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(73) Patenthaver: **Global Blood Therapeutics, Inc., 181 Oyster Point Blvd., South San Francisco, CA 94080, USA**

(72) Opfinder: **METCALF, Brian, 297 Lakefield Place, Moraga, CA 94556, USA**
CHUANG, Chihyuan, 460 Bayview Avenue, Millbrae, CA 94030, USA
WARRINGTON, Jeffrey, 1936 Playa Street, San Mateo, CA 94403, USA
PAULVANNAN, Kumar, 6974 Blue Hill Drive, San Jose, CA 95129, USA
JACOBSON, Matthew, 370 Arkansas St., San Francisco, CA 94107, USA
HUA, Lan, 2747 De Medio Ct., Apt 103B, Mountain View, CA 94040, USA
MORGAN, Bradley, 120 Rimer Dr., Moraga, CA 94556, USA

(74) Fuldmægtig i Danmark: **Zacco Denmark A/S, Arne Jacobsens Allé 15, 2300 København S, Danmark**

(54) Benævnelse: **Mellemprodukter til opnåelse af substituerede benzaldehydforbindelser og fremgangsmåder til anvendelse deraf ved øgning af vævsoxygenering**

(56) Fremdragne publikationer:
ROLAN P E ET AL: "The pharmacokinetics, tolerability and pharmacodynamics of tucaresol (589C80); 4[2-formyl-3-hydroxyphenoxymethyl] benzoic acid), a potential anti-sickling agent, following oral administration to healthy subjects", BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, BLACKWELL SCIENTIFIC PUBL, GB, vol. 35, no. 4, 1 April 1993 (1993-04-01), pages 419-425, XP002000120, ISSN: 0306-5251
OSHEIZA ABDULMALIK ET AL: "Crystallographic analysis of human hemoglobin elucidates the structural basis of the potent and dual antisickling activity of pyridyl derivatives of vanillin", ACTA CRYSTALLOGRAPHICA SECTION D BIOLOGICAL CRYSTALLOGRAPHY, vol. 125, no. 11, 1 November 2011 (2011-11-01), pages 788-928, XP055203573, ISSN: 0907-4449, DOI: 10.1107/S0907444911036353
NNAMANI I N ET AL: "Pyridyl derivatives of benzaldehyde as potential antisickling agents", CHEMISTRY & BIODIVERSITY, HELVETICA CHIMICA ACTA, ZUERICH, CH, vol. 5, no. 9, 1 September 2008 (2008-09-01), pages

Fortsættes ...

1762-1769, XP002732217, ISSN: 1612-1872, DOI: 10.1002/CBDV.200890165 [retrieved on 2008-09-24]

DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention generally relates to intermediates useful for preparing substituted benzaldehydes and tautomers or pharmaceutically acceptable salts thereof that act as allosteric modulators of hemoglobin.

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 (SHMF) was found to be a potent hemoglobin modulator both *in vitro* and *in vivo.* Transgenic mice producing human HbS that were treated with SHMF were found to have significantly improved survival times when exposed to extreme hypoxia (5% oxygen). Under these hypoxic conditions, the SHMF treated mice were also found to have reduced amounts of hypoxia-induced sickled red blood cells as compared to the non-treated mice.

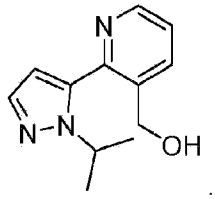
[0005] A need exists for therapeutics that can shift the equilibrium between the deoxygenated and oxygenated states of Hb to treat disorders that are mediated by Hb or by abnormal Hb such as HbS. A need also exists for therapeutics to treat disorders that would benefit from

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.

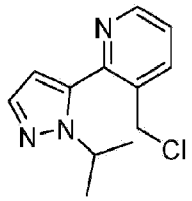
[0006] Rolan, P E et al., British Journal Of Clinical Pharmacology, vol. 35, no. 4, pages 419-425 (1993) discusses tucaresol for use in the treatment of sickle cell anaemia. Osheiza Abdulmalik et al., Acta Crystallographica Section D Biological Crystallography, vol. 125, no. 11, pages 788-928 (2011) discusses derivatives of vanillin for use in the treatment of sickle cell anaemia.

BRIEF SUMMARY OF THE INVENTION

[0007] The present invention provides, in one aspect, a compound of formula:



[0008] In another aspect, the present invention provides a compound of formula:



or a hydrochloric acid salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0009] As used herein, the below terms have the following meanings unless specified otherwise.

[0010] 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 (CH2Cl2), DIBAL = diisobutylaluminum hydride, DMF = dimethyl formamide, EtOAc = ethyl acetate, g = gram, H2 = hydrogen; H2O = water; HBr = hydrogen bromide; HCl = hydrogen chloride, HPLC = high

pressure liquid chromatography, h = hour, LAH = lithium aluminum hydride (LiAlH4); 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, Na2CO3 = 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.

[0011] 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.

[0012] "Alkoxy" refers to -O(alkyl) where alkyl as defined herein. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy, and the like.

[0013] "Alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, fully saturated aliphatic hydrocarbon radical having the number of carbon atoms designated. For example, "C_{1-8}alkyl" refers to a hydrocarbon radical straight or branched, containing from 1 to 8 carbon atoms that is derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Alkyl includes branched chain isomers of straight chain alkyl groups such as isopropyl, t-butyl, isobutyl, sec-butyl, and the like. Representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. Further representative alkyl groups include straight and branched chain alkyl groups having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms.

[0014] "Alkenyl" refers to a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical having the number of carbon atoms indicated in the prefix and containing at least one double bond, but no more than three double bonds. For example, C_{2-8}alkenyl is meant to include, ethenyl, propenyl, 1,3-butadienyl and the like.

[0015] "Alkynyl" means a linear monovalent hydrocarbon radical or a branched monovalent hydrocarbon radical containing at least one triple bond and having the number of carbon atoms indicated in the prefix. The term "alkynyl" is also meant to include those alkyl groups having one triple bond and one double bond. For example, C_{2-8}alkynyl is meant to include ethynyl, propynyl and the like.

[0016] The term "allosteric modulators" refers to compounds that bind to hemoglobin to modulate its affinity for oxygen. The allosteric modulators may act to stabilize or destabilize a particular hemoglobin conformation. The modulators may stabilize the relaxed R state. Alternatively, the modulators may destabilize the tense T state. The allosteric modulators may destabilize one conformation while stabilizing another. In some such scenarios, 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. The allosteric modulators may inhibit the polymerization of HbS and the sickling of red blood cells. The binding of the allosteric modulators to hemoglobin may occur through covalent or non-covalent interactions. An allosteric modulator may react through its aldehyde substituent with an amine group on a hemoglobin amino acid side chain to form a Schiff base.

[0017] "Amino" refers to a monovalent radical $-NH_2$.

[0018] "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.

[0019] "Bond" when used as an element in a Markush group means that the corresponding group does not exist, and the groups of both sides are directly linked.

[0020] "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.

[0021] The term "hemoglobin" as used herein refers to any hemoglobin protein, including normal hemoglobin (Hb) and sickle hemoglobin (HbS).

[0022] "Heteroaryl" refers to a cyclic or polycyclic radical having at least one aromatic ring and from one to five ring heteroatom selected from N, O, and S, and optionally one or more oxo (=O) substituents attached to one or more carbon ring atoms, and wherein the nitrogen and sulfur ring atoms are optionally oxidized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom or through a carbon atom and can contain 5 to 10 carbon atoms. Heteroaryl groups include polycyclic aromatic ring(s) fused to non-aromatic cycloalkyl or heterocycloalkyl groups, and where the point of attachment to the remainder of the molecule can be through any suitable ring atom of any ring. In a polycyclic heteroaryl group, the ring heteroatom(s) can be in either an aromatic or non-aromatic ring or both. The term "aromatic ring" include any ring having at least one planar resonance structure where 2n+2 pi electrons are delocalized about the ring. Examples of heteroaryl groups include, but are not limited to, imidazopyridinyl groups, pyrrolopyridinyl groups, pyrazolopyridinyl groups, triazolopyridinyl groups, pyrazolopyrazinyl groups, pyridinyl groups, pyrazinyl groups, oxazolyl groups, imidazolyl groups, triazolyl groups, tetrazolyl groups, pyrazolyl groups, quinolinyl

groups, isoquinolinyl groups, indazolyl groups, benzooxazolyl groups, naphthyridinyl groups, and quinoxalinyl groups. Other non-limiting examples of heteroaryl groups include xanthine, hypoxanthine, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, benzopyrazolyl, 5-indolyl, azaindole, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, 6-quinolyl 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl and 4-pyrimidyl. "Bicyclic heteroaryl" refers to a heteroaryl radical that contains two rings.

[0023] 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.

[0024] "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 "haloCl-8alkyl" 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, the term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms. The haloakyl, haloalkenyl, haloalkynyl, and haloalkoxy groups may have from one to 5 or from one to 3 halo atoms. Examples of haloalkoxy groups include difluoromethoxy and trifluoromethoxy. The halo atoms of the haloalkenyl and haloalkynyl groups may be attached to the aliphatic portions of these groups.

[0025] 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.

[0026] "Oxo" refers to the divalent atom =O.

[0027] 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.

[0028] 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 the allosteric modulators described herein 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 the allosteric modulators described herein 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 allosteric modulators described herein contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0029] 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.

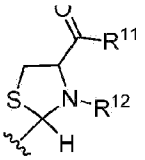
[0030] The term "pharmaceutically acceptable carrier or excipient" means a carrier or excipient

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" includes both one and more than one such carrier or excipient.

[0031] 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.

[0032] "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.

[0033] 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. The aldehyde protecting group may be a five or six membered cyclic acetal formed from condensation of the aldehyde with ethylene or propylene glycol. The aldehyde protecting group may be an imine or hydroxyimine. The aldehyde protecting groups of the present disclosure also include prodrug groups that convert the aldehyde to a prodrug, where the aldehyde is formed *in vivo* as the active agent under physiological conditions upon administration of the prodrug. The prodrug group can also serve to increase the bioavailability of the aldehyde. The prodrug group may be hydrolyzed *in vivo* to the aldehyde. The aldehyde protecting group may be a thiazolidine or N-acetylthiazolidine prodrug group. The aldehyde protecting group may be a thiazolidine prodrug group disclosed in US 6,355,661. The modulators described 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. The modulators may have 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.

[0034] 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).

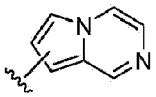
[0035] The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. Preferably the subject is a human.

[0036] "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.

[0037] 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 may be applied preventively, prophylactically, pallatively or remedially.

[0038] 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.

[0039] The term "wavy line" signifies the point of attachment of the substituent to the remainder of the molecule. When the wavy line is not depicted as being specifically appended to a specific ring atom, the point of attachment can be to any suitable atom of the substituent. For example, the wavy line in the following structure:



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

[0040] 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.

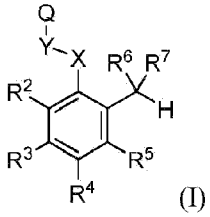
[0041] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with isotopes, such as for example deuterium (^{2}H), tritium (^{3}H) or carbon-14 (^{14}C). 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.

[0042] 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 akyl group that is substituted with alkoxy and "hydoxyalkyl" refers to an akyl group that is substituted with hydroxy. For both of these substituents, the point of attachment is at the alkyl group.

[0043] 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

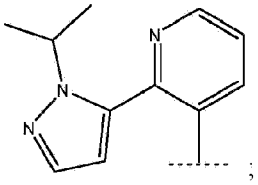
[0044] The intermediates of the present invention are useful in preparing compounds of Formula (I):



(I)

or a tautomer or pharmaceutically acceptable salt thereof,

wherein Q is



;

Y is CH_2;

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, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3, where z is 0, 1, 2, 3, 4, 5, or 6; or R^5 is $-(CH_2)_pR^{5a}$ where p is 0 or 1 and R^{5a} is OH;

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

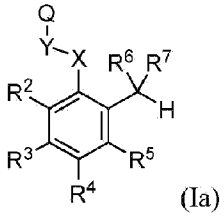
each R^b is independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and C_{2-8} alkynyl, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

each R^d 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 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.

[0045] In compounds of Formula (I), z may be 0. Alternatively, z may be 1. Alternatively, z may be 2. Alternatively, z may be 3. Alternatively, z may be 4. Alternatively, z may be 5. Alternatively, z may be 6.

[0046] The compound of Formula (I) may be a compound of Formula (Ia):



(Ia)

or a tautomer or pharmaceutically acceptable salt thereof,

wherein Q, Y and X are as described above;

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

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^d 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 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.

[0047] In the compounds of Formula (I), R^6 and R^7 may together form oxo.

[0048] In the compounds of Formula (I), R^6 and R^7 may together form a thiazolidine.

[0049] In compounds of Formula (I), R^2 may be H.

[0050] In compounds of Formula (I), R^3 may be H.

[0051] In compounds of Formula (I), R^5 may be H.

[0052] In compounds of Formula (I), R^4 may be C_{1-8}alkoxy.

[0053] In compounds of Formula (I), R^2, R^3, R^5 may be H and R^4 may be C_{1-8}alkoxy.

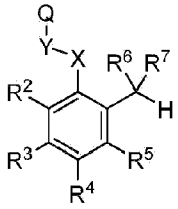
[0054] In compounds of Formula (I), R^4 may be methoxy.

[0055] In compounds of Formula (I), R^4 may be haloalkoxy. In compounds of Formula (I), R^4 may be $OCHF_2$. In compounds of Formula (I), R^4 may be OCF_3.

[0056] In compounds of Formula (I), R^2, R^3, R^4, and R^5 may be H.

[0057] In compounds of Formula (I), one of R^2, R^3, R^4, and R^5 may be selected from the group consisting of $-O(CH_2)_zOH$, $-O(CH_2)_zO(C_{1-8}alkyl)$, $-O(CH_2)_zNH_2$, $-O(CH_2)_zNH(C_{1-8}alkyl)$, and $-O(CH_2)_zN(C_{1-8}alkyl)(C_{1-8}alkyl)$ where z is 0, 1, 2, 3, 4, 5, or 6.

[0058] The compound of Formula (I) may be a compound according to Formula (Ib):



(Ib)

or a tautomer or pharmaceutically acceptable salt thereof,

wherein Q, Y and X are as described above;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halo, R^b, OR^d, $-O(CH_2)_zOR^d$, $-O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, NO_2, CO_2R^d, $CONR^dR^d$, $C(O)R^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3, where z is 0, 1, 2, 3, 4, 5, or 6; or R^5 is $-(CH_2)_pR^{5a}$ where p is 0 or 1 and R^{5a} is OH;

R^4 is hydrogen;

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

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

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^d 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 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.

[0059] In some compounds of formula (Ib), or a tautomer or pharmaceutically acceptable salt thereof, R^6 and R^7 together form oxo.

[0060] In some compounds of formula (Ib), or a tautomer or pharmaceutically acceptable salt thereof, R^5 is selected from the group consisting of hydrogen and OR^d.

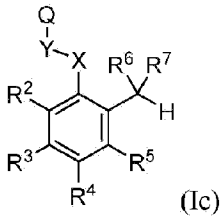
[0061] In some compounds of formula (Ib), or a tautomer or pharmaceutically acceptable salt thereof, R^5 is selected from the group consisting of hydroxy and fluoro.

[0062] In some compounds of formula (Ib), R^2 and R^3 are independently selected from the group consisting of hydrogen, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, CO_2R^d, $CONR^dR^d$, and $C(O)R^d$, where z is 1, 2, or 3.

[0063] In some compounds of formula (Ib), R^2 and R^3 are H.

[0064] In some compounds of formula (Ib), z is 0. In some compounds of formula (Ib), z is 1. In some compounds of formula (Ib), z is 2. In some compounds of formula (Ib), z is 3. In some compounds of formula (Ib), z is 4. In some compounds of formula (Ib), z is 5. In some compounds of formula (Ib), z is 6.

[0065] The compound of Formula (I) may be a compound according to Formula (Ic):



(Ic)

or a tautomer or pharmaceutically acceptable salt thereof, wherein:

Q, Y and X are as described above;

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

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

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

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^d 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 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.

[0066] In some compounds of formula (Ic), z is 1. In other compounds of formula (Ic), z is 2. In still other compounds of formula (Ic), z is 3.

[0067] In some compounds of formula (Ic), R^2 is selected from the group consisting of H and OR^d; R^3 is selected from the group consisting of H, CN, halo, and OR^d; R^4 is selected from the group consisting of H, CN, and OR^d; and R^5 is H.

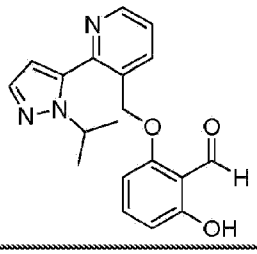
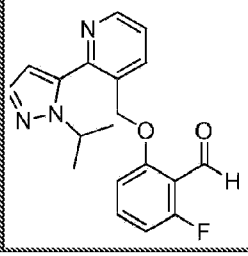
[0068] In some compounds of formula (Ic), R^4 is methoxy.

[0069] In some compounds of formula (Ic), R^5 is selected from the group consisting of hydroxy and fluoro.

[0070] In some compounds of formula (Ic), R^6 and R^7 together form oxo.

[0071] The compound of Formula (I) may be 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
54		2-fluoro-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde

[0072] The compound of Formula (I) may be selected from:

2-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxybenzaldehyde,

2-hydroxy-6-((2-(1-isopropyl-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,

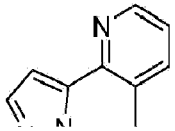
or a tautomer or pharmaceutically acceptable salt thereof.

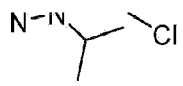
[0073] Compounds of Formula (I) described herein, or a tautomer or pharmaceutically acceptable salt thereof, are useful in the preparation of a pharmaceutical composition.

[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] The compounds of the present invention are useful as intermediate compounds used in the preparation of the compounds of Formula (I) described above.

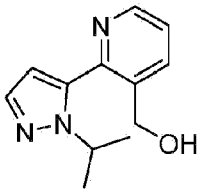
[0076] For example, Scheme I shows a synthetic route for the synthesis of the compounds of Formula (I) using the intermediates of the present invention. Phenol **1.1** is contacted with intermediate **1.2** in the presence of base under ether forming conditions to give ether **1.3,** where Lg represents a leaving group such as a halogen leaving group. In this case, intermediate **1.2** is:



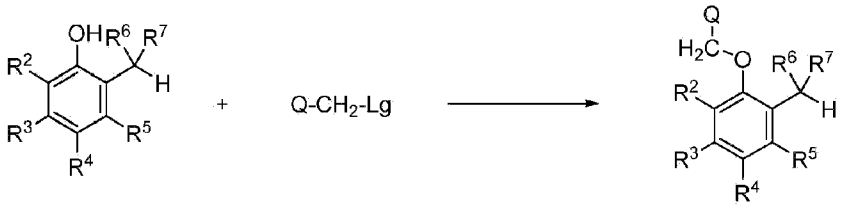


or a hydrochloric acid salt thereof.

The compounds of Formula (I) can also 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. In this case, intermediate **1.2** is:



Scheme I



1.1 **1.2** **1.3**

[0077] One skilled in the art will recognize that in certain syntheses 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.

[0078] 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.

[0079] 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 containing a compound of Formula (I) and Methods of Administration

[0080] Depending on the intended mode of administration, pharmaceutical compositions comprising a compound of Formula (I) 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] The pharmaceutical compositions 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.

[0085] Typically, the pharmaceutical composition 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.

[0086] The pharmaceutical composition may additionally contain one or more other pharmacologically active agents in addition to a compound of Formula (I).

[0087] Dosage forms containing effective amounts of the modulators are within the bounds of routine experimentation. A therapeutically effective dose may vary depending upon the route of administration and dosage form. The representative compound or compounds of Formula (I) 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

[0088] Compounds of Formula (I) are suitable 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 Formula (I) or a tautomer or pharmaceutically acceptable salt thereof.

[0089] Compounds of Formula (I) are suitable 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 Formula (I) or a tautomer or pharmaceutically acceptable salt thereof.

[0090] Compounds of Formula (I) are suitable 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 Formula (I) or a tautomer or pharmaceutically acceptable salt thereof.

V. Examples

[0091] The following examples are offered to illustrate, but not to limit, the claimed invention. In particular, the synthetic processes below exemplify the use of the compounds of the present invention as intermediates in the synthesis of compounds of Formula (I).

PREPARATIVE EXAMPLES

[0092] 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.

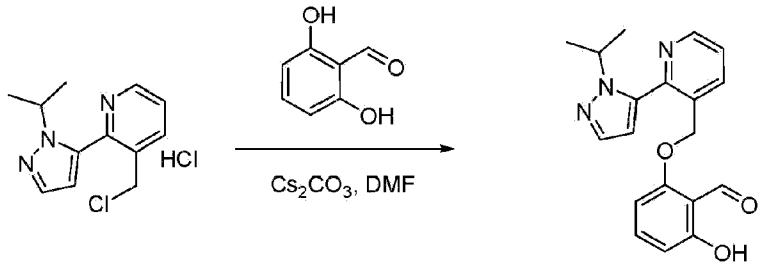
[0093] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0094] 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.

[0095] 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).

[0096]

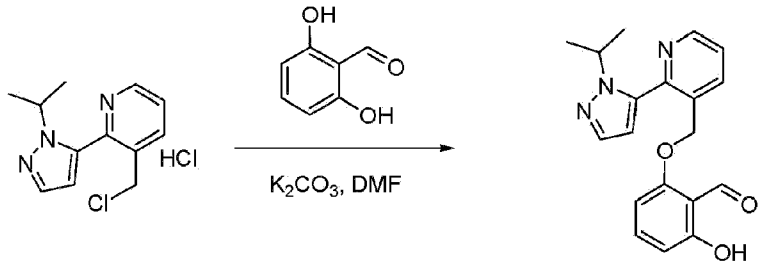


[0097] A mixture of 2,6-dihydroxybenzaldehyde (1.96 g, 14.2 mmol, 2 eq.) and Cs_2CO_3 (7.5 g, 21.3 mmol, 3 eq.) in DMF (180 mL) was stirred at rt for 30 min. To this mixture was added 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride (1.93 g, 7.1 mmol, 1eq.) at rt. The mixture was 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, $CDCl_3$) 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 2. Preparation of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 43).

[0098]

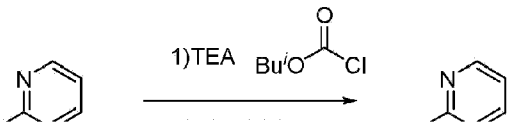


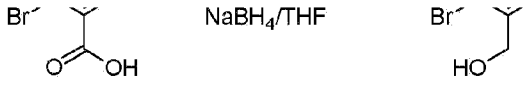
[0099] A mixture of 2,6-dihydroxybenzaldehyde (1.58 g, 11.47 mmol, 2 eq.) and K_2CO_3 (2.4 g, 17.22 mmol, 3 eq.) in DMF (150 mL) was stirred at rt for 10 min. To this mixture was added 3-(chloromethyl)-2-(1-isopropyl-1H-pyrazol-5-yl)pyridine hydrochloride (1.56 g, 5.74 mmol, 1eq.) at rt. The mixture 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-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-2-methoxybenzaldehyde.

Step 1:

[0100]

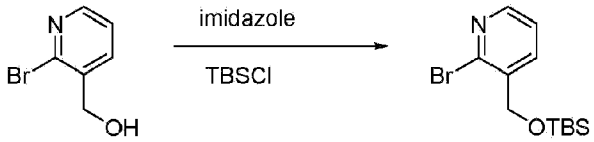




[0101] To a solution of 2-bromonicotinic acid (4.0 g, 20 mmol) and triethylamine (3.34 mL, 24 mmol, 1.2 eq.) in THF (100 mL) was added i-butyl chloroformate (3.12 mL, 24 mmol, 1.2 eq.) at 0 °C. The mixture was stirred at 0 °C for 10 min and filtered. To this filtrate was added a suspension of $NaBH_4$ (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

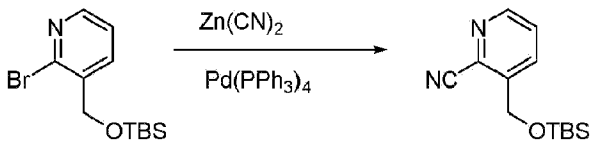
[0102]



[0103] 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 TBSCl (19.2 g, 150.7 mmol, 1.2 eq.) at rt. The mixture was stirred at rt for 1 h and diluted with a mixture of water (100 mL) and EtOAc (300 mL). The organic layer was washed with $NH_4Cl_{(sat.)}$ solution and brine, dried over 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

[0104]

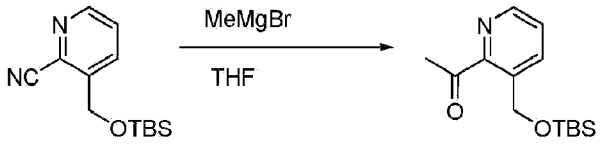


[0105] A mixture of 2-bromo-3-((tert-butyldimethylsilyloxy)methyl)pyridine (30.1 g, 100.0 mmol, 1 eq.) and $Zn(CN)_2$ (23.5 g, 200.0 mmol, 2.0 eq.) in DMF (100.0 mL) was purged with N_2 for 5 min and added $Pd(PPh_3)_4$ (5.78 g, 5.0 mmol, 0.05 eq.). The mixture was heated at 120 °C for 2 h under N_2, 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:

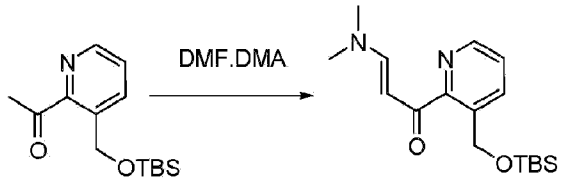
[0106]



[0107] 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:

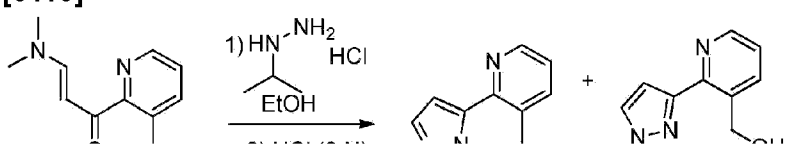
[0108]

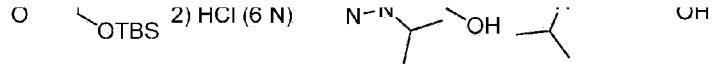


[0109] 1-(3-((tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)ethanone (10.8 g, 40.75 mmol) in dimethoxy-N,N-dimethylmethanamine (15.0 mL) was heated to reflux for 3 days. The mixture was concentrated and used for next step without further purification. LRMS ($M+H^+$) m/z 321.1.

Step 6:

[0110]

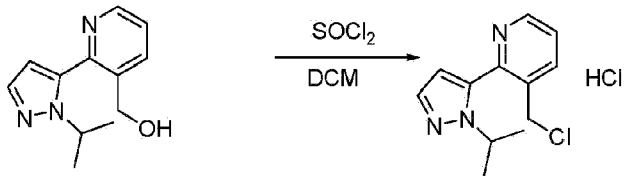




[0111] To *(E)*-1-(3-((tert-butyldimethylsilyloxy)methyl)pyridin-2-yl)-3-(dimethylamino)prop-2-en-1-one (crude, 1.03 g, 3.22 mmol, 1 eq.) in EtOH (10 mL) was added isopropylhydrazine hydrochloride (430 mg, 3.86 mmol, 1.2 eq.). The mixture was heated at 80 °C for 2 h, cooled, added HCl (6 N, 0.5 mL), 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: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.0 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 1.8 Hz, 1H), 7.39 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.37 (d, *J* = 1.8 Hz, 1H), 4.67 (s, 2H), 4.55 (sep, *J* = 6.6 Hz 1H), 1.98-2.05 (br, 1H), 1.47 (d, *J* = 6.6 Hz, 6H). LRMS ($M+H^+$) m/z 218.1 Data for (2-(1-isopropyl-1H-pyrazol-3-yl)pyridin-5-yl)methanol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (dd, *J*= 4.8, 1.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.23 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.99 (dd, *J* = 8.0, 6.5 Hz, 1H), 6.07 (t, *J* = 7.6 Hz, 1H), 4.67 (d, *J* = 7.6 Hz, 2H), 4.58 (sep, *J* = 6.7 Hz, 1H), 1.60 (d, *J* = 6.7 Hz, 1H). LRMS ($M+H^+$) m/z 218.1.

Step 7:

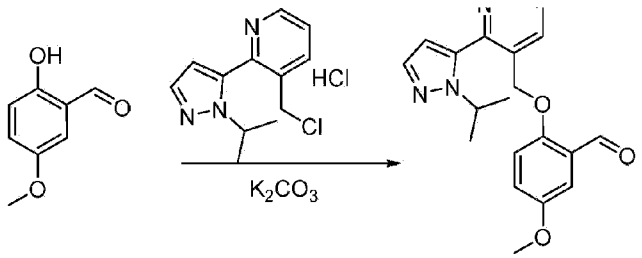
[0112]



[0113] 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:

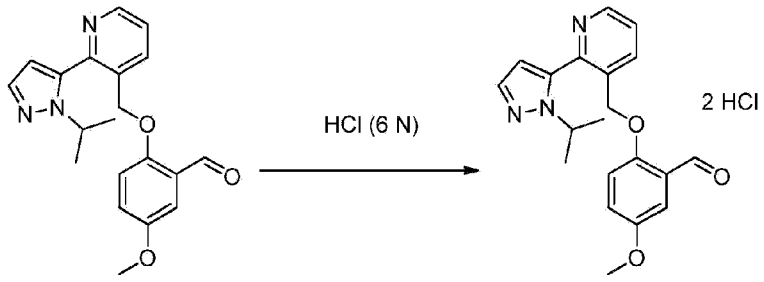
[0114]



[0115] 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:

[0116]



[0117] 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 Benzaldehyde Derivatives.

[0118] 2-Fluoro-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde (Compound 54) was prepared according to the methods described above. ^{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 OF COMPOUNDS OF FORMULA (I)

Reference Example 5. Modulation of Hemoglobin Oxygen affinity by Substituted Benzaldehyde CompoundsAssay Procedure.

[0119] 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.

Reference Example 6. Modulation of Hemoglobin Oxygen affinity by Substituted Benzaldehyde CompoundsAssay Results.

[0120] 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.

Reference Example 7. Polymerization Assay.

[0121] 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.

[0122] 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	†

Reference Example 8. R/T Assay

[0123] 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.

[0124] 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.

[0125] 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	+++

Reference Example 9. Whole Blood Assay

[0126] 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 pO_2. 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.

[0127] 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	+

Reference Example 10. Pharmacokinetic Study of Compound 43 (HCl salt)

I.V. STUDY

[0128] 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 cone (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

Compound 43 7.8mpk IV in rat						
	blood cone (uM)			plasma conc (uM)		
time (min)	A	B	C	A	B	C
30	283	333	292	no sample	8.66	7.1
60	256	203	285	612	7.52	7.22
120	263	274	280	3.92	6.02	5.22
240	248	225	259	3.72	5.24	5.88
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
tl/2 beta	min	749.0	619.1
CL	ml/min/kg	0.08	4.45
Vss	L/kg	0.09	4.11
AUClast	min*umol/L	215846.3	4114.8

ORAL STUDY

[0129] 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	227	44	100	227
Tmax	min	320.00	720.00		200.00	680.00	
Cmax	umol/L	381.33	1096.67	2.88	14.79	44.53	3.01
AUClast	min*umol/L	395638.27	1384101.11	3.50	12517.54	52836.17	422

[0130] 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

Cited references

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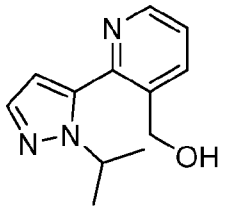
PATENTKRAV

1. Forbindelse med formlen:



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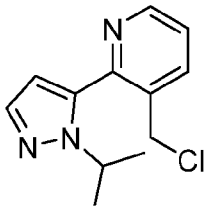
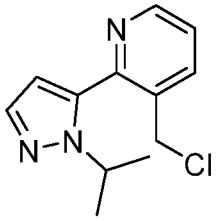


eller et saltsyresalt deraf.

3. Forbindelse ifølge krav 2, hvor forbindelsen er:



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