, any of the six substitutable carbon atoms.

[0039] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space am termed "stereoisomers". "Stereoisomer" and "stereoisomers" refer to compounds that exist in different stereoisomeric forms if they possess one or more asymmetric centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Stereoisomers include enantiomers and diastereomers. Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (−)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture". Unless otherwise indicated, the description is intended to include individual stereoisomers well as mixtures. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of Advanced Organic Chemistry, 4th edition J. March, John Wiley and Sons, New York 1992) differ in the chirality of one or more stereocenters.

[0040] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with isotopes, such as for example deuterium (^{2}H), tritium (^{3}H) iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

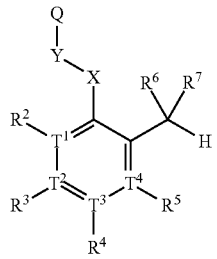
[0041] Unless indicated otherwise the nomenclature of substituents that am not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "alkoxyalkyl" refers to an akyl group that is substituted with alkoxy and "hydoxyalkyl" refers to an akyl group that is substituted with hydroxy. For both of these substituents the point of attachment is at the alkyl group.

[0042] It is understood that the definitions and formulas provided herein are not intended to include impermissible substitution patterns (e.g., methyl substituted with 5 fluoro groups). Such impermissible substitution patterns are well known to the skilled artisan.

II. Hemoglobin Modulators

[0043] In one group of embodiments, provided is a compound of Formula (I):

(I)



or a tautomer or pharmaceutically acceptable salt thereof,

[0044] wherein Q is selected from the group consisting of aryl, heteroaryl, and heterocycloalkyl, each optionally substituted with one to three R^a;

[0045] Y is O or $CR^{1a}R^{1b}$, where R^{1a} is H or halo and R^{1b} is selected from the group consisting of H, halo, and OH;

[0046] X is selected from the group consisting of O, $>CH(CH_2)_nR^8$, and $C(R^9)_2$ where n is 0 or 1, R^8 is OH, and R^9 is independently H or halo; or Y—X taken together is —NHC(O)— or —C(O)NH—;

[0047] R^2, R^3, R^4, and R^5 are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_2OR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3; or R^5 is $—(CH_2)_pR^{5a}$ where p is 0 or 1 and R^{5a} is OH;

[0048] R^6 and R^7 together form oxo or an aldehyde protecting group, or R^6 together with R^{1b}, R^8, or R^5 forms a cyclic ether where one of R^{1b}, R^8, or R^{5a} is O, R^6 is a bond, and R^7 is selected from the group consisting of OH, C_{1-8}alkoxy, and haloC_{1-8}alkoxy;

[0049] T^1, T^2, T^3, and T^4 are independently C or N provided that at least one of T^1, T^2, T^3, and T^4 is N and at least one of T^1, T^2, T^3, and T^4 is C;

[0050] each R^a is independently selected from the group consisting of halo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, $—(CH_2)_kOC(O)R^e$, $—(CH_2)_kSR^d$, CN, NO_2, $—(CH_2)_kCO_2(C_{1-8}alkyl)OH$, $—(CH_2)_kCO_2(C_{1-8}alkyl)(heteroaryl)C(O)(C_{1-8}alkyl)$, $—(CH_2)_kCO_2R^d$, $—(CH_2)_kCONR^dR^d$, $(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^d(O)_2R^e$, $—(CH_2)_kC(O)R^d$, $—(CH_2)_kOC(O)NR^dR^d$, $—NR^d(CH_2)_uOR^d$, $—NR^d(CH_2)_uNR^dR^d$, $—NR^d(CH_2)_uNR^dC(O)R^e$, $—NR^d(CH_2)_uNR^dC(O)_2R^e$, $—NR^d(CH_2)_uNR^dS(O)_2R^e$, $—(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^dC(O)_2R^d$, $—(CH_2)_kNR^dC(O)NR^dR^d$, $—(CH_2)_kS(O)R^e$, $—(CH_2)_kS(O)_2R^e$, $—(CH_2)_kNR^dS(O)_2R^e$, $—C(O)(CH_2)_kNR^dS(O)_2R^e$, $—(CH_2)_kC(O)NR^dS(O)_2R^e$, $—(CH)_kS(O)_2NR^dR^d$, N_3, $—(CH_2)_karyl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_karyl$ optionally substituted with one to three R^c, $—(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c, and $—NR(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6;

[0051] each R^b is independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and C_{2-8}alkynyl, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

[0052] each R^c is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkanyl, C_{2-8}alkynyl, haloC_{2-8}alkynyl, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, NO_2, $(CH_2)_mCO_2R^f$, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, N_3, $(R^f)_mSiC_{1-8}$alkyl, heteroaryl optionally substituted with one to three R^h, cycloalkyl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

[0053] each R^h is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, OR^j, OC(O)R, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, $C(O)R^j$, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^i$, $NR^jC(O)_2R^i$, $NR^jC(O)NR^jR^j$, $S(O)R^i$, $S(O)_2R^i$, $NR^jS(O)_2R^i$, and $S(O)_2NR^jR^j$;

[0054] R^d, R^f, and R^j are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl; and

[0055] R^e, R^g, and R^i are each independently selected from the group consisting of C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl;

[0056] In one group of embodiments, X and Y are not both O.

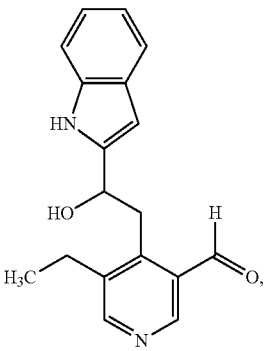
[0057] In one group of embodiments, when X is O, R^{1b} is not OH.

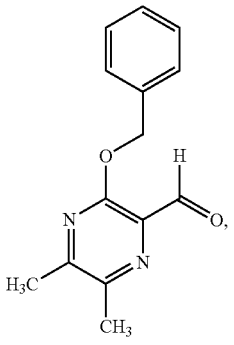
[0058] In one group of embodiments, when Y is O, and n is 0, R^8 is not OH.

[0059] In one group of embodiments, z is 0. In another group of embodiments, z is 1. In yet another group of embodiments, z is 2. In still another group of embodiments, z is 3.

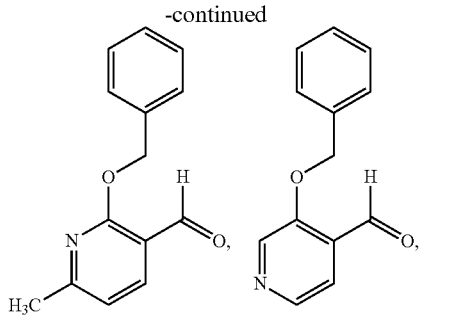
[0060] In one group of embodiments, when R^6 and R^7 together are oxo, Y is CH_2, X is O or CH_2, and R^5 is H, halo, OH, CHO, or OCH_3, then Q is V or W.

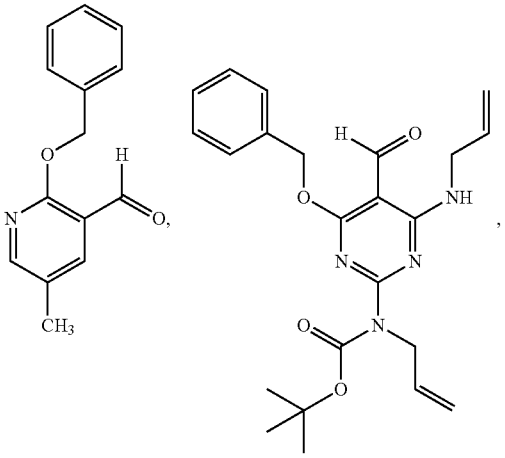
[0061] In one group of embodiments, the compound is not

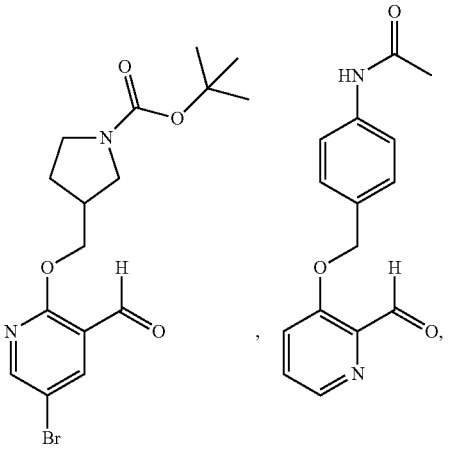


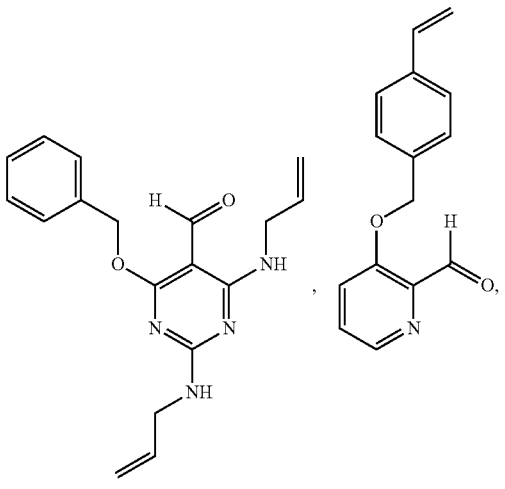


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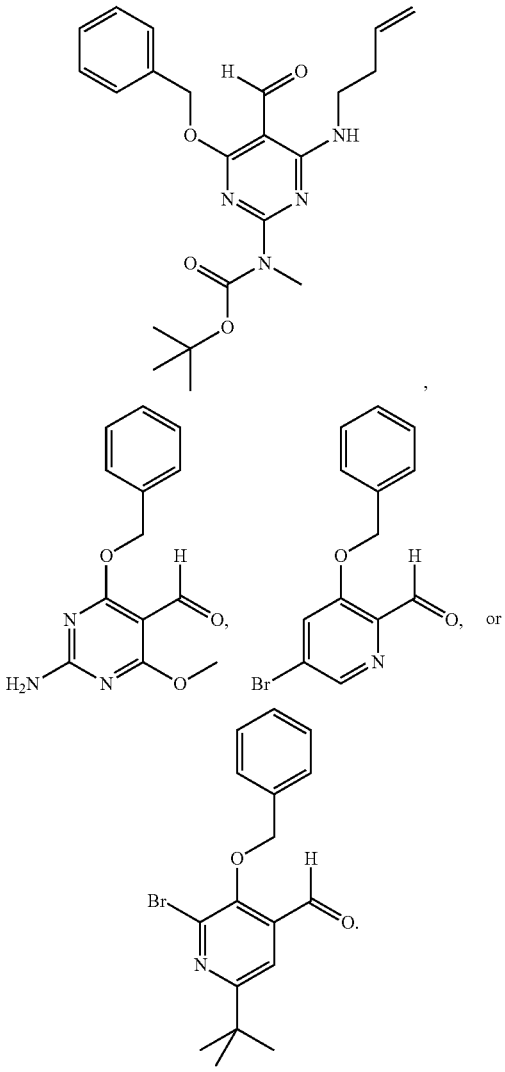




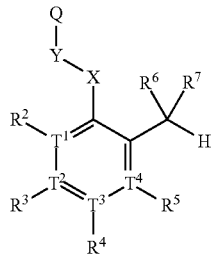




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[0062] In one group of embodiments, provided is a compound of Formula (Ia):



(Ia)

or a tautomer or pharmaceutically acceptable salt thereof,

[0063] wherein Q is selected from the group consisting of aryl, heteroaryl, and heterocycloalkyl, each optionally substituted with one to three R^a;

[0064] Y is O or $CR^{1a}R^{1b}$, where R^{1a} is H or halo and R^{1b} is selected from the group consisting of H, halo, and OH;

[0065] X is selected from the group consisting of O, $>CH(CH)_nR^8$, and $C(R^9)_2$ where a is 0 or 1, R^8 is OH, and R^9 is independently H or halo; or Y—X taken together is —NHC(O) or —C(O)NH—;

[0066] R^2, R^3, R^4, and R^5 are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3; or R^5 is $—(CH_2)_pR^{5a}$ where p is 0 or 1 and R^{5a} is OH;

[0067] R^6 and R^7 together form oxo or an aldehyde protecting group, or R^6 together with R^{1b}, R^8, or R^5 forms a cyclic ether where one of R^{1b}, R^8, or R^{5a} is O, R^6 is a bond, and R^7 is selected from the group consisting of OH, C_{1-8}alkoxy, and haloC_{1-8}alkoxy;

[0068] T^1, T^2, T^3, and T^4 are independently C or N provided that at least one of T^1, T^2, T^3, and T^4 is N and at least one of T^1, T^2, T^3, and T^4 is C;

[0069] each R^a is independently selected from the group consisting of halo, R^b, OR^d, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, $NR^dC(O)R^e$, $NR^dC(O)_2R^d$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, N_3, aryl optionally substituted with one to three R^c, heteroaryl optionally substituted with one to three R^c, and heterocycloalkyl optionally substituted with one to three R^c, and

[0070] each R^b is independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and C_{2-8}alkynyl, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

[0071] each R^c is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkanyl, C_{2-8}alkynyl, haloC_{2-8}alkynyl, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, NO_2, CO_2R^f, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, and N_3 where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

[0072] each R^d, R^f is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl; and

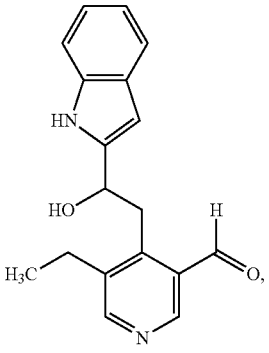
[0073] each R^e, R^g is independently selected from the group consisting of C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl;

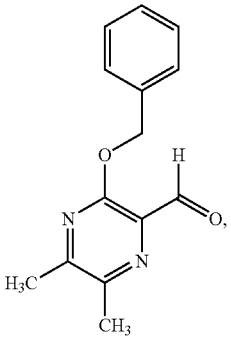
[0074] provided that X and Y are not both O;

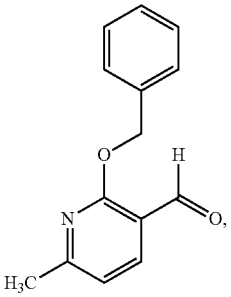
[0075] provided that when X is O, R^{1b} is not OH;

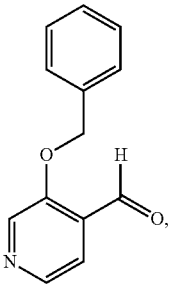
[0076] provided that when Y is O, and n is 0, R^g is not OH.

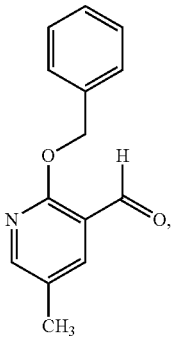
[0077] In one group of embodiments, the compound is not:

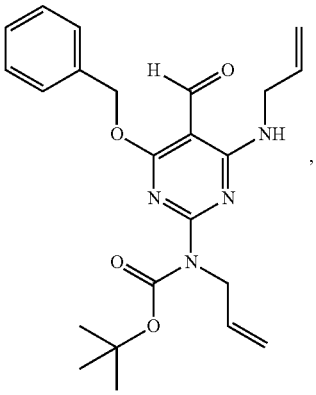


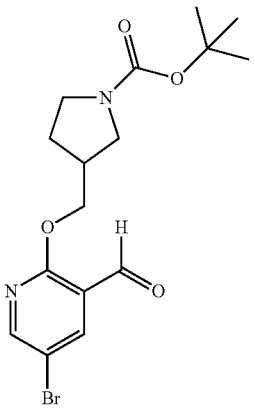


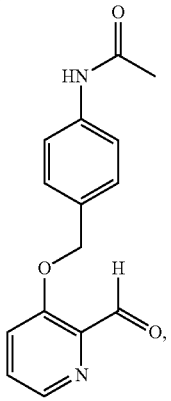




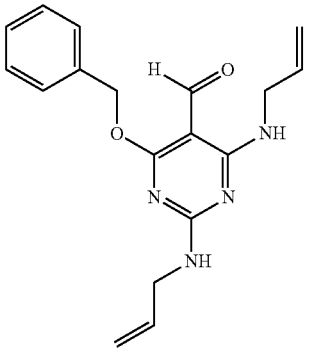


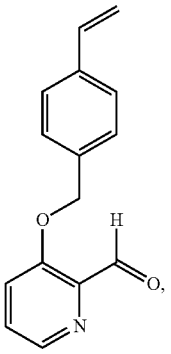


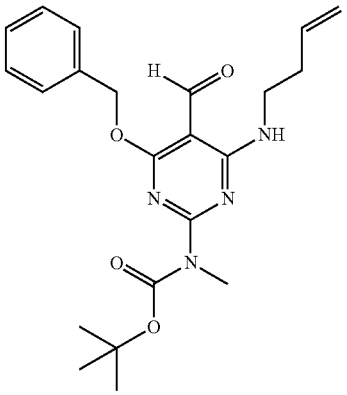


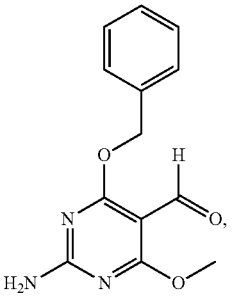


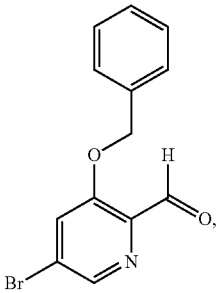
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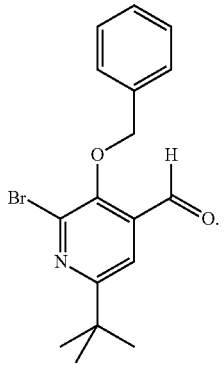






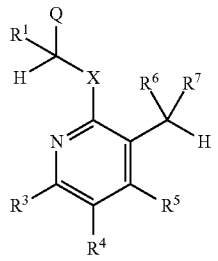


or



[0078] In one group of embodiments, provided is a compound having Formula (Ia)

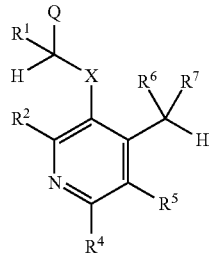
(Ia)



or a tautomer or pharmaceutically acceptable salt thereof.

[0079] In one group of embodiments, provided is a compound having Formula (Ib)

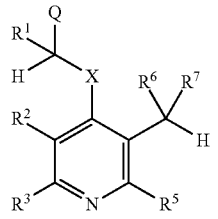
(Ib)



or a tautomer or pharmaceutically acceptable salt thereof.

[0080] In one group of embodiments, provided is a compound having Formula (Ic):

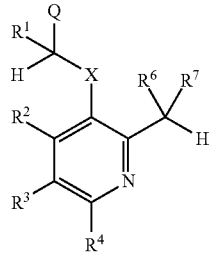
(Ic)



or a tautomer or pharmaceutically acceptable salt thereof.

[0081] In one group of embodiments, provided is a compound having Formula (Id):

(Id)

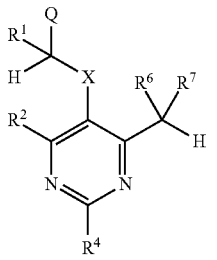


or a tautomer or pharmaceutically acceptable salt thereof.

[0082] In one group of embodiments, at least two of T^1, T^2, T^3, and T^4 are N.

[0083] In one group of embodiments, provided is a compound having Formula (Ie), (If), (Ig), or (Ih):

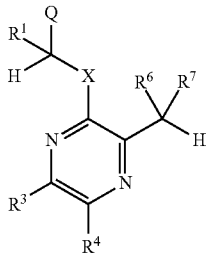
(Ie)



or a tautomer or pharmaceutically acceptable salt thereof.

[0084] In one group of embodiments, provided is a compound having Formula (If):

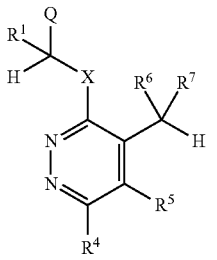
(If)



or a tautomer or pharmaceutically acceptable salt thereof.

[0085] In one group of embodiments, provided is a compound having Formula (Ig):

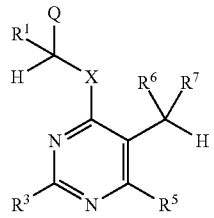
(Ig)



or a tautomer or pharmaceutically acceptable salt thereof.

[0086] In one group of embodiments, provided is a compound having Formula (h):

(Ih)



or a tautomer or pharmaceutically acceptable suit thereof.

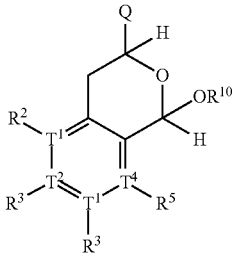
[0087] In one group of embodiments, R^6 and R^7 together form oxo.

[0088] In one group of embodiments, R^6 and R^7 together form a thiazolidine.

[0089] In one group of embodiments, R^6 together with R^{1b}, R^8, or R^5 forms a cyclic ether where one of R^{1b}, R^8, or R^{5a} is O, R^6 is a bond, and R^7 is selected from the group consisting of OH, C_{1-8}alkoxy, and haloC_{1-8}alkoxy.

[0090] In one group of embodiments, provided is a compound having Formula (Ii):

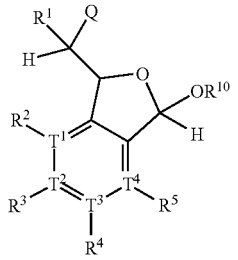
(Ii)



or a tautomer or pharmaceutically acceptable salt thereof, wherein R^{10} is selected from the group consisting of H, C_{1-8}alkyl, and haloC_{1-8}alkyl.

[0091] In one group of embodiments, provided is a compound having Formula (Ij):

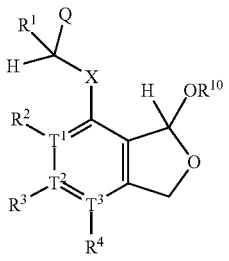
(Ij)



or a tautomer or pharmaceutically acceptable salt thereof, wherein R^{10} is selected from the group consisting of H, C_{1-8}alkyl, and haloC_{1-8}alkyl.

[0092] In one group of embodiments, provided is a compound having Formula (Ik):

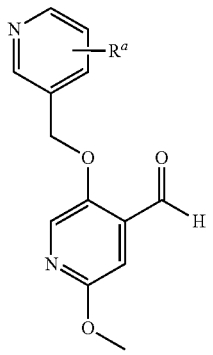
(Ik)



or a tautomer or pharmaceutically acceptable salt thereof, wherein R^{10} is selected from the group consisting of H, C_{1-8}alkyl, and haloC_{1-8}alkyl.

[0093] In one group of embodiments, provided is a compound having Formula (Il):

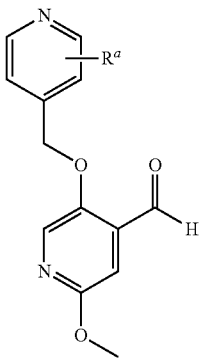
(Il)



or a tautomer or pharmaceutically acceptable salt thereof.

[0094] In one group of embodiments, provided is a compound having Formula (Im):

(Im)



or a tautomer or pharmaceutically acceptable salt thereof.

[0095] In one group embodiments, at least one R^a is heteroaryl optionally substituted with one to three R^c.

[0096] In one group of embodiments at least one R^a is heteroaryl attached to Q at the ring atom adjacent to ring atom bearing Y.

[0097] In one group of embodiments at least one R^a is heteroaryl substituted with at least one C_{1-8}alkyl. In one group of embodiments at least one R^a heteroaryl is substituted with at least one methyl.

[0098] In one group of embodiments at least one R^a is pyrazolyl substituted with at least one C_{1-8}alkyl. In one group of embodiments at least one R^a is pyrazoyl substituted with at least one C_{1-8}alkyl. In one group of embodiments, at least one R^a is pyrazol-5-yl. In one group of embodiments, at least one R^a is 4-methyl-pyrazol-5-yl.

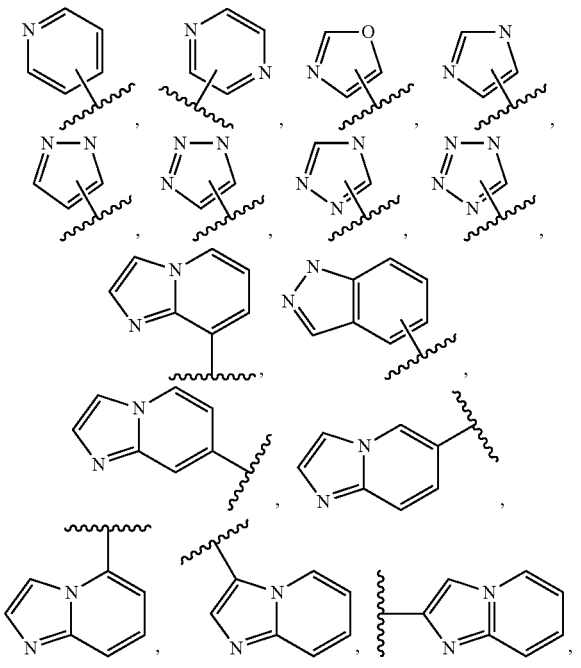
[0099] In one group of embodiments, Q is a heteroaryl or heterocycloalkyl group optionally substituted with one to three R^a.

[0100] In one group of embodiments, Q is a bicyclic heteroaryl or heterocycloalkyl group optionally substituted with one to three R^a.

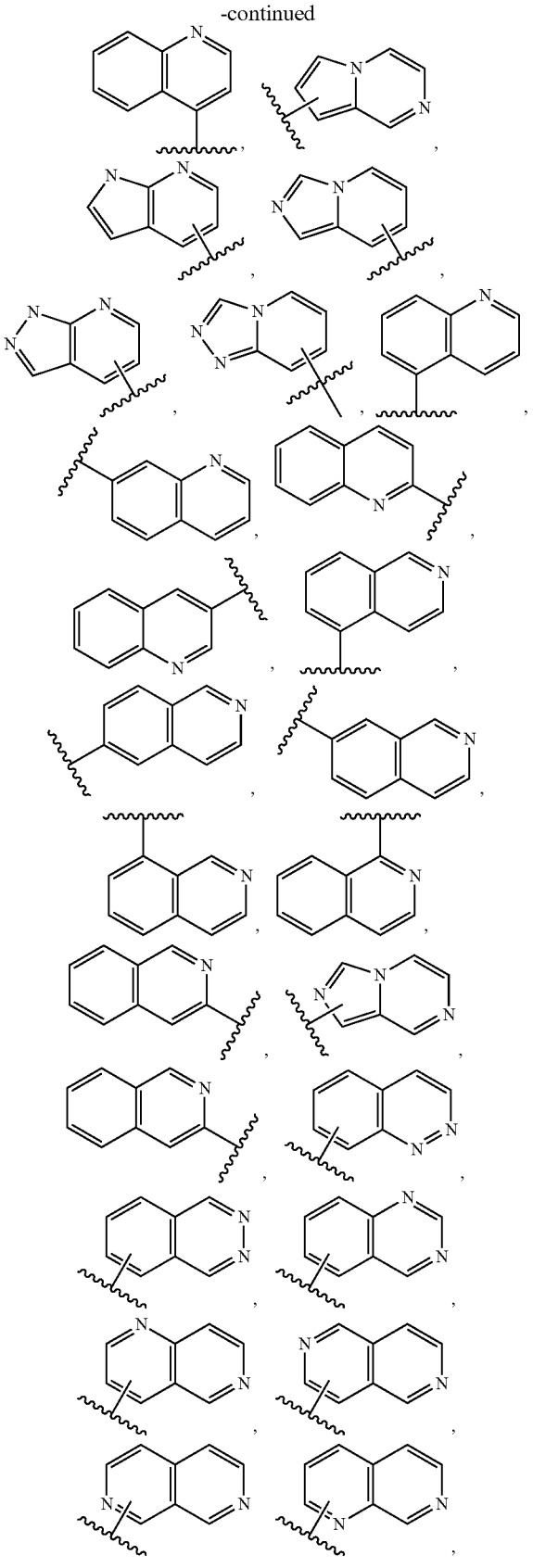
[0101] In one group of embodiments, Q is a bicyclic heteroaryl group optionally substituted with one to three R^a.

[0102] In one group of embodiments, Q is a bicyclic heteroaryl group substituted with one to three R^a. In one group of embodiments, Q is isoquinolin-4-yl optionally substituted with one to three R^a wherein at least one R^a is heteroaryl optionally substituted with one to three R^c. In one group of embodiments at least one R^a is heteroaryl attached to said Q at the ring atom adjacent to ring atom bearing Y. In one group of embodiments at least one R^a is heteroaryl substituted with at least one C_{1-8}alkyl. In one group of embodiments at least one R^a heteroaryl is substituted with at least one methyl. In one group of embodiments at least one R^a is pyrazolyl substituted with at least one C_{1-8}alkyl. In one group of embodiments at least one R^a is pyrazoyl substituted with at least one methyl. In one group of embodiments, R^a is pyrazol-5-yl. In one group of embodiments, R^a is 4-methyl-pyrazol-5-yl.

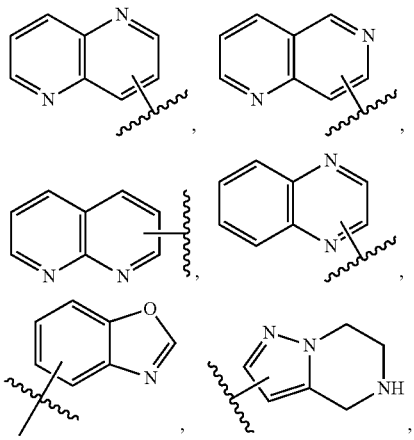
[0103] In one group of embodiments, Q is selected from the group consisting of



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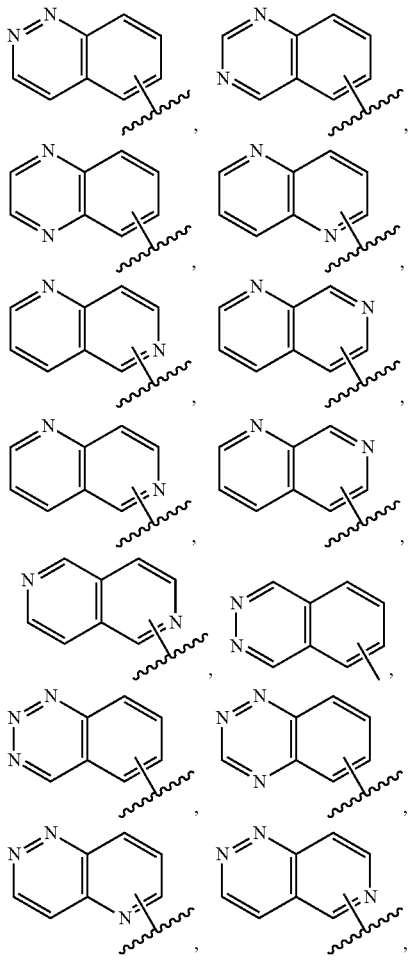


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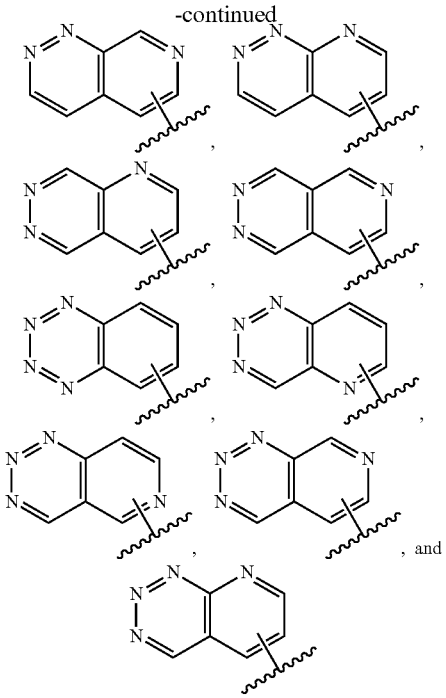


naphthalene containing two to four ring nitrogen atoms, each optionally substituted with one to three R^a and wherein the wavy line signifies the point of attachment to Y.

[0104] In one group of embodiments, Q is selected from the group consisting of



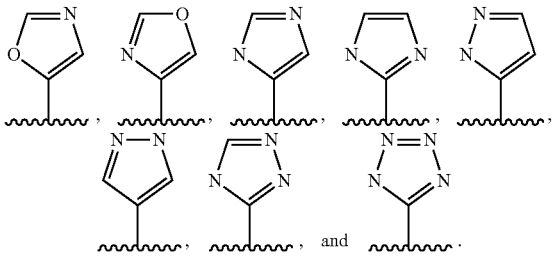
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, and

wherein Q is optionally substituted with one to three R^a.

[0105] In one group of embodiments, Q is selected from the group consisting of



[0106] In one group of embodiments, Q is substituted with $CONR^dR^d$, NR^dR^d, or heteroaryl optionally substituted with one to three R^c. In one group of embodiments, Q is substituted with heteroaryl having one to two nitrogen ring atoms.

[0107] In one group of embodiments, Q is not unsubstituted pyridin-2-yl, unsubstituted pyridin-3-yl, or unsubstituted pyridine-4-yl. In one group of embodiments, Q is pyridin-2-yl, pyridin-3-yl, or pyridine-4-yl, each of which is substituted with one to three R^c.

[0108] In one group of embodiments, Q is pyridin-2-yl, pyridin-3-yl, or pyridine-4-yl, said Q is optionally substituted with CN or $CONR^dR^d$.

[0109] In one group of embodiments, Q is pyridin-2-yl, pyridin-3-yl, or pyridine-4-yl, said Q is optionally substituted with one to three R^a wherein at least one R^a is heteroaryl optionally substituted with one to three R^c. In one group of embodiments at least one R^a is heteroaryl attached to said Q at the ring atom adjacent to ring atom bearing Y. In one group of embodiments at least one R^a is heteroaryl substituted with at least one C_{1-8}alkyl. In one group of

embodiments at least one R^a heteroaryl is substituted with at least one methyl. In one group of embodiments at least one R^a is pyrazolyl substituted with at least one C_{1-8}alkyl. In one group of embodiments at least one R^a is pyrazoyl substituted with at least one methyl. In one group of embodiments, R^a is pyrazol-5-yl. In one group of embodiments, R^a is 4-methyl-pyrazol-5-yl.

[0110] In one group of embodiments, Q is substituted with at least one R^a selected from the group consisting of —$(CH_2)_kOH$, —$(CH_2)_kNH_2$, —$(CH_2)_kNH(C_{1-8}alkyl)$, —$(CH_2)_kN(C_{1-8}alkyl)(C_{1-8}alkyl)$, —$(CH_2)_kNHC(C_{1-8}alkyl)$, —$(CH_2)_kN(C_{1-8}alkyl)C(O)(C_{1-8}alkyl)$, —$(CH_2)_kNHC(O)_2(C_{1-8}alkyl)$, —$(CH_2)_kN(C_{1-8}alkyl)C(O)_2(C_{1-8}alkyl)$, —$(CH_2)_kNHS(O)_2(C_{1-8}alkyl)$, —$(CH_2)_kN(C_{1-8}alkyl)S(O)_2(C_{1-8}alkyl)$, and —$(CH_2)_k$heterocycloalkyl optionally substituted with one to three R^c where k is selected f on the group consisting of 0, 1, 2, 3, 4, 5, and 6. In some embodiments the heterocycloalkyl group is morpholino or piperazinyl optionally substituted with alkyl, —$C(O)C_{1-8}$alkyl, —$C(O)_2C_{1-8}$alkyl, or —$S(O)_2C_{1-8}$alkyl.

[0111] In one group of embodiments, Q is substituted with at least one R^a selected from the group consisting of —$NR^d(CH_2)_kOH$, —$NR^d(CH_2)_kNH_2$, $NR^d(CH_2)_kNH(C_{1-8}alkyl)$, —$NR^d(CH_2)_kN(C_{1-8}akyl)(C_{1-8}alkyl)$, —$NR^d(CH_2)_kNHC(O)(C_{1-8}alkyl)$, —$NR^d(CH_2)_kN(C_{1-8}alkyl)C(O)(C_{1-8}alkyl)$, —$NR^d(CH_2)_kNHC(O)_2(C_{1-8}alkyl)$, —$NR^d(CH_2)_kN(C_{1-8}alkyl)C(O)_2(C_{1-8}alkyl)$, —$NR^d(CH_2)_kNHS(O)_2(C_{1-8}alkyl)$, —$NR^d(CH_2)_kN(C_{1-8}alkyl)S(O)_2(C_{1-8}alkyl)$, and —$NR^d(CH_2)_k$heterocycloalkyl optionally substituted with one to three R^c where k is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6. In some embodiments, R^d is H or C_{1-8}alkyl. In some embodiments the heterocycloalkyl group is morpholino or piperazinyl optionally substituted with alkyl, —$C(O)C_{1-8}$alkyl, —$C(O)_2C_{1-8}$alkyl, or —$S(O)_2C_{1-8}$alkyl.

[0112] In one group of embodiments, Q is substituted with at least one R^a selected from the group consisting of $O(CH_2)_kOH$, $O(CH_2)_kNH_2$, $O(CH_2)_kNH(C_{1-8}alkyl)$, $O(CH_2)_kN(C_{1-8}alkyl)(C_{1-8}alkyl)$, $O(CH_2)_kNHC(O)(C_{1-8}alkyl)$, $O(CH_2)_kN(C_{1-8}alkyl)C(O)(C_{1-8}alkyl)$, $O(CH_2)_kNHC(O)_2(C_{1-8}alkyl)$, $O(CH_2)_kN(C_{1-8}alkyl)C(O)_2(C_{1-8}alkyl)$, $O(CH_2)_kNHS(O)_2(C_{1-8}alkyl)$, $O(CH_2)_kN(C_{1-8}alkyl)S(O)_2(C_{1-8}alkyl)$, and $O(CH_2)_k$heterocycloalkyl optionally substituted with one to three R^c where k is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6. In some embodiments the heterocycloalkyl group is morpholino or piperazinyl optionally substituted with alkyl, —$C(O)C_{1-8}$alkyl, —$C(O)_2C_{1-8}$alkyl, or —$S(O)_2C_{1-8}$alkyl.

[0113] In one group of embodiments, T^1 is C and R^2 is H.

[0114] In one group of embodiments, T^2 is C and R^3 is H.

[0115] In one group of embodiments, T^4 is C and R^5 is H.

[0116] In one group of embodiments, T^3 is C and R^4 is C_{1-8}alkoxy.

[0117] In one group of embodiments, R^2, R^3, R^5 when present are H and R^4 is C_{1-8} alkoxy.

[0118] In one group of embodiments, R^4 is methoxy.

[0119] In one group of embodiments, R^4 is haloalkoxy. In one group of embodiments, R^4 is $OCHF_2$. In one group of embodiments, R^4 is OCF_3.

[0120] In one group of embodiments, R^2, R^3, R^4, and R^5 when present are H.

[0121] In one group of embodiments, one of R^2, R^3, R^4, and R^5 is selected from the group consisting of —$O(CH_2)_zOH$, —$O(CH_2)_zNH_2$, —$O(CH_2)_zNH(C_{1-8}alkyl)$, and —$O(CH_2)_zN(C_{1-8}alkyl)(C_{1-8}alkyl)$ where z is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6.

[0122] In one group of embodiments, X is O.

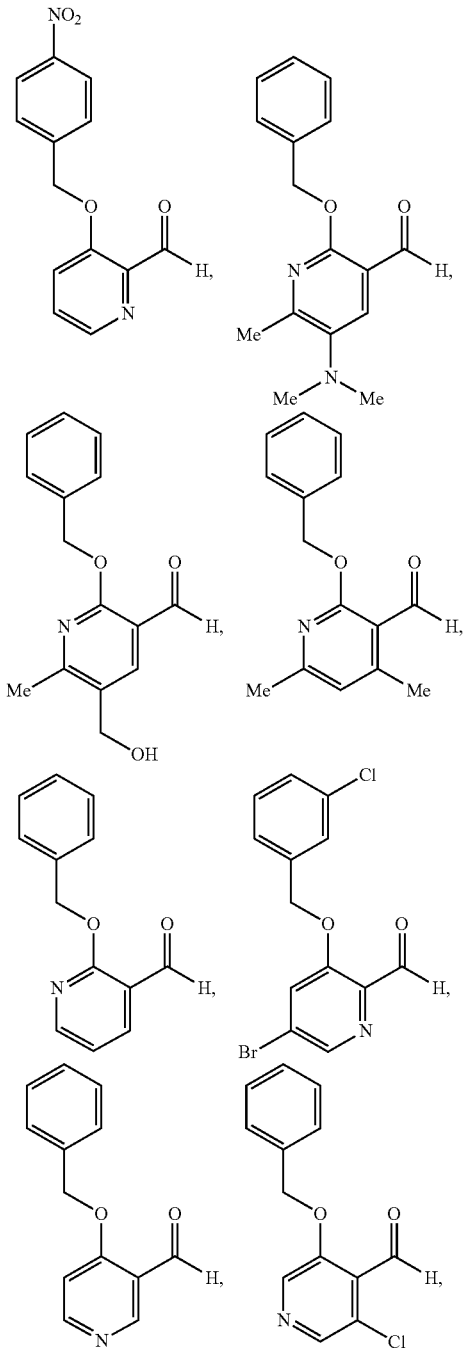
[0123] In one group of embodiments, CH_2.

[0124] In one group of embodiments, X is $C(R^9)_2$ and at least one of R^9 is F.

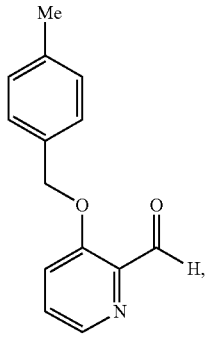
[0125] In one group of embodiments, Y is CH_2.

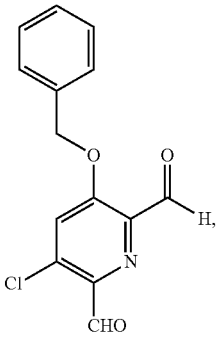
[0126] In one group of embodiments, Y is $CR^{1a}R^{1b}$ and at least one of R^{1a} or R^{1b} is F.

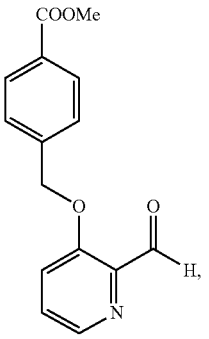
[0127] In one group of embodiments, the compound is not:

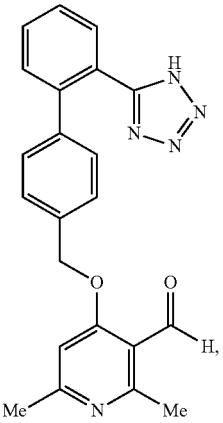


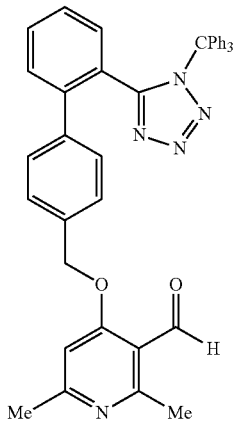
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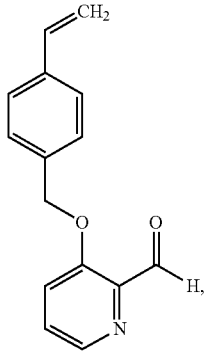




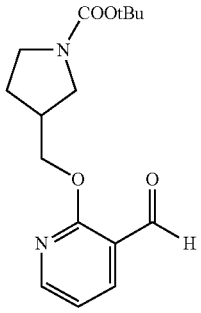




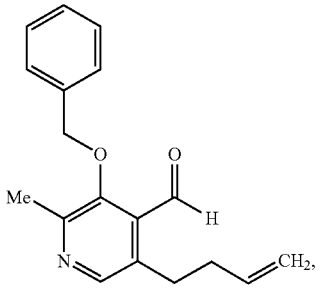




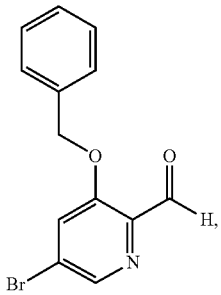
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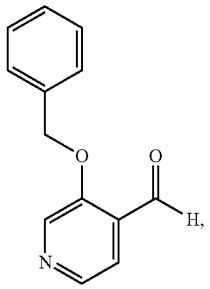


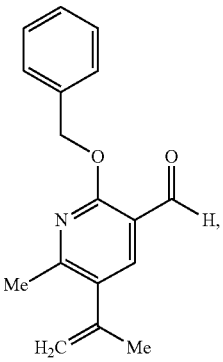
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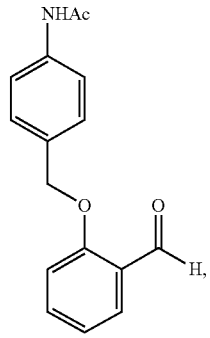


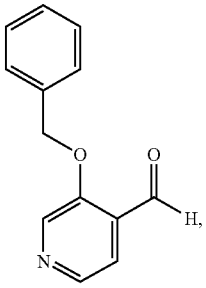
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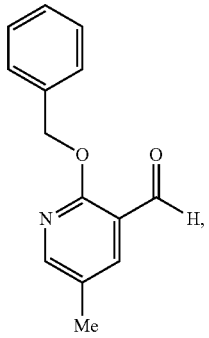


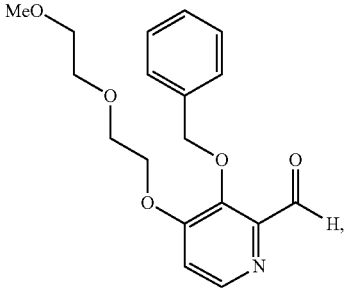


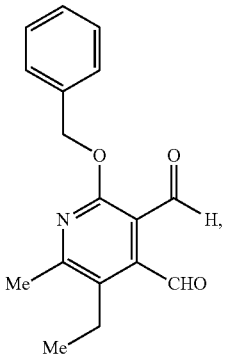


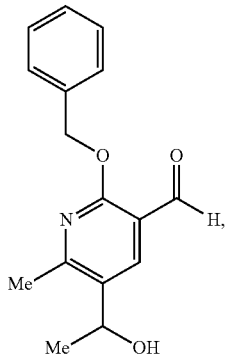




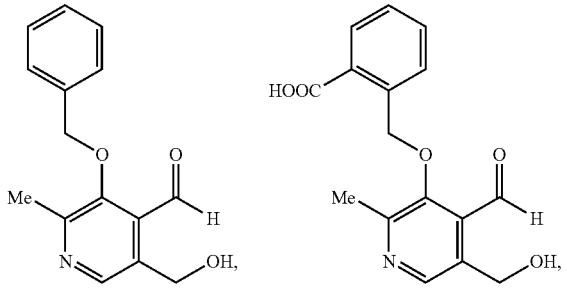


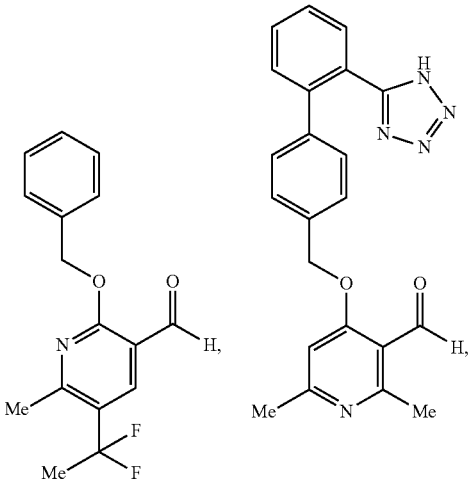


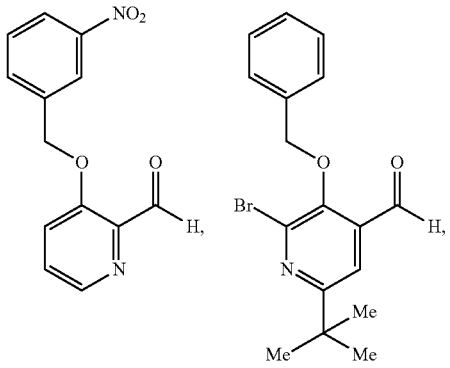


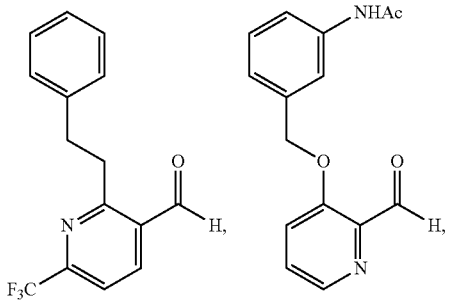


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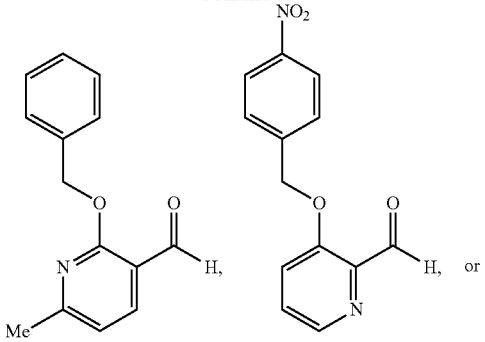


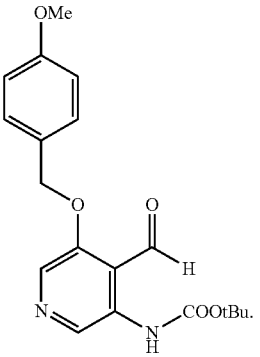






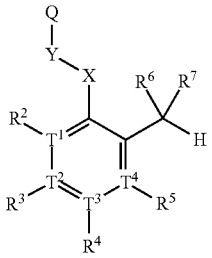
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[0128] In another group of embodiments, the invention provides compounds of Formula (Ib):

(Ib)



or a tautomer or pharmaceutically acceptable salt thereof, wherein:

[0129] Q is selected from the group consisting of aryl, heteroaryl, and heterocycloalkyl, each optionally substituted with one to three R^a;

[0130] Y is O or CH_2;

[0131] X is O or CH_2;

[0132] R^2 and R^3 are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^d$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 0, 1, 2, or 3;

[0133] R^4 is absent or selected from the group consisting of hydrogen, R^b, OR^d, $O(CH_2)_zR^d$, where z is 0, 1, 2, or 3;

[0134] R^5 is absent or selected from the group consisting of hydrogen, halo, R^b, and OR^d;

[0135] R^6 and R^7 together form oxo or an aldehyde protecting group;

[0136] T^1, T^2, T^3, and T^4 are independently C or N provided that at least one of T^1, T^2, T^3, and T^4 is N and at least one of T^1, T^2, T^3, and R^4 is C;

[0137] each R^a is independently selected from the group consisting of halo, oxo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, $—(CH_2)_kOC(O)R^e$, $—(CH_2)_kSR^e$, CN, NO_2, $—(CH_2)_kCO_2(C_{1-8}alkyl)OH$, $—(CH_2)_kCO_2(C_{1-8}alkyl)(heteroaryl)C(O)(C_{1-8}alkyl)$, $—(CH_2)_kCO_2R^d$, $—(CH_2)_kCONR^dR^d$, $—(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^dC(O)_2R^e$, $—(CH_2)_kC(O)R^d$, $—(CH_2)_kOC(O)NR^dR^d$, $—NR^d(CH_2)_uOR^d$, $—NR^d(CH_2)_uNR^dR^d$, $—NR^d(CH_2)_uNR^dC(O)R^e$, $—NR^d(CH_2)_uNR^dC(O)_2R^e$, $—NR^d(CH_2)_uNR^dS(O)_2R^e$, $—(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^dC(O)_2R^d$, $—(CH_2)_kNR^dC(O)NR^dR^d$, $—(CH_2)_kS(O)R^e$, $—(CH_2)_kS(O)_2R^e$, $—(CH_2)_kNR^dS(O)_2R^e$, $—C(O)(CH_2)_kNR^dS(O)_2R^e$, $—(CH_2)_kC(O)NR^dS(O)_2R^e$, $—(CH)_kS(O)_2NR^dR^d$, N_3, $—(CH_2)_karyl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_karyl$ optionally substituted with one to three R^c, $—(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c, and $—NR(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6;

[0138] each R^b is independently selected from the group consisting of $C_{1-8}alkyl$, $C_{2-8}alkenyl$, and $C_{2-8}alkynyl$, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

[0139] each R^c is independently selected from the group consisting of halo, $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, $C_{2-8}alkenyl$, $haloC_{2-8}alkanyl$, $C_{2-8}alkynyl$, $haloC_{2-8}alkynyl$, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, NO_2, $(CH_2)_mCO_2R^f$, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, N_3, $(R^f)_mSiC_{1-8}alkyl$, heteroaryl optionally substituted with one to three R^h, cycloalkyl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

[0140] each R^h is independently selected from the group consisting of halo, $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, OR^j, OC(O)R, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, $C(O)R^j$, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^i$, $NR^jC(O)_2R^i$, $NR^jC(O)NR^jR^j$, $S(O)R^i$, $S(O)_2R^i$, $NR^jS(O)_2R^i$, and $S(O)_2NR^jR^j$;

[0141] R^d, R^f, and R^j are each independently selected from the group consisting of hydrogen, $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, C_{2-8} alkenyl, $haloC_{2-8}alkenyl$, $C_{2-8}alkynyl$, and $haloC_{2-8}alkynyl$; and

[0142] R^e, R^g, and R^i are each independently selected from the group consisting of $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, C_{2-8} alkenyl, $haloC_{2-8}alkenyl$, C_{2-8} alkynyl, and $haloC_{2-8}alkynyl$;

[0143] provided that X and Y are not both O;

[0144] provided that when Q is phenyl and R^4 is $C_{1-8}alkyl$ or $C_{2-8}alkenyl$, Q is substituted with at least one R^a;

[0145] provided that when R^5 is halo, Q is substituted with at least 1 R^a;

[0146] provided that when R^5 is R^b, Q is not phenyl; and

[0147] provided that when R^2, R^3, R^4, and R^5 are H and Q is phenyl, Q is substituted with at least one R^a selected from 4-carboxy, 3-carboxy, and (C_{1-8} alkyl 3-carboxylate).

[0148] In one group of embodiments, the invention provides compounds of Formula Ib wherein R^2 and R^3 are independently absent or selected from the group consisting of hydrogen, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^d$, CO_2R^d, $CONR^dR^d$, and $C(O)R^d$, where z is 1, 2, or 3.

[0149] In one group of embodiments, the invention provides compounds of Formula Ib wherein at least one z is 0. In another group of embodiments, at least one z is 1. In yet another group of embodiments, at least one z is 2. In still another group of embodiments, at least one z is 3. In another group of embodiments, no z is 0.

[0150] In one group of embodiments, the invention provides compounds of Formula Ib wherein T^2 is N; T^1, T^3, and T^4 are C; R^2 and R^5 are H; R^3 is absent; and R^4 is $C_{1-8}alkoxy$.

[0151] In one group of embodiments, the invention provides compounds of Formula Ib wherein T^2 is N; T^1, T^2, and T^3 are C; R^2 and R^5 are H; R^4 is absent; and R^5 is selected from hydroxy and $C_{1-8}alkoxy$.

[0152] In one group of embodiments, the invention provides compounds of Formula Ib wherein T^4 is N; T^1, T^2, and T^3 are C; R^2 and R^3 are H; R^5 is absent; and R^4 is selected from $C_{1-8}alkyl$ and $C_{1-8}alkoxy$.

[0153] In one group of embodiments, the invention provides compounds of Formula Ib wherein T^1 is N; T^2, T^3, and T^4 are C; R^3, R^4, and R^5 are H; and R^2 is absent.

[0154] In one group of embodiments, the invention provides compounds of Formula Ib wherein T^2 is N; T^1, T^3, and T^4 an C; R^2, R^4, and R^5 are H; and R^4 is absent.

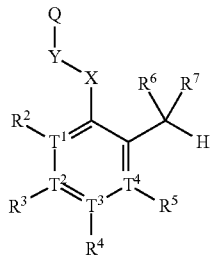
[0155] In one group of embodiments, the invention provides compounds of Formula Ib wherein T^3 is N; T^1, T^2, and T^4 are C; R^2, R^3, and R^5 are H; and R^4 is absent.

[0156] In one group of embodiments, the invention provides compounds of Formula Ib wherein T^4 is N; T^1, T^2, and T^3 are C; R^2, R^3, and R^4 are H; and R^5 is absent.

[0157] In one group of embodiments, the invention provides compounds of Formula Ib wherein Q is selected from an imidazopyridinyl group, a pyrrolopyridinyl group, a pyrazolopyridinyl group, a triazolopyridinyl group, a pyrazolopyrazinyl group, a pyridinyl group, a pyrazinyl group, an oxazolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a pyrazolyl group, a quinolinyl group, an isoquinolinyl group, an indazolyl group, a benzooxazolyl group, a naphthyridinyl group, and a quinoxalinyl group; and wherein Q is optionally substituted with one to three R^a.

[0158] In another group of embodiments, the invention provides compounds of Formula Ic:

(c)



or a tautomer or pharmaceutically acceptable salt thereof, wherein:

[0159] Y is CH_2;

[0160] X is O or CH_2;

[0161] T^1, T^2, T^3 and T^4 are C or N, provided that no more than one of T^1, T^2, T^3, and T^4 is N;

[0162] Q is selected from the group consisting of

[0163] i) heteroaryl optionally substituted with one to three R^a; wherein

[0164] R^2, R^3, R^4, and R^5, are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^b, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)NR^dR^d$, and N_3 where z is 1, 2, or 3;

[0165] ii) aryl substituted with one to three $-(CH_2)_kCO_2R^d$; wherein

[0166] R^2 and R^5 are independently absent or selected from the group consisting of hydrogen, halo, OR^b, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3;

[0167] R^3 and R^4 are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3;

[0168] iii) unsubstituted aryl, wherein

[0169] R^2, R^3, and R^4, are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3; and

[0170] R^5 is absent or is OR^d; and

[0171] iv) heterocycloalkyl, optionally substituted with one to three R^a; wherein

[0172] R^2, R^3, R^4, and R^5, are independently absent or selected from the group consisting of hydrogen, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3;

[0173] R^6 and R^7 together form oxo or an aldehyde protecting group;

[0174] each R^a is independently selected from the group consisting of halo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, $-(CH_2)_kOC(O)R^e$, $-(CH_2)_kSR^d$, CN, NO_2, $-(CH_2)_kCO_2(C_{1-8}alkyl)OH$, $-(CH_2)_kCO_2(C_{1-8}alkyl)(heteroaryl)C(O)(C_{1-8}alkyl)$, $-(CH_2)_kCO_2R^d$, $-(CH_2)_kCONR^dR^d$, $-(CH_2)_kNR^dC(O)R^e$, $-NR^d(CH_2)_uNR^dR^d$, $-NR^d(CH_2)_uNR^dC(O)R^e$, $-NR^d(CH_2)_uNR^dC(O)_2R^e$, $-NR^d(CH_2)_uNR^dS(O)_2R^e$, $-(CH_2)_kNR^dC(O)R^e$, $-(CH_2)_kNR^dC(O)_2R^e$, $-NR^d(CH_2)_uNR^dC(O)NR^dR^d$, $-(CH_2)_kS(O)R^e$, $-(CH_2)_kS(O)_2R^e$, $-(CH_2)_kNR^dS(O)_2R^e$, $-C(O)(CH_2)_kNR^dS(O)_2R^e$, $-(CH_2)_kC(O)NR^dS(O)_2R^e$, $-(CH_2)_kS(O)_2NR^dR^d$, N_3, $-(CH_2)_karyl$ optionally substituted with one to three R^c, $-NR^d(CH_2)_karyl$ optionally substituted with one to three R^c, $-(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $-NR^d(CH_2)$, heteroaryl optionally substituted with one to three R^c, $-(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c, an $-NR^d(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5 or 6;

[0175] each R^b is independently selected from the group consisting of $C_{1-8}alkyl$, $C_{2-8}alkenyl$, and $C_{2-8}alkynyl$, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

[0176] each R^c is independently selected from the group consisting of halo, $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, $C_{2-8}alkenyl$, $haloC_{2-8}alkenyl$, $C_{2-84}alkynyl$, $haloC_{2-8}alkynyl$, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, NO_2, $(CH_2)_mCO_2R^f$, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^f$, $S(O)_2NR^fR^f$, N_3, $(R^f)_mSiC_{1-8}alkyl$, heteroaryl optionally substituted with one to three R^h, cycloalkyl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

[0177] each R^h is independently selected from the group consisting of halo, $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, OR^j, OC(O)R, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, $C(O)R^j$, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^i$, $NR^jC(O)_2R^i$, $NR^jC(O)NR^jR^j$, $S(O)R^i$, $S(O)_2R^i$, $NR^jS(O)R^i$ and $S(O)NR^jR^j$;

[0178] R^d, R^f, and R^j are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, $haloC_{1-8}akyl$, C_{2-8} alkenyl, $haloC_{1-8}alkenyl$, C_{2-8} alkynyl, and $haloC_{2-8}alkynyl$; and

[0179] R^e, R^g, and R^i are each independently selected from the group consisting of $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, C_{2-8} alkenyl, $haloC_{1-8}alkenyl$, C_{2-8} alkynyl, and $haloC_{2-8}alkynyl$.

[0180] In one group of embodiments, the invention provides compounds of Formula Ic, wherein R^6 and R^7 together form oxo.

[0181] In one group of embodiments, the invention provides compounds of Formula Ic, wherein R^2 and R^3 are independently absent or selected from the group consisting of hydrogen. R^b, OR^d, $O(CH_2)OR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, CO_2R^d, $CONR^dR^d$, and $C(O)R^d$, where z is 1, 2, or 3.

[0182] In one group of embodiments, the invention provides compounds of Formula Ic, wherein T^2 is N; R^2 and R^5 are H; R^3 is absent; and R^4 is $C_{1-8}alkoxy$, $haloC_{1-8}alkoxy$, and $O(CH_2)_2C_{1-8}alkyl$.

[0183] In one group of embodiments, the invention provides compounds of Formula Ic, wherein T^2 is N; R^2 and R^4 are H; R^3 is absent; and R^5 is selected from hydroxy and $C_{1-8}alkoxy$.

[0184] In one group of embodiments, the invention provides compounds of Formula Ic, wherein T^4 is N; R^2 and R^3 are H; R^5 is absent; and R^4 is selected from $C_{1-8}alkyl$ and $C_{1-8}alkoxy$.

[0185] In one group of embodiments, the invention provides compounds of Formula Ic, wherein T^1 is N; R^3, R^4, and R^5 are H; and R^2 is absent.

[0186] In one group of embodiments, the invention provides compounds of Formula Ic, wherein T^2 is N; R^2, R^4, and R^5 are H; and R^3 is absent.

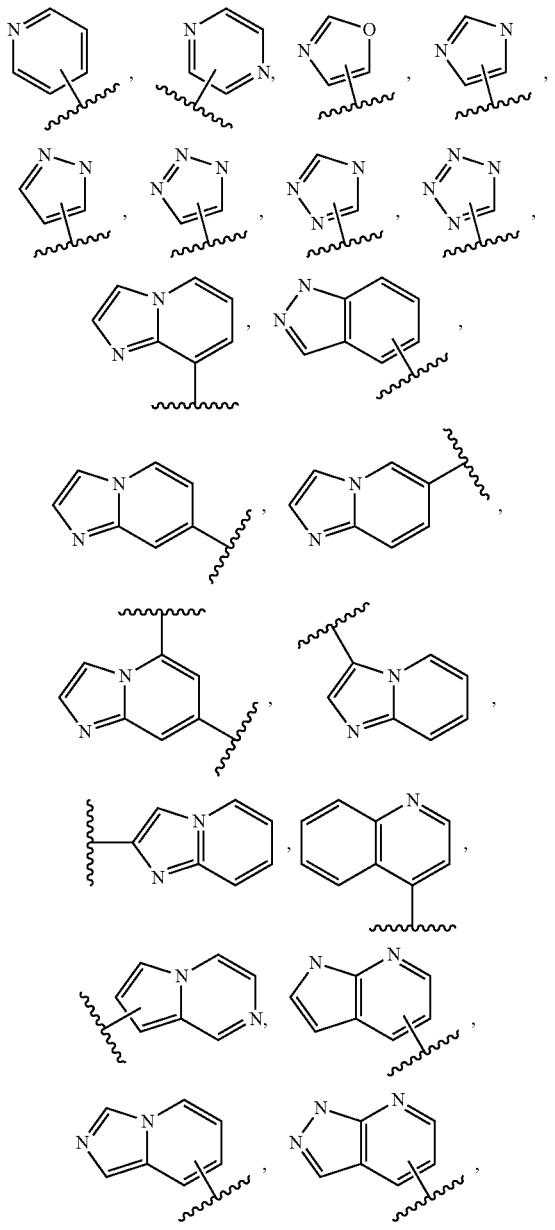
[0187] In one group of embodiments, the invention provides compounds of Formula Ic, wherein T^3 is N; R^2, R^3, and R^5 are H; and R^4 is absent.

[0188] In one group of embodiments, the invention provides compounds of Formula Ic, wherein T^4 is N; R^2, R^3, and R^4 are H; and R^5 is absent.

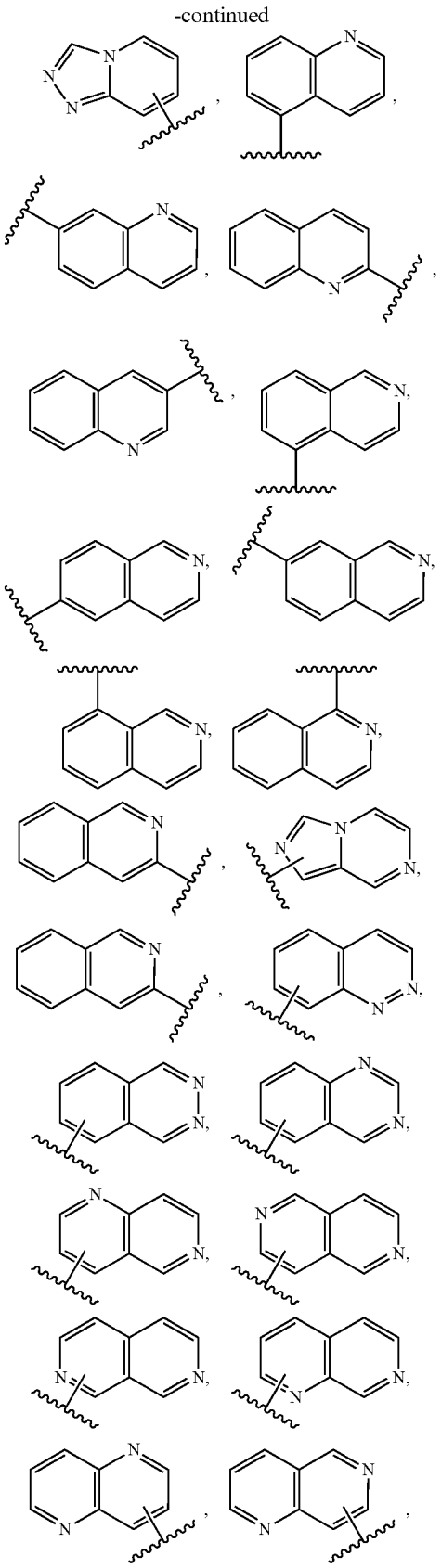
[0189] In one group of embodiments, the invention provides compounds of Formula Ic, or another group of

embodiments of Formula Ic that is disclosed herein, wherein Q is selected from the group consisting of an imidazopyridinyl group, a pyrrolopyridinyl group, a pyrazolopyridinyl group, a triazolopyridinyl group, a pyrazolopyrazinyl group, a pyridinyl group, a pyrazinyl group, an oxazolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a pyrazolyl group, a quinolinyl group, an isoquinolinyl group, an indazolyl group, a benzooxazolyl group, a naphthyridinyl group, and a quinoxalinyl group; and wherein Q is optionally substituted with one to three R^a.

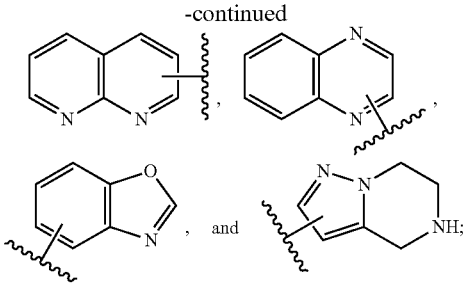
[0190] In one group of embodiments, the invention provides compounds of Formula Ic, or another group of embodiments of Formula Ic that is disclosed herein, wherein Q is selected from the group consisting of:



-continued



-continued



and wherein Q is optionally substituted with one to three R^a.

[0191] In one group of embodiments, the invention provides compounds of Formula Ic wherein at least one z is 0. In another group of embodiments, at least one z is 1. In yet another group of embodiments, at least one z is 2. In still another group of embodiments, at least one z is 3. In another group of embodiments, no z is 0.

[0192] In certain embodiments, the compounds of Formula I, Ib and Ic, or tautomers or pharmaceutically acceptable salts thereof, are selected from Table 1 below.

TABLE 1

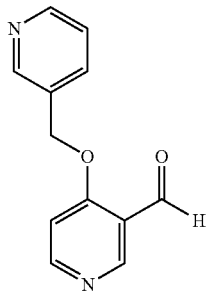
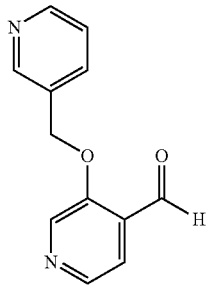
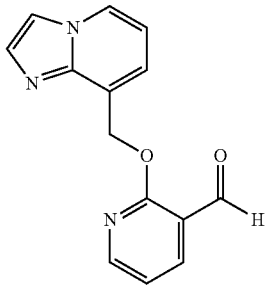
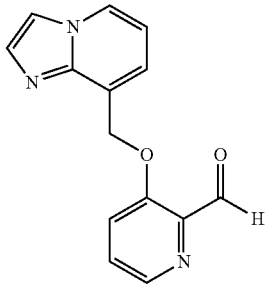
Compound	Structure	Name
1		4-(pyridin-3-ylmethoxy)nicotinaldehyde
2		3-(pyridin-3-ylmethoxy)isonicotinaldehyde
3		2-(imidazo[1,2-a]pyridin-8-ylmethoxy)nicotinaldehyde
4		3-(imidazo[1,2-a]pyridin-8-ylmethoxy)picolinaldehyde

TABLE 1-continued

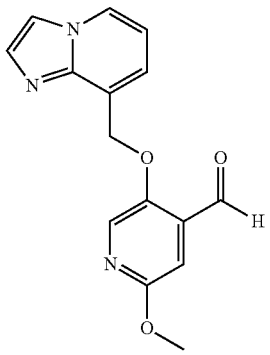
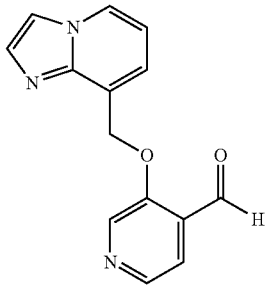
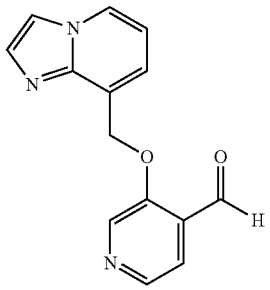
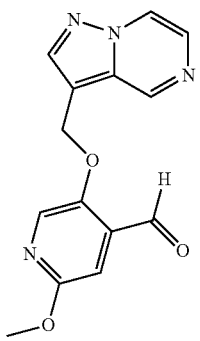
Compound	Structure	Name
5		5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde
6		3-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde
7		3-(imidazo[1,5-a]pyridin-8-ylmethoxy)isonicotinaldehyde
8		2-methoxy-5-(pyrazolo[1,5-a]pyrazin-3-ylmethoxy)isonicotinaldehyde

TABLE 1-continued

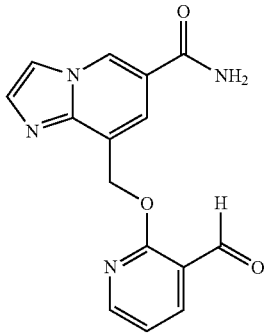
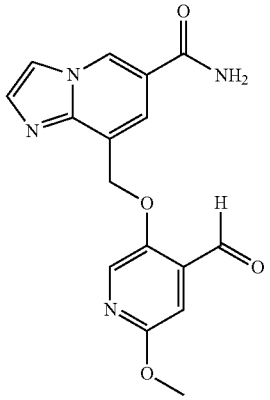
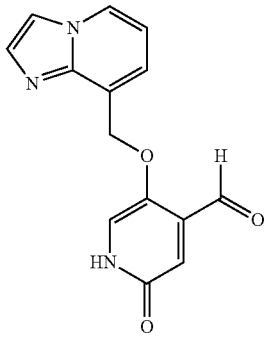
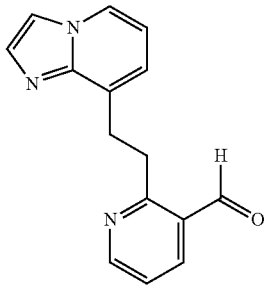
Compound	Structure	Name
9		8-((3-formylpyridin-2-yloxy)methyl)imidazo[1,2-a]pyridine-6-carboxamide
10		8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-6-carboxamide
11		5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde
12		2-(2-(imidazo[1,2-a]pyridin-8-yl)ethyl)nicotinaldehyde

TABLE 1-continued

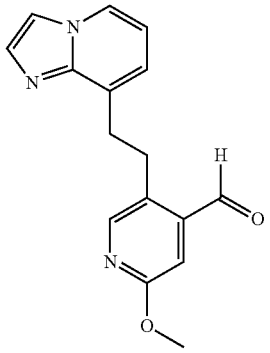
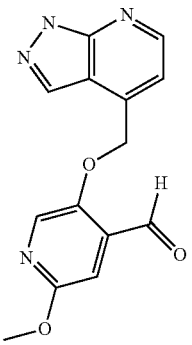
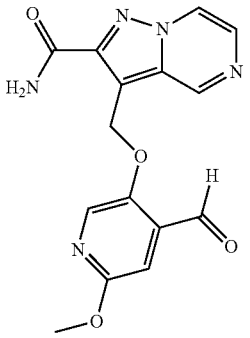
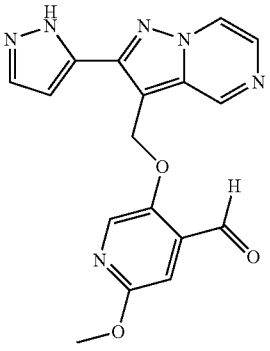
Compound	Structure	Name
13		5-(2-(imidazo[1,2-a]pyridin-8-yl)ethyl)-2-methoxyisonicotinaldehyde
14		5-((1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde
15		3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyrazolo[1,5-a]pyrazine-2-carboxamide
16		5-((2-(1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrazin-3-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

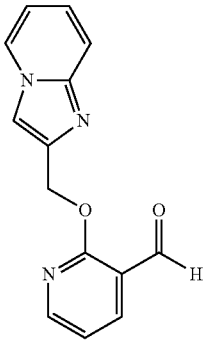
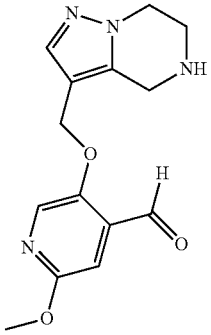
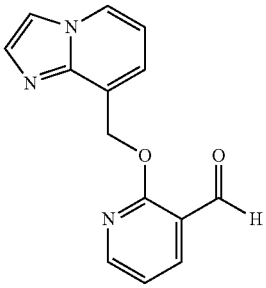
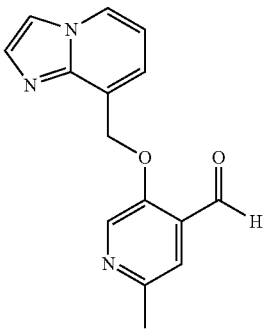
Compound	Structure	Name
17		2-(imidazo[1,2-a]pyridin-2-ylmethoxy)nicotinaldehyde
18		2-methoxy-5-((4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methoxy)isonicotinaldehyde
19		2-(imidazo[1,2-a]pyridin-8-ylmethoxy)nicotinaldehyde
20		5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methylisonicotinaldehyde

TABLE 1-continued

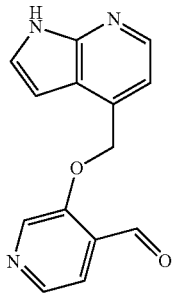
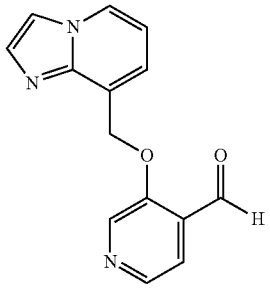
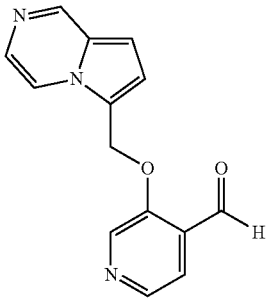
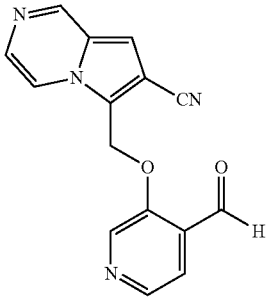
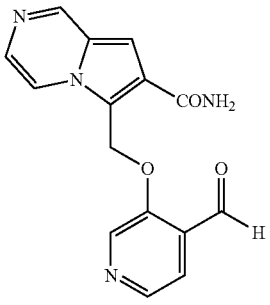
Compound	Structure	Name
21		3-((1H-pyrrolo[2,3-b]pyridin-4-yl)methoxy)isonicotinaldehyde
22		3-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde
23		3-(pyrrolo[1,2-a]pyrazin-6-ylmethoxy)isonicotinaldehyde
24		6-((4-formylpyridin-3-yloxy)methyl)pyrrolo[1,2-a]pyrazine-7-carbonitrile
25		6-((4-formylpyridin-3-yloxy)methyl)pyrrolo[1,2-a]pyrazine-7-carboxamide

TABLE 1-continued

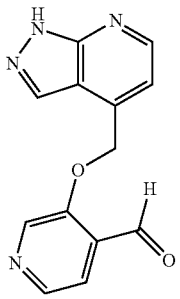
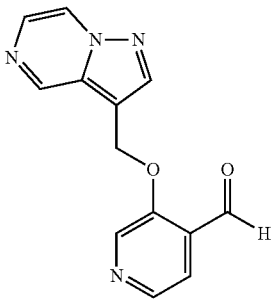
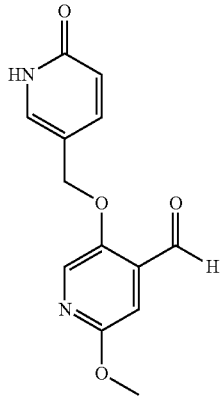
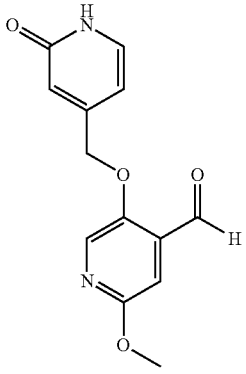
Compound	Structure	Name
26		3-((1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)isonicotinaldehyde
27		3-(pyrazolo[1,5-a]pyrazin-3-ylmethoxy)isonicotinaldehyde
28		2-methoxy-5-((6-oxo-1,6-dihydropyridin-3-yl)methoxy)isonicotinaldehyde
29		2-methoxy-5-((2-oxo-1,2-dihydropyridin-4-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

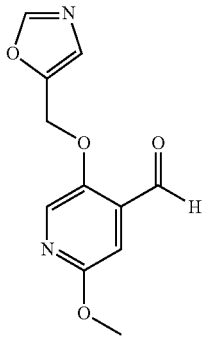
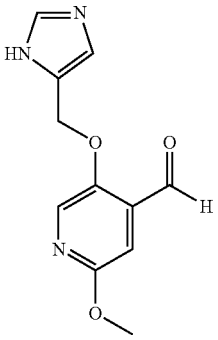
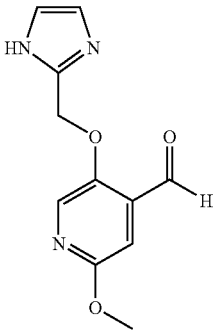
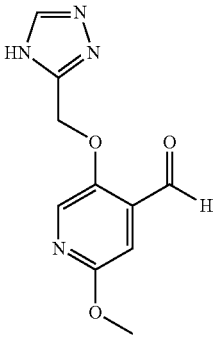
Compound	Structure	Name
30		2-methoxy-5-(oxazol-5-ylmethoxy)isonicotinaldehyde
31		5-((1H-imidazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde
32		5-((1H-imidazol-2-yl)methoxy)-2-methoxyisonicotinaldehyde
33		5-((4H-1,2,4-triazol-3-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

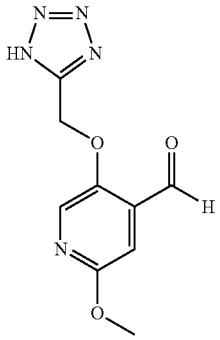
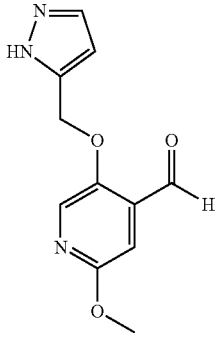
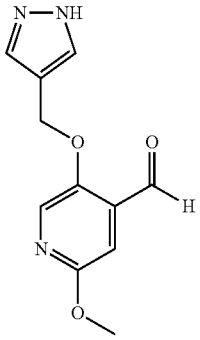
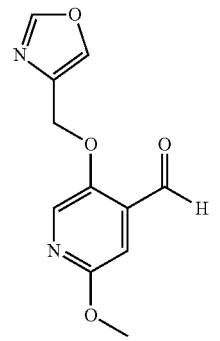
Compound	Structure	Name
34		5-((1H-tetrazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde
35		5-((1H-pyrazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde
36		5-((1H-pyrazol-4-yl)methoxy)-2-methoxyisonicotinaldehyde
37		2-methoxy-5-(oxazol-4-ylmethoxy)isonicotinaldehyde

TABLE 1-continued

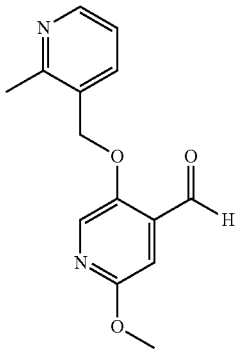
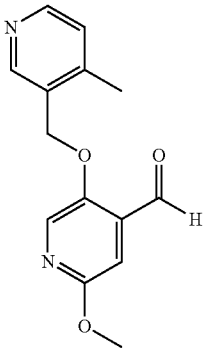
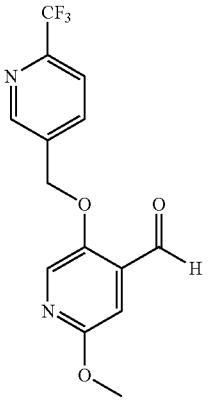
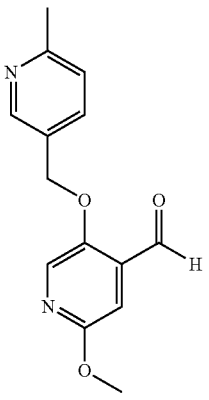
Compound	Structure	Name
38		2-methoxy-5-((2-methylpyridin-3-yl)methoxy)isonicotinaldehyde
39		2-methoxy-5-((4-methylpyridin-3-yl)methoxy)isonicotinaldehyde
40		2-methoxy-5-((6-(trifluoromethyl)pyridin-3-yl)methoxy)isonicotinaldehyde
41		2-methoxy-5-((6-methylpyridin-3-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

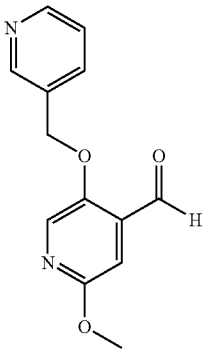
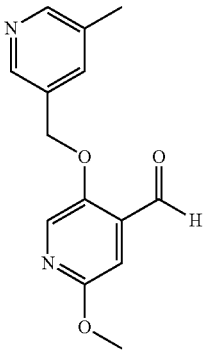
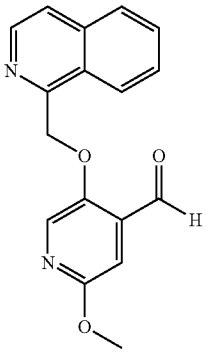
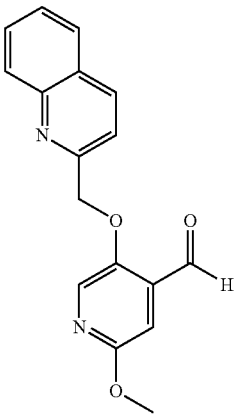
Compound	Structure	Name
42		2-methoxy-5-(pyridin-3-ylmethoxy)isonicotinaldehyde
43		2-methoxy-5-((5-methylpyridin-3-yl)methoxy)isonicotinaldehyde
44		5-(isoquinolin-1-ylmethoxy)-2-methoxyisonicotinaldehyde
45		2-methoxy-5-(quinolin-2-ylmethoxy)isonicotinaldehyde

TABLE 1-continued

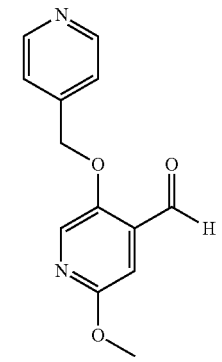
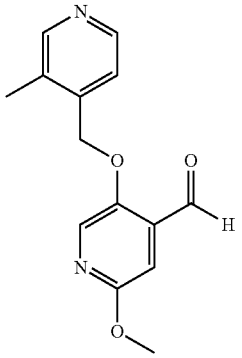
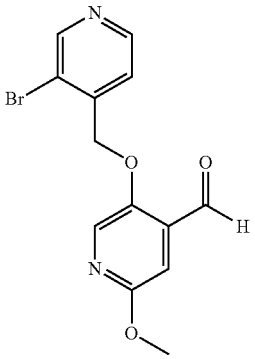
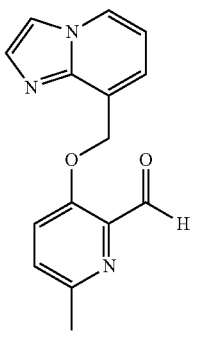
Compound	Structure	Name
46		2-methoxy-5-(pyridin-4-ylmethoxy)isonicotinaldehyde
47		2-methoxy-5-((3-methylpyridin-4-yl)methoxy)isonicotinaldehyde
48		5-((3-bromopyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde
49		3-(imidazo[1,2-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde

TABLE 1-continued

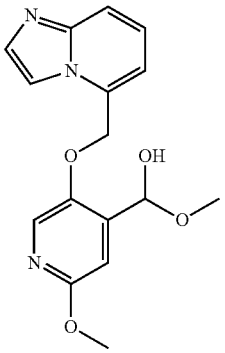
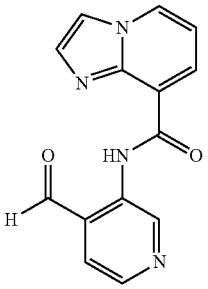
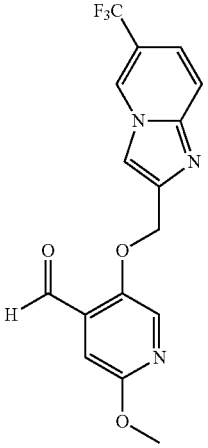
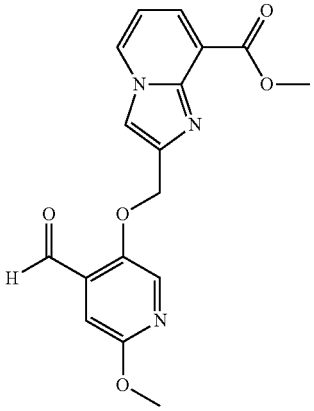
Compound	Structure	Name
50		(5-(imidazo[1,2-a]pyridin-5-ylmethoxy)-2-methylpyridin-4-yl)(methoxy)methanol
51		N-(4-formylpyridin-3-yl)imidazo[1,2-a]pyridine-8-carboxamide
52		2-methoxy-5-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methoxy)isonicotinaldehyde
53		methyl 2-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxylate

TABLE 1-continued

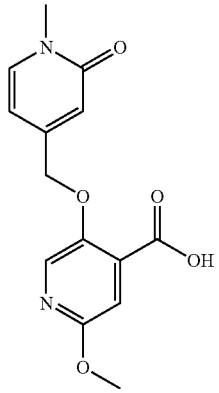
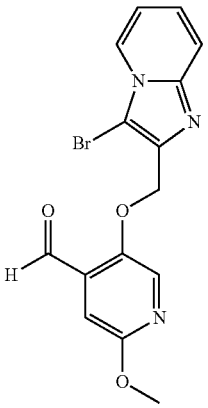
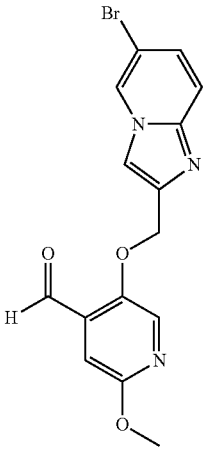
Compound	Structure	Name
54		2-methoxy-5-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)isonicotinaldehyde
55		5-((3-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde
56		5-((6-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

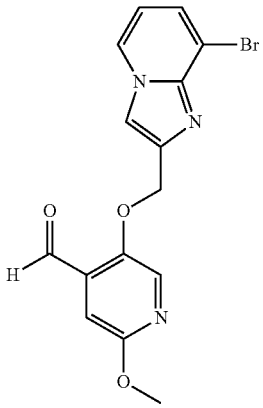
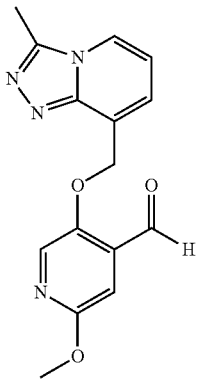
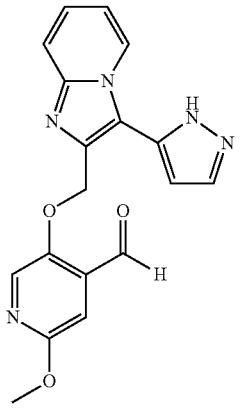
Compound	Structure	Name
57		5-((8-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde
58		2-methoxy-5-((3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)methoxy)isonicotinaldehyde
59		5-((3-(1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

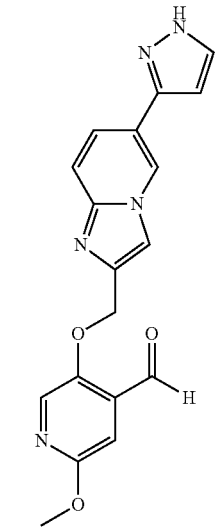
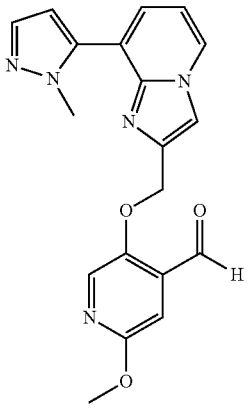
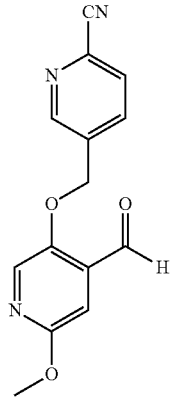
Compound	Structure	Name
60		5-((6-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde
61		2-methoxy-5-((8-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)isonicotinaldehyde
62		5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinonitrile

TABLE 1-continued

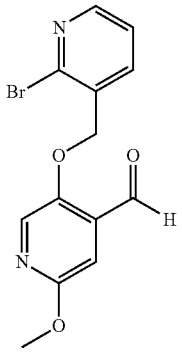
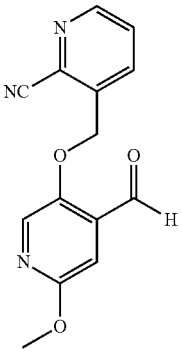
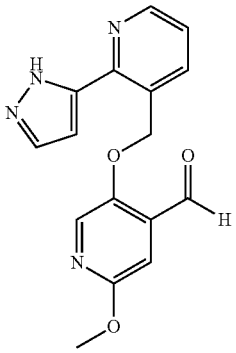
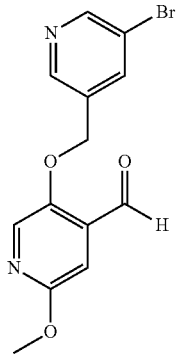
Compound	Structure	Name
63		5-((2-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
64		3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinonitrile
65		5-((2-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
66		5-((5-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

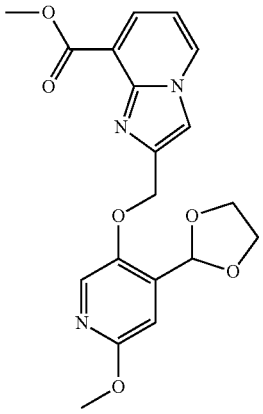
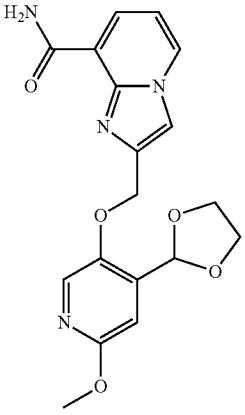
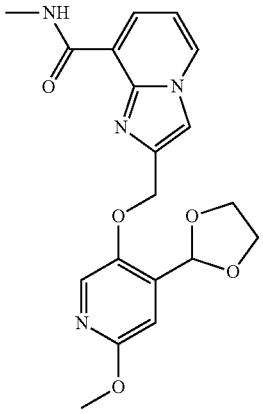
Compound	Structure	Name
67		methyl 2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxylate
68		2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxamide
69		2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)-N-methylimidazo[1,2-a]pyridine-8-carboxamide

TABLE 1-continued

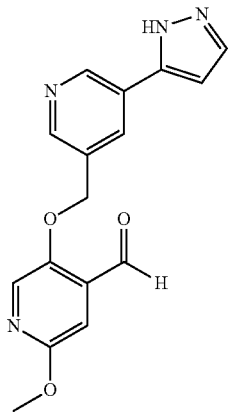
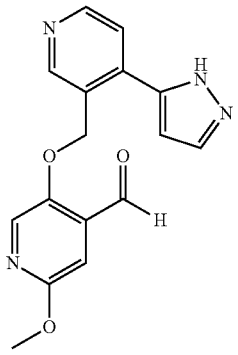
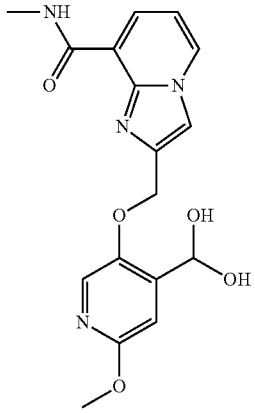
Compound	Structure	Name
70		5-((5-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
71		5-((4-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
72		2-((4-(dihydroxymethyl)-6-methoxypyridin-3-yloxy)methyl)-N-methylimidazo[1,2-a]pyridine-8-carboxamide

TABLE 1-continued

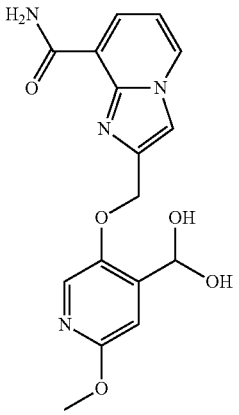
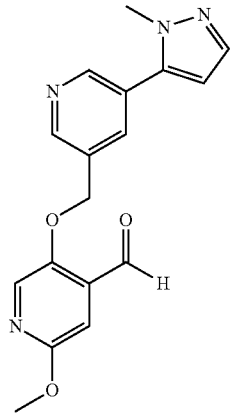
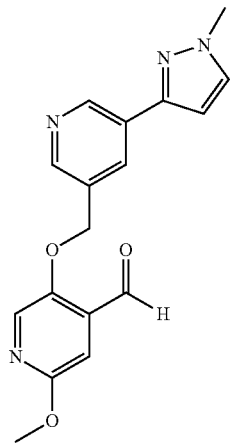
Compound	Structure	Name
73		2-((4-(dihydroxymethyl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxamide
74		2-methoxy-5-((5-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
75		2-methoxy-5-((5-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

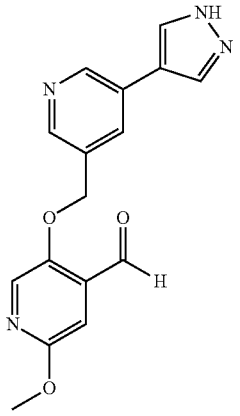
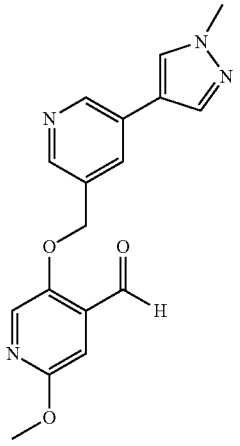
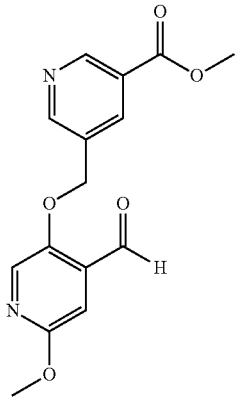
Compound	Structure	Name
76		5-((5-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
77		2-methoxy-5-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
78		methyl 5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinate

TABLE 1-continued

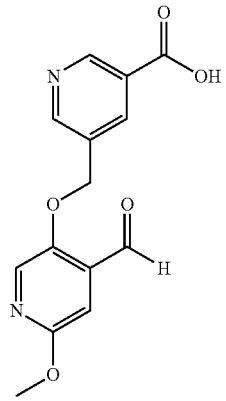
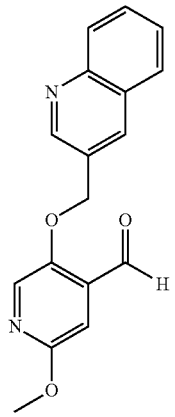
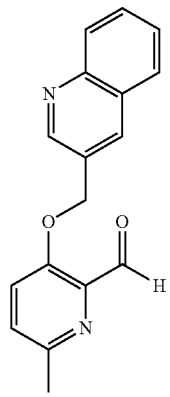
Compound	Structure	Name
79		5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinic acid
80		2-methoxy-5-(quinolin-3-ylmethoxy)isonicotinaldehyde
81		6-methyl-3-(quinolin-3-ylmethoxy)picolinaldehyde

TABLE 1-continued

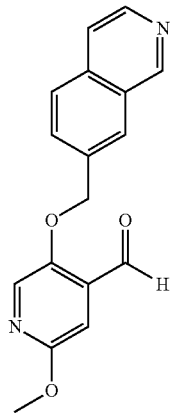
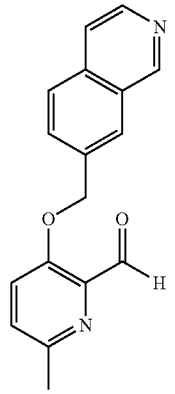
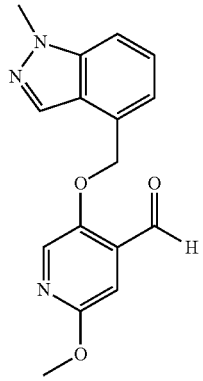
Compound	Structure	Name
82		5-(isoquinolin-7-methoxy)-2-methoxyisonicotinaldehyde
83		3-(isoquinolin-7-methoxy)-6-methylpicolinaldehyde
84		2-methoxy-5-((1-methyl-1H-indazol-4-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

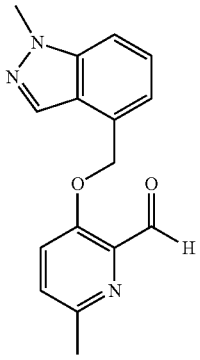
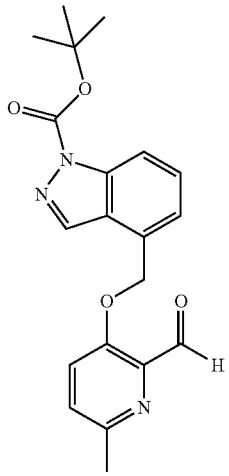
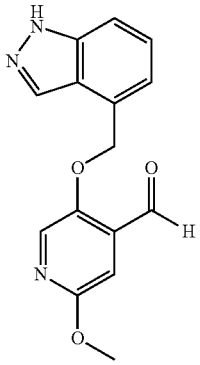
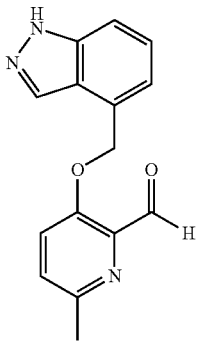
Compound	Structure	Name
85		6-methyl-3-((1-methyl-1H-indazol-4-yl)methoxy)picolinaldehyde
86		tert-butyl 4-((2-formyl-6-methylpyridin-3-yloxy)methyl)-1H-indazole-1-carboxylate
87		5-((1H-indazol-4-yl)methoxy)-2-methoxyisonicotinaldehyde
88		3-((1H-indazol-4-yl)methoxy)-6-methylpicolinaldehyde

TABLE 1-continued

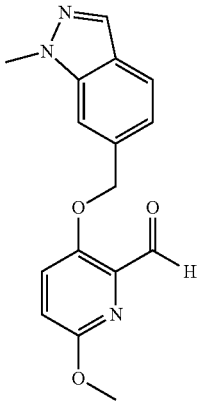
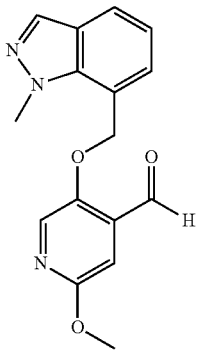
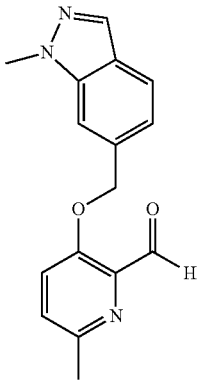
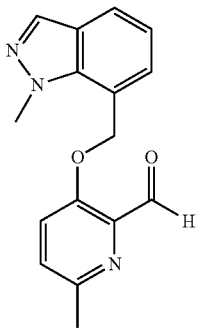
Compound	Structure	Name
89		6-methoxy-3-((1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde
90		2-methoxy-5-((1-methyl-1H-indazol-7-yl)methoxy)isonicotinaldehyde
91		6-methyl-3-((1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde
92		6-methyl-3-((1-methyl-1H-indazol-7-yl)methoxy)picolinaldehyde

TABLE 1-continued

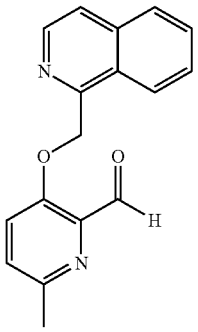
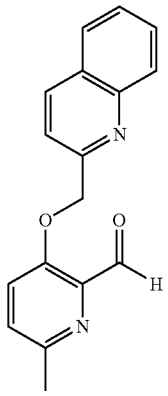
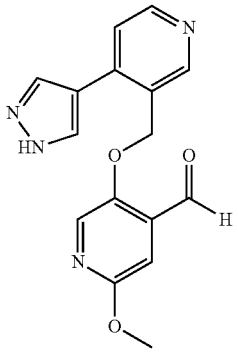
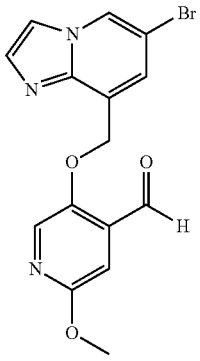
Compound	Structure	Name
93		3-(isoquinolin-1-ylmethoxy)-6-methylpicolinaldehyde
94		6-methyl-3-(quinolin-2-ylmethoxy)picolinaldehyde
95		5-((4-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
96		5-((6-bromoimidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

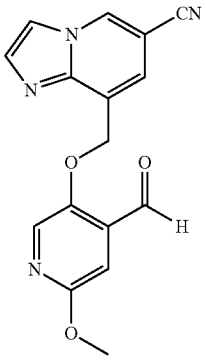
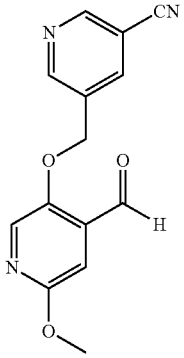
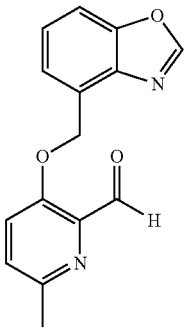
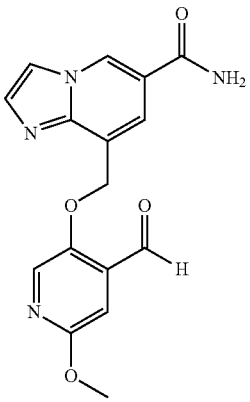
Compound	Structure	Name
97		8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-6-carbonitrile
98		5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinonitrile
99		3-(benzo[d]oxazol-4-ylmethoxy)-6-methylpicolinaldehyde
100		8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-6-carboxamide

TABLE 1-continued

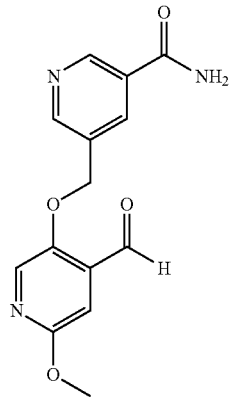
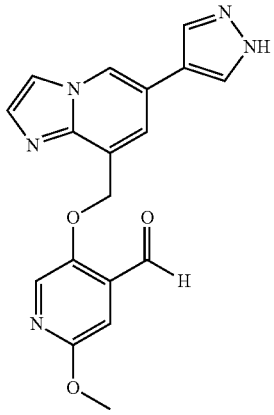
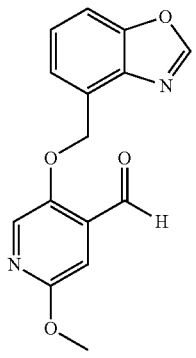
Compound	Structure	Name
101		5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinamide
102		5-((6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde
103		5-(benzo[d]oxazol-4-ylmethoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

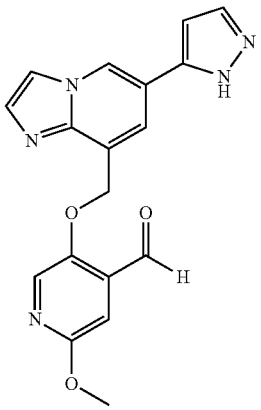
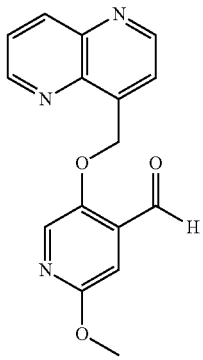
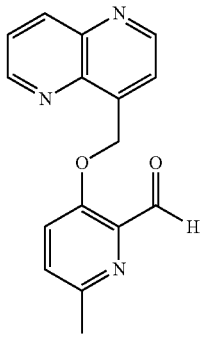
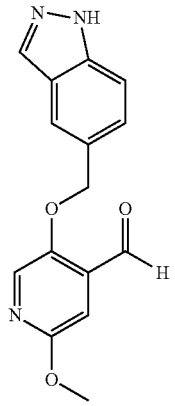
Compound	Structure	Name
104		5-((6-(1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde
105		5-((1,5-naphthyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde
106		3-((1,5-naphthyridin-4-yl)methoxy)-6-methylpicolinaldehyde
107		5-((1H-indazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

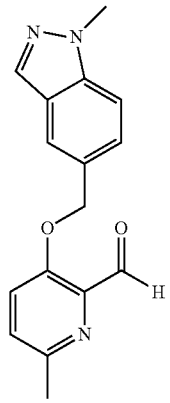
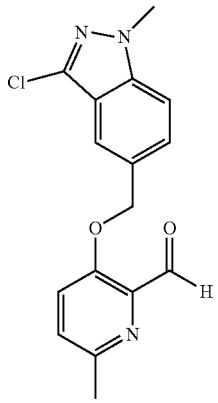
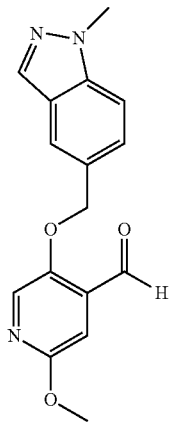
Compound	Structure	Name
108		6-methyl-3-((1-methyl-1H-indazol-5-yl)methoxy)picolinaldehyde
109		3-((3-chloro-1-methyl-1H-indazol-5-yl)methoxy)-6-methylpicolinaldehyde
110		2-methoxy-5-((1-methyl-1H-indazol-5-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

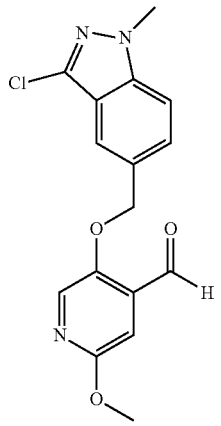
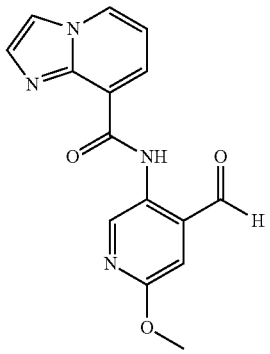
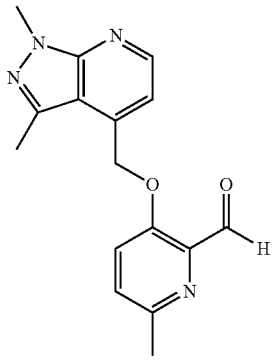
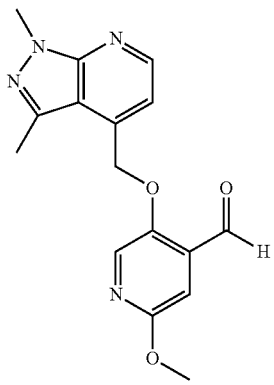
Compound	Structure	Name
111		5-((3-chloro-1-methyl-1H-indazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde
112		N-(4-formyl-6-methoxypyridin-3-yl)imidazo[1,2-a]pyridine-8-carboxamide
113		3-((1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-6-methylpicolinaldehyde
114		5-((1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

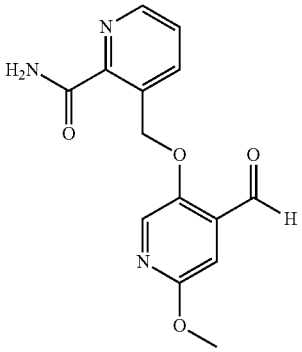
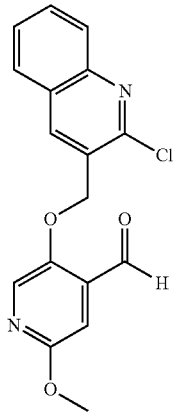
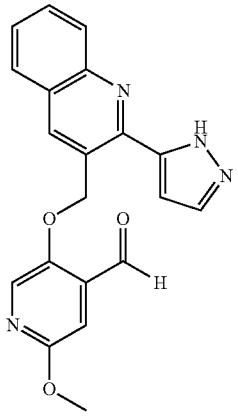
Compound	Structure	Name
115		3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinamide
116		5-((2-chloroquinolin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
117		5-((2-(1H-pyrazol-5-yl)quinolin-3-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

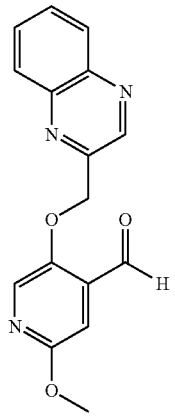
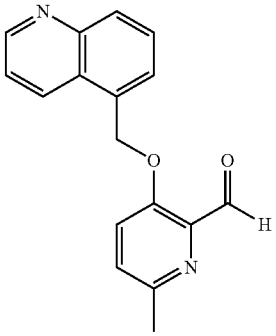
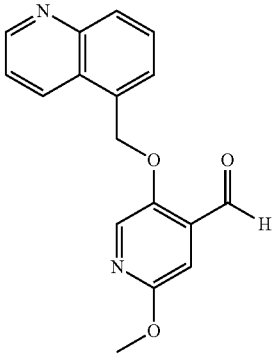
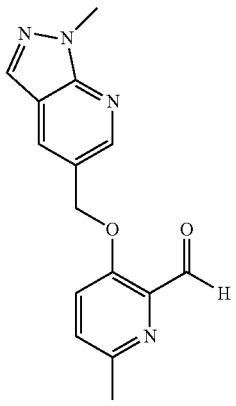
Compound	Structure	Name
118		2-methoxy-5-(quinoxalin-2-ylmethoxy)isnoicotinaldehyde
119		6-methyl-3-(quinolin-5-ylmethoxy)picolinaldehyde
120		2-methoxy-5-(quinolin-5-ylmethoxy)isonicotinaldehyde
121		6-methyl-3-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methoxy)picolinaldehyde

TABLE 1-continued

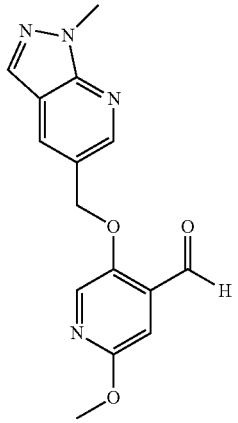
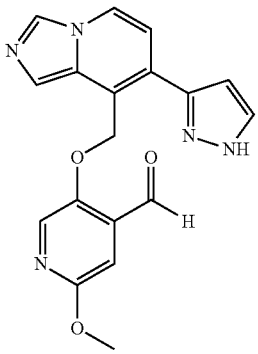
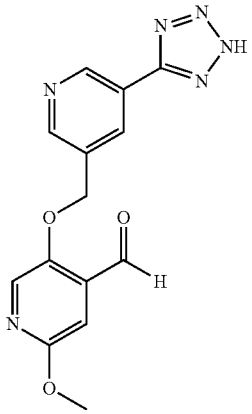
Compound	Structure	Name
122		2-methoxy-5-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methoxy)isonicotinaldehyde
123		5-((7-(1H-pyrazol-3-yl)imidazo[1,5-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde
124		5-((5-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

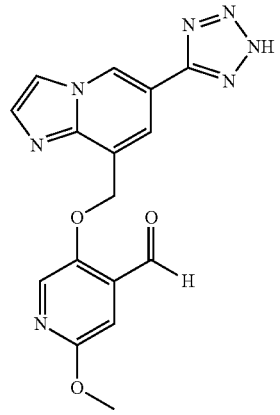
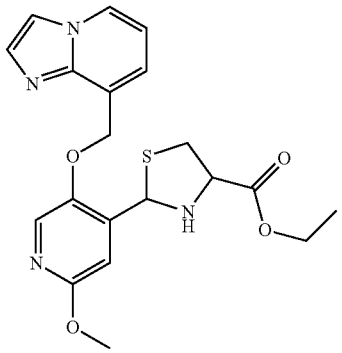
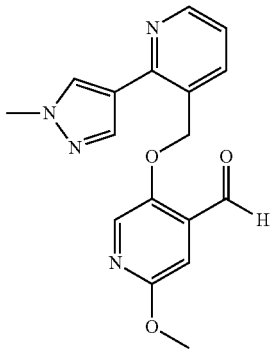
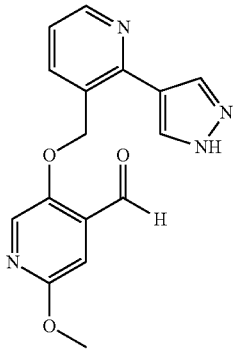
Compound	Structure	Name
125		5-((6-(2H-tetrazol-5-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde
126		ethyl 2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidine-4-carboxylate
127		2-methoxy-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
128		5-((2-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

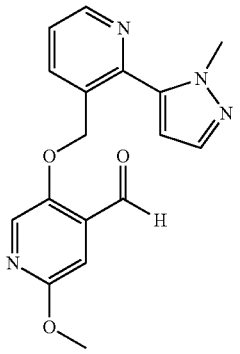
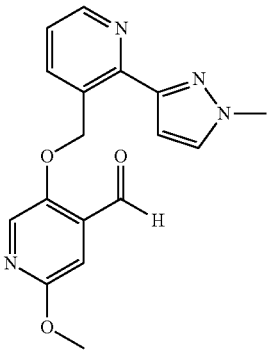
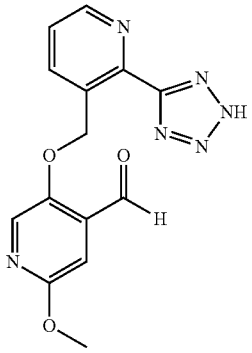
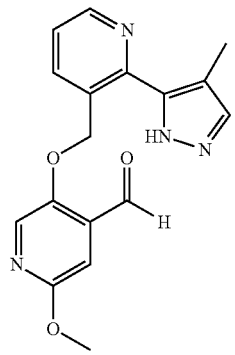
Compound	Structure	Name
129		2-methoxy-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
130		2-methoxy-5-((2-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
131		5-((2-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
132		2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

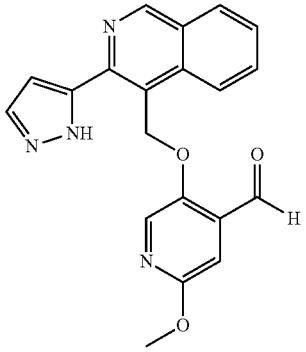
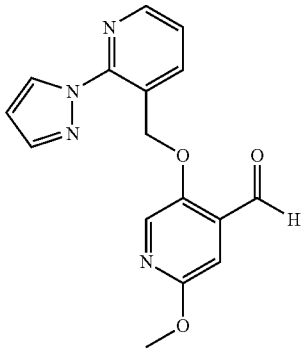
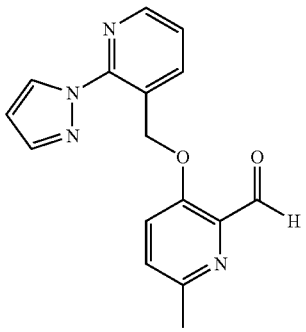
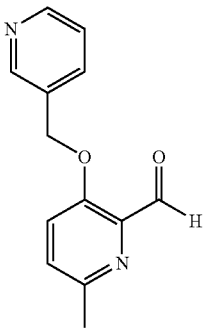
Compound	Structure	Name
133		5-((3-(1H-pyrazol-5-yl)isoquinolin-4-yl)methoxy)-2-methoxyisonicotinaldehyde
134		5-((2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
135		3-((2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde
136		6-methyl-3-(pyridin-3-ylmethoxy)picolinaldehyde

TABLE 1-continued

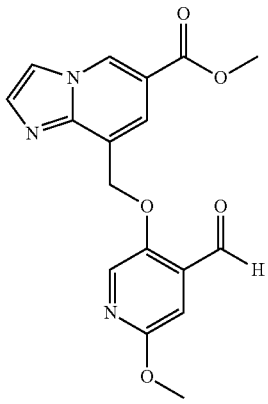
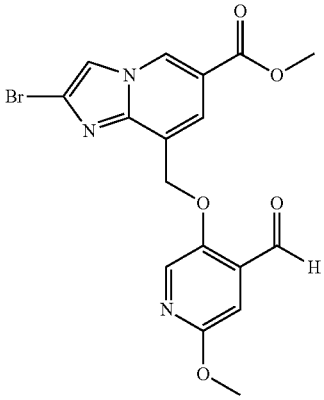
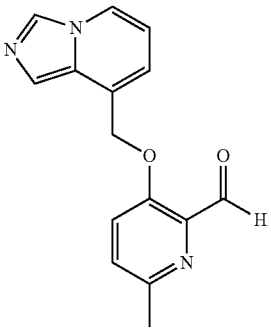
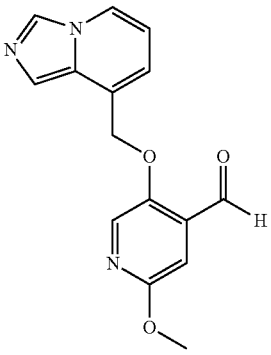
Compound	Structure	Name
137		methyl 8-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)imidazo[1,2-a]pyridine-6-carboxylate
138		methyl 2-bromo-8-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)imidazo[1,2-a]pyridine-6-carboxylate
139		3-(imidazo[1,5-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde
140		5-(imidazo[1,5-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

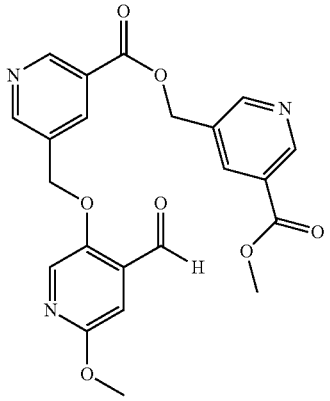
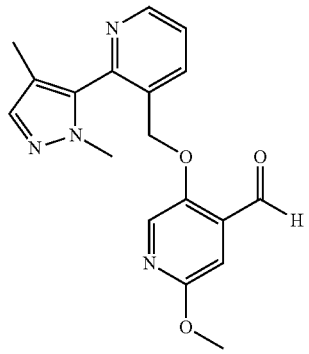
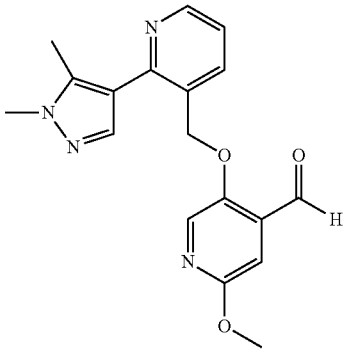
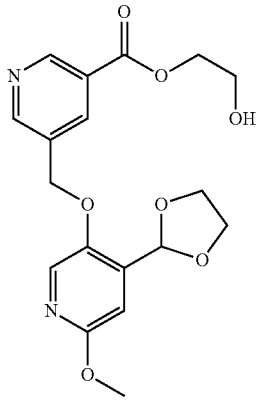
Compound	Structure	Name
141		(5-(methoxycarbonyl)pyridin-3-yl)methyl 5-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)nicotinate
142		5-((2-(1,4-dimethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
143		5-((2-(1,5-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
144		2-hydroxyethyl 5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate

TABLE 1-continued

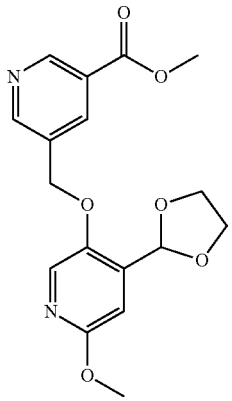
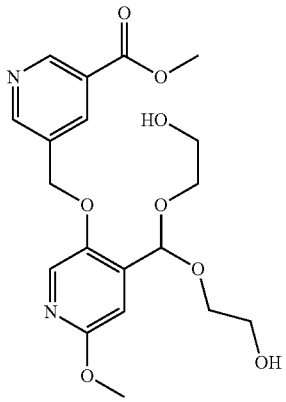
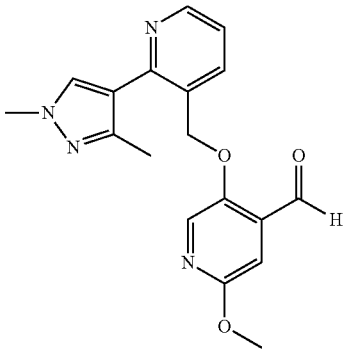
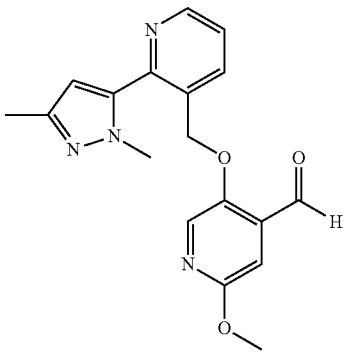
Compound	Structure	Name
145		methyl 5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate
146		methyl 5-(((4-(bis(2-hydroxyethoxy)methyl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate
147		5-((2-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
148		5-((2-(1,3-dimethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

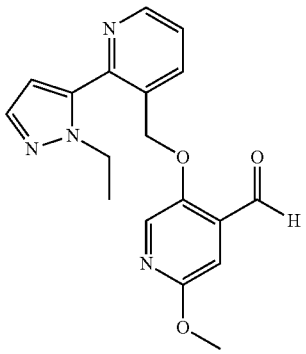
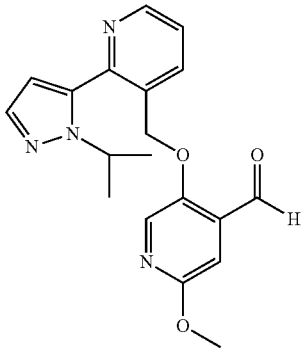
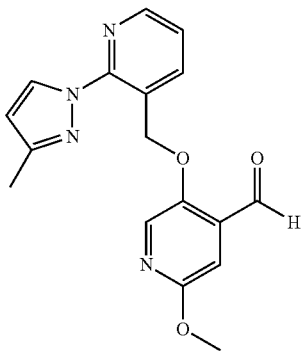
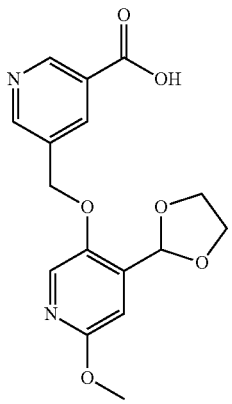
Compound	Structure	Name
149		5-((2-(1-ethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
150		5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
151		2-methoxy-5-((2-(3-methyl-1H-pyraozl-1-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
152		5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinic acid

TABLE 1-continued

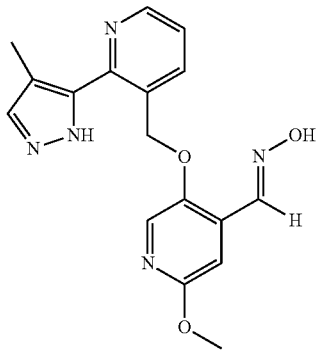
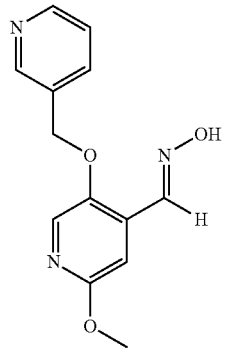
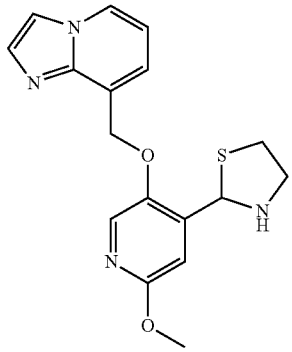
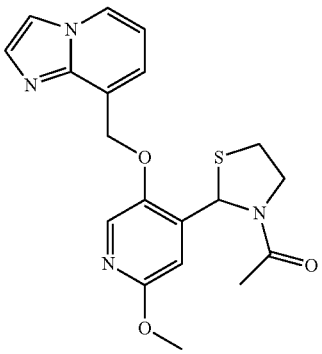
Compound	Structure	Name
153		(E)-2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde oxime
154		(E)-2-methoxy-5-(pyridin-3-ylmethoxy)isonicotinaldehyde oxime
155		2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidine
156		1-(2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidin-3-yl)ethanone

TABLE 1-continued

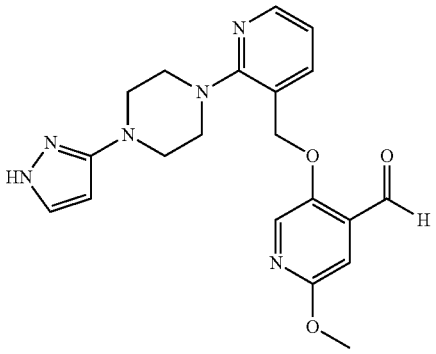
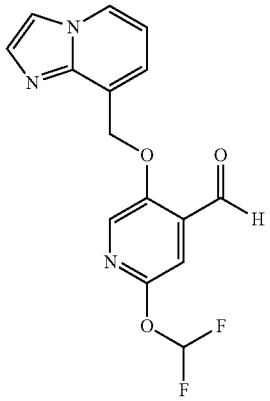
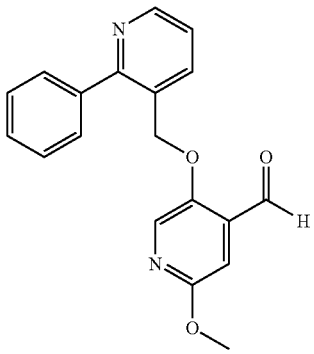
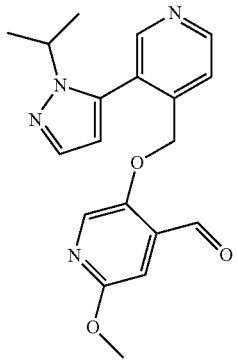
Compound	Structure	Name
157		5-((2-(4-(1H-pyrazol-3-yl)piperazin-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
158		2-(difluoromethoxy)-5-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde
159		2-methoxy-5-((2-phenylpyridin-3-yl)methoxy)isonicotinaldehyde
160		5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

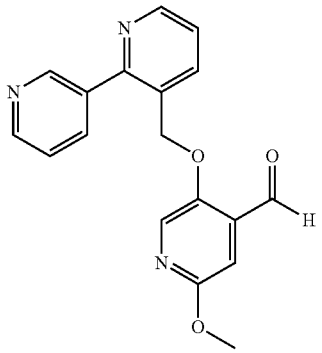
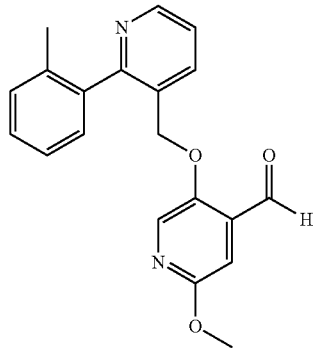
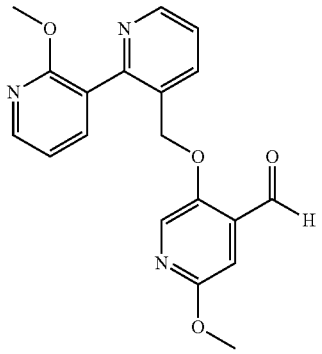
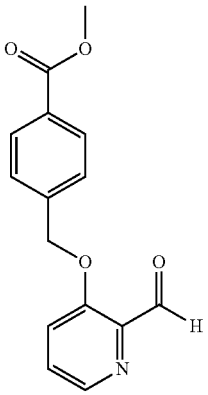
Compound	Structure	Name
161		5-([2,3'-bipyridin]-3-ylmethoxy)-2-methoxyisonicotinaldehyde
162		2-methoxy-5-((2-(o-tolyl)pyridin-3-yl)methoxy)isonicotinaldehyde
163		2-methoxy-5-((2'-methoxy-[2,3'-bipyridin]-3-yl)methoxy)isonicotinaldehyde
164		methyl 4-(((2-formylpyridin-3-yl)oxy)methyl)benzoate

TABLE 1-continued

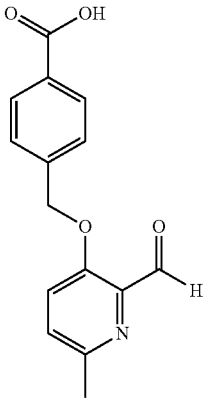
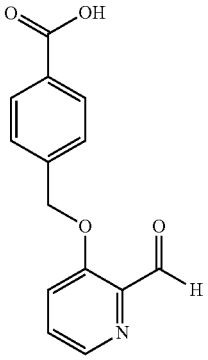
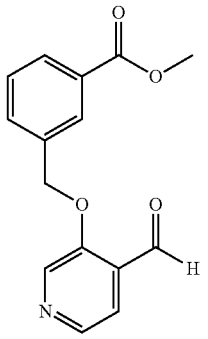
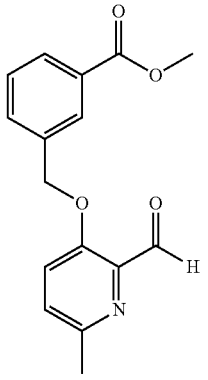
Compound	Structure	Name
165		4-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid
166		4-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid
167		methyl 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoate
168		methyl 3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoate

TABLE 1-continued

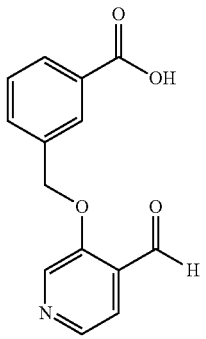
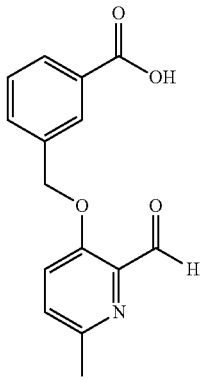
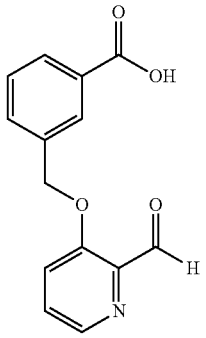
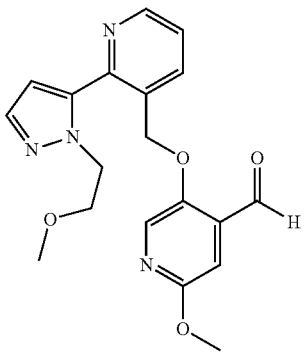
Compound	Structure	Name
169		3-(((4-formylpyridin-3-yl)oxy)methyl)benzoic acid
170		3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid
171		3-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid
172		2-methoxy-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

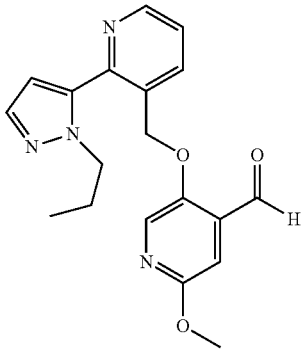
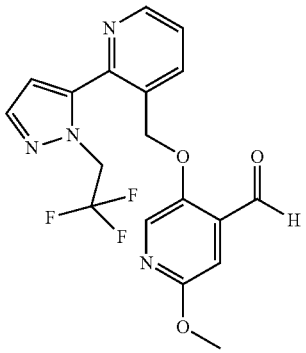
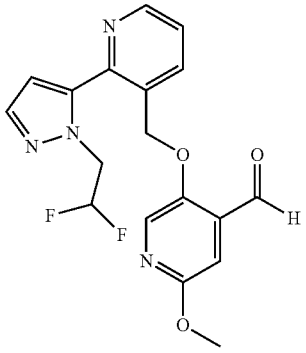
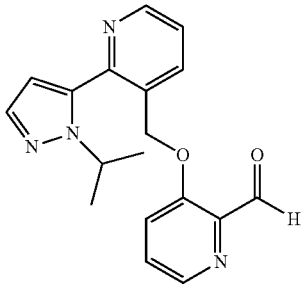
Compound	Structure	Name
173		2-methoxy-5-((2-(1-propyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
174		2-methoxy-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
175		5-((2-(1-(2,2-diflurooethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
176		3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)picolinaldehyde

TABLE 1-continued

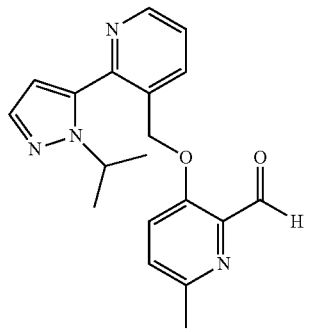
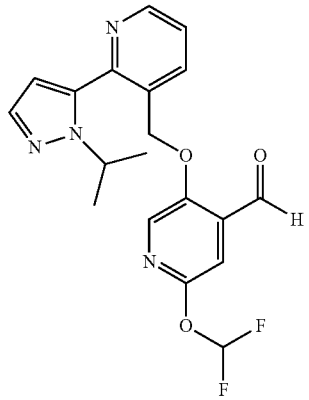
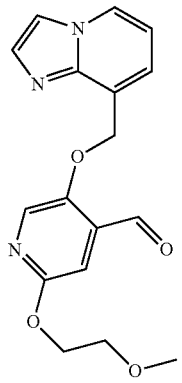
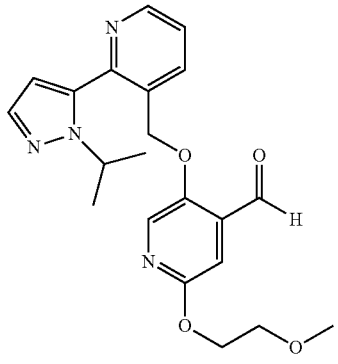
Compound	Structure	Name
177		3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde
178		2-(difluoromethoxy)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
179		5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-(2-methoxyethoxy)isonicotinaldehyde
180		5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-(2-methoxyethoxy)isonicotinaldehyde

TABLE 1-continued

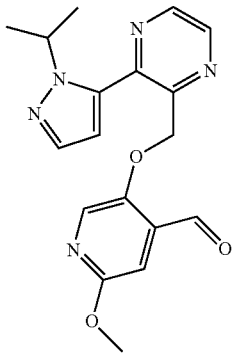
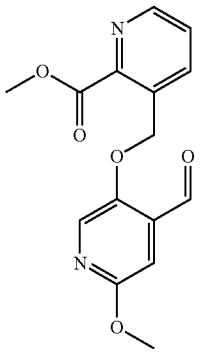
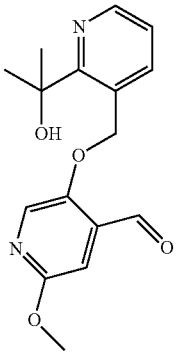
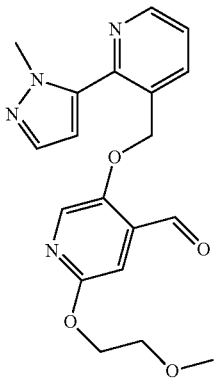
Compound	Structure	Name
181		5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyrazin-2-yl)methoxy)-2-methoxyisonicotinaldehyde
182		3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinate
183		5-((2-(2-hydroxypropan-2-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
184		2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

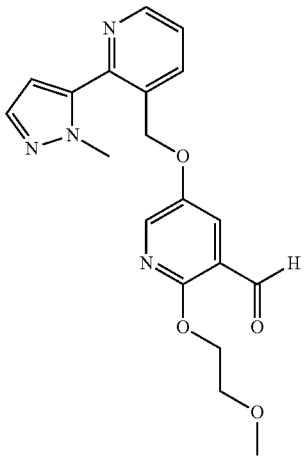
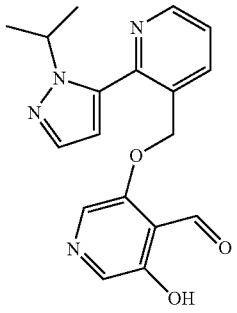
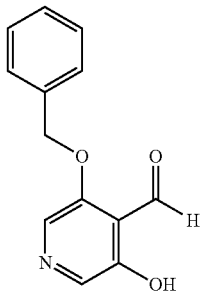
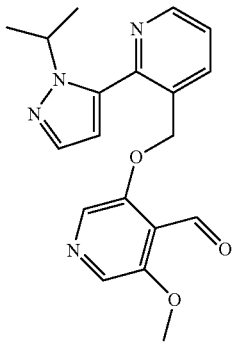
Compound	Structure	Name
185		2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)nicotinaldehyde
186		3-hydroxy-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
187		3-(benzyloxy)-5-hydroxyisonicotinaldehyde
188		3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxyisonicotinaldehyde

TABLE 1-continued

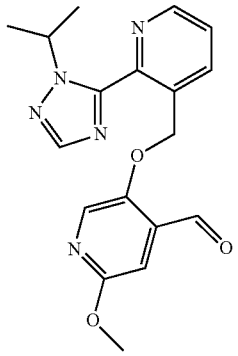
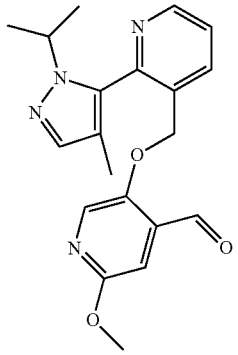
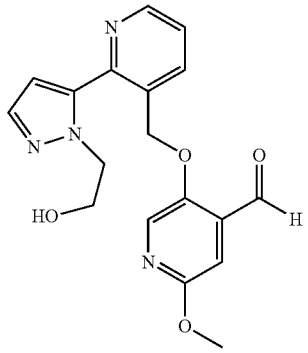
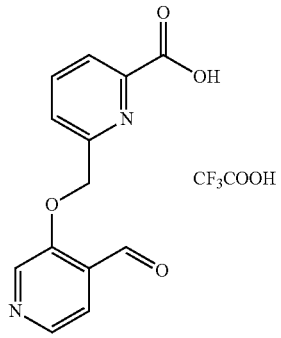
Compound	Structure	Name
189		5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
190		5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
191		5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
192		2,2,2-trifluoroacetic acid:6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid (1:1)

TABLE 1-continued

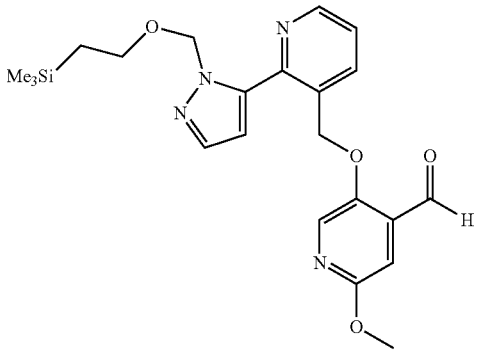
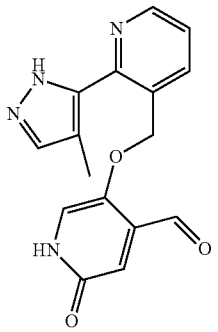
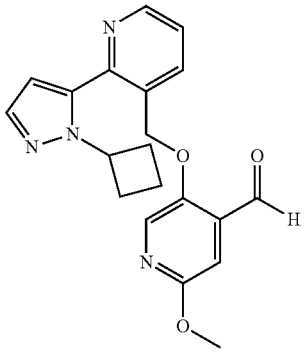
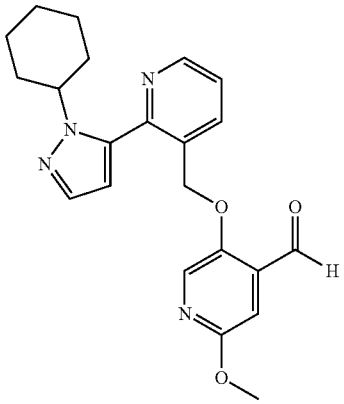
Compound	Structure	Name
193		2-methoxy-5-((2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
194		5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde
195		5-((2-(1-cyclobutyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
196		5-((2-(1-cyclohexyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde

TABLE 1-continued

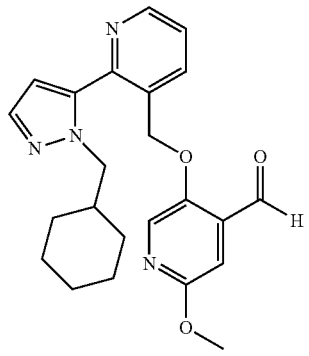
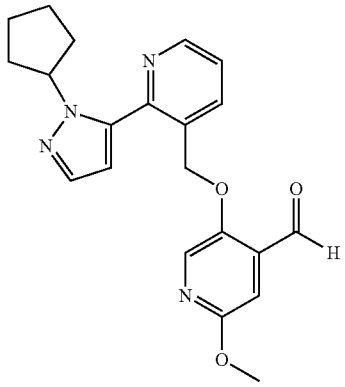
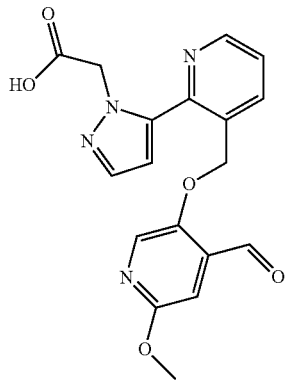
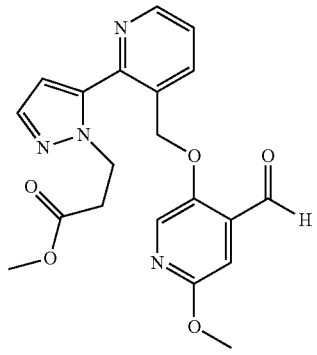
Compound	Structure	Name
197		5-((2-(1-(cyclohexylmethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
198		5-((2-(1-cyclopentyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde
199		2-(5-(3-((4-fomryl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetic acid
200		methyl 3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate

TABLE 1-continued

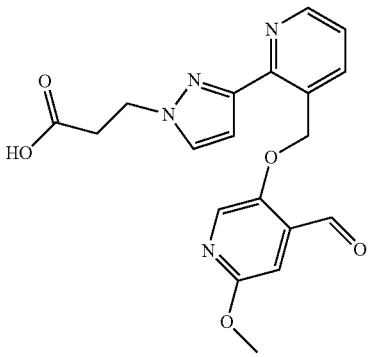
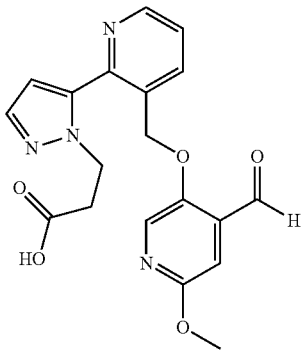
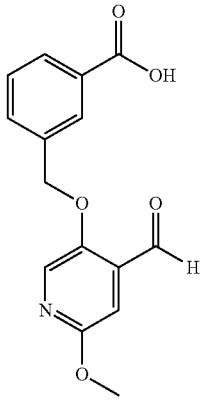
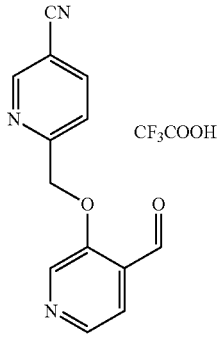
Compound	Structure	Name
201		3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid
202		3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid
203		3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)benzoic acid
204		6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinonitrile 2,2,2-trifluoroacetate

TABLE 1-continued

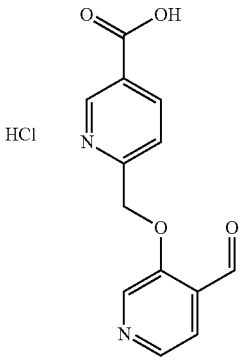
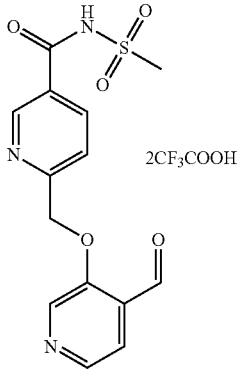
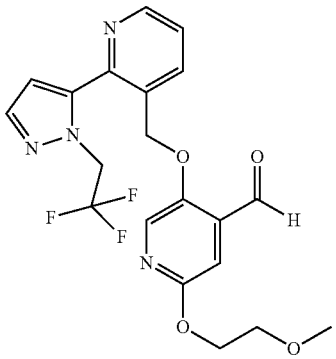
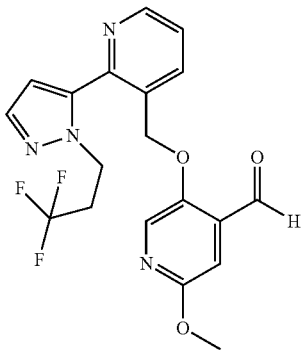
Compound	Structure	Name
205		6-(((4-formylpyriidn-3-yl)oxy)methyl)nicotinic acid hydrochloride
206		2,2,2-trifluoroacetic acid:6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide (2:1)
207		2-(2-methoxyethoxy)-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
208		2-methoxy-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

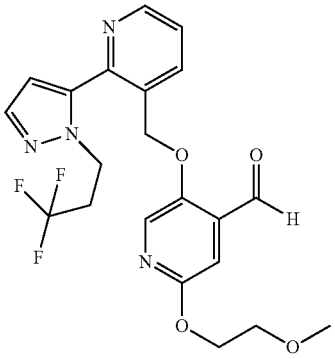
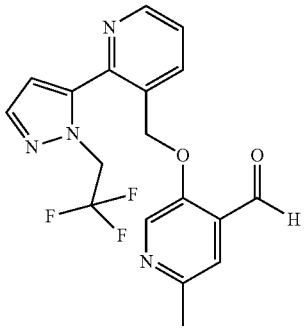
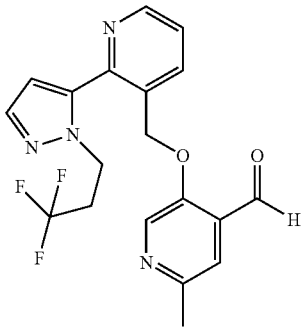
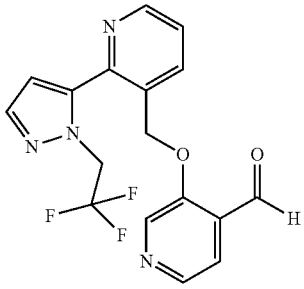
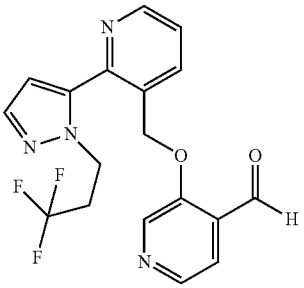
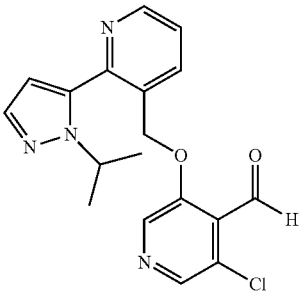
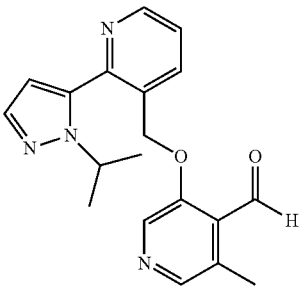
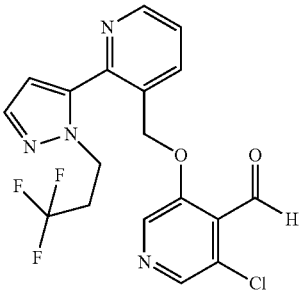
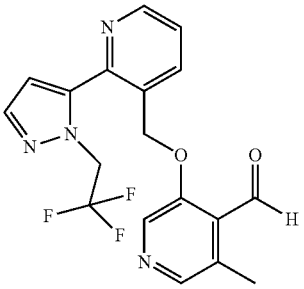
Compound	Structure	Name
209		2-(2-methoxyethoxy)-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
210		2-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
211		2-methyl-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
212		3-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde

TABLE 1-continued

Compound	Structure	Name
213		3-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
214		3-chloro-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
215		3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methylisonicotinaldehyde
216		3-chloro-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde
217		3-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde

[0193] In one group of embodiments, the compound is selected from 5-hydroxy-2-(2-methoxyethoxy)isonicotinaldehyde (Compound 218), S-hydroxy-2-(2-methoxyethoxy) nicotinaldehyde (Compound 219), 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (Compound 220), 5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (Compound 221), or a tautomer or pharmaceutically acceptable salt thereof.

[0194] In one group of embodiments, the compound is selected from:

[0195] 5-imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde,

[0196] 2-methoxy-5-((5-methylpyridin-3-yl)methoxy) isonicotinaldehyde,

[0197] 5-(isoquinolin-1-ylmethoxy)-2-methoxyisonicotinaldehyde,

[0198] 2-methoxy-5-(quinolin-2-ylmethoxy)isonicotinaldehyde,

[0199] 2-methoxy-5-(pyridin-4-ylmethoxy)isonicotinaldehyde,

[0200] 3-(imidazo[1,2-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde,

[0201] methyl 2-((4-formyl-6-methoxypyridin-3-yloxy) methyl)imidazo[1,2-a]pyridine-8-carboxylate,

[0202] 2-methoxy-5-((3-methyl-[1,2,4]triazolo[4,3-a] pyridin-8-yl)methoxy)isonicotinaldehyde,

[0203] 5-((2-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0204] 5-((2-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0205] 5-(5-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0206] 2-methoxy-5-((5-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0207] 5-((4-formyl-6-methoxypyridin-3-yloxy)methyl) nicotinic acid,

[0208] 2-methoxy-5-(quinolin-3-ylmethoxy)isonicotinaldehyde,

[0209] 2-methoxy-5-((1-methyl-1H-indazol-4-yl) methoxy)isonicotinaldehyde,

[0210] tert-butyl 4-((2-formyl-6-methylpyridin-3-yloxy) methyl)-1H-indazole-1-carboxylate,

[0211] 6-methyl-3-((1-methyl-1H-indazol-6-yl)methoxy) picolinaldehyde,

[0212] 6-methyl-3-((1-methyl-1H-indazol-7-yl)methoxy) picolinaldehyde,

[0213] 3-(isoquinolin-1-ylmethoxy)-6-methylpicolinaldehyde,

[0214] 5-(benzo[d]oxazol-4-ylmethoxy)-2-methoxyisonicotinaldehyde,

[0215] 3-((1,5-naphthyridin-4-yl)methoxy)-6-methylpicolinaldehyde,

[0216] 6-methyl-3-((1-methyl-1H-indazol-5-yl)methoxy) picolinaldehyde,

[0217] 6-methyl-3-(quinolin-5-ylmethoxy)picolinaldehyde,

[0218] 2-methoxy-5-(quinolin-5-ylmethoxy)isonicotinaldehyde,

[0219] 2-methoxy-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0220] 2-methoxy-5-((2-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0221] 5-((2 (2H-tetrazol-5-yl)pyridin-3-yl)methyoxy-2-methoxyisonicotinaldehyde,

[0222] 2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0223] 5-((3-(1H-pyrazol-5-yl)isoquinolin-4 yl)methoxy-2-methoxyisonicotinaldehyde,

[0224] 5-((2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0225] 5-(imidazo[1,5-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde,

[0226] 5-((2-(1,5-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotialdehyde,

[0227] 5-((2-(1-ethyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,

[0228] 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,

[0229] 2-(difluoromethoxy)-5-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde,

[0230] 2-methoxy-5-((2-phenylpyridin-3-yl)methoxy) isonicotinaldehyde,

[0231] 5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl) methoxy)-2-methoxyisonicotinaldehyde,

[0232] 5-([2,3'-bipyridin]-3-ylmethoxy)-2 methoxyisonicotinaldehyde,

[0233] 2-methoxy-5-((2-(o-tolyl)pyridin-3-yl)methoxy) isonicotinaldehyde,

[0234] 2-methoxy-5-((2'-methoxy-[2,3'-bipyridin]-3-yl) methoxy)isonicotinaldehyde,

[0235] 4-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl) benzoic acid,

[0236] 4-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,

[0237] methyl 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoate,

[0238] methyl 3-(((2-formyl-6-methylpyridin-3-yl)oxy) methy)benzoate,

[0239] 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoic acid,

[0240] 3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl) benzoic acid,

[0241] 3-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,

[0242] 2-methoxy-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0243] 2-methoxy-5-((2-(1-propyl-1H-pyrazol-yl)pyridin-3 yl)methoxy)isonicotinaldehyde,

[0244] 2-methoxy-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0245] 5-((2-(1-(2,2-difluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0246] 3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)picolinaldehyde,

[0247] 3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-6-methylpicolinaldehyde,

[0248] 2-(difluoromethoxy)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0249] 5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,

[0250] 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,

[0251] 5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyrazin-2-yl) methoxy)-2-methoxyisonicotinaldehyde,

[0252] 3-((4-formyl-6-methoxypyridin-3-yloxy)methyl) picolinate,

[0253] 5-((2-(2-hydroxypropan-2-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,

[0254] 2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0255] 2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)nicotinaldehyde,

[0256] 3-hydroxy-5-((2-(1-isopropyl-1H-pyrazol-5-yl) pyridin-3-yl) methoxy)isonicotinaldehyde,

[0257] 3-(benzyloxy)-5-hydroxyisonicotinaldehyde,

[0258] 3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-5-methoxyisonicotinaldehyde,

[0259] 5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0260] 5-((2-(1-isopropyl-4-methyl-1-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,

[0261] 5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0262] 6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid,

[0263] 2,2,2-trifluoroacetic acid: 6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid (1:1),

[0264] 2-methoxy-5-((2-(1-((2-(trimethylsilyl)ethoxy) methyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0265] 5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde,

[0266] 5-((2-(1-cyclobutyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,

[0267] 5-((2-(1-cyclohexyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,

[0268] 5-((2-(1-cyclohexylmethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0269] 5-((2-(1-cyclopentyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

[0270] 2-(5-(3-(((4-formyl-6-methoxypyridin-3-yloxy) methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetic acid,

[0271] methyl 3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate,

[0272] 3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy) methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,

[0273] 3-(5-(3-((4-formyl-6-methoxypyridin-3-yl)oxy) methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,

[0274] 3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl) benzoic acid,

[0275] 6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinonitrile 2,2,2-trifluoroacetate,

[0276] 6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid,

[0277] 6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid hydrochloride,

[0278] 6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide,

[0279] 2,2,2-trifluoroacetic acid 6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide (2:1), 2-(2-methoxyethoxy)-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-methoxy)isonicotinaldehyde,

[0280] 2-methoxy-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0281] 2-(2-methoxyethoxy)-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0282] 2-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0283] 2-methyl-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0284] 3-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl) pyridin-3-yl)methoxy)isonicotinaldehyde,

[0285] 3-((2-(1-(3,3,3-tritluoropropyl)-1H-pyrazol-5-yl) pyridin-3-yl)methoxy)isonicotinaldehyde,

[0286] 3-chloro-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

[0287] 3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-5-methylisonicotinaldehyde,

[0288] 3-chloro-5-((2-(1-(3,3,3-trifluoropropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde, and

[0289] 3-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

or a tautomer or pharmaceutically acceptable salt thereof.

[0290] In one group of embodiments, provided is a pharmaceutical composition comprising a compound of any of the above embodiments or a tautomer or pharmaceutically acceptable salt thereof.

[0291] In one group of embodiments, provided is a compound in any of the Examples or Tables. In another group of embodiments, provided are any combinations of subembodiments as disclosed herein including any combination of elements disclosed herein including the a selection of any single elements.

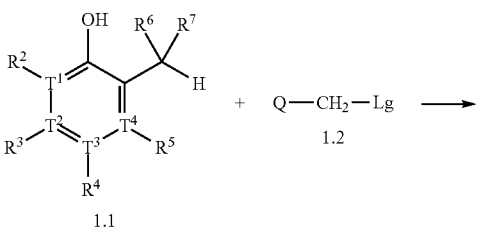
[0292] The compounds of the present invention may be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples.

[0293] In one group of embodiments provided is an intermediate compound used in the preparation of the compounds disclosed herein.

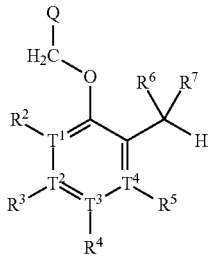
[0294] In one group of embodiments, provided are methods for preparing the compounds disclosed herein.

[0295] For example, Scheme I shows a synthetic route for the synthesis of the compounds of Formula (I) where X is O and Y is CH_2. Phenol 1.1 is contacted with intermediate 1.2 in the presence of base under ether forming conditions to give ether 1.3, where Lg represents a leaving group such as a halogen leaving group. Conversely, when X is O and Y is CH_2, the compounds of Formula (I) can be prepared using the appropriate starting materials where the OH moiety of intermediate 1.1 is replaced with a leaving group and the Lg group of intermediate 1.2 is replaced with an OH group.

Scheme I



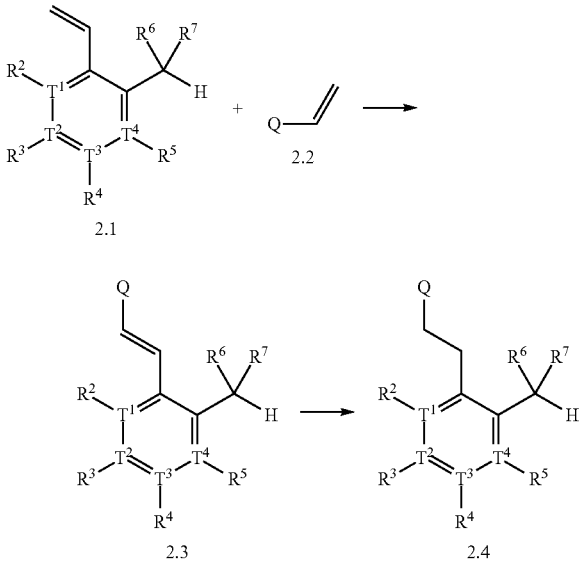
-continued



1.3

[0296] Scheme II shows an example of a synthetic route for the synthesis of the compounds of Formula (I) where X and Y are CH_2. Alkene 2.1 is contacted with alkene 2.2 under metathesis forming conditions in the presence of an appropriate transition metal catalyst. Suitable catalysts include ruthenium catalysts such as Grubbs' catalyst. Product 2.3 is then hydrogenated to give compound 2.4.

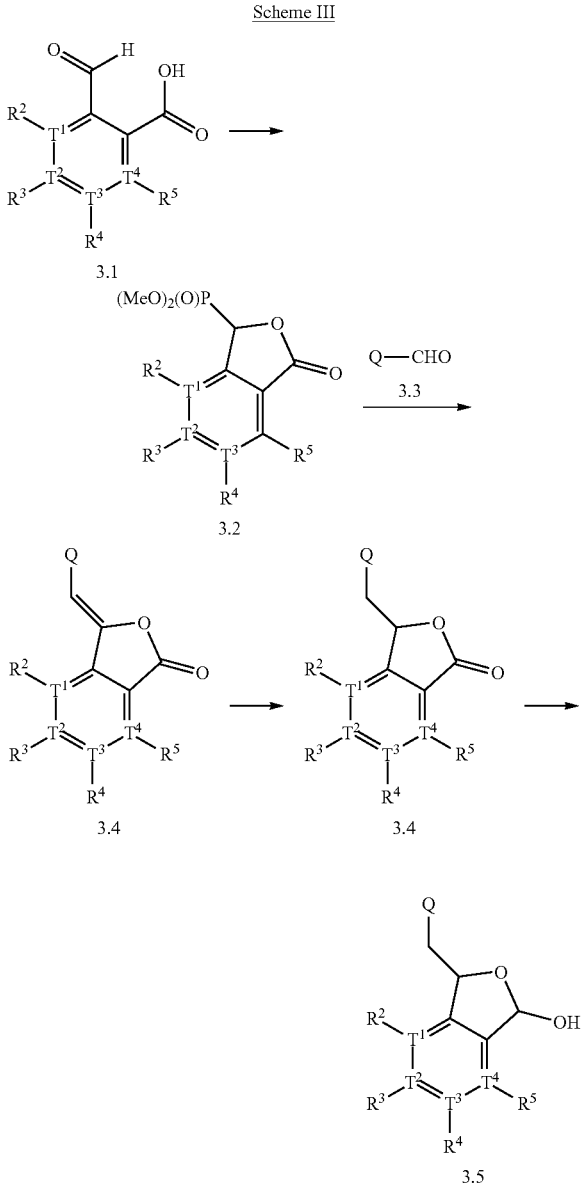
Scheme II



2.1 2.2 2.3 2.4

[0297] Scheme III shows an example of a synthetic route for the synthesis of the compounds of Formula (I) where R^6 together with R^{1b} form a cyclic ether. Compound 3.1, is reacted with diethylphosphite and a base such as sodium methoxide to give intermediate 3.2, that is then condensed with aldehyde 3.3 to give alkene 3.4. Treatment of the alkene with H_2 under hydrogenation conditions gives lactose 3.4, which is then reduced with a suitable reducing agent such as $LiBHEt_3$ to give cyclic hemiacetal 3.5.

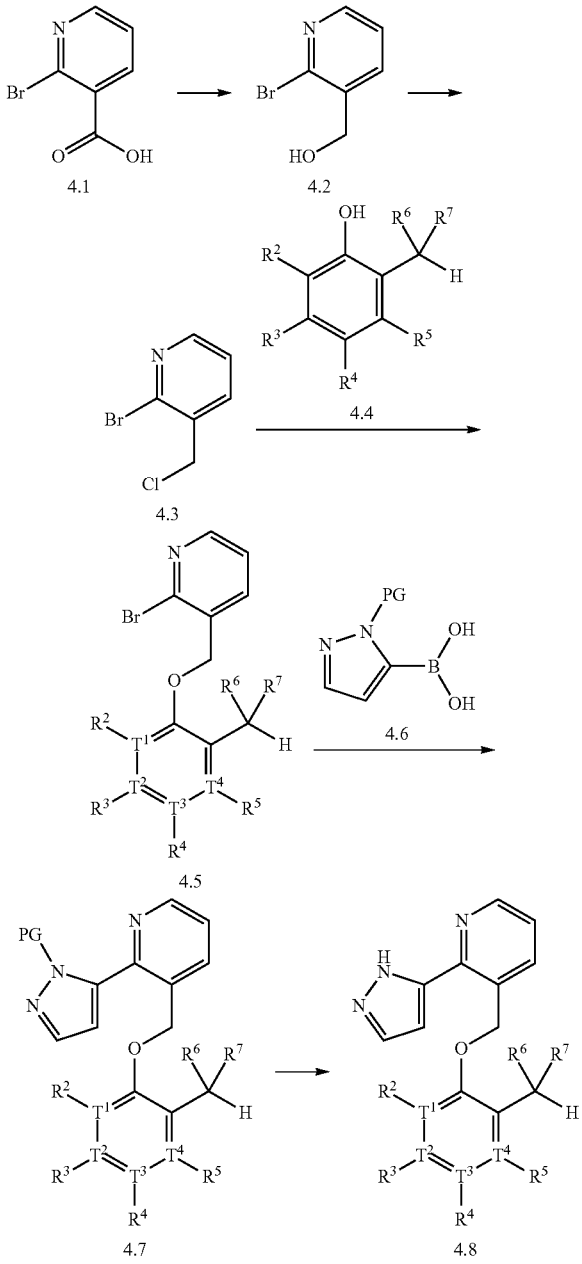
Scheme III



3.1 3.2 3.3 3.4 3.4 3.5

[0298] Scheme IV shows an example of synthesis of the compounds of Formula (I) where Q is pyridine-3-yl and R^a heteroaryl. Acid 4.1 is reduced to alcohol 4.2 using known methods such as by forming the anhydride (e.g. treatment with triethylamine and i-butyl chloroformate) followed by reduction with $NaBH_4$. Alcohol 4.2 is converted to chloride 4.3 such as by treatment with thionyl chloride. Coupling of the halide with alcohol 4.4 under ether forming conditions gives the precursor 4.5 that can be functionalized with a variety to heteroaryl R^a groups. For example, 4.5 can be coupled with pyrazole 4.6 under known organometallic coupling conditions (e.g. $Pd(PPh_3)_4$) to give 4.7, where PG is a nitrogen protecting group such as a silyl protecting group that can be removed to give the product 4.8.

Scheme IV



[0299] One skilled in the art will recognize that in certain embodiments it may be advantageous to use a protecting group strategy. The protecting group can be removed using methods known to those skilled in the art.

[0300] The compounds of the present invention may generally be utilized as the free base. Alternatively, the compounds of this invention may be used in the form of acid addition salts.

[0301] It is understood that in another group of embodiments, any of the above embodiments may also be combined with other embodiments listed herein, to form other embodiments of the invention. Similarly, it is understood that in other embodiments, listing of groups includes embodiments wherein one or more of the elements of those groups is not included.

III. Compositions and Methods of Administration

[0302] Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, preferably in unit dosage form suitable for single administration of a precise dosage. In addition to an effective amount of the active compound(s), the compositions may contain suitable pharmaceutically-acceptable excipients, including adjuvants which facilitate processing of the active compounds into preparations which can be used pharmaceutically. "Pharmaceutically acceptable excipient" refers to an excipient or mixture of excipients which does not interfere with the effectiveness of the biological activity of the active compound(s) and which is not toxic or otherwise undesirable to the subject to which it is administered.

[0303] For solid compositions, conventional excipients include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmacologically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in water or an aqueous excipient, such as, for example, water, saline, aqueous dextrose, and the like, to form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary excipients such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc.

[0304] For oral administration, the composition will generally take the form of a tablet or capsule, or it may be an aqueous or nonaqueous solution, suspension or syrup. Tablets and capsules are preferred oral administration forms. Tablets and capsules for oral use will generally include one or more commonly used excipients such as lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. When liquid suspensions are used, the active agent may be combined with emulsifying and suspending excipients. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional excipients for incorporation into an oral formulation include preservatives, suspending agents, thickening agents, and the like.

[0305] Injectable formulations can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solubilization or suspension in liquid prior to injection, or as emulsions or liposomal formulations. The sterile injectable formulation may also be a sterile injectable solution or a suspension in a nontoxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, Ringers solution and isotonic sodium chloride solution. In addition, sterile, fixed oils, fatty esters or polyols are conventionally employed as solvents or suspending media.

[0306] The pharmaceutical compositions of this invention may also be formulated in lyophilized form for parenteral administration. Lyophilized formulations may be reconstituted by addition of water or other aqueous medium and then further diluted with a suitable diluent prior to use. The liquid

formulation is generally a buffered, isotonic, aqueous solution. Examples of suitable diluents are isotonic saline solution, 5% dextrose in water, and buffered sodium or ammonium acetate solution. Pharmaceutically acceptable solid or liquid excipients may be added to enhance or stabilize the composition, or to facilitate preparation of the composition.

[0307] Typically, a pharmaceutical composition of the present invention is packaged in a container with a label, or instructions, or both, indicating use of the pharmaceutical composition in the treatment of the indicated disease.

[0308] The pharmaceutical composition may additionally contain one or more other pharmacologically active agents in addition to a compound of this invention.

[0309] Dosage forms containing effective amounts of the modulators are within the bounds of routine experimentation and within the scope of the invention. A therapeutically effective dose may vary depending upon the route of administration and dosage form. The representative compound or compounds of the invention is a formulation that exhibits a high therapeutic index. The therapeutic index is the dose ratio between toxic and therapeutic effects which can be expressed as the ratio between LD_{50} and ED_{50}. The LD_{50} is the dose lethal to 50% of the population and the ED_{50} is the dose therapeutically effective in 50% of the population. The LD_{50} and ED_{50} are determined by standard pharmaceutical procedures in animal cell cultures or experimental animals. It should be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex and diet of the patient, and the time of administration, rate of excretion, drug combination, judgment of the treating physician and severity of the particular disease being treated. The amount of active ingredient(s) will also depend upon the particular compound and other therapeutic agent, if present, in the composition.

IV Methods

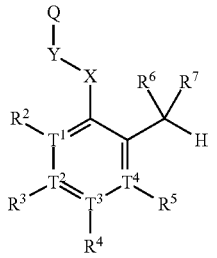
[0310] In one group of embodiments, provided is a method for increasing tissue oxygenation, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the above embodiments or a tautomer or pharmaceutically acceptable salt thereof.

[0311] In one group of embodiments, provided is a method for treating a condition associated with oxygen deficiency, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the above embodiments or a tautomer or pharmaceutically acceptable salt thereof.

[0312] In one group of embodiments, provided is a method for treating sickle cell disease, cancer, a pulmonary disorder, stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, acute respiratory disease syndrome, and a wound, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the above embodiments or a tautomer or pharmaceutically acceptable salt thereof.

[0313] In one group of embodiments, provided is a method for increasing tissue oxygenation or for treating a condition associated with oxygen deficiency, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound Formula (II):

(II)



or a tautomer or pharmaceutically acceptable salt thereof,

[0314] wherein Q is selected from the group consisting of aryl, heteroaryl, and heterocycloalkyl, each optionally substituted with one to three R^a;

[0315] Y is O or $CR^{1a}R^{1b}$, where R^{1a} is H or halo and R^{1b} is selected from the group consisting of H, halo, and OH;

[0316] X is selected from the group consisting of O, $>CH(CH_2)_nR^8$, and $C(R^9)_2$ where n is 0 or 1, R^8 is OH, and R^9 is independently H or halo; or Y—X taken together is —NHC(O)— or —C(O)NH—;

[0317] R^2, R^3, R^4, and R^5 are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^d$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 0, 1, 2, or 3; or R^5 is $—(CH_2)_pR^{5a}$ where p is 0 or 1 and R^{5a} is OH;

[0318] R^6 and R^7 together form oxo or an aldehyde protecting group, or R^6 together with R^{1b}, R^8, or R^5 forms a cyclic ether where one of R^{1b}, R^8, or R^{5a} is O, R^6 is a bond, and R^7 is selected from the group consisting of OH, C_{1-8}alkoxy, and haloC_{1-8}alkoxy;

[0319] T^1, T^2, T^3, and T^4 are independently C or N provided that at least one of T^1, T^2, T^3, and T^4 is N and at least one of T^1, T^2, T^3, and T^4 is C;

[0320] each R^a is independently selected from the group consisting of halo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, $—(CH_2)_kOC(O)R^e$, $—(CH_2)_kSR^d$, CN, NO_2, $—(CH_2)_kCO_2(C_{1-8}alkyl)OH$, $—(CH_2)_kCO_2(C_{1-8}alkyl)(heteroaryl)C(O)(C_{1-8}alkyl)$, $—(CH_2)_kCO_2R^d$, $—(CH_2)_kCONR^dR^d$, $(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^d(O)_2R^e$, $—(CH_2)_kC(O)R^d$, $—(CH_2)_kOC(O)NR^dR^d$, $—NR^d(CH_2)_uOR^d$, $—NR^d(CH_2)_uNR^dR^d$, $—NR^d(CH_2)_uNR^dC(O)R^e$, $—NR^d(CH_2)_uNR^dC(O)_2R^e$, $—NR^d(CH_2)_uNR^dS(O)_2R^e$, $—(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^dC(O)_2R^d$, $—(CH_2)_kNR^dC(O)NR^dR^d$, $—(CH_2)_kS(O)R^e$, $—(CH_2)_kS(O)_2R^e$, $—(CH_2)_kNR^dS(O)_2R^e$, $—C(O)(CH_2)_kNR^dS(O)_2R^e$, $—(CH_2)_kC(O)NR^dS(O)_2R^e$, $—(CH)_kS(O)_2NR^dR^d$, N_3, $—(CH_2)_karyl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_karyl$ optionally substituted with one to three R^c, $—(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c, and $—NR(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6;

[0321] each R^b is independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl and C_{2-8}alkynyl, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

[0322] each R^c is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, C_{2-8}alkynyl, haloC_{2-8}alkynyl, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, NO_2, $(CH_2)_mCO_2R^f$, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, N_3, $(R^f)_mSiC_{1-8}$alkyl, heteroaryl optionally substituted with one to three R^h, cycloalkyl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

[0323] each R^h is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, OR^j, OC(O)R, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, $C(O)R^j$, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^i$, $NR^jC(O)_2R^i$, $NR^jC(O)NR^jR^j$, $S(O)R^i$, $S(O)_2R^i$, $NR^jS(O)_2R^i$, and $S(O)_2NR^jR^j$;

[0324] R^d, R^f, and R^j are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl; and

[0325] R^e, R^g, and R^i are each independently selected from the group consisting of C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl;

[0326] provided that X and Y are not both O;

[0327] provided that when X is O, R^{1b} is not OH; and

[0328] provided that when Y is O, and n is O, R^8 is not OH.

[0329] In one group of embodiments, provided is a method of any of the groups of embodiments disclosed herein, wherein at least one z is 0. In another group of embodiments, at least one z is 1. In yet another group of embodiments, at least one z is 2. In still another group of embodiments, at least one z is 3. In another group of embodiments, no z is 0.

V. Examples

[0330] The following examples are offered to illustrate, but not to limit, the claimed invention.

PREPARATIVE EXAMPLES

[0331] The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley & Sons: New York, 1967-2004. Volumes 1-22; *Rodd's Chemistry of Carbon Compounds*, Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and Organic Reactions, Wiley & Sons: New York, 2005, Volumes 1-65.

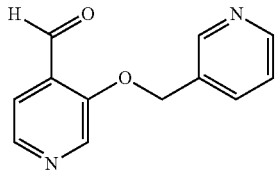
[0332] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0333] Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about −78° C. to about 150° C., more preferably from about 0° C. to about 125° C., and most preferably and conveniently at about room (or ambient) temperature, e.g., about 20° C. to about 75° C.

[0334] Referring to the examples that follow, compounds of the present invention were synthesized using the methods described herein, or other methods known in the art.

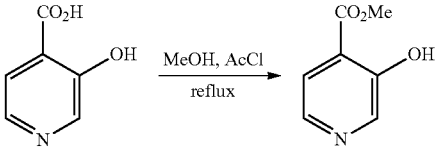
Example 1. Preparation of 3-(pyridin-3-ylmethoxy)isonicotinaldehyde

[0335]



Step 1:

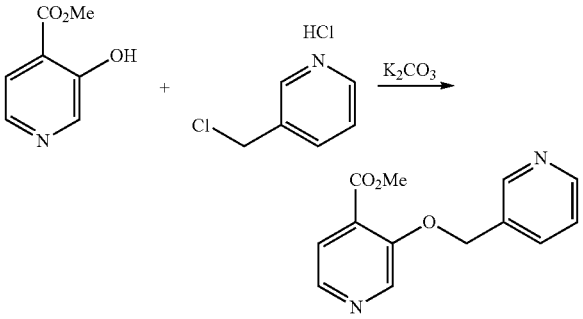
[0336]



[0337] Acetyl chloride (20 mL) was added dropwise to methanol (200 mL) at 0° C. After the addition, the reaction mixture was stirred at this temp for 15 min and then 4.0 g of the acid was added. The reaction mixture was heated at reflux for 12 h. Methanol was removed to give a residue, which was then carefully neutralized with sq. sat. $NaHCO_3$ and then extracted with EtOAc (3×). The organic layers were combined, dried and evaporated to give the ester as a yellow solid, which was used in the next step without further purification.

Step 2:

[0338]

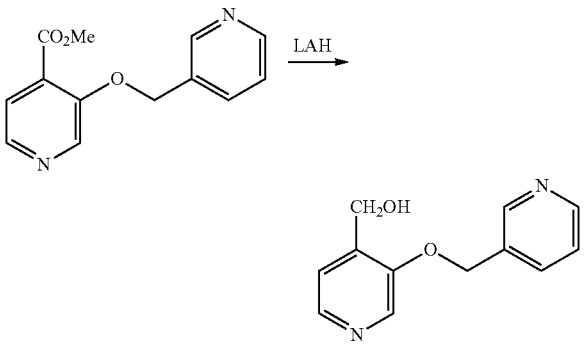


[0339] A mixture of chloride (300 mg 1.5 mmol, 1.0 eq), hydroxypyridine (230 mg, 1.5 mmol, 1.0 eq) and potassium carbonate (621 mg, 4.5 mmol, 3.0 eq) were taken in DMF (10 mL) and the reaction mixture was heated at 80° C. for 4 h. Solvent was removed and the crude was purified by

column chromatography (Hexane/EtOAc to EtOAc/MeOH) to provide the coupled product.

Step 3:

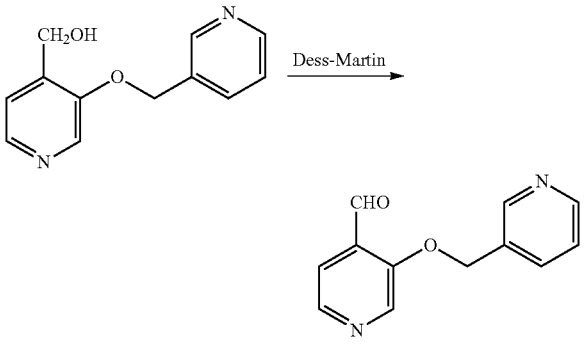
[0340]



[0341] To an ice cold solution of ester (1.5 mmol, 1.0 eq) in THF (15 mL) was slowly added LAH solution (1.5 mL, 2M solution in THF) and the reaction mixture was stirred at this temp for 30 min. Then excess ethyl acetate was added slowly to quench excess LAH. Then water (1 mL), 15% NaOH (1 mL) and water (3 mL) were added and stirred at rt for 30 min. The clear solution was filtered and the solid was washed with ethyl acetate (3×). The organic layers were combined, dried and evaporated to give the crude alcohol, which was used in the next step without further purification.

Step 4:

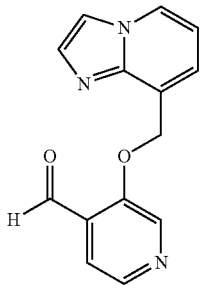
[0342]



[0343] To a solution of the above alcohol (1.5 mmol, 1.0 eq) in DCM (15 mL) was added Dess-Martin reagent (2.25 mmol, 454 mg, 1.5 eq) and the reaction mixture was stirred at it for 1 h. Solution was diluted with 25 mL DCM and then a 1:1 mixture of sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ was added and stirred for 30 min to get two clear layers. Aqueous layer was separated and washed with DCM (3×). Organic layer was dried and evaporated to give a crude product, which was purified by column chromatography (EtOAc/MeOH). NMR (400 MHz, $CDCl_3$): δ 5.35 (s, 2H), 7.49 (m, 1H), 7.60 (d, 1H), 8.02 (m, 1H), 8.25 (m, 1H), 8.38 (s, 1H), 8.53 (m, 1H), 8.70 (m, 1H), 10.58 (s, 1H); MS: exact mass calculated for $C_{12}H_{10}N_2O_2$, 214.07; m/z found, 215 $[M+H]^+$.

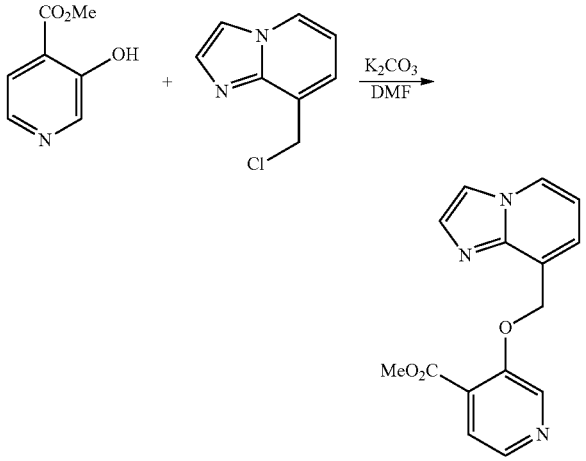
Example 2. Preparation of 3-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde

[0344]



Step 1:

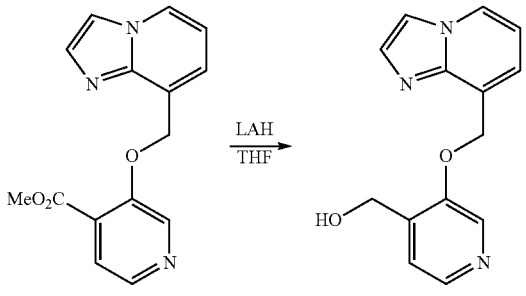
[0345]



[0346] To a DMF (15 mL) solution of the chloride (300 mg, 1.5 mmol, 1.0 eq) and phenol (230 mg, 1.5 mmol, 1.0 eq) was added K_2CO_3 (621 mg, 4.5 mmol, 3.0 eq) and the reaction mixture was heated at 80-90° C. for 5 h. Solvent was removed and the residue was purified by column chromatography (EtOAc/MeOH) to give the alkylation product. MS: exact mass calculated for $C_{15}H_{13}N_3O_3$, 283.10; m/z found, 284 $[M+H]^+$.

Step 2:

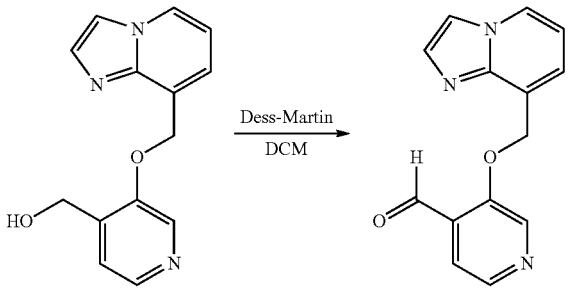
[0347]



[0348] To a cooled solution of the ester (1.5 mmol, 1.0 eq) in THF (15 mL) was slowly added LAH in THF (1.5 mL, 2.0 M solution in THF, 2.0 eq) and the reaction mixture was stirred at this temperature for 30 min. Excess ethyl acetate was added very slowly followed by water (1.0 mL), 15% NaOH (1.0 mL) and water (3.0 mL) and the mixture was stirred at it for 30 min. The solution was filtered and the solid was washed with ethyl acetate (3×). Combined organic layers were dried and evaporated to provide the alcohol, which was used in the next step without further purification. MS: exact mass calculated for $C_{14}H_{13}N_3O$, 255.10; m/z found, 256 $[M+H]^+$.

Step 3:

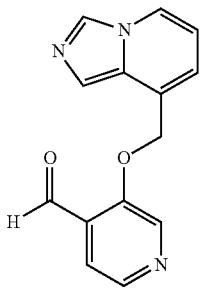
[0349]



[0350] To a solution of the above alcohol (1.5 mmol, 1.0 eq) in DCM (15 mL) was added Des-Martin reagent (2.25 mmol, 954 mg, 1.5 eq) and the reaction mixture was stirred at rt for 1 h. The reaction was then diluted with 25 mL DCM and then a 1:1 mixture of sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ was added and stirred for 30 min to get two clear layers. The aqueous layer was separated and washed with DCM (3×). The organic layer was dried and evaporated to give a crude product which was purified by column chromatography (EtOAc/MeOH). MS: exact mass calculated for $C_{14}H_{11}N_3O_2$, 253.09; m/z found, 254 $[M+H]^+$.

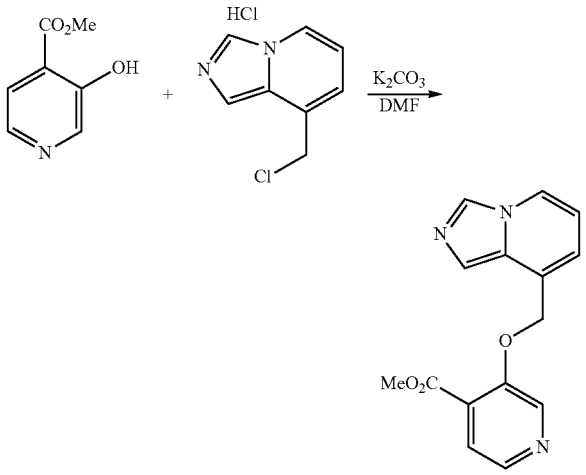
Example 3. Preparation of 3-(imidazo[1,5-a]pyridin-8-ylmethoxy)isonicotinaldehyde

[0351]



Step 1:

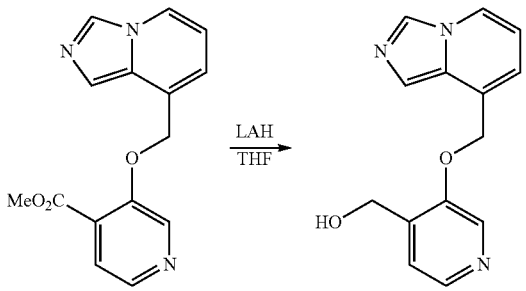
[0352]



[0353] To a solution of chloride (200 mg, 1.0 mmol, 1.0 eq), and phenol (153 mg, 1.0 mmol, 1.0 eq) in DMF (15 mL) was added K_2CO_3 (414 mg, 3.0 mmol, 3.0 eq) and the reaction mixture was heated at 80-90° C. for 5 h. Solvent was removed and the residue was purified by column chromatography (EtOAc/MeOH) to give the alkylation product. MS: exact mass calculated for $C_{15}H_{13}N_3O_3$, 283.10; m/z found, 284 $[M+H]^+$.

Step 2:

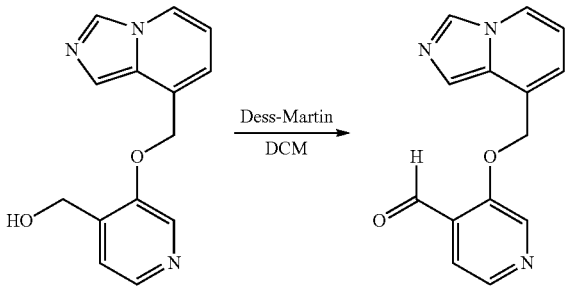
[0354]



[0355] To a cooled solution of the ester (1.0 mmol, 1.0 eq) in THF (15 mL) was slowly added LAH in THF (4 mmol, 2.0 mL, 2.0 M solution in THF, 4.0 eq) and the reaction mixture was stirred at this temperature for 30 min. Excess ethyl acetate was added very slowly followed by water (1.0 mL), 15% NaOH (1.0 mL) and water (3.0 mL) and the mixture was stirred at rt for 30 min. Filtered and the solid was washed with ethyl acetate (3×). Combined organic layers were dried and evaporated to provide the alcohol, which was used in the next step without further purification. MS: exact mass calculated for $C_{14}H_{13}N_3O_2$, 255.10; m/z found, 286 $[M+H]^+$.

Step 3:

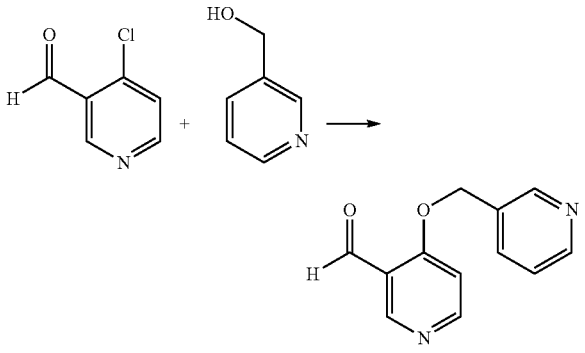
[0356]



[0357] To a cooled solution of the ester (1.0 mmol, 1.0 eq) in THF (15 mL) was slowly added LAH in THF (4 mmol, 2.0 mL, 2.0 M solution in THF, 4.0 eq) and the reaction mixture was stirred at this temperature for 30 min. Excess ethyl acetate was added very slowly followed by water (1.0 mL), 1% NaOH (1.0 mL) and water (3.0 mL) and the mixture was stirred at rt for 30 min. Reaction was filtered and the solid was washed with ethyl acetate (3×). Combined organic layers were dried and evaporated to provide the alcohol, which was used in the next step without further purification. MS: exact mass calculated for $C_{14}H_{13}N_3O_2$, 255.10; m/z found, 286 $[M+H]^+$.

Example 4. Preparation of 4-(pyridin-3-ylmethoxy)nicotinaldehyde

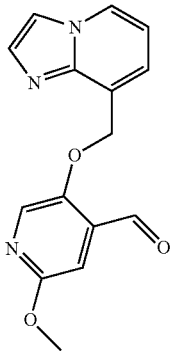
[0358]



[0359] 4-chloro-3-pyridine aldehyde (1.0 g, 7 mmol, 1.0 eq), 3-hydroxymethyl pyridine (5.4 g, 49.45 mmol, 7 eq) and p-toluenesulfonic acid mon hydrate (1.3 g, 7.0 mmol, 1.0 eq) in benzene (30 mL) were heated using a Dean-Stark trap for 24 h. Solvent was removed and purified by column chromatography to provide the alkylation product. MS: exact mass calculated for $C_{12}H_{10}N_2O_2$, 214.22; m/z found, 215 $[M+H]^+$.

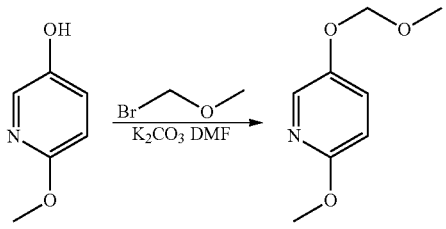
Example 5. Preparation of 5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde (Compound 5)

[0360]



Step 1:

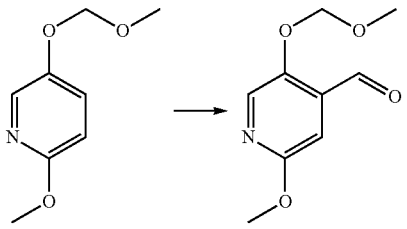
[0361]



[0362] To a mixture of 6-methoxypyridin-3-ol (25 g, 0.2 mol) and K_2CO_3 (82.8 g, 0.6 mol) in DMF (250 mL) was added bromomethyl methyl ether (30 g, 0.24 mmol) slowly at rt for a period of 1 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified on silica gel with 25% EtOAc/hexanes eluent to give 2-methoxy-5-(methoxymethoxy)pyridine (20 g, 59%) as a colorless oil. LRMS ($M+H^+$) m/z 170.1

Step 2:

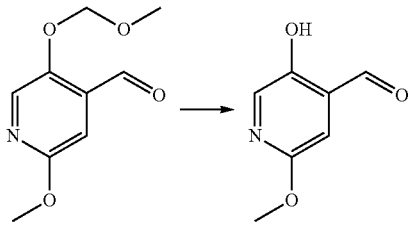
[0363]



[0364] To a solution of 2-methoxy-5-(methoxymethoxy) pyridine (20 g, 0.12 mol) in THF was added diisopropylamine (0.24 g, 2.4 mmol). The solution was cooled to −40° C. followed by addition of MeLi (3M/THF, 72 mL, 0.216 mol) slowly. The resulting mixture was warmed to 0° C., stirred at 0° C. for 3 h, cooled back down to −40° C. and added N-formylpiperidine (24 mL, 0.216 mol). After stirring at −40° C. for 2 h, the mixture was quenched with a mixed solution of HCl (37%, 120 mL) and THF (250 mL). The temperature was then raised to it and diluted with water (200 mL) and EtOAc (200 mL). The pH of the mixture was adjusted to 8-9 with solid K_2CO_3 and extracted with EtOAc (300 mL) twice. The organic layer was combined, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel with 25% EtOAc/hexanes as eluent to give 2-methoxy-5-(methoxymethoxy)isonicotinaldehyde (10 g, 42%) as a pale yellow oil. ^{1}H NMR (400 MHz; CD_3OD) 7.90 (s, 1H), 6.92 (s, 1H), 5.64 (s, 1H), 5.20 (s, 2H), 3.84 (s, 3H), 3.48 (s, 3H).

Step 3:

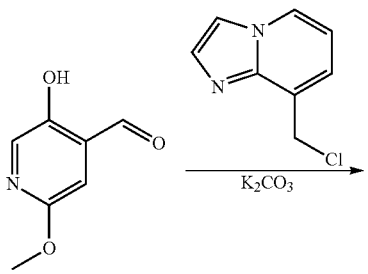
[0365]



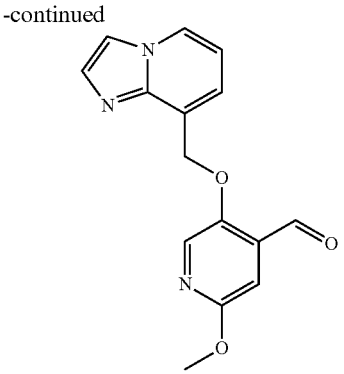
[0366] To a solution of 2-methoxy-5-(methoxymethoxy) isonicotinaldehyde (10 g, 0.05 mol) in THF (100 mL) was added 3 N HCl (150 mL). The reaction was stirred at 50° C. for 30 min, cooled to rt, and diluted with water (100 mL). The mixture was neutralized to pH 7-8 and extracted with EtOAc (200 mL) three times. The organic layer was dried over Na_2SO_4 and concentrated to give 5-hydroxy-2-methoxyisonicotinaldehyde (4.2 g, 55%) as a yellow solid. ^{1}H NMR (400 MHz; DMSO) δ=10.31 (s, 1H), 8.03 (s, 1H), 6.89 (s, 1H), 3.80 (s, 3H).

Step 4:

[0367]



-continued



[0368] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (723.6 mg, 4.7 mmol), 8-(chloromethyl)-imidazol[1,2-a]pyridine (785 mg, 4.7 mmol), and K_2CO_3 (1.9 g, 14.1 mmol) in DMF (20 mL) was heated at microwave reactor at 125° C. for 15 min. The mixture was filtered and concentrated. The residue was purified on silica gel (50-100% EtOAc in hexanes) to give 5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde (500 mg, 38%) as an off-white solid. ^{1}H NMR (400 MHz; DMSO) δ=10.37 (s, 1H), 8.58 (d, 1H), 8.39 (s, 1H), 8.02 (s, 1H), 7.61 (s, 1H), 7.44 (d, 1H), 6.98 (s, 1H), 6.93 (t, 1H), 5.61 (s, 2H), 3.84 (s, 3H). LRMS ($M+H^+$) m/z 284.0.

[0369] Examples 6-13 were synthesized according to Example 5.

Example 6. Preparation of 2-methoxy-5-((5-methylpyridin-3-yl)methoxy)isonicotinaldehyde (Compound 43)

[0370] ^{1}H NMR (400 MHz, CDCl3) δ 10.43 (s, 1H), 8.69 (s, 1H), 8.56 (s, 1H), 8.09 (s, 1H), 7.94 (s, 1H), 7.15-7.09 (m, 1H), 5.29 (s, 2H), 3.94 (s, 3H), 2.51 (s, 3H), 1H NMR (400 MHz, CDCl3) δ 10.43 (s, 1H), 8.69 (s, 1H), 8.56 (s, 1H), 8.09 (s, 1H), 7.94 (s, 1H), 7.15-7.09 (m, 1H), 5.29 (s, 2H), 3.94 (s, 3H), 2.51 (s, 3H).

Example 7. Preparation of 5-(isoquinolin-1 ylmethoxy)-2-methoxyisonicotinaldehyde (Compound 44)

[0371] ^{1}H NMR (400 MHz, CDCl3) δ 10.40 (s, 1H), 8.54 (d, J=5.7 Hz, 1H), 8.30 (s, 1H), 8.31 (d, J=8.6 Hz, 1H), 7.90 (d, J=8.4 Hz, 1H), 7.78-7.63 (m, 3H), 7.07 (d, J=0.5 Hz, 1H), 5.82 (s, 2H), 3.91 (s, 3H).

Example 8. Preparation of 2-methoxy-5-(quinolin-2 ylmethoxy)isonicotinaldehyde (Compound 45)

[0372] ^{1}H NMR (400 MHz, CDCl3) δ 10.61 (s, 1H), 8.26 (d, J=8.5 Hz, 1H), 8.12 (s, 1H), 8.10 (d, J=8.5 Hz, 1H), 7.87 (dd, J=8.2, 1.1 Hz, 1H), 7.78 (ddd, J=8.4, 6.9, 1.4 Hz, 1H), 7.67 (d, J=8.5 Hz, 1H), 7.60 (ddd, J=8.1, 7.0, 1.1 Hz, 1H), 7.13 (s, 1H), 5.52 (s, 2H), 3.91 (s, 3H).

Example 9. Preparation of 2-methoxy-5-(pyridin-4-ylmethoxy)isonicotinaldehyde (Compound 46)

[0373] ^{1}H NMR (400 MHz, CDCl3) δ 10.44 (s, 1H), 8.59 (d, J=6.0 Hz, 2H), 7.92 (s, 1H), 7.30 (d, =6.0 Hz, 2H), 7.06 (s, 1H), 5.16 (s, 2H), 3.84 (s, 3H).

Example 10. 3-(imidazo[1,2-a]pyridin-8-yl-methoxy)-6-methylpicolinaldehyde (Compound 49)

[0374] ^{1}H NMR (400 MHz, DMSO) δ 10.22 (s, 1H), 8.56 (d, J=6.7 Hz, 1H), 8.02 (s, 1H), 7.82 (d, J=8.7 Hz, 1H), 7.60 (s, 1H), 7.53 (d, J=8.7 Hz, 1H), 7.47 (d, J=6.7 Hz, 1H), 6.96 (t, J=6.9 Hz, 1H), 5.59 (s, 2H), 2.49 (s, 3H).

Example 11. Preparation of methyl 2-((4-formyl-6 methoxypyridin-3 yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxylate (Compound 53)

[0375] ^{1}H NMR (400 MHz, CDCl3) δ 10.52 (s, 1H), 8.32 (dd, J=6.7, 1.3 Hz, 1H), 8.17 (s, 1H), 8.03 (dd, J=7.2, 1.3 Hz, 1H), 7.76 (s, 1H), 7.11 (s, 1H), 6.94 (t, J=7.0 Hz, 1H), 5.53 (s, 2H), 4.06 (s, 3H), 3.93 (s, 3H).

Example 12. Preparation of 2-methoxy-5-((3-methyl-[1,2,4]triazolo[4,3]pyridin-8-yl)methoxy) isonicotinaldehyde (Compound 58)

[0376] ^{1}H NMR (400 MHz, CDCl3) δ 10.53 (s, 1H), 8.14 (s, 1H), 7.89 (d, J=6.9 Hz, 3H), 7.44 (dd, J=6.8, 1.1 Hz, 1H), 7.11 (s, 1H), 6.94 (t, J=6.9 Hz, 1H), 5.67 (s, 2H), 3.92 (s, 3H), 2.80 (s, 3H).

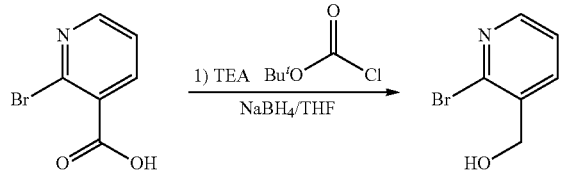
Example 13. Preparation of 5-((2-(1H-pyrazol-1-yl) pyridin-3 yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 134)

[0377] ^{1}H NMR (400 MHz, CDCl3) δ 10.47 (s, 3H), 8.53 (d, J=2.1 Hz, 1H), 8.48 (d, J=4.7 Hz, 1H), 8.19 (d, J=7.8 Hz, 1H), 8.10 (s, 3H), 7.75 (s, 1H), 7.35 (dd, J=7.7, 4.7 Hz, 1H), 7.12 (s, 1H), 6.51 (dd, J=2.5, 1.8 Hz, 1H), 5.75 (s, 2H), 3.93 (s, 3H).

Example 14. Preparation of 5-(2-(1H-pyrazol-5-yl) pyridin-3 yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 65)

Step 1:

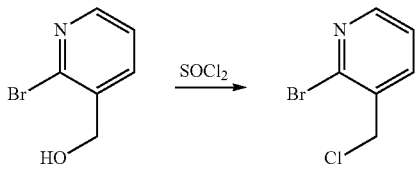
[0378]



[0379] To a solution of 2-bromonicotinic acid (4.0 g, 20 mmol) and triethylamine (3.34 mL, 24 mmol, 1.2 eq.) in THF (100 mL) was added i-butyl chloroformate (3.12 mL, 24 mmol, 1.2 eq.) at 0° C. The mixture was stirred at 0° C. for 10 min and filtered. To this filtrate was added a suspension of $NaBH_4$ (1.52 g, 40 mmol, 2 eq.) in water (1.0 mL) at 0° C. The mixture was stirred for 30 min, added water (3 mL), continued to stir for 2 h, and concentrated to dryness. The crude was purified on silica gel using a mixture of ethylacetate and hexanes as eluent to give (2-bromopyridin-3-yl)methanol (3.4 g, 90%) as a white solid. LRMS (M+H$^+$) m/z 188.0.

Step 2:

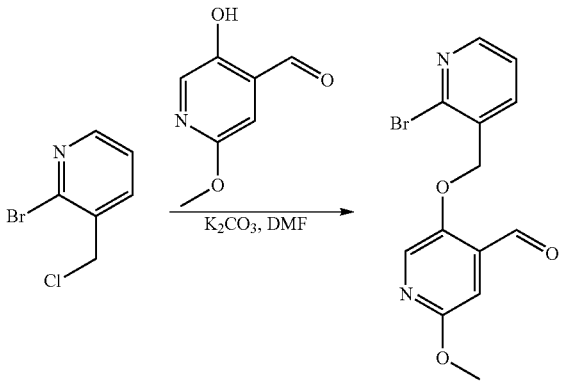
[0380]



[0381] To (2-bromopyridin-3-yl)methanol (380 mg, 2 mmol) in DCM (5 mL) was added $SOCl_2$ (1 mL) at rt. The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give an off-white solid (480 mg), which was used for next step without further purification.

Step 3:

[0382]

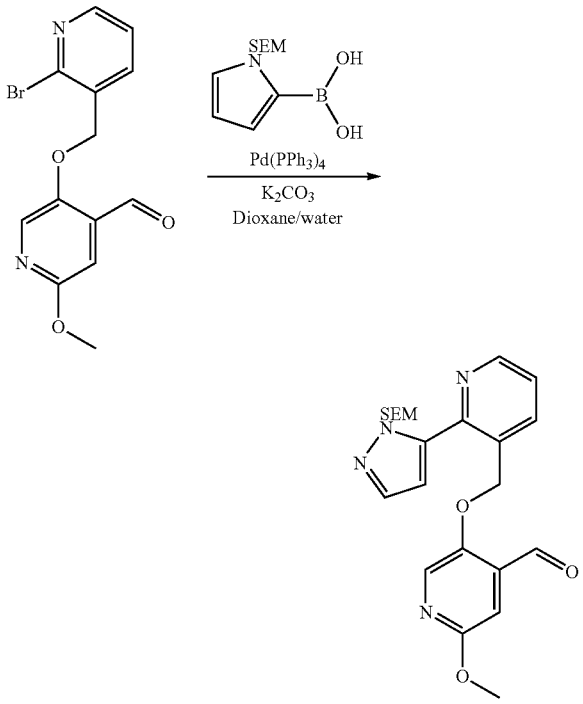


[0383] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (306 mg, 2 mmol, 1 eq.), 2-bromo-3-(chloromethyl) pyridine (crude above, 2 mmol), and K_2CO_3 (828 mg, 6 mmol, 3 eq.) in DMF (1.0 mL) was heated at 50° C. for 2 h. The mixture was cooled and added to water (50 mL) dropwise. The precipitate was filtered, washed with water, dried under high vacuo to give 5-((2-bromopyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde (350 mg, 85%) as an yellow solid.

[0384] ^{1}H NMR (400 MHz; $CDCl_3$) δ=10.51 (s, 1H), 8.42 (dd, 1H), 8.09 (s, 1H), 7.91 (d, 1H), 7.40 (dd, 1H), 7.15 (s, 1H), 5.27 (s, 2H), 3.95 (s, 3H). LRMS (M+H$^+$) m/z 323.0.

Step 4:

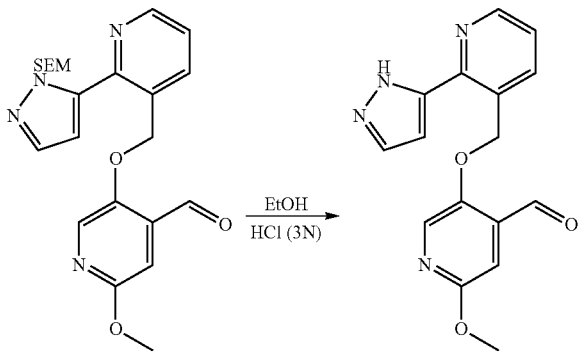
[0385]



[0386] 5-((2-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (258 mg, 0.8 mmol, 1 equiv), 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-ylboronic aid (233 mg, 0.96 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (92 mg, 0.08 mmol, 0.1 equiv). K_2CO_3 (331 mg, 2.4 mmol, 3 equiv) in a round bottom flask were added dioxane (8 mL) and water (2 mL). The mixture was heated 2 h at 90° C., cooled, filtered, and concentrated. The crude was purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 2-methoxy-5-((2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (208 mg, 79%) as a white solid. ^1H NMR (40 MHz; $CDCl_3$) δ=10.54 (s, 1H), 8.85 (d, 1H), 8.18 (d, 1H), 8.03 (s, 1H), 7.73 (d, 1H), 7.56 (dd, 1H), 7.21 (s, 1H), 6.60 (d, 1H), 5.79 (s, 2H), 5.27 (s, 2H), 4.01 (s, 3H), 3.65 (t, 2H), 0.88 (t, 2H), 0.05 (s, 9H). LRMS ($M+H^+$) m/z 441.2.

Step 5:

[0387]



[0388] To 2-methoxy-5-((2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (120 mg, 0.27 mmol, 1 equiv) suspended in EtOH (1 mL) was added HCl (1.0 mL, 3 N). The solution turned homogeneous and the mixture was stirred at rt overnight. The EtOH was partially removed by blowing in N_2 gas and the precipitate was collected. The solid was washed with acetonitrile and EtOAc and dried under high vacuo to give 5-((2-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde dihydrochloride (100 mg, 96%) as a white solid. ^1H NMR (400 MHz; DMSO, 80° C.) δ=10.27 (s, 1H), 8.68 (br, 1H), 8.32 (br, 1H), 8.22 (s, 1H), 7.82 (br, 1H), 7.57 (br, 1H), 7.00 (br, 2H), 5.75 (s, 2H), 3.89 (s, 3H). LRMS ($M+H^+$) m/z 311.1.

[0389] Examples 15-22 we synthesized according to Example 14.

Example 15. Preparation of 5-((2-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 63)

[0390] ^1H NMR (400 MHz, CDCl3) δ 10.51 (s, 1H), 8.41 (dd, J=4.7, 1.8 Hz, 1H), 8.09 (s, 1H), 7.91 (dd, J=7.6, 1.6 Hz, 1H), 7.39 (dd, J=7.6, 4.8 Hz, 1H), 7.15 (s, 1H), 5.27 (s, 2H), 3.95 (s, 3H).

Example 16. Preparation of 5-((5-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 66)

[0391] ^1H NMR (400 MHz, CDCl3) δ 10.47 (s, 1H), 8.73 (s, 1H), 8.65 (s, 1H), 8.07 (s, 1H), 7.99 (s, 1H), 7.15 (s, 1H), 5.22 (s, 2H), 3.95 (d, J=0.8 Hz, 3H).

Example 17. Preparation of 2-methoxy-5-((5-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 74)

[0392] ^1H NMR (400 MHz, CDCl3) δ 10.44 (s, 1H), 8.75 (dd, J=9.0, 2.1 Hz, 2H), 8.11 (s, 1H), 7.88 (t, J=2.1 Hz, 1H), 7.58 (d, J=1.9 Hz, 1H), 7.13 (s, 1H), 6.43 (d, J=1.9 Hz, 1), 5.30 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H).

Example 18. Preparation of 5-((2-(1,5-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 143)

[0393] ^1H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.69 (dd, J=4.8, 1.7 Hz, 1H), 7.94 (s, 1H), 7.92 (dd, J=7.8, 1.7 Hz, 1H), 7.57 (s, 1H), 7.29 (dd, J=7.8, 4.8 Hz, 2H), 7.10 (s, 1H), 5.24 (s, 2H), 3.92 (s, 3H), 3.88 (s, 3H), 2.42 (s, 3H).

Example 19. Preparation of 5-((2-(1-ethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 149)

[0394] ^1H NMR (400 MHz, CDCl3) δ 10.32 (s, 1H), 8.68 (dd, J=4.8, 1.6 Hz, 1H), 7.95 (dd, J=7.9, 1.6 Hz, 1H), 7.84 (s, 1H), 7.50 (d, J=1.9 Hz, 1H), 7.36 (dd, J=7.9, 4.8 Hz, 1H), 7.03 (s, 1H), 6.32 (d, J=1.9 Hz, 1H), 5.09 (s, 2H), 4.21 (q, J=7.2 Hz, 2H), 3.83 (s, 3H), 1.32 (t, J=7.2 Hz, 3H).

Example 20. Preparation of 2-methoxy-5-(2-phenylpyridin-3-yl)methoxy)isonicotinaldehyde (Compound 159)

[0395] ^{1}H NMR (400 MHz, CDCl3) δ 10.26 (s, 1H), 8.63 (dd, J=4.8, 1.6 Hz, 1H), 7.88 (dd, J=7.8, 1.6 Hz, 1H), 7.78 (s, 1H), 7.48-7.44 (m, 2H), 7.41-7.34 (m, 3H), 7.28 (dd, J=7.8, 4.8 Hz, 1H), 6.99 (s, 1H), 5.12 (s, 2H), 3.80 (s, 3H).

Example 21. Preparation of 2-methoxy-5-((2-(o-tolyl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 162)

[0396] ^{1}H NMR (400 MHz, CDCl3) δ 10.36 (s, 1H), 8.71 (dd, J=4.8, 1.6 Hz, 1H), 7.99 (dd, J=7.8, 1.6 Hz, 1H), 7.80 (s, 1H), 7.40 (dd, J=7.8, 4.8 Hz, 1H), 7.36-7.29 (m, 2H), 7.28-7.23 (m, 1H), 7.23-7.18 (n, 1H), 7.06 (s, 1H), 4.98 (s, 2H), 3.89 (s, 3H), 2.13 (s, 3H).

Example 22. Preparation of 2-methoxy-5-((2'-methoxy-[2,3'-bipyridin]-3-yl)methoxy)isonicotinaldehyde (Compound 163)

[0397] ^{1}H NMR (400 MHz, CDCl3) δ 10.31 (s, 1H), 8.71 (dd, J=4.8, 1.4 Hz, 1H), 8.28 (dd, J=5.0, 1.9 Hz, 1H), 7.96 (dd, J=7.8, 0.9 Hz, 1H), 7.82 (s, 1H), 7.74 (dd, J=7.3, 1.9 Hz, 1H), 7.41 (dd, J=7.8, 4.8 Hz, 1H), 7.09-7.03 (m, 2H), 5.14 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H).

Example 23. Preparation of 2-methoxy-5-((2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl) pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 193)

[0398] ^{1}H NMR (400 MHz, CDCl3) δ 10.54 (s, 1H), 8.84 (dd, J=4.8, 1.6 Hz, 1H), 8.14 (dd, J=7.9, 1.6 Hz, 1H), 8.03 (s, 1H), 7.72 (d, J=1.7 Hz, 1H), 7.55 (dd, J=7.9, 4.8 Hz, 1H), 7.21 (s, 1H), 6.60 (d, J=1.8 Hz, 1H), 5.79 (s, 2H), 5.27 (s, 2H), 4.01 (s, 3H), 3.66-3.59 (m, 2H), 0.92-0.80 (m, 2H), 0.00 (s, 9H).

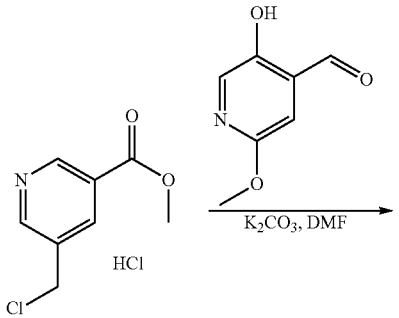
Example 24. Preparation of 2-methoxy-5-(quinolin-3-ylmethoxy)isonicotinaldehyde (Compound 80)

[0399] ^{1}H NMR (400 MHz, CDCl3) δ 10.50 (s, 1H), 9.03 (d, J=2.2 Hz, 1H), 8.27 (d, J=1.3 Hz, 1H), 8.17 (d, J=8.5 Hz, 1H), 8.15 (s, 1H), 7.89 (d, J=8.1 Hz, 1H), 7.79 (ddd, J=8.4, 6.9, 1.4 Hz, 1H), 7.63 (ddd, J=8.1, 7.0, 1.2 Hz, 1H), 7.14 (s, 1H), 5.42 (s, 2H), 3.94 (s, 3H).

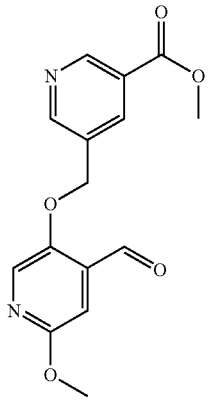
Example 25. Preparation of 5-((4-formyl-6-methoxypyridin-3 yloxy)methyl)nicotinic acid (Compound 79)

Step 1

[0400]



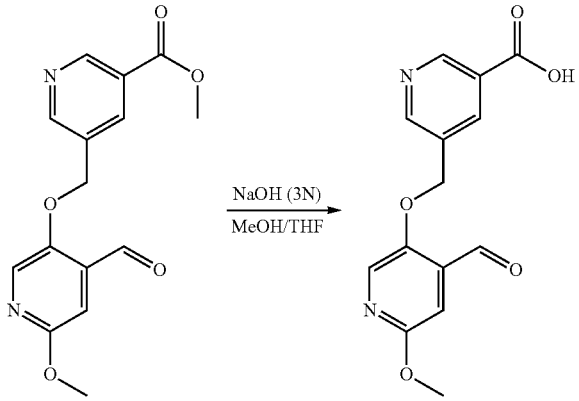
-continued



[0401] A mixture of 5-hydroxy-2 methoxyisonicotinaldehyde (352 mg, 2.29 mmol, 1 eq.), methyl 5-(chloromethyl) nicotinate hydrochloride (506 mg, 2.29 mmol, 1 eq.), and K_2CO_3 (1.26 g, 9.16 mmol, 4 eq.) in DMF (8.0 mL) was heated at 60° C. for 3 h. The mixture was cooled and added into water (50 mL) dropwise. The precipitate was filtered, washed with water, and dried to give methyl 5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinate (350 mg, 85%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.47 (s, 1H), 9.26 (d, J=2.0 Hz, 1H), 8.90 (d, J=2.2 Hz, 1H), 8.42 (t, J=2.1 Hz, 1H), 8.09 (s, 1H), 7.15 (s, 1H), 5.29 (s, 2H), 4.01 (s, 3H), 3.95 (s, 3H). LRMS (M+H$^+$) m/z 303.1.

Step 2

[0402]



[0403] To 5-((4-formyl-6-methoxypyridin-3-yloxy) methyl)nicotinate (96 mg, 0.32 mmol, 1 eq) in a mixture of MeOH/THF (1/3, 8.0 mL) was added NaOH (3 N, 1.7 mL, 5.1 mmol, 16 eq.). The mixture was stirred at rt for 2 h, acidified to pH 3, extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give 5-((4-formyl-6-methoxypyridin-3-yloxy) methyl)nicotinic acid (86 g, 93%) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 13.55 (s, 1H), 10.34 (s, 1H), 9.06 (d, J=1.9 Hz, 1H), 8.96 (d, J=2.0 Hz, 1H), 8.42 (t, J=2.0 Hz, 1H), 8.34 (s, 1H), 7.02 (s, 1H), 5.44 (s, 2H), 3.86 (s, 3H). LRMS (M+H$^+$) m/z 289.1.

[0404] Examples 26-35 were synthesized according to the procedure in Example 25.

Example 26. Preparation of methyl 4-(((3-formylpyridin-3-yl)oxy)methoxy)benzoate (Compound 164)

[0405] ^{1}H NMR (400 MHz, CDCl3) δ 10.44 (s, 1H), 8.46 (dd, J=4.3, 0.6 Hz, 1H), 8.11 (d, J=8.1 Hz, 2H), 7.58 (d, J=8.0 Hz, 2H), 7.50-7.40 (m, 2H), 5.33 (s, 2H), 3.95 (s, 3H).

Example 27. Preparation of 4-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid (Compound 165)

[0406] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.16 (d, J=8.2 Hz, 2H), 7.61 (d, J=8.1 Hz, 2H), 7.33 (d, J=1.8 Hz, 2H), 5.32 (s, 2H), 2.61 (s, 3H).

Example 28. Preparation of 4-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid (Compound 166)

[0407] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.38 (dd, J=4.3, 1.2 Hz, 1H), 8.08 (d, J=8.3 Hz, 2H), 7.54 (d, J=8.2 Hz, 2H), 7.42-7.32 (m, 2H), 5.26 (s, 2H).

Example 29. Preparation of methyl 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoate (Compound 167)

[0408] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.64 (s, 1H), 8.46 (d, J=4.7 Hz, 1H), 8.16 (s, 1H), 8.08 (d, J=7.8 Hz, 1H), 7.71-7.61 (m, 21H), 7.54 (t, J=7.7 Hz, 1H), 5.38 (s, 2H), 3.96 (s, 3H).

Example 30. Preparation of methyl 3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoate (Compound 168)

[0409] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.11 (s, 1H), 8.02 (d, J=7.8 Hz, 1H), 7.70 (d, J=7.8 Hz, 1H), 7.50 (t, J=7.7 Hz, 1H), 7.35 (d, J=8.7 Hz, 1H), 7.29 (d, J=8.7 Hz, 1H), 5.26 (s, 2H), 3.93 (s, 3H).

Example 31. Preparation of 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoic acid (Compound 169)

[0410] ^{1}H NMR (400 MHz, DMSO) δ 13.21-12.87 (br, 1H), 10.45 (s, 1H), 8.82 (s, 1H), 8.43 (d, J=4.8 Hz, 1H), 8.11 (s, 1H), 7.94 (d, J=7.6 Hz, 1H), 7.81 (d, J=7.1 Hz, 1H), 7.63-7.46 (m, 2H), 5.52 (s, 2H).

Example 32 Preparation of 3-(((2-formyl-6-methylpyridin-3 yl)oxy)methyl)benzoic acid (Compound 170)

[0411] ^{1}H NMR (400 MHz, DMSO) δ 12.83 (s, 1H), 9.99 (s, 1H), 7.87 (s, 1H), 7.71 (d, J=7.8 Hz, 1H), 7.60-7.50 (m 2H), 7.38-7.30 (m, 2H), 5.16 (s, 2H).

Example 33. Preparation of 3-((2 formylpyridin-3 yl)oxy)methyl)benzoic acid (Compound 171)

[0412] ^{1}H NMR (400 MHz, DMSO) δ 13.04 (s, 1H), 10.23 (s, 1H), 8.40 (d, J=4.4 Hz, 1H), 8.10 (s, 1H), 7.93 (d, J=7.7 Hz, 1H), 7.84 (d, J=8.5 Hz, 1H), 7.80 (d, J a 7.7 Hz, 1H), 7.68 (dd, J=8.6, 4.4 Hz, 1H), 7.57 (t, J=7.7 Hz, 1H), 5.41 (s, 2H).

Example 34. Preparation of 3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)benzoic acid (Compound 203)

[0413] ^{1}H NMR (400 MHz, CDCl3) δ 10.27 (s, 1H), 7.97 (s, 1H), 7.89 (d, J=7.8 Hz, 1H), 7.85 (s, 1H), 7.48 (d, J=7.7 Hz, 1H), 7.32 (t, J=7.7 Hz, 1H), 6.89 (s, 1H), 5.05 (s, 2H), 3.69 (s, 3H).

Example 35. Preparation of tert-butyl 4-((2-formyl-6-methylpyridin-3-yloxy)methyl)-1H-indazol-1-carboxylate (Compound 86)

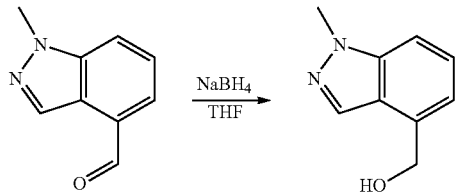
[0414] The title compound was prepared as for Example 34 above.

[0415] ^{1}H NMR (400 MHz, CDCl3) δ 10.35 (s, 1H), 8.40 (s, 1H), 8.23 (d, J=8.6 Hz, 1H), 7.57 (dd, J=8.4, 7.3 Hz, 1H), 7.43 (d, J=7.2 Hz, 1H), 7.37 (d, J=8.6 Hz, 1H), 7.30 (d, J=8.6, 1H), 5.58 (s, 2H), 2.58 (s, 3H), 1.75 (s, 9H).

Example 36. Preparation of 5-methoxy-2-((1 methyl-1H-indazol-4-yl)methoxy)isonicotinaldehyde (Compound 115)

Step 1

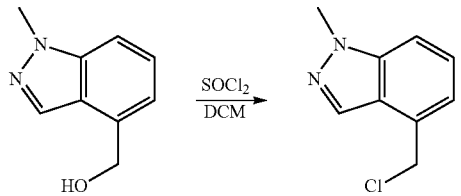
[0416]



[0417] To a mixture of 1-methyl-1H-indazole-4-carbaldehyde (180 mg, 1.12 mol) in THF (10 mL) was added $NaBH_4$ (85 mg, 2.24 mmol) at r.t. The reaction mixture was stirred at r.t. for 1 h, acidified to pH 3, and extracted with EtOAc. The combined organic layer was washed with saturated sodium bicarbonate solution and brine, dried over Na_2SO_4, filtered, and concentrated to give a crude solid (191 mg), which was used for next step without further purification.

Step 2

[0418]

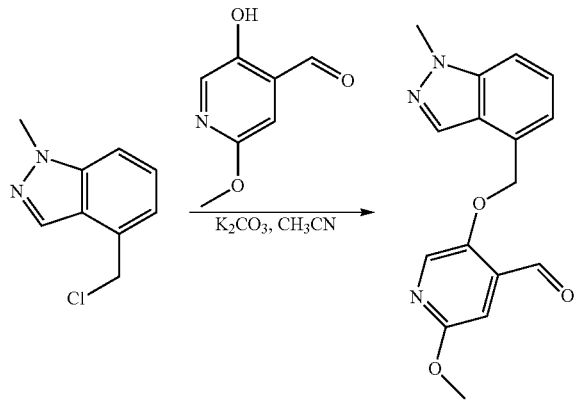


[0419] To (1-methyl-1H-indazol-4-yl)methanol (191 mg) in DCM (5 mL) was added $SOCl_2$ (2 mL) at rt. The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried

under vacuum to give an off-white solid (210 mg), which was used for next step without further purification.

Step 3

[0420]



[0421] A mixture of 2-hydroxy-5-methoxyisonicotinaldehyde (170 mg, 1.12 mmol), 4-(chloromethyl)-1-methyl-1H-indazole (1.12 mmol), and K_2CO_3 (618 mg, 4.48 mmol) is refluxed in CH_3CN (20 mL) for 2 h. The mixture is filtered and the solid is washed with DCM. The filtrate is concentrated and purified on silica gel using a mixture of EtOAc and MeOH as eluent to give 5-methoxy-2-(1-methyl-1H-indazol-4-yl)methoxy)isonicotinaldehyde as a white solid.

[0422] Examples 37-45 were prepared according to Example 36.

Example 37. Preparation of 2-methoxy-5-((1-methyl-1H-indazol-4-yl)methoxy)isonicotinaldehyde (Compound 84)

[0423] ^{1}H NMR (400 MHz, CDCl3) δ 10.46 (s, 1H), 8.13 (s, 1H), 8.09 (s, 1H), 7.48-7.38 (m, 2H), 7.22 (dd, J=6.0, 0.8 Hz, 1H), 7.10 (s, 1H), 5.55 (s, 2H), 4.13 (s, 3H), 3.91 (s, 3H).

Example 38. Preparation of 6-methyl-3-((1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde (Compound 91)

[0424] ^{1}H NMR (400 MHz, CDCl3) δ 10.43 (s, 1H), 7.98 (d, J=0.9 Hz, 1H), 7.75 (dd, J=8.3, 0.8 Hz, 1H), 7.60 (d, J=0.8 Hz, 1H), 7.39 (d, J=8.9 Hz, 1H), 7.30 (d, J=9.0 Hz, 1H), 7.18 (dd, J=8.3, 1.3 Hz, 1H), 5.37 (s, 2H), 4.10 (s, 3H), 2.58 (s, 31).

Example 39. Preparation of 6-methyl-3-((1-methyl-1H-indazol-7-yl)methoxy)picolinaldehyde (Compound 92)

[0425] ^{1}H NMR (400 MHz, CDCl3) δ 10.8 (s, 1H), 8.02 (s, 1H), 7.77 (dd, J=8.1, 1.0 Hz, 1H), 7.49 (d, J=8.6 Hz, 1H), 7.38 (dd, J=7.0, 1.0 Hz, 1H), 7.34 (d, J=8.6 Hz, 1H), 7.12 (dd, J=8.1, 7.0 Hz, 1H), 5.56 (s, 2H), 4.35 (s, 3H), 2.60 (s, 3H).

Example 40. Preparation of 3-(isoquinolin-1-yl-methoxy)-6-methylpicolinaldehyde (Compound 93)

[0426] ^{1}H NMR (400 MHz, CDCl3) δ 10.36 (s, 1H), 8.52 (d, J=5.7 Hz, 1H), 8.48 (d, J=9.2 Hz, 1H), 7.88 (d, J=7.5 Hz, 1H), 7.77-7.66 (m, 4H), 7.27 (d, J=8.9 Hz, 1H), 5.86 (s, 2H), 2.55 (s, 3H).

Example 41. Preparation of 5-(benzo[d]oxazol-4-ylmethoxy)-2-methoxyisonicotinaldehyde (Compound 103)

[0427] ^{1}H NMR (400 MHz, CDCl3) δ 10.51 (s, 1H), 8.18 (d, J=7.3 Hz, 2H), 7.63 (dd, J=8.1, 1.0 Hz, 1H), 7.52 (d, J=7.1 Hz, 1H), 7.46 (t, J=7.8 Hz, 1H), 7.11 (d, J=0.5 Hz, 1H), 5.65 (s, 2H), 3.92 (s, 3H).

Example 42. Preparation of 3-((1,5-naphthyridin-4 yl)methoxy)-6-methylpicolinaldehyde (Compound 106)

[0428] ^{1}H NMR (400 MHz, CDCl3) δ 10.41 (s, 1H), 9.15 (d. J=2.1 Hz, 1H), 9.05 (dd, J=4.2, 1.6 Hz, 1H), 8.52 (d, J=1.1 Hz, 1H), 8.47 (d, J=8.5 Hz, 1H), 7.71 (dd, J=8.5, 4.2 Hz, 1H), 7.44 (d, J=8.6 Hz, 1H), 7.35 (d, J=8.6 Hz, 1H), 5.50 (s, 2H), 2.62 (s, 3H).

Example 43. Preparation of 6-methyl-3-((1-methyl-1H-indazol-5-yl)methoxy)picolinaldehyde (Compound 10)

[0429] ^{1}H NMR (400 MHz, CDCl3) δ 10.43 (s, 1H), 8.01 (s, 1H), 7.81 (s, 1H), 7.50 (d, J=8.7 Hz, 1H), 7.45 (d, J=8.7 Hz, 1H), 7.42 (d, J=8.6 Hz, 1H), 7.30 (d, J=8.6 Hz, 1H), 5.34 (s, 2H), 4.11 (d, J=0.5 Hz, 3H), 2.59 (s, 3H).

Example 44. Preparation of 6-methyl-3-(quinolin-5-ylmethoxy)picolinaldehyde (Compound 119)

[0430] ^{1}H NMR (400 MHz, DMSO) δ 10.13 (s, 1H), 8.96 (dd, J=4.2, 1.6 Hz, 1H), 8.64 (d, J=8.4 Hz, 1H), 8.04 (d, J=8.4 Hz, 1N), 7.97 (d, J=8.7 Hz, 1H), 7.91 (d, J=7.2 Hz, 1H), 7.80 (dd, J=8.4, 7.1 Hz, 1H), 7.61 (dd, J=8.6.4.2 Hz, 1H), 7.58 (d, J=8.8 Hz, 1H), 5.78 (s, 2H), 2.49 (s, 3H).

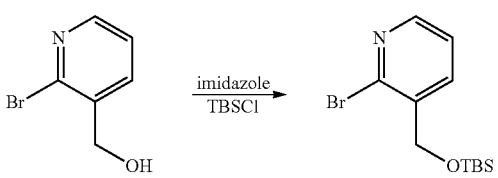
Example 45. Preparation of 2-methoxy-5-(quinolin-5-ylmethoxy)isonicotinaldehyde (Compound 120)

[0431] ^{1}H NMR (400 MHz, CDCl3) δ 10.23 (s, 1H), 8.94 (dd, J=4.3, 1.5 Hz, 1H), 8.43 (d, J=8.5 Hz, 1H), 8.16 (d, J=14.1 Hz, 1H), 8.13 (s, 2H), 7.68 (dd, J=8.3, 7.2 Hz, 1H), 7.61 (d, J=6.7 Hz, 1H), 7.47 (dd, J=8.6, 4.3 Hz, 1H), 7.02 (s, 1H), 5.56 (s, 2H), 3.84 (s, 3H).

Example 46 Preparation of 2-methoxy-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 129)

Step 1

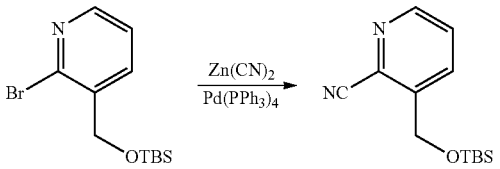
[0432]



[0433] To a mixture of (2-bromopyridin-3-yl)methanol (20.0 g, 106.4 mmol, eq.; refer to example 14) and imidazole (14.5 g, 212.8 mmol, 2 eq.) in DMF (50.0 mL) was added TBSCl (19.2 g, 150.7 mmol, 1.2 eq.) at rt. The mixture was stirred at rt for 1 h and diluted with a mixture of water (100 mL) and EtOAc (300 mL). The organic layer was washed with $NH_4Cl_{(sat.)}$ solution and brine, dried over N_2SO_4, concentrated, and purified on silica gel using 10% EtOAc/hexanes as eluent to give 2-bromo-3-((tert-butyldimethylsilyloxy)methyl)pyridine (30.1 g, 94%) as a colorless oil. LRMS ($M+H^+$) m/z 302.0.

Step 2

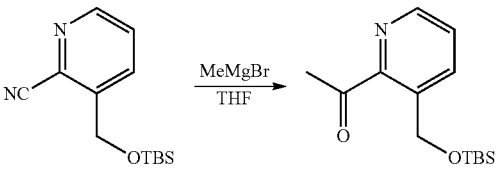
[0434]



[0435] A mixture of 2-bromo-3-((tert-butyldimethylsilyloxy)methyl)pyridine (30.1 g, 100.0 mmol, 1 eq.) and $Zn(CN)_2$ (23.5 g, 200.0 mmol, 2.0 eq.) in DMF (100.0 mL) was purged with N_2 for 5 min and added $Pd(PPh_3)_4$ (5.78 g, 5.0 mmol, 0.05 eq.). The mixture was heated at 120° C. for 2 h under N_2, cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 3-((tert-butyldimethylsilyloxy)methyl)picolinonitrile (20.4 g, 82%) as a colorless oil. LRMS ($M+H^+$) m/z 249.1.

Step 3:

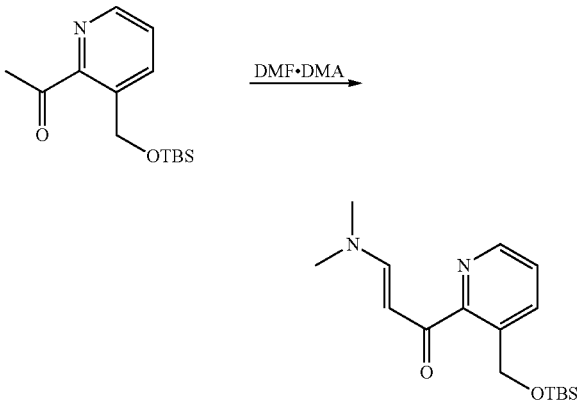
[0436]



[0437] Methylmagnesium bromide (3M/ether, 41.0 mL, 123.4 mmol) was added to a stirred solution of 3-((tert-butyldimethylsilyloxy)methyl)picolinonitrile (20.4 g, 82.25 mmol) in THF (100.0 mL) at −78° C. The reaction mixture was warm to rt, quenched with aqueous citric acid solution, and extracted with EtOAc (50 mL) twice. The combined organic layers were washed with $NaHCO_{3\ (sat)}$ solution and brine, dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc/hexanes as eluent to give 1-(3-((tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)ethanone (12.9 g, 59%) as a colorless oil. LRMS ($M+H^+$) m/z 266.2.

Step 4:

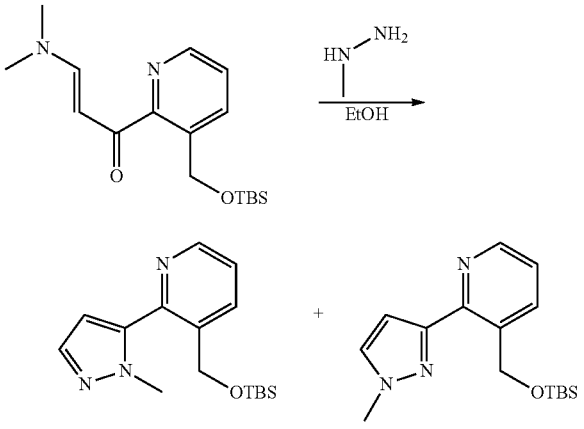
[0438]



[0439] 1-(3-((tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)ethanone (10.8 g, 40.75 mmol) in dimethoxy-N,N-dimethylmethanamine (15.0 mL) was heated to reflux for 3 days. The mixture was concentrated and used for next step without further purification. LRMS ($M+H^+$) m/z 321.1.

Step 5

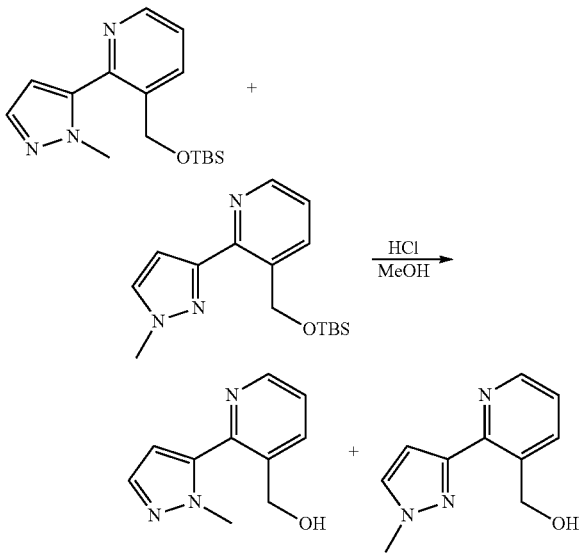
[0440]



[0441] To (E)-1-(3-((tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)-3-(dimethylamino)prop-2-en-1-one (crude above, 966.4 mg, 3.02 mmol, 1 eq.) in EtOH (10 mL) was added methylhydrazine (1.0 mL) at it. The mixture was heated at 80° C. for 2 h, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give a mixture of regio-isomers (420 mg; 46% for 2 steps). LRMS ($M+H^+$) m/z 304.2.

Step 6

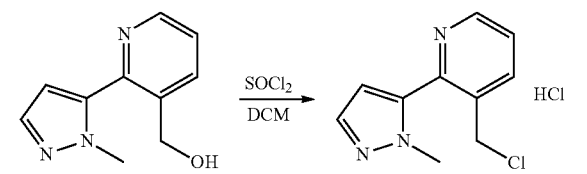
[0442]



[0443] To a mixture of 3-((tert-butyldimethylsilyloxy) methyl)-2-(1-methyl-1H-pyrazol-5-yl)pyridine and 3-((tert-butyldimethylsilyloxy)methyl)-2-(1-methyl-1H-pyrazol-3-yl)pyridine (420 mg, 1.38 mmol) in MeOH (20 mL) was added HCl (4 N, 2.0 mL). The mixture was stirred at rt for 1 h, concentrated, and diluted with EtOAc (50 mL) and $NaHCO_{3\ (sat)}$ solution (10 mL). The layers were separated and aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using EtOAc as eluent to give (2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl) methanol (187 mg, 72%) and (2-(1-methyl-1H-pyrazol-3-yl)pyridin-5-yl)methanol (55 mg, 21%) as white solids. Data for 2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methanol: ^1H NMR (400 MHz; $CDCl_3$) 8.58 (d, 1H), 7.91 (d, 1H), 7.46 (s, 1H), 7.30 (dd, 1H), 6.36 (s, 1H), 4.62 (d, 2H), 3.83 (s, 3H), 2.1 (t, 1H). LRMS ($M+H^+$) m/z 190.1; data for (2-(1-methyl-1H-pyrazol-3-yl)pyridin-5-yl)methanol: ^1H NMR (400 MHz; $CDCl_3$) 8.60 (d, 1H), 7.70 (d, 1H), 7.47 (s, 1H), 7.22 (dd, 1H), 6.99 (s, 1H), 5.91 (t, 1H), 4.68 (d, 2H), 4.01 (s, 3H). LRMS ($M+H^+$) m/z 190.1

Step 7

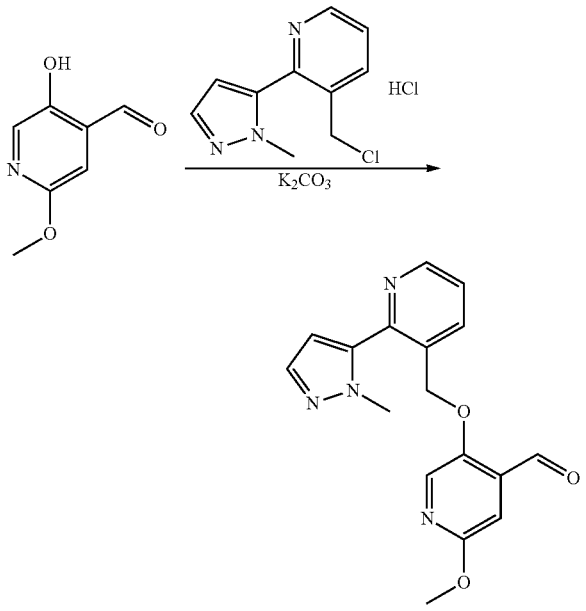
[0444]



[0445] To (2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl) methanol (182 mg, 0.96 mmol) in DCM (5 mL) was added $SOCl_2$ (1.5 mL) at it. The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give 3-(chloromethyl)-2-(1-methyl-1H-pyrazol-5-yl)pyridine (236 mg) as an off-white solid, which was used for next step without further purification.

Step 8

[0446]



[0447] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (147 mg, 0.96 mmol, 1 eq.), 3-(chloromethyl)-2-(1-methyl-1H-pyrazol-5-yl)pyridine hydrochloride (236 mg, 0.96 mmol, 1 eq.), and K_2CO_3 (532 mg, 3.85 mmol, 3 eq.) in DMF (3.0 mL) was heated at 70° C. for 2 h. The mixture was cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 2-methoxy-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)isonicotinaldehyde (232.5 mg, 75%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.77 (dd, J=4.7, 1.7 Hz, 1H), 8.03 (dd, J=7.9, 1.7 Hz, 1H), 7.93 (s, 1H), 7.55 (d, J=1.9 Hz, 1H), 7.44 (dd, J=7.9, 4.8 Hz, 1H), 7.11 (d, J=0.4 Hz, 1H), 6.43 (d, J=1.9 Hz, 1H), 5.20 (s, 2H), 3.97 (s, 3H), 3.92 (s, 3H). LRMS ($M+H^+$) m/z 325.1.

[0448] 1H NMR (400 MHz, CDCl3) δ 10.40 (s, 1H), 8.77 (dd, J=4.7, 1.7 Hz, 1H), 8.03 (dd, J=7.9, 1.7 Hz, 1H), 7.93 (s, 1H), 7.55 (d, J=1.9 Hz, 1H), 7.44 (dd, J=7.9, 4.8 Hz, 1H), 7.11 (d, J=0.4 Hz, 1H), 6.43 (d, J=1.9 Hz, 1H), 5.20 (s, 2H), 3.97 (s, 3H), 3.92 (s, 3H).

Example 47. Preparation of 2-methoxy-5-((2-(1-methy-1H-pyrazol-3-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 130)

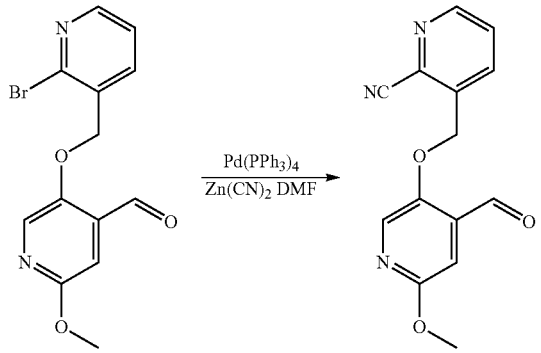
[0449] The title compound was prepared according to the procedure in Example 46.

[0450] ^{1}H NMR (400 MHz, CDCl3) δ 10.49 (s, 1H), 8.66 (dd, J=4.7, 1.3 Hz, 1H), 8.11 (s, 1H), 8.03 (dd, J=7.8, 1.0 Hz, 1H), 7.45 (d, J=2.3 Hz, 1H), 7.31 (dd, J=7.9, 4.8 Hz, 1H), 7.13 (s, 1H), 6.97 (d, J=2.0 Hz, 1H), 5.73 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H).

Example 48 Preparation of 5-((2-(2H-tetrazol-5-yl) pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 131)

Step 1:

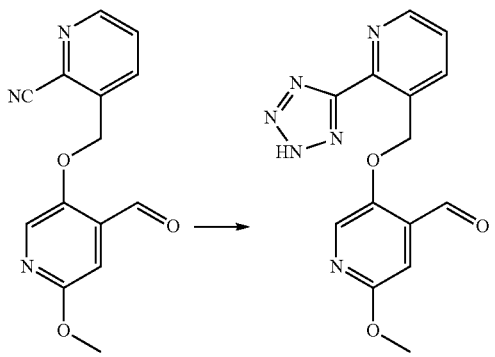
[0451]



[0452] To a mixture of 5-((2-bromopyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde (100 mg, 0.31 mmol, 1 equiv), Zn $(CN)_2$ (71 mg, 0.62 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (72 mg, 0.06 mmol, 0.2 equiv) in a 5 mL microwave tube was added DMF (2 mL). The mixture was heated 15 min at 125° C. in a microwave reactor. The solid was filtered off and the filtrate was concentrated to dryness. The crude was purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinonitrile (71 mg, 84%) as a white solid. ^{1}H NMR (400 MHz; $CDCl_3$) δ=10.54 (s, 1H), 8.86 (d, 1H), 8.22 (s, 1H), 8.20 (d, 1H), 7.74 (dd, 1H), 6.37 (s, 1H), 5.52 (s, 2H), 4.04 (s, 3H). LRMS ($M+H^+$) m/z 270.1.

Step 2:

[0453]

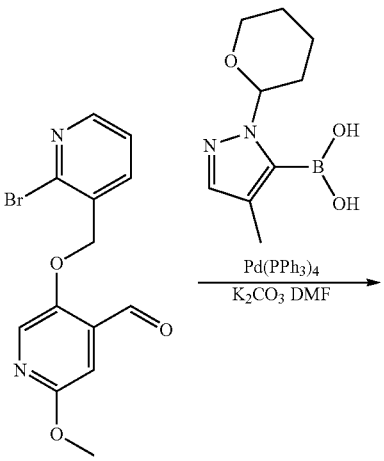


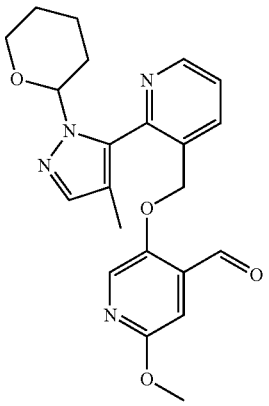
[0454] To TEA hydrochloride salt (123 mg, 0.89 mmol, 4 equiv.) and 3-((4-formyl-6-methoxypyridin-3-yloxy) methyl)picolinonitrile (70 mg, 0.26 mmol, 1 equiv.) in chlorobenzene (5.0 mL) was added NaN_3 (48 mg, 0.89 mmol, 4 equiv.) at rt. The mixture was heated to 110° C. for 2 h, cooled to rt, and added water (5.0 mL). The precipitate was filtered and washed with EtOAc and water and dried under high vacuo to give 5-((2-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde as a white solid. ^{1}H NMR (400 MHz; DMSO) δ=10.23 (s, 1H), 8.61 (d, 1H), 8.16 (s, 1H), 8.10 (d, 1H), 7.38 (dd, 1H), 6.96 (s, 1H) 5.73 (s, 2H), 3.83 (s, 3H). LRMS ($M+H^+$) m/z 313.0.

Example 49. Preparation of 2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 132)

Step 1:

[0455]

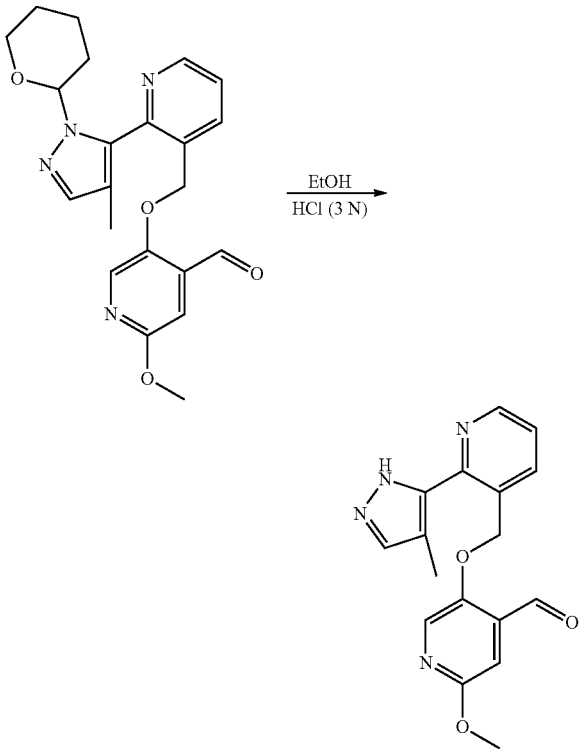




[0456] To a mixture of 5-((2-bromopyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde (100 mg, 0.31 mmol, 1 equiv), 4-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-ylboronic acid (98 mg, 0.47 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (70 mg, 0.06 mmol, 0.2 equiv), K_2CO_3 (171 mg, 1.24 mmol, 4 equiv) in a 5 mL microwave tube was added DMF (2 mL). The mixture was heated 30 min at 125° C. in a microwave reactor. The solid was filtered off and the filtrate was concentrated to dry ness. The crude was purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 2-methoxy-5-((2-(4-methyl-1-(tetrahydro-2H-pyran-2-yl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (110 mg, 87%) as a colorless oil. LRMS ($M+H^+$) m/z 409.2.

Step 2:

[0457]

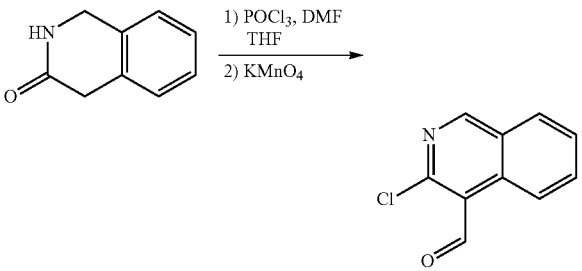


[0458] To 2-methoxy-5-((2-(4-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (110 mg, 0.27 mmol, 1 equiv) suspended in EtOH (1 mL) was added HCl (1.0 mL, 3 N). The solution turned homogeneous and the mixture was stirred at rt overnight. The EtOH was partially removed by blowing in N_2 gas and basified to pH 9. The aqueous solution was extracted with EtOAc three times. The organic layer was dried over Na_2SO_4 and concentrated. The crude was purified on silica gel using a mixture of MeOH and DCM as eluent to give 2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (40 mg, 46%) as a white solid. ^1H NMR (400 MHz; $CDCl_3$) δ=10.45 (s, 1H), 8.76 (d, 1H), 8.07 (br, 1H), 8.05 (s, 1H), 7.53 (s, 1H), 7.40 (dd, 1H), 7.13 (s, 1H), 5.52 (br, 2H), 3.98 (s, 3H). LRMS ($M+H^+$) m/z 325.1.

Example 50. Preparation of 5-((3-(1H-pyrazol-5-yl) isoquinolin-4-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 133)

Step 1:

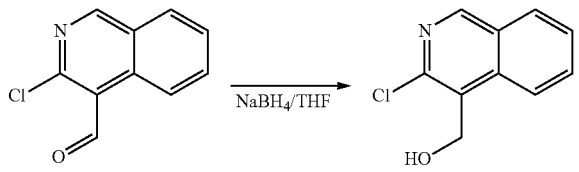
[0459]



[0460] To a mixture of $POCl_3$ (0.73 mL, 7.85 mmol, 3.8 eqiv.) and DMF (0.6 g, 8.16 mmol, 4.0 equiv.) in THF was added 1,2-dihydroisoquinolin-3(4H)-one at 0° C. in portions for 5 min. The mixture was continued to stir at 0° C. for 1 h and poured into a mixture of 2 N NaOH (20 mL), ice (20 g), and toluene (20 mL). The organic phase was separated and the aqueous layer was extracted with toluene one more time. The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated to half of its volume at low temperature in vacuo. To this mixture was added 2 N H_2SO_4 (20 mL) under vigorous stirring followed by ground $KMnO_4$ in portions. The mixture was continued to stir for another 4 h. The organic phase was separated, dried over Na_2SO_4, and concentrated to give 3-chloroisoquinolin-4-carbaldehyde (220 mg, 50% pure) as a oil, which was used for next step without further purification. LRMS ($M+H^+$) m/z 192.0.

Step 2:

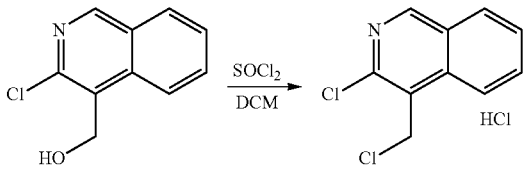
[0461]



[0462] To 3-chloroisoquinoline-4-carbaldehyde (220 mg, crude) in THF (10 mL) was added $NaBH_4$ (155 mg, 4.08 mmol) at 0° C. The reaction mixture was stirred at 0° C. for 1 h, acidified to pH 3, and extracted with EtOAc. The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried over Na_2SO_4, filtered, and concentrated to give a crude solid. The crude was purified on silica gel using a mixture of EtOAc and hexanes as eluent to give (3-chloroisoquinolin-4-yl)methanol (92 mg, 24% for three steps). LRMS ($M+H^+$) m/z 194.0.

Step 3:

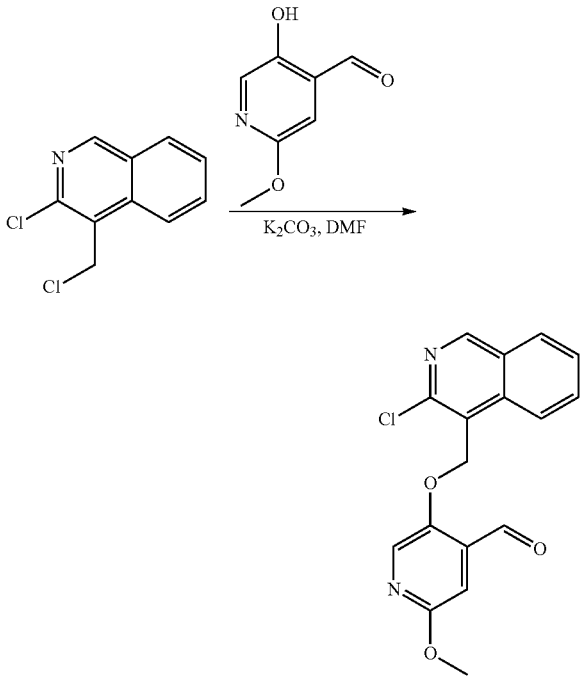
[0463]



[0464] To (3-chloroisoquinolin-4-yl)methanol (92 mg, 0.48 mmol) in DCM (5 mL) was added $SOCl_2$ (mL) at rt The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give an off-white solid (120 mg), which was used for next step without further purification.

Step 4:

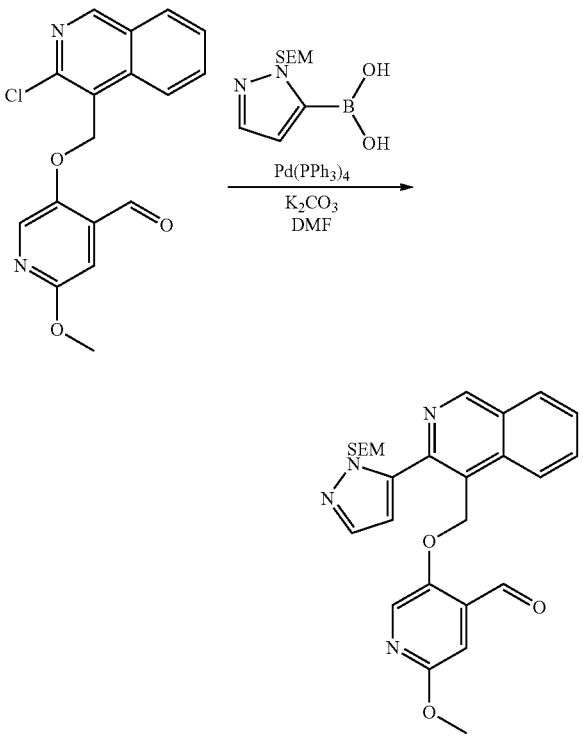
[0465]



[0466] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (73 mg, 0.48 mmol, 1 eq.), 3-chloro-4-(chloromethyl) isoquinoline (crude above, 0.48 mmol), and K_2CO_3 (265 meg, 1.92 mmol, 4 eq.) in DMF (2.0 mL) was heated at 60° C. for 1 h. The mixture was cooled, filtered, concentrated to dryness. The crude was purified on silica gel using a mixture of EtOAc and hexanes to give 5-((3-chloroisoquinolin-4-yl) methoxy)-2-methoxyisonicotinaldehyde (22 mg, 14%) as an yellow solid. ^1H NMR (400 MHz; $CDCl_3$) δ=10.19 (s, 1H), 9.05 (s, 1H), 8.23 (s, 1H) 8.06 (d, 1H), 7.98 (d, 1H), 7.76 (t, 1H), 7.63 (t, 1H), 7.01 (s, 1H), 5.72 (s, 2H), 3.87 (s, 3H). LRMS ($M+H^+$) m/z 329.1.

Step 5:

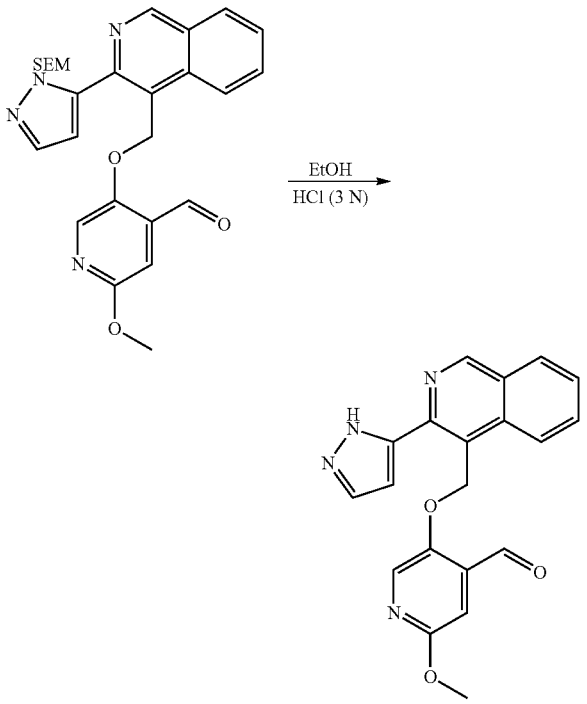
[0467]



[0468] To a mixture of 5-((3-chloroisoquinolin-4-yl) methoxy)-2-methoxyisonicotinaldehyde (18 g, 0.05 mmol, 1 equiv), 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-ylboronic acid (20 mg, 0.08 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol, 0.2 equiv), K_2CO_3 (30 mg, 0.22 mmol, 4 equiv) in a 5 mL microwave tube were added DMF (2 mL). The mixture was heated 30 min at 125° C. in a microwave reactor. The solid was filtered off and the filtrate was concentrated to dryness. The crude was purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 2-methoxy-5-((3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)isoquinolin-4-yl)methoxy)isonicotinaldehyde (10 mg, 38%) as a white solid. LRMS ($M+H^+$) m/z 491.1.

Step 6:

[0469]

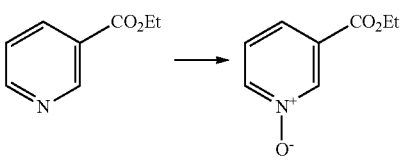


[0470] To 2-methoxy-5-((3-(1-((2-(trimethylsilyl)ethoxy) methyl)-1H-pyrazol-5-yl)isoquinolin-4-yl)methoxy)isonicotinaldehyde (10 mg, 0.02 mmol, 1 equiv) suspended in EtOH (1 mL) was added HCl (0.1 mL, 3 N). The solution turned homogeneous and the mixture was stirred at rt overnight. The EtOH was partially removed by blowing in N_2 gas and basified to pH 9. The aqueous solution was extracted with EtOAc three times. The organic layer was dried over Na_2SO_4 and concentrated. The crude was purified on silica gel using MeOH and DCM as eluent to give 5-((3-(1H-pyrazol-5-yl)isoquinolin-4-yl)methoxy)-2-methoxyisonicotinaldehyde (6.0 mg, 83%) as a white solid. ^1H NMR (400 MHz; $CDCl_3$) δ=10.17 (s, 1H), 9.25 (s, 1H), 8.18 (s, 1H), 8.05 (d, 1H), 7.99 (d, 1H), 7.73 (t, 1H), 7.60-7.68 (m, 2H), 7.03 (s, 1H), 6.70 (d, 1H), 5.85 (s, 2H), 3.85 (s, 3H). LRMS ($M+H^+$) m/z 361.1.

Example 51. Preparation of 2-(imidazo[1,5-a]pyridin-8-ylmethoxy)-5-methoxyisonicotinaldehyde

Step 1:

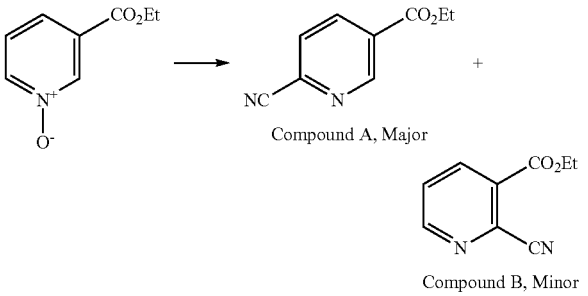
[0471]



[0472] To a cold solution of 3-ethoxycarbonylpyridine (25 g, 165.4 mmol, 1 eq) in DCM was slowly added mCPBA (70% wt, 198.5 mmol) and the reaction mixture was stirred at rt overnight. Reaction was cooled and diluted with DCM and then neutralized with slow addition of sat. $NaHCO_3$. Aqueous layer was washed with DCM (3×) and the combined organic layer was dried and evaporated to give a residue, which was purified by column chromatography (EtOAc/MeOH) to give 3-ethoxycarbonylpyridine N-oxide (13.6 g). MS: exact mass calculated for $C_8H_9NO_3$, 167.06; m/z found, 168 $[M+H]^+$.

Step 2:

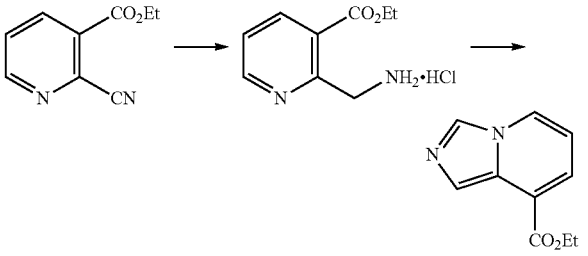
[0473]



[0474] To a solution of 3-ethoxycarbonylpyridine N-oxide in 330 mL of DCM were added trimethylsilyl cyanide (TMSCN) (11.0 g, 65.9 mmol, 1.0 eq) and dimethylcarbamoyl chloride (7.1 g, 65.9 mmol, 1.0 eq) and the reaction mixture was stirred at rt for 2 days. Then 10% K_2CO_3 was slowly added to make the reaction mixture basic. Organic layer was separated, dried and evaporated to provide the crude, which was purified by column chromatography to provide compounds A (5.7 g) and B (3.5 g).

Steps 3 and 4:

[0475]



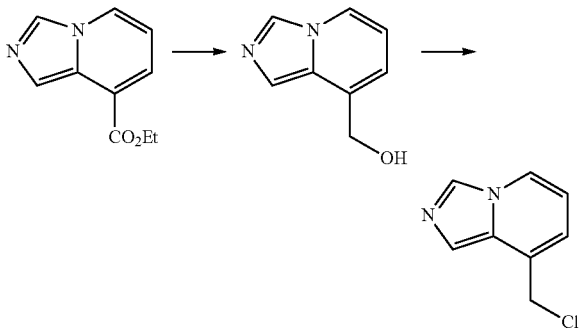
[0476] To a solution of ethyl 2-cyano-3-pyridinecarboxylate (2.5 g) and cone. HCl (5 mL) in 150 mL ethanol was added 10% Pd/C (wet, 250 mg) and the reaction mixture was hydrogenated using a hydrogen balloon and stirred for 12 h. The reaction was filtered through celite and ethanol was evaporated to give ethyl 2-(aminomethyl)-3-pyridinecarboxylate HCl as a white solid which was used in the next step without further purification.

[0477] A mixture of 44.8 mL of acetic anhydride and 19.2 mL of formic acid was heated in a 50-60° C. oil bath

temperature for 3 h and then cooled to rt to give formic-acetic anhydride, which was then slowly added to the solid ethyl 2-(aminomethyl)-3-pyridinecarboxylate HCl and then stirred at for 8 h. Excess reagent was evaporated to give a residue, which was neutralized by very slow addition of sat. $NaHCO_3$ solution. Solution was extracted with DCM, dried and evaporated to provide ethyl imidazo[1,5-a]pyridine-8-carboxylate as a yellow solid (crude weight 2.7 g). MS: exact mass calculated for $C_{10}H_{10}N_2O_2$, 190.07; m/z found, 191 $[M+H]^+$.

Steps 5 and 6:

[0478]

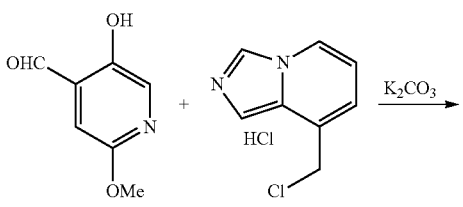


[0479] To a cold solution of lithium aluminum hydride (1.62 g, 42.4 mmol, 4.0 eq) in THF (50 mL) was added the crude ethyl imidazo[1,5-a]pyridine-8-carboxylate (2.7 g, 14.2 mmol, 1.0 eq) and the reaction mixture was heated at reflux for 2 h. The reaction was cooled and water (1.7 mL), 15% NaOH (1.7 mL) and water (5.1 mL) were slowly added. Solution was diluted with excess EtOAc and stirred at rt for 30 min. The solution was filtered and the solid was washed with ethyl acetate. Organic layers were combined, dried and solvent was removed to give crude imidazo[1,5-a]pyridine-8-methanol, which was purified by column chromatography (EtOAc/Hexane). MS: exact mass calculated for $C_8H_8N_2O$, 148.06; m/z found, 149 $[M+H]^+$.

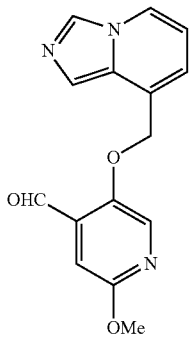
[0480] To a solution of imidazo[1,5-a]pyridine-8-methanol (800 mg) in chloroform (50 mL) was slowly added thionyl chloride (10 mL) and the reaction mixture was stirred at rt for 8 h. Chloroform was removed and the residue was then taken in toluene and toluene was evaporated (3×) to give a solid, which was used in the next step without further purification. MS: exact mass calculated for $C_3H_7ClN_2$, 166.03; m/z found, 167 $[M+H]^+$.

Step 7:

[0481]



-continued



[0482] To a solution of chloride (1.25 mmol, 1.0 eq), and hydroxynicotinaldehyde (1.25 mmol, 1.0 eq) in DMF (10 mL) is added K_2CO_3 (3.0 eq) and the reaction mixture was heated at 80-90° C. for 5 h. Solvent is removed and the residue is purified by column chromatography (EtOAc/MeOH).

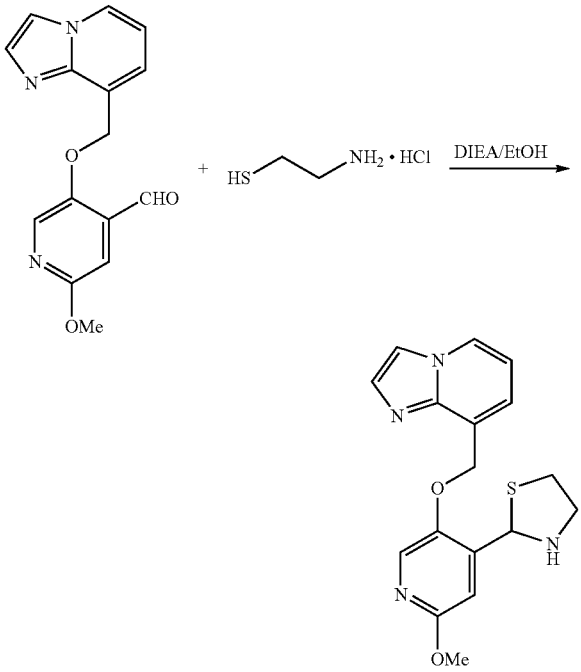
Example 52. Preparation of 5-(imidazo[1,5-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde (Compound 140)

[0483] The title compound was prepared according to the procedure in Example 51.

[0484] ^1H NMR (400 MHz, CDCl3) δ 10.47 (s, 1H), 8.21 (s, 1H), 8.11 (s, 1H), 7.97 (d, J=7.0 Hz, 1H), 7.52 (s, 1H), 7.12 (s, 1H), 6.87 (t, J=8.1 Hz, 1H), 6.62 (t, J=6.8 Hz, 1H), 5.37 (s, 2H), 3.92 (s, 3H).

Example 53. Preparation of 2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidine (Compound 155)

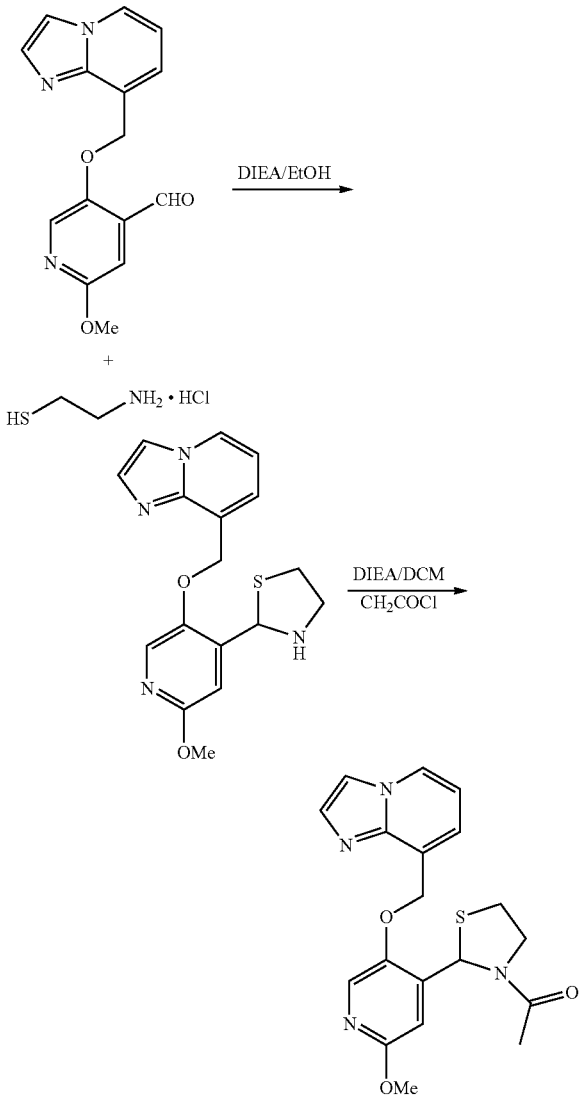
[0485]



[0486] To a solution of aldehyde (0.326 g, 1.15 mmol, 1 eq) and DIEA (0.15 g 1.15 mmol, 1.0 eq) in EtOH (4 mL) was added cysteamine.HCl (135 ma, 1.15 mmol, 1.0 eq) and the reaction mixture was stirred at rt for 24 h. The reaction mixture was diluted with water and the solid was filtered, washed (water) and dried. The crude was purified by column chromatography (DCM/MeOH) to give the pure material. MS: exact mass calculated for $C_{17}H_{18}N_4O_2S$, 342.12; m/z found, 343 $[M+H]^+$.

Example 54. Preparation of 1-(2-(5-(imidazo[1,2-a] pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidin-3-yl)ethanone (Compound 156)

[0487]

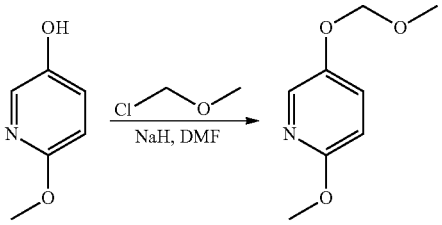


[0488] To a solution of aldehyde (0.900 g, 3.18 mmol, 1 eq) and DIEA) (0.45 g, 3.5 mmol, 1.1 eq) in EtOH (11 mL) was added cysteamine.HCl (0.398 g, 3.5 mmol, 1.1 eq) and the reaction mixture was stirred at rt for 24 h. Solvent was removed and the crude was directly used in the next step. To a solution of crude thiazoline (3.18 mmol) and DIEA (1.5 eq) in DCM (25 mL) at 0° C. was added acetyl chloride (1.2 eq) drop wise and the reaction mixture was stirred at room temperate for 24 h. The reaction mix was diluted with DCM and washed with saturated aq. NaHCO3. The organic layer was dried and solvent was removed to give the crude amide, which was purified by column chromatography (EtOAc/MeOH) to give the amide. MS: exact mass calculated for C19H20N4O3S, 384.13; m/z found, 385 [M+H]+.

Example 55. Preparation of 5-hydroxy-2-methoxyisonicotinaldehyde

Step 1

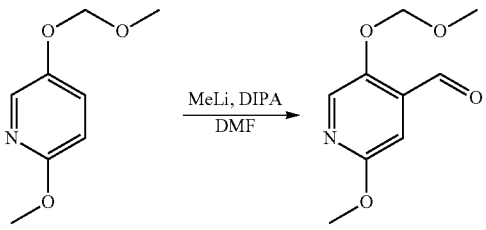
[0489]



[0490] To a solution of 6-methoxypyridin-3-ol (20 g, 0.16 mol, 1 eq.) in DMF (200 mL) was added NaH (60% in mineral oil; 9.6 g, 0.24 mol, 1.5 eq.) at 0-5° C. portion-wise. Upon the completion of addition, the mixture was continued to stir at 0-5° C. for 15 min. added chloromethyl methyl ether (15.5 g, 0.19 mol 1.2 eq.), stirred at 0-5° C. for another 20 min. and quenched with $NH_4Cl_{(sat.)}$ solution. The aqueous layer was extracted with EtOAc (3×100 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4, concentrated, and purified on silica gel using 25% EtOAc/hexanes as eluent to give 2-methoxy-5-(methoxymethoxy)pyridine (24.1 g, 89.3%) as a colorless oil. ^1H NMR (400 MHz; CDCl3) 7.97 (d, 1H), 7.35 (dd, 1H), 6.70 (d, 1H), 5.12 (s, 2H), 3.91 (s, 3H), 3.51 (s, 3H). LRMS ($M+H^+$) m/z 170.1

Step 2

[0491]

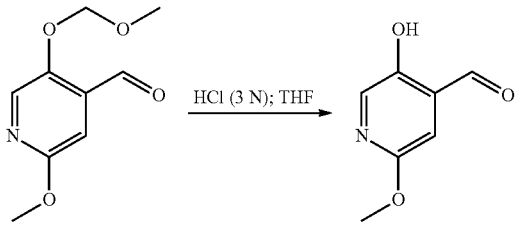


[0492] To a mixture of 2-methoxy-5-(methoxymethoxy) pyridine (30 g, 0.178 mol, 1 eq.) and diisopropylamine (507 uL, 3.6 mmol, 0.02 eq.) in THF (500 mL) was added methyl lithium (1.6 M/THF, 200 mL, 0.32 mol, 1.8 eq.) at −40° C. Upon the completion of addition, the mixture was warmed to 0° C., continued to stir at 0° C. for 3 h, cooled back down to −40° C. and added DMF (24.7 mL, 0.32 mol, 1.8 eq.)

slowly. The mixture was then stirred at −40° C. for 1 h, quenched with a mixture of HCl (12 N, 120 mL) and THF (280 mL), warmed to rt, and added water (200 mL). The pH of the mixture was adjusted to pH 8-9 with solid K_2CO_3. The aqueous layer was extracted with EtOAc (300 mL) twice. The combined organic layers were dried over Na_2SO_4 and concentrated to give 2-methoxy-5-(methoxymethoxy)isonicotinaldehyde (33.5 g, 95.7%) as a brown solid, which was used for next step without further purification. ^{1}H NMR (400 MHz; CD_3OD) 7.90 (s, 1H), 6.92 (s, 1H), 5.64 (s, 1H), 5.20 (s, 2H), 3.84 (s, 3H), 3.48 (s, 3H). LRMS ($M+H^+$) m/z 198.1

Step 3

[0493]

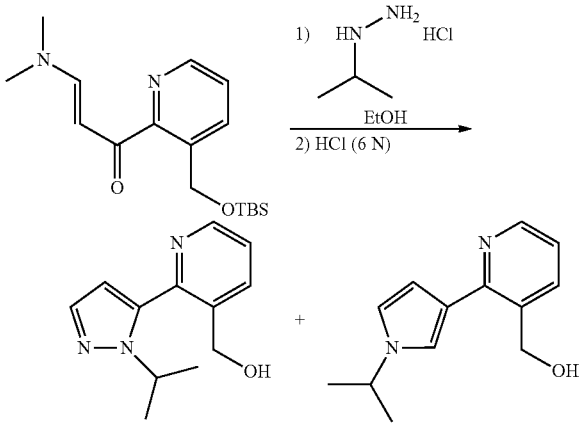


[0494] To a solution of 2-methoxy-5-(methoxymethoxy) isonicotinaldehyde (33.5 g, 0.17 mol, 1 eq.) in THF (150 mL) was added HCl (3 N, 250 mL, 4.4 eq.). The reaction was stirred at 50° C. for 1 h, cooled to rt, and diluted with water (500 mL). The mixture was neutralized to pH 7-8 with solid K_2CO_3. The pale yellow solid was collected, washed with water, and dried to give 5-hydroxy-2-methoxyisonicotinaldehyde (17.9 g, 74.6%) as a pale yellow solid. ^{1}H NMR (400 MHz; DMSO) δ=10.31 (s, 1H), 8.03 (s, 1H), 6.89 (s, 1H), 3.80 (s, 3H). LRMS ($M+H^+$) m/z 154.0.

Example 56. Preparation of 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 150)

Step 1:

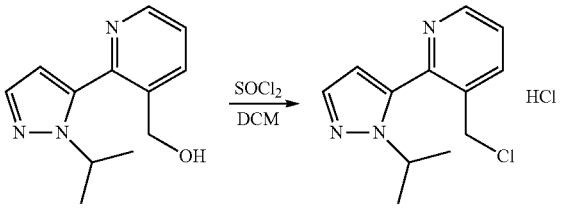
[0495]



[0496] To (E)-1-(3-((tert-butyldimethylsilyloxy)methyl) pyridin-2-yl)-3-(dimethylamino)prop-2-en-1-one (crude, 1.03 g, 3.22 mmol, 1 eq.; refer to Example 46) in EtOH (10 mL) was added isopropylhydrazine hydrochloride (430 mg, 3.86 mmol, 1.2 eq.). The mixture was heated at 80° C. for 2 h, cooled, added HCl (6 N, 0.5 mL), and stirred O/N. The mixture was concentrated and diluted with EtOAc (80 mL) and $NaHCO_{3(sat)}$ (10 mL) solution. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using EtOAc as eluent to give (2-(1-isopropyl-1H-pyrazol-5-yl) pyridin-3-yl)methanol (500 mg, 71%) and (2-(1-isopropyl-1H-pyrazol-3-yl)pyridin-5-yl)methanol (55 mg, 25%) as pale yellow oils. Data for 2-(1-isopropyl-1 H-pyrazol-5-yl) pyridin-3-yl)methanol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, J=4.7, 1.5 Hz, 1H), 8.0 (d, J=7.8 Hz, 1H), 7.61 (d, J=1.8 Hz, 1H), 7.39 (dd, J=7.8, 4.8 Hz, 1H), 6.37 (d, J=1.8 Hz, 1H), 4.67 (s, 2H), 4.55 (sep, J=6.6 Hz, 1H), 1.98-2.05 (br, 1H), 1.47 (d, J=6.6 Hz, 6H). LRMS ($M+H^+$) m/z 218.1 Data for (2-(1-isopropyl-1H-pyrazol-3-yl)pyridin-5-yl)methanol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, J=4.8, 1.6 Hz, 1H), 7.72 (d, J=7.6 Hz, 1H), 7.55 (d, J=2.4 Hz, 1H), 7.23 (dd, J=7.6, 4.8 Hz, 1H), 6.99 (dd, J=8.0, 6.5 Hz, 1H), 6.07 (t, J=7.6 Hz, 1H), 4.67 (d, J=7.6 Hz, 2H), 4.58 (sep, J=6.7 Hz, 1H), 1.60 (d, J=6.7 Hz, 1H), LRMS ($M+H^+$) m/z 218.1

Step 2:

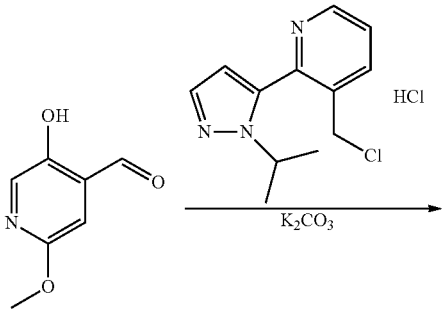
[0497]



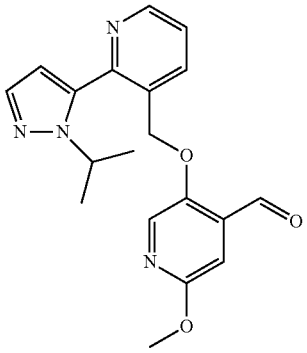
[0498] To (2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methanol (560 mg, 2.58 mmol) in DCM (10 mL) was added $SOCl_2$ (3.0 mL) at rt. The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridin hydrochloride (700 mg) as an off-white solid, which was used for next step without further purification.

Step 3:

[0499]



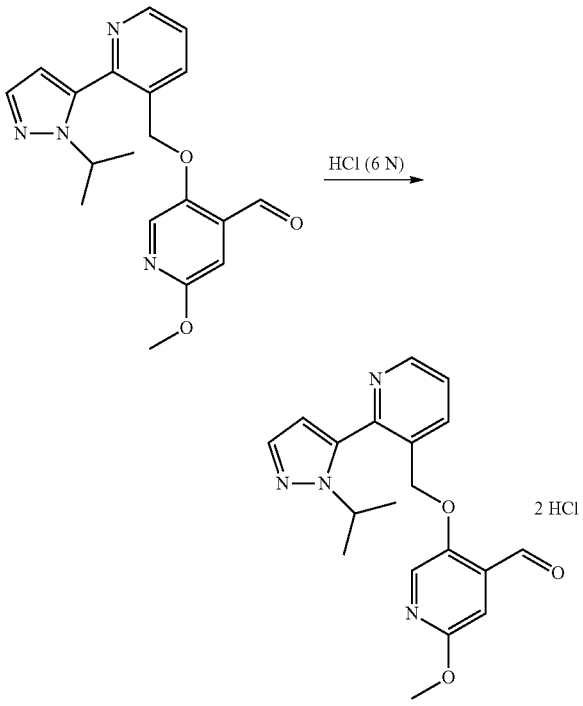
-continued



[0500] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (395 mg, 2.58 mmol, 1 eq.), 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride (700 mg, 2.58 mmol, 1 eq.), and K_2CO_3 (1.4 g, 10.32 mmol, 4 eq.) in DMF (10.0 mL) was heated at 70° C. for 2 h. The mixture was cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (590 mg, 65%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.76 (dd, J=4.7, 1.6 Hz, 1H), 8.04 (dd, J=7.9, 1.6 Hz, 1H), 7.90 (s, 1H), 7.61 (d, J=1.8 Hz, 1H), 7.44 (dd, J=7.9, 4.8 Hz, 1H), 7.10 (s, 1H), 6.37 (d, J=1.8 Hz, 1H), 5.14 (s, 2H), 4.65 (sep, J=6.6 Hz, 1H), 3.91 (s, 3H), 1.49 (d, J=6.6 Hz, 6H). LRMS (M+H$^+$) m/z 353.1.

Step 4:

[0501]



[0502] 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (980 mg, 2.78 mmol, 1 eq.) in HCl (6 N, 9.2 mL, 20 eq.) solution was freeze at −78° C. The mixture was lyophilized O/N to give 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde bis-hydrochloride as a yellow solid. ^{1}H NMR (400 MHz, D_2O) δ 8.85 (dd, J=5.7, 1.3 Hz, 1H), 3.78 (d, J=8.2 Hz, 1H), 8.12 (dd, J=8.1, 5.7 Hz, 1H), 7.76 (s, 1H), 7.72 (d, J=2.0 Hz, 1H), 7.46 (s, 1H), 6.6 (d, J=2.1 Hz, 1H), 6.09 (s, 1H), 5.09 (s, 2H), 4.24 (sep, J=6.6 Hz, 1H), 4.04 (s, 3H), 1.26 (d, J=6.6 Hz, 7H). LRMS (M+H$^+$) m/z 353.1.

[0503] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 3.76 (dd, J=4.7, 1.6 Hz, 1H), 8.04 (dd, J=7.9, 1.6 Hz, 1H), 7.90 (s, 1H), 7.61 (d, J=1.8 Hz, 1H), 7.44 (dd, J=7.9, 4.8 Hz, 1H), 7.10 (s, 1H), 6.37 (d, J=1.8 Hz, 1H), 5.14 (s, 2H), 4.65 (hept, J=6.6 Hz, 1H), 3.91 (s, 3H), 1.49 (d, J=6.6 Hz, 6H).

[0504] Examples 57-62 were prepared according to the procedure in Example 55.

Example 57. Preparation of 2-methoxy-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-5 yl)pyridin-3-yl) methoxy)isonicotinaldehyde (Compound 172)

[0505] ^{1}H NMR (400 MHz, DMSO) δ 3.04 (s, 1H), 10.23 (s, 1H), 8.40 (d, J=4.4 Hz, 1H), 8.10 (s, 1H), 7.93 (d, J=7.7 Hz, 1H), 7.84 (d, J=0.5 Hz, 1H), 7.80 (d, J=7.7 Hz, 1H), 7.68 (dd, J=8.6, 4.4 Hz, 1H), 7.57 (t, J=7.7 Hz, 1H), 5.41 (s, 2H).

Example 58. Preparation of 2-methoxy-5-((2-(1 propy-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound) 173)

[0506] ^{1}H NMR (400 MHz, CDCl3) δ 10.41 (s, 1H), 8.76 (dd, J=4.7, 1.6 Hz, 1H), 8.04 (dd, J=7.9, 1.3 Hz, 1H), 7.93 (s, 1H), 7.57 (d, J=1.8 Hz, 1H), 7.44 (dd, J=7.9, 4.8 Hz, 1H), 7.11 (s, 1H), 6.41 (d, J=1.9 Hz, 1H), 5.17 (s, 2H), 4.23 (t, J=7.4 Hz, 2H), 3.92 (s, 3H), 1.80 (sex., J=7.4 Hz, 2H), 0.81 (t, J=7.4 Hz, 3H).

Example 59. Preparation of 2-methoxy-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)isonicotinaldehyde (Compound 174)

[0507] ^{1}H NMR (400 MHz, CDCl3) δ 10.33 (s, 1H), 8.67 (dd, J=4.8, 1.6 Hz, 1H), 7.97 (dd, J=7.9, 1.4 Hz, 1H), 7.91 (s, 1H) 7.59 (d, J=1.9 Hz, 1H), 7.38 (dd, J=7.9, 4.8 Hz, 1H), 7.05 (s, 1H), 6.47 (d, J=1.9 Hz, 1H), 5.17 (q, J=8.6 Hz, 2H), 5.11 (s, 2H), 3.85 (s, 3H).

Example 60. Preparation of 5-((2-(1-(2,2-difluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 175)

[0508] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.66 (dd, J=4.8, 1.6 Hz, 1H), 7.96 (dd, J=7.9, 1.4 Hz, 1H), 7.87 (s, 1H), 7.55 (d, J=1.9 Hz, 1H), 7.36 (dd, J=7.9, 4.8 Hz, 1H), 7.02 (s, 1H), 6.42 (d, J=1.9 Hz, 1H), 6.11 (tt, J=56.0, 4.4 Hz, 1H), 5.11 (s, 2H), 4.67 (td, J=13.4, 4.4 Hz, 2H), 3.83 (s, 3H).

Example 61. Preparation of 3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)picolinaldehyde (Compound 176)

[0509] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.76 (dd, J=4.7, 1.6 Hz, 1H), 8.47 (dd, J=4.4, 1.0 Hz, 1H), 8.32 (dd, J=7.9, 1.5 Hz, 1H), 7.64 (d, J=1.8 Hz, 1H), 7.49 (td,

J=8.3, 4.6 Hz, 2H), 7.31 (d, J=8.5 Hz, 1H), 6.39 (d, J=1.8 Hz, 1H), 5.15 (s, 2H), 4.65 (sep, J=6.6 Hz, 1H), 1.49 (d, J=6.6 Hz, 6H).

Example 62. Preparation of 3-((2-((1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde (Compound 177)

[0510] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.75 (dd, J=4.7, 1.3 Hz, 1H), 8.29 (d, J=7.9 Hz, 1H), 7.64 (d, J=1.7 Hz, 1H), 7.48 (dd, J=7.9, 4.8 Hz, 1H), 7.31 (d, J=8.6 Hz, 1H), 7.20 (d, J=8.6 Hz, 1H), 6.38 (d, J=1.7 Hz, 1H), 5.11 (s, 2H), 4.64 (sep, J=6.6 Hz, 1H), 2.61 (s, 3H), 1.49 (d, J=6.6 Hz, 6H).

Example 63. Preparation of 5-((2-(1-cyclobutyl-1H-pyrazol-5-yl)pyridin-3 yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 195)

[0511] ^{1}H NMR (400 MHz, CDCl3) δ 10.31 (s, 1H), 8.68 (dd, J=4.8, 1.6 Hz, 1H), 7.94 (dd, J=7.9, 1.6 Hz, 1H), 7.79 (s, 1H), 7.54 (d, J=1.81 Hz, 1H), 7.36 (dd, J=7.9, 4.8 Hz, 1H), 7.01 (s, 1H), 6.30 (d, J=1.8 Hz, 1H), 5.05 (s, 2H), 4.77 (quin, J=8.4 Hz, 1H), 3.82 (s, 3H), 2.74-2.56 (m, 2H), 2.32-2.15 (m, 2H), 1.87-1.73 (m, 1H), 1.72-1.59 (m, 1H).

Example 64. Preparation of 5-((2-(1-cyclohexyl-1H-pyrazol-5-yl)pyridin-3 yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 196)

[0512] ^{1}H NMR (400 MHz, CDCl3) δ 10.33 (s, 1H), 8.68 (dd, J=4.7, 1.5 Hz, 1H), 7.96 (dd, J=7.9.1.2 Hz, 1H), 7.81 (s, 1H), 7.51 (d, J=1.8 Hz, 1H), 7.36 (dd, J=7.9, 4.8 Hz, 1H), 7.02 (s, 1H) 6.28 (d, J=1.8 Hz, 1H), 5.05 (s, 2H), 4.10 (quin, J=7.6 Hz, 1H), 3.83 (s, 3H), 1.96-1.83 (m, J=2.9 Hz, 4H), 1.3-1.68 (m, 2H), 1.68-1.45 (m, 2H), 1.33-1.06 (m, 2H).

Example 65. Preparation of 5-((2-(1-(cyclohexylmethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 197)

[0513] ^{1}H NMR (400 MHz, CDCl3) δ 10.43 (s, 1H), 8.76 (dd, J=4.7, 1.4 Hz, 1H), 8.04 (dd, J=7.9, 1.0 Hz, 1H), 7.93 (s, 1H), 7.58 (d, J=1.7 Hz, 1H), 7.45 (dd, J=7.9, 4.8 Hz, 1H), 7.11 (s, 1H), 6.40 (d, J=1.8 Hz, 1H), 5.16 (s, 2H), 4.13 (d, J=7.3 Hz, 2H), 3.92 (s, 3H), 1.92-1.74 (m, 1H), 1.60 (dd, J=8.2, 4.5 Hz, 3H), 1.47 (d, J=11.4 Hz, 2H), 1.21-0.98 (m, 3H), 0.91-0.71 (m, 2H).

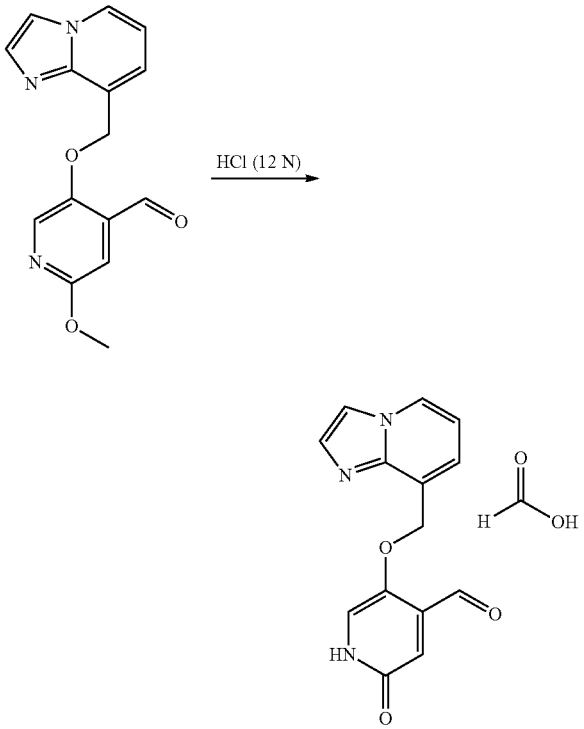
Example 66. Preparation of 3-((2-(1-cyclopentyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 198)

[0514] ^{1}H NMR (400 MHz, CDCl3) δ 10.42 (s, 1H), 8.77 (dd, J=4.7, 1.5 Hz, 1H), 8.04 (dd, J=7.9, 1.2 Hz, 1H), 7.90 (s, 1H), 7.60 (d, J=1.8 Hz, 1H), 7.45 (dd, J=7.9, 4.81 Hz, 1H), 7.11 (s, 1H), 6.38 (d, J=1.9 Hz, 1H), 5.15 (s, 2H), 4.74 (quin, J=7.5 Hz, 1H), 3.92 (s, 3H), 2.23-1.85 (m, 6H), 1.63-1.51 (m, 2H).

Example 67. Preparation of 2-(difluoromethoxy)-5-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde (Compound 138)

Step 1:

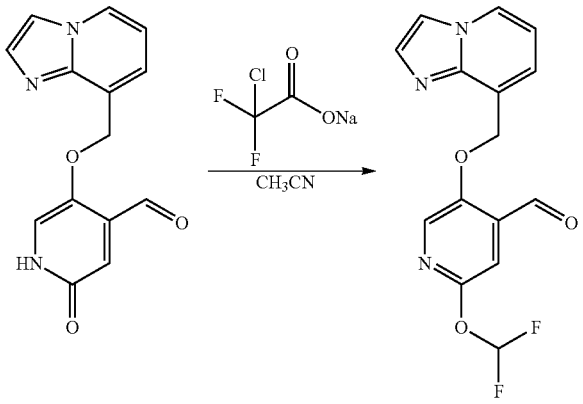
[0515]



[0516] To 5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde (300 mg, 0.84 mmol, 1 equiv) in a vial was added HCl (6 N, 1 mL, 6 mmol). The mixture was concentrated, dried under vaccum at 60° C. O/N, cooled to rt, and dissolved in NaOH (3 N, 5 mL), filtered, and washed with EtOAc twice. The pH of the aqueous layer was adjust to pH 6-7, filtered, and purified by RP-HPLC (Gemini 21.2×150 mm) with a mixture of CH_3CN and water (0.1% HCOOH) as eluent to give 5-(imidazo[1,2-a]pyridin-8-yl-methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde formate (82.5 mg, 31%) as an yellow solid. ^{1}H NMR (400 MHz, D_2O) δ 8.56 (d, J=7.1 Hz, 1H), 8.32 (s, 1H), 8.01 (d, J=2.1 Hz, 1H), 7.83 (d, J=7.2 Hz, 1H), 7.81 (t, J=2.1 Hz, 1H), 7.31 (t, J=7.2 Hz, 1H), 7.27 (s, 1H), 6.68 (s, 1H), 5.94 (s, 1H), 5.32 (s, 2H). LRMS ($M+H^+$) m/z 270.1.

Step 2:

[0517]



[0518] To 5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (100 mg, 0.37 mmol, 1 equiv) in CH_3CN (10 mL) was added sodium 2-chloro-2,2-difluoroacetate (84.5 mg, 0.56 mmol, 1.5 eq.). The mixture was stirred at rt O/N and concentrated. The crude was purified on silica gel using 10% MeOH/DCM as eluent to give 2-(difluoromethoxy)-5-(imidazo[1,2-a]pyridin-8-yl-methoxy)isonicotinaldehyde (6.0 mg, 5%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.14 (s, 1H), 8.10 (d, J=7.0 Hz, 1H), 7.61 (s, 2H), 7.44 (t, J=60.0 Hz, 1H), 7.24-7.27 (m, 2H), 6.79 (t, J=7.0 Hz, 1H), 5.63 (s, 2H). LRMS ($M+H^+$) m/z 320.0.

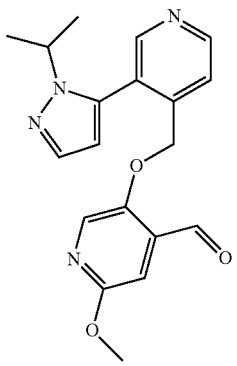
Example 68. Preparation of 2-(difluoromethoxy)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)isonicotinaldehyde (Compound 178)

[0519] The title compound was prepared according to the procedure in Example 67.

[0520] ^1H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.80 (d, J=3.7 Hz, 1H), 8.03 (d, J=8.0 Hz, 1H), 7.95 (s, 1H), 7.63 (d, J=1.6 Hz, 1H), 7.47 (dd, J=7.9, 4.8 Hz, 1H), 7.33 (t, J=72.8 Hz, 1H), 6.37 (d, J=1.7 Hz, 1H), 5.21 (s, 2H), 4.67 (sep, J=6.6 Hz, 1H), 1.50 (d, J=6.6 Hz, 6H).

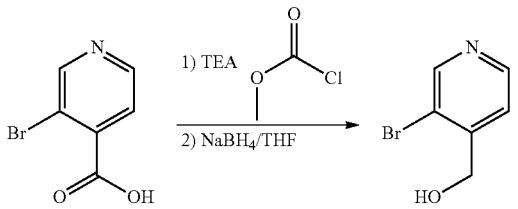
Example 69 Preparation of 5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 160)

[0521]



Step 1:

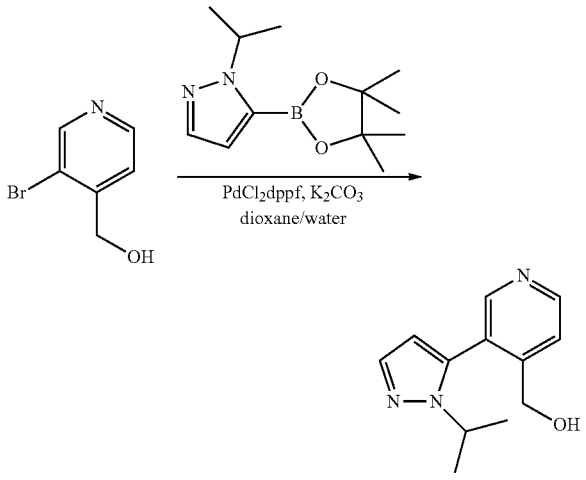
[0522]



[0523] To a mixture of 3-bromoisonicotinic acid (2.5 g, 12.37 mmol, 1 eq.) and TEA (3.44 mL, 24.75 mmol, 2.0 eq.) in THF (100 mL) was added methyl chloroformate (1.2 mL, 14.85 mmol, 1.2 eq.) at 0° C. The mixture was stirred at 0° C. for 10 min and filtered. To this filtrate was added a suspension of $NaBH_4$ (0.95 g, 24.75 mmol, 2 eq.) in water (1.0 mL) at 0° C. The mixture was stirred at 0° C. for 1 h, quenched with $NH_4Cl_{(aq)}$ solution, extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give (3-bromopyridin-4-yl)methanol (1.2 g, 52%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.37 (d, J=4.9 Hz, 1H), 7.37 (d, J=4.9 Hz, 1H), 4.61 (d, J=0.5 Hz, 2H), 2.3 (t, J=5.5 Hz, 1H), LRMS ($M+H^+$) m/z 133.0.

Step 2:

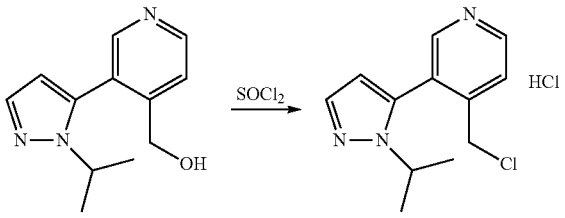
[0524]



[0525] To a mixture of (3-bromopyridin-4-yl)methanol (150 mg, 0.3 mmol, 1 eq.), 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (226 mg, 0.96 mmol, 1.2 eq.), $Pd(dppf)Cl_2$ (58 mg, 0.08 mmol, 0.1 eq.), and K_2CO_2 (331 mg, 3.0 mmol, 3 eq.) in a RB flask were added dioxane (6 mL) and water (2 mL). The mixture was heated at 100° C. for 2 h, cooled, filtered, and concentrated. The crude was purified on silica gel using a mixture of EtOAc and hexanes as eluent to give (3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl)methanol (75 mg, 43%) as a yellow oil. LRMS ($M+H^+$) m/z 213.1.

Step 3:

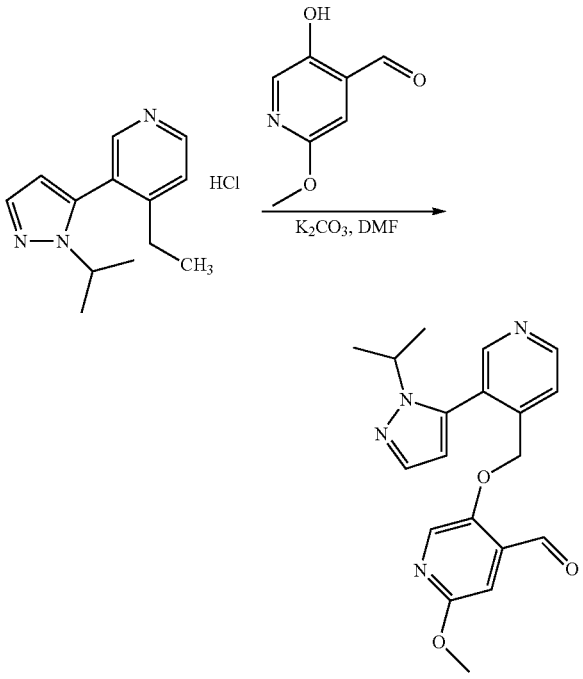
[0526]



[0527] (3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl) methanol (75 mg, 0.35 mmol) in $SOCl_2$ (5 mL) was heated at 60° C. for 30 ruin and concentrated. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give a brown solid (95 mg) which was used for next step without further purification.

Step 4:

[0528]



[0529] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (79 mg, 0.52 mmol, 1.5 eq.), 4-(chloromethyl)-3-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride (crude above, 0.35 mmol), and K_2CO_3 (145 mg, 1.05 mmol, 3 eq.) in DMF (10.0 mL) was heated at 100° C. for 2 h. The mixture was cooled, filtered, concentrated, and purified on RP-HPLC (Gemini 21.2×150 mm) twice using a mixture of CH_3CN/water (0.1% HCOOH) as eluent to give 5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde (6.0 mg, 5%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.63 (s, 1H), 8.42 (s, 1H), 7.67 (s, 1H), 7.54 (s, 1H), 7.52 (d, J=1.7 Hz, 1H), 6.96 (s, 1H), 6.15 (d, J=1.8 Hz, 1H), 4.87 (s, 2H), 4.06 (sep, J=6.6 Hz, 1H), 3.75 (s, 3H), 1.31 (d, J=6.6 Hz, 6H). LRMS ($M+H^+$) m/z 353.1.

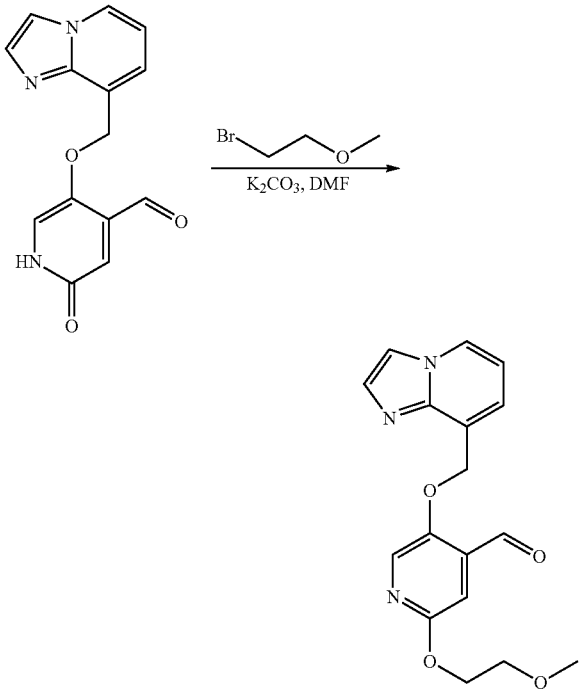
Example 70. Preparation of 5-([2,3'-bipyridin]-3-ylmethoxy)-2-methoxyisonicotinaldehyde (Compound 161)

[0530] The title compound was prepared according to the procedure in Example 69.

[0531] ^1H NMR (400 MHz, CDCl3) δ 10.36 (s, 1H), 8.85 (d, J=1.7 Hz, 1H), 8.78 (dd, J=4.8, 1.6 Hz, 1H), 8.71 (dd, J=4.8, 1.5 Hz, 1H), 8.02 (dd, J=7.8, 1.5 Hz, 1H), 7.96 (dt, J=7.9, 1.9 Hz, 1H), 7.90 (s, 1H), 7.49-7.42 (m, 2H), 7.10 (s, 1H), 5.21 (s, 2H), 3.91 (s, 3H).

Example 71. Preparation of 5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-(2-methoxyethoxy)isonicotinaldehyde (Compound 179)

[0532]



[0533] To a mixture of 5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (100 mg, 0.37 mmol, 1 equiv) and K_2CO_3 (153.2 mg, 1.11, 3.0 eq.) in DMF (5 mL) was added 1-bromo-2-methoxyethane (154.3 mg, 1.11 mmol, 3.0 eq.). The mixture was stirred at rt O/N, filtered, concentrated, and purified on silica gel using 10% MeOH/DCM as eluent to give 5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-(2-methoxyethoxy)isonicotinaldehyde (6.0 mg, 5%) as an yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.08 (d, J=6.8 Hz, 1H), 8.06 (s, 1H), 7.60 (dd, J=6.8, 1.2 Hz, 2H), 7.27 (dd, J=6.9, 1.0 Hz, 1H), 7.09 (s, 1H), 6.78 (t, J=6.9 Hz, 1H), 5.58 (s, 2H), 4.35 (dd, J=5.4, 3.9 Hz, 2H), 3.66 (dd, J=5.4, 3.9 Hz, 2H), 3.36 (s, 3H). LRMS ($M+H^+$) m/z 328.1.

Example 72. Preparation of 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-(2-methoxyethoxy)isonicotinaldehyde (Compound 180)

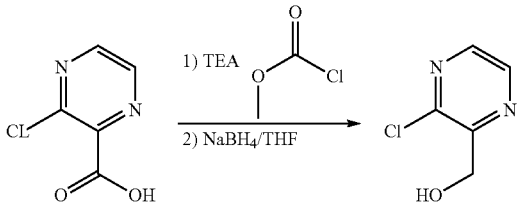
[0534] The title compound was prepared according to the procedure in Example 71.

[0535] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H) 8.76 (dd, J=4.7, 1.5 Hz, 1H), 8.04 (dd, J=7.9, 1.2 Hz, 1H), 7.87 (s, 1H), 7.61 (d, J=1.8 Hz, 1H), 7.44 (dd, J=7.9, 4.8 Hz, 1H), 7.16 (s, 1H), 6.37 (d, J=1.8 Hz, 1H), 5.14 (s, 2H), 4.65 (sep. J=6.6 Hz, 1H), 4.42 (t, J=4.8 Hz, 2H), 3.74 (t, J=4.8 Hz, 2H), 3.44 (s, 3H), 1.49 (d, J=6.6 Hz, 6H).

Example 73. Preparation of 5-((3-(1-isopropyl-1H pyrazol-5-yl)pyrazin-1-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 181)

Step 1:

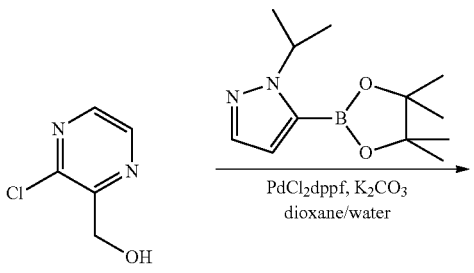
[0536]



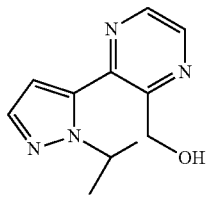
[0537] To a solution of 3-chloropyrazine-2-carboxylic acid (2.0 g, 12.70 mmol, 1.0 eq.) and TEA (3.50 mL, 25.40 mmol, 2.0 eq.) in THF (50 mL) was added methyl chloroformate (1.2 mL, 15.20 mmol, 1.2 eq.) at 0° C. The mixture was stirred at 0° C. for 10 min and filtered. To this filtrate was added a suspension of NaBH (0.97 g, 25.40 mol, 2 eq.) in water (1.0 mL) at 0° C. The mixture was stirred at 0° C. for 1 h, quenched with $NH_4Cl_{(aq)}$ solution, and extracted with EtOAc twice. The combined organic layers were dried over N_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give (3-chloropyrazin-2-yl)methanol (400 mg, 22%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 8.58 (d, J=2.5 Hz, 1H), 8.38 (4, J=2.5 Hz, 1H), 4.84 (s, 2H). LRMS ($M+H^+$) m/z 145.1.

Step 2:

[0538]



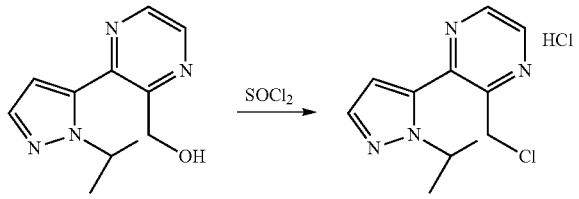
-continued



[0539] To a mixture of (3-chloropyrazin-2-yl)methanol (200 mg, 1.4 mmol, 1 eq.), 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (393 mg, 1.67 mmol, 1.2 eq.). $Pd(dppf)Cl_2$ (102 mg, 0.14 mmol, 0.1 eq.), and K_2CO_3 (580 mg, 4.2 mmol, 3 eq.) in a RB flask were added dioxane (6 mL) and water (2 mL). The mixture was heated at 100° C. for 1 h, cooled to rt, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give (3-(1-isopropyl-1H-pyrazol-5-yl) pyrazin-2-yl)methanol (110 mg, 36%) as a yellow oil. LRMS ($M+H^+$) m/z 219.1.

Step 3:

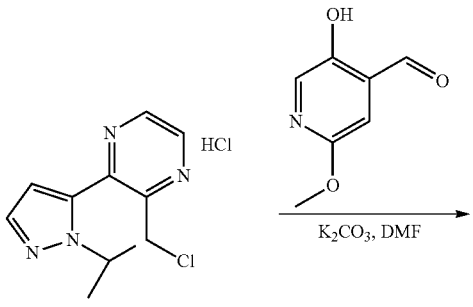
[0540]



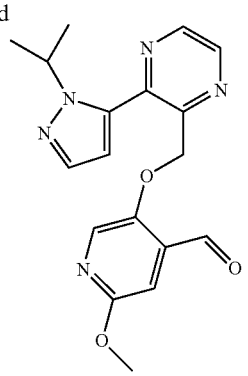
[0541] 3-(1-isopropyl-1H-pyrazol-5-yl)pyrazin-2-yl) methanol (75 mg, 0.35 mmol) in $SOCl_2$ (5 mL) was heated at 60° C. for 30 min and concentrated. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give a brown solid (95 mg), which was used for next step without further purification.

Step 4:

[0542]



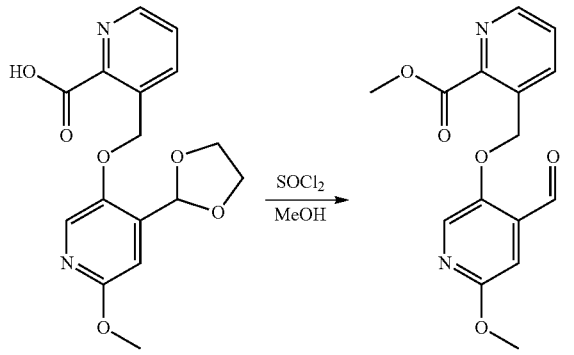
-continued



[0543] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (110 mg, 0.60 mmol, 1.2 eq.), 2-(chloromethyl)-3-(1-isopropyl-1H-pyrazol-5-yl)pyrazine hydrochloride (crude above, 0.5 mmol, 1 eq.), and K_2CO_3 (207 mg, 1.50 mol, 3 eq.) in DMF (15.0 mL) was heated at 100° C. for 30 min. The mixture was cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyrazin-2-yl) methoxy)-2-methoxyisonicotinaldehyde (12.0 mg, 68%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.73 (d, J=2.4 Hz, 1H), 8.65 (d, J=2.4 Hz, 1H), 8.05 (s, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.06 (s, 1H), 6.49 (d, J=1.9 Hz, 1H), 5.32 (s, 2H), 4.68 (sep, J=6.6 Hz, 1H), 3.89 (s, 2H), 1.48 (d, J=6.6 Hz, 6H). LRMS (M+H$^+$) m/z 354.1.

Example 74. Preparation of methyl 3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinate (Compound 182)

[0544]

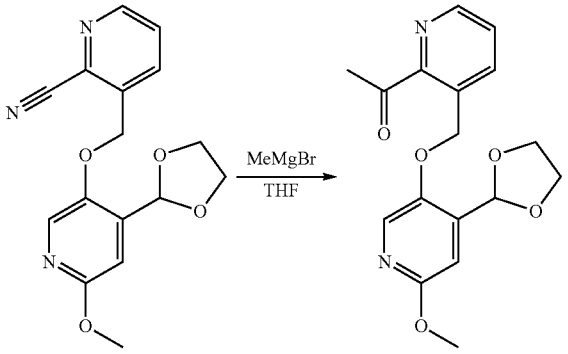


[0545] To 3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)picolinic acid (55 mg, 0.17 mmol, 1 equiv) in MeOH (15 mL) was added $SOCl_2$ (5.0 mL). The mixture was heated to reflux O/N, concentrated, and neutralized to pH 8-9 with $NaHCO_{3(sat.)}$ solution. The aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give methyl 3-((4-formyl-6-methoxypyridin-3-yloxy) methyl)picolinate (31.5 mg, quantitative yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.67 (dd, J=4.6, 1.5 Hz, 1H), 8.14 (dd, J=8.0, 1.5 Hz, 1H), 8.03 (s, 1H), 7.51 (dd, J=8.0, 4.6 Hz, 1H), 7.06 (s, 1H), 5.60 (s, 2H), 3.95 (s, 3H), 3.85 (s, 3H). LRMS (M+H$^+$) m/z 303.1.

Example 75. Preparation of 5-((2-2-hydroxypropan-2-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 183)

Step 1:

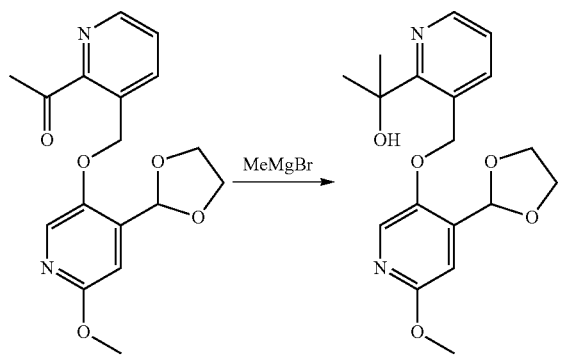
[0546]



[0547] Methylmagnesium bromide (3M/ether, 2.0 mL, 5.65 mmol, 1.5 eq.) was added to a stirred solution of 3-((4-(3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl) picolinonitrile (1180 mg, 3.76 mmol, 1 eq.) in THF (10.0 mL) at −78° C. After addition, the reaction mixture was allowed to warm to rt and quenched with aqueous citric acid solution. The aqueous layer was extracted with EtOAc (30 mL) twice. The combined organic layers were washed with $NaHCO_{3(sat)}$ solution and brine, dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 1-(3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)ethanone (776 mg, 63%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J=4.0 Hz, 1H), 8.26 (d, J=7.9 Hz, 1H), 7.82 (s, 1H), 7.54 (dd, J=8.0, 4.0 Hz, 1H), 6.95 (s, 1H), 6.23 (s, 1H), 5.59 (s, 2H), 4.22-4.04 (m, 4H), 3.90 (s, 3H), 2.79 (s, 3H). LRMS (M+H$^+$) m/z 331.1.

Step 2:

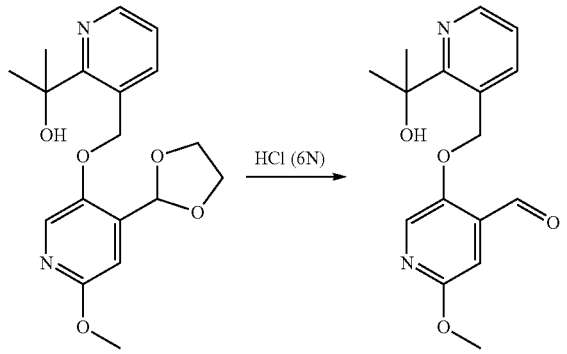
[0548]



[0549] Methylmagnesium bromide (3M/ether, 0.25 mL, 0.75 mmol, 3.0 eq.) was added to a stirred solution of 1-(3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy) methyl)pyridin-2-yl)propan-1-one (82 mg, 0.25 mmol, 1 eq.) in THF (5.0 mL) at −78° C. After addition, the reaction mixture was warm to it and quenched with aqueous citric acid solution. The aqueous layer was extracted with EtOAc (20 mL) twice. The combined organic layers were washed with $NaHCO_{3(sat)}$ solution and brine, dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 2-(3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)propan-2-ol (38 mg, 44%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, J=7.7, 1.6 Hz, 1H), 7.84 (dd, J=7.7, 1.5 Hz, 1H), 7.74 (s, 1H), 7.18 (dd, J=7.7, 4.7 Hz, 1H), 6.84 (s, 1H), 6.01 (s, 1H), 5.27 (s, 2H), 4.07-3.88 (m, 4H), 3.82 (s, 3H), 1.55 (s, 6H). LRMS ($M+H^+$) m/z 347.1.

Step 3:

[0550]

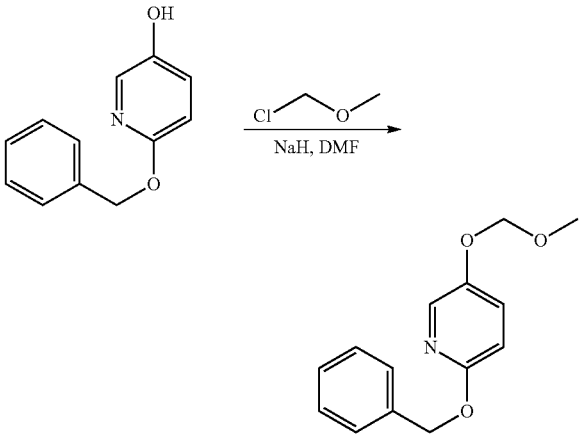


[0551] To 2-(3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)propan-2-ol (30 mg 0.087 mmol, 1 eq.) in a RB flask was added HCl (6 N, 3.0 mL). The mixture was warmed to 40° C. O/N, cooled to rt, neutralized to pH 7-8 with $NaHCO_{3(sat)}$ solution, and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 5-((2-(2-hydroxypropan-2-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (10.2 mg, 99%) as a pale-yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.46 (dd, J=4.7, 1.6 Hz, 1H), 7.99 (s, 1H), 7.86 (dd, J=7.8, 1.5 Hz, 1H), 7.24 (dd, J=7.8, 4.7 Hz, 1H), 7.05 (s, 1H), 5.37 (s, 2H), 3.85 (s, 3H), 1.57 (s, 6H). LRMS ($M+H^+$) m/z 303.1.

Example 76. Preparation of 5-hydroxy-2-(2-methoxyethoxy)isonicotinaldehyde and 5-hydroxy 2-(2-methoxyethoxy)nicotinaldehyde

Step 1

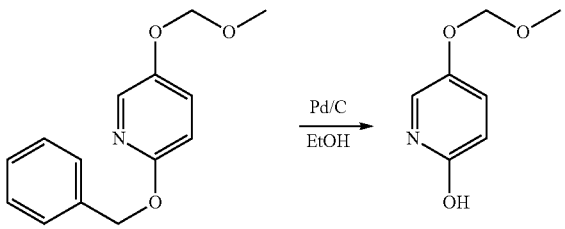
[0552]



[0553] To a solution of 6-(benzyloxy)pyridin-3-ol (2.0 g, 10 mmol, 1 eq.) in DMF (20 mL) was added NaH (60% in mineral oil; 0.6 g, 15 mmol, 1.5 eq.) at 0-5° C. portion-wise. Upon the completion of addition, the mixture was continued to stir at 0-5° C. for 15 min, added chloromethyl methyl ether (0.88 g, 11 mmol, 1.1 eq.), stirred at 0-5° C. for another 20 min, and quenched with $NH_4Cl_{(sat.)}$ solution. The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with water and brine, dried over Na_2SO_4, concentrated, and purified on silica gel using 25% EtOAc/hexanes as eluent to give 2-(benzyloxy)-5-(methoxymethoxy)pyridine (2.1 g, 87%) as a colorless oil. LRMS ($M+H^+$) m/z 246.1

Step 2

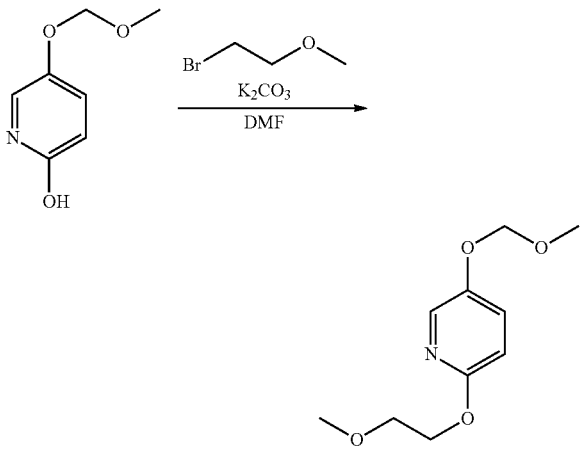
[0554]



[0555] To 2-(benzyloxy)-5-(methoxymethoxy)pyridine (1.8 g, 8.71 mol) in EtOH was added Pd/C (1.0 g). The mixture was charged with H_2 (15 psi), stirred at it for 45 min, filtered, and concentrated to give 5-(methoxymethoxy)pyridin-2-ol (1.35 g, quantitative yield) as a pale yellow solid. LRMS ($M+H^+$) m/z 156.1

Step 3

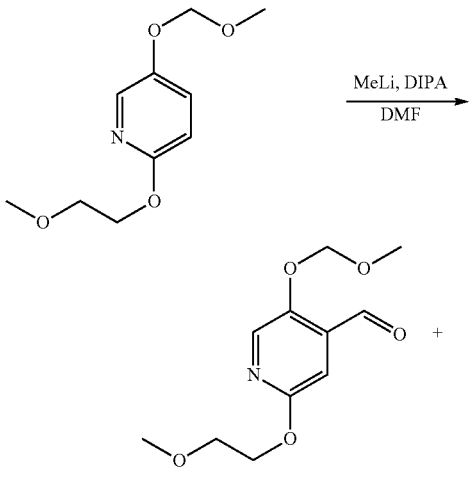
[0556]



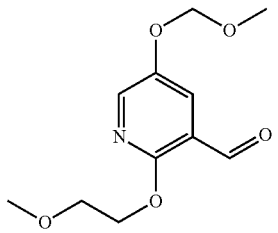
[0557] To a mixture of 5-(methoxymethoxy)pyridin-2-ol (1.35 g, 8.71 mmol, 1 eq.) and K_2CO_3 (6.01 g, 43.6 mmol, 5.0 eq.) in DMF (30.0 mL) was added 1-bromo-2-methoxyethane (3.61 g, 26.1 mmol, 3 eq.). The mixture was heated at 60° C. for 2 h, cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 2-(2-methoxyethoxy)-5-(methoxymethoxy)pyridine (500 mg, 27%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J=3.0 Hz, 1H), 7.35 (ddd, J=8.9, 3.0, 1.0 Hz, 1H), 6.76 (dd, J=8.9, 1.0 Hz, 1H), 5.11 (s, 2H), 4.48-4.40 (m, 2H), 3.79-3.71 (m, 2H), 3.50 (s, 3H), 3.45 (s, 3H). LRMS ($M+H^+$) m/z 214.1.

Step 4

[0558]



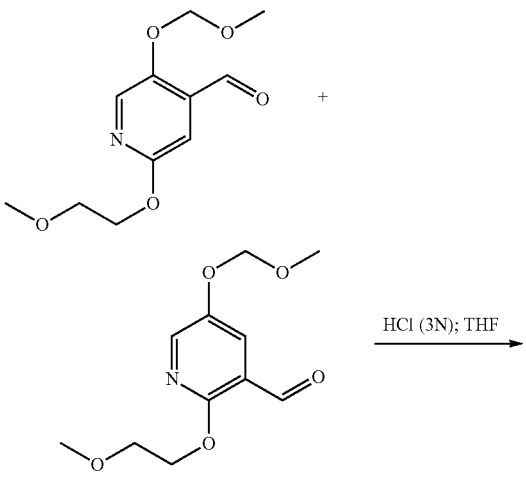
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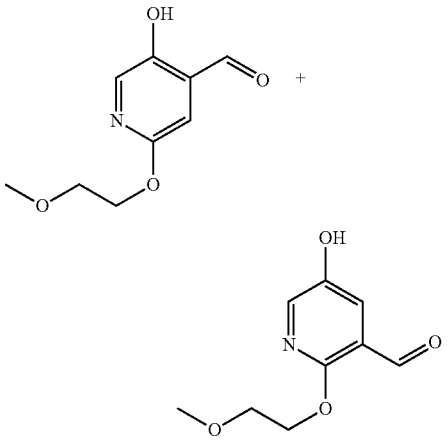
[0559] To a mixture of 2-(2-methoxyethoxy)-5-(methoxymethoxy)pyridine (1.34 g, 6.3 mol, 1 eq.) and diisopropylamine (17.5 uL, 0.13 mmol, 0.02 eq.) in THF (50 mL) was added methyl lithium (1.6 M/THF, 7 mL, 11.3 mol, 1.8 eq.) at −40° C. Upon the completion of addition, the mixture was warmed to 0° C., continued to stir at 0° C. for 3 h, cooled back down to −40° C., and added DMF (0.83 mL, 11.3 mol, 1.8 eq.) slowly. The mixture was then stirred at −40° C. for 1 h, quenched with a mixture of HCl (12 N, 12 mL) and THF (28 mL), warmed to rt, and added water (20 mL). The pH of the mixture was adjusted to pH 8-9 with solid K_2CO_3. The aqueous layer was extracted with EtOAc (30 mL) twice. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give a mixture of 2-(2-methoxyethoxy)-5-(methoxymethoxy)isonicotinaldehyde and 2-(2-methoxyethoxy)-5-(methoxymethoxy)nicotinaldehyde (5/1, 1.27 g, 83.6%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.23 (s, 1H), 7.16 (s, 1H), 5.27 (s, 2H), 4.46 (dd, J=5.4, 3.9 Hz, 2H), 4.14 (q, J=7.1 Hz, 1H), 3.77-3.71 (m, 2H), 3.56 (s, 3H), 3.46 (s, 3H) and ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.18 (d, J=3.2 Hz, 1H), 7.85 (d, J=3.1 Hz, 1H), 5.16 (s, 2H), 4.64-4.57 (m, 2H), 3.85-3.79 (m, J=5.4, 4.0 Hz, 2H), 3.50 (s, 3H), 3.46 (s, 3H); LRMS ($M+H^+$) m/z 242.1.1

Step 5

[0560]



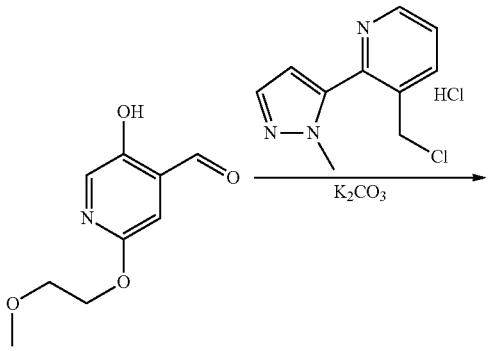
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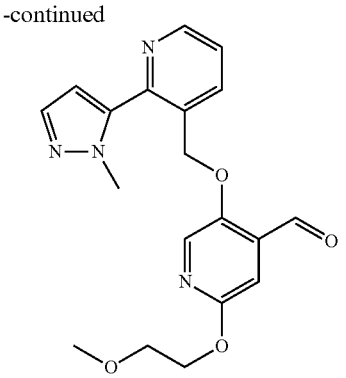
[0561] To a solution of 2-methoxy-5-(methoxymethoxy) isonicotinaldehyde (1.27 g, 5.29 mol) in THF (S mL) was added HCl (3 N, 4 mL). The reaction was stirred at 50° C. for 1 h, cooled to rt, and diluted with water (5 mL). The mixture was neutralized to pH 748 with solid K_2CO_3 and the aqueous layer was extracted with EtOAc (100 mL) twice. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes to give 5-hydroxy-2-(2-methoxyethoxy) isonicotinaldehyde (630 mg, 60%) and 5-hydroxy-2-(2-methoxyethoxy)nicotinaldehyde (120 mg, 11%). Data for 5-hydroxy-2-(2-methoxyethoxy)isonicotinaldehyde: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 9.50 (s, 1H), 8.07 (s, 1H), 7.02 (s, 1H), 4.51-4.39 (m, 2H), 3.81-3.72 (m, 2H), 3.47 (s, 3H). LRMS ($M+H^+$) m/z 198.1. Data for and 5-hydroxy-2-(2-methoxyethoxy)nicotinaldehyde: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.3 (s, 1H), 7.99 (d, J=3.2 Hz, 1H), 7.58 (d, J=3.2 Hz, 1H), 7.18-7.07 (br, 1H), 4.54 (dd, J=5.4, 3.7 Hz, 2H), 3.84 (dd, J=5.4, 3.7 Hz, 2H), 3.49 (s, 3H). LRMS ($M+H^+$) m/z 198.1

Example 77. Preparation of 2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrol-5-yl)pyridin-3-yl)methoxy) isonicotinaldehyde (Compound 184)

[0562]



-continued



[0563] A mixture of 5-hydroxy-2-(2-methoxyethoxy) isonicotinaldehyde (125 mg, 0.63 mmol, 1 eq.), 3-(chloromethyl)-2-(1-methyl-1H-pyrazol-5-yl)pyridine hydrochloride salt (120 mg, 0.63 mmol, 1 eq.), and Cs_2CO_3 (410 mg, 1.26 mmol, 2 eq.) in DMF (3.0 mL) was heated at 60° C. for 2 h. The mixture was cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (59 mg, 25%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.59 (dd, J=4.7, 1.6 Hz, 1H), 7.87 (dd, J=7.9, 1.3 Hz, 1H), 7.73 (s, 1H), 7.38 (d, J=1.9 Hz, 1H), 7.27 (dd, J=7.9, 4.8 Hz, 1H), 7.00 (s, 1H), 6.25 (d, J=1.9 Hz, 1H), 5.02 (s, 2H), 4.26 (dd, J=5.4, 3.9 Hz, 21H), 3.80 (s, 3H), 3.57 (dd, J=5.4, 3.9 Hz, 2H), 3.28 (s, 3H). LRMS ($M+H^+$) m/z 387.1.

Example 78. Preparation of 2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)nicotinaldehyde (Compound 185)

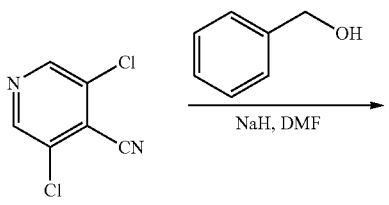
[0564] The title compound was prepared according to the procedure in Example 77.

[0565] ^{1}H NMR (400 MHz, CDCl3) δ 10.38 (s, 1H), 8.74 (dd, J=4.7, 1.5 Hz, 1H), 8.07 (d, J=3.3 Hz, 1H), 7.98 (dd, J=7.9, 1.2 Hz, 1H), 7.64 (d, J=3.3 Hz, 1H), 7.53 (d, J=0.9 Hz, 1H), 7.41 (dd, J=7.9, 4.8 Hz, 1H), 6.41 (d, J=1.9 Hz, 1H), 5.04 (s, 2H), 4.62-4.51 (m, 2H), 3.96 (s, 3H), 3.82-3.76 (m, 2H), 3.45 (s, 3H).

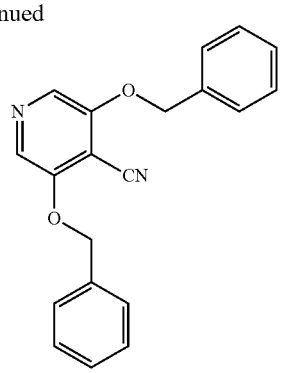
Example 79. Preparation of 3-hydroxy-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy) isonicotinaldehyde (Compound 186)

Step 1:

[0566]



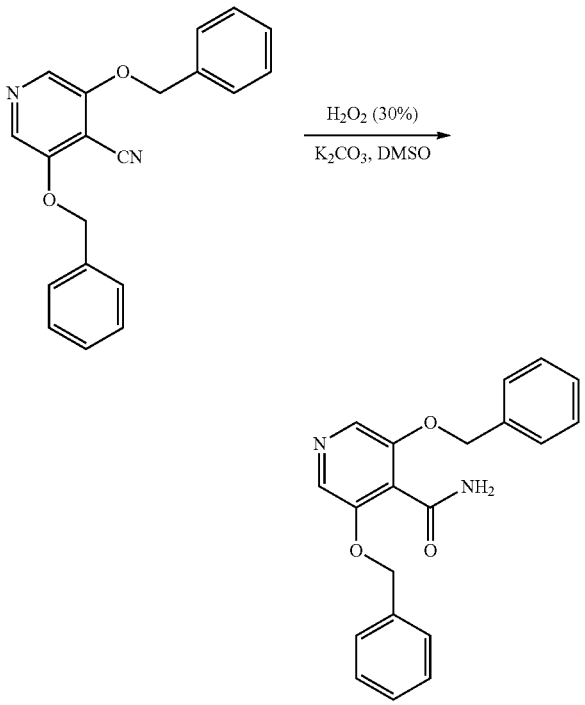
-continued



[0567] To a mixture of NaH (60% in mineral oil) (2.77 g, 69.25 mmol, 2.5 eq.) in DMF (40.0 mL) was added benzyl alcohol (6.6 g, 61.0 mmol, 2.2 eq.) at 0° C. The mixture was stirred at 0° C. for 10 min. added 3,5-dichloroisonicotinonitrile (4.8 g, 27.7 mmol, 1 eq.), continued to stir at 0° C. for 30 min, gradually warm to rt, stirred at rt O/N, and quenched with $NH_4Cl_{(sat)}$ solution. The aqueous layer was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over N_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes s eluent to give 3,5-bis(benzyloxy)isonicotinonitrile (4.94 g, 56%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 2H), 7.58-7.30 (m, 10H), 5.33 (s, 4H). LRMS ($M+H^+$) m/z 317.1

Step 2:

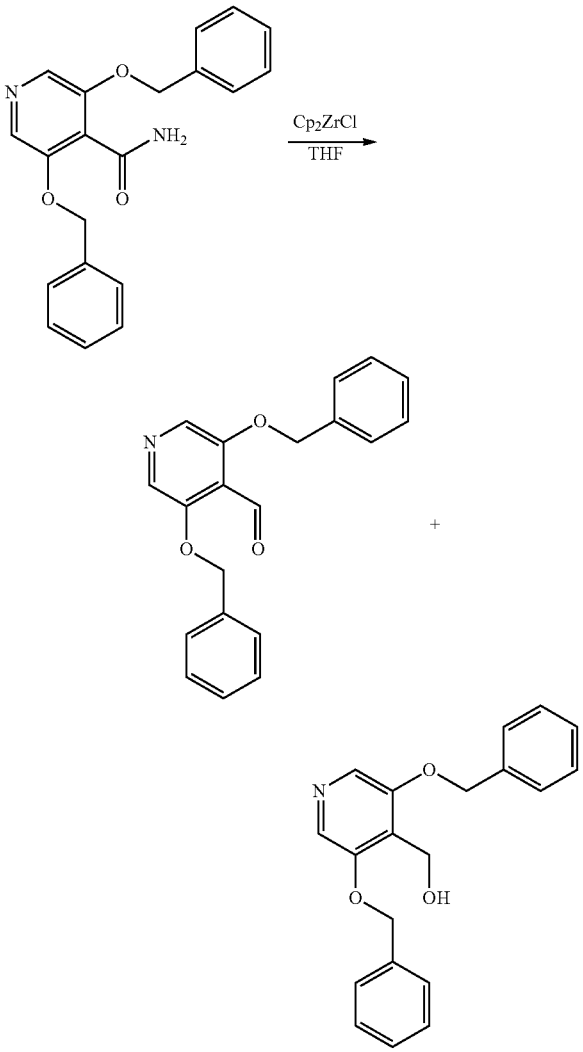
[0568]



[0569] To a mixture of 3,5-bis(benzyloxy)isonicotinonitrile (2.5 g, 7.9 mmol, 1 eq.) and K_2CO_3 (4.37 g, 31.6 mmol, 4 eq.) in DMSO (10 mL) was added H_2O (30% in water, 2.0 mL) at rt. The mixture was stirred at rt O/N and added water (50 mL). The solid was collected and dried to give 3,5-bis(benzyloxy)isonicotinamide (2.2 g, 83%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 2H), 7.59-7.33 (m, 10H), 5.83 (s, 2H), 5.25 (s, 4H), 4.81 (s, 2H). LRMS ($M+H^+$) m/z 335.1

Step 3:

[0570]

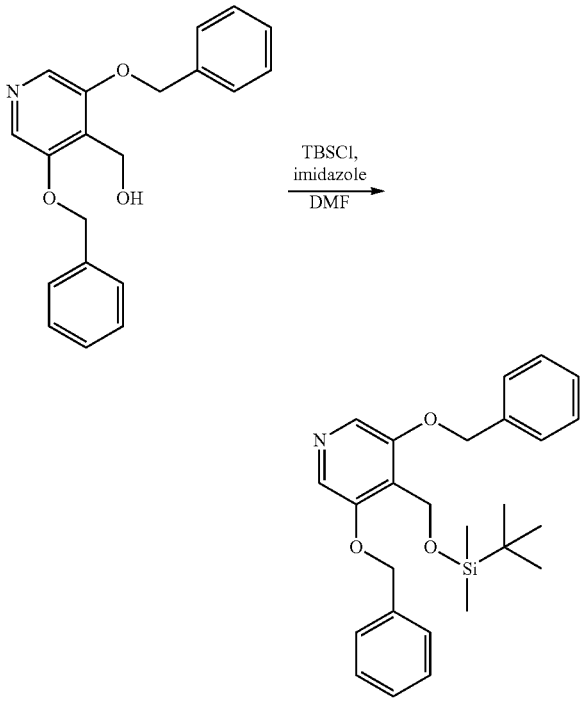


[0571] To 3,5-bis(benzyloxy)isonicotinamide (1.6 g, 4.79 mmol) in THF (30 mL) was added Cp2ZrCl (3.7 g, 14.4 mmol, 3 eq.) at rt. The mixture was stirred at rt for 2 h, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 3,5-bis(benzyloxy) isonicotinaldehyde (580 mg, 38%) and (3,5-bis(benzyloxy) pyridin-4-yl)methanol (710 mg, 46%) as white solids. Data for aldehyde ^1H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.13 (s, 2H), 7.51-7.22 (m, 10H), 5.21 (s, 4H); LRMS

(M+H$^+$) m/z 320.1. Data for alcohol ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 2H), 7.58-7.34 (m, 10H), 5.22 (s, 4H), 4.87 (s, 1H). LRMS (M+H$^+$) m/z 322.1.

Step 4:

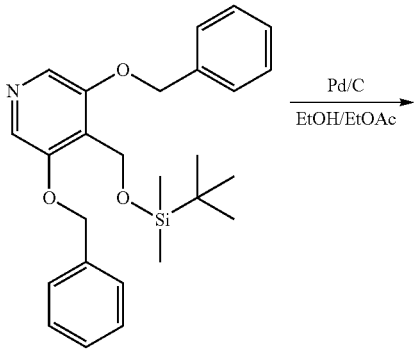
[0572]



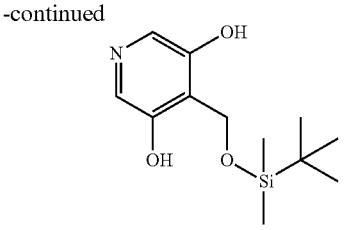
[0573] To a solution of (3,5-bis(benzyloxy)pyridin-4-yl) methanol (910 mg, 2.83 mmol) and imidazole (385 mg, 5.66 mmol) in DMF (10.0 mL) was added TBSCl (513 mg, 3.4 mmol) at it. The mixture was stirred at rt for 1 h and diluted with a mixture of water (10 mL) and EtOAc (40 mL). The organic layer was washed with $NH_4Cl_{(sat.)}$ solution and brine, dried over Na_2SO_4, concentrated, and purified on silica gel using 10% EtOAc hexanes as eluent to give 3,5-bis(benzyloxy)-4-((tert-butyldimethylsilyloxy)methyl) pyridine (728 mg, 59%) as an off-white solid. LRMS (M+H$^+$) m/z 436.3.

Step 5:

[0574]



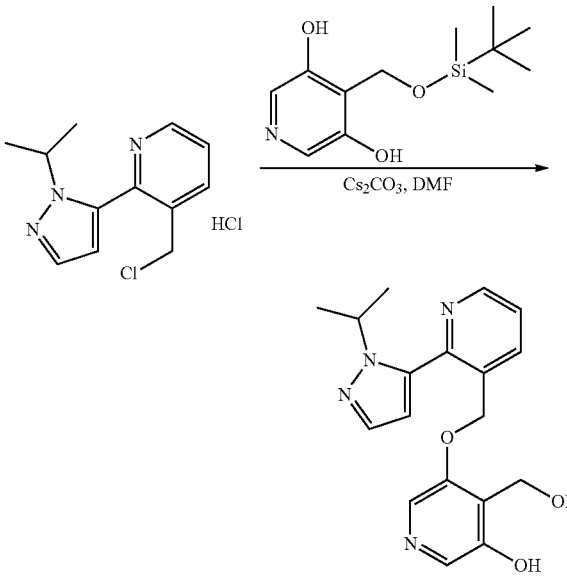
-continued



[0575] To 3,5-bis(benzyloxy)-4-((tert-butyldimethylsilyloxy)methyl)pyridine (720 mg, 1.66 mmol, 1 eq.) in a mixture of EtOAc/EtOH (5/2, 28 mL) was added Pd/C (400.0 mg). The mixture was charged with H_2 (60 psi), stirred at rt for 2 h. filtered, and concentrated to give 4-((tert-butyldimethylsilyloxy)methyl)pyridine-3,5-diol as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 2H), 4.91 (s, 2H), 0.73 (s, 9H), −0.00 (s, 6H). LRMS (M+H$^+$) m/z 256.1.

Step 6:

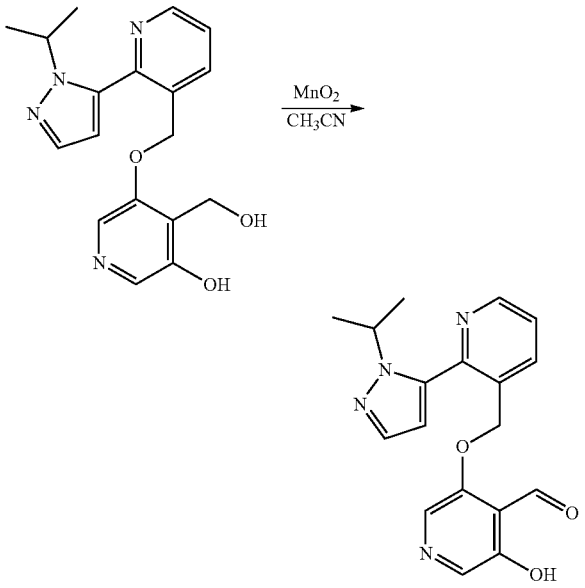
[0576]



[0577] A mixture of 4-((tert butyldimethylsilyloxy) methyl)pyridine-3,5-diol (100 mg, 0.39 mmol, 2 eq.) and Cs_2CO_3 (381 mg 1.17 mmol, 3 eq.) in DMF (15 mL) was stirred at rt for 30 min. To this mixture was added 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride (53 mg, 0.39 mmol, 1 eq.) at rt. The mixture was continued to stir at rt O/N, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 4-(hydroxymethyl)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)pyridin-3-ol (36 mg, 27%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dt, J=33.0, 16.5 Hz, 1H), 7.72 (d, J=1.6 Hz, 1H), 7.69 (s, 1H), 7.47 (s, 1H), 7.33 (s, 1H), 7.21 (dd, J=7.8, 4.8 Hz, 1H), 6.10 (d, J=1.8 Hz, 1H), 4.84 (s, 2H), 4.68 (s, 1H), 4.44 (sep. 6.6 Hz, 1H), 1.24 (d, J=6.6 Hz, 6H), LRMS (M+H$^+$) m/z 341.1

Step 7:

[0578]



[0579] To 4-(hydroxymethyl)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)pyridin-3-ol (26 mg, 0.076 mmol, 1 eq.) in CH_3CN (10 mL) was added MnO_2 (66 mg, 0.76 mmol, 10 eq.). The mixture was heated to 46° C. with stirring O/N, cooled to rt, filtered, and concentrated to give 3-hydroxy-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 11.06 (s, 1H), 10.35 (s, 1H), 8.70 (dd, J=4.7, 1.5 Hz, 1H), 8.11 (s, 1H), 7.89 (dd, J=7.9, 1.1 Hz, 1H), 7.80 (s, 1H), 7.53 (d, J=1.8 Hz, 1H), 7.36 (dd, J=7.9, 4.8 Hz, 1H), 6.27 (d, J=1.8 Hz, 1H), 5.14 (s, 2H), 4.61 (sep, J=6.6 Hz, 1H), 1.41 (d, J=6.6 Hz, 6H). LRMS ($M+H^+$) m/z 339.1

Example 80. Preparation of 3-(benzyloxy)-5-hydroxyisonicotinaldehyde (Compound 187)

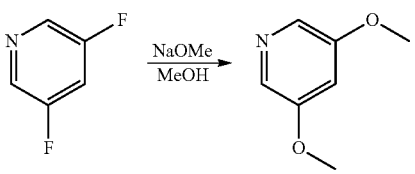
[0580] The title compound was prepared according to the procedure in Example 79.

[0581] ^1H NMR (400 MHz, $CDCl_3$) δ 11.08 (s, 1H), 10.41 (s, 1H), 8.08 (s, 1H), 7.99 (s, 1H), 7.39-7.28 (m, 5H), 5.18 (s, 2H).

Example 81. Preparation of 3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxyisonicotinaldehyde (Compound 188)

Step 1:

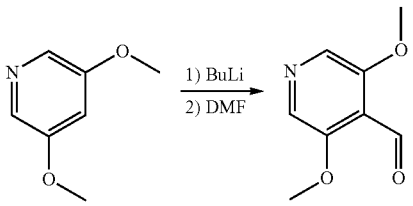
[0582]



[0583] To a solution of 3,5-difluoropyridine (5.4 g, 46.8 mmol, 1 eq.) in MeOH (45 mL) was added NaOMe (7.5 g, 140.4 mmol). The mixture was divided into three microwave tubes and individually heated at 135° C. for 1 h in a microwave reactor. The three tubes were combined, concentrated, and diluted with a mixture EtOAc (100 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude was re-dissolved in MeOH (45 mL) and added NaOMe (7.5 g, 140.4 mmol). The mixture was again divided into three microwave tubes and individually heated at 135° C. for 1 h in a microwave reactor. The three tubes were combined and concentrated. The crude was dissolved in a mixture of EtOAc (200 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 3,5-dimethoxypyridine (3.73 g, 57%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J=2.4 Hz, 2H), 6.76 (t, J=2.4 Hz, 1H), 3.88 (s, 6H). LRMS ($M+H^+$) m/z 140.1.

Step 2:

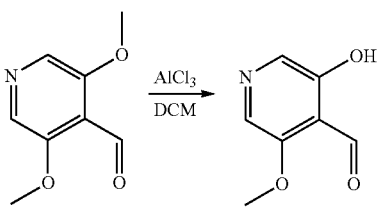
[0584]



[0585] To a solution of 3,5-dimethoxypyridine (3.6 g, 25.90 mmol, 1 eq.) in THF (80 mL) was added BuLi (3M/hexanes, 13.0 mL, 38.85 mmol, 1.5 eq.) at −20° C. The mixture was warmed to 0° C., stirred at 0° C. for 30 min, cooled back down to −78° C., and added DMF (3.8 g& 51.8 mmol, 2 eq.). The mixture was gradually warmed to 0° C., quenched with $NH_4Cl_{(sat.)}$ solution, and diluted with EtOAc. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 3,5-dimethoxyisonicotinaldehyde (2.7 g, 62%) as a yellow solid. LRMS ($M+H^+$) m/z 168.1.

Step 3:

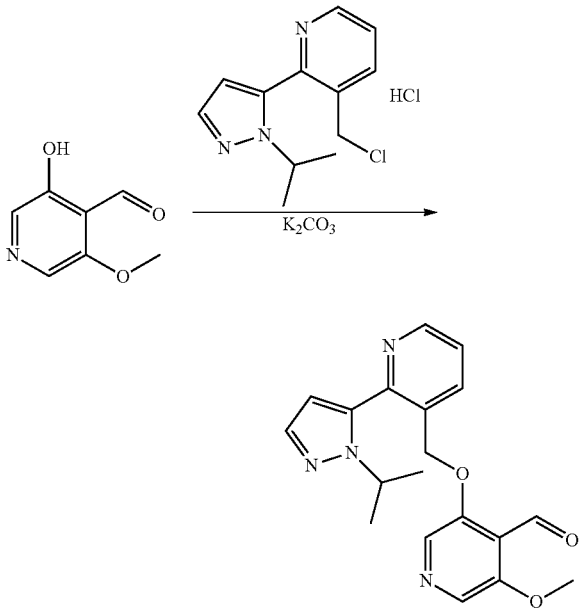
[0586]



[0587] To a solution of 3,5-dimethoxyisonicotinaldehyde (2.7 g, 16.16 mmol, 1 eq.) in DCM (100 mL) was added $AlCl_3$ (4.31 g, 32.32 mmol, 2.0 eq.) at rt. The mixture was reflux O/N, cooled to rt, and added into ice (200 g). The aqueous layer was extracted with DCM three times. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 3-hydroxy-5-methoxyisonicotinaldehyde (420 mg, 17%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 10.26 (s, 1H), 7.96 (s, 1H), 7.80 (s, 1H), 3.84 (s, 3H). LRMS ($M+H^+$) m/z 154.1.

Step 4:

[0588]

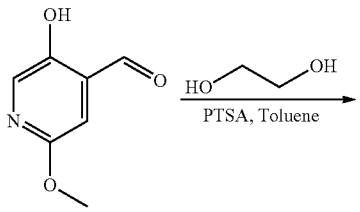


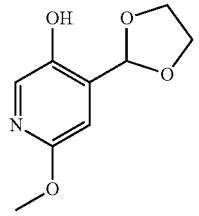
[0589] A mixture of 3-hydroxy-5-methoxyisonicotinaldehyde (30 mg, 0.20 mmol, 1 eq.), 3-(chlormethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride (54 mg, 0.20 mmol, 1 eq.), and K_2CO_3 (110 mg, 0.80 mmol, 4 eq.) in DMF (2.0 mL) was heated at 70° C. for 2 h. The mixture was cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes to give 3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxyisonicotinaldehyde (30 mg, 43%) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.65 (dd, J=4.7, 1.1 Hz, 1H), 8.13 (s, 1H), 8.11 (dd, J=7.9, 1.1 Hz, 1H), 7.96 (s, 1H), 7.54 (d, J=1.7 Hz, 1H), 7.37 (dd, J=7.9, 4.8 Hz, 1H), 6.29 (d, J=1.7 Hz, 1H), 5.11 (s, 2H), 4.55 (sep, J=6.6 Hz, 1H), 3.95 (s, 3H), 1.40 (d, J=6.6 Hz, 6H). LRMS ($M+H^+$) m/z 353.1.

Example 82. Preparation of 5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)methoxy)-2-methoxy-isonicotinaldehyde (Compound 189)

Step 1:

[0590]

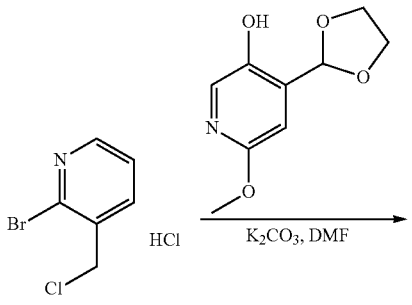




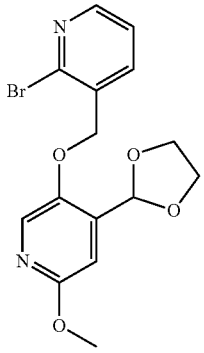
[0591] To S-hydroxy-2-methoxyisonicotinaldehyde (1.0 g, 6.54 mmol, 1.0 eq.) in toluene (50.0 mL) were added ethane-1,2-diol (10.0 mL) and PTSA (248 mg, 1.31 mmol, 0.2 eq.). The mixture was heated to reflux O/N, cooled to rt, neutralized to pH 8, and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give 4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-ol (980 mg, 76%) as an off-white solid. LRMS ($M+H^+$) m/z 198.1.

Step 2:

[0592]



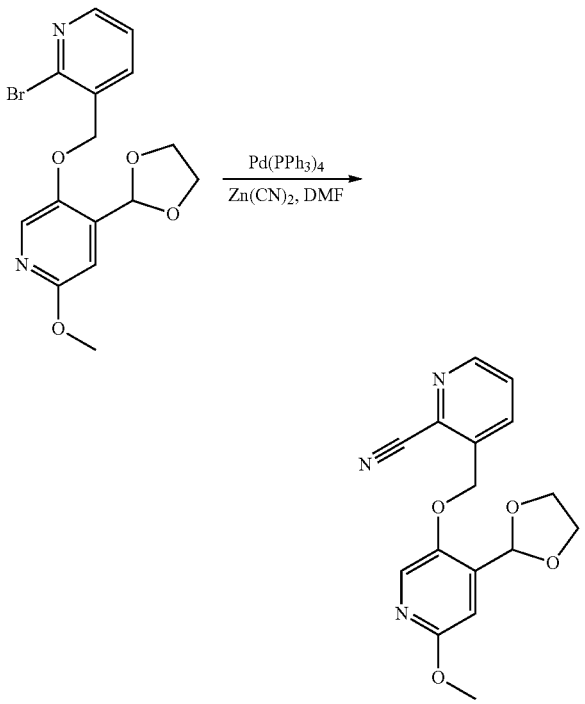
-continued



[0593] A mixture of 4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-ol (980 mg, 4.97 mmol, 1 eq.), 2-bromo-3-(chloromethyl)pyridine hydrochloride (1.2 g, 4.93 mmol, 1 eq.) and K_2CO_3 (2.7 g, 19.88 mmol, 4 eq.) in DMF (10.0 mL) was heated at 70° C. for 2 h. The mixture was cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 5-((2-bromopyridin-3-yl)methoxy)-4-(1,3-dioxolan-2-yl)-2-methoxypyridine (1.21 g, 66%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, J=4.7, 1.9 Hz, 1H), 7.83 (dd, J=7.6, 1.9 Hz, 1H), 7.74 (s, 1H), 7.25 (dd, J=7.6, 4.8 Hz, 1H), 6.86 (s, 1H), 6.10 (s, 1H), 5.09 (s, 2H), 4.07-3.93 (m, 4H), 3.82 (s, 3H). LRMS ($M+H^+$) m/z 367.0.

Step 3:

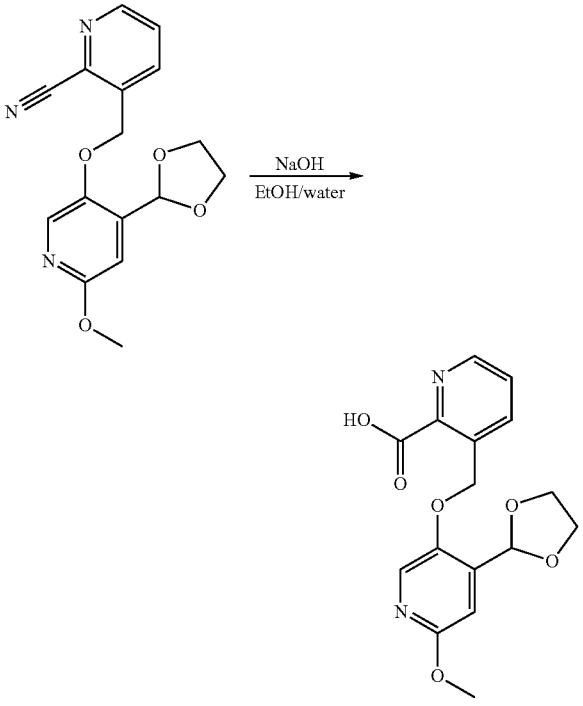
[0594]



[0595] A mixture of 5-((2-bromopyridin-3-yl)methoxy)-4-(1,3-dioxolan-2-yl)-2-methoxypyridine (1.1 g, 3.0 mmol, 1 eq.), Zn $(CN)_2$ (704 mg, 6.0 mmol, 2.0 eq.), and $Pd(PPh_3)$. (346 mg, 0.3 mmol, 0.2 eq.) in DMF (10 mL) was heated at 125° C. for 2 h under N_2. The mixture was cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)picolinonitrile (820 mg, 84%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J=4.6 Hz, 1H), 8.12 (dd, J=8.0, 0.7 Hz, 1H), 7.88 (s, 1H), 7.60 (dd, J=8.0, 4.7 Hz, 1H), 6.95 (s, 1H), 6.16 (s, 1H), 5.37 (s, 2H), 4.18-4.00 (m, 4H), 3.92 (s, 3H). LRMS ($M+H^+$) m/z 314.1.

Step 4:

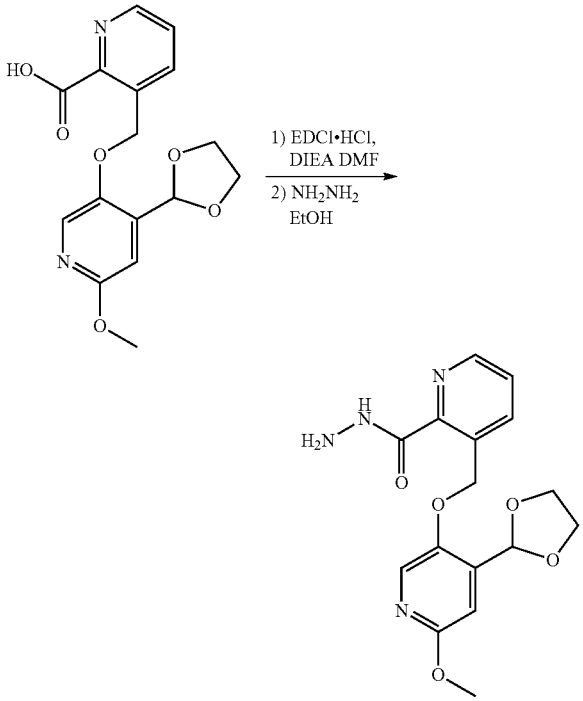
[0596]



[0597] To 3-((4-(1,3-dioxolan 2-yl)-6-methoxypyridin-3-yloxy)methyl)picolinonitrile (150 mg, 0.48 mol, 1 eq.) in a mixture of EtOH/water (5/1, 12 mL) was added NaOH (192 mg, 4.8 mmol, 10 eq.). The mixture was heated to reflux O/N, partially concentrated, added ice, and acidified to pH 3 with $HCl_{(conc.)}$. The solid was collected and dried to give 3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)picolinic acid (145 mg, 91%) as a white solid. ^{1}H NMR (400 MHz, MeOD) δ 8.38-8.48 (br, 1H), 8.28-8.35 (br, 1H), 7.76 (s, 1H), 7.50-7.70 (br, 1H), 6.81 (s, 1H), 6.04 (s, 1H), 5.50-5.64 (br, 2H), 4.03-3.87 (m, 3H), 3.75 (s, 3H). LRMS ($M+H^+$) m/z 333.0.

Step 5:

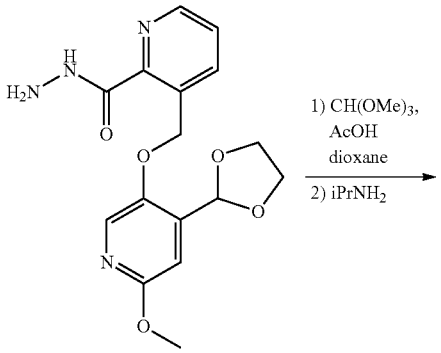
[0598]



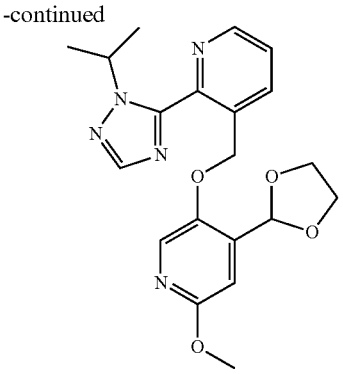
[0599] To a mixture of 3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)picolinic acid (145 mg, 0.44 mmol, 1 eq.) and EDCI.HCl (169 mg, 0.88 mmol, 2 eq.) in DMF (3.0 mL) was added DIEA (146 uL, 0.81 mmol, 2 eq.). The mixture was stirred at rt for 1 h and purified by RP-HPLC (Gemini 21.2×150 mm) using a mixture of CH_3CN and water to isolate the urea intermediate. The fractions were concentrated and dissolved in EtOH (5.0 mL). To this mixture was added hydrazine (0.5 mL) at it. The mixture was stirred at t for 1 h. partially concentrated, and diluted with water (10 mL). The solid was collected, washed with water, and dried to give 3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)picolinohydrazide (97 mg, 64% for two steps) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.51 (d, J=4.6 Hz, 1H), 8.24 (d, J=7.9 Hz, 1H), 7.85 (s, 1H), 7.51 (dd, J=8.0, 4.6 Hz, 1H), 6.95 (s, 1H), 6.24 (s, 1H), 5.80 (s, 2H), 4.20-4.06 (m, 4H), 3.90 (s, 3H). LRMS ($M+H^+$) m/z 347.1.

Step 6:

[0600]



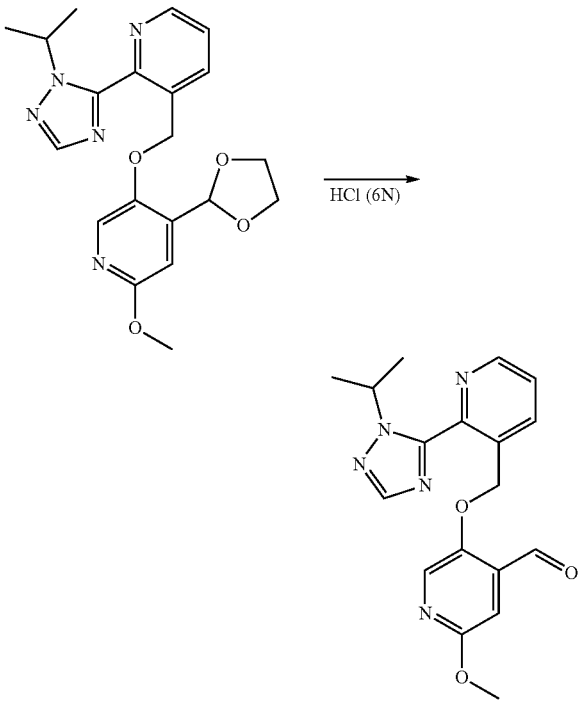
-continued



[0601] To a mixture of 3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)picolinohydrazide (90 mg, 0.26 mmol, 1 eq.) and AcOH (0.4 mL) in dioxane (2.0 mL) was added $CH(OMe)_3$ (0.4 mL). The mixture was sealed and heated at 110° C. for 1 h, cooled to rt, and added isopropyl amine (0.4 mL). The mixture was re-sealed, heated at 110° C. O/N, concentrated, and purified on RP-HPLC (Gemini 21.2×150 mm) using a mixture of CH_3CN and water as eluent to give 4-(1,3-dioxolan-2-yl)-5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)methoxy)-2-methoxypyridine (68 mg, 66%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J=4.7, 1.2 Hz, 1H), 8.41 (s, 1H), 8.24 (dd, J=8.0, 1.2 Hz, 1H), 7.76 (s, 1H), 7.45 (dd, J=8.0, 4.7 Hz, 1H), 6.90 (s, 1H), 6.17 (s, 1H), 5.61 (s, 2H), 5.30 (sep, J=6.7 Hz, 1H), 4.17-4.02 (m, 4H), 3.88 (s, 3H), 1.55 (d, J=6.7 Hz, 6H). LRMS ($M+H^+$) m/z 398.2.

Step 7:

[0602]

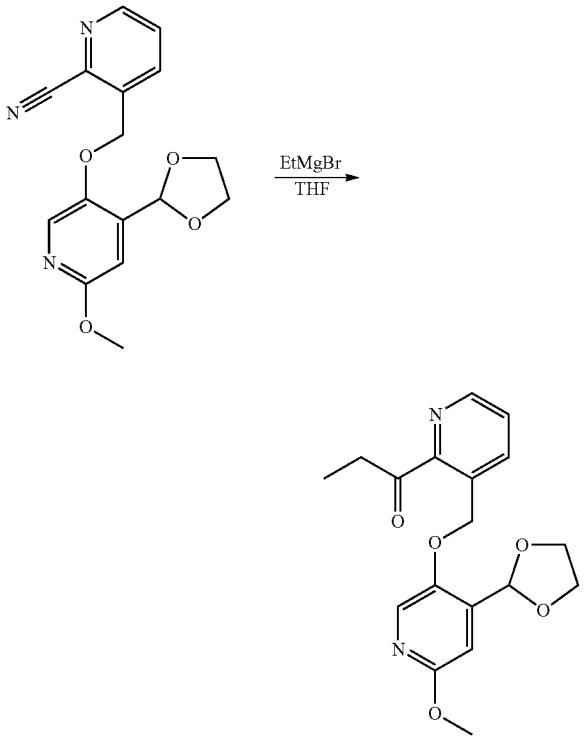


[0603] To 4-(1,3-dioxolan-2 yl)-5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)methoxy)-2-methoxypyridine (60 mg, 0.15 mmol, 1 eq.) in a RB flask was added HCl (6 N, 2.0 mL). The mixture was warmed to 40° C. O/N, cooled to rt, neutralized to pH 7-8 with $NaHCO_{3(sat)}$ solution, and extracted with EtOAc three times. The combined organic layers we washed with brine dried over Na_2SO_4, and concentrated to give 5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl) pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (52.2 mg, 99%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.62 (dd, J=4.6, 1.2 Hz, 1H), 8.33 (s, 1H), 8.11 (dd, J=8.0, 1.2 Hz, 1H), 7.98 (s, 1H), 7.40 (dd, J=8.0, 4.7 Hz, 1H), 6.99 (s, 1H), 5.62 (s, 2H), 5.28 (sep. J=6.7 Hz, 1H), 3.82 (s, 3H), 1.46 (d, J=6.7 Hz, 6H). LRMS ($M+H^+$) m/z 354.1.

Example 83. Preparation of 5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 190)

Step 1:

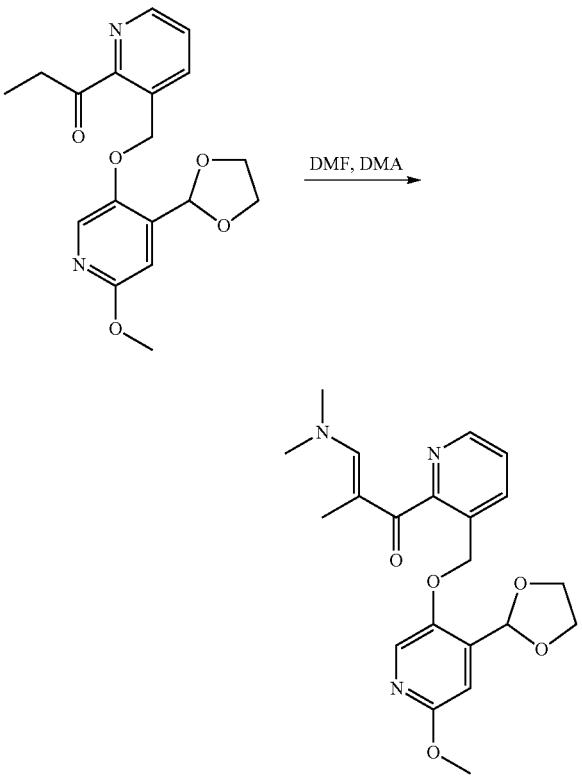
[0604]



[0605] Ethylmagnesium bromide (3M/ether, 1.53 mL, 4.60 mmol, 1.5 eq.) was added to a stirred solution of 3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy) methyl)picolinonitrile (960 mg, 3.01 mmol, 1 eq.) in THF (15.0 mL) at −78° C. After addition, the reaction mixture was allowed to warm to rt and quenched with aqueous citric acid solution. The aqueous layer was extracted with EtOAc (2×30 mL). The combined organic layers were washed with $NaHCO_{3(sat)}$ solution and brine, dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 1-(3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)propen-1-one (611 mg, 58%) as a colorless oil. LRMS ($M+H^+$) m/z 345.1.

Step 2:

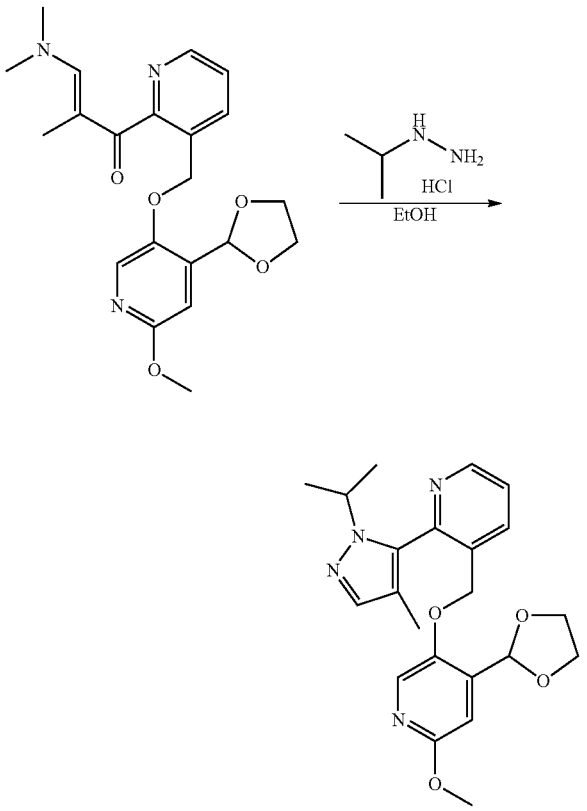
[0606]



[0607] 1-(3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)propan-1-one (600 mg, 1.74 mmol) in dimethoxy-N,N-dimethylmethanamine (10.0 mL) was heated to reflux O/N. The mixture was concentrated to give (E)-1-(3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-3-(dimethylamino)-2-methyl-prop-2-en-1-one, which was used for next step without further purification. LRMS ($M+H^+$) m/z 400.2.

Step 3:

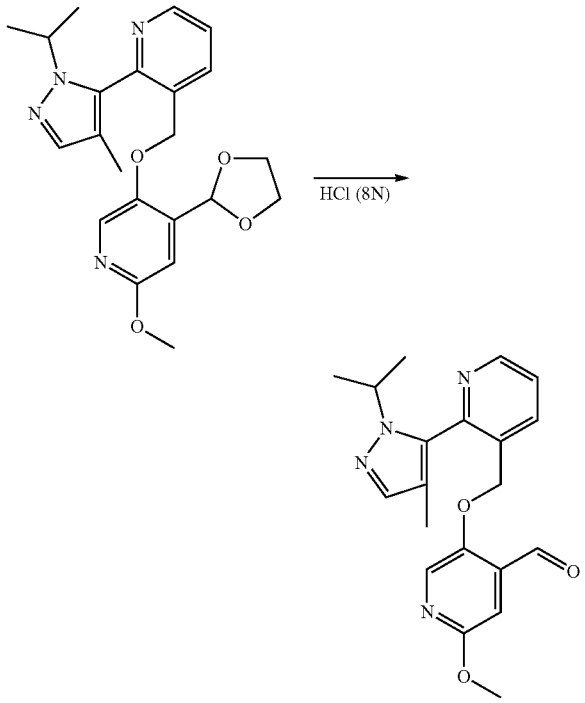
[0608]



[0609] To (E)-1-(3-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-3-(dimethylamino)-2-methylprop-2-en-1-one (crude, 230 mg, 0.58 mmol, 1 eq.) in EtOH (5 mL) was added isopropylhydrazine hydrochloride (128 mg, 1.16 mmol, 2 eq.) at rt. The mixture was heated at 80° C. for 2 h cooled to rt, concentrated, and diluted with a mixture of EtOAc (5 mL) and $NaHCO_{3(sat}$ (10.0 mL) solution. The layer were separated and aqueous layer was extracted with EtOAc throe times. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 4-(1,3-dioxolan 2-yl)-5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxypyridine (48 mg, 20% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, J=4.7, 1.4 Hz, 1H), 8.12 (d, J=8.1 Hz, 1H), 7.62 (s, 1H), 7.49-7.44 (m, 2H), 6.91 (s, 1H), 6.11 (s, 1H), 4.85-5.01 (m, 2H), 4.30-3.98 (m, 5H), 3.88 (s, 3H), 1.94 (s, 3M), 1.50 (d, J=6.7 Hz, 3H), 1.39 (d, J=6.7 Hz, 3H). LRMS ($M+H^+$) m/z 411.2.

Step 4:

[0610]



[0611] To 4-(1,3-dioxolan-2-yl)-5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxypyridine (41 mg, 0.1 mmol, 1 eq.) in a RB flask was added HCl (6 N, 2.0 mL). The mixture was warmed to 40° C. O/N, cooled to rt, neutralized to pH 7-8 with $NaHCO_{3(sat)}$ solution, and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (333 mg, 99%) as an pale-yellow oil ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.71 (dd, J=4.7, 1.6 Hz, 1H), 7.99 (dd, J=7.9, 1.5 Hz, 1H), 7.76 (s, 1H), 7.40 (dd, J=7.1, 4.7 Hz, 1H), 7.39 (s, 1H), 7.01 (s, 1H), 4.86-4.99 (m, 2H), 4.12 (sep, J=6.7, 1H), 3.82 (s, 3H), 1.86 (s, 3H), 1.40 (d, J=767 Hz, 3H), 1.29 (d, J=6.7 Hz, 3H). LRMS ($M+H^+$) m/z 367.1.

Example 84. Preparation of 5-((2-(1-((2-hydroxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde (Compound 191)

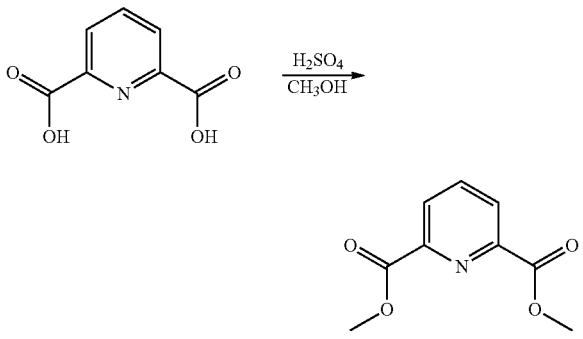
[0612] The title compound was prepared according to the procedure in Example 83.

[0613] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.50 (dd, J=4.8, 1.6 Hz, 1H), 7.89 (dd, J=7.9, 1.5 Hz, 1H), 7.72 (s, 1H), 7.42 (d, J=1.9 Hz, 1H), 7.27 (dd, J=7.9, 4.9 Hz, 1H), 6.90 (s, 1H), 6.26 (d, J=1.9 Hz, 1H), 5.34 (s, 1H), 5.04 (s, 2H), 4.24-4.16 (m 2H), 3.94-3.85 (m, 2H), 3.70 (s, 3H).

Example 85. Synthesis of 2,2,2-trifluoracetic acid: 6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid (1:1) (Compound 192)

Step 1:

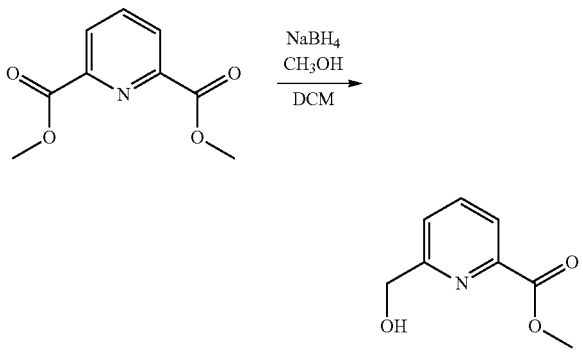
[0614]



[0615] Into a 25-mL round-bottom flask, was placed a solution of pyridine-2,6-dicarboxylic acid (1 g, 5.98 mmol, 1.00 equiv) in methanol (12.5 mL). Sulfuric acid (2.5 mL) was added to the reaction mixture. The resulting solution was stirred overnight at 70° C., and then it was quenched by the addition of 10 mL of water. The pH value of the solution was adjusted to 7 with sodium carbonate. The resulting solution was extracted with 2×25 mL of dichloromethane, and the combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 0.95 g (81%) of 2,6-dimethyl pyridine-2,6-dicarboxylate as a white solid

Step 2:

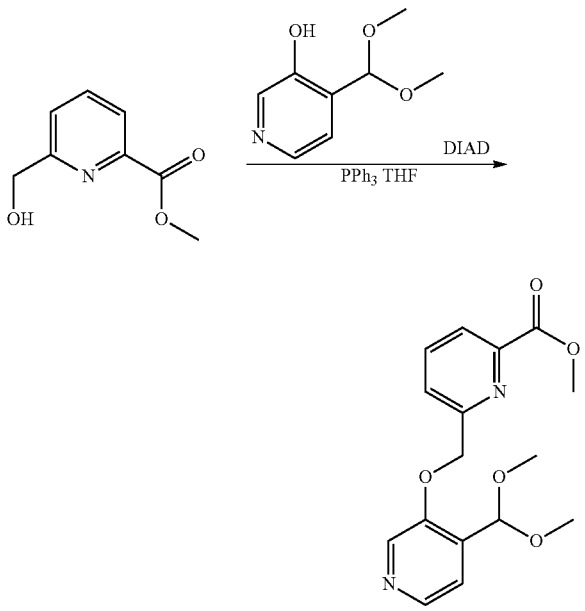
[0616]



[0617] Into a 100-mL round-bottom flask, was placed a solution of 2,6-dimethyl pyridine-2,6-dicarboxylate (950 mg, 4.87 mmol, 1.00 equiv) in a solvent mixture of methanol (33.2 mL) and dichloromethane (14.2 ml). $NaBH_4$ (185 mg, 5.02 mmol, 1.00 equiv) was added to the reaction mixture in several batches at 0° C. The resulting solution was stirred overnight at room temperature, and then it was quenched by the addition of 50 mL of NH_4Cl (aq.). The resulting solution was extracted with 2×50 mL of dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1-2:1) as eluent to yield 750 mg (92%) of methyl 6-(hydroxymethyl)pyridine-2-carboxylate as a white solid.

Step 3:

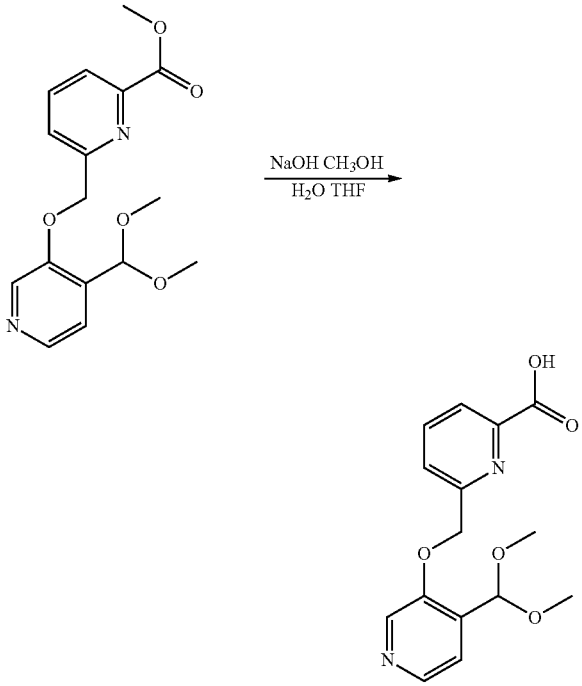
[0618]



[0619] Into a 50-mL round-bottom flask, which was purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl 6-(hydroxymethyl)pyridine-2-carboxylate (300 mg, 1.79 mmol, 1.00 equiv) in tetrahydrofuran (15 mL), 4-(Dimethoxymethyl)pyridin-3-ol (304.2 mg, 1.80 mmol, 1.00 equiv), and triphenylphosphane (615 mg, 2.34 mmol, 1.30 equiv) was added to the reaction mixture. This was followed by the addition of DIAD (473.1 mg, 2.34 mmol, 1.30 equiv) dropwise at 0° C. The resulting solution was stirred overnight at room temperature, and then it was quenched by the addition of 10 mL of water. The resulting solution was extracted with 2×50 mL of ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5-1:1) as eluent to yield 340 mg (60%) of methyl 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl)pyridino-2-carboxylate as a white solid.

Step 4:

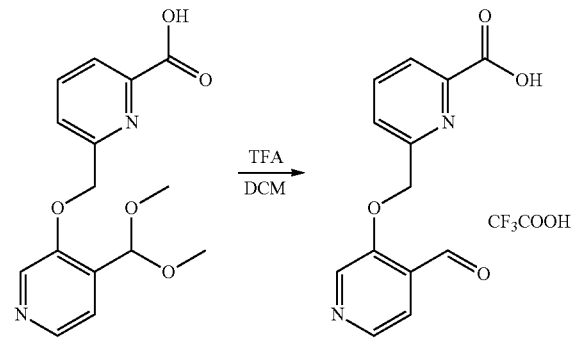
[0620]



[0621] Into a 100-mL round-bottom flask, was placed methyl 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl) pyridine-2-carboxylate (310 mg, 0.97 mmol, 1.00 equiv) and sodium hydroxide (117 mg, 2.93 mmol, 3.00 equiv) in a solvent mixture of methanol (10 mL), water (10 mL) and tetrahydrofuran (10 mL). The resulting solution was stirred overnight at room temperature. The pH value of the solution was adjusted to 4-5 with hydrogen chloride (1 mol/L). The resulting solution was extracted with 3×20 mL of isopropal/DCM(1/3) and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 230 mg (78%) of 6-([[4-(dimethoxymethyl) pyridin-3-yl]oxy]methyl)pyridine-2-carboxylic acid as a white solid.

Step 5:

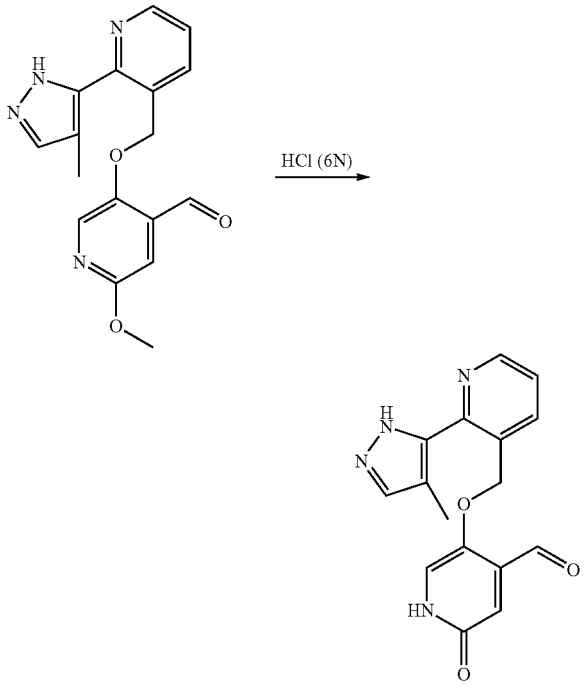
[0622]



[0623] Into an 8-mL sealed tube, was placed a solution of 6-(([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl)pyridine-2-carboxylic acid (150 mg, 0.49 mmol, 1.00 equiv) in dichloromethane (4 mL) and trifluoroacetic acid (2 mL). The resulting solution was stirred for 3.5 h at 45° C. in an oil bath. The resulting mixture was concentrated under vacuum. The crude product (100 mg) was purified by Prep-HPLC with the following conditions (2#-Analyse HPLC-SHIMADZU(HPLC-10)): Column, SunFire Prep C18 OBD Column, 5 um, 19*150 mm; mobile phase, water with 0.05% TFA and MeCN (10% MeCN up to 35% in 4 min, up to 100% in 1 min, down to 10% in 1 min); Detector, Waters2545 UvDector 254&220 nm. This resulted in 49 mg (38%) of 6-[[(4-formylpyridin-3-yl)oxy]methyl]pyridine-2-carboxylic acid as a light yellow solid. LC-MS-PH-GBT-ZL-HS-19-0 (ES, m/z): 259 $[M+1]^+$ H-NMR-PH-GBT-ZL-HS-19-0 (300 MHz, DMSO, ppm): 10.52 (s, 1H), 8.92 (s, 1H), 8.52 (d, J=4.8 Hz, 1H), 8.09 (m, 2H), 7.95 (m, 1H), 7.76 (d, J=4.8 Hz, 1H), 5.61 (s, 2H).

Example 86 Preparation of 5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (Compound 194)

[0624]



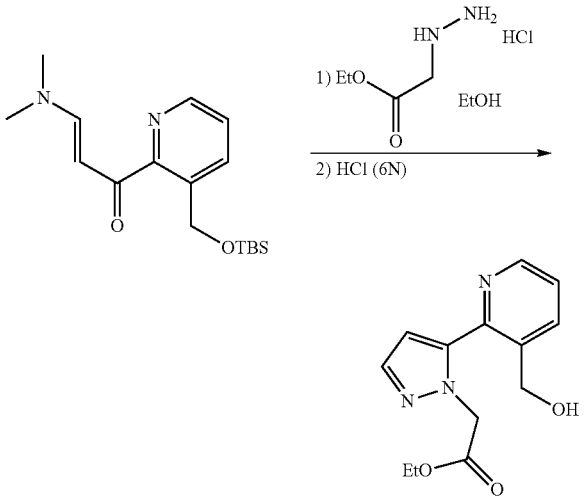
[0625] To 2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl) pyridin-3-yl)methoxy)isonicotinaldehyde (862 mg, 2.66 mmol, 1 equiv) suspended in water (5.0 mL) was added HCl (6 N, 4.43 mL, 26.6 mmol, 10 eq.). Once the mixture turned into a homogeneous solution, it was freeze at −78° C. to an solid and pump under high vaccum O/N. The yellow solid was continued to pump at 45° C. for 20 h. dissolved in water

(2.0 mL), and basified to pH 11 with NaOH (2 N). The aqueous layer was washed with DCM three times and the pH of the mixture was adjusted to pH 6-7. The solid was collected and dried to give 5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde (180 mg, 44% based on 50% recovered of SM) as a white solid. ^{1}H NMR (400 MHz, DMSO at 90° C.) δ 10.14 (s, 1H), 8.63 (s, 1H), 8.09-8.03 (br, 1H), 7.56-7.50 (br, 2H), 7.42-7.35 (br, 1H), 6.70 (s, 1H), 5.39 (s, 2H), 2.18 (s, 3H). LRMS (M+H$^+$) m/z 311.1.

Example 87. Preparation of 2-(5-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetic acid (Compound 199)

Step 1

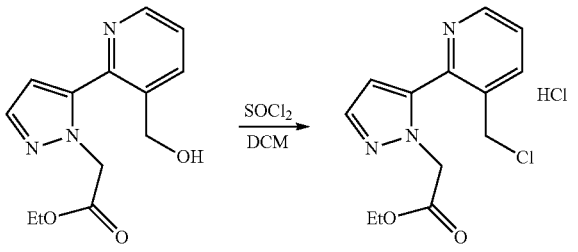
[0626]



[0627] To (E)-1-(3-((tert-butyldimethylsilyloxy)methyl) pyridin-2-yl)-(dimethyl)pyridin-2-yl)-3-dimethylamino) prop-2-en-1-one (crude, 350 mg, 1.09 mmol, 1 eq.) in EtOH (10 mL) was added ethyl 2-hydrazinylacetate hydrochloride (338 mg, 2.18 mmol, 2.0 eq.). The mixture was heated at 80° C. for 2 h, cooled to rt, added HCl (6 N, 0.5 mL), and stirred O/N. The mixture was concentrated, and diluted with a mixture of EtOAc (50 mL) and $NaHCO_{3(sat)}$ (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, concentrated, and purified on silica gel using EtOAc as eluent to give ethyl 2-(5-(3-(hydroxymethyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetate (212 mg, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (dd, J=4.7, 1.6 Hz, 1H), 7.97 (dd, J=7.8, 1.4 Hz, 1H), 7.64 (d, J=1.9 Hz, 1H), 7.36 (dd, J=7.8, 4.8 Hz, 1H), 6.56 (d, J=1.9 Hz, 1H), 5.21 (s, 2H), 4.79 (d, J=5.8 Hz, 2H), 4.09 (q, J=7.1 Hz, 2H), 2.54 (t, J=6.0 Hz, 1H), 1.18 (t, J=7.1 Hz, 3H). LRMS (M+H$^+$) m/z 262.1

Step 2

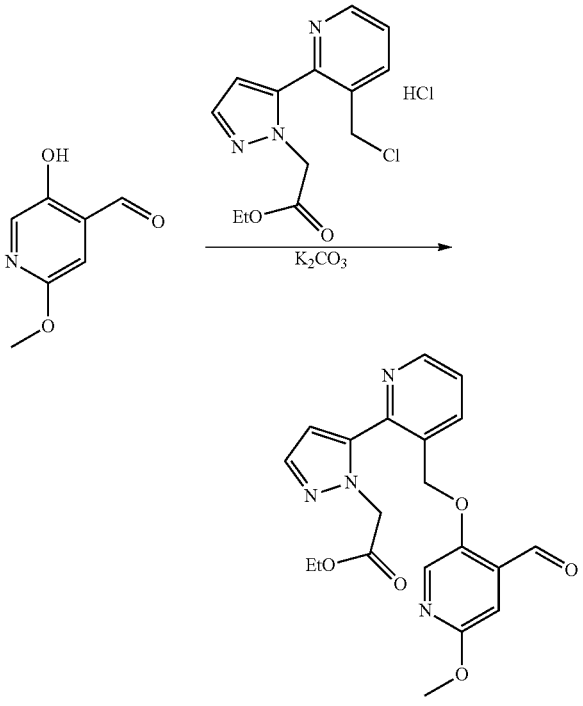
[0628]



[0629] To ethyl 2-(5-(3-(hydroxymethyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetate (182 mg, 0.70 mmol) in DCM (10 mL) was added $SOCl_2$ (3.0 mL) at rt. The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give ethyl 2-(5-(3-(chloromethyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetate hydrochloride (220 mg) as an off-white solid, which was used for next step without further purification.

Step 3

[0630]

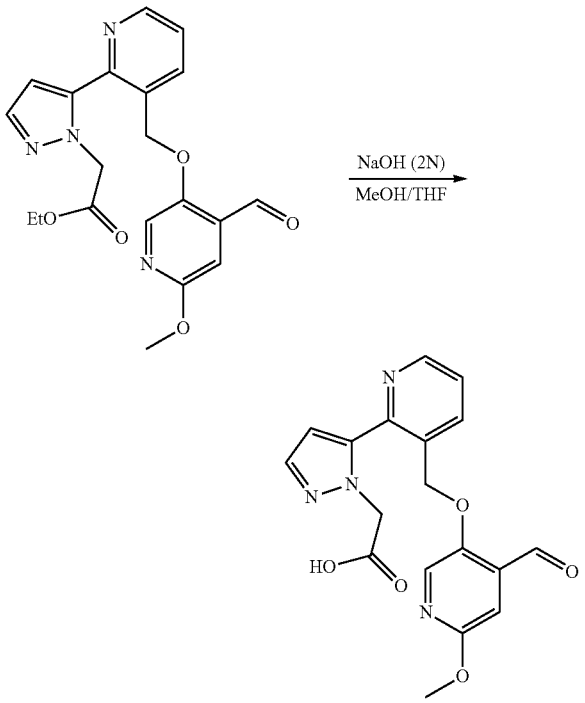


[0631] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (107 mg, 0.70 mmol, 1 eq.), ethyl 2-(5-(3-(chloromethyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetate hydrochloride (220 mg, 0.70 mmol, 1 eq.), and K_2CO_3 (386 mg, 2.8 mmol, 4 eq.) in DMF (6.0 mL) was heated at 70° C. for 2 h. The mixture was cooled, filtered, concentrated, and purified on

silica gel using a mixture of EtOAc and hexanes as eluent to give ethyl 2-(5-(3-((4-formyl-6-methoxypyridin-3-yloxy) methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetate (261 mg, 94%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.69 (d, J, 3.8 Hz, 1H), 8.02 (s, 1H), 8.01 (d, J=7.5 Hz, 1H), 7.63 (d, J=1.6 Hz, 1H), 7.40 (dd, J=7.6, 4.0 Hz, 1H), 7.13 (s, 1H), 6.53 (d, J=1.6 Hz, 1H), 5.30 (s, 2H), 5.28 (s, 2H), 4.12 (q, J=7.1 Hz, 2H), 3.93 (s, 3H), 1.18 (t, J=7.1 Hz, 3H). LRMS ($M+H^+$) m/z 397.1.

Step 4

[0632]



[0633] To ethyl 2-(5-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetate (182 mg, 0.46 mmol, 1 eq.) in a mixture of MeOH/THF (1/5, 12.0 mL) was added NaOH (2N, 2.3 mL, 4.6 mmol, 10 eq.). The mixture was stirred at rt for 2 h, acidified to pH 3, and extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give 2-(5-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetic acid (135.1 mg, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.71 (d, J=4.7 Hz, 1H), 8.13 (d, J=7.8 Hz, 1H), 7.97 (s, 1H), 7.66 (d, J=1.6 Hz, 1H), 7.52 (dd, J=7.9, 4.9 Hz, 1H), 7.13 (s, 1H), 6.56 (d, J=1.7 Hz, 1H), 5.31 (s, 2H), 5.14 (s, 2H), 3.91 (s, 3H). LRMS ($M+H^+$) m/z 369.1.

[0634] Examples 88 and 89 were prepared according to example 87 above.

Example 88. Preparation of methyl 3-(5-(3-(((4-formyl-6-methoxypyridin-3-2)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate (Compound 200)

[0635] ^{1}H NMR (400 MHz, CDCl3) δ 10.44 (s, 1H), 8.75 (dd, J=4.8, 1.6 Hz, 1H), 8.05 (dd, J=7.9, 1.4 Hz, 1H), 7.99 (s, 1H), 7.58 (d, J=1.9 Hz, 1H), 7.44 (dd, J=7.9, 4.8 Hz, 1H), 7.12 (s, 1H), 6.41 (d, J=1.9 Hz, 1H), 5.21 (s, 2H), 4.55 (t, J=7.1 Hz, 2H), 3.92 (s, 3H), 3.62 (s, 3H), 3.00 (t, J=7.1 Hz, 2H).

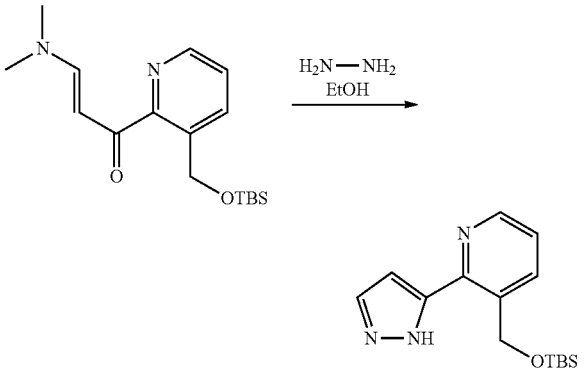
Example 89. Preparation of 3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid (Compound 202)

[0636] ^{1}H NMR (400 MHz, CDCl3) δ 10.33 (s, 1H), 8.66 (dd, J=4.8, 1.6 Hz, 1H), 7.96 (dd, J=7.9, 1.5 Hz, 1H), 7.83 (s, 1H), 7.53 (d, J=1.9 Hz, 1H), 7.37 (dd, J=7.9, 4.8 Hz, 1H), 7.02 (s, 1H), 6.33 (d, J=1.9 Hz, 1H), 5.13 (s, 2H), 4.49 (t, J=6.5 Hz, 2H), 3.81 (s, 3H), 2.94 (t, J=6.5 Hz, 2H).

Example 90. Preparation of 3-(3-(3-((4 formyl-6-methoxypyridin-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid (Compound 201)

Step 1

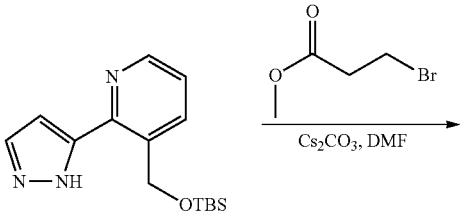
[0637]



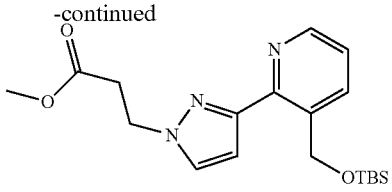
[0638] To (E)-1-(3-((tert-butyldimethylsilyloxy)methyl) pyridin-2-yl)-3-(dimethylamino)prop-2-en-1-one (crude, 350 mg, 1.09 mmol, 1 eq.) in EtOH (5 mL) was added hydrazine (140 mg, 4.36 mmol, 4 eq.). The mixture was heated at 80° C. for 2 h, cooled, concentrated, and purified on silica gel using EtOAc as eluent to give 3-((tort-butyldimethylsilyloxy)methyl)-2-(1H-pyrazol-5-yl)pyridine (232 mg, 90%) as a white solid. LRMS ($M+H^+$) m/z 290.1

Step 2

[0639]



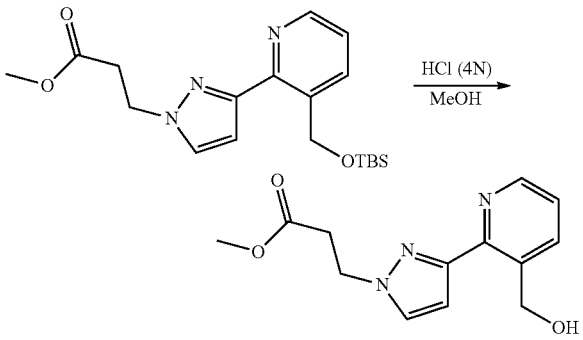
-continued



[0640] To a mixture of 3-((tert-butyldimethylsilyloxy) methyl)-2-(1H-pyrazol-5-yl)pyridine (140 mg, 0.48 mmol, 1 eq.) and Cs_2CO_3 (312 mg, 0.96 mmol, 2 eq.) in DMF (3 mL) was added methyl 3-bromopropanoate (122 mg, 0.73 mmol, 1.5 eq.). The mixture was stirred at rt for 6 h, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give methyl 3-(3-(3-((tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate (110 mg, 61%). LRMS ($M+H^+$) m/z 376.1.

Step 3

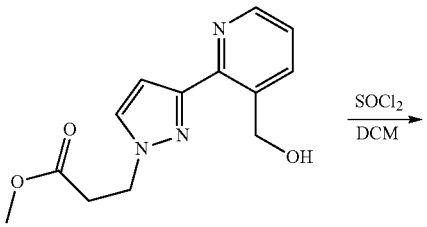
[0641]



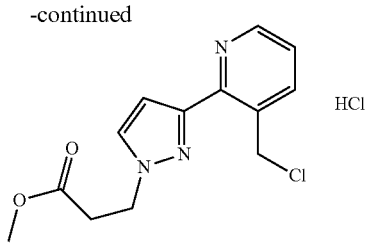
[0642] To methyl 3-(3-(3-((tert-butyldimethylsilyloxy) methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate in MeOH (10 mL) was added HCl (2 N, 1.2 mL, 10 eq.). The mixture was stirred at rt for 4 h, concentrated, neutralized to pH 7-8 with $NaHCO_{3(sat)}$ solution, and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated, and purified on silica gel using EtOAc as eluent to give methyl 3-(3-(3-(hydroxymethyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate (51 mg, 67%) as an oil. LRMS ($M+H^+$) m/z 262.1.

Step 4

[0643]



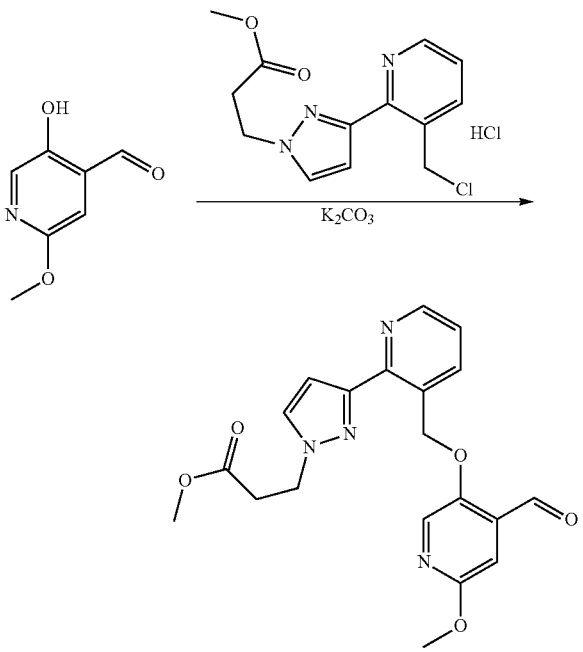
-continued



[0644] To methyl 3-(3-(3-(hydroxymethyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate (51 mg, 0.20 mmol) in DCM (5 mL) was added $SOCl_2$ (1.0 mL) at rt. The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give methyl 3-(3-(3-(chloromethyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate hydrochloride (63 mg) as an off-white solid, which was used for next step without further purification.

Step 5

[0645]

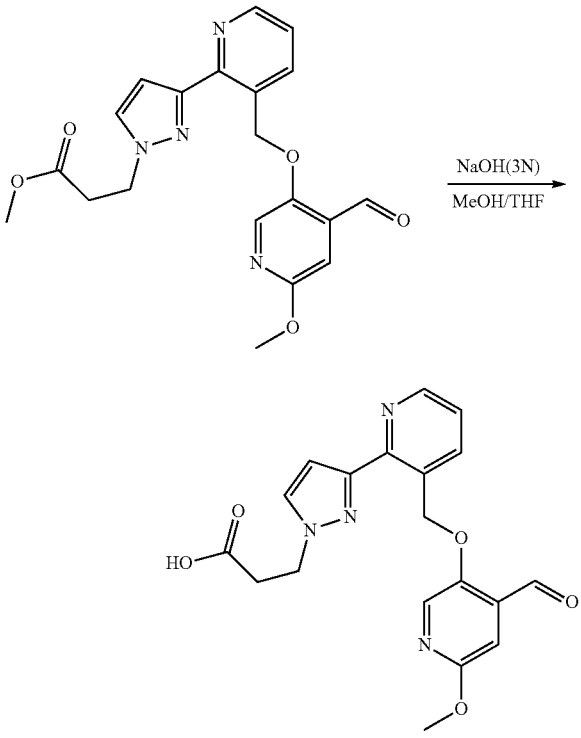


[0646] A mixture of 5-hydroxy-2-methoxyisonicotinaldehyde (30 mg, 0.20 mmol, 1 eq.), methyl 3-(3-(3-(chloromethyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate hydrochloride (63 mg, 0.20 mmol, 1 eq.), and K_2CO_3 (100 mg, 10.32 mmol, 4 eq.) in DMF (5.0 mL) was heated at 70° C. for 2 h. The mixture was cooled, filtered, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give methyl 3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin 2-yl)-1H-pyrazol-1-yl)propanoate

(88 mg, quantitative yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.65 (dd, J=4.7, 0.9 Hz, 1H), 8.09 (s, 1H), 8.02 (dd, J=7.8, 0.8 Hz, 1H), 7.53 (d, J=2.3 Hz, 1H), 7.31 (dd, J=7.9, 4.8 Hz, 1H), 7.12 (s, 1H), 6.96 (d, J=2.3 Hz, 1H), 5.71 (s, 2H), 4.46 (t, J=6.6 Hz, 2H), 3.93 (s, 3H), 3.69 (s, 3H), 2.91 (t, J=6.6 Hz, 2H). LRMS ($M+H^+$) m/z 397.1.

Step 6

[0647]

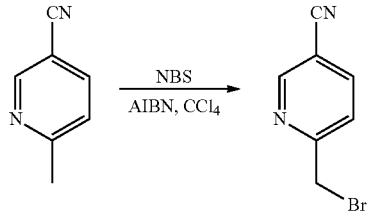


[0648] To methyl 3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate (72 mg, 0.18 mmol, 1 eq.) in a mixture of MeOH/THF (1/6, 6.0 mL) was added NaOH (3 N, 0.6 mL, 1.8 mmol, 10 eq.). The mixture was stirred at rt for 2 h, acidified to pH 3, extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give 3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propenoic acid (53.4 mg, 78%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.57 (d, J=4.6 Hz, 1H), 8.08 (s, 1H), 7.95 (d, J=7.8 Hz, 1H), 7.46 (d, J=2.3 Hz, 1H), 7.23 (dd, J=7.9, 4.6 Hz, 1H), 7.03 (s, 1H), 6.85 (d, J=2.3 Hz, 1H), 5.64 (s, 2H), 4.42 (t, J=6.1 Hz, 2H), 3.83 (s, 3H), 2.86 (t, J=6.1 Hz, 21). LRMS ($M+H^+$) m/z 383.1.

Example 91. Preparation of 6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinonitrile 2,2,2-trifluoroacetate (Compound 204)

Step 1:

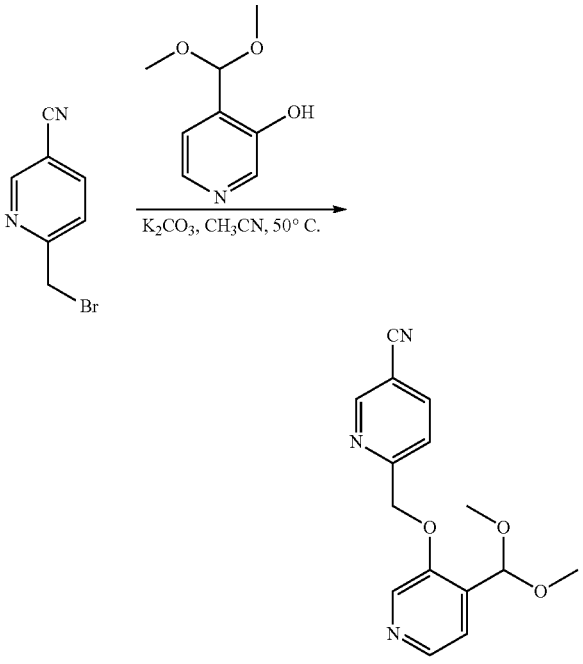
[0649]



[0650] Into a 250-mL round-bottom flask, was placed a solution of 6-methylpyridine-3-carbonitrile (8 g, 67.72 mmol, 1.00 equiv) in CCl4 (125 mL). N-Bromosuccinimide (13.4 g, 75.29 mmol, 1.10 equiv), and AIBN (480 mg, 2.92 mmol, 0.04 equiv) were added to the reaction solution. The resulting solution was stirred for 5 h at 85° C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5) as eluent to yield 5 g (37%) of 6-(bromomethyl) pyridine-3-carbonitrile as a beige solid.

Step 2:

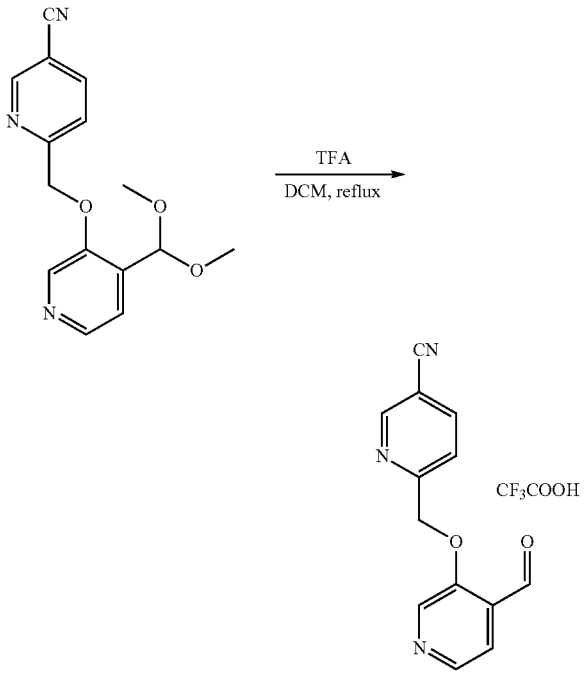
[0651]



[0652] Into a 250-mL round-bottom flask, was placed a solution of 6-(bromomethyl)pyridine-3-carbonitrile (3 g, 15.23 mmol, 1.00 equiv) in CH3CN (100 mL). Potassium carbonate (4.24 g, 30.68 mmol, 2.00 equiv) and 4-(dimethoxymethyl)pyridin-3-ol (2.83 g, 16.73 mmol, 1.10 equiv) were added to the reaction mixture. The resulting solution was stirred for 2 h at 50° C., and then it was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:3) as eluent to furnish 1.4 g (32%) of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl)pyridine-3-carbonitrile as a red solid.

Step 2:

[0653]



[0654] Into an 8-mL vial, was placed a solution of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl)pyridine-3-carbonitrile (100 mg, 0.35 mmol, 1.00 equiv) in a mixture of dichloromethane (2 mL) and trifluoroacetic acid (1 mL). The resulting solution was stirred for 5 h at 45° C., and then it was concentrated under vacuum. The crude product (50 mg) was purified by Prep-HPLC with the following conditions (Prep-HPLC-010): Column, SunFire Prep C18 OBD Column, 5 um, 19*150 mm; mobile phase, Water and MeCN (10.0% MeCN up to 40.0% in 3 min, up to 100.0% in 2 min, down to 10.0% in 1 min); Detector, Waters2545 UvDector 254&220 nm. This resulted in 8 mg (10%) of 6-[[(4-formylpyridin-3-yl)oxy]methyl]pyridine-3-carbonitrile as a white solid. LC-MS-PH-GBT-ZL-HS-13-0: (ES, m/z): 258 [M+1+18]+. H-NMR-PH-GBT-ZL-HS-13-0: (300 MHz, DMSO, ppm): 10.48 (s, 1H), 9.06 (s, 1H), 8.80 (s, 1H), 8.47 (m, 2H), 7.94 (d, J=8.1 Hz, 1H), 7.65 (d, J=5.1 Hz, 1H), 5.69 (s, 2H).

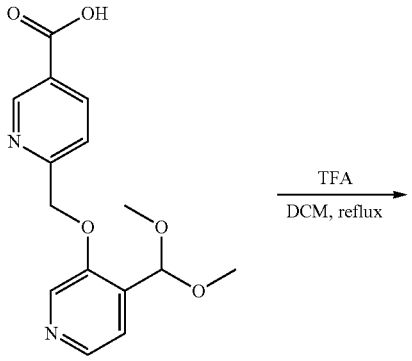
Example 92. Preparation of 6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid hydrochloride (Compound 205)

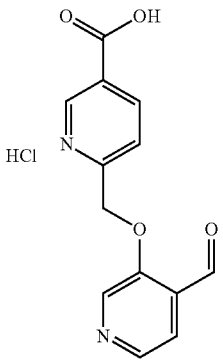
Step 1:

[0655] Into a 100-mL round-bottom flask, was placed a solution of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl)pyridine-3-carbonitrile (1 g, 3.51 mmol, 1.00 equiv) in water (30 mL). Sodium hydroxide (1.4 g, 35.00 mmol, 10.00 equiv) was added to the reaction. The resulting solution was stirred for 4 h at 90° C. The pH value of the solution was adjusted to 4-5 with hydrogen chloride (aq. 3 mol/L). The resulting solution was extracted with 3×200 ml of ethyl acetate. The aqueous layer was extracted again with 3×200 ml of tetrahydrofuran. The combined organic layers were concentrated under vacuum. This resulted in 1 g (94%) of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl)pyridine-3-carboxylic acid as a yellow solid.

Step 2:

[0656]



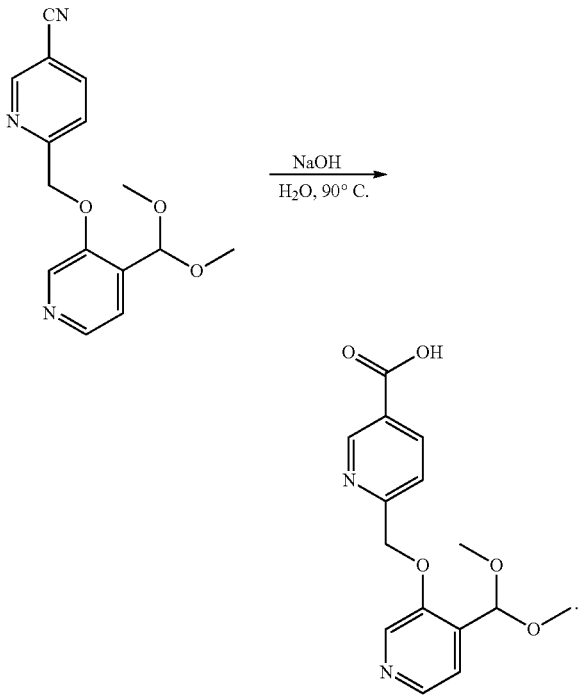


[0657] Into an 8-mL vial, was placed a solution of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl)pyridine-3-carboxylic acid (100 mg, 0.33 mmol, 1.00 equiv) in a solvent mixture of dichloromethane (2 mL) and trifluoroacetic acid (1 mL). The resulting solution was stirred for 3 h at 40° C., and then it was concentrated under vacuum. The crude product (70 mg) was purified by Prep-HPLC with the following conditions (Prep-HPLC-010): Column, SunFire Prep C18 OBD Column, 5 um, 19*150 mm; mobile phase, water (0.05% HCl) and MeCN (10.0% MeCN up to 40.0% in 3 min, up to 100.0% in 2 min, down to 10.0% in 1 min); Detector, Waters2545 UvDector 254&220 nm. This resulted in 30 mg (31%) of 6-[[(4-formylpyridin-3-yl)oxy]methyl] pyridine-3-carboxylic acid hydrochloride as a white solid. The compound exhibited a melting point of 192-194. LC-MS-PH-GBT-ZL-HS-14-0: (ES, m/z): 259 $[M+1]^+$/277 $[M+1+18]^+$. H-NMR-PH-GBT-ZL-HS-14-0: (300 MHz, DMSO, ppm): 13.42 (s, 1H), 10.48 (s, 1H), 9.03 (s, 1H), 8.74 (s, 1H), 8.40 (d, J=4.8 Hz, 1H), 8.30 (dd, J=8.1 Hz, 1H), 7.80 (d, J=8.7 Hz, 1H), 7.57 (d, J=4.8 Hz, 1H), 5.55 (s, 2H).

Example 93. Preparation of 2,2,2-trifluoroacetic acid: 6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide (2:1) (Compound 206)

Step 1:

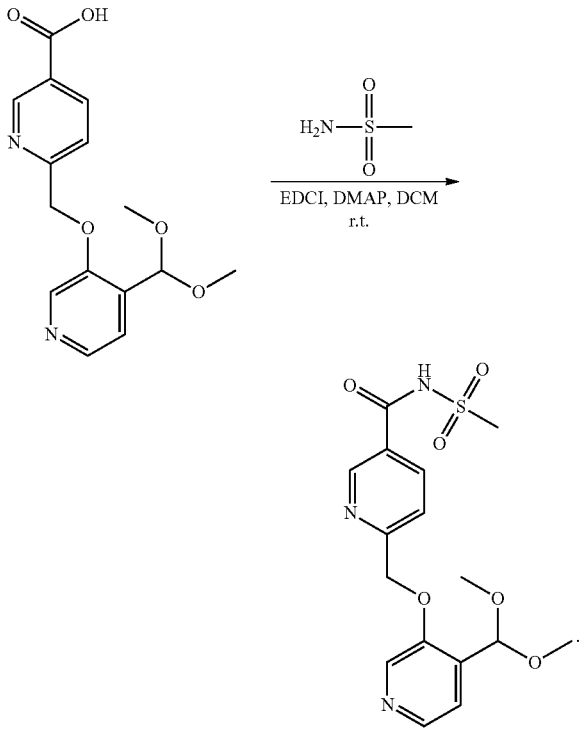
[0658]



[0659] Into a 100-mL round-bottom flask, was placed a solution of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy] methyl)pyridine-3-carbonitrile (1 g, 3.51 mmol, 1.00 equiv) and sodium hydroxide (1.4 g, 35.00 mmol, 10.00 equiv) in water (30 mL). The resulting solution was stirred for 4 h at 90° C. The pH value of the solution was adjusted to 4-5 with hydrogen chloride (3 mol/L). The resulting solution was extracted with 3×200 mL of ethyl acetate and 3×200 ml of tetrahydrofuran. The combined organic layers were concentrated under vacuum. This resulted in 1 g (94%) of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy]methyl)pyridine-3-carboxylic acid as a yellow solid.

Step 2.

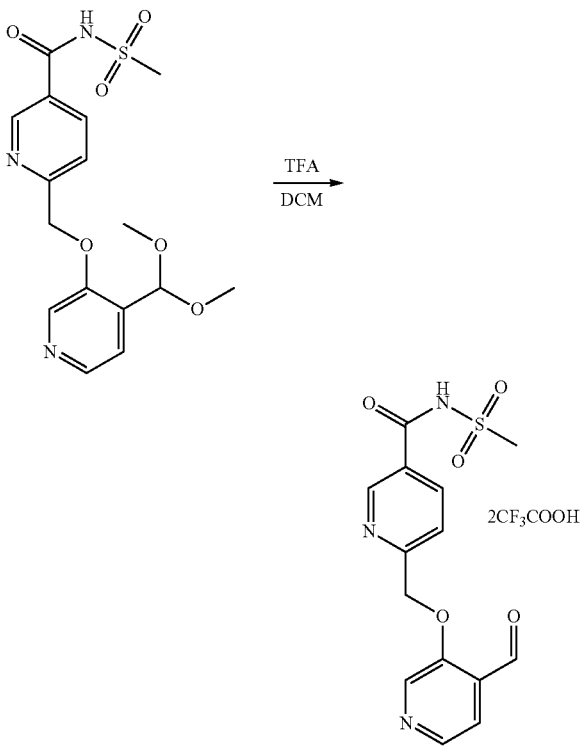
[0660]



[0661] Into a 100-mL round-bottom flask, was placed a solution of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy] methyl)pyridine-3-carboxylic acid (200 mg, 0.66 mmol, 1.00 equiv) in dichloromethane (30 mL). EDCI (190 mg, 0.99 mmol, 1.50 equiv), 4-dimethylaminopyridine (120 mg, 0.98 mmol, 1.50 equiv), and methanesulfonamide (80 mg, 0.84 mmol, 1.20 equiv) were added to the reaction mixture. The resulting solution was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with MeOH:DCM (1:10) as eluent. This resulted in 200 mg (80%) of 6-([[4-(dimethoxymethyl)pyridin-3-yl]oxy] methyl)-N-methanesulfonylpyridine-3-carboxamide as a yellow solid.

Step 3:

[0662]



[0663] Into a 50-mL round-bottom flask, which was purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 6-([4-(dimethoxymethyl)pyridin-3-yl)oxy]methyl)-N-methanesulfonylpyridine-3-carboxamide (80 mg, 0.21 mmol, 1.00 equiv) in dichloromethane (5 mL), and trifluoroacetic acid (2 mL). The resulting solution was stirred for 3 h at 40'C in an oil bath, and then it was concentrated under vacuum. The crude product (60 mg) was purified by Flash-Prep-HPLC with the following conditions (CombiFlash-1): Column, CIS silica gel; mobile phase, CH_3CN/H_2O=1/99 increasing to CH_3CN/H_2O=40/60 within 20 min; Detector, UV 254 nm. This resulted in 20 mg (17%) of 6-[[(4-formylpyridin-3-yl)oxy]methyl]-N-methanesulfonylpyridine-3-carboxamide; bis(trifluoroacetic acid) as a white solid. The compound exhibited a melting point of 102-104° C. LC-MS: (ES, m/z): 336 [M+1]+/354 [M+1+18]+. H-NMR (300 MHz, DMSO, ppm): 10.53 (s, 1H), 9.07 (s, 1H), 8.78 (s, 1H), 8.43 (d, J=4.5 Hz, 1H), 8.36 (dd, J=8.1 Hz, 1H), 7.84 (d, J=8.4 Hz, 1H), 7.62 (d, J=4.5 Hz, 1H), 5.60 (s, 2H), 337 (s, 3H).

Example 94. Preparation of Substituted Isonicotinaldehydes

[0664] Compounds 207-217 were prepared according to the methods described above.

[0665] 2-(2-methoxyethoxy)-5-((2-((2-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 207). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.67 (dd, J=4.8, 1.6 Hz, 1H), 7.97 (dd, J=7.9, 1.5 Hz, 1H), 7.87 (s, 1H), 7.59 (d, J=1.9 Hz, 1H), 7.38 (dd, J=7.9, 4.8 Hz, 1H), 7.11 (s, 1H), 6.47 (d, J=1.9 Hz, 1H), 5.17 (q, J=8.6 Hz, 2H), 5.10 (s, 2H), 4.39-4.32 (m, 2H), 3.70-3.63 (m, 2H), 3.37 (s, 3H).

[0666] 2-methoxy-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 208). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.77 (dd, J=4.7, 1.6 Hz, 1H), 8.06 (dd, J=7.9, 1.6 Hz, 1H), 7.97 (s, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.46 (dd, J=7.9, 4.8 Hz, 1H), 7.13 (s, 1H), 6.46 (d, J=1.9 Hz, 1H), 5.21 (s, 2H), 4.61-4.49 (m, 2H), 3.93 (s, 3H), 2.95-2.79 (m, 2H).

[0667] 2-(2-methoxyethoxy)-5-((2-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 209). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.76 (dd, J=4.7, 1.6 Hz, 1H), 8.06 (dd, J=7.9, 1.6 Hz, 1H), 7.93 (s, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.45 (dd, J=7.9, 4.8 Hz, 1H), 7.19 (s, 1H), 6.45 (d, J=1.9 Hz, 1H), 5.20 (s, 2H), 4.63-4.48 (m, 2H), 4.48-436 (m, 2H), 3.75 (dd, J=5.4, 3.9 Hz, 2H), 3.45 (s, 3H), 3.01-2.69 (m, 2H).

[0668] 2-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 210). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.64 (dd, J=4.7, 1.6 Hz, 1H), 8.16 (dd, J=7.9, 1.5 Hz, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.38 (dd, J=7.9, 4.8 Hz, 1H), 7.21 (d, J=8.6 Hz, 1H), 7.10 (d, J=8.6 Hz, 1H), 6.47 (d, J=1.9 Hz, 1H), 5.19 (q, J=8.6 Hz, 2H), 5.12 (d, J=6.1 Hz, 2H), 2.51 (s, 3H).

[0669] 2-methyl-5-((2-(1-(3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 211). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.75 (dd, J=4.7, 1.7 Hz, 1H), 8.27 (dd, J=7.9, 1.6 Hz, 1H), 7.62 (d, J=1.9 Hz, 1H), 7.49 (dd, J=7.9, 4.8 Hz, 1H), 7.33 (d, J=8.6 Hz, 1H), 7.24 (d, J=8.6 Hz, 1H), 6.46 (d, J=1.9 Hz, 1H), 5.18 (s, 2H), 4.61-4.44 (m, 2H), 2.96-2.75 (m, 2H), 2.62 (s, 3H).

[0670] 3-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl) pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 212). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.65 (dd, J=4.7, 1.5 Hz, 1H), 8.38 (dd, J=4.4, 1.0 Hz, 1H), 8.19 (dd, J=7.9, 1.0 Hz, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.43-7.33 (m, 2H), 7.21 (d, J=8.6 Hz, 1H), 6.48 (d, J=1.9 Hz, 1H), 5.19 (q, J=8.6 Hz, 2H), 5.15 (s, 2H).

[0671] 3-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl) pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 213). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.66 (dd, J=4.7, 1.6 Hz, 1H), 8.39 (dd, J=4.5, 1.1 Hz, 1H), 8.21 (dd, J=7.9, 1.6 Hz, 1H), 7.53 (d, J=1.9 Hz, 1H), 7.44-7.37 (m, 2H), 7.26 (d, J=8.5 Hz, 1H), 6.37 (d, J=1.9 Hz, 1H), 5.13 (s, 21H), 4.49-4.40 (m, 2H), 2.87-2.64 (m, 2H).

[0672] 3-chloro-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 214). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.77 (dd, J=4.7, 1.6 Hz, 1H), 8.41 (s, 1H), 8.28 (s, 1H), 8.13 (dd, J=7.9, 1.3 Hz, 1H), 7.63 (d, J=1.8 Hz, 1H), 7.47 (dd, J=7.9, 4.8 Hz, 1H), 6.37 (d, J=1.8 Hz, 1H), 5.23 (s, 2H), 4.66 (sep, J=6.6 Hz, 1H), 1.49 (d, J=6.6 Hz, 6H).

[0673] 3-(2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-5-methylisonicotinaldehyde (Compound 215). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.69 (dd, J=4.7, 1.5 Hz, 1H), 8.18 (d, J=3.7 Hz, 2H), 7.92 (dd, J=7.9, 1.2 Hz, 1H), 7.53 (d, J=1.8 Hz, 1H), 7.36 (dd, J=7.9, 4.8 Hz, 1H), 7.19 (s, 1H), 6.29 (d, J=1.8 Hz, 1H), 5.14 (s, 2H), 4.59 (sep, J=6.6 Hz, 1H), 1.41 (d, J=6.6 Hz, 6H).

[0674] 3-chloro-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Com-

pound 216). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.67 (dd, J=4.7, 1.5 Hz, 1H), 8.35 (s, 1H), 8.26 (s, 1H), 8.06 (dd, J=7.9, 1.3 Hz, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.40 (dd, J=7.9, 4.8 Hz, 1H), 6.47 (d, J=1.9 Hz, 1H), 5.21-5.10 (m, 4H).

[0675] 3-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde (Compound 217). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.77 (dd, J=4.7, 1.3 Hz, 1H), 8.35 (s, 1H), 8.30 (s, 1H), 8.04 (d, J=7.9 Hz, 1H), 7.69 (d, J=1.9 Hz, 1H), 7.47 (dd, J=7.9, 4.8 Hz, 1H), 6.55 (d, J=1.9 Hz, 1H), 534-5.22 (m, 4H), 2.57 (s, 3H).

In Vitro Testing

Example 95. Modulation of Hemoglobin Oxygen Affinity by Heteroaryl Aldehydes—Assay Procedure

[0676] Oxygen equilibrium curves (OEC) in purified Hemoglobin S (HbS) were measured by the change in p50, the partial pressure of oxygen at which the home binding sites in the HbS sample are 50% saturated with oxygen. HbS was purified by a modified procedure (Antonini and Brunori, 1971; Heomoglobin and Myoglobin in their Reactions with Ligands; North Holland Publishing Company; Amsterdam, London) from blood obtained from homozygous sickle cell patients though the Hemoglobinopathy Center at Children's Hospital Oakland Research Institute (CHORI) with Institutional Review Board approval. Oxygen equilibrium curves were carried out with a HEMOX analyzer, (TCS Scientific, New Hope, Pa.). Five hundred μL of 250 μM purified HbS were diluted into 4.5 mL of HEMOX buffer (30 mM TES, 130 mM NaCl, 5 mM KCl, pH=7.4) resulting in a final hemoglobin concentration of 25 μM. The compounds were added at the final desired concentrations. The mixture was incubated for 45 min at 37° C. and then transferred to the Hemox sample chamber. The samples were saturated with oxygen by flushing with compressed air for 10 minutes. The samples were then flushed with pure nitrogen and the absorbance of deoxy-Hb was recorded as a function of the solution pO_2. The oxygen equilibrium data was then fit to the Hill Model to obtain values for p50. The deoxygenation curves for both HbS alone (control) and HbS in the presence of compound were collected with the TCS software. The p50 for purified Hbs was typically 13.8±1.6. Delta p50 values were obtained from the p50 value for control minus the p50 value for HbS treated with compound divided by the p50 value for the control. A positive delta p50 value corresponds to a left shifted curve and a lower p50 value relative to control, indicating that the compound acts to modulate HbS to increase its affinity for oxygen.

Example 96. Modulation of Hemoglobin Oxygen Affinity by Heteroaryl Aldehydes—Assay Results

[0677] The compounds of Table 1 that were where tested in the assay above were all found to have positive delta p50 values. Delta p50% is calculated from [[p50(HbS)−p50(HbS treated with compound)]/p50(HbS)]×100. Table 2 below lists the delta p50% values where + indicates a delta p50% of between 0 and 29. ++ indicates a delta p50% of between 30 and 50, and +++ indicates a delta p50% of 50 or greater. Unless noted otherwise, the compounds in Table 2 were tested at 30 μM.

TABLE 2

delta p50 %

Compound	delta p50
1	+
2	++ (100 μM)
3	+
4	+
5	++
6	+
7	+
12	+ (100 μM)
38	+
39	+
40	+ (100 μM)
41	+
42	+
43	++
44	+++
45	+++
46	++
47	+
48	++ (100 μM)
49	++
50	+
51	+
52	+ (100 μM)
53	++
54	++ (100 μM)
55	+ (100 μM)
56	+ (100 μM)
57	++ (100 μM)
58	++
59	+
61	+
62	+
63	+++
64	+
65	++
66	++
68	+
69	+
70	+
71	+
72	+
73	+
74	++
75	+
76	+
77	+
78	+
79	++
80	++
81	+
82	+
83	+
84	++
85	+
86	++
87	+
88	+
89	+
90	+
91	++
92	++
93	++
94	+
95	+
96	+
97	+
98	+
99	+
100	+
101	+
102	+
103	++
104	+

TABLE 2-continued

delta p50 %	
Compound	delta p50
105	+
106	++
107	+
108	++
109	+
110	+
111	+
112	+
113	+
114	+
115	+
116	+
117	+
118	+
119	++
120	++
121	+
122	+
123	+
124	+
125	+
126	+
127	+
128	+
129	++
130	++
131	++
132	+++
133	++
134	++
135	+
136	+
137	+
138	+
139	+
140	++
141	+
142	+
143	++
149	+++
150	+++
158	++
159	+++
160	+++
161	++
162	+++
163	+++
164	++
165	++
169	++
172	++
173	+++
174	+++
175	+++
176	+++
177	+++
178	++
179	++
180	+++
181	+++
183	+++
184	++
186	+++
187	++
188	+++
189	++
190	+++
191	+++
193	++
194	++
195	+++
196	+++
197	++

TABLE 2-continued

delta p50 %	
Compound	delta p50
198	+++
199	+++
200	++
201	++
202	+++
203	+++

Example 97. Polymerization Assay

[0678] Polymerization assays are carried out in vitro using purified HBS exchanged into 1.8 M potassium phosphate buffer at pH 7.4. Using a slightly modified protocol (Antonini and Brunori, 1971), HbS is purified by the CRO VIRUSYS, from blood obtained from homozygous sickle cell patients through the Hemoglobinopathy Center at Children's Hospital Oakland Research Institute (CHORI) with Institutional Review Board approval. Compounds are prepared in 100% DMSO and a desired amount is added to 50 μM of purified HBS at a final DMSO concentration of 0.3%. Final potassium phosphate concentration is adjusted to 1.8 M using a combination of 2.5 M potassium phosphate stock solution and water at pH 7.4. The reaction mixture is incubated for an hour at 37° C. and then transferred into a 24-well plate for deoxygenation in a glove box containing 99.5% nitrogen and 0.5% oxygen. The 24-well plate is not covered and incubated at 4° C. on a plate cooler inside the glove box for one and a half hours. Fifty μL of the reaction mixture is transferred into a 96-well plate and the absorbance at 700 nm is measured every minute for one hour at 37° C. in a plate reader located inside the glove box. A plot of the absorbance against time is fitted using a Boltzman sigmoidal fit and the delay time (from zero to time at half Vmax) is measured. To compare and rank compounds, delay times are expressed as percent delay (% DT), which is defined as the difference in delay times for HBS/compound and HBS alone multiplied by 100 and divided by the delay time for HBS alone.

[0679] Compounds listed below have been tested in the polymerization assay. Activity ranges are defined by the number of dagger (†) symbols indicated. † denotes activity ≥40% but ≤80%; †† denotes activity >80% but ≤120%; ††† denotes activity >120% but ≤140%; †††† denotes activity >160%.

TABLE 3

% delta Delay	
Compound	% delta Delay
5	†
108	
130	†
132	
91	
149	†
150	†††
158	†
179	
159	††
160	††
161	

TABLE 3-continued

% delta Delay	
Compound	% delta Delay
162	††
173	†
174	††
195	†††
197	†
198	†
175	††
162	††
203	††
163	††
181	†††
206	†††
178	†
180	†
199	†††
176	†
177	†
202	†††
187	††
164	†††
165	†††
169	†††
186	††††
188	†††
189	†††
190	†††

Example 98. R/T Assay

[0680] A relaxed-to-tense transition assay ("R/T assay") was used to determine the ability of substituted benzaldehyde compounds to maintain the high-oxygen affinity relaxed (R) state of hemoglobin under deoxygenated conditions. This ability can be expressed as a "delta R" value (i.e., the change in the time-period of the R state after hemoglobin is treated with a compound, as compared to the period without treatment with the compound). Delta R is the % R to remaining after the compounds treatment compared with no treatment (e.g. if R % without treatment is 8% while with treatment with a target compound is 48% R at 30 μM, then % R is 40% for that compound.

[0681] A mixture of HbS/A was purified from blood obtained from homozygous sickle cell patients though the Hemoglobinopathy Center at Children's Hospital Oakland Research Institute (CHORI) with Institutional Review Board approval. HbS/A (at a final concentration of 3 μM) was incubated for 1 hr at 37° C. in presence or absence of compounds in 50 μM potassium phosphate buffer, pH=7.4 and 30 μM 2, 3 diphosphoglycerate (DPG) in 96 well plates in a final volume of 160 μl. Compounds were added at different concentrations (3 μM to 100 μM final concentrations). Plates were covered with a Mylar film. After incubation was completed the Mylar cover was removed and the plates were placed in a Spectrostar Nano plate reader previously heated at 37° C. Five minutes later, N_2 (flow rate=20 L/min) was flowed through the spectrophotometer. Spectroscopic measurements (300 nm to 700 nm) were taken every 5 min for 2 hours. Data analysis was performed by using linear regression from the data retrieved for all wavelengths.

[0682] Table 4 below lists the delta R values where + indicates a delta R of between 0 and 30, ++ indicates a delta R of between 30 and 50, and +++ indicates a delta R of 50 or greater.

[0683] Unless noted otherwise, the compounds in Table 2 were tested at 30 μM.

TABLE 4

delta R	
Compound	delta R
5	++
43	+ (9 μM)
45	++ (9 μM)
46	+ (9 μM)
53	+ (9 μM)
58	+ (9 μM)
63	++ (9 μM)
193	+ (9 μM)
65	+ (9 μM)
66	++ (9 μM)
79	++ (9 μM)
80	+++ (9 μM)
84	++ (9 μM)
86	+ (9 μM)
91	+++ (9 μM)
92	+ (9 μM)
93	+ (9 μM)
103	++ (9 μM)
108	+++ (9 μM)
119	++ (9 μM)
120	++ (9 μM)
129	++ (9 μM)
130	++ (9 μM)
131	+ (9 μM)
132	++
133	++ (9 μM)
134	+ (9 μM)
140	+ (9 μM)
143	+ (9 μM)
149	+ (9 μM)
150	+++
194	+ (9 μM)
158	+ (9 μM)
179	+ (9 μM)
159	++
160	+
161	+ (9 μM)
172)	+ (9 μM)
191	+ (9 μM)
173	+++
195	+++
174	++
196	++
197	+ (9 μM)
198	++
175	++
162	+++
203	+ (9 μM)
163	++
181	+ (9 μM)
206	+ (9 μM)
178	+ (9 μM)
180	++
199	+ (9 μM)
176	+ (9 μM)
177	+ (3 μM)
183	++
184	++
200	+ (9 μM)
201	+ (9 μM)
202	+ (9 μM)
187	+++ (9 μM)
164	++ (9 μM)
165	+ (9 μM)
169	++ (9 μM)
186	+++

Example 99. Whole Blood Assay

[0684] Oxygen Equilibrium Curves (OEC) of whole blood before and after treatment with different concentrations of substituted benzaldehyde compounds were performed as follows using a HEMOX analyzer (TCS Scientific, New Hope, Pa.). Blood samples from homozygous sickle cell patients were obtained though the Hemoglobinopathy Center at Children's Hospital Oakland Research Institute (CHORI) with Institutional Review Board approval. The hematocrit was adjusted to 20% using autologous plasma and the blood samples were incubated for 1 hour at 37° C. in absence or presence of compounds. 100 μl of these samples were added to 5 mL of Hemox buffer (30 mM TES, 130 mM NaCl, 5 mM KCl, pH=7.4) at 37° C. and then transferred to the Hemox sample chamber. The samples were saturated with oxygen by flushing with compressed air for 10 minutes. The samples were then flushed with pure nitrogen and the respective absorbances of oxy- and deoxy-Hb are recorded as a function of the solution pO2. The oxygen equilibrium data were then fitted to the Hill Model to obtain values for p50. The deoxygenation curves for both whole blood alone (control) and whole blood in the presence of the compound were collected with the TCS software.

[0685] Table 5 below lists the delta p50% values where + indicates a delta p50% of between 0 and 29, ++ indicates a delta p50% of between 30 and 50, and +++ indicates a delta p50% of 50 or greater. Unless noted otherwise, the compounds in Table 2 were tested at 1000 μM. A positive delta p50 value corresponds to a left shifted curve and a lower p50 value relative to control, indicating that the compound acts to modulate HbS to increase its affinity for oxygen.

TABLE 5

delta p50 % Values for Whole Blood Assay	
Compound	delta p50 %
5	+
44	+
58	+
65	+
74	++
79	+
80	+
92	+
93	+
103	+
106	+
108	+
120	+
129	++
130	++
131	+
132	++
133	+
140	+
143	+
149	+++
150	+++
194	+
158	+
179	++
159	+++
160	+++
191	+++
173	+++
174	+++
195	+++
196	++

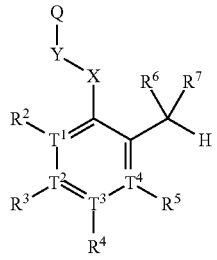
TABLE 5-continued

delta p50 % Values for Whole Blood Assay	
Compound	delta p50 %
197	+++
198	+++
175	+++
162	+++
209	+
163	+++
181	+++
206	+++
178	++
180	+++
199	+
176	+++
177	+++
183	+++
184	+++
200	+++
201	+
202	+
187	+
164	++
165	+
169	++
186	+++
188	+++
189	+++
190	+++

[0686] All patents, patent applications, publications and presentations referred to herein are incorporated by reference in their entirety. Any conflict between any reference cited herein and the teaching of this specification is to be resolved in favor of the latter. Similarly, any conflict between an art-recognized definition of a word or phrase and a definition of the word or phrase as provided in this specification is to be resolved in favor of the latter.

What is claimed is:

1. A compound of Formula (I):



(I)

or a tautomer or pharmaceutically acceptable salt thereof, wherein

Q is selected from the group consisting of aryl, heteroaryl, and heterocycloalkyl, each optionally substituted with one to three R^a;

Y is O or $CR^{1a}R^{1b}$, where R^{1a} is H or halo and R^{1b} is selected from the group consisting of H, halo, and OH;

X is selected from the group consisting of O, >CH $(CH_2)_nR^8$, and $C(R^9)_2$ where n is 0 or 1, R^8 is OH, and R^9 is independently H or halo; or Y—X taken together —NHC(O)— or —C(O)NH—;

R^2, R^3, R^4, and R^5 are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_2OR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3; or R^5 is $—(CH_2)_pR^{5a}$ where p is 0 or 1 and R^{5a} is OH;

R^6 and R^7 together form oxo or an aldehyde protecting group, or R^6 together with R^{1b}, R^8, or R^5 forms a cyclic ether where one of R^{1b}, R^8, or R^{5a} is O, R^6 is a bond, and R^7 is selected from the group consisting of OH, C_{1-8}alkoxy, and haloC_{1-8}alkoxy;

T^1, T^2, T^3, and T^4 are independently C or N provided that at least one of T^1, T^2, T^3, and T^4 is N and at least one of T^1, T^2, T^3, and T^4 is C;

each R^a is independently selected from the group consisting of halo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, $—(CH_2)_kOC(O)R^e$, $—(CH_2)_kSR^d$, CN, NO_2, $—(CH_2)_kCO_2(C_{1-8}alkyl)OH$, $—(CH_2)_kCO_2(C_{1-8}alkyl)(heteroaryl)C(O)(C_{1-8}alkyl)$, $—(CH_2)_kCO_2R^d$, $—(CH_2)_kCONR^dR^d$, $(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^d(O)_2R^e$, $—(CH_2)_kC(O)R^d$, $—(CH_2)_kOC(O)NR^dR^d$, $—NR^d(CH_2)_uOR^d$, $—NR^d(CH_2)_uNR^dR^d$, $—NR^d(CH_2)_uNR^dC(O)R^e$, $—NR^d(CH_2)_uNR^dC(O)_2R^e$, $—NR^d(CH_2)_uNR^dS(O)_2R^e$, $—(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^dC(O)_2R^d$, $—(CH_2)_kNR^dC(O)NR^dR^d$, $—(CH_2)_kS(O)R^e$, $—(CH_2)_kS(O)_2R^e$, $—(CH_2)_kNR^dS(O)_2R^e$, $—C(O)(CH_2)_kNR^dS(O)_2R^e$, $—(CH_2)_kC(O)NR^dS(O)_2R^e$, $—(CH)_kS(O)_2NR^dR^d$, N_3, $—(CH_2)_karyl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_karyl$ optionally substituted with one to three R^c, $—(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c, and $—NR(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6;

each R^b is independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and C_{2-8}alkynyl, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

each R^e is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkanyl, C_{2-8}alkynyl, haloC_{2-8}alkynyl, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, NO_2, $(CH_2)_mCO_2R^f$, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, N_3, $(R^f)_mSiC_{1-8}$alkyl, heteroaryl optionally substituted with one to three R^h, cycloalkyl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

each R^h is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, OR^j, $OC(O)R$, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, $C(O)R^j$, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^i$, $NR^jC(O)_2R^i$, $NR^jC(O)NR^jR^j$, $S(O)R^i$, $S(O)_2R^i$, $NR^jS(O)_2R^i$, and $S(O)_2NR^jR^j$;

R^d, R^f, and R^j are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl; and

R^e, R^g, and R^i are each independently selected from the group consisting of C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl;

provided that X and Y are not both O;

provided that when X is O, R^{1b} is not OH; and

provided that when Y is O, and n is 0, R^g is not OH.

2. A according to claim **1**, or a tautomer or pharmaceutically acceptable salt thereof, wherein:

Y is CH_2;

X is O or CH_2;

T_1, T^2, T^3, and T^4 are C or N, provided that no more than one of T^1, T^2, T^3, and T^4 is N;

Q is selected from the group consisting of

i) heteroaryl optionally substituted with one to three R^a; wherein

R^2, R^3, R^4, and R^5, are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^b, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, and N_3 where z is 1, 2, or 3;

ii) aryl substituted with one to three $—(CH_2)_kCO_2R^d$; wherein

R^2 and R^5 are independent absent or selected from the group consisting of hydrogen, halo, OR^b, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3;

R^3 and R^4 are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3;

iii) unsubstituted aryl, wherein

R^2, R^3, and R^4, are independently absent or selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3; and

R^5 is absent or is OR^d; and

iv) heterocycloalkyl, optionally substituted with one to three R^a; wherein

R^2, R^3, R^4, and R^5, are independently absent or selected from the group consisting of hydrogen, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3;

R^6 and R^7 together form oxo or an aldehyde protecting group;

each R^a is independently selected from the group consisting of halo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, $—(CH_2)_kOC(O)R^e$, $—(CH_2)_kSR^d$, CN, NO_2, $—(CH_2)_kCO_2(C_{1-8}alkyl)OH$, $—(CH_2)_kCO_2(C_{1-8}alkyl)(heteroaryl)C(O)(C_{1-8}alkyl)$, $—(CH_2)_kCO_2R^d$, $—(CH_2)_kCONR^dR^d$, $—(CH_2)_kNR^dC(O)R^e$, $—NR^d(CH_2)_uNR^dR^d$, $—NR^d(CH_2)_uNR^dC(O)R^e$, $—NR^d(CH_2)_uNR^dC(O)_2R^e$, $—NR^d(CH_2)_uNR^dS(O)_2R^e$, $—(CH_2)_kNR^dC(O)R^e$, $—(CH_2)_kNR^dC(O)_2R^e$, $—NR^d(CH_2)_uNR^dC(O)NR^dR^d$, $—(CH_2)_kS(O)R^e$, $—(CH_2)_kS(O)_2R^e$, $—(CH_2)_kNR^dS(O)_2R^e$, $—C(O)(CH_2)_kNR^dS(O)_2R^e$, $—(CH_2)_kC(O)NR^dS(O)_2R^e$, $—(CH_2)_kS(O)_2NR^dR^d$, N_3, $—(CH_2)_karyl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_karyl$ optionally substituted with one to three R^c, $—(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—NR^d(CH_2)_kheteroaryl$ optionally substituted with one to three R^c, $—(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c, an $—NR^d(CH_2)_kheterocycloalkyl$ optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5 or 6;

each R^b is independently selected from the group consisting of $C_{1-8}alkyl$, $C_{2-8}alkenyl$, and $C_{2-8}alkynyl$, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

each R^e is independently selected from the group consisting of halo, $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, $C_{2-8}alkenyl$, $haloC_{2-8}alkenyl$, C_{2-8} alkynyl, $haloC_{2-8}alkynyl$, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, NO_3, $(CH_2)_mCO_2R^f$, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, N_3, $(R^f)_mSiC_{1-8}alkyl$, heteroaryl optionally substituted with one to three R^h, cycloalkyl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

each R^h is independently selected from the group consisting of halo, $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, OR^j, OC(O)R, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, C(O)RR, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^i$, $NR^hC(O)_2R^i$, $NR^jC(O)NR^hR^j$, $S(O)R^i$, $S(O)_2R^i$, $NR^jS(O)_2R^i$, and $S(O)_2NR^jR^j$;

R^d, R^f and R^j are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, $haloC_{1-8}alkyl$, C_{2-8} alkenyl, $haloC_{2-8}alkenyl$, C_{2-8} alkynyl, and $haloC_{2-8}alkynyl$; and

R^e, R^h, and R^i are each independently selected from the group consisting of $C_{1-8}alkyl$, $haloC_{1-8}alkyl$, C_{2-8} alkenyl, $haloC_{2-8}alkenyl$, C_{2-8} alkynyl, and $haloC_{2-8}alkynyl$.

3. A compound according to claim **2**, or a tautomer or pharmaceutically acceptable salt thereof, wherein R^6 and R^7 together form oxo.

4. A compound according to claim **2** wherein R^2 and R^3 are independently absent or selected from the group consisting of hydrogen, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, CO_2R^d, $CONR^dR^d$, and $C(O)R^d$, where z is 1, 2, or 3.

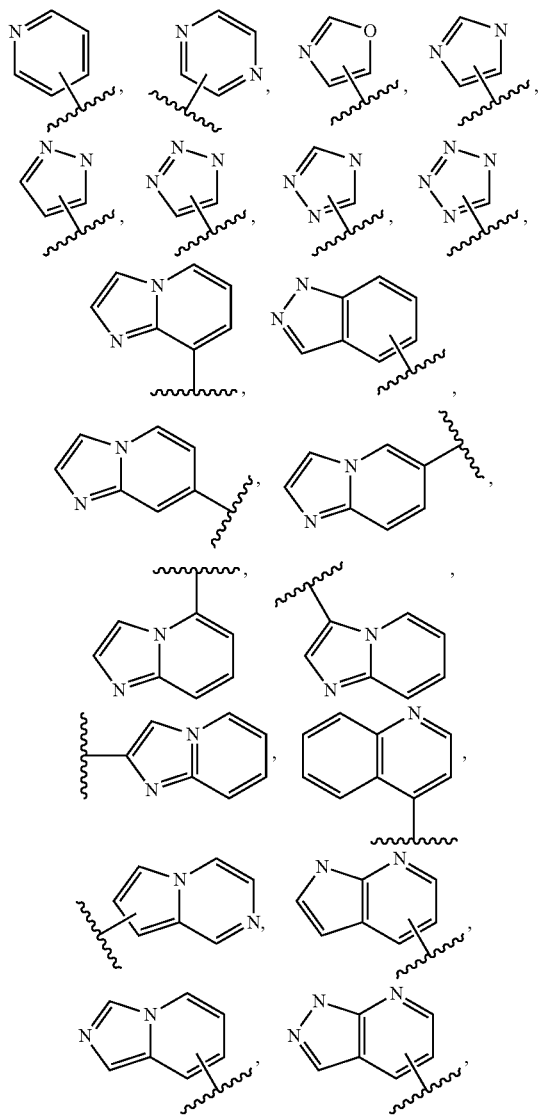
5. A compound according to claim **2**, wherein T^2 is N; R^2 and R^5 are H; R^3 is absent; and R^4 is $C_{1-8}alkoxy$, $haloC_{1-8}alkoxy$, and $O(CH_2)_2C_{1-8}alkyl$.

6. A compound according to claim **2**, wherein T^2 is N; R^2 and R^4 are H; R^3 is absent; and R^5 is selected from hydroxy and $C_{1-8}alkoxy$.

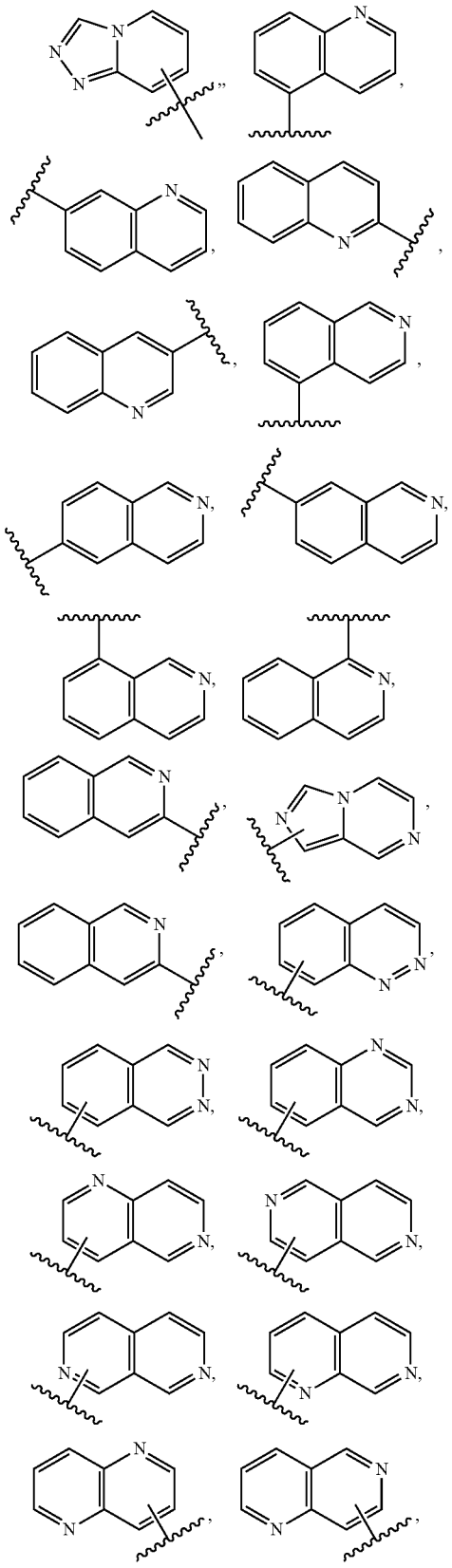
7. A compound according to claim **2**, wherein T^4 is N; R^2 and R^3 are H; R^5 is absent; and R^4 is selected from $C_{1-8}alkyl$ and $C_{1-8}alkoxy$.

8. A compound according to any of claims **5-7**, wherein Q is selected from the group consisting of an imidazopyridinyl group, a pyrrolopyridinyl group, a pyrazolopyridinyl group, a triazolopyridinyl group, a pyrazolopyrazinyl group, a pyridinyl group, a pyrazinyl group, an oxazolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a pyrazolyl group, a quinolinyl group, an isoquinolinyl group, an indazolyl group, a benzooxazolyl group, a naphthyridinyl group, and a quinoxalinyl group; and wherein Q is optionally substituted with one to three R^a.

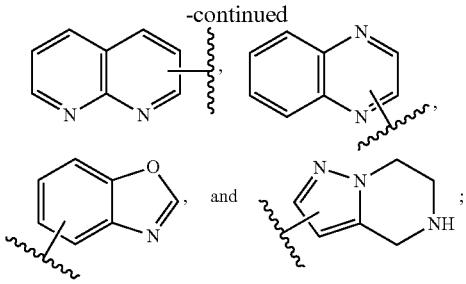
9. A compound according to any of claims **5-7**, wherein Q is selected from the group consisting of:



-continued



-continued



and wherein Q is optionally substituted with one to three R^a.

10. A compound accorrding to claim **2**, wherein T^1 is N; R^3, R^4, and R^5 are H; and R^2 is absent.

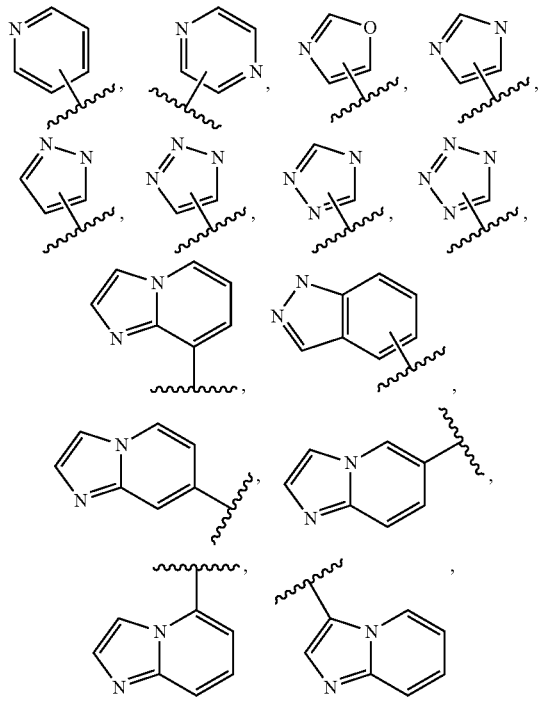
11. A compound according to claim **2**, wherein T^2 is N; R^2, R^4, and R^5 are H; and R^3 is absent.

12. A compound according to claim **2**, wherein T^3 is N; R^2, R^3, and R^5 are H; and R^4 is absent.

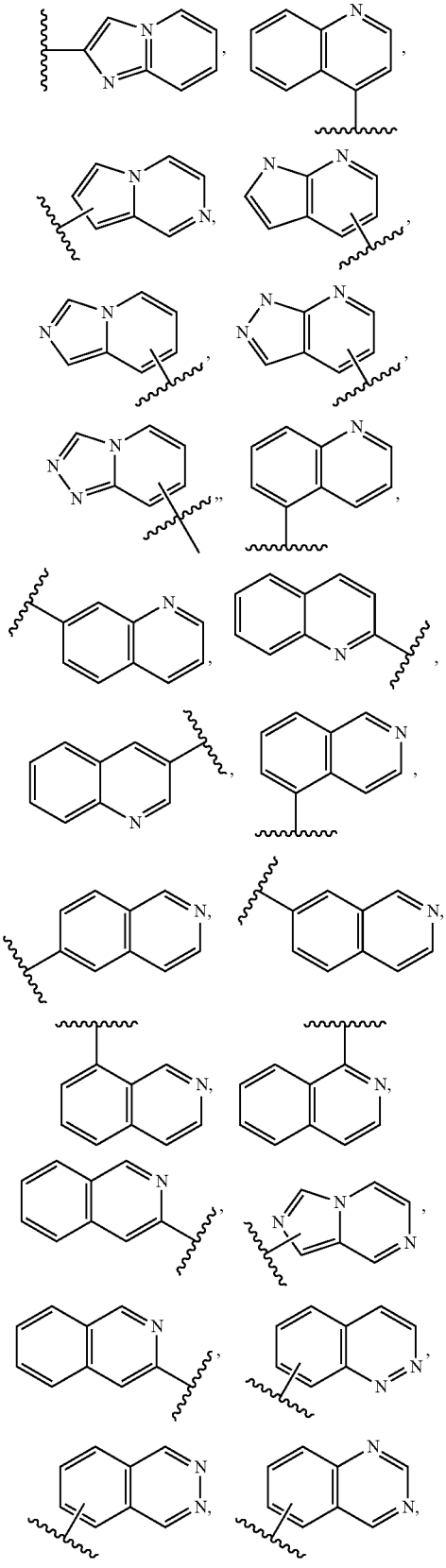
13. A compound according to claim **2**, wherein T^4 is N; R^2, R^3, and R^4 are H; and R^5 is absent.

14. A compound according to any of claims **10-13**, wherein Q is selected front the group consisting of an imidazopyridinyl group, a pyrrolopyridinyl group, a pyrazolopyridinyl group, a thiazolopyridinyl group, a pyrazolopyrazinyl group, a pyridinyl group, a pyrazinyl group, an oxazolyl group, an imidazolyl group, a triazolyl group, a tetrazolyl group, a pyrazolyl group, a quinolinyl group, an isoquinolinyl group, an indazolyl group, a benzooxazolyl group, a naphthyridinyl group, and a quinoxalinyl group; and Q is optionally substituted with one to three R^a.

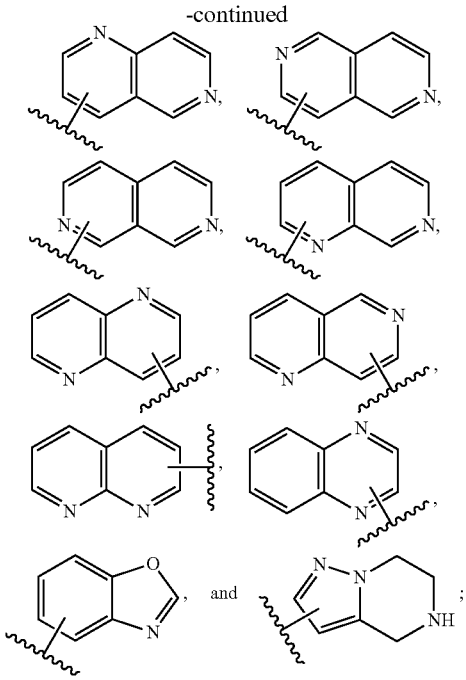
15. A compound according to any of claims **10-13**, wherein Q is selected from the group consisting of:



-continued



-continued



and wherein Q is optionally substituted with one to three R^a.

16. A compound of claim **2** selected from the group consisting of:

4-(pyridin-3-ylmethoxy)nicotinaldehyde,

3-(pyridin-3-ylmethoxy)isonicotinaldehyde,

2-(imidazo[1,2-a]pyridin-8-ylmethoxy)nicotinaldehyde,

3-(imidazo[1,2-a]pyridin-8-ylmethoxy)picolinaldehyde,

5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-1-methoxyisonicotinaldehyde,

3-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde,

3-(imidazo[1,5-a]pyridin-8-ylmethoxy)isonicotinaldehyde,

2-methoxy-5-(pyrazolo[1,5-a]pyrazin-3-ylmethoxy) isonicotinaldehyde,

8-((3-formylpyridin-2-yloxy)methyl)imidazo[1,2-a]pyridine-6-carboxamide,

8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo [1,2-a]pyridine-6-carboxamide,

5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde,

2-(2-(imidazo[1,2-a]pyridin-8-yl)ethyl)nicotinaldehyde,

5-(2-(imidazo[1,2-a]pyridin-8-yl)ethyl)-2-methoxyisonicotinaldehyde,

5-((1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,

3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyrazolo [1,5-a]pyrazine-2-carboxamide,

5-((2-(1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrazine-3-yl) methoxy)-2-methoxyisonicotinaldehyde,

2-(imidazo[1,2-a]pyridin-2-ylmethoxy)nicotinaldehyde,

2-methoxy-5-((4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methoxy)isonicotinaldehyde,

2-(imidazo[1,2-a]pyridin-8-ylmethoxy)nicotinaldehyde,

5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methylisonicotinaldehyde,

3-((1H-pyrrolo[2,3-b]pyridin-4-yl)methoxy)isonicotinaldehyde,
3-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde,
3-(pyrrolo[1,2-a]pyrazin-6-ylmethoxy)isonicotinaldehyde,
6-((4-formylpyridin-3-yloxy)methyl)pyrrolo[1,2-a]pyrazine-7-carbonitrile,
6-((4-formylpyridin-3-yloxy)methyl)pyrrolo[1,2-a]pyrazine-7-carboxamide,
3-((1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)isonicotinaldehyde,
3-(pyrazolo[1,5-a]pyrazin-3-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((6-oxo-1,6-dihydropyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-oxo-1,2-dihydropyridin-4-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-(oxazol-5-yl)methoxy)isonicotinaldehyde,
5-((1H-imidazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1H-imidazol-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((4H-1,2,4-triazol-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1H-tetrazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1H-pyrazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1H-pyrazol-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-(oxazol-4-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((2-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((4-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((6-(trifluoromethyl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((6-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-(pyridin-3-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((5-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
5-(isoquinolin-1-ylmethoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-(quinolin-2-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-(pyridin-4-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((3-methylpyridin-4-yl)methoxy)isonicotinaldehyde,
5-((3-bromopyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-(imidazo[1,2-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde,
(5-(imidazo[1,2-a]pyridin-5-ylmethoxy)-2-methoxypyridin-4-yl)(methoxy)methanol,
N-(4-formylpyridin-3-yl)imidazo[1,2-a]pyridine-8-carboxamide,
2-methoxy-5-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methoxy)isonicotinaldehyde,
methyl 2-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxylate,
2-methoxy-5-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)isonicotinaldehyde,
5-((3-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((6-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((8-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)methoxy)isonicotinaldehyde,
5-((3-(1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((6-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((8-((1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)isonicotinaldehyde,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinonitrile,
5-((2-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinonitrile,
5-((2-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((5-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
methyl 2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxylate,
2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxamide,
2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)-N-methylimidazo[1,2-a]pyridine-8-carboxamide,
5-((5-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((4-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-((4-(dihydroxymethyl)-6-methoxypyridin-3-yloxy)methyl)-N-methylimidazo[1,2-a]pyridine-8-carboxamide,
2-((4-(dihydroxymethyl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxamide,
2-methoxy-5-((5-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((5-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-(5-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
methyl 5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinate,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinic acid,
2-methoxy-5-(quinolin-3-ylmethoxy)isonicotinaldehyde,
6-methyl-3-(quinolin-3-ylmethoxy)picolinaldehyde,
5-(isoquinolin-7-ylmethoxy)-2-methoxyisonicotinaldehyde,
3-(isoquinolin-7-ylmethoxy)-6-methylpicolinaldehyde,
2-methoxy-5-((1-methyl-1H-indazol-4-yl)methoxy)isonicotinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-4-yl)methoxy)picolinaldehyde,
tert butyl 4-((2-formyl-6-methylpyridin-3-yloxy)methyl)-1H-indazole-1-carboxylate,

5-((1H-indazol-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((1H-indazol-4-yl)methoxy)-6-methylpicolinaldehyde,
6-methoxy-3-((1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde,
2-methoxy-5-((1-methyl-1H-indazol-7-yl)methoxy)isonicotinaldehyde,
6-methoxy-3-(1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-7-yl)methoxy)picolinaldehyde,
3-(isoquinolin-1-ylmethoxy)-6-methylpicolinaldehyde,
6-methyl-3-(quinolin-2-ylmethoxy)picolinaldehyde,
5-((4-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((6-bromoimidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-6-carbonitrile,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinonitrile,
3-(benzo[d]oxazol-4-ylmethoxy)-6-methylpicolinaldehyde,
8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-6-carboxamide,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinamide,
5-((6-((1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-(benzo[d]oxazol-4-ylmethoxy)-2-methoxyisonicotinaldehyde,
5-((6-(1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1,5-naphthyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((1,5-naphthyridin-4-yl)methoxy)-6-methylpicolinaldehyde,
5-((1H-indazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-5-yl)methoxy)picolinaldehyde,
3-((3-chloro-1-methyl-1H-indazol-5-yl)methoxy)-6-methylpicolinaldehyde,
2-methoxy-5-(1-methyl-1H-indazol-5-yl)methoxy)isonicotinaldehyde,
5-((3-chloro-1-methyl-1H-indazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
N-(4-formyl-6-methoxypyridin-3-yl)imidazo[1,2-a]pyridine-8-carboxamide,
3-(1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-6-methylpicolinaldehyde,
5-((1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinamide,
5-((2-chloroquinolin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1H-pyrazol-5-yl)quinolin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-(quinoxalin-2-ylmethoxy)isonicotinaldehyde,
6-methyl-3-(quinolin-5-ylmethoxy)picolinaldehyde,
2-methoxy-5-(quinolin-5-ylmethoxy)isonicotinaldehyde,
6-methyl-3-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methoxy)picolinaldehyde,
2-methoxy-5-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methoxy)isonicotinaldehyde,
5-((7-(1H-pyrazol-3-yl)imidazo[1,5-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((5-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((6-(2H-tetrazol-5-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
ethyl 2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidine-4-carboxylate,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-1-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxyl)isonicotinaldehyde,
5-((2-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((3-(1H-pyrazol-5-yl)isoquinolin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-(2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde,
6-methyl-3-(pyridin-3-ylmethoxy)picolinaldehyde,
methyl 8-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)imidazo[1,2-a]pyridine-6-carboxylate,
methyl 2-bromo-8-(((4-formyl-6-methoxypyridin-3-yl)oxy)methy)imidazo[1,2-a]pyridine-6-carboxylate,
3-(imidazo[1,5-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde,
5-(imidazo[1,5-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde,
(5-(methoxycarbonyl)pyridin-3-yl)methyl 5-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)nicotinate,
5-((2-(1,4-dimethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1,5-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-hydroxyethyl 5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate,
methyl 5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate,
methyl 5-(((4-(bis(2-hydroxyethoxy)methyl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate,
5-((2-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1,3-dimethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-ethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(3-methyl-1H-pyrazol-1-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinic acid,

(E)-2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde oxime,
(E)-2-methoxy-5-(pyridin-3-ylmethoxy)isonicotinaldehyde oxime,
2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidine,
1-(2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidin-3-yl)ethanone, 5-((2-(4-(1H-pyrazol-3-yl)piperazin-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(difluoromethoxy)-5-(imidazo[1,2-a]pyridin-8-yl(methoxy)isonicotinaldehyde,
2-methoxy-5-((2-phenylpyridin-3-yl)methoxy)isonicotinaldehyde,
5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-([2,3'-bipyridin]-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(o-tolyl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2'-methoxy-[2,3'-bipyridin]-3-yl)methoxy)isonicotinaldehyde,
4-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid,
4-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,
methyl 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoate,
methyl 3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoate,
3-(((4-formylpyridin-3-yl)oxy)methyl)benzoic acid,
3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid,
3-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,
2-methoxy-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-propyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-(2,2,2-trifluoromethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(1-(2,2-difluoromethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)picolinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde,
2-(difluoromethoxy)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,
5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,
5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyrazin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinate,
5-(2-(2-hydroxypropan-2-yl)pyridin-3-yl)methoxy-2-methoxyisonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)nicotinaldehyde,
3-hydroxy-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-(benzyloxy)-5-hydroxyisonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxyisonicotinaldehyde,
5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)ethoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid,
2,2,2-trifluoroacetic acid: 6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid (1:1),
2-methoxy-5-((2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde,
5-((2-(1-cyclobutyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclohexyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-(cyclohexylmethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclopentyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(5-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetic acid,
methyl 3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate,
3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,
3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,
3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)benzoic acid,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinonitrile 2,2,2-trifluoroacetate,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid hydrochloride,
6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide,
2,2,2-trifluoroacetic acid 6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide (2:1), 2-(2-methoxyethoxy)-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methyl-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-chloro-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methylisonicotinaldehyde,

3-chloro-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde, and
3-methyl-5-((2-(1-(2,2,2-trifluoromethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
or a tautomer or pharmaceutically acceptable salt thereof.

17. A compound of claim **2** selected from the group consisting of;

5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((5-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
5-(isoquinolin-1-ylmethoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-(quinolin-2-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-(pyridin-4-ylmethoxy)isonicotinaldehyde,
3-(imidazo[1,2-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde,
methyl 2-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridin-8-carboxylate,
2-methoxy-5-((3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)methoxy)isonicotinaldehyde,
5-((2-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((5-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((5-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinic acid,
2-methoxy-5-(quinolin-3-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((1-methyl-1H-indazol-4-yl)methoxy)isonicotinaldehyde,
tert-butyl 4-(2-formyl-6-methylpyridin-3-yloxy)methyl)-1H-indazole-1-carboxylate,
6-methyl-3-((1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-7-yl)methoxy)picolinaldehyde,
3-(isoquinolin-1-ylmethoxy)-6-methylpicolinaldehyde,
5-(benzo[d]oxazol-4-ylmethoxy)-2-methoxyisonicotinaldehyde,
3-((1,5-naphthyridin-4-yl)methoxy)-6-methylpicolinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-5-yl)methoxy)picolinaldehyde,
6-methyl-3-(quinolin-5-ylmethoxy)picolinaldehyde,
2-methoxy-5-(quinolin-5-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((3-(1H-pyrazol-5-yl)isoquinolin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-(imidazo[1,5-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1,5-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-ethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(difluoromethoxy)-5-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((2-phenylpyridin-3-yl)methoxy)isonicotinaldehyde,
5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-([2,3'-bipyridin]-3-ylmethoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(o-tolyl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2'-methoxy-[2,3'-bipyridin]-3-yl)methoxy)isonicotinaldehyde,
4-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid,
4-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,
methyl 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoate,
methyl 3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoate,
3-(((4-formylpyridin-3-yl)oxy)methyl)benzoic acid,
3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid,
3-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,
2-methoxy-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-propyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxyisonicotinaldehyde,
2-methoxy-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(1-(2,2-difluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)picolinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde,
2-(difluoromethoxy)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,
5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,
5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyrazin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinate,
5-((2-(2-hydroxypropan-2-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)nicotinaldehyde,
3-hydroxy-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-(benzyloxy)-5-hydroxyisonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxyisonicotinaldehyde,
5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,

5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid
2,2,2-trifluoroacetic acid: 6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid (1:1),
2-methoxy-5-((2-(1-(((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)pyridin-3-3-yl)methoxy)isonicotinaldehyde,
5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy-2-oxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde,
5-((2-(1-cyclobutyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclohexyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclohexylmethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclopentyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(5-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetic acid,
methyl 3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate,
3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,
3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,
3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)benzoic acid,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinonitrile 2,2,2-trifluoroacetate,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid hydrochloride,
6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide,
2,2,2-trifluoroacetic acid: 6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide (2:1), 2-(2-methoxyethoxy)-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methyl-5-((2-(1-(2,2,2-trifluoromethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methyl-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-chloro-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methylisonicotinaldehyde,
3-chloro-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde, and
3-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
or a tautomer or pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound of any of the preceding claims or a tautomer or pharmaceutically acceptable salt thereof.

19. A method for increasing tissue oxygenation, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the preceding claims or a tautomer or pharmaceutically acceptable salt thereof.

20. A method for treating a condition associated with oxygen deficiency, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the preceding claims or a tautomer or pharmaceutically acceptable salt thereof.

21. The method of claim **20**, wherein the condition is selected from the group consisting of sickle cell disease, cancer, a pulmonary disorder, stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, acute respiratory disease syndrome, and a wound.

22. The method according to any of claims **19**-**21** wherein the compound is selected from the group consisting of:
4-(pyridin-3-ylmethoxy)nicotinaldehyde,
3-(pyridin-3-ylmethoxy)isonicotinaldehyde,
2-(imidazo[1,2-a]pyridin-8-ylmethoxy)nicotinaldehyde,
3-(imidazo[1,2-a]pyridin-8-ylmethoxy)picolinaldehyde,
5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-1-methoxyisonicotinaldehyde,
3-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde,
3-(imidazo[1,5-a]pyridin-8-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-(pyrazolo[1,5-a]pyrazin-3-ylmethoxy)isonicotinaldehyde,
8-((3-formylpyridin-2-yloxy)methyl)imidazo[1,2-a]pyridine-6-carboxamide,
8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-6-carboxamide,
5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde,
2-(2-(imidazo[1,2-a]pyridin-8-yl)ethyl)nicotinaldehyde,
5-(2-(imidazo[1,2-a]pyridin-8-yl)ethyl)-2-methoxyisonicotinaldehyde,
5-((1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyrazolo[1,5-a]pyrazine-2-carboxamide,
5-((2-(1H-pyrazol-5-yl)pyrazolo[1,5-a]pyrazine-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(imidazo[1,2-a]pyridin-2-ylmethoxy)nicotinaldehyde,
2-methoxy-5-((4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-yl)methoxy)isonicotinaldehyde,
2-(imidazo[1,2-a]pyridin-8-ylmethoxy)nicotinaldehyde,
5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methylisonicotinaldehyde,
3-((1H-pyrrolo[2,3-b]pyridin-4-yl)methoxy)isonicotinaldehyde,
3-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde,
3-(pyrrolo[1,2-a]pyrazin-6-ylmethoxy)isonicotinaldehyde,
6-((4-formylpyridin-3-yloxy)methyl)pyrrolo[1,2-a]pyrazine-7-carbonitrile,
6-((4-formylpyridin-3-yloxy)methyl)pyrrolo[1,2-a]pyrazine-7-carboxamide,

3-((1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)isonicotinaldehyde,
3-(pyrazolo[1,5-a]pyrazin-3-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((6-oxo-1,6-dihydropyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-oxo-1,2-dihydropyridin-4-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-(oxazol-5-yl)methoxy)isonicotinaldehyde,
5-((1H-imidazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1H-imidazol-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((4H-1,2,4-triazol-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1H-tetrazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1H-pyrazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1H-pyrazol-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-(oxazol-4-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((2-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((4-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((6-(trifluoromethyl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((6-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-(pyridin-3-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((5-methylpyridin-3-yl)methoxy)isonicotinaldehyde,
5-(isoquinolin-1-ylmethoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-(quinolin-2-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-(pyridin-4-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((3-methylpyridin-4-yl)methoxy)isonicotinaldehyde,
5-((3-bromopyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-(imidazo[1,2-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde,
(5-(imidazo[1,2-a]pyridin-5-ylmethoxy)-2-methoxypyridin-4-yl)(methoxy)methanol,
N-(4-formylpyridin-3-yl)imidazo[1,2-a]pyridine-8-carboxamide,
2-methoxy-5-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methoxy)isonicotinaldehyde,
methyl 2-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxylate,
2-methoxy-5-((1-methyl-2-oxo-1,2-dihydropyridin-4-yl)methoxy)isonicotinaldehyde,
5-((3-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((6-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((8-bromoimidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)methoxy)isonicotinaldehyde,
5-((3-(1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((6-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((8-((1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methoxy)isonicotinaldehyde,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinonitrile,
5-((2-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinonitrile,
5-((2-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((5-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
methyl 2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxylate,
2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxamide,
2-((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yloxy)methyl)-N-methylimidazo[1,2-a]pyridine-8-carboxamide,
5-((5-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((4-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-((4-(dihydroxymethyl)-6-methoxypyridin-3-yloxy)methyl)-N-methylimidazo[1,2-a]pyridine-8-carboxamide,
2-((4-(dihydroxymethyl)-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-8-carboxamide,
2-methoxy-5-((5-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((5-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-(5-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((5-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
methyl 5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinate,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinic acid,
2-methoxy-5-(quinolin-3-ylmethoxy)isonicotinaldehyde,
6-methyl-3-(quinolin-3-ylmethoxy)picolinaldehyde,
5-(isoquinolin-7-ylmethoxy)-2-methoxyisonicotinaldehyde,
3-(isoquinolin-7-ylmethoxy)-6-methylpicolinaldehyde,
2-methoxy-5-((1-methyl-1H-indazol-4-yl)methoxy)isonicotinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-4-yl)methoxy)picolinaldehyde,
tert butyl 4-((2-formyl-6-methylpyridin-3-yloxy)methyl)-1H-indazole-1-carboxylate,
5-((1H-indazol-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((1H-indazol-4-yl)methoxy)-6-methylpicolinaldehyde,
6-methoxy-3-((1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde,
2-methoxy-5-((1-methyl-1H-indazol-7-yl)methoxy)isonicotinaldehyde,
6-methoxy-3-(1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-7-yl)methoxy)picolinaldehyde,

3-(isoquinolin-1-ylmethoxy)-6-methylpicolinaldehyde,
6-methyl-3-(quinolin-2-ylmethoxy)picolinaldehyde,
5-((4-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((6-bromoimidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-6-carbonitrile,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinonitrile,
3-(benzo[d]oxazol-4-ylmethoxy)-6-methylpicolinaldehyde,
8-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridine-6-carboxamide,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinamide,
5-((6-((1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-(benzo[d]oxazol-4-ylmethoxy)-2-methoxyisonicotinaldehyde,
5-((6-(1H-pyrazol-5-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((1,5-naphthyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((1,5-naphthyridin-4-yl)methoxy)-6-methylpicolinaldehyde,
5-((1H-indazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-5-yl)methoxy)picolinaldehyde,
3-((3-chloro-1-methyl-1H-indazol-5-yl)methoxy)-6-methylpicolinaldehyde,
2-methoxy-5-(1-methyl-1H-indazol-5-yl)methoxy)isonicotinaldehyde,
5-((3-chloro-1-methyl-1H-indazol-5-yl)methoxy)-2-methoxyisonicotinaldehyde,
N-(4-formyl-6-methoxypyridin-3-yl)imidazo[1,2-a]pyridine-8-carboxamide,
3-(1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-6-methylpicolinaldehyde,
5-((1,3-dimethyl-1H-pyrazolo[3,4-b]pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinamide,
5-((2-chloroquinolin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1H-pyrazol-5-yl)quinolin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-(quinoxalin-2-ylmethoxy)isonicotinaldehyde,
6-methyl-3-(quinolin-5-ylmethoxy)picolinaldehyde,
2-methoxy-5-(quinolin-5-ylmethoxy)isonicotinaldehyde,
6-methyl-3-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methoxy)picolinaldehyde,
2-methoxy-5-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)methoxy)isonicotinaldehyde,
5-((7-(1H-pyrazol-3-yl)imidazo[1,5-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((5-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((6-(2H-tetrazol-5-yl)imidazo[1,2-a]pyridin-8-yl)methoxy)-2-methoxyisonicotinaldehyde,
ethyl 2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidine-4-carboxylate,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-1-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxyl)isonicotinaldehyde,
5-((2-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((3-(1H-pyrazol-5-yl)isoquinolin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-(2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde,
6-methyl-3-(pyridin-3-ylmethoxy)picolinaldehyde,
methyl 8-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)imidazo[1,2-a]pyridine-6-carboxylate,
methyl 2-bromo-8-(((4-formyl-6-methoxypyridin-3-yl)oxy)methy)imidazo[1,2-a]pyridine-6-carboxylate,
3-(imidazo[1,5-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde,
5-(imidazo[1,5-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde,
(5-(methoxycarbonyl)pyridin-3-yl)methyl 5-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)nicotinate,
5-((2-(1,4-dimethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1,5-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-hydroxyethyl 5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate,
methyl 5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate,
methyl 5-(((4-(bis(2-hydroxyethoxy)methyl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinate,
5-((2-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1,3-dimethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-ethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(3-methyl-1H-pyrazol-1-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-(((4-(1,3-dioxolan-2-yl)-6-methoxypyridin-3-yl)oxy)methyl)nicotinic acid,
(E)-2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde oxime,
(E)-2-methoxy-5-(pyridin-3-ylmethoxy)isonicotinaldehyde oxime,
2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidine,
1-(2-(5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxypyridin-4-yl)thiazolidin-3-yl)ethanone, 5-((2-(4-(1H-pyrazol-3-yl)piperazin-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(difluoromethoxy)-5-(imidazo[1,2-a]pyridin-8-yl(methoxy)isonicotinaldehyde,

2-methoxy-5-((2-phenylpyridin-3-yl)methoxy)isonicotinaldehyde,
5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-([2,3'-bipyridin]-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(o-tolyl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2'-methoxy-[2,3'-bipyridin]-3-yl)methoxy)isonicotinaldehyde,
methyl-4-(((2-formylpyridin-3-yl)oxy)methyl)benzoate,
4-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid,
4-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,
methyl 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoate,
methyl 3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoate,
3-(((4-formylpyridin-3-yl)oxy)methyl)benzoic acid,
3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid,
3-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,
2-methoxy-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-propyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-(2,2,2-trifluoromethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(1-(2,2-difluoromethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)picolinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde,
2-(difluoromethoxy)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,
5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,
5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyrazin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinate,
5-(2-(2-hydroxypropan-2-yl)pyridin-3-yl)methoxy-2-methoxyisonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)nicotinaldehyde,
3-hydroxy-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-(benzyloxy)-5-hydroxyisonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxyisonicotinaldehyde,
5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)ethoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid,
2,2,2-trifluoroacetic acid: 6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid (1:1),
2-methoxy-5-((2-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde,
5-((2-(1-cyclobutyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclohexyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-(cyclohexylmethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclopentyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(5-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)acetic acid,
methyl 3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate,
3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,
3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,
3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)benzoic acid,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinonitrile 2,2,2-trifluoroacetate,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid hydrochloride,
6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide,
2,2,2-trifluoroacetic acid 6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide (2:1),
2-(2-methoxyethoxy)-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methyl-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-chloro-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methylisonicotinaldehyde,
3-chloro-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde, and
3-methyl-5-((2-(1-(2,2,2-trifluoromethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,

or a tautomer or pharmaceutically acceptable salt thereof.

23. The method of claim **22**, wherein the compound is selected from the group consisting of:

5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((5-methylpyridin-3-yl)methoxy)isonicotinaldehyde,

5-(isoquinolin-1-ylmethoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-(quinolin-2-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-(pyridin-4-ylmethoxy)isonicotinaldehyde,
3-(imidazo[1,2-a]pyridin-8-ylmethoxy)-6-methylpicolinaldehyde,
methyl 2-((4-formyl-6-methoxypyridin-3-yloxy)methyl)imidazo[1,2-a]pyridin-8-carboxylate,
2-methoxy-5-((3-methyl-[1,2,4]triazolo[4,3-a]pyridin-8-yl)methoxy)isonicotinaldehyde,
5-((2-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((5-bromopyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((5-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((4-formyl-6-methoxypyridin-3-yloxy)methyl)nicotinic acid,
2-methoxy-5-(quinolin-3-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((1-methyl-1H-indazol-4-yl)methoxy)isonicotinaldehyde,
tert-butyl 4-(2-formyl-6-methylpyridin-3-yloxy)methyl)-1H-indazole-1-carboxylate,
6-methyl-3-((1-methyl-1H-indazol-6-yl)methoxy)picolinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-7-yl)methoxy)picolinaldehyde,
3-(isoquinolin-1-ylmethoxy)-6-methylpicolinaldehyde,
5-(benzo[d]oxazol-4-ylmethoxy)-2-methoxyisonicotinaldehyde,
3-((1,5-naphthyridin-4-yl)methoxy)-6-methylpicolinaldehyde,
6-methyl-3-((1-methyl-1H-indazol-5-yl)methoxy)picolinaldehyde,
6-methyl-3-(quinolin-5-ylmethoxy)picolinaldehyde,
2-methoxy-5-(quinolin-5-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-methyl-1H-pyrazol-3-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(2H-tetrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((3-(1H-pyrazol-5-yl)isoquinolin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1H-pyrazol-1-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-(imidazo[1,5-a]pyridin-8-ylmethoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1,5-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-ethyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(difluoromethoxy)-5-(imidazo[1,2-a]pyridin-8-ylmethoxy)isonicotinaldehyde,
2-methoxy-5-((2-phenylpyridin-3-yl)methoxy)isonicotinaldehyde,
5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyridin-4-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-([2,3'-bipyridin]-3-ylmethoxy)-2-methoxyisonicotinaldehyde,
2-methoxy-5-((2-(o-tolyl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2'-methoxy-[2,3'-bipyridin]-3-yl)methoxy)isonicotinaldehyde,
methyl 4-(((2-formylpyridin-2-yl)oxy)methyl)benzoate,
4-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid,
4-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,
methyl 3-(((4-formylpyridin-3-yl)oxy)methyl)benzoate,
methyl 3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoate,
3-(((4-formylpyridin-3-yl)oxy)methyl)benzoic acid,
3-(((2-formyl-6-methylpyridin-3-yl)oxy)methyl)benzoic acid,
3-(((2-formylpyridin-3-yl)oxy)methyl)benzoic acid,
2-methoxy-5-((2-(1-(2-methoxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methoxy-5-((2-(1-propyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxyisonicotinaldehyde,
2-methoxy-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-((2-(1-(2,2-difluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((2(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)picolinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-6-methylpicolinaldehyde,
2-(difluoromethoxy)-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
5-(imidazo[1,2-a]pyridin-8-ylmethoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,
5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-(2-methoxyethoxy)isonicotinaldehyde,
5-((3-(1-isopropyl-1H-pyrazol-5-yl)pyrazin-2-yl)methoxy)-2-methoxyisonicotinaldehyde,
3-((4-formyl-6-methoxypyridin-3-yloxy)methyl)picolinate,
5-((2-(2-hydroxypropan-2-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)nicotinaldehyde,
3-hydroxy-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-(benzyloxy)-5-hydroxyisonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxyisonicotinaldehyde,
5-((2-(2-isopropyl-2H-1,2,4-triazol-3-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-(2-hydroxyethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid
2,2,2-trifluoroacetic acid: 6-(((4-formylpyridin-3-yl)oxy)methyl)picolinic acid (1:1),
2-methoxy-5-((2-(1-(((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-5-yl)pyridin-3-3-yl)methoxy)isonicotinaldehyde,
5-((2-(4-methyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy-2-oxy)-2-oxo-1,2-dihydropyridine-4-carbaldehyde,

5-((2-(1-cyclobutyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclohexyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclohexylmethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxyisonicotinaldehyde,
5-((2-(1-cyclopentyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-2-methoxyisonicotinaldehyde,
2-(5-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl) pyridin-2-yl)-1H-pyrazol-1-yl)acetic acid,
methyl 3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy) methyl)pyridin-2-yl)-1H-pyrazol-1-yl)propanoate,
3-(3-(3-((4-formyl-6-methoxypyridin-3-yloxy)methyl) pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,
3-(5-(3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl) pyridin-2-yl)-1H-pyrazol-1-yl)propanoic acid,
3-(((4-formyl-6-methoxypyridin-3-yl)oxy)methyl)benzoic acid,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinonitrile 2,2,2-trifluoroacetate,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid,
6-(((4-formylpyridin-3-yl)oxy)methyl)nicotinic acid hydrochloride,
6-(((4-formylpyridin-3-yl)oxy)methyl)-N-(methylsulfonyl)nicotinamide,
2,2,2-trifluoroacetic acid: 6-(((4-formylpyridin-3-yl)oxy) methyl)-N-(methylsulfonyl)nicotinamide (2:1), 2-(2-methoxyethoxy)-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy) isonicotinaldehyde,
2-methoxy-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-(2-methoxyethoxy)-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methyl-5-((2-(1-(2,2,2-trifluoromethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
2-methyl-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-chloro-5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde,
3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl) methoxy)-5-methylisonicotinaldehyde,
3-chloro-5-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)isonicotinaldehyde, and
3-methyl-5-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl) pyridin-3-yl)methoxy)isonicotinaldehyde,
or a tautomer or pharmaceutically acceptable salt thereof.

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