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(54) Benævnelse: **Substituerede benzaldehydforbindelser og fremgangsmåder til anvendelse deraf ved øgning af vævsiltning**

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DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention generally relates to substituted benzaldehydes and tautomers or pharmaceutically acceptable salts thereof that act as allosteric modulators of hemoglobin, methods and intermediates for their preparation, pharmaceutical compositions comprising the modulators, and said substituted benzaldehydes and tautomers or pharmaceutically acceptable salts thereof for use in treating disorders mediated by hemoglobin and disorders that would benefit from increased tissue oxygenation.

BACKGROUND OF THE INVENTION

[0002] 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.

[0003] 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, 2008 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.

[0004] US 7,160,910 discloses 2-furfuraldehydes and related compounds that are also allosteric modulators of hemoglobin. One particular compound 5-hydroxymethyl-2-furfuraldehyde (5HMF) was found to be a potent hemoglobin modulator both *in vitro* 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.

[0005] 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.

[0006] Rolan, P E et al., British Journal Of Clinical Pharmacology, vol. 35, no. 4, pages 419-425 (1993) discusses tucaresol for use in the treatment of sickle cell anaemia. Osheiza Abdulmalik et al., Acta Crystallographica Section D Biological Crystallography, vol. 125, no. 11, pages 788-928 (2011) discusses derivatives of vanillin for use in the treatment of sickle cell anaemia. Nnamani I N et al., Chemistry & Biodiversity, Helvetica Chimica Acta, vol. 5, no. 9, pages 1762-1769 (2008) discusses pyridyl derivatives of benzaldehyde for use in the treatment of sickle cell anaemia. Glasson, C R K et al., Australian Journal of Chemistry, vol. 65, pages 1371-1376 (2012) discloses the compound 2-((5'-methyl-[2,2'-bipyridin]-5-yl)methoxy)benzaldehyde as a synthetic precursor to a "pseudo cage" compound which chelates to metal ions.

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 said allosteric modulators. In other aspects, provided are allosteric modulators of hemoglobin for use in the treatment of the human or animal body. In some aspects, the allosteric modulators of hemoglobin are for use in treating disorders mediated by hemoglobin or for use in a method for increasing tissue oxygenation for treating disorders that would benefit from increased oxygenation, such methods comprising administering the allosteric modulators to a subject in need thereof.

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, DMF = dimethyl formamide, EtOAc = ethyl acetate, 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; 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, TEA = triethylamine, THF = tetrahydrofuran, TFA = trifluoroacetic acid, TLC = thin layer chromatography, and TMS = trimethylsilyl.

[0010] It is noted here 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 is 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, "$C_{1\text{-}8}$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, $C_{2\text{-}8}$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, $C_{2\text{-}8}$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 part 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] "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 as ring members. "$C_{u'-v'}$cycloalkenyl" refers to cycloalkenyl groups having u' to v' carbon atoms as ring members.

[0019] The term "hemoglobin" as used herein refers to any hemoglobin protein, including normal hemoglobin (Hb) and sickle hemoglobin (HbS).

[0020] "Heteroaryl" refers to a cyclic or polycyclic radical having at least one aromatic ring and from one to five ring heteroatoms 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.

[0021] 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, piperazine-2-one, piperazin-1-oxide, piperidine, morpholine, piperazine, isoxazoline, pyrazoline, imidazoline, pyrrolidine, and the like.

[0022] "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 "halo$C_{1\text{-}8}$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 haloakyl, 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.

[0023] 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 situations where the

heteroaryl group is substituted with an alkyl group and situations where the heteroaryl group is not substituted with the alkyl group.

[0024] "Oxo" refers to the divalent atom =O.

[0025] 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.

[0026] The term "pharmaceutically acceptable salts" 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 as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine 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 arginate 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.

[0027] 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.

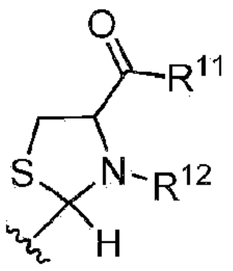
[0028] The term "pharmaceutically acceptable carrier or excipient" means a carrier or excipient that is useful in preparing a pharmaceutical composition that is generally safe, nontoxic and neither biologically nor otherwise undesirable, and includes a carrier or excipient that is acceptable for veterinary 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.

[0029] 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.

[0030] "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. 1-8, 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-ethanesulfonyl ("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.

[0031] 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. An aldehyde protecting group may be a five or six membered cyclic acetal formed from condensation of the aldehyde with ethylene or propylene glycol. An aldehyde protecting group may be an imine or hydroxyimine. The term "aldehyde protecting groups" also includes 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. A prodrug group may be hydrolyzed *in vivo* to the aldehyde. An aldehyde protecting group may be a thiazolidine or N-acetylthiazolidine prodrug group. An aldehyde protecting group may be a thiazolidine prodrug

group disclosed in US 6,355,661. The modulators provided herein may be condensed with L-cysteine or a L-cysteine derivative to form the corresponding thiazolidine protected aldehyde prodrug. The thiazolidine may have 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, cycloacyloxy, phenol, phenoxy, pyridinyl, pyrrolidinyl, amino, amido, hydroxy, alkoxy, cycloalkoxy, F, Cl, Br, NO_2, cyano, sulfuryl, and the like. Also disclosed herein 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.

[0032] 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).

[0033] 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.

[0034] "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.

[0035] 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.

[0036] 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.

[0037] 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 are 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 as 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.

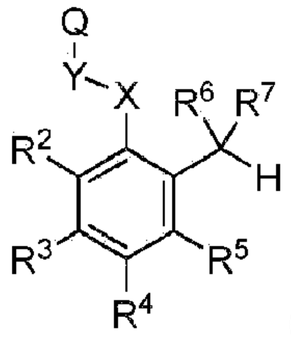
[0038] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with isotopes, such as for example deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) 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.

[0039] Unless indicated otherwise, the nomenclature of substituents that are 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 alkyl group that is substituted with alkoxy and "hydroxyalkyl" refers to an alkyl group that is substituted with hydroxy. For both of these substituents, the point of attachment is at the alkyl group.

[0040] 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

[0041] In one group of embodiments, provided is a compound of Formula (I):



(I)

or a tautomer or pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body,

wherein Q is pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, said Q being substituted with one to three R^a wherein at least one R^a is heteroaryl optionally substituted with one to three R^c;

Y is $CR^{1a}R^{1b}$, wherein R^{1a} is H or halo and R^{1b} is H or halo, optionally wherein at least one of R^{1a} and R^{1b} is F;

X is O;

R^2, R^3, R^4, and R^5 are independently 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;

R^6 and R^7 together form oxo;

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;

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^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, 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;

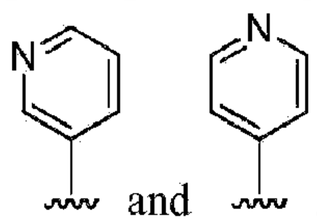
each R^d and R^f is independently selected from the group consisting of hydrogen, C_{1-8} alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl; and

each R^e and 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.

[0042] In one group of embodiments, Y is CH_2 and R^5 is H, halo, OH, CHO, or OCH_3.

[0043] 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.

[0044] In one group of embodiments, Q is selected from the group consisting of



.

[0045] 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.

[0046] 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 is heteroaryl 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 pyrazolyl 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.

[0047] In one group of embodiments, Q is substituted with at least one R^a selected from the group consisting of OH, $NHC(O)(C_{1-8}alkyl)$,$N(C_{1-8}alkyl)C(O)(C_{1-8}alkyl)$, $-NHC(O)_2(C_{1-8}alkyl)$, $-N(C_{1-8}alkyl)C(O)_2(C_{1-8}alkyl)$, $NHS(O)_2(C_{1-8}alkyl)$, $N(C_{1-8}alkyl)S(O)_2(C_{1-8}alkyl)$, and heterocycloalkyl optionally substituted with one to three R^c. In some embodiments the heterocycloalkyl group is morpholino or piperazinyl optionally substituted with C_{1-8}alkyl,-$C(O)C_{1-8}$alkyl, $-C(O)_2C_{1-8}$alkyl, or $-S(O)_2C_{1-8}$alkyl.

[0048] In one group of embodiments, Q is substituted with CN or $CONR^dR^d$.

[0049] In one group of embodiments, R^2 is H.

[0050] In one group of embodiments, R^3 is H.

[0051] In one group of embodiments, R^5 is H.

[0052] In one group of embodiments, R^4 is $C_{1\text{-}8}$alkoxy.

[0053] In one group of embodiments, R^2, R^3, R^5 are H and R^4 is $C_{1\text{-}8}$alkoxy.

[0054] In one group of embodiments, R^4 is methoxy.

[0055] 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.

[0056] In one group of embodiments, R^2, R^3, R^4, and R^5 are H.

[0057] In one group of embodiments, Y is CH_2.

[0058] In one group of embodiments, Y is $CR^{1a}R^{1b}$ and at least one of R^{1a} or R^{1b} is F.

[0059] In other embodiments, the invention provides a compound of Formula (I) or a tautomer or pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body, wherein:

Y is CH_2;

R^4 is hydrogen;

R^5 is selected from the group consisting of hydrogen, halo, and OR^d; and

provided that if R^5 is OR^d, then R^a is not oxo, oxido, or halo.

[0060] In this group of embodiments, R^5 may be selected from the group consisting of hydrogen and OR^d.

[0061] In this group of embodiments, R^5 may be selected from the group consisting of hydroxy and fluoro.

[0062] In this group of embodiments, R^2 and R^3 may independently be selected from the group consisting of hydrogen, R^b, OR^d, $OC(O)R^e$, CO_2R^d, $CONR^dR^d$, and $C(O)R^d$.

[0063] In this group of embodiments, R^2 and R^3 may be H.

[0064] In other embodiments, the invention provides a compound according to Formula (I), or a tautomer or pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body, wherein:

Y is CH_2; and

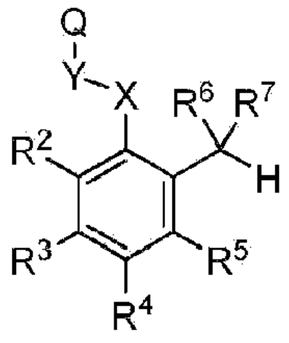
R^5 is selected from the group consisting of halo and OR^d.

[0065] In this group of embodiments, R^4 may be methoxy.

[0066] In this group of embodiments, Q may be pyridine-3-yl.

[0067] In this group of embodiments, R^5 may be selected from the group consisting of hydroxy and fluoro.

[0068] The invention further provides a compound of Formula (I):



(I)

or a tautomer or pharmaceutically acceptable salt thereof, wherein

Q is pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl, said Q being substituted with one to three R^a wherein at least one R^a is heteroaryl optionally substituted with one to three R^c;

Y is $CR^{1a}R^{1b}$, wherein R^{1a} is H or halo and R^{1b} is H or halo, optionally wherein at least one of R^{1a} and R^{1b} is F;

X is O;

R^2, R^3, R^4, and R^5 are independently 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;

R^6 and R^7 together form oxo;

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;

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

each R^c is independently selected from the group consisting of halo, $C_{1\text{-}8}$alkyl, halo$C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$alkenyl, halo$C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$alkynyl, halo$C_{2\text{-}8}$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;

each R^d and R^f is independently selected from the group consisting of hydrogen, $C_{1\text{-}8}$ alkyl, halo$C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$ alkenyl, halo$C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$ alkynyl, and halo$C_{2\text{-}8}$alkynyl; and

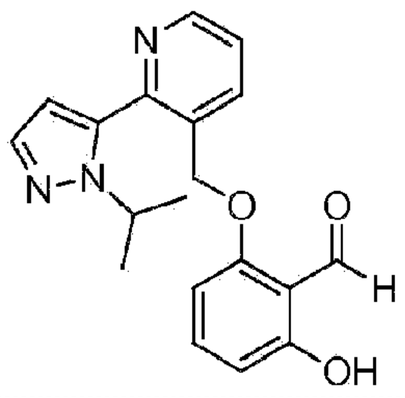
each R^e and R^g is independently selected from the group consisting of $C_{1\text{-}8}$alkyl, halo$C_{1\text{-}8}$alkyl, $C_{2\text{-}8}$ alkenyl, halo$C_{2\text{-}8}$alkenyl, $C_{2\text{-}8}$ alkynyl, and halo$C_{2\text{-}8}$alkynyl,

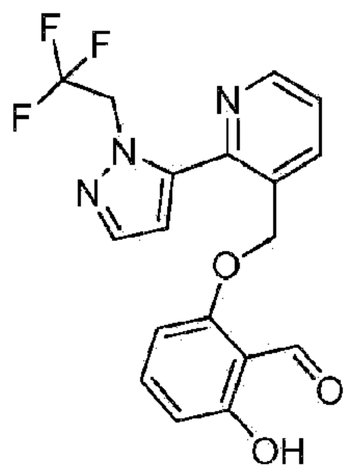
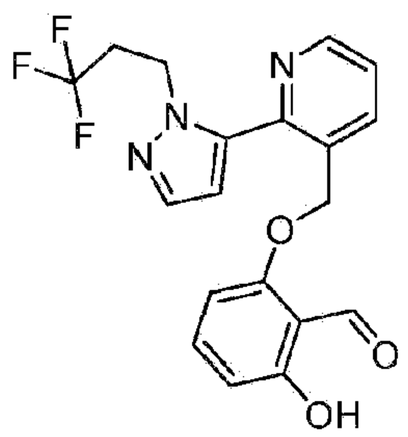
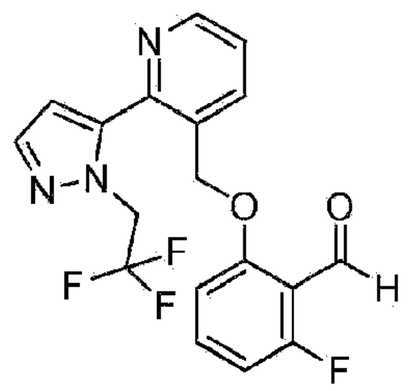
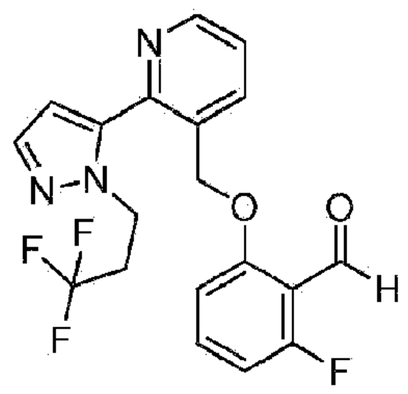
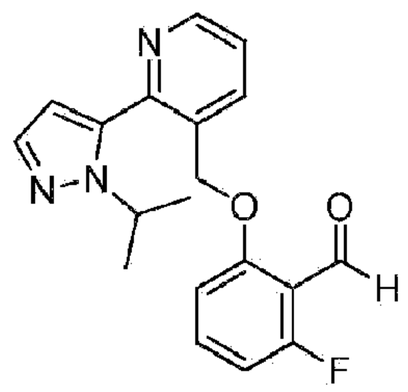
provided that the compound is other than 2-((5'-methyl-[2,2'-bipyridin]-5-yl)methoxy)benzaldehyde.

[0069] In this embodiment, the preferred identities of the moieties Q, Y, R^2, R^3, R^4, R^5, R^a, R^c and R^d are as set out in any of the embodiments above.

[0070] In one group of embodiments, a compound is selected from Table 1 below or a tautomer or pharmaceutically acceptable salt thereof.

Table 1

Compound	*Structure*	*Name*
43		2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde

Compound	*Structure*	*Name*
50		2-hydroxy-6-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde
51		2-hydroxy-6-((2-(1-(3,3,3-trifluoropropyl)-1 H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde
52		2-fluoro-6-((2-(1-(2,2,2-trifluoroethyl)-1 H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde
53		2-fluoro-6-((2-(1-(3,3,3-trifluoropropyl)-1 H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde
54		2-fluoro-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde

[0071] In one group of embodiments, the compound is selected from:

2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde,

2-hydroxy-6-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde,

2-hydroxy-6-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde,

2-fluoro-6-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde,

2-fhioro-6-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde, and

2-fluoro-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde,

or a tautomer or pharmaceutically acceptable salt thereof.

[0072] 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.

[0073] 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.

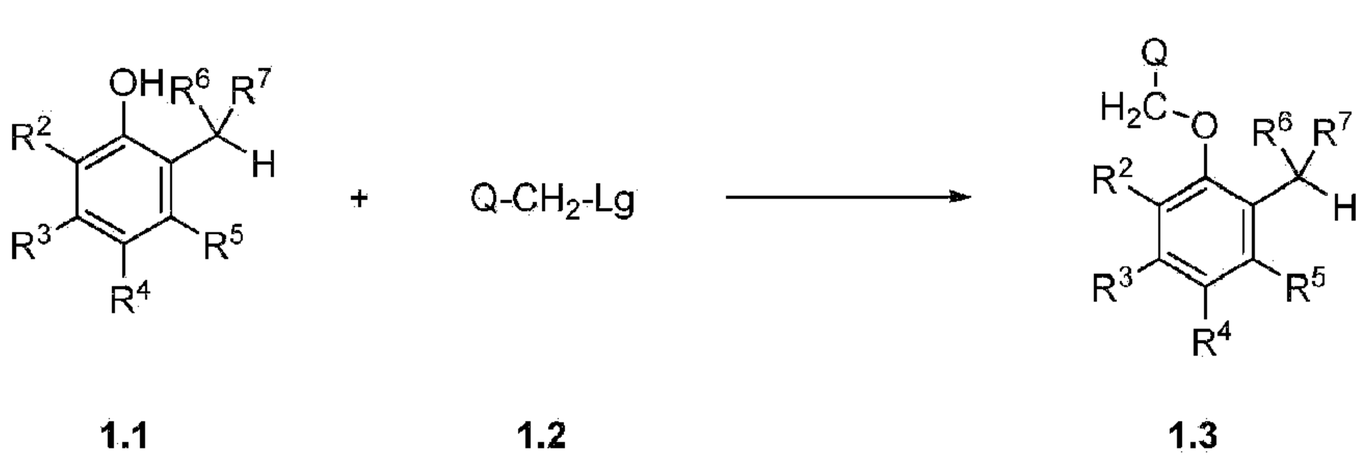
[0074] The compounds of the present invention may be prepared by known organic synthesis techniques, including the methods described in more detail in the Examples.

[0075] Also disclosed herein are intermediate compounds used in the preparation of the compounds disclosed herein.

[0076] Also disclosed herein are methods for preparing the compounds disclosed herein.

[0077] 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.

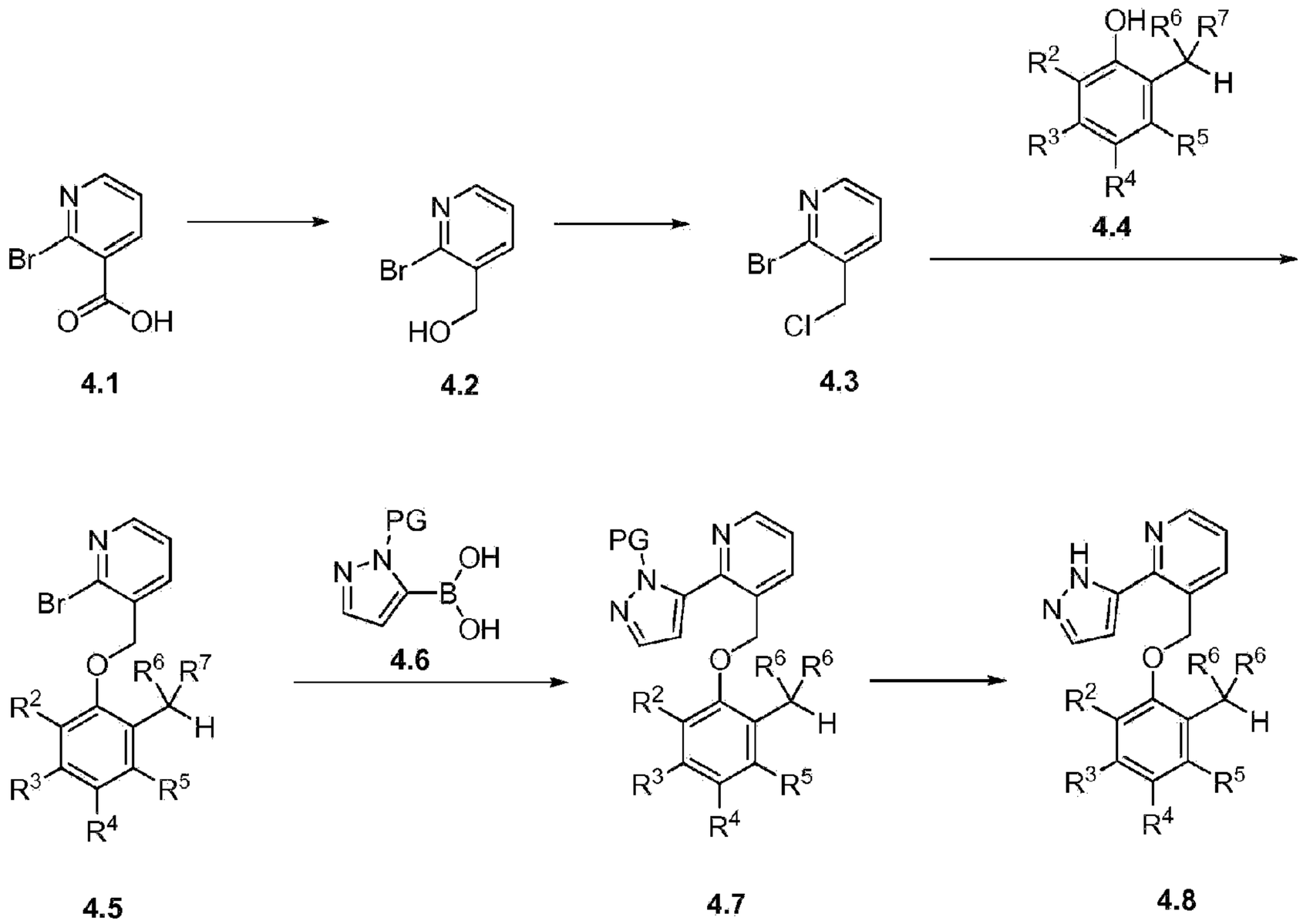
Scheme I



1.1 **1.2** **1.3**

[0078] Scheme II shows an example of synthesis of the compounds of Formula (I) where Q is pyridine-3-yl and R^a is 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 II



[0079] 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.

[0080] In one group of embodiments, certain of the compounds disclosed herein may generally be utilized as the free base. Alternatively, certain of the compounds may be used in the form of acid addition salts.

[0081] 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

[0082] 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.

[0083] 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.

[0084] 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.

[0085] 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, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils, fatty esters or polyols are conventionally employed as solvents or suspending media.

[0086] 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.

[0087] 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.

[0088] The pharmaceutical composition may additionally contain one or more other pharmacologically active agents in addition to a compound of this invention.

[0089] 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

[0090] The present invention also provides a compound of Formula (I) as disclosed herein for use in 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.

[0091] The present invention also provides a compound of Formula (I) as disclosed herein for use in 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.

[0092] The present invention also provides a compound of Formula (I) as disclosed herein for use in 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.

V. Examples

[0093] The following examples are offered to illustrate, but not to limit, the claimed invention. Compounds falling outside the scope of the claims are included for reference purposes only.

PREPARATIVE EXAMPLES

[0094] 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.

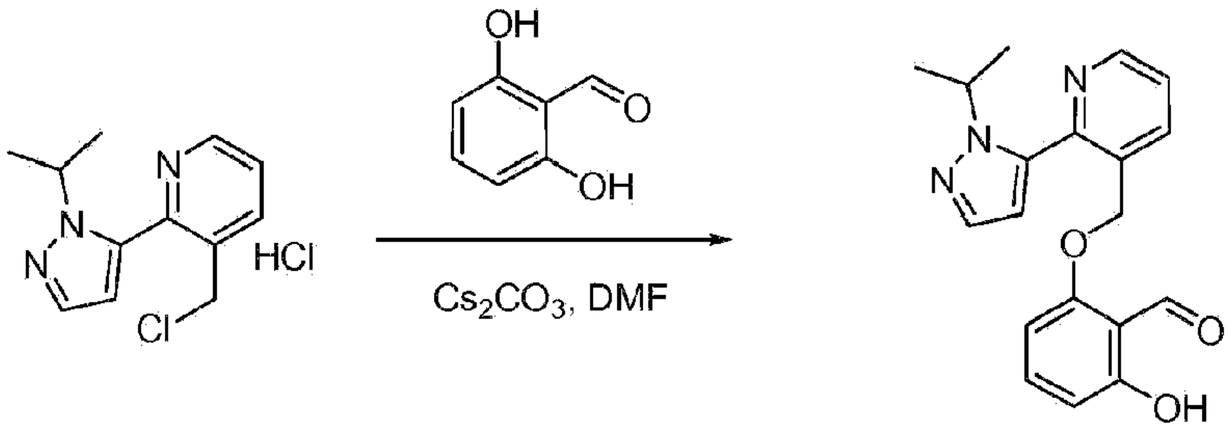
[0095] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0096] 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.

[0097] 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 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 43).

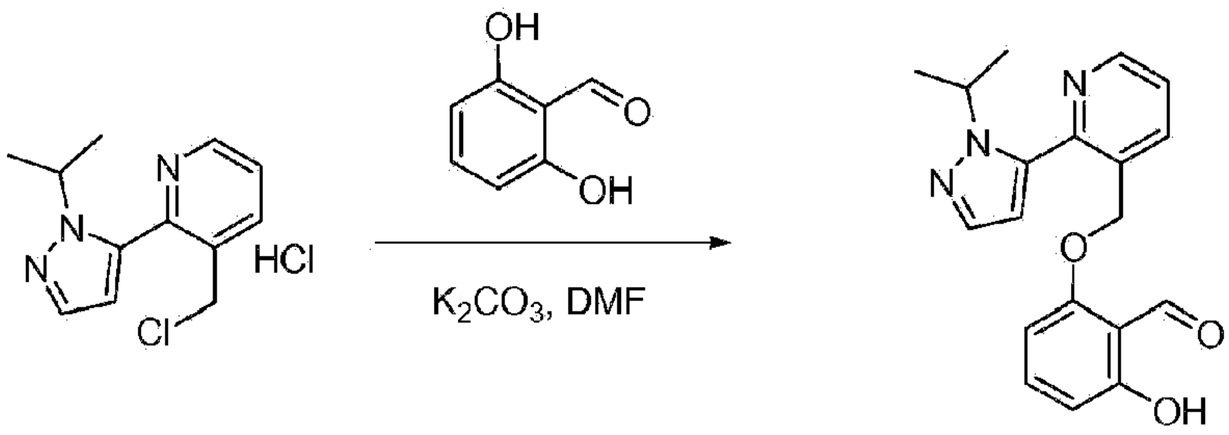
[0098]



[0099] A mixture of 2,6-dihydroxybenzaldehyde (1.96 g, 14.2 mmol, 2 eq.) and Cs_2CO_3 (7.5 g, 21.3 mmol, 3 eq.) in DMF (180 mL) was stirred at rt for 30 min. To this mixture was added 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride (1.93 g, 7.1 mmol, 1eq.) 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 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (920 mg, 37%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 8 11.96 (s, 1H), 10.40 (s, 1H), 8.77 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.49 - 7.34 (m, 2H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.37 (d, *J* = 1.8 Hz, 1H), 6.29 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 2H), 4.67 (sep, *J* = 6.7 Hz, 1H), 1.50 (d, *J* = 6.6 Hz, 6H). LRMS ($M+H^+$) m/z 338.1

Example 2. Alternative preparation of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 43).

[0100]

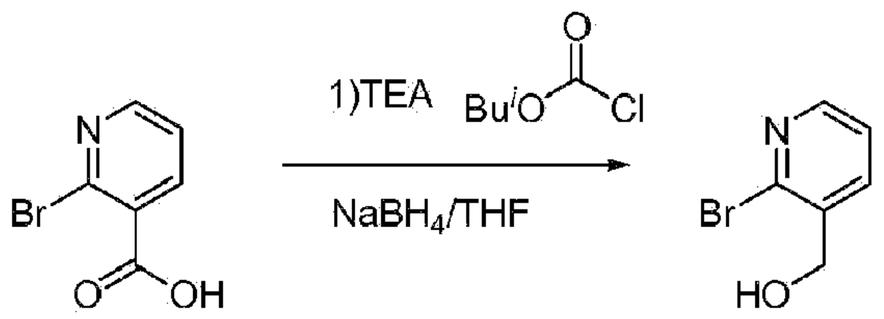


[0101] A mixture of 2,6-dihydroxybenzaldehyde (1.58 g, 11.47 mmol, 2 eq.) and K_2CO_3 (2.4 g, 17.22 mmol, 3 eq.) in DMF (150 mL) was stirred at rt for 10 min. To this mixture was added 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride (1.56 g, 5.74 mmol, 1eq.) at rt. The mixture was heated at 50 °C for 2 h, filtered, concentrated and purified on silica gel using a mixture of EtOAc and hexanes as eluent to give 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (1.71 g, 88%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 10.40 (s, 1H), 8.77 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 1.8 Hz, 1H), 7.49 - 7.34 (m, 2H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.37 (d, *J* = 1.8 Hz, 1H), 6.29 (d, *J* = 8.2 Hz, 1H), 5.10 (s, 2H), 4.67 (sep, *J* = 6.7 Hz, 1H), 1.50 (d, *J* = 6.6 Hz, 6H). LRMS ($M+H^+$) m/z 338.1

Example 3. Preparation of 5-((2-(1-isopropyl-1 H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxybenzaldehyde.

Step 1:

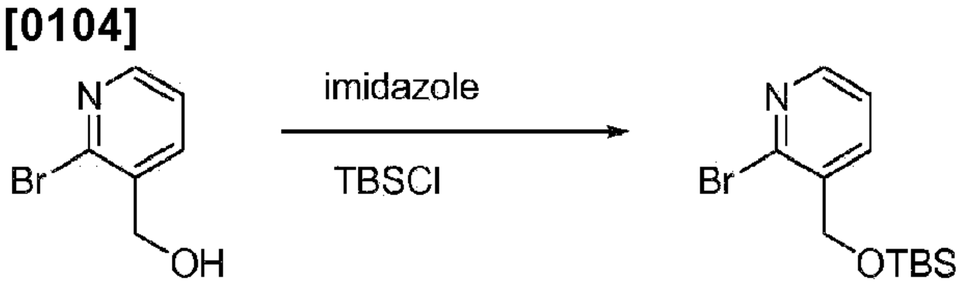
[0102]



[0103] 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

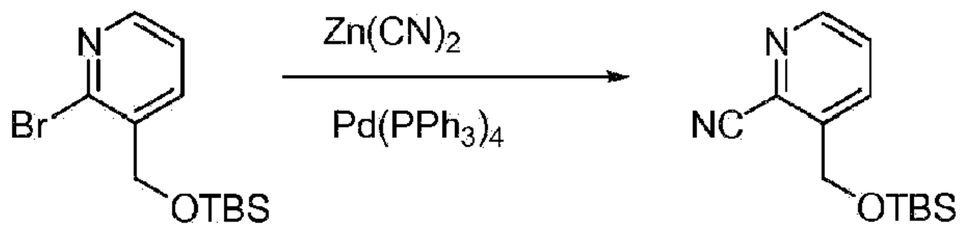
[0104]



[0105] To a mixture of (2-bromopyridin-3-yl)methanol (20.0 g, 106.4 mmol, 1 eq.) and imidazole (14.5 g, 212.8 mmol, 2 eq.) in DMF (50.0 mL) was added TBSC1 (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 Na_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 3

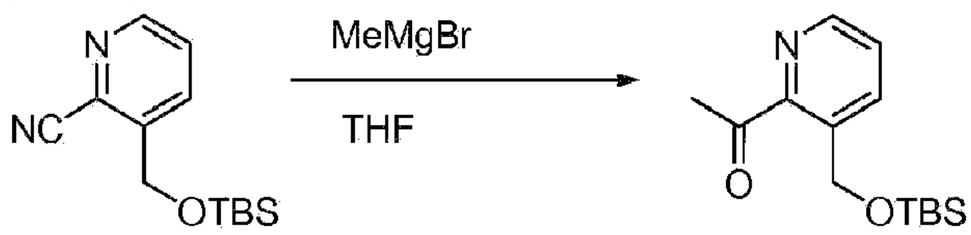
[0106]



[0107] 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 4:

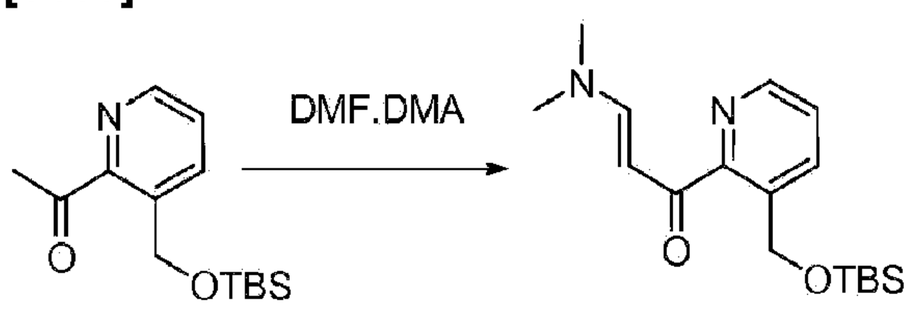
[0108]



[0109] 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 5:

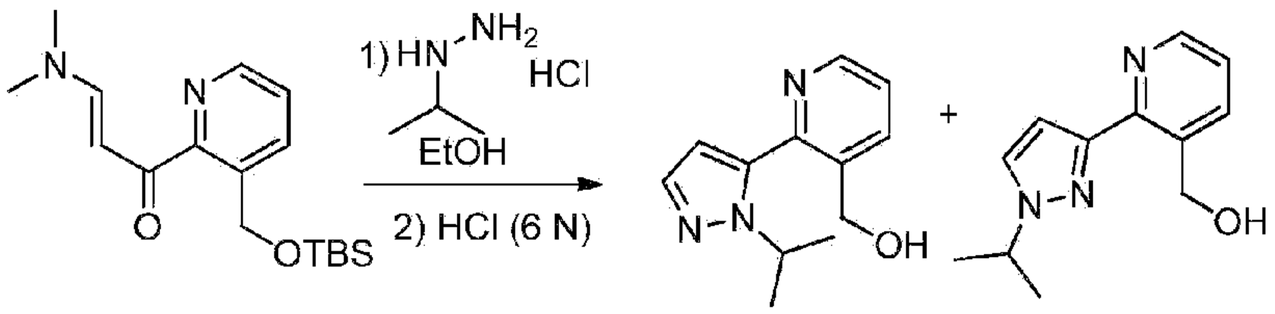
[0110]



[0111] 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 6:

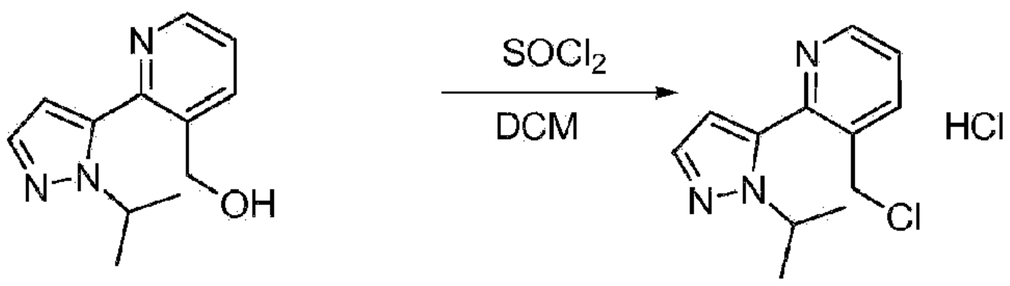
[0112]



[0113] 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.) 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-1H-pyrazol-5-yl)pyridin-3-yl)methanol: ^1H 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: ^1H 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 7:

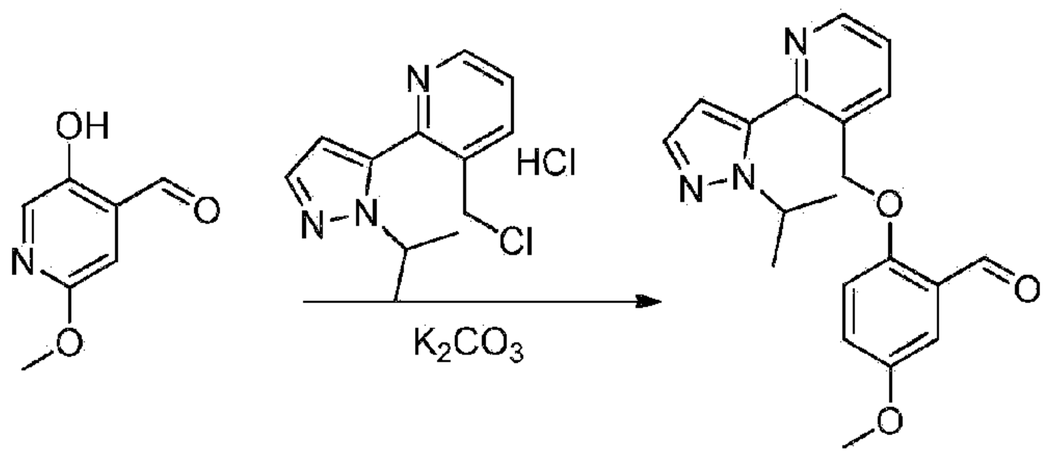
[0114]



[0115] To (2-(1-iospropyl-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)pyridine hydrochloride (700 mg) as an off-white solid, which was used for next step without further purification.

Step 8:

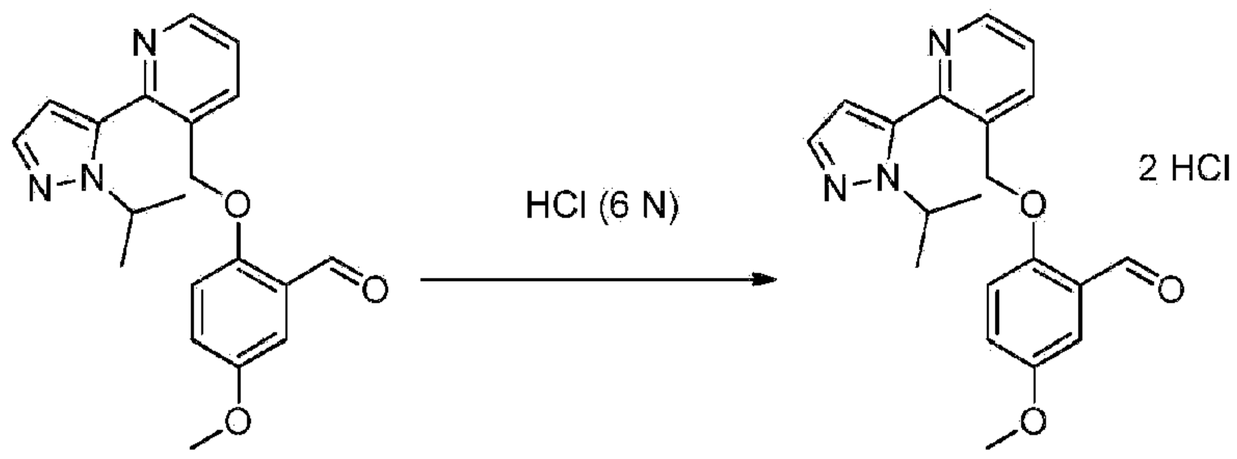
[0116]



[0117] A mixture of 5-hydroxy-2-methoxybenzaldehyde (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-methoxybenzaldehyde (590 mg, 65%) as an off-white solid.

Step 9:

[0118]

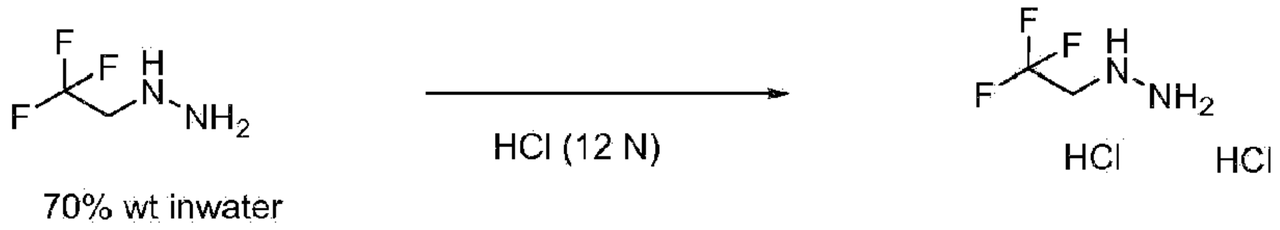


[0119] 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxybenzaldehyde (980 mg, 2.78 mmol, 1 eq.) in HCl (6 N, 9.2 mL, 20 eq.) solution was frozen at -78 °C. The mixture was lyophilized O/N to give 5-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxybenzaldehyde as a yellow solid.

Example 4. Preparation of 2-hydroxy-6-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 50).

Step 1:

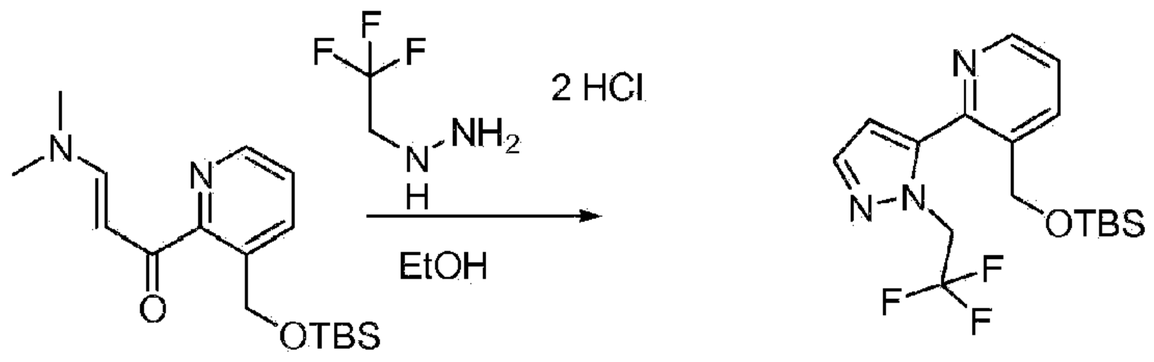
[0120]



[0121] To (3,3,3-trifluoroethyl)hydrazine (25 g, 50% wt in water, 153.5 mmol, 1 eq.) in a RB flask (250 mL) was added HCl (12 N, 25.6 mL, 307.0 mmol, 2 eq.). The mixture was concentrated to give (3,3,3-trifluoroethyl)hydrazine dihydrochloride (1.07 g) as a yellow solid. LRMS (M+H) m/z 129.1.

Step 2:

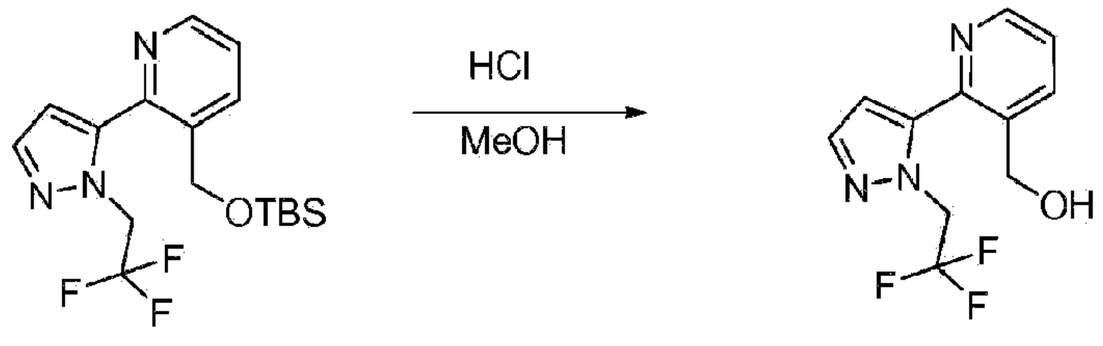
[0122]



[0123] To *(E)*-1-(3-((tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)-3-(dimethylamino)prop-2-en-1-one (crude above, 5.91 g, 18.44 mmol, 1 eq.) in EtOH (20 mL) was added (3,3,3-trifluoroethyl)hydrazine dihydrochloride (4.13 g, crude above, 22.13 mmol, 1.2 eq.) at rt. The mixture was heated at 80 °C 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 a mixture of EtOAc and hexanes as eluent to give 3-((tert-butyldimethylsilyloxy)methyl)-2-(1-(3,3,3-trifluoroethyl)-1H-pyrazol-5-yl)pyridine (5.90 g; 86% for 2 steps). LRMS ($M+H^+$) m/z 372.2.

Step 3:

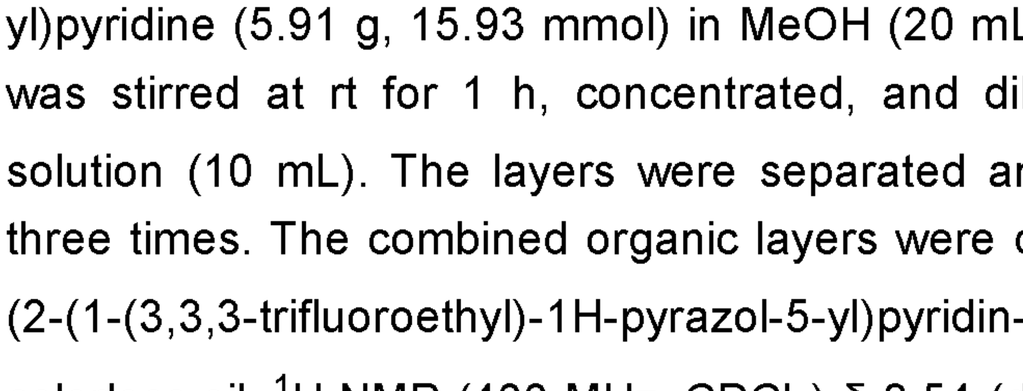
[0124]



[0125] To 3-((tert-butyldimethylsilyloxy)methyl)-2-(1-(3,3,3-trifluoroethyl)-1H-pyrazol-5-yl)pyridine (5.91 g, 15.93 mmol) in MeOH (20 mL) was added HCl (4 N, 8.0 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, and concentrated to give (2-(1-(3,3,3-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methanol (4.1 g, quantitative yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.92 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.30 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.50 (d, *J* = 1.9 Hz, 1H), 5.09 (q, *J* = 8.6 Hz, 2H), 4.63 (s, 2H), 1.76 (s, 1H). LRMS ($M+H^+$) m/z 272.1

Step 4:

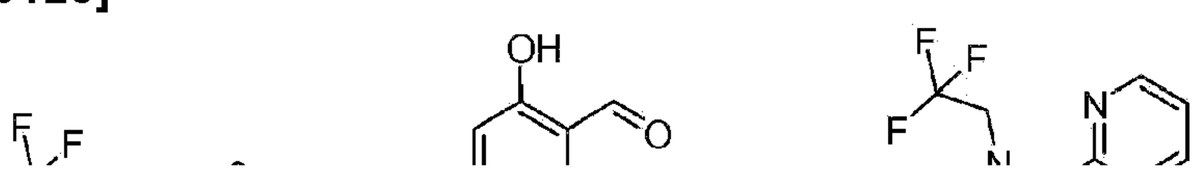
[0126]

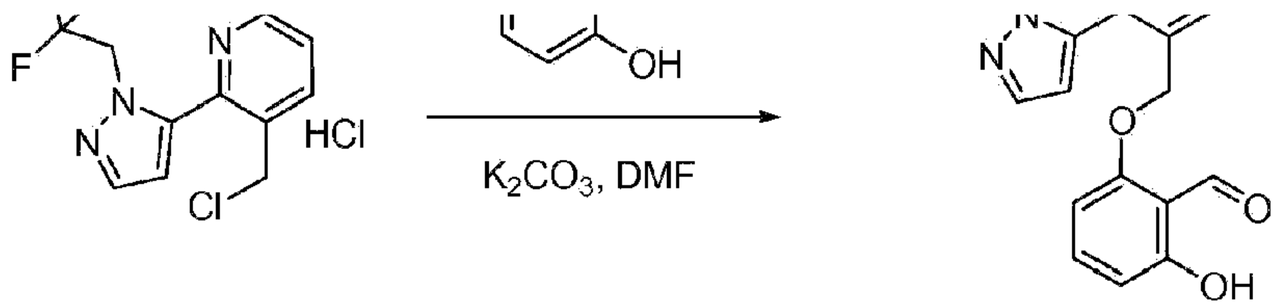


[0127] To (2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methanol (408 mg, 1.59 mmol) in DCM (5 mL) was added $SOCl_2$ (1.5 mL) at rt. The reaction mixture was stirred at rt for 4 h and concentrated to dryness. The crude solid was suspended in toluene and concentrated to dryness. The process was repeated three times and dried under vacuum to give 3-(chloromethyl)-2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridine hydrochloride (498 mg) as an off-white solid, which was used for next step without further purification.

Step 5:

[0128]



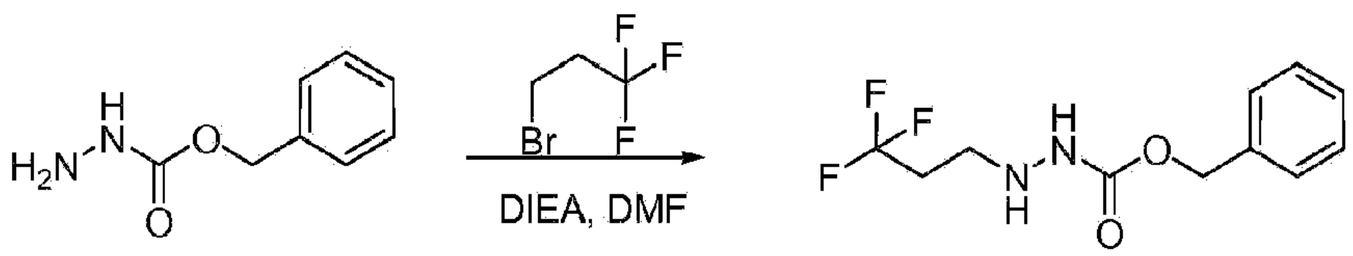


[0129] A mixture of 2,6-dihydroxybenzaldehyde (438 mg, 11.47 mmol, 2 eq.) and K_2CO_3 (2.4 g, 17.22 mmol, 3 eq.) in DMF (150 mL) was stirred at rt for 10 min. To this mixture was added 3-(chloromethyl)-2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridine hydrochloride (498 mg, 1.59 mmol, 1eq.) at rt. The mixture was heated at 50 °C for 2 h, filtered, concentrated and purified on silica gel using a mixture of EtOAc and hexanes as eluent to 2-hydroxy-6-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (338.4 mg, 56%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (s, 1H), 10.41 (s, 1H), 8.76 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.69 (d, *J* = 1.9 Hz, 1H), 7.49 - 7.39 (m, 2H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.53 (d, *J* = 1.9 Hz, 1H), 6.32 (d, *J* = 8.3 Hz, 1H), 5.30 (q, *J* = 8.6 Hz, 2H), 5.17 (s, 2H). LRMS ($M+H^+$) m/z 378.1

Example 5. Preparation of 2-hydroxy-6-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 51).

Step 1:

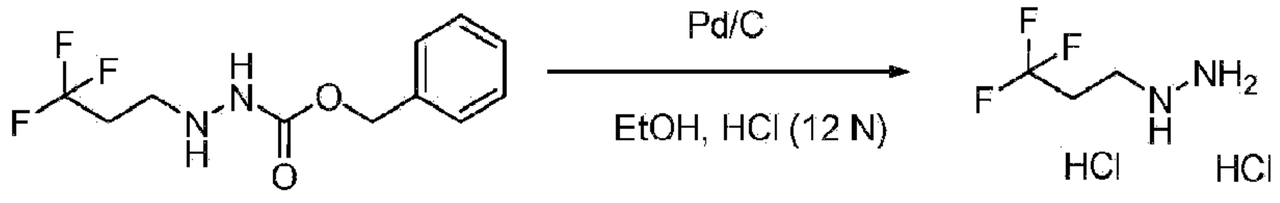
[0130]



[0131] To a mixture of benzyl hydrazinecarboxylate (5.0 g, 30.3 mmol, 1 eq.) and DIEA (15.0 mL, 90.9 mmol, 3 eq.) in DMF (20 mL) was added 3,3,3-trifluoropropyl bromide (10.7 g 60.6 mmol, 2 eq.) at rt. The mixture was heated at 80 °C for 20 h, concentrated, and purified on silica gel using a mixture of EtOAc and hexanes as eluent to benzyl 2-(3,3,3-trifluoropropyl)hydrazinecarboxylate (4.2 g; 53%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 - 7.17 (m, 5H), 6.11 (s, 1H), 5.01 (s, 2H), 4.00 (s, 1H), 3.00 (dd, *J* = 12.2, 7.1 Hz, 2H), 2.17 (qt, *J* = 10.8, 7.3 Hz, 2H). LRMS ($M+H^+$) m/z 263.1

Step 2:

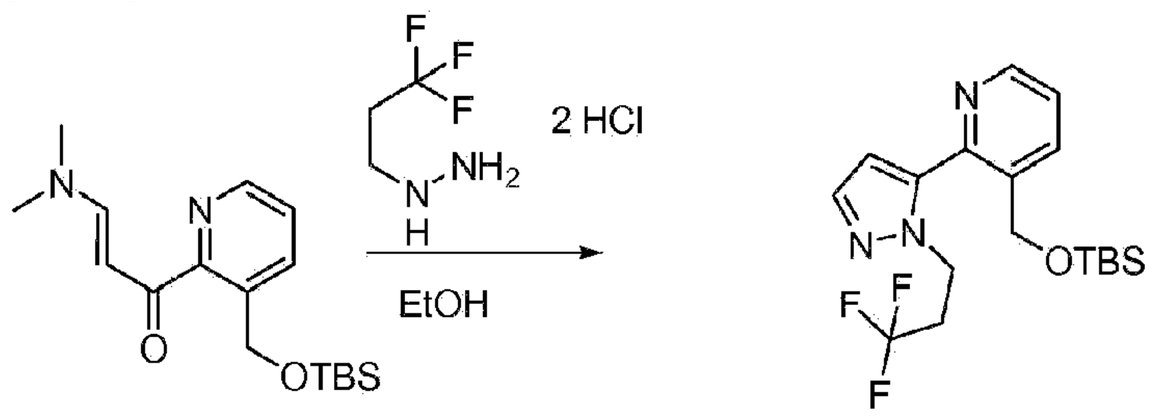
[0132]



[0133] To benzyl 2-(3,3,3-trifluoropropyl)hydrazinecarboxylate (1.7 g, 6.49 mmol, 1 eq.) in a mixture of EtOH (30 mL) were added Pd/C (1.0 g) and HCl (12 N, 2.0 mL). The mixture was charged with H_2 (60 psi), stirred at rt for 1 h, filtered, and concentrated to give (3,3,3-trifluoropropyl)hydrazine dihydrochloride (1.07 g) as a yellow solid. LRMS (M+H) m/z 129.1.

Step 3:

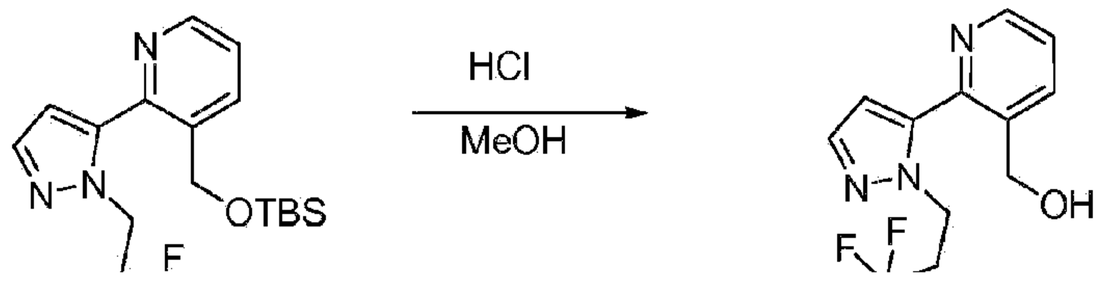
[0134]

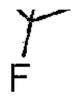


[0135] To *(E)*-1-(3-((tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)-3-(dimethylamino)prop-2-en-1-one (crude above, 1.73 g, 5.41 mmol, 1 eq.) in EtOH (10 mL) was added (3,3,3-trifluoropropyl)hydrazine dihydrochloride (1.30 g, crude above, 6.49 mmol, 1.2 eq.) at rt. The mixture was heated at 80 °C for 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 a mixture of EtOAc and hexanes as eluent to give 3-((tert-butyldimethylsilyloxy)methyl)-2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridine (1.58 g; 76% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.96 - 7.88 (m, 1H), 7.51 (d, *J* = 1.9 Hz, 1H), 7.29 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.34 (d, *J* = 1.9 Hz, 1H), 4.62 (s, 2H), 4.45 - 4.33 (m, 2H), 2.82 - 2.61 (m, 2H), 0.85 (s, 8H), -0.00 (s, 5H). LRMS ($M+H^+$) m/z 386.2.

Step 4:

[0136]

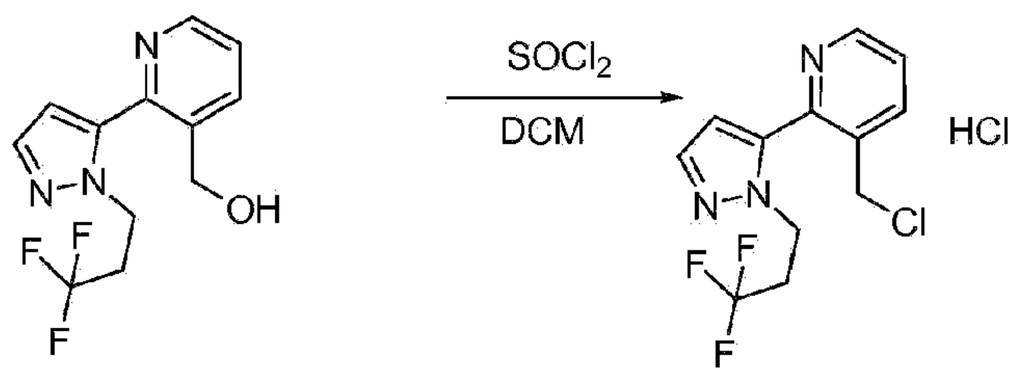




[0137] To 3-((tert-butyldimethylsilyloxy)methyl)-2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridine (1.58 g, 4.1 mmol) in MeOH (20 mL) was added HCl (4 N, 4.0 mL). The mixture was stirred at rt for 1 h, concentrated, and diluted with EtOAc (50 mL) and $NaHCO_{3(sat)}$ solution (10 mL). The layers were separated and aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over Na_2SO_4, and concentrated to give (2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methanol (1.1 g, 99%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.00 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.38 (dd, *J* = 7.9, 4.8 Hz, 1H), 6.48 (d, *J* = 1.9 Hz, 1H), 4.69 (s, 2H), 4.51 - 4.43 (m, 2H), 2.85 - 2.72 (m, 2H), 2.70 (s, 1H). LRMS ($M+H^+$) m/z 272.1.

Step 5:

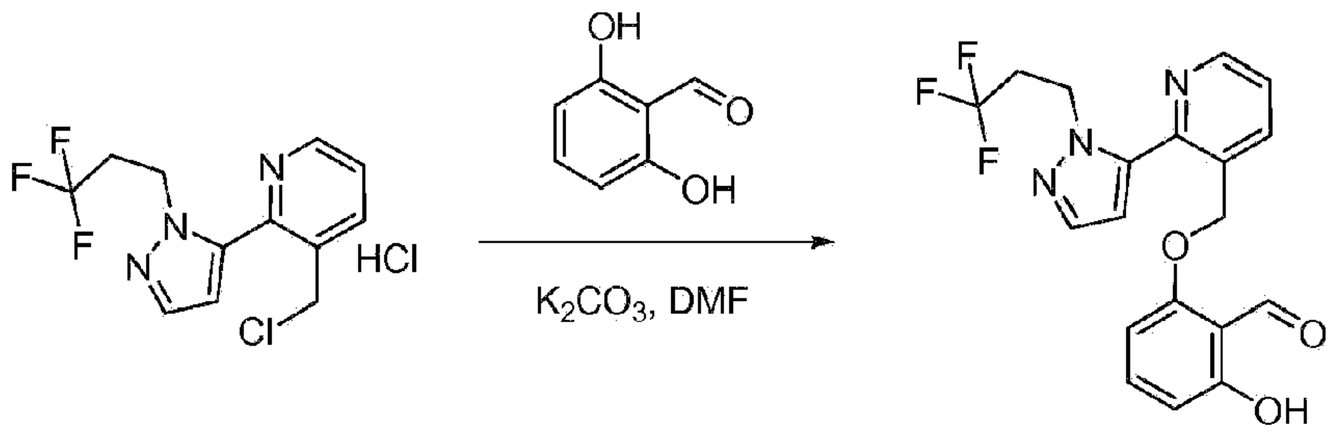
[0138]



[0139] To (2-(1-(2,2,2-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methanol (140 mg, 0.52 mmol) in DCM (5 mL) was added $SOCl_2$ (2.0 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-(2,2,2-trifluoropropyl)-1H-pyrazol-5-yl)pyridine hydrochloride (498 mg) as an off-white solid, which was used for next step without further purification.

Step 6:

[0140]



[0141] A mixture of 2,6-dihydroxybenzaldehyde (144 mg, 1.04 mmol, 2 eq.) and K_2CO_3 (214 mg, 1.56 mmol, 3 eq.) in DMF (20 mL) was stirred at rt for 10 min. To this mixture was added 3-(chloromethyl)-2-(1-(2,2,2-trifluoropropyl)-1H-pyrazol-5-yl)pyridine hydrochloride (168 mg, 0.52 mmol, 1eq.) at rt. The mixture was heated at 50 °C for 2 h, filtered, concentrated and on RP-HPLC (Gemini 21.2 x 150 mm) using a mixture of CH_3CN and water as eluent to give 2-hydroxy-6-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (53.5 mg, 26%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.98 (s, 1H), 10.38 (s, 1H), 8.77 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.49 - 7.39 (m, 2H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.44 (d, *J* = 1.9 Hz, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 5.15 (s, 2H), 4.56 (dd, *J* = 8.3, 6.7 Hz, 2H), 3.02 - 2.72 (m, 2H). LRMS ($M+H^+$) m/z 392.1.

Example 6. Preparation of Benzaldehyde Derivatives.

[0142] Compounds 52-54 were prepared according to the methods described above.

[0143] 2-Fluoro-6-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 52). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.74 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.21 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.54 - 7.41 (m, 2H), 6.82 (dd, *J* = 10.0, 8.6 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.56 (d, *J* = 1.9 Hz, 1H), 5.28 (q, *J* = 8.6 Hz, 2H), 5.20 (s, 2H).

[0144] 2-Fluoro-6-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 53). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.75 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.22 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.62 (d, *J* = 1.9 Hz, 1H), 7.54 - 7.42 (m, 2H), 6.83 (dd, *J* = 10.0, 8.7 Hz, 1H), 6.73 (d, *J* = 8.5 Hz, 1H), 6.46 (d, *J* = 1.9 Hz, 1H), 5.19 (s, 2H), 4.59 - 4.51 (m, 2H), 2.96 - 2.76 (m, 2H).

[0145] 2-Fluoro-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 54). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.66 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.13 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.46 - 7.29 (m, 2H), 6.72 (dd, *J* = 10.0, 8.7 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.29 (d, *J* = 1.8 Hz, 1H), 5.03 (s, 2H), 4.56 (sep, *J* = 6.7 Hz, 1H), 1.40 (d, *J* = 6.6 Hz, 6H).

IN VITRO TESTING

Example 7. Modulation of Hemoglobin Oxygen affinity by Substituted Benzaldehyde Compounds-Assay Procedure.

[0146] Oxygen equilibrium curves (OEC) in purified Hemoglobin S (HbS) were measured by the change in p50, the partial pressure of oxygen at which the heme 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 8. Modulation of Hemoglobin Oxygen affinity by Substituted Benzaldehyde Compounds-Assay Results.

[0147] 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)] X 100.

Example 9. Polymerization Assay.

[0148] 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.

[0149] 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%.

Compound	*% delta Delay*
43	††
4-((2-formyl-3-hydroxyphenoxy)methyl)benzoic acid	††
2-((3-(2H-tetrazol-5-yl)benzyl)oxy)-6-hydroxybenzaldehyde	†
2-((4-(2H-tetrazol-5-yl)benzyl)oxy)-6-hydroxybenzaldehyde	††
methyl 4-((2-formylphenoxy)methyl)benzoate	†
4-((2-formylphenoxy)methyl)benzoic acid	††
methyl 3-((2-formylphenoxy)methyl)benzoate	†
2-bromo-3-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde	†

Example 10. RIT Assay

[0150] A relaxed-to-tense transition assay ("R/T assay") was used to determine the ability of substituted benzaldehyde compounds to mantain 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 comound). 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.

[0151] 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.

[0152] Table 2 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. Unless noted otherwise, the compounds in Table 2 were tested at 9 µM.

Table 2. delta R

Compound	*delta R (%)*
43	+++ (30 µm)
2-(imidazo[1,2-a]pyridin-2-ylmethoxy)-5-methoxybenzaldehyde	++
5-methoxy-2-(quinolin-5-ylmethoxy)benzaldehyde	++
5-methoxy-2-((8-methylimidazo[1,2-a]pyridin-2-yl)methoxy)benzaldehyde	+
2-((1H-indazol-4-yl)methoxy)-5-methoxybenzaldehyde	++
5-methoxy-2-(pyridin-3-ylmethoxy) benzaldehyde	+
4-((2-formyl-3-hydroxyphenoxy)methyl)benzoic acid	+++ (30 µm)
2-((3-(2H-tetrazol-5-yl)benzyl)oxy)-6-hydroxybenzaldehyde	+++
2-((4-(2H-tetrazol-5-yl)benzyl)oxy)-6-hydroxybenzaldehyde	+++

Example 11. Whole Blood Assay

[0153] 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.

[0154] Table 3 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. The compounds in Table 3 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 3. delta p50% Values for Whole Blood Assay

Compound	*delta p50%*
43	+++
4-((2-formyl-3-hydroxyphenoxy)methyl)benzoic acid	+
2-((3-(2H-tetrazol-5-yl)benzyl)oxy)-6-hydroxybenzaldehyde	+
2-((4-(2H-tetrazol-5-yl)benzyl)oxy)-6-hydroxybenzaldehyde	+

Example 12. Pharmacokinetic Study of Compound 43 (HCl salt)

I.V. STUDY

[0155] Sprague Dawley rats were treated with 7.8 mg/kg of Compound 43 dissolved in 10%DMA:50%PEG:16%ca vitron. At specified time points 10 μL of whole blood/plasma was removed from rats and treated with 490 μl pH 3 buffer + 500 μL ACN/IS, then shaken for 1 hour, centrifuged for 10 minutes at 57 rpm at 4°C. The supernatant was transferred to a filter plate and centrifuged at 2000 rpm for 1 minute at 4°C. The samples were then analyzed by LC-MS/MS monitoring parent aldehyde. Concentrations in blood and plasma are shown in Table 4. Key P/K parameters are shown in Table 5.

Table 4

Compound 43 7.8mpk IV in rat						
	blood conc (uM)			plasma conc (uM)		
time (min)	A	B	C	A	B	C
0	BLLOQ	BLLOQ	BLLOQ	BLLOQ	BLLOQ	BLLOQ
5	259	246	281	7.56	8.68	7.44
15	287	341	285	8.38	8.42	7.16
30	283	333	292	no sample	8.66	7.1
60	256	203	285	6.12	7.52	7.22
120	263	274	280	3.92	6.02	5.22
240	248	225	259	3.72	5.24	5.88

Compound 43 7.8mpk IV in rat						
	blood conc (uM)			plasma conc (uM)		
time (min)	A	B	C	A	B	C
480	118	136	22.9	2.06	2.66	3.15
1440	81.1	85	70.8	1.07	1.38	1.51

Table 5

Compound 43 7.8mpk IV in rat			
		Blood	Plasma
t1/2 beta	min	749.0	619.1
CL	ml/min/kg	0.08	4.45
Vss	L/kg	0.09	4.11
AUClast	min*µmol/L	215846.3	4114.8

ORAL STUDY

[0156] SD Rats were treated by gavage with 44 mg/kg and 100 mg/kg dissolved in 10%DMA:90% PEG. At specified time points blood was taken and worked up as described above in the IV Study. Key Parameters are shown in Table 6.

Table 6

Compound 43 :2 PO in rats							
Blood					Plasma		
				ratio			ratio
dose	mg/kg	44	100	2.27	44	100	2.27
Tmax	min	320.00	720.00		200.00	680.00	
Cmax	µmol/L	381.33	1096.67	2.88	14.79	44.53	3.01
AUClast	min*µmol/L	395638.27	1384101.11	3.50	12517.54	52836.17	4.22

[0157] 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.

REFERENCES CITED IN THE DESCRIPTION

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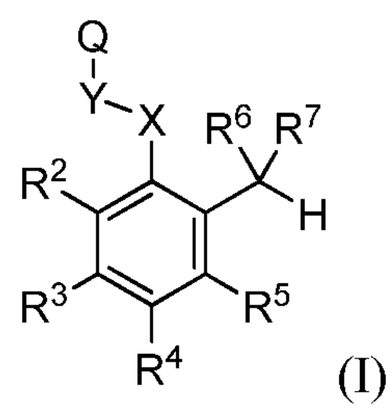
PATENTKRAV

1. Forbindelse med formlen (I):



(I)

eller en tautomer eller et farmaceutisk acceptabelt salt deraf, til anvendelse i behandlingen af menneske- eller dyrelegeme,

hvor Q er pyridin-2-yl, pyridin-3-yl, eller pyridin-4-yl, hvor Q er substitueret med ét til tre R^a, hvor mindst ét R^a er heteroaryl eventuelt substitueret med ét til tre R^c;

Y er $CR^{1a}R^{1b}$, hvor R^{1a} er H eller halo og R^{1b} er H eller halo, eventuelt hvor mindst ét af R^{1a} og R^{1b} er F;

X er O;

R^2, R^3, R^4 og R^5 uafhængigt er udvalgt fra gruppen bestående af 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, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$ og N^3; eller R^5 er $-(CH_2)_pR^{5a}$, hvor p er 0 eller 1 og R^{5a} er OH;

R^6 og R^7 sammen danner oxo;

hver R^a er uafhængigt udvalgt fra gruppen bestående af 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 eventuelt substitueret med ét til tre R^c, heteroaryl eventuelt substitueret med ét til tre R^c, og heterocycloalkyl eventuelt substitueret med ét til tre R^c;

hver R^b er uafhængigt udvalgt fra gruppen bestående af C_{1-8}-alkyl, C_{2-8}-alkenyl og C_{2-8}-alkynyl, der hver eventuelt er uafhængigt substitueret med ét til tre halo, OR^d eller NR^dR^d;

hver R^c er uafhængigt udvalgt fra gruppen bestående af 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, CO_2R^f, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2Rg$, $S(O)_2NR^fR^f$ og N^3, hvor m er udvalgt fra gruppen bestående af 0, 1, 2, 3, 4, 5 og 6;

hver R^d og R^f er uafhængigt udvalgt fra gruppen bestående af hydrogen, C_{1-8}-alkyl, haloC_{1-8}-alkyl, C_{2-8}-alkenyl, haloC_{2-8}-alkenyl, C_{2-8}-alkynyl og haloC_{2-8}-alkynyl; og

hver R^e og R^g er uafhængigt udvalgt fra gruppen bestående af C_{1-8}-alkyl, haloC_{1-8}-alkyl, C_{2-8}-alkenyl, haloC_{2-8}-alkenyl, C_{2-8}-alkynyl og haloC_{2-8}-alkynyl.

2. Forbindelse til anvendelse ifølge krav 1, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor Q er substitueret med ét til tre R^a, hvor mindst ét R^a er heteroaryl eventuelt substitueret med ét til tre R^c, og hvor heteroaryldelen er bundet til Q ved ringatomet stødende op til det ringatom, der bærer Y.

3. Forbindelse til anvendelse ifølge krav 1 eller 2, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor Q er substitueret med heteroaryl med ét eller to nitrogenringatomer.

4. Forbindelse til anvendelse ifølge krav 1, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor

Q er pyridin-3-yl substitueret med ét til tre R^a;

Y er $CR^{1a}R^{1b}$, hvor R^{1a} er H og R^{1b} er H;

R^2, R^3, R^4 og R^5 uafhængigt er udvalgt fra gruppen bestående af hydrogen, halo og OR^d;

mindst ét R^a er heteroaryl eventuelt substitueret med ét til tre R^c; og hver R^c er uafhængigt udvalgt fra gruppen bestående af C_{1-4}-alkyl og haloC_{1-4}-alkyl.

5. Forbindelse til anvendelse ifølge krav 4, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor Q er substitueret med heteroaryl med ét eller to nitrogenringatomer.

6. Forbindelse til anvendelse ifølge krav 4 eller 5, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor mindst ét R^a er bundet til Q ved ringatomet stødende op til det ringatom, der bærer Y.

7. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 4-6, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor mindst ét R^a er heteroaryl substitueret med mindst ét C_{1-4}-alkyl.

8. Forbindelse til anvendelse ifølge krav 7, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor mindst ét R^a er pyrazolyl substitueret med mindst ét C_{1-4}-alkyl.

9. Forbindelse til anvendelse ifølge krav 4 udvalgt fra gruppen bestående af:

2-hydroxy-6-((2-(1-(2,2,2-trifluorethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyd,

2-hydroxy-6-((2-(1-(3,3,3-trifluorpropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyd,

2-fluor-6-((2-(1-(2,2,2-trifluorethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyd,

2-fluor-6-((2-(1-(3,3,3-trifluorpropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyd og

2-fluor-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyd

eller en tautomer eller et farmaceutisk acceptabelt salt deraf.

10. Forbindelse til anvendelse ifølge krav 1, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor heteroarylet er udvalgt fra gruppen bestående af en imidazopyridinylgruppe, en pyrrolopyridinylgruppe, en pyrazolopyridinylgruppe, en triazolopyridinylgruppe, en pyrazolopyrazinylgruppe, en pyridinylgruppe, en pyrazinylgruppe, en oxazolylgruppe, en imidazolylgruppe,

en triazolylgruppe, en tetrazolylgruppe, en pyrazolylgruppe, en quinolinylgruppe, en isoquinolinylgruppe, en indazolylgruppe, en benzooxazolylgruppe, en naphthyridinylgruppe og en quinoxalinylgruppe.

11. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-10, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, der er til anvendelse i en fremgangsmåde til øgning af vævsiltning.

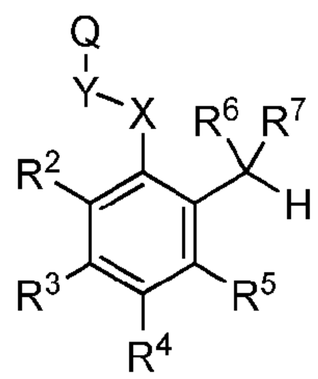
12. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-10, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, der er til anvendelse i en fremgangsmåde til behandling af en tilstand forbundet med oxygendeficiens.

13. Forbindelse til anvendelse ifølge krav 12, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor tilstanden er udvalgt fra gruppen bestående af cancer, en lungeforstyrrelse, apopleksi, højdesyge, ulcer, liggesår, Alzheimers sygdom, akut respiratorisk sygdomssyndrom og et sår.

14. Forbindelse til anvendelse ifølge et hvilket som helst af kravene 1-10, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, der er til anvendelse i en fremgangsmåde til behandling af seglcellesygdom.

15. Forbindelse til anvendelse ifølge krav 13, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor tilstanden er en lungeforstyrrelse.

16. Forbindelse med formlen (I):



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eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor

Q er pyridin-2-yl, pyridin-3-yl eller pyridin-4-yl, hvor Q er substitueret med ét til tre R^a, hvor mindst ét R^a er heteroaryl eventuelt substitueret med ét til tre R^c;

Y er $CR^{1a}R^{1b}$, hvor R^{1a} er H eller halo og R^{1b} er H eller halo, eventuelt hvor mindst ét af R^{1a} og R^{1b} er F;

X er O;

R^2, R^3, R^4 og R^5 uafhængigt er udvalgt fra gruppen bestående af 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, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$ og N^3; eller R^5 er $-(CH_2)^pR^{5a}$, hvor p er 0 eller 1 og R^{5a} er OH;

R^6 og R^7 sammen danner oxo;

hver R^a er uafhængigt udvalgt fra gruppen bestående af 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 eventuelt substitueret med ét til tre R^c, heteroaryl eventuelt substitueret med ét til tre R^c og heterocycloalkyl eventuelt substitueret med ét til tre R^c;

hver R^b er uafhængigt udvalgt fra gruppen bestående af C_{1-8}-alkyl, C_{2-8}-alkenyl og C_{2-8}-alkynyl, der hver eventuelt er uafhængigt substitueret med ét til tre halo, OR^d eller NR^dR^d;

hver R^c er uafhængigt udvalgt fra gruppen bestående af 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, CO_2R^f, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$ og N_3, hvor m er udvalgt fra gruppen bestående af 0, 1, 2, 3, 4, 5 og 6;

hver R^d og R^f er uafhængigt udvalgt fra gruppen bestående af hydrogen, C_{1-8}-alkyl, haloC_{1-8}-alkyl, C_{2-8} alkenyl, haloC_{2-8}-alkenyl, C_{2-8}-alkynyl og haloC_{2-8}-alkynyl; og

hver R^e og R^g er uafhængigt udvalgt fra gruppen bestående af C_{1-8}-alkyl, haloC_{1-8}-alkyl, C_{2-8}-alkenyl, haloC_{2-8}-alkenyl, C_{2-8}-alkynyl, og haloC_{2-8}-alkynyl, forudsat forbindelsen er andet end 2-((5'-methyl-[2,2'-bipyridin]-5-yl)methoxy)benzaldehyd.

17. Forbindelse ifølge krav 16, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, hvor Q, Y, R^2, R^3, R^4, R^5, R^a og R^c er som defineret i et hvilket som helst af kravene 2-10.

18. Farmaceutisk sammensætning, der omfatter en forbindelse ifølge krav 16 eller 17, eller en tautomer eller et farmaceutisk acceptabelt salt deraf, og en farmaceutisk acceptabel excipiens.