COMPOUNDS AND USES THEREOF FOR THE MODULATION OF HEMOGLOBIN

FIELD OF THE INVENTION

[0001] This invention provides compounds and pharmaceutical compositions suitable as allosteric modulators of hemoglobin, methods and intermediates for their preparation, and methods for their use in treating disorders mediated by hemoglobin and disorders that would benefit from tissue and/or cellular oxygenation.

STATE OF THE ART

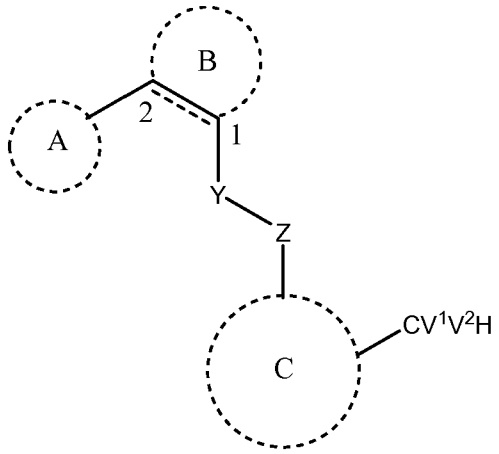
[0002] Sickle cell disease is a disorder of the red blood cells, found particularly among those of African and Mediterranean descent. The basis for sickle cell disease is found in sickle hemoglobin (HbS), which contains a point mutation relative to the prevalent peptide sequence of hemoglobin (Hb).

[0003] Hemoglobin (Hb) transports oxygen molecules from the lungs to various tissues and organs throughout the body. Hemoglobin binds and releases oxygen through conformational changes. Sickle hemoglobin (HbS) contains a point mutation where glutamic acid is replaced with valine, allowing HbS 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. US 7, 160,910 discloses compounds that are allosteric modulators of hemoglobin. However, a need exists for additional therapeutics that can treat disorders that are mediated by Hb or by abnormal Hb such as HbS.

SUMMARY OF THE INVENTION

[0004] This invention relates generally to compounds and pharmaceutical compositions suitable as allosteric modulators of hemoglobin. In some aspects, this invention relates to methods for treating disorders mediated by hemoglobin and disorders that would benefit from tissue and/or cellular oxygenation.

[0005] In certain aspects of the invention, a compound of formula (I) is provided:



(I)

or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein

ring A is an optionally substituted 4-10 membered cycloalkyl or 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

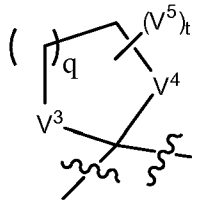
ring B is a C_6-C_{10} aryl or 5-10 membered heteroaryl having 1-3 nitrogen atoms, preferably 1-2 nitrogen atoms and more preferably 1 nitrogen atom, or oxidized versions thereof, wherein the aryl or heteroaryl is optionally substituted;

 is a single or a double bond;

each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{12}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O; R^{12} is hydrogen or C_1-C_6 alkyl; provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and provided that Y and Z are both not heteroatoms or oxidized forms thereof;

ring C is C_6-C_{10} aryl, optionally substituted;

V^1 and V^2 independently are C_1-C_6 alkoxy; or V^1 and V^2 together with the carbon atom they are attached to form a ring of formula:



wherein each V^3 and V^4 are independently O, S, or NH, provided that when one of V^3 and V^4 is S, the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60}, where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 0, 1, 2, or 4; or CV^1V^2 is C=V, wherein V is O, NOR^{80}, or $NNR^{81}R^{82}$;

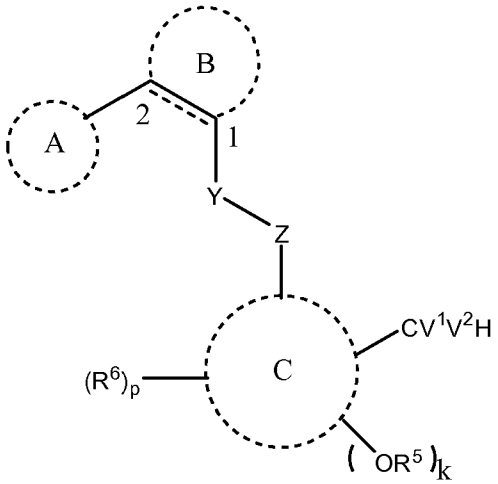
R^{80} is optionally substituted C_1-C_6 alkyl;

R^{81} and R^{82} independently are selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, COR^{83}, or CO_2R^{84};

R^{83} is hydrogen or optionally substituted C_1-C_6 alkyl; and

R^{84} is optionally substituted C_1-C_6 alkyl.

[0006] In certain aspects of the invention, a compound of formula (IA) is provided:



(IA)

wherein R^5 is hydrogen, C_1-C_6 alkyl or a prodrug moiety R, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo;

R^6 is halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 S(O)-, C_1-C_6 $S(O)_2$-,wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo; or

R^6 is 4-10 membered cycloalkyl or heterocycle substituted with an R'R'N- moiety wherein each R' is independently C_1-C_6 alkyl or hydrogen;

k is 0 or 1;

p is 0, 1, 2 or 3;

and the remaining variables are defined as above.

[0007] In further aspects of the invention, a composition is provided comprising any of the compounds described herein, and at least a pharmaceutically acceptable excipient.

[0008] In still further aspects of the invention, a method is provided for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

[0009] In further aspects of the invention, a method is provided for treating oxygen deficiency associated with sickle cell anemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0010] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a solvent" includes a plurality of such solvents.

[0011] As used herein, the term "comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition or process consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0012] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood

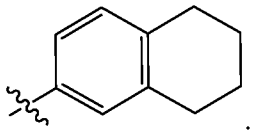
as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations. Each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. The term "about" when used before a numerical designation, e.g., temperature, time, amount, and concentration, including range, indicates approximations which may vary by (+) or (-) 10 %, 5 % or 1 %.

[0013] As used herein, C_m-C_n, such as C_1-C_{12}, C_1-C_8, or C_1-C_6 when used before a group refers to that group containing m to n carbon atoms.

[0014] The term "alkoxy" refers to –O-alkyl. The term alkylthio is –S-alkyl.

[0015] The term "alkyl" refers to monovalent saturated aliphatic hydrocarbyl groups having from 1 to 30 carbon atoms (i.e., C_1-C_{30} alkyl) or 1 to 22 carbon atoms (i.e., C_1-C_{22} alkyl), 1 to 8 carbon atoms (i.e., C_1-C_8 alkyl), or 1 to 4 carbon atoms. This term includes, by way of example, linear and branched hydrocarbyl groups such as methyl (CH_3-), ethyl (CH_3CH_2-), *n*-propyl ($CH_3CH_2CH_2$-), isopropyl ($(CH_3)_2CH$-), *n*-butyl ($CH_3CH_2CH_2CH_2$-), isobutyl ($(CH_3)_2CHCH_2$-), *sec*-butyl ($(CH_3)(CH_3CH_2)CH$-), *t*-butyl ($(CH_3)_3C$-), *n*-pentyl ($CH_3CH_2CH_2CH_2CH_2$-), and neopentyl ($(CH_3)_3CCH_2$-).

[0016] The term "aryl" refers to a monovalent, aromatic mono- or bicyclic ring having 6-10 ring carbon atoms. Examples of aryl include phenyl and naphthyl. The condensed ring may or may not be aromatic provided that the point of attachment is at an aromatic carbon atom. For example, and without limitation, the following is an aryl group:

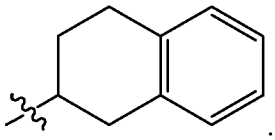


[0017] The term "-CO_2H ester" refers to an ester formed between the –CO_2H group and an alcohol, preferably an aliphatic alcohol. A preferred example included –CO_2R^E, wherein R^E is alkyl or aryl group optionally substituted with an amino group.

[0018] The term "chiral moiety" refers to a moiety that is chiral. Such a moiety can possess one or more asymmetric centers. Preferably, the chiral moiety is enantiomerically enriched, and more preferably a single enantiomer. Non limiting examples of chiral

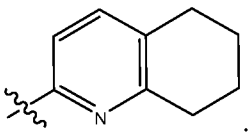
moieties include chiral carboxylic acids, chiral amines, chiral amino acids, such as the naturally occurring amino acids, chiral alcohols including chiral steroids, and the likes.

[0019] The term "cycloalkyl" refers to a monovalent, preferably saturated, hydrocarbyl mono-, bi-, or tricyclic ring having 3-12 ring carbon atoms. While cycloalkyl, refers preferably to saturated hydrocarbyl rings, as used herein, it also includes rings containing 1-2 carbon-carbon double bonds. Nonlimiting examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamentyl, and the like. The condensed rings may or may not be non-aromatic hydrocarbyl rings provided that the point of attachment is at a cycloalkyl carbon atom. For example, and without limitation, the following is a cycloalkyl group:



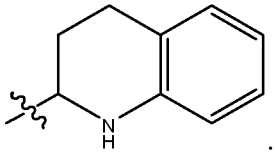
[0020] The term "halo" refers to F, Cl, Br, and/or I.

[0021] The term "heteroaryl" refers to a monovalent, aromatic mono-, bi-, or tricyclic ring having 2-16 ring carbon atoms and 1-8 ring heteroatoms selected preferably from N, O, S, and P and oxidized forms of N, S, and P, provided that the ring contains at least 5 ring atoms. Nonlimiting examples of heteroaryl include furan, imidazole, oxadiazole, oxazole, pyridine, quinoline, and the like. The condensed rings may or may not be a heteroatom containing aromatic ring provided that the point of attachment is a heteroaryl atom. For example, and without limitation, the following is a heteroaryl group:



[0022] The term "heterocyclyl" or heterocycle refers to a non-aromatic, mono-, bi-, or tricyclic ring containing 2-12 ring carbon atoms and 1-8 ring heteroatoms selected preferably from N, O, S, and P and oxidized forms of N, S, and P, provided that the ring contains at least 3 ring atoms. While heterocyclyl preferably refers to saturated ring systems, it also includes ring systems containing 1-3 double bonds, provided that the ring is non-aromatic. Nonlimiting examples of heterocyclyl include, azalactones, oxazoline, piperidinyl, piperazinyl, pyrrolidinyl, tetrahydrofuranyl, and tetrahydropyranyl. The

condensed rings may or may not contain a non-aromatic heteroatom containing ring provided that the point of attachment is a heterocyclyl group. For example, and without limitation, the following is a heterocyclyl group:



[0023] The term "hydrolyzing" refers to breaking an R^H–O-CO-, R^H-O-CS-, or an R^H–O-SO_2- moiety to an R^H–OH, preferably by adding water across the broken bond. A hydrolyzing is performed using various methods well known to the skilled artisan, non limiting examples of which include acidic and basic hydrolysis.

[0024] The term "oxo" refers to a C=O group, and to a substitution of 2 geminal hydrogen atoms with a C=O group.

[0025] The term "optionally substituted" refers to a substituted or unsubstituted group. The group may be substituted with one or more substituents, such as e.g., 1, 2, 3, 4 or 5 substituents. Preferably, the substituents are selected from the group consisting of oxo, halo, -CN, NO_2, -N_2+, -CO_2R^{100}, -OR^{100}, -SR^{100}, -SOR^{100}, -SO_2R^{100}, -$NR^{101}R^{102}$, -$CONR^{101}R^{102}$, -$SO_2NR^{101}R^{102}$, C_1-C_6 alkyl, C_1-C_6 alkoxy, -CR^{100}=$C(R^{100})_2$, -CCR^{100}, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl and C_2-C_{12} heteroaryl, wherein each R^{100} independently is hydrogen or C_1-C_8 alkyl; C_3-C_{12} cycloalkyl; C_3-C_{10} heterocyclyl; C_6-C_{12} aryl; or C_2-C_{12} heteroaryl; wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 halo, 1-3 C_1-C_6 alkyl, 1-3 C_1-C_6 haloalkyl or 1-3 C_1-C_6 alkoxy groups. Preferably, the substituents are selected from the group consisting of chloro, fluoro, -OCH_3, methyl, ethyl, *iso*-propyl, cyclopropyl, vinyl, ethynyl, -CO_2H, -CO_2CH_3, -OCF_3, -CF_3 and -$OCHF_2$.

[0026] R^{101} and R^{102} independently is hydrogen; C_1-C_8 alkyl, optionally substituted with -CO_2H or an ester thereof, C_1-C_6 alkoxy, oxo, -CR^{103}=$C(R^{103})_2$, -CCR, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, or C_2-C_{12} heteroaryl, wherein each R^{103} independently is hydrogen or C_1-C_8 alkyl; C_3-C_{12} cycloalkyl; C_3-C_{10} heterocyclyl; C_6-C_{12} aryl; or C_2-C_{12} heteroaryl; wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups or 1-3 halo groups, or R^{101} and R^{102} together with the nitrogen atom they are attached to form a 5-7 membered heterocycle.

[0027] The term "pharmaceutically acceptable" refers to safe and non-toxic for *in vivo*, preferably, human administration.

[0028] The term "pharmaceutically acceptable salt" refers to a salt that is pharmaceutically acceptable.

[0029] The term "salt" refers to an ionic compound formed between an acid and a base. When the compound provided herein contains an acidic functionality, such salts include, without limitation, alkali metal, alkaline earth metal, and ammonium salts. As used herein, ammonium salts include, salts containing protonated nitrogen bases and alkylated nitrogen bases. Exemplary, and non-limiting cations useful in pharmaceutically acceptable salts include Na, K, Rb, Cs, NH_4, Ca, Ba, imidazolium, and ammonium cations based on naturally occurring amino acids. When the compounds utilized herein contain basic functionality, such salts include, without limitation, salts of organic acids, such as carboxylic acids and sulfonic acids, and mineral acids, such as hydrogen halides, sulfuric acid, phosphoric acid, and the likes. Exemplary and non-limiting anions useful in pharmaceutically acceptable salts include oxalate, maleate, acetate, propionate, succinate, tartrate, chloride, sulfate, bisalfate, mono-, di-, and tribasic phosphate, mesylate, tosylate, and the likes.

[0030] The terms "treat", "treating" or "treatment", as used herein, include alleviating, abating or ameliorating a disease or condition or one or more symptoms thereof, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting or suppressing the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or suppressing the symptoms of the disease or condition, and are intended to include prophylaxis. The terms also include relieving the disease or conditions, e.g., causing the regression of clinical symptoms. The terms further include achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the individual, notwithstanding that the individual is still be afflicted with the underlying disorder. For prophylactic benefit, the compositions are administered to an individual at

risk of developing a particular disease, or to an individual reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

[0031] The terms "preventing" or "prevention" refer to a reduction in risk of acquiring a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease). The terms further include causing the clinical symptoms not to develop, for example in a subject at risk of suffering from such a disease or disorder, thereby substantially averting onset of the disease or disorder.

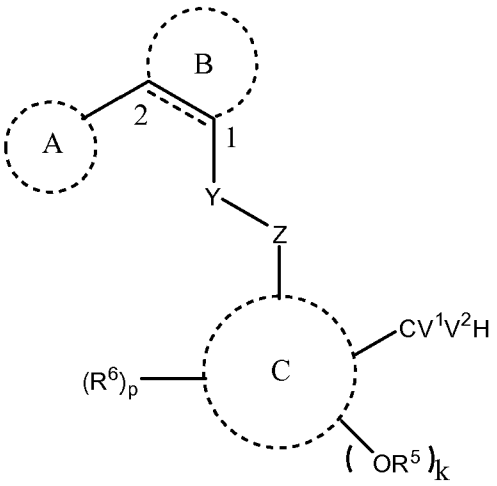
[0032] The term "effective amount" refers to an amount that is effective for the treatment of a condition or disorder by an intranasal administration of a compound or composition described herein. In some embodiments, an effective amount of any of the compositions or dosage forms described herein is the amount used to treat a disorder mediated by hemoglobin or a disorder that would benefit from tissue and/or cellular oxygenation of any of the compositions or dosage forms described herein to a subject in need thereof.

[0033] The term "carrier" as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells, *e.g.*, red blood cells, or tissues.

[0034] As used herein, a "prodrug" is a compound that, after administration, is metabolized or otherwise converted to an active or more active form with respect to at least one property. To produce a prodrug, a pharmaceutically active compound can be modified chemically to render it less active or inactive, but the chemical modification is such that an active form of the compound is generated by metabolic or other biological processes. A prodrug may have, relative to the drug, altered metabolic stability or transport characteristics, fewer side effects or lower toxicity. For example, see the reference Nogrady, 1985, Medicinal Chemistry A Biochemical Approach, Oxford University Press, New York, pages 388-392. Prodrugs can also be prepared using compounds that are not drugs.

Compounds

[0035] In certain aspects of the invention, a compound of formula (I) is provided:



(I)

or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof,

wherein

ring A is an optionally substituted 4-10 membered cycloalkyl or 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

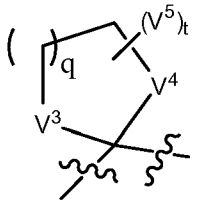
ring B is a C_6-C_{10} aryl or 5-10 membered heteroaryl having 1-3 nitrogen atoms, preferably 1-2 nitrogen atoms and more preferably 1 nitrogen atom, or oxidized versions thereof, wherein the aryl or heteroaryl is optionally substituted;

 is a single or a double bond;

each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{12}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O; R^{12} is hydrogen or C_1-C_6 alkyl; provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and provided that Y and Z are both not heteroatoms or oxidized forms thereof;

ring C is C_6-C_{10} aryl;

V^1 and V^2 independently are C_1-C_6 alkoxy; or V^1 and V^2 together with the carbon atom they are attached to form a ring of formula:



wherein each V^3 and V^4 are independently O, S, or NH, provided that when one of V^3 and V^4 is S, the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60}, where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 0, 1, 2, or 4; or CV^1V^2 is C=V, wherein V is O, NOR^{80}, or $NNR^{81}R^{82}$;

R^5 is hydrogen, C_1-C_6 alkyl or a prodrug moiety R, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo;

R^6 is halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 S(O)-, C_1-C_6 $S(O)_2$-,wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo; or

R^6 is 4-10 membered cycloalkyl or heterocycle substituted with an R'R'N- moiety wherein each R' is independently C_1-C_6 alkyl or hydrogen;

R^{80} is optionally substituted C_1-C_6 alkyl;

R^{81} and R^{82} independently are selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, COR^{83}, or CO_2R^{84};

R^{83} is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{84} is optionally substituted C_1-C_6 alkyl;

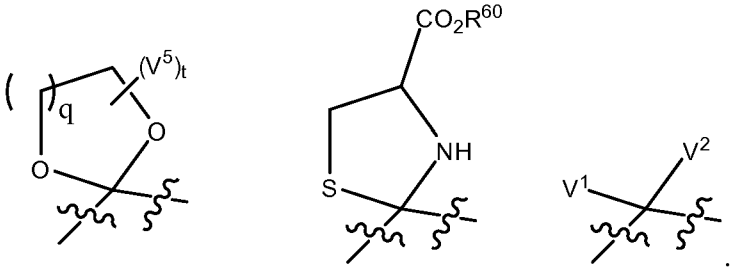
k is 0 or 1; and

p is 0, 1, 2 or 3.

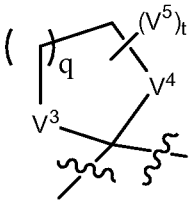
[0036] In certain embodiments, t is 0. In certain embodiments, t is 1. In certain embodiments, t is 2. In certain embodiments, t is 3.

[0037] Preferably, in certain embodiments, Y and Z are both not a heteroatom or a heteroatom containing moiety. Preferably, one of Y and Z is a methylene or substituted methylene and the other is a heteroatom or a heteroatom containing moiety. More preferably, Y is an alkylene, and Z is a heteroatom or a heteroatom containing moiety, which, yet more preferably is oxygen.

[0038] Preferably, V^1 and V^2 together with the carbon atom they are attached to form a ring of formula:

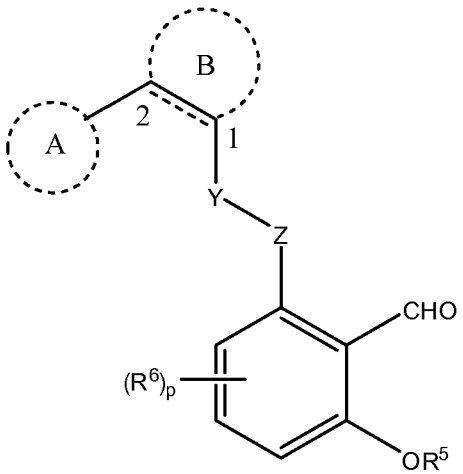


[0039] In some embodiments, V^1 and V^2 independently are C_1-C_6 alkoxy; or V^1 and V^2 together with the carbon atom they are attached to form a ring of formula:



wherein each V^3 and V^4 are independently O, S, or NH, provided that when one of V^3 and V^4 is S the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60}, where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 0, 1, 2, or 4; or CV^1V^2 is C=V, wherein V is O, and wherein the remaining variables are defined herein.

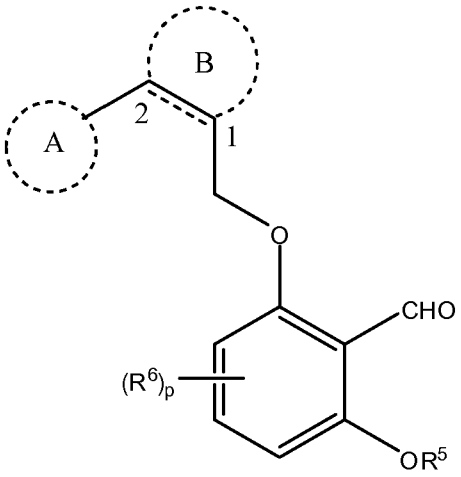
[0040] In certain aspects of the invention, the compound of Formula (I) is of Formula (II):



(II)

wherein the remaining variables are defined herein.

[0041] In certain aspects of the invention, the compound of Formula (I) is of Formula (IIA):



(II)

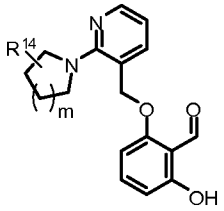
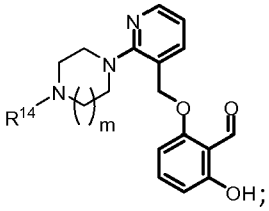
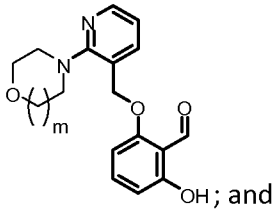
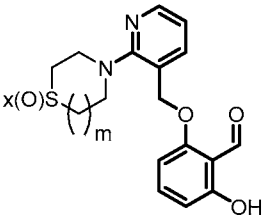
wherein

the variables are defined herein.

[0042] In some embodiments, ring A is optionally substituted with 1-3: halo, C_1-C_6 alkyl, COR^{15} and/or $COOR^{15}$; wherein R^{15} is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl containing up to 5 ring heteroatoms, or optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S.

[0043] In some embodiments, ring B is optionally substituted with 1-3: halo, C_1-C_6 alkyl COR^{15} and/or $COOR^{15}$; wherein R^{15} is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl containing up to 5 ring heteroatoms, or optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S.

[0044] In some embodiments, the compound is selected from the group consisting of




; and

;

or an N oxide thereof, wherein

R^{14} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, COR^{15} or $COOR^{15}$;

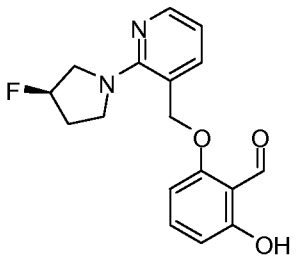
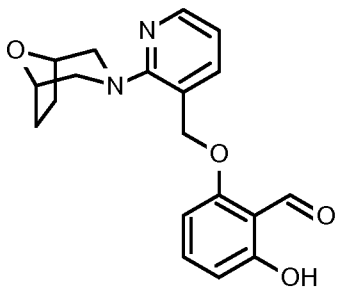
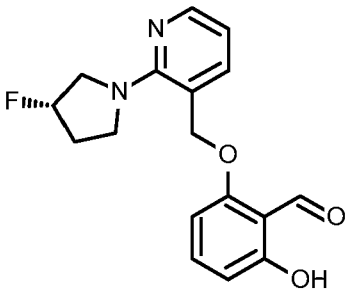
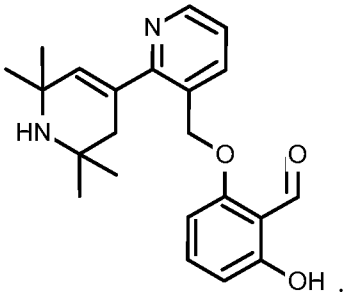
R^{15} is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl containing up to 5 ring heteroatoms, or optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

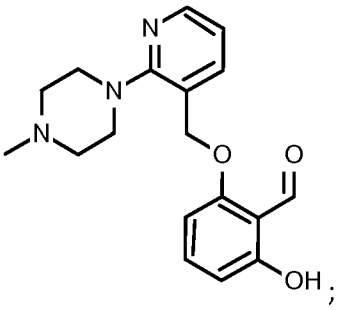
x is 0, 1, or 2;

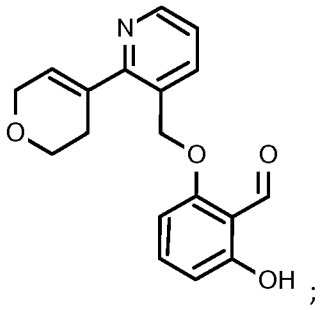
p is 0, 1, and 2; and

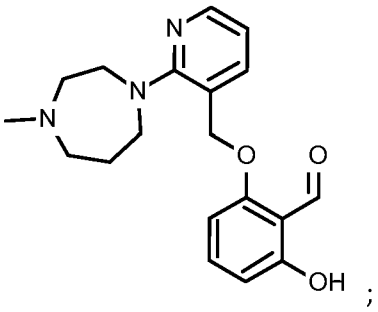
m is 0, 1 or 2.

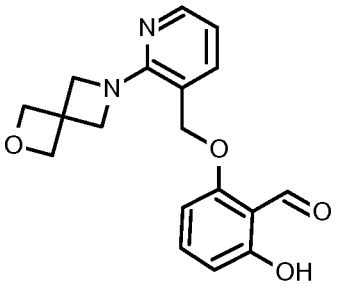
[0045] In one embodiment, the compound is

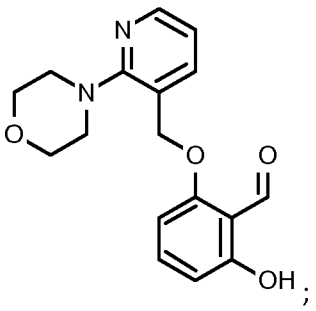


;

;

;


;


;


;


; and


;

or a prodrug thereof, or a pharmaceuticlaly acceptable salt of each thereof.

[0046] Other compounds provided herein are included in the Examples section.

Prodrug Moiety

[0047] In one aspect, **R** is hydrogen, a phosphate or a diphosphate containing moiety, or another promoiety or prodrug moiety. Preferably the prodrug moiety imparts at least a 2 fold, more preferably a 4 fold, enhanced solubility and/or bioavailability to the active moiety (where R is hydrogen), and more preferably is hydrolyzed in vivo. The promoieties are structurally and functionally defined herein.

[0048] In one embodiments, **R** is $-COR^{90}$, CO_2R^{91}, or $CONR^{92}R^{93}$ wherein R^{90} and R^{91} independently are C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 4-9 membered heterocycle, or a 5-10 membered heteroaryl, each containing at least 1 basic nitrogen moiety; and R^{92} and R^{93} independently are C_1-C_6 alkyl; C_3-C_8 cycloalkyl, 4-9 membered heterocycle, or a 5-10 membered heteroaryl, each containing at least 1 basic nitrogen moiety; or R^{92} and R^{93}

together with the nitrogen atom they are bonded to for a 4-9 member heterocycle substituted with at least 1 amino, C_1-C_6 alkyl amino, or di C_1-C_6 alkylamino group.

[0049] In certain embodiments, R is $-C(O)R^{31}$, $C(O)OR^{31}$, or $CON(R^{13})_2$,

each R^{31} is independently a C_1-C_6 alkyl; C_3-C_8 cycloalkyl, 4-9 membered heterocycle, or a 5-10 membered heteroaryl, containing at least 1 basic nitrogen moiety; and

each R^{13} independently are C_1-C_6 alkyl; C_3-C_8 cycloalkyl, 4-9 membered heterocycle, or a 5-10 membered heteroaryl, containing at least 1 basic nitrogen moiety; or 2 R^{13} together with the nitrogen atom they are bonded to for a 4-9 member heterocycle substituted with at least 1 amino, C_1-C_6 alkyl amino, or di C_1-C_6 alkylamino group.

[0050] In one aspect, **R** is $C(O)OR^{31}$, $C(S)OR^{31}$, $C(O)SR^{31}$ or COR^{31}, wherein R^{31} is as defined herein.

[0051] In one embodiment, R^{31} is a group of the formula $(CR^{32}R^{33})_eNR^{34}R^{35}$, wherein

each R^{32} and R^{33} is independently H, a C_1-C_8 alkyl, C_3-C_9 heterocyclyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_3-C_9 heteroaryl or R^{32} and R^{33} together with the carbon atom they are bond to form a C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_3-C_9 heterocyclyl or C_3-C_9 heteroaryl ring system, or 2 adjacent R^{32} moieties or 2 adjacent R^{33} moieties together with the carbon atom they are bond to form a C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_3-C_9 heterocyclyl or C_3-C_9 heteroaryl ring system;

each R^{34} and R^{35} is a C_1-C_8 alkyl, C_3-C_9 heterocyclyl, C_3-C_8 cycloalkyl, or R^{34} and R^{35} together with the nitrogen atom they are bond to form a C_3-C_8 cycloalkyl or C_3-C_9 heterocyclyl ring system;

each heterocyclic and heteroaryl ring system is optionally substituted with C_1-C_3 alkyl, -OH, amino and carboxyl groups; and

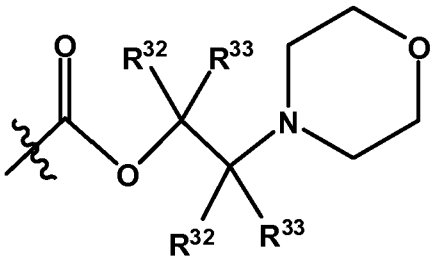
e is an integer of from 1 to 4.

[0052] In some less preferred embodiments R^{34} and R^{35} can be hydrogen.

[0053] In one embodiment, the subscript e is preferably 2 and each R^{32} and R^{33} is preferably independently selected from the group, H, CH_3, and a member in which R^{32} and R^{33} are joined together to form a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or 1,1-dioxo-hexahydro-lΔ^6-thiopyran-4-yl or tetrahydropyran-4-yl group.

[0054] With regard to the prodrug group, preferred embodiments are compounds wherein $NR^{34}R^{35}$ is morpholino.

[0055] In one embodiment, **R** is:



wherein

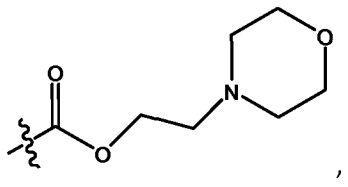
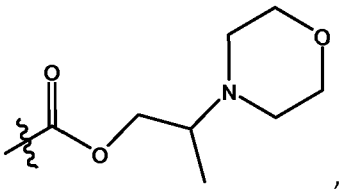
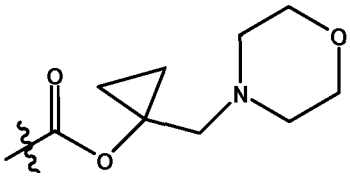
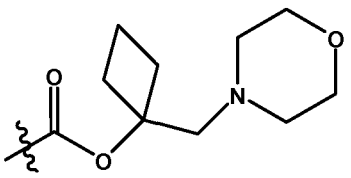
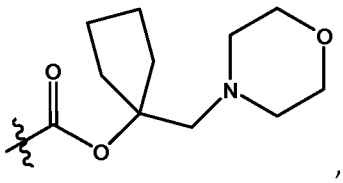
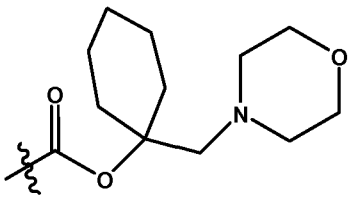
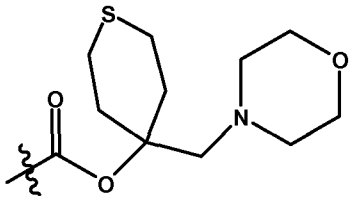
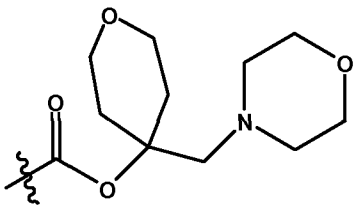
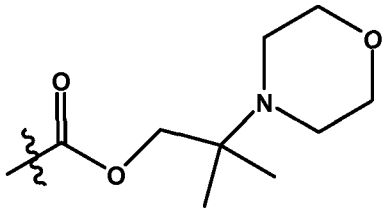
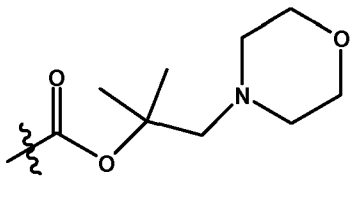
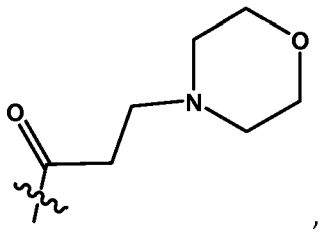
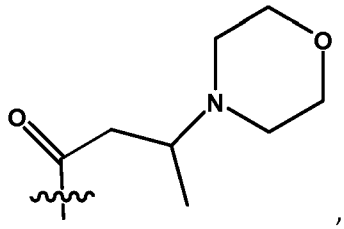
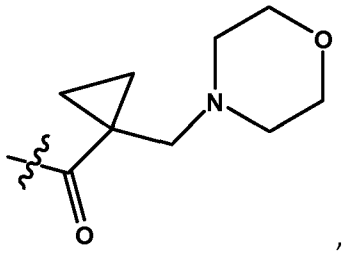
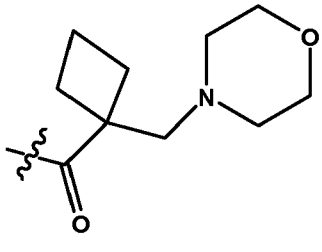
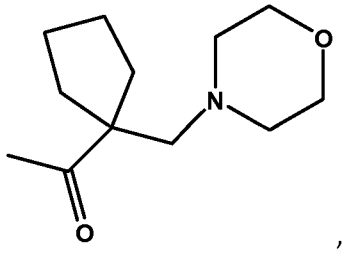
each R^{32} and R^{33} is independently H, C_1-C_8 alkyl, or optionally, if both present on the same substituent, may be joined together to form a C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_3-C_9 heterocyclyl or C_3-C_9 heteroaryl ring system.

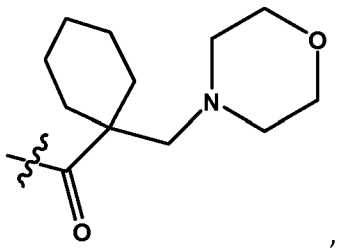
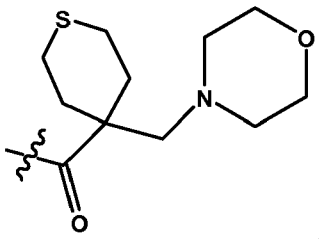
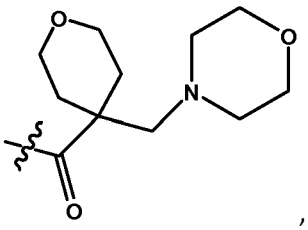
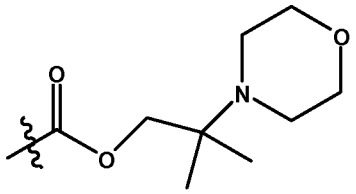
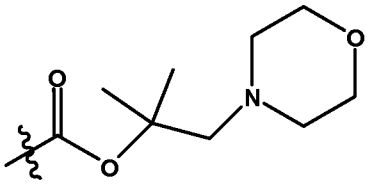
[0056] Within this embodiment, each R^{32} and R^{33} is independently, H, CH_3, or are joined together to form a cyclopropyl, cyclopbutyl, cyclopentyl, cyclohexyl, 1,1-dioxo- hexahydro-$1\lambda^6$-thiopyran-4-yl or tetrahydropyran-4-yl group.

[0057] In a preferred embodiment, linkage of the prodrug moiety to the rest of the active molecule is stable enough so that the serum half life of the prodrug is from about 8 to about 24 hours.

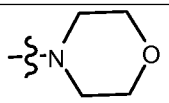
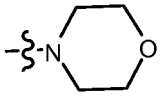
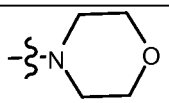
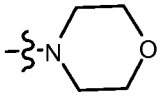
[0058] In an embodiment of the invention, the prodrug moiety comprises a tertiary amine having a pKa near the physiological pH of 7.5. Any amines having a pKa within 1 unit of 7.5 are suitable alternatives amines for this purpose. The amine may be provided by the amine of a morpholino group. This pKa range of 6.5 to 8.5 allows for significant concentrations of the basic neutral amine to be present in the mildly alkaline small intestine. The basic, neutral form of the amine prodrug is lipophilic and is absorbed through the wall of the small intestine into the blood. Following absorption into the bloodstream, the prodrug moiety is cleaved by esterases which are naturally present in the serum to release an active compound.

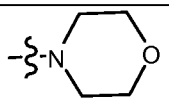
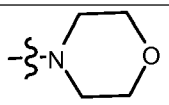
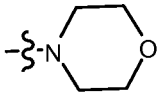
[0059] Examples of **R** include, without limitation:


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and
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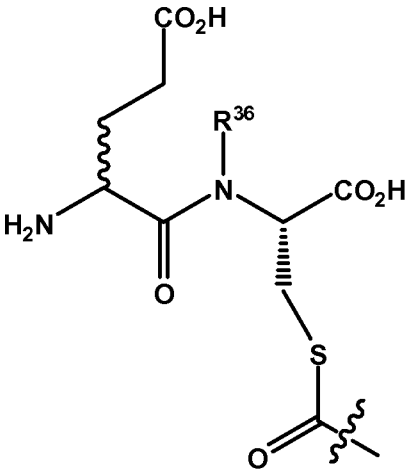
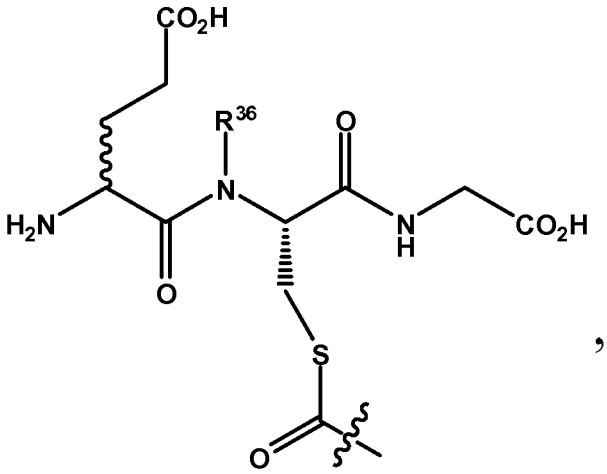
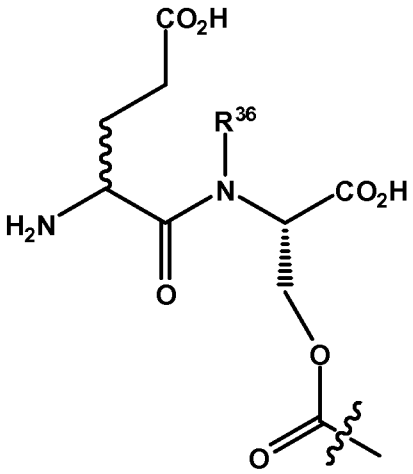
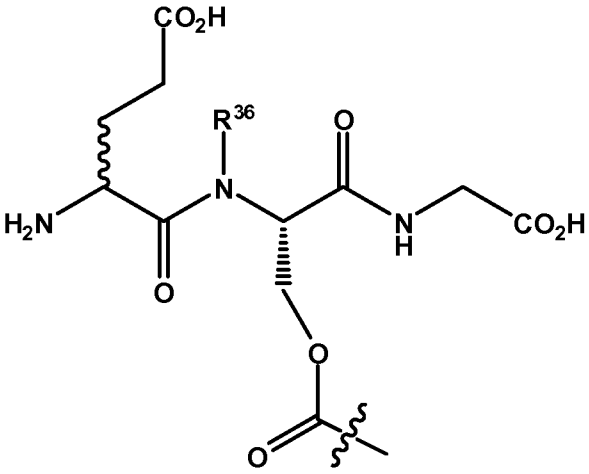
[0060] In another embodiment, R is as tabulated below:

R	m	R^{34}	R^{35}	$NR^{34}R^{35}$
$C(O)(CH_2)_mNR^{34}R^{35}$	1	Me	Me	
$C(O)(CH_2)_mNR^{34}R^{35}$	2	Me	Me	
$C(O)(CH_2)_mNR^{34}R^{35}$	3	Me	Me	
$C(O)(CH_2)_mNR^{34}R^{35}$	4	Me	Me	
$C(O)(CH_2)_mNR^{34}R^{35}$	1			
$C(O)(CH_2)_mNR^{34}R^{35}$	2			
$C(O)(CH_2)_mNR^{34}R^{35}$	3			
$C(O)(CH_2)_mNR^{34}R^{35}$	4			
$C(O)O(CH_2)_mNR^{34}R^{35}$	2	Me	Me	
$C(O)O(CH_2)_mNR^{34}R^{35}$	3	Me	Me	
$C(O)O(CH_2)_mNR^{34}R^{35}$	4	Me	Me	

$C(O)O(CH_2)_mNR^{34}R^{35}$	2			
$C(O)O(CH_2)_mNR^{34}R^{35}$	3			
$C(O)O(CH_2)_mNR^{34}R^{35}$	4			
$P(O)(OH)_2$				

an N oxide thereof, or a pharmaceutically acceptable salt of each thereof.

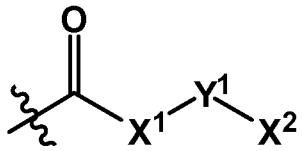
[0061] In another aspect, **R** is,


,

,

or


wherein

R^{36} is lower alkyl (*e.g.* C_1-C_6 alkyl).

[0062] In yet another aspect, **R** is:



wherein X^1, Y^1 and X^2 are as defined herein.

[0063] In one embodiment, X^1 is selected from the group consisting of O, S and NR^{37} wherein R^{37} is hydrogen or C_1-C_6 alkyl;

Y^1 is $-C(R^{38})_2$ or a sugar moiety, wherein each R^{38} is independently hydrogen or C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl;

X^2 is selected from the group consisting of halogen, C_1-C_6 alkoxy, diacylglycerol, amino, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, C_1-C_6 alkylthio, a PEG moiety, a bile acid moiety, a sugar moiety, an amino acid moiety, a di-or tri-peptide, a PEG carboxylic acid, and –U-V wherein

U is O or S; and

V is selected from the group consisting of C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, C_3-C_9 heteroaryl, $C(W^2)X^3$, $PO(X^3)_2$, and SO_2X^3;

wherein W^2 is O or NR^{39}

wherein R^{39} is hydrogen or C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 hetrocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl; and

each X^3 is independently amino, hydroxyl, mercapto, C_1-C_6 alkyl, heteroalkyl, cycloalkyl, hetrocyclyl, aryl, or heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, C_1-C_6 alkylthio, a bile acid based alkoxy group, a sugar moiety, a PEG moiety, and $-O-CH_2-CH(OR^{40})CH_2X^4R^{40}$,

wherein:

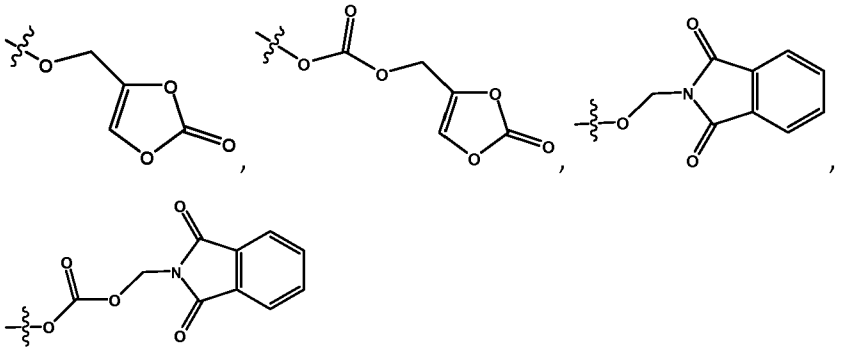
X^4 is selected from the group consisting of O, S, S=O, and SO_2; and

each R^{40} is independently C_{10}-C_{22} alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl, C_1-C_8 alkylene, or C_1-C_8 heteroalkylene.

[0064] Each heterocyclic and heteroaryl ring system is optionally substituted with C_1-C_3 alkyl, -OH, amino and carboxyl groups.

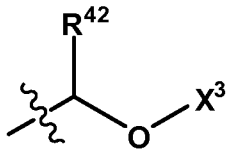
[0065] In one embodiment, the present invention utilizes the following Y^1 groups: CH_2, CHMe, CH(isopropyl), CH(tertiarybutyl), $C(Me)_2$, $C(Et)_2$, $C(isopropyl)_2$, and $C(propyl)_2$.

[0066] In another embodiment, the present invention utilizes the following X^2 groups:



-OMe, -OEt, -O-isopropyl, O-isobutyl, O-tertiarybutyl, -O-COMe, -O-C(=O)(isopropyl), -O-C(=O)(isobutyl), -O-C(=O)(tertiarybutyl), -O-C(=O)-NMe_2, -O-C(=O)-NHMe, -O-C(=O)-NH_2, -O-C(=O)-N(H)-CH(R^{41})-CO_2Et wherein R^{41} is a side chain C_1-C_6 alkyl, or C_3-C_9 heterocyclyl group selected from the side chain groups present in essential amino acids; -O-P(=O)$(OMe)_2$, -O-P(=O)$(O\text{-isopropyl})_2$, and –O-P(=O)$(O\text{-isobutyl})_2$. Each heterocyclic is optionally substituted with one or more, preferably, 1-3, C_1-C_3 alkyl, -OH, amino and/or carboxyl groups.

[0067] In another embodiment, In one embodiment, **R** is:



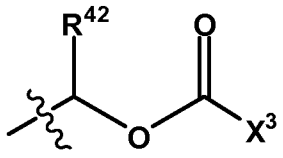
wherein

X^3 is independently C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl; and

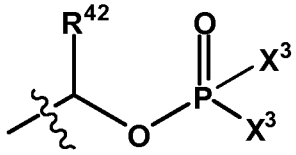
R^{42} is independently hydrogen or C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl.

[0068] Each heterocyclic is optionally substituted with one or more, preferably, 1-3, C_1-C_3 alkyl, -OH, amino and/or carboxyl groups.

[0069] In one embodiment, **R** is:



, or



wherein

each X^3 is independently amino, hydroxyl, mercapto, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, C_1-C_6 alkylthio, a bile acid based alkoxy group, a sugar moiety, a PEG moiety, and -O-CH_2-$CH(OR^{40})CH_2X^4R^{40}$,

wherein:

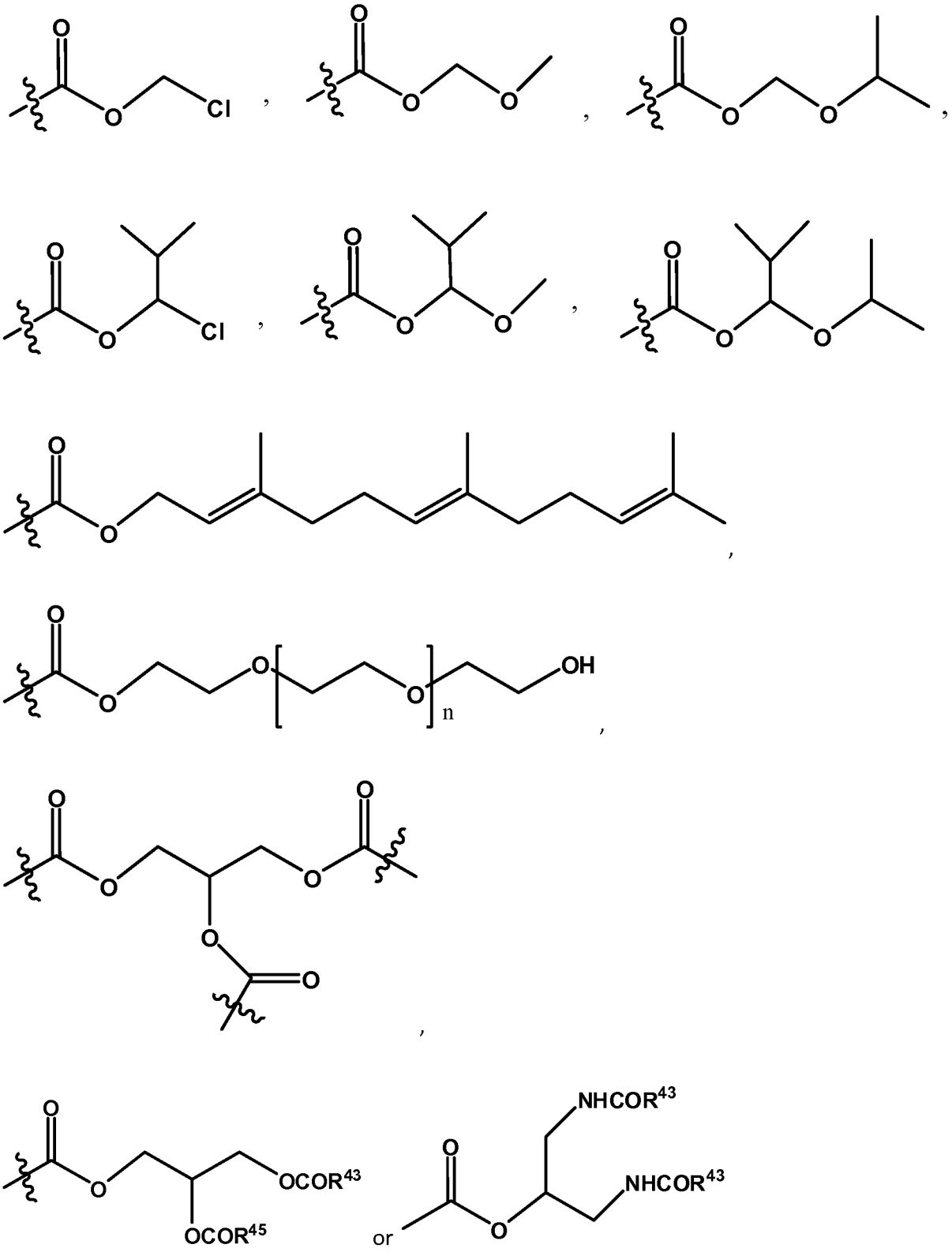
X^4 is selected from the group consisting of O, S, S=O, and SO_2; and

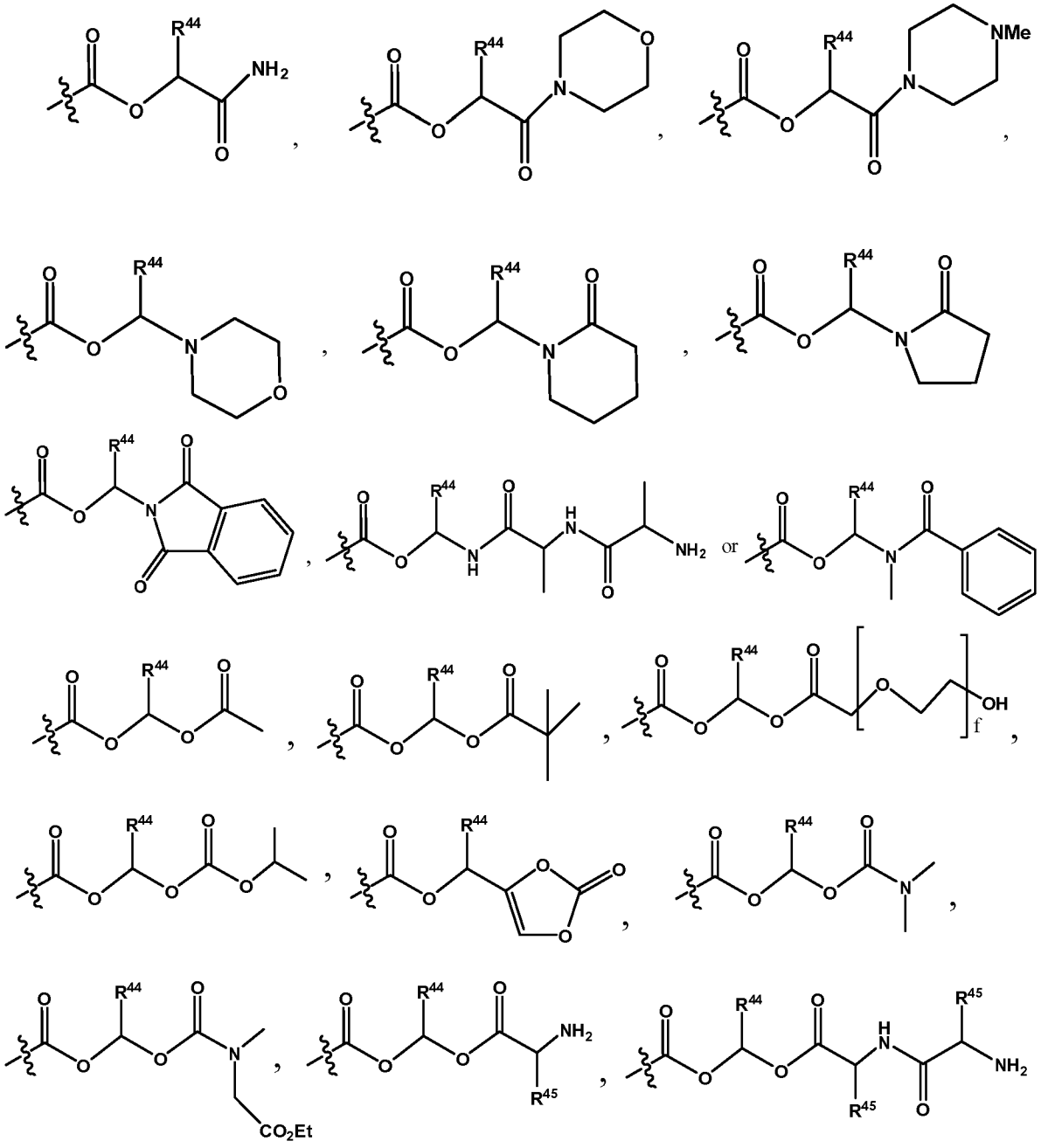
each R^{40} is independently C_{10}-C_{22} alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, C_3-C_9 heteroaryl, C_1-C_8 alkylene, or C_1-C_8 heteroalkylene; and

R^{42} is independently hydrogen or C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl.

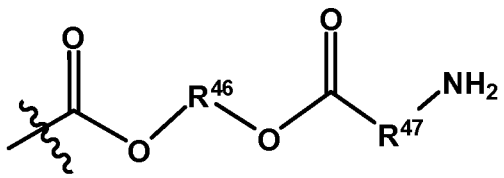
[0070] In some embodiments, R^{42} is independently hydrogen or C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl; and each X^3 independently is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl, C_1-C_6 alkoxy, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, or C_1-C_6 alkylthio.

[0071] In some embodiments, **R** is represented by the following structures:

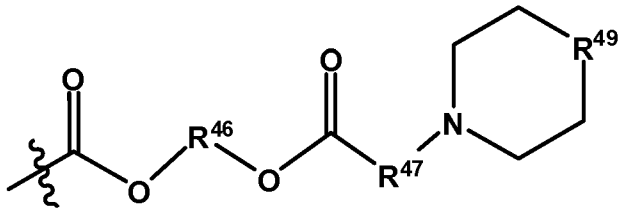




wherein, in the above examples, R^{43} is C_{10}-C_{22} alkyl or alkylene, R^{44} is H or C_1-C_6 alkyl and R^{45} represents side chain alkyl groups present in naturally occurring alpha amino acids;

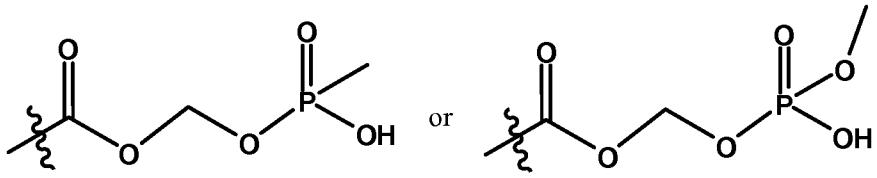


wherein R^{46} is $(CH_2)_n$, f=2-4, and CO-R^{47}-NH_2 represents an aminoacyl group; or



wherein R^{46} is $(CH_2)_n$, n=2-4, R^{47} is $(CH_2)_n$, n=1-3 and R^{49} is O or NMe.

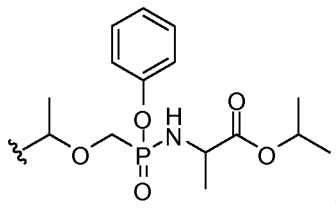
[0072] In one embodiment, **R** is:



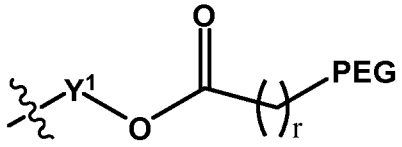
[0073] In one aspect, **R** is -C($R^{200}R^{201}$)O($R^{202}R^{203}$)P(O)OR^{204}N$R^{205}R^{206}$, wherein each R^{200}, R^{201}, R^{202}, R^{203}, R^{204} R^{205} and R^{206} is independently H, a C_1-C_8 alkyl, C_3-C_9 heterocyclyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, C_3-C_9 heteroaryl, wherein each alkyl, heterocyclyl, cycloalkyl, aryl, and heteroaryl is optionally substituted.

[0074] In some embodiments, **R** is -CH(R^{201})OCH_2P(O)OR^{204}NHR^{206}, wherein R^{201} is C_1-C_8 alkyl, R^{204} is phenyl, optionally substituted. In one embodiment, R^{206} is -CHR^{207}C(O)OR^{208} wherein R^{207} is selected from the group consisting of the naturally occurring amino acid side chains and CO_2H esters thereof and R^{208} is C_1-C_8 alkyl. In one embodiment, R^{206} is C_1-C_6 alkyl, optionally susbtitued with 1-3, CO_2H, SH, NH_2, C_6-C_{10} aryl, and C_2-C_{10} heteroaryl.

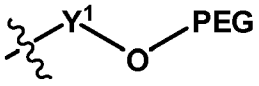
[0075] In some embodiments, **R** is:



[0076] In one embodiment, **R** is:



r = 0 to 12

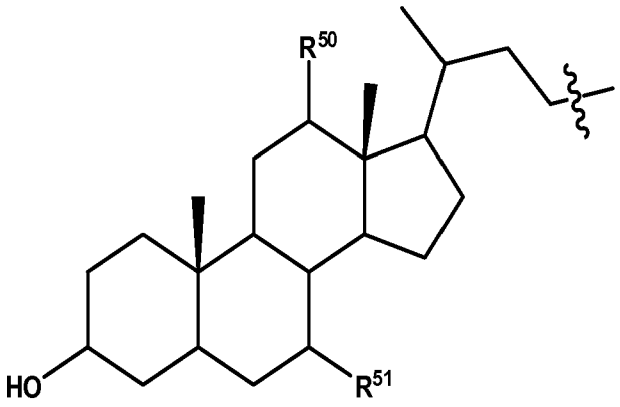


, or

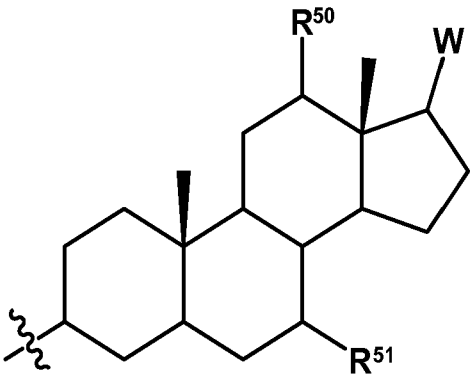
wherein Y^1 is $-C(R^{38})_2$, wherein each R^{38} is independently hydrogen or C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl.

[0077] Various polyethylene glycol (PEG) moieties and synthetic methods related to them that can be used or adapted to make compounds of the invention are described in U.S. Patent Nos. 6,608,076; 6,395,266; 6,194,580; 6,153,655; 6,127,355; 6,111,107; 5,965,566; 5,880,131; 5,840,900; 6,011,042 and 5,681,567.

[0078] In one embodiment, **R** is



or



wherein

R^{50} is -OH or hydrogen;

R^{51} is -OH, or hydrogen;

W is- $CH(CH_3)W^1$;

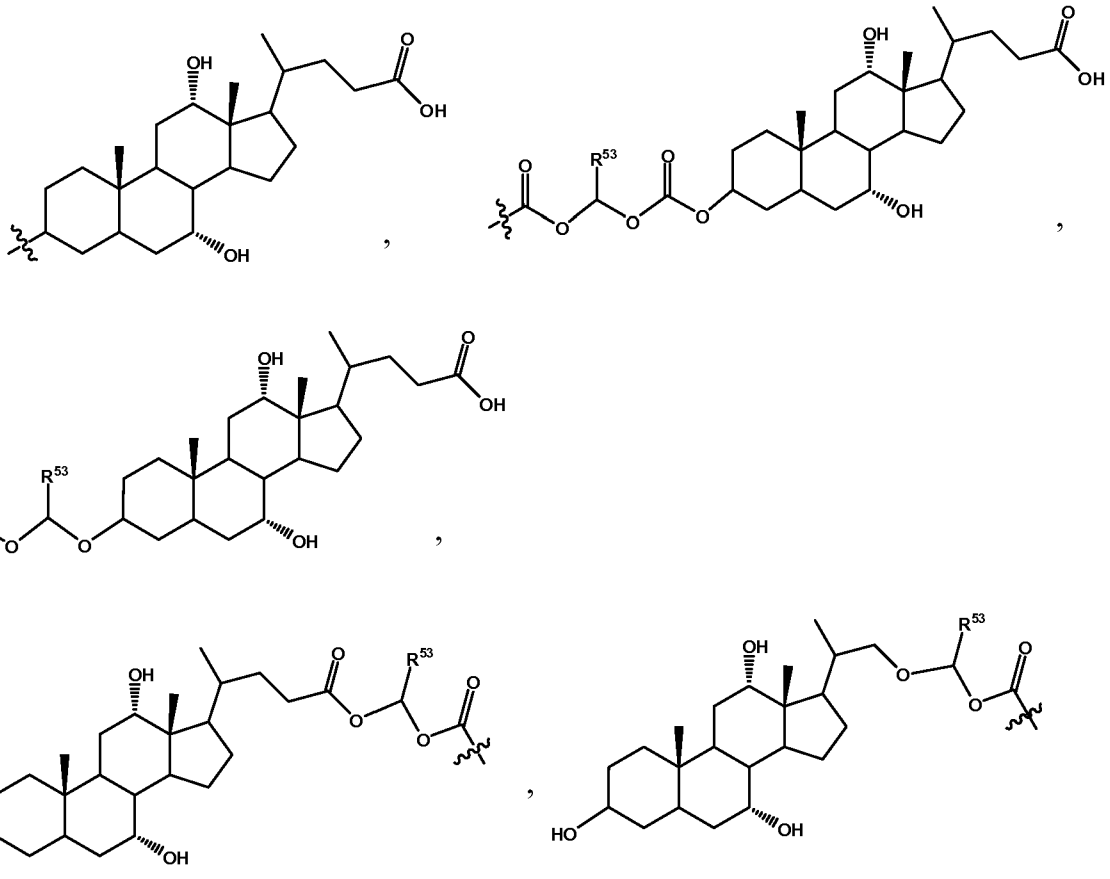
wherein W^1 is a substituted C_1-C_8 alkyl group containing a moiety which is optionally negatively charged at physiological pH,

said moiety is selected from the group consisting of CO_2H, SO_3H, SO_2H, $-P(O)(OR^{52})(OH)$, $-OP(O)(OR^{52})(OH)$, and OSO_3H,

wherein R^{52} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl.

[0079] Each heterocyclic and heteroaryl ring system is optionally substituted with one or more, preferably 1-3, C_1-C_3 alkyl, -OH, amino and/or carboxyl groups.

[0080] In one embodiment, **R** is:



wherein R^{53} is H or C_1-C_6 alkyl.

[0081] In another aspect, **R** is SO_3H.

[0082] In another aspect, **R** comprises a cleavable linker, wherein the term "cleavable linker" refers to a linker which has a short half life in vivo. The breakdown of the linker Z in a compound releases or generates the active compound. In one embodiment, the cleavable linker has a half life of less than ten hours. In one embodiment, the cleavable linker has a half life of less than an hour. In one embodiment, the half life of the cleavable linker is between one and fifteen minutes. In one embodiment, the cleavable linker has at least one connection with the structure: C*- C(=X*)X*-C* wherein C* is a substituted or unsubstituted methylene group, and X* is S or O. In one embodiment, the cleavable linker has at least one C*-C(=O)O-C* connection. In one embodiment, the cleavable linker has at least one C*-C(=O)S-C* connection. In one embodiment, the cleavable linker has at least one -C(=O)N*-C*-SO_2-N*-connection, wherein N* is -NH- or C_1-C_6 alkylamino. In one embodiment, the cleavable linker is hydrolyzed by an esterase enzyme.

[0083] In one embodiment, the linker is a self-immolating linker, such as that disclosed in U.S. patent publication 2002/0147138, to Firestone; PCT Appl. No. US05/08161 and PCT Pub. No. 2004/087075. In another embodiment, the linker is a substrate for enzymes. See generally Rooseboom et al., 2004, Pharmacol. Rev. 56:53-102.

Pharmaceutical Compositions

[0084] In further aspects of the invention, a composition is provided comprising any of the compounds described herein, and at least a pharmaceutically acceptable excipient.

[0085] In another aspect, this invention provides a composition comprising any of the compounds described herein, and a pharmaceutically acceptable excipient.

[0086] Such compositions can be formulated for different routes of administration. Although compositions suitable for oral delivery will probably be used most frequently, other routes that may be used include transdermal, intravenous, intraarterial, pulmonary, rectal, nasal, vaginal, lingual, intramuscular, intraperitoneal, intracutaneous, intracranial, and subcutaneous routes. Suitable dosage forms for administering any of the compounds described herein include tablets, capsules, pills, powders, aerosols, suppositories, parenterals, and oral liquids, including suspensions, solutions and emulsions. Sustained release dosage forms may also be used, for example, in a transdermal patch form. All

dosage forms may be prepared using methods that are standard in the art (see e.g., Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton Pa. 1980).

[0087] Pharmaceutically acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of this invention. Such excipients may be any solid, liquid, semi-solid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art. Pharmaceutical compositions in accordance with the invention are prepared by conventional means using methods known in the art.

[0088] The compositions disclosed herein may be used in conjunction with any of the vehicles and excipients commonly employed in pharmaceutical preparations, e.g., talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous solvents, oils, paraffin derivatives, glycols, etc. Coloring and flavoring agents may also be added to preparations, particularly to those for oral administration. Solutions can be prepared using water or physiologically compatible organic solvents such as ethanol, 1,2-propylene glycol, polyglycols, dimethylsulfoxide, fatty alcohols, triglycerides, partial esters of glycerin and the like.

[0089] Solid pharmaceutical excipients include starch, cellulose, hydroxypropyl cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. In certain embodiments, the compositions provided herein comprises one or more of α-tocopherol, gum arabic, and/or hydroxypropyl cellulose.

[0090] In one embodiment, this invention provides sustained release formulations such as drug depots or patches comprising an effective amount of a compound provided herein. In another embodiment, the patch further comprises gum Arabic or hydroxypropyl cellulose separately or in combination, in the presence of alpha-tocopherol. Preferably, the hydroxypropyl cellulose has an average MW of from 10,000 to 100,000. In a more preferred embodiment, the hydroxypropyl cellulose has an average MW of from 5,000 to 50,000.

[0091] Compounds and pharmaceutical compositions of this invention maybe used alone or in combination with other compounds. When administered with another agent, the co-administration can be in any manner in which the pharmacological effects of both are manifest in the patient at the same time. Thus, co-administration does not require that a single pharmaceutical composition, the same dosage form, or even the same route of administration be used for administration of both the compound of this invention and the other agent or that the two agents be administered at precisely the same time. However, co-administration will be accomplished most conveniently by the same dosage form and the same route of administration, at substantially the same time. Obviously, such administration most advantageously proceeds by delivering both active ingredients simultaneously in a novel pharmaceutical composition in accordance with the present invention.

Methods of Treatment

[0092] In aspects of the invention, a method is provided for increasing tissue and/or cellular oxygenation, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

[0093] In aspects of the invention, a method is provided for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

[0094] In aspects of the invention, a method is provided for treating a condition associated with oxygen deficiency, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

[0095] In further aspects of the invention, a method is provided for treating oxygen deficiency associated with sickle cell anemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

[0096] In further aspects of the invention, a method is provided for treating sickle cell disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any of the compounds or compositions described herein. In still further aspects of the invention, a method is provided for treating 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 compounds or compositions described herein.

Synthetic Methods

[0097] Certain methods for making the compounds described herein are also provided. The reactions are preferably carried out in a suitable inert solvent that will be apparent to the skilled artisan upon reading this disclosure, for a sufficient period of time to ensure substantial completion of the reaction as observed by thin layer chromatography, ^{1}H-NMR, etc. If needed to speed up the reaction, the reaction mixture can be heated, as is well known to the skilled artisan. The final and the intermediate compounds are purified, if necessary, by various art known methods such as crystallization, precipitation, column chromatography, and the likes, as will be apparent to the skilled artisan upon reading this disclosure.

[0098] An illustrative and non-limiting method for synthesizing a compound of formula (I), is schematically shown below.

In the following Schemes, (A), (B) and (C) refer to rings A, B and C as described herein.

X and X^5 each represent a leaving group and are independently selected from Cl, F, Br, and I.

X^6 represents CHR^{14}, NR^{14}, O, S(O)x ; wherein x is 0, 1, or 2;

Y^5 represents a leaving group selected from Cl, F, Br, I, OSO_2R^{17} and OSO_2Ar;

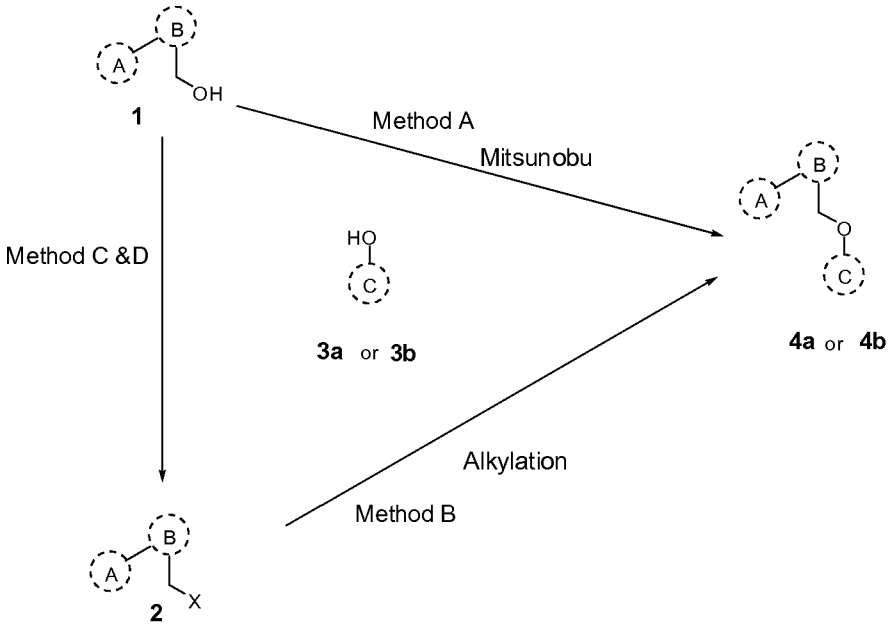
R^{17} is C_1-C_6 alkyl;

n is 0, 1, or 2;

Ar is phenyl optionally substituted with 1-3 halo or C_1-C_4 alkyl groups.

Where variables already used in the structures hereinabove are used in the shcemes, the context makes it unambiguous as to what the variable refers to.

General Synthetic Scheme 1A



[0099] General method A for preparing aryloxy ether analogs (4a) from substituted methylene alcohol (1) and hydroxyl aryl aldehyde derivative (3a). A hydroxyl arylaldehyde derivative (**3a**) (0.1-2 mmol) mixture with substituted methylene alcohol (**1**) (0.8 to 1.2eq) and PPh_3 (1-1.5eq) in anhydrous THF (1-10mL) was stirred under nitrogen until complete dissolution. The solution was cooled to 0 ^oC on ice bath and DIAD or DEAD (1.1 eq) in THF or toluene was added dropwise over a 1-20 min period. The ice cooling bath was allowed to expire over 90 min and the mixture was stirred at RT for 2-48 hours. The mixture was stirred for 10 min, then filtered through a pad of silica. The silica was washed with ethyl acetate 2-20mL. The combined filtrates were evaporated and the residue was dried on highvac. The residue was purified by preparative HPLC or flash silica gel chromatography.

[0100] General method B for preparing aryloxy ether analogs (4a) from substituted methylene halide (2) and hydroxyl aryl aldehyde derivatives (3a). A mixture of hydroxyl arylaldehyde derivatives (**3a**) (0.1-2 mmol, 1-4 eq.), substituted methylene chloride or bromide (**2**) (1eq), and K_2CO_3 (2-5 eq.) (catalytic amount of NaI or Bu_4NI may also be added) in DMF or acetonitrile (1 to 10 mL) was stirred at RT or heating up to 120 ^oC for 0.5-8 h

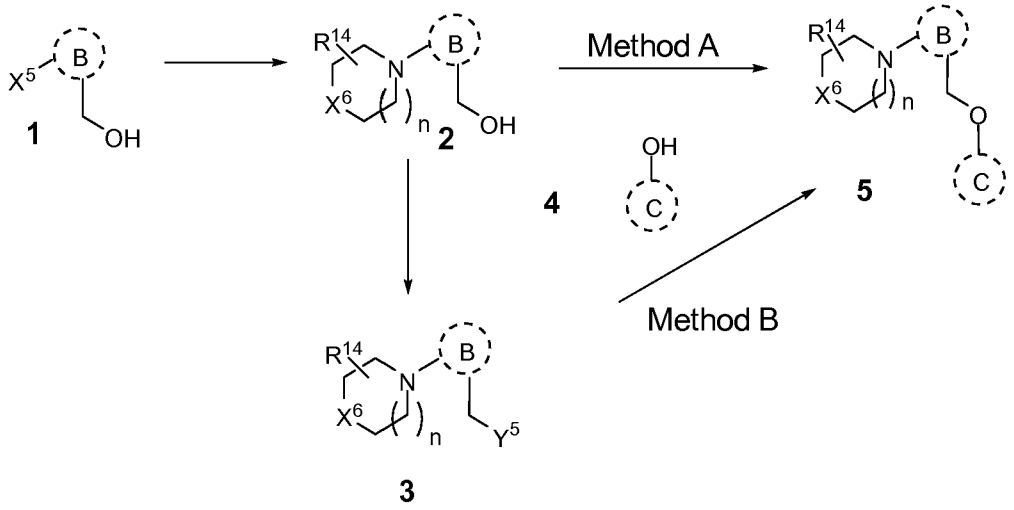
under nitrogen atmosphere. In workup A, water was added to the reaction mixture, the precipitated product was collected, washed with water, and then subjected to preparative HPLC or flash silica gel chromatography purification. In workup B (for products that did not precipitate), diluted HCl or aqueous NH_4Cl was added at 0 ^oC to adjusted the pH to ~7, the reaction mixture was partitioned between ethyl acetate or dichloromethane and aqueous sodium chloride and the organic layer separated, dried, and solvent removed under vacuum to afford crude product which was purified by automated silica gel column chromatography using appropriate solvents mixture (e.g., ethyl acetate/hexanes).

[0101] General method C for preparing substituted methylene chloride (2a). To a solution of substituted methylene alcohol (**1**) (0.1 to 2 mmol) in DCM (1-10 mL) was added $SOCl_2$ dropwise (2eq to 5eq) at 0 ^oC or RT. The reaction mixture was stirred at RT for 10min to 6 h, or until reaction is judged complete (LC/MS). The reaction mixture is concentrated to dryness over a rotavap. The crude chloride residue was suspended in toluene, sonicated and concentrated to dryness. The process was repeated three times and dried under vacuum to give the substituted methylene chloride (**2**), usually as an off-white solid, which was used for next step without further purification. Alternatively, a solution of aqueous 1N Na_2CO_3 is then added to produce a solution of pH~ 8. the mixture was extracted with DCM (3 x10-50mL), dried over sodium sulfate, and concentrated to the crude substituted methylene chloride (**2a**), which is then purified by column chromatography on silica gel (0-100% ethyl acetate-hexanes).

[0102] General method D for preparing substituted methylene bromide (2b). To a solution of substituted methylene alcohol (**1**) (0.1 to 2 mmol) in DCM (1-10 mL) was added Ph_3PBr_2 dropwise (2eq to 5eq) at 0 ^oC or RT. The reaction mixture was stirred at RT for 10 min to 2 h, or until reaction is judged complete (LC/MS). The reaction mixture is concentrated to dryness over a rotavap. The residue purified by column chromatography on silica gel (0-100% ethyl acetate-hexanes) to afford the pure bromide **2b**.

[0103] Similarly, N-linked heterocyclic analogs (compound **5**) can also be synthesized from amination procedures developed by Buchwald and Hartwig.

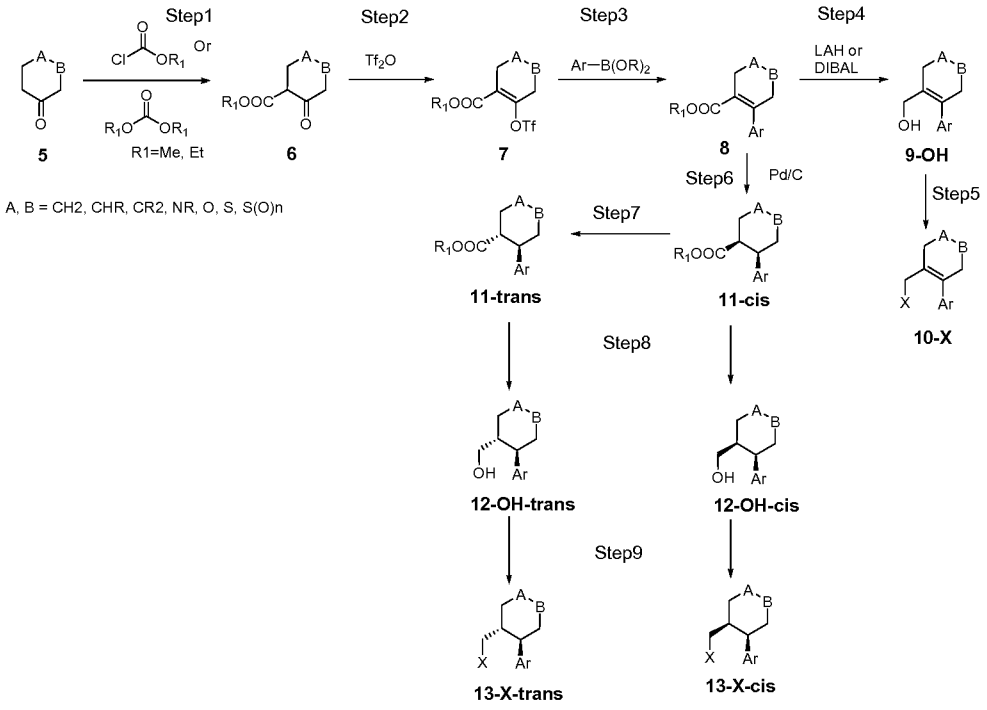
Scheme 1B



[0104] Protected amides of formula -$CONHR^{95}$ and -$CONHOR^{95}$ can be converted e.g., hydrolyzed to the corresponding amides according to methods known to the skilled artisan.

$C_{19}H_{23}N_3O_3$: 342.2.

[0105] General Synthetic Scheme 2 (six membered ring)

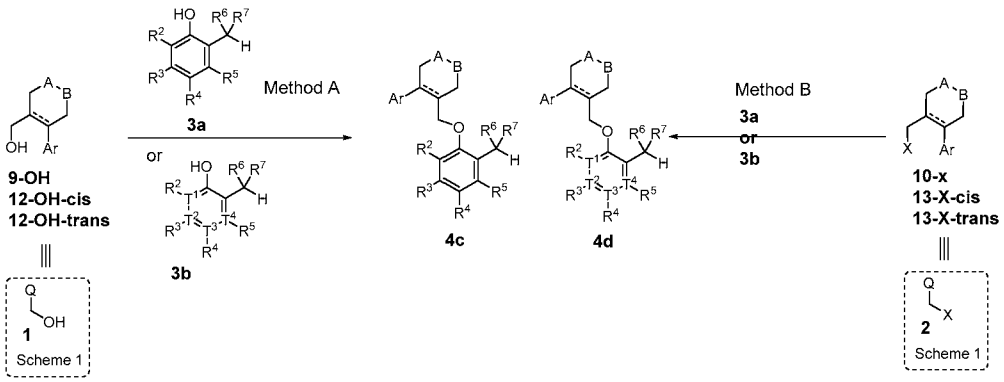


[0106] **General method E (Scheme 2) for preparing heterocyclic methylene derivatives 9, 10, 12 and 13.** Condensation of heterocyclic ketone analog **5** with chlorformate or dialkyl carbonate gives (hetero)cyclic beta-ketone ester **6** (Step 1). The ketone ester **6** is converted

to the triflate intermediate **7** by treating with a triflating agent (e.g, triflic anhydride) in the presence of an organic base such as Hunig's base (Step 2). Suzuki coupling of the triflate **7** with a boronic acid or ester affords heterocyclohexene carboxylate **8** (Step 3). Subsequent reduction of the ester group by LAH or DIBAL gives the corresponding alcohol **9-OH** (Step 4). Further reaction of the alcohol **9-OH** with thionyl chloride, Ph_3PBr_2 (or CBr_4-Ph_3P or PBr_3), or alkyl/aryl sufonyl chloride produces the corresponding **10-X** chloride, bromide or sulfonate (Step 5).

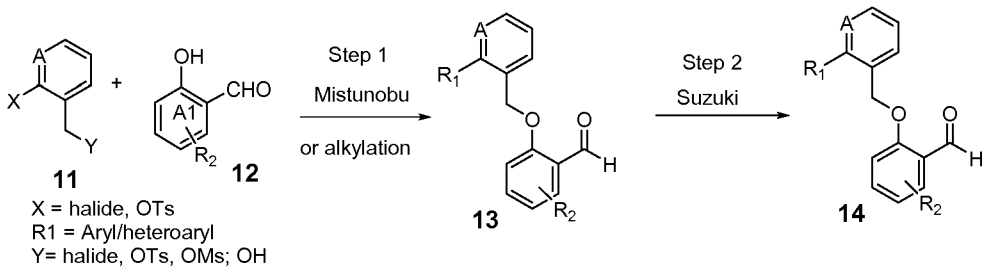
[0107] Alternatively, the double bond of heterocyclohexene carboxylate **8** is reduced to give the *cis*-heterocyclohexane **11-cis** carboxylate under palladium catalyzed hydrogenation conditions (Step 6). Reduction of the ester group of **11-cis** by LAH or DIBAL yields cis-alcohol **12-OH-cis** (Step 8). Conversion of the alcohol **12-OH-cis** to its chloride, bromide or sulfonate (such as mesylate, tosylate) **13-X-cis** can be achieved by reacting with thionyl chloride, or Ph_3PBr_2, or sufonyl chloride (such as mesyl chloride or tosyl chloride) (Step 9). The *cis*-cyclohexane carboxylate **11-cis** can also be isomerized to the thermodynamically more stable trans-isomer **11-trans** by the treatment with an alcoholic alkoxide (e.g., ethoxide) solution. Analogously, transformation of **11-trans** ester to **12-trans** alcohol and **13-X-trans** halide is accomplished by applying conditions of Step 8 and Step9 (Scheme 2) similar to these for the corresponding cis-isomers.

Scheme 3



[0108] Coupling of the (hetero)cyclic methylene derivatives **9**, **10, 12** and **13** with hydroxyl (hetero)arylaldehyde derivatives (**3a/3b**) (see, e.g., Scheme 3) by general method A or B affords the corresponding aryloxy/heteroarylether analogs (**4c** and **4d**).

General Synthetic Scheme 4

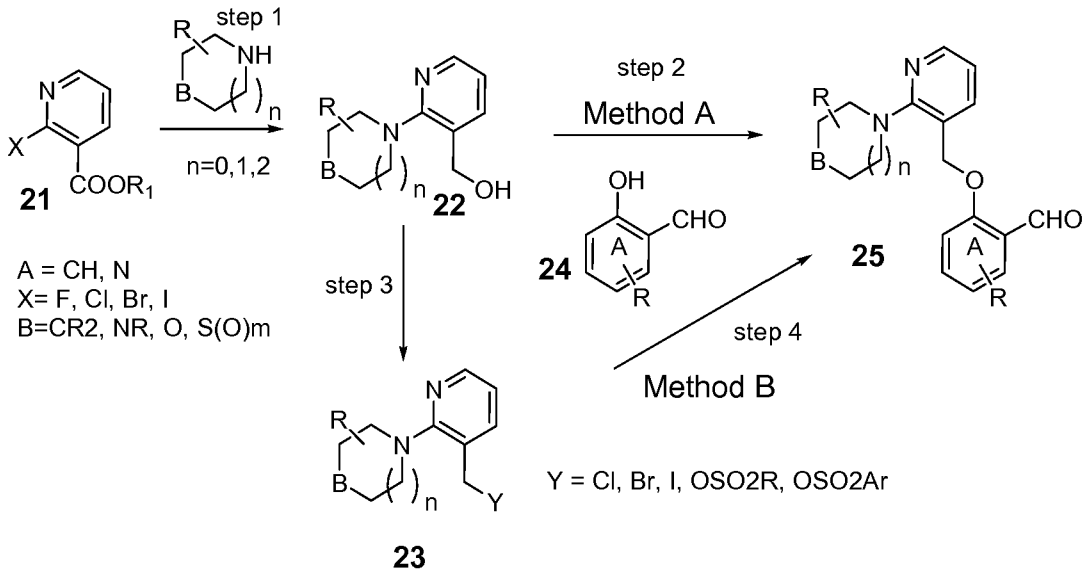


[0109] Step 1a-Compound **13** can is synthesized via O-alkylation of phenol aldehyde **12** with alkyl halide **11** (Y=halide, OTs, OMs). A mixture of hydroxyl (hetero)arylaldehyde derivatives (**12**) (0.1-2 mmol, 1-4 eq.), substituted methylene chloride or bromide (**11**) (1eq), and K_2CO_3 (2-5 eq.) (catalytic amount of NaI or Bu_4NI may also be added) in DMF, acetonitrile, NMP or DMSO (1 to 10 mL) was stirred at RT or heating up to 120 ^oC for 1-24 h under nitrogen atmosphere. In workup A, water was added to the reaction mixture, the precipitated product was collected, washed with water, and then subjected to preparative HPLC or flash silica gel chromatography purification. In workup B (for products that did not precipitate), diluted HCl or aqueous NH_4Cl was added at 0 ^oC to adjusted the pH to ~7, the reaction mixture was partitioned between ethyl acetate or dichloromethane and aqueous sodium chloride and the organic layer separated, dried, and solvent removed under vacuum to afford crude product which was purified by automated silica gel column chromatography using appropriate solvents mixture (e.g., ethyl acetate/hexanes).

[0110] Step 1b-Alternatively, compound **13** is made by coupling of phenol aldehyde **12** with alcohol **1** (Y=OH) under Mitsunobu conditions. A hydroxyl (hetero)arylaldehyde derivatives (**12**) (0.1-2 mmol) mixture with substituted methylene alcohol (**11,** Y=OH) (0.8 to 1.2eq) and (polymer-supported)/PPh_3 (1-1.5eq) in anhydrous THF (1-10mL) was stirred under nitrogen until complete dissolution. The solution was cooled to 0 ^oC on ice bath and DIAD or DEAD (1.1 eq) in THF or toluene was added drop wise over a 1-20 min period. The ice cooling bath was allowed to expire over 90 min and the mixture was stirred at RT for 2-48 hours. The mixture was stirred for 10 min, then filtered through a pad of silica. The silica was washed with ethyl acetate 2-20mL. The combined filtrates were evaporated and the residue was dried on highvac. The residue was purified by preparative HPLC or flash silica gel chromatography.

[0111] Step 2. To a solution of (2-chloropyridin-3-yl)methanol or (2-bromopyridin-3-yl)methanol (1-100mmol) and appreciate bronic acid or ester (0.8 to 1.5 eq) in dioxane (2-200 mL) was added a solution of sodium bicarbonate (3 eq) in water (1-100 mL), followed by the addition of $Pd(dppf)Cl_2$ (5 to 10mol%). After heating at 100 °C for 4-24 h, the reaction mixture was cooled and diluted with EtOAc, organic layer was washed with water, brine, dried and concentrated to give crude product, which was purified by column chromatography.

General Synthetic Scheme 5



[0112] Compound **25** can be prepared from 2-halonicotinate through a series organic transformations that involve displacement with cyclic amine and reduction of ester to give hydroxymethylene derivative **22** (step 1). The final product can be synthesized via either direct Mitsunobu reaction of **22** with phenol aldehyde **24** or conversion of the alcohol **22** to halide **23** followed by O-alkylation of phenol **24** with **23**.

Prodrug Synthesis

[0113] Syntheses of the ester prodrugs start with the free carboxylic acid bearing the tertiary amine. The free acid is activated for ester formation in an aprotic solvent and then reacted with a free alcohol group in the presence of an inert base, such as triethyl amine, to provide the ester prodrug. Activating conditions for the carboxylic acid include forming the acid chloride using oxalyl chloride or thionyl chloride in an aprotic solvent, optionally with a catalytic amount of dimethyl formamide, followed by evaporation. Examples of aprotic

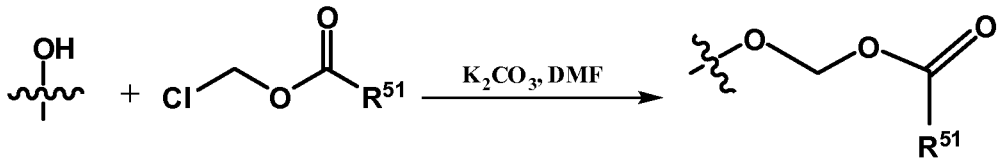
solvents, include, but are not limited to methylene chloride, tetrahydrofuran, and the like. Alternatively, activations can be performed in situ by using reagents such as BOP (benzotriazol-l-yloxytris(dimethylamino) phosphonium hexafluorolphosphate, and the like (see Nagy et al., 1993, Proc. Natl. Acad. Sci. USA 90:6373-6376) followed by reaction with the free alcohol. Isolation of the ester products can be affected by extraction with an organic solvent, such as ethyl acetate or methylene chloride, against a mildly acidic aqueous solution; followed by base treatment of the acidic aqueous phase so as to render it basic; followed by extraction with an organic solvent, for example ethyl acetate or methylene chroride; evaporation of the organic solvent layer; and recrystalization from a solvent, such as ethanol. Optionally, the solvent can be acidified with an acid, such as HCl or acetic acid to provide a pharmaceutically acceptable salt thereof. Alternatively the crude reaction can be passed over an ion exchange column bearing sulfonic acid groups in the protonated form, washed with deionized water, and eluted with aqueous ammonia; followed by evaporation.

[0114] Suitable free acids bearing the tertiary amine are commercially available, such as 2-(N-morpholino)-propionic acid, N,N- dimethyl-beta-alanine, and the like. Non- commercial acids can be synthesized in straightforward manner via standard literature procedures.

[0115] Carbonate and carbamate prodrugs can be prepared in an analogous way. For example, amino alcohols and diamines can be activated using activating agents such as phosgene or carbonyl diimidazole, to provide an activated carbonates, which in turn can react with the alcohol and/or the phenolic hydroxy group on the compounds utilized herein to provide carbonate and carbamate prodrugs.

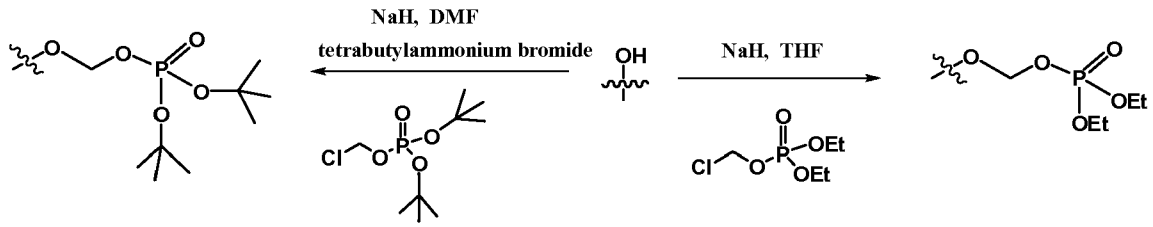
[0116] Various protecting groups and synthetic methods related to them that can be used or adapted to make compounds of the invention can be adapted from the references Testa et al., Hydrolysis in Drug and Prodrug Metabolism, June 2003, Wiley- VCH, Zurich, 419-534 and Beaumont et al., Curr. Drug Metab. 2003, 4:461-85.

[0117] Provided herein is a method of synthesizing an acyloxymethyl version of a prodrug by adapting a method from the reference Sobolev et al., 2002, J. Org. Chem. 67:401-410.

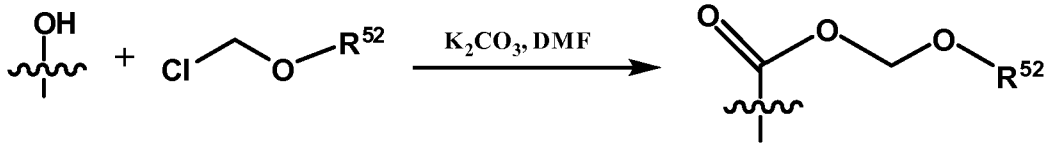


R^{51} is C_1-C_6 alkyl.

[0118] Provided herein is a method for synthesizing a phosphonooxymethyl version of a prodrug by adapting a method from Mantyla et al., 2004, J. Med. Chem. 47:188-195.



[0119] Provided herein is a method of synthesizing an alkyloxymethyl version of a prodrug



R^{52} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_9 heterocyclyl, C_6-C_{10} aryl, or C_3-C_9 heteroaryl.

Examples

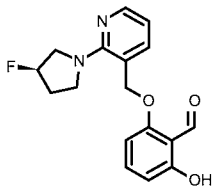
[0120] The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims will occur to those skilled in the art.

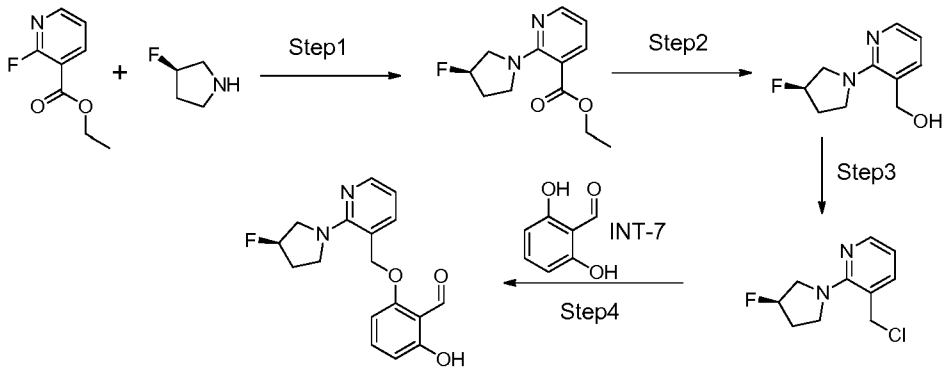
[0121] In the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

°C = degrees Celsius

RT	=	Room temperature
min	=	minute(s)
h	=	hour(s)
µL	=	Microliter
mL	=	Milliliter
mmol	=	Millimole
eq	=	Equivalent
mg	=	Milligram
MS	=	Mass spectrometry
LC-MS	=	Liquid chromatography–mass spectrometry
HPLC	=	High performance liquid chromatography
NMR	=	Nuclear magnetic resonance
EtOAc	=	Ethyl acetate
Ph_3PBr_2	=	Triphenylphosphine dibromide
DMF	=	N, N-Dimethylformamide
DCM	=	Dichloromethane
DMSO	=	Dimethyl sulfoxide
THF	=	Tetrahydrofuran
DIAD	=	Diisopropyl azodicarboxylate
DEAD	=	Diethyl azodicarboxylate

[0122] Preparation of 2-[[2-[(3R)-3-fluoropyrrolidin-1-yl]pyridin-3-yl]methoxy]-6-hydroxybenzaldehyde





[0123] Step 1: (R)-ethyl 2-(3-fluoropyrrolidin-1-yl)nicotinate. To a solution of ethyl 2-fluoronicotinate (0.074 g, 0.48 mmol) in DMF (0.3 mL) was added diisopropylethyl amine (0.25 mL, 1.4 mmol), and (*R*)-3-fluoropyrrolidine (0.090 g, 0.72 mmol). The resulting mixture was irradiated with microwaves (100 ^{o}C) for 1h and loaded directly onto a silica column. Eluting the column with EtOAc/hexanes (0-100%) provided (*R*)-ethyl 2-(3-fluoropyrrolidin-1-yl)nicotinate as a clear oil (0.100 g, 94% yield); MS (ESI) m/z 239 $[M+H]^+$.

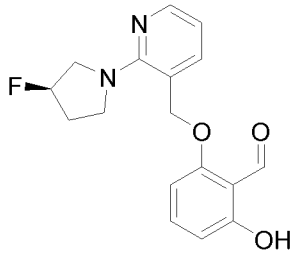
[0124] Step 2: (*R*)-(2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methanol. To a cooled (0 ^{o}C) solution of (*R*)-methyl 2-(3-fluoropyrrolidin-1-yl)nicotinate in THF (5 mL) was added a solution of lithium aluminum hydride (1M in THF). The reaction mixture was stirred for 1h and then 20 µL of H_2O was added followed by 20 µL of 15% NaOH (aq) and then 60 µL of additional water. The slurry was stirred for 1h and filtered and the resulting residue was washed with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromotography (EtOAc/hexanes,0-100%) provided (*R*)-(2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methanol (0.081 g, 92% yield). MS (ESI) m/z 197 $[M+H]^+$.

[0125] Step 3: (*R*)-3-(chloromethyl)-2-(3-fluoropyrrolidin-1-yl)pyridine. To a cooled (0 ^{o}C) solution of (*R*)-(2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methanol (0.081 g, 0.38 mmol) in dichloromethane was added $SOCl_2$ (0.450 g, 3.8 mmol) and the reaction mixture was allowed to warm to ambient temperature. After 1 h, the reaction mixture was concentrated and azeotroped with toluene to provide (*R*)-3-(chloromethyl)-2-(3-fluoropyrrolidin-1-yl)pyridine (0.080 g, 92%) as a clear oil. MS (ESI) m/z 215 $[M+H]^+$.

[0126] Step 4: (*R*)-2-((2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde. To a solution of (*R*)-3-(chloromethyl)-2-(3-fluoropyrrolidin-1-yl)pyridine (0.080 g, 0.35 mmol) and 2,6-dihydroxybenzaldehyde (0.130 g, 0.94 mmol) in DMF was added potassium carbonate (0.190 g, 1.4 mmol) and the reaction mixture was

heated (60 °C). After 30 minutes, the DMF was removed and the resulting residue was reconstituted in CH_2Cl_2 and filtered through a plug of silica (EtOAc/hexanes, 1:1). Purification Prep-HPLC provided (*R*)-2-((2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (8 mg, 5% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (dd, *J* = 8.4, 0.7 Hz, 1H), 10.21 (d, *J* = 0.5 Hz, 1H), 8.10 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.71 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 6.73 (dd, *J* = 8.6, 0.7 Hz, 1H), 6.71 (dd, *J* = 7.4, 5.0 Hz, 1H), 6.53 (dt, *J* = 8.4, 0.7 Hz, 1H), 5.40 (dd, *J* = 54.2, 3.3 Hz, 1H), 5.28 (d, *J* = 11.3 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 3.91 – 3.56 (m, 4H), 2.21 – 1.93 (m, 2H); MS (ESI) m/z 317 $[M+H]^+$.

GBT883



[0127] GBT883- **(*R*)-2-((2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde.** The compound was prepared from ethyl 2-fluoronicotinate and (*R*)-3-fluoropyrrolidine according to scheme 5, reaction steps 1, 3 and 4.

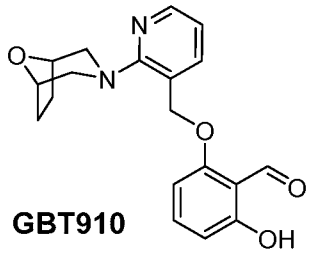
[0128] Step 1a: To a solution of ethyl 2-fluoronicotinate (0.074 g, 0.48 mmol) in DMF (0.3 mL) was added diisopropylethyl amine (0.25 mL, 1.4 mmol), and (*R*)-3-fluoropyrrolidine (0.090 g, 0.72 mmol). The resulting mixture was irradiated with microwaves (100 °C) for 1h and loaded directly onto a silica column. Eluting the column with EtOAc/hexanes (0-100%) provided (*R*)-ethyl 2-(3-fluoropyrrolidin-1-yl)nicotinate as a clear oil (0.100 g, 94% yield). MS (ES) for $C_{12}H_{15}FN_2O_2$: 225 (MH^+).

[0129] Step 1b: To a cooled (0 °C) solution of (*R*)-methyl 2-(3-fluoropyrrolidin-1-yl)nicotinate in THF (5 mL) was added a solution of lithium aluminum hydride (1M in THF). The reaction mixture was stirred for 1h and then 20 µL of H2O was added followed by 20 µL of 15% NaOH (aq) and then 60 µL of additional water. The slurry was stirred for 1h and filtered and the resulting residue was washed with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromotography (EtOAc/hexanes,0-100%) provided (*R*)-(2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methanol (0.081 g, 92% yield). MS (ES) for $C_{10}H_{13}FN_2O$: 197 (MH^+).

[0130] Step 3: To a cooled (0 °C) solution of (*R*)-(2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methanol (0.081 g, 0.38 mmol) in dichloromethane was added $SOCl_2$ (0.450 g, 3.8 mmol) and the reaction mixture was allowed to warm to ambient temperature. After 1 h, the reaction mixture was concentrated and azeotroped with toluene to provide (*R*)-3-(chloromethyl)-2-(3-fluoropyrrolidin-1-yl)pyridine (0.080 g, 92%) as a clear oil. MS (ES) for $C_{10}H_{12}ClFN_2$: 215 (MH^+).

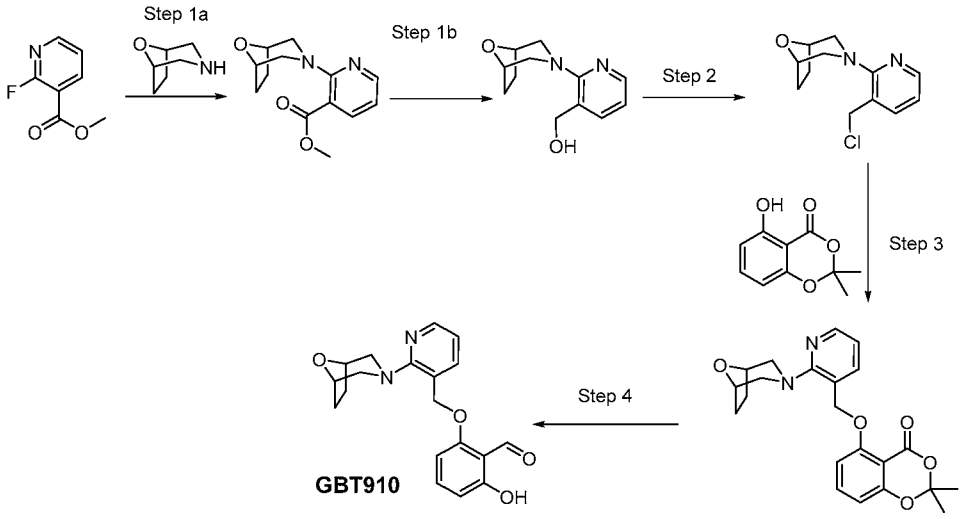
[0131] Step 4. To a solution of (*R*)-3-(chloromethyl)-2-(3-fluoropyrrolidin-1-yl)pyridine (0.080 g, 0.35 mmol) and 2,6-dihydroxybenzaldehyde (0.130 g, 0.94 mmol) in DMF was added potassium carbonate (0.190 g, 1.4 mmol) and the reaction mixture was heated (60 °C). After 30 minutes, the DMF was removed and the resulting residue was reconstituted in CH_2Cl_2 and filtered through a plug of silica (EtOAc/hexanes, 1:1). Purification Prep-HPLC provided (*R*)-2-((2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (8 mg, 5% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 11.71 (dd, *J* = 8.4, 0.7 Hz, 1H), 10.21 (d, *J* = 0.5 Hz, 1H), 8.10 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.71 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 6.73 (dd, *J* = 8.6, 0.7 Hz, 1H), 6.71 (dd, *J* = 7.4, 5.0 Hz, 1H), 6.53 (dt, *J* = 8.4, 0.7 Hz, 1H), 5.40 (dd, *J* = 54.2, 3.3 Hz, 1H), 5.28 (d, *J* = 11.3 Hz, 1H), 5.17 (d, *J* = 12.0 Hz, 1H), 3.91 – 3.56 (m, 4H), 2.21 – 1.93 (m, 2H). MS (ES) for $C_{17}H_{17}FN_2O_3$: 317 (MH^+).

GBT910



GBT910

[0132] GBT910- **2-((2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde.** The compound was prepared from ethyl 2-fluoronicotinate and 8-oxa-3-azabicyclo[3.2.1]octane according to reaction scheme below.



[0133] **Step 1a:** To a solution of ethyl 2-fluoronicotinate (0.15 g, 0.97 mmol) in NMP (0.5 mL) was added diisopropylethyl amine (0.50 mL, 2.9 mmol), and 8-oxa-3-azabicyclo[3.2.1]octane (0.17 g, 0.72 mmol). The resulting mixture was irradiated with microwaves (100 °C) for 1h and loaded directly onto a silica column. Eluting the column with EtOAc/hexanes (0-100%) provided methyl 2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)nicotinate as a clear oil (0.100 g, 42% yield). MS (ES) for $C_{13}H_{16}N_2O_3$: 249 (MH^+).

[0134] **Step 1b:** To a cooled (0 °C) solution of 2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)nicotinate (0.10 g, 0.40 mmol) in THF (5 mL) was added a solution of lithium aluminum hydride (1.2 mL, 1M in THF). The reaction mixture was stirred for 1h and then 20 µL of H_2O was added followed by 20 µL of 15% NaOH (aq) and then 60 µL of additional H_2O. The slurry was stirred for 1h, filtered and the resulting residue was washed with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to yield (2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)methanol (0.070 g, 79% yield). MS (ES) for $C_{12}H_{16}N_2O_2$: 221 (MH^+).

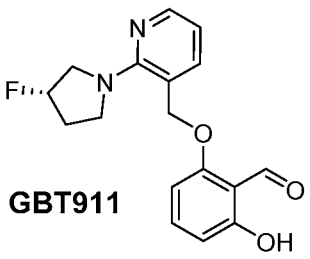
[0135] **Step 2:** To a cooled (0 °C) solution of (2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)methanol (0.070 g, 0.32 mmol) in dichloromethane was added $SOCl_2$ (0.23 mL, 3.2 mmol) and the reaction mixture was allowed to warm to ambient temperature. After 1 h, the reaction mixture was concentrated and azeotroped with toluene three times to provide 3-(3-(chloromethyl)pyridin-2-yl)-8-oxa-3-azabicyclo[3.2.1]octane (0.075 g, 98%) as a clear oil. MS (ES) for $C_{12}H_{15}ClN_2O$: 239 (MH^+).

[0136] **Step 3:** To a solution of provide 3-(3-(chloromethyl)pyridin-2-yl)-8-oxa-3-azabicyclo[3.2.1]octane (0.080 g, 0.35 mmol) and 5-hydroxy-2,2-dimethyl-4H-

benzo[d][1,3]dioxin-4-one (0.061 g, 0.31 mmol) in DMF was added cesium carbonate (0.307 g, .94 mmol) and the reaction mixture was heated (60 °C). After 30 minutes, the reaction mixture was partitioned between EtOAc and saturated aqueous sodium bicarbonate and the aqueous layer was extracted two times with EtOAc. Combined organic layers were washed with brine, dried over $MGSO_4$ and concentrated in vacuo. Purification by silica gel chromatography yielded 5-((2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)methoxy)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (112 mg, 90% yield). MS (ES) for $C_{22}H_{24}N_2O_5$: 397 (MH^+).

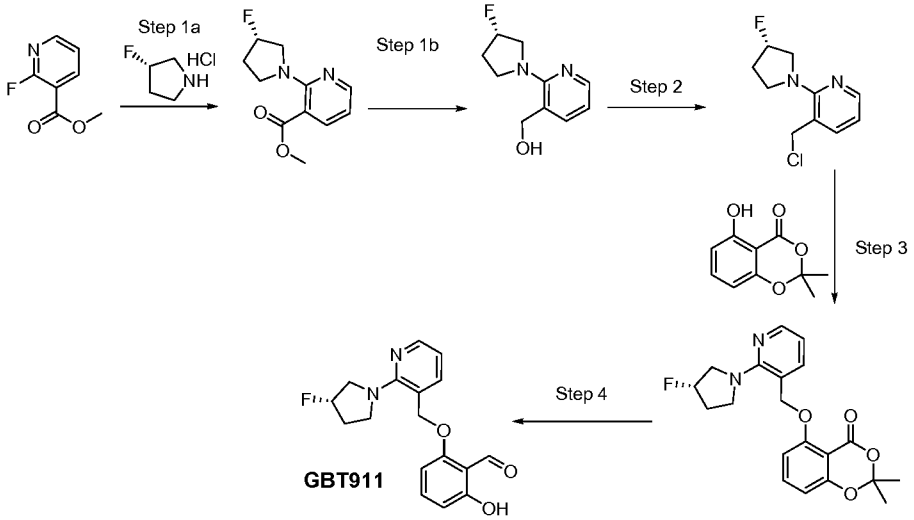
[0137] Step 4: To a cooled (-78 °C) solution of 5-((2-(3-oxa-8-azabicyclo[3.2.1]octan-8-yl)pyridin-3-yl)methoxy)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (0.11 g, 0.28 mmol) in CH_2Cl_2 was added DIBAL-H (0.85 mL, 1M in CH_2Cl_2) and reaction mixture was allowed to warm to ambient temperature over 3 hours. The reaction mixture was then cooled (-78 °C) and MeOH was added followed by saturated potassium sodium tartrate solution (300 µL). This mixture was stirred for 2 hours at ambient temperature and filtered over Celite. The resulting solution was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and washed two times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by preparatory HPLC resulted in 2-((2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (0.025 g, 25% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.95 (s, 1H), 10.39 (d, *J* = 0.6 Hz, 1H), 8.32 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.74 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.40 (t, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 8.3 Hz, 1H), 5.15 (s, 2H), 4.47 – 4.40 (m, 2H), 3.33 (dd, *J* = 12.5, 2.0 Hz, 2H), 3.03 (dd, *J* = 12.3, 1.4 Hz, 2H), 2.13 – 1.94 (m, 4H). MS (ES) for $C_{19}H_{20}N_2O_4$: 341 (MH^+).

GBT911



GBT911

[0138] GBT911- **2-((2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde.** The compound was prepared from ethyl 2-fluoronicotinate and (*S*)-3-fluoropyrrolidine according to reaction scheme below.



[0139] **Step 1a:** To a solution of ethyl 2-fluoronicotinate (0.090 g, 0.58 mmol) in DMF (0.3 mL) was added diisopropylethyl amine (0.51 mL, 2.9 mmol), and (*S*)-3-fluoropyrrolidine (0.10 g, 1.2 mmol). The resulting mixture was irradiated with microwaves (100 ^{o}C) for 1h and loaded directly onto a silica column. Eluting the column with EtOAc/hexanes (0-100%) provided (*S*)-ethyl 2-(3-fluoropyrrolidin-1-yl)nicotinate as a clear oil (0.100 g, 46% yield). MS (ES) for $C_{12}H_{15}FN_2O_2$: 225 (MH^+).

[0140] **Step 1b:** To a cooled (0 ^{o}C) solution of (*S*)-methyl 2-(3-fluoropyrrolidin-1-yl)nicotinate (0.20 g, 0.87 mmol) in THF (5 mL) was added a solution of lithium aluminum hydride (2.6 mL, 1M in THF). The reaction mixture was stirred for 1h and then 20 µL of H_2O was added followed by 20 µL of 15% NaOH (aq) and then 60 µL of additional H_2O. The slurry was stirred for 1h, filtered and the resulting residue was washed with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromotography (EtOAc/hexanes,0-100%) provided (*S*)-(2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methanol (0.165 g, 97% yield). MS (ES) for $C_{10}H_{13}FN_2O$: 197 (MH^+).

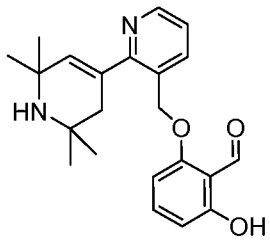
[0141] **Step 2:** To a cooled (0 ^{o}C) solution of (*S*)-(2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methanol (0.081 g, 0.77 mmol) in dichloromethane was added $SOCl_2$ (0.92 g, 7.7 mmol) and the reaction mixture was allowed to warm to ambient temperature. After 1 h, the reaction mixture was concentrated and azeotroped with toluene to provide (*S*)-3-

(chloromethyl)-2-(3-fluoropyrrolidin-1-yl)pyridine (0.180 g, 99%) as a clear oil. MS (ES) for $C_{10}H_{12}ClFN_2$: 215 (MH^+).

[0142] **Step 3:** To a solution of provide (*S*)-3-(chloromethyl)-2-(3-fluoropyrrolidin-1-yl)pyridine (0.085 g, 0.40 mmol) and 5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (0.12 g, 0.59 mmol) in DMF was added cesium carbonate (0.39 g, 0.12 mmol) and the reaction mixture was heated (60 ^oC). After 30 minutes, the reaction mixture was partitioned between EtOAc and saturated aqueous sodium bicarbonate and the aqueous layer was extracted two times with EtOAc. Combined organic layers were washed with brine, dried over $MGSO_4$ and concentrated in vacuo. Purification by silica gel chromatography yielded (*S*)-5-((2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methoxy)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (120 mg, 81% yield). MS (ES) for $C_{20}H_{21}FN_2O_4$: 373 (MH^+).

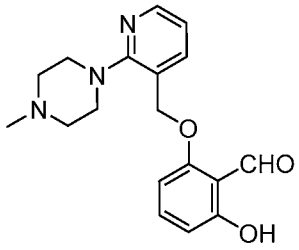
[0143] **Step 4:** To a cooled (-78 ^oC) solution of (*S*)-5-((2-(3-fluoropyrrolidin-1-yl)pyridin-3-yl)methoxy)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (0.085 g, 0.23 mmol) in CH_2Cl_2 was added DIBAL-H (0.68 mL, 1M in CH_2Cl_2) and reaction mixture was allowed to warm to ambient temperature over 3 hours. The reaction mixture was then cooled (-78 ^oC) and MeOH was added followed by saturated potassium sodium tartrate solution (300 µL). This mixture was stirred for 2 hours at ambient temperature and filtered over Celite. The resulting solution was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and washed two times with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification by preparatory HPLC resulted in 2-((2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde (0.020 g, 28% yield). ^1H NMR (400 MHz, Chloroform-*d*) δ 11.97 (s, 1H), 10.34 (s, 1H), 8.21 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.56 (ddd, *J* = 7.4, 1.9, 0.5 Hz, 1H), 7.42 (t, *J* = 8.4 Hz, 1H), 6.75 (dd, *J* = 7.4, 4.8 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 9.0 Hz, 1H), 5.24 (dt, *J* = 53.0, 3.9, 3.3 Hz, 1H), 5.16 (d, *J* = 11.4 Hz, 1H), 5.05 (d, *J* = 11.4 Hz, 1H), 3.97 – 3.60 (m, 4H), 2.37 – 1.96 (m, 2H). MS (ES) for $C_{17}H_{17}FN_2O_3$: 317 (MH^+).

GBT001028

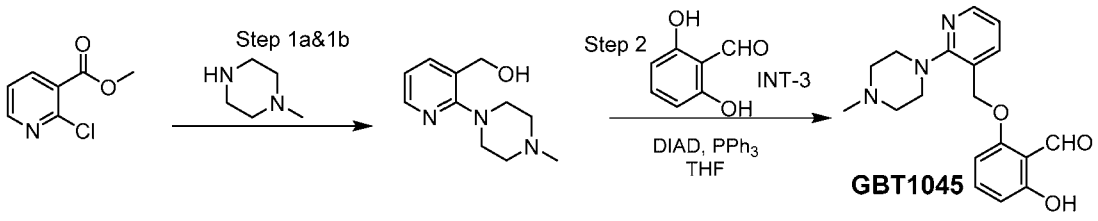


[0144] GBT1028 - **2-hydroxy-6-((2',2',6',6'-tetramethyl-1',2',3',6'-tetrahydro-[2,4'-bipyridin]-3-yl)methoxy)benzaldehyde.** The compound was prepared by Suzuki coupling of 2,2,6,6-tetramethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine and 2-((2-bromopyridin-3-yl)methoxy)-6-(methoxymethoxy)benzaldehyde according to scheme 4, reaction step 2; the MOM ether protecting group was removed by treating with conc HCl (2eq) in THF. The product HCl salt was obtained as brown solid after silica gel chromatography. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 10.30 (s, 1H), 9.21 (s, 2H), 8.62 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.24 – 8.16 (m, 1H), 7.58 – 7.46 (m, 2H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.94 (d, *J* = 1.8 Hz, 1H), 5.26 (s, 2H), 3.66 – 3.54 (m, 2H), 1.56 – 1.37 (m, 12H); MS (ES, *m/z*) 367.38 $[M+1]^+$.

GBT1045



[0145] **GBT1045-2-hydroxy-6-((2-(4-methylpiperazin-1-yl)pyridin-3-yl)methoxy)benzaldehyde.** The compound was prepared from methyl 2-chloronicotinate and methylpiperazine according to scheme 5, reaction steps 1 and 2.



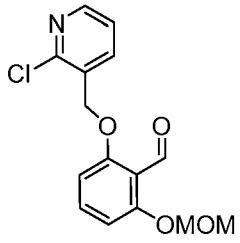
[0146] **Step 1a:** Into a 100-mL round-bottom flask, was placed a solution of methyl 2-chloropyridine-3-carboxylate (2.0 g, 11.66 mmol, 1.00 equiv) in N,N-dimethylformamide (40 mL). 1-methylpiperazine (1.75 g, 17.47 mmol, 1.50 equiv), potassium carbonate (3.30 g,

23.88 mmol, 2.00 equiv), 18-crown-6 (200 mg, 0.06 equiv) were added to the reaction. The resulting solution was stirred overnight at 100°C. The reaction mixture was cooled to room temperature. The resulting solution was diluted with 30 mL of H_2O, and then it was extracted with 5x30 mL of ethyl acetate. The combined organic layers were concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (10:1) as eluent. This resulted in 2.7 g (98%) of methyl 2-(4-methylpiperazin-1-yl)pyridine-3-carboxylate as a yellow oil.

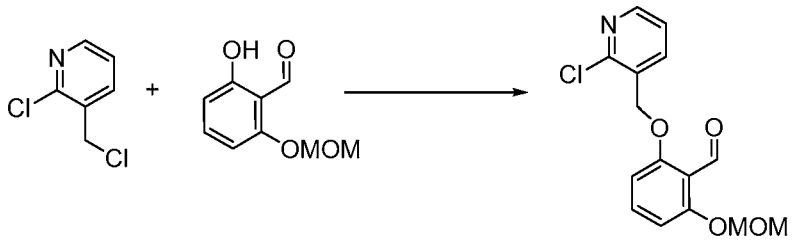
[0147] **Step 1b:** Into a 100-mL round-bottom flask, was placed a solution of methyl 2-(4-methylpiperazin-1-yl)pyridine-3-carboxylate (1.3 g, 5.53 mmol, 1.00 equiv) in tetrahydrofuran (40 mL). This was followed by the addition of $AlLiH_4$ (315 mg, 8.30 mmol, 1.50 equiv) at 0°C. The resulting solution was stirred for 5 h at 0°C, and then it was quenched by the addition of 0.5 mL of water, 1.5 ml of NaOH(15%) and 0.5 ml of water. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (1:1) as eluent. This resulted in 500 mg (44%) of [2-(4-methylpiperazin-1-yl)pyridin-3-yl]methanol as a yellow solid.

[0148] **Step 2:** Into a 50-mL round-bottom flask, was placed a solution of [2-(4-methylpiperazin-1-yl)pyridin-3-yl]methanol (200 mg, 0.96 mmol, 1.00 equiv) in tetrahydrofuran (20 mL). 2,6-Dihydroxybenzaldehyde (200 mg, 1.45 mmol, 1.50 equiv) and PPh_3 (380 mg, 1.45 mmol, 1.50 equiv) were added to the reaction. This was followed by the addition of DIAD (293 mg, 1.45 mmol, 1.50 equiv) at 0°C. The resulting solution was stirred overnight at room temperature, and then it was concentrated under vacuum. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Prep-HPLC-010): Column, SunFire Prep C18 OBD Column, 5um, 19*150mm,; mobile phase, water with 0.05%TFA and MeCN (25.0% MeCN up to 42.0% in 13 min, up to 95.0% in 2 min, down to 25.0% in 2 min); Detector, Waters2545 UvDector 254&220nm. This resulted in 67.9 mg (21%) of 2-hydroxy-6-[[2-(4-methylpiperazin-1-yl)pyridin-3-yl]methoxy]benzaldehyde as a yellow oil; ^{1}HNMR (400MHz, $CDCl_3$, *ppm*): 11.98 (s, 1H), 10.43 (s, 6H), 8.35(m, 1H), 7.77(d, *J*=5.7Hz, 1H), 7.42(m, 1H), 7.03 (m, 1H), 6.58(d, *J*=6.3Hz, 1H), 6.43(d, *J*=6.0Hz, 1H), 5.18(d, *J*=7.8Hz, 2H), 3.26 (m, 4H), 2.64 (s, 4H), 2.40 (s, 3H) 1.42-2.09(m, 8H); MS (ES, *m/z*): 328 $[M+1]^+$.

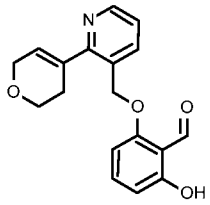
GBT1249



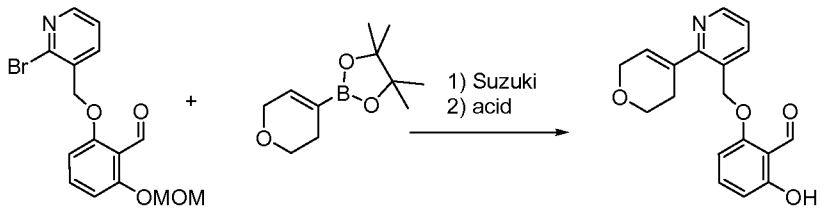
[0149] GBT1249- **2-((2-chloropyridin-3-yl)methoxy)-6-(methoxymethoxy)benzaldehyde.** The compound was prepared by O-alkylation of 2-hydroxy-6-(methoxymethoxy)benzaldehyde and 2-chloro-3-(chloromethyl)pyridine. The product as white solid was obtained after flash column purification. ^{1}HNMR (400MHz, $CDCl_3$, *ppm*): 10.65(s, 1H), 8.37(d, *J*=5.7Hz, 1H), 7.49(t, *J*=6.3Hz, 1H), 7.39(t, *J*=4.5Hz, 1H), 7.28(s, 1H), 6.90(d, *J*=6.3Hz, 1H), 6.75(d, *J*=6.3Hz, 1H), 5.32(s, 2H), 5.21(s, 2H), 3.54(s, 3H); MS (ES, *m/z*): 308[M+1]$^+$



GBT001046

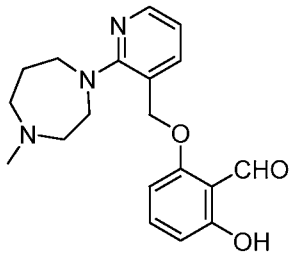


[0150] GBT1046- **2-((2-(3,6-dihydro-2H-pyran-4-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde**.

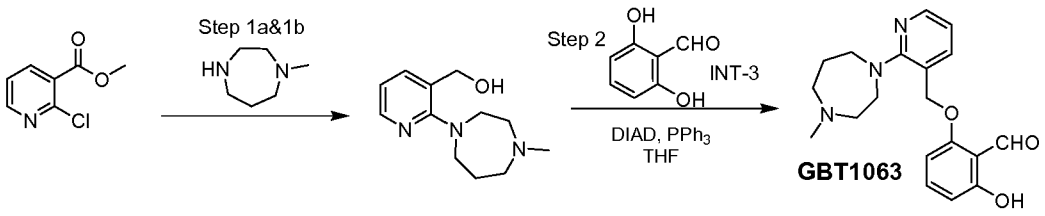


[0151] The compound was prepared by Suzuki coupling of 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and 2-((2-bromopyridin-3-yl)methoxy)-6-(methoxymethoxy)benzaldehyde according to scheme 4, reaction step 2; the MOM ether protecting group was removed by treating with conc HCl (2eq) in THF. The product was obtained as light brown solid after silica gel chromatography. ^{1}H NMR (400 MHz, Chloroform-d) d 11.93 (d, J = 0.6 Hz, 1H), 10.37 (s, 1H), 8.84 (s, 1H), 8.56 (d, J = 7.2 Hz, 1H), 7.89 (s, 1H), 7.46 (t, J = 8.3 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 6.36 (d, J = 7.6 Hz, 2H), 5.29 (s, 2H), 4.43 (s, 2H), 4.08 (t, J = 4.5 Hz, 2H), 2.80 (s, 2H); MS (ES, *m/z*) 312.33 $[M+1]^+$.

GBT1063



[0152] GBT1063- 2-hydroxy-6-((2-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl)methoxy)benzaldehyde. The compound was prepared from methyl 2-chloronicotinate and 1-methyl-1,4-diazepane according to scheme 5, reaction steps 1 and 2.



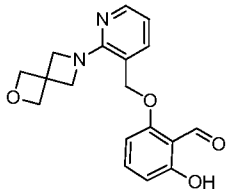
[0153] Step 1a: Into a 100-mL round-bottom flask, was placed a solution of methyl 2-chloropyridine-3-carboxylate (2.0 g, 11.66 mmol, 1.00 equiv) in N,N-dimethylformamide (40 mL). 1-methyl-1,4-diazepane (2.0 g, 17.51 mmol, 1.50 equiv), potassium carbonate (3.3 g, 23.88 mmol, 2.00 equiv), and 18-crown-6 (200 mg, 0.06 equiv) were added to the reaction. The resulting solution was stirred overnight at 100°C. The reaction mixture was cooled to room temperature, and then it was diluted with 40 mL of H_2O. The resulting solution was extracted with 5x30 mL of ethyl acetate and the combined organic layers were concentrated under vacuum. The residue was applied onto a silica gel column with

dichloromethane/methanol (10:1) as eluent. This resulted in 2.65 g (91%) of methyl 2-(4-methyl-1,4-diazepan-1-yl)pyridine-3-carboxylate as a yellow oil.

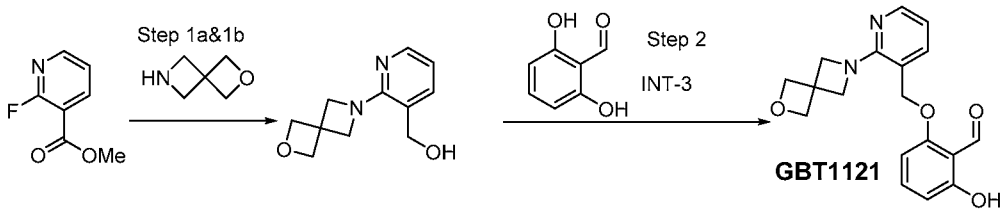
[0154] **Step 1b:** Into a 100-mL round-bottom flask, was placed a solution of methyl 2-(4-methyl-1,4-diazepan-1-yl)pyridine-3-carboxylate (1.2 g, 4.81 mmol, 1.00 equiv) in tetrahydrofuran (40 mL). This was followed by the addition of $LiAlH_4$ (500 mg, 13.18 mmol, 2.00 equiv) at 0°C. The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 0.5 mL of water, 1.5 mL of 15% NaOH,0.5 mL of H_2O. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (3:1) as eluent. This resulted in 800 mg (75%) of [2-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl]methanol as a yellow oil.

[0155] **Step 2:** Into a 50-mL round-bottom flask, was placed a solution of [2-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl]methanol (300 mg, 1.36 mmol, 1.00 equiv) in tetrahydrofuran (25 mL). 2,6-Dihydroxybenzaldehyde (280 mg, 2.03 mmol, 1.50 equiv) and PPh_3 (532 mg, 2.03 mmol, 1.50 equiv) were added to the reaction. This was followed by the addition of DIAD (410 mg, 2.03 mmol, 1.50 equiv) at 0°C. The resulting solution was stirred overnight at room temperature, and then it was concentrated under vacuum. The crude product (300 mg) was purified by Prep-HPLC with the following conditions (Prep-HPLC-010): Column, Gemini-NX 150*21.20mm C18 AXIA Packed, 5um 110A; mobile phase, water with 0.05%TFA and MeCN (10.0% MeCN up to 50.0% in 5 min); Detector, nm. This resulted in 159.5 mg (34%) of 2-hydroxy-6-[[2-(4-methyl-1,4-diazepan-1-yl)pyridin-3-yl]methoxy]benzaldehyde as a yellow oil; ^{1}HNMR (400MHz, DMSO+D_2O, *ppm*): 10.29 (s, 1H), 8.19 (d, *J*=2.7Hz, 1H), 7.95 (d, *J*=5.4Hz, 1H), 7.52 (m, 1H),7.08(m, 1H), 6.66 (d, *J*=6.3Hz, 1H), 6.57 (d, *J*=0.9Hz, 1H), 5.21(s, 2H), 3.74(s, 2H), 3.45(m, 6H), 2.84(s, 3H), 2.11 (d, *J*=3.9Hz, 2H); (ES, *m/z*): 342 $[M+1]^+$.

GBT001121



[0156] GBT1121- 2-((2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde. The compound was prepared from methyl 2-fluoronicotinate and 2-oxa-6-azaspiro[3.3]heptane according to scheme 5, reaction steps 1 and 2.



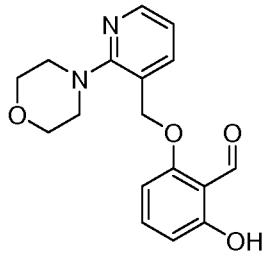
[0157] Step 1a: Methyl 2-fluoronicotinate (0.3 g, 1.93 mmol) and 2-oxa-6-azaspiro[3.3]heptane oxalate (0.55 g, 2.9 mmol) were combined with DMF (3 ml). N,N-diisopropylethylamine (2 ml, 11.6 mmol) was added and the mixture was heated in a microwave reactor (120 ^{o}C, 1 h). Ethyl acetate (100 ml) and water (50 ml) were added to the cooled solution and the phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined organic phases were washed with water (30 ml) and a saturated aqueous sodium chloride solution (30 ml), and dried over sodium sulfate. After evaporation, the residue was purified by silica gel chromatography (5 – 80% ethyl acetate/hexanes) to give 0.27 g (59%) of methyl 2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)nicotinate as a white solid. MS (ESI) m/z 235 $[M+H]^+$.

[0158] Step 1b: Methyl 2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)nicotinate (0.26 g, 1.1 mmol) was dissolved in THF (5 ml) and stirred in an ice bath. Lithium aluminum hydride (2.2 ml of a 1M THF solution) was added dropwise. The reaction was stirred to 25 ^{o}C over 2 h. Water (0.084 ml) was carefully added followed by 15% aqueous sodium hydroxide solution (0.084 ml) and water (0.25 ml). The mixture was stirred for 30 m then filtered, rinsed with THF (10 ml) and the solvent evaporated to give 226 mg (98%) of (2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)methanol which was used directly in the next step. MS (ESI) m/z 207 $[M+H]^+$.

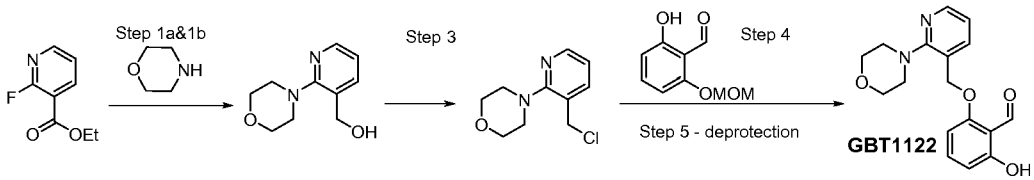
[0159] Step 2: 2-(2-Oxa-6-azaspiro[3.3]heptan-6-yl)pyridin-3-yl)methanol (0.12 g, 0.582 mmol) 2,6-dihydroxybenzaldehyde (96 mg, 0.7 mmol) and triphenylphosphine-polystyrene resin (0.63 g, 0.76 mmol) were combined with THF (3 ml), and stirred in an ice bath. Diisopropylazodicarboxylate (0.15 ml, 0.76 mmol) was added dropwise and the reaction was stirred to 25 ^{o}C over 16 h. The reaction was filtered, rinsed with THF (10 ml) and evaporated. The resulting residue was purified by silica gel chromatography (0 – 75 % ethyl acetate/dichloromethane) to give 31 mg (16%) of 2-((2-(2-oxa-6-azaspiro[3.3]heptan-6-

yl)pyridin-3-yl)methoxy)-6-hydroxybenzaldehyde as a white solid after lyophilization from acetonitrile/water. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.97 (s, 1H), 10.36 (s, 1H), 8.21 (dd, *J* = 1.65, 4.92 Hz, 1H), 7.51 (dd, *J* = 1.68, 7.37 Hz, 1H), 7.44 (t, *J* = 8.38 Hz, 1H), 6.76 (dd, *J* = 4.95, 7.34 Hz, 1H), 6.60 (d, *J* = 8.49 Hz, 1H), 6.42 (d, *J* = 8.28 Hz, 1H), 4.96 (s, 2H), 4.81 (s, 4H), 4.27 (s, 4H). MS (ESI) m/z 327 $[M+H]^+$.

GBT001122



[0160] GBT1122- 2-Hydroxy-6-((2-morpholinopyridin-3-yl)methoxy)benzaldehyde. The compound was prepared from ethyl 2-fluoronicotinate and morpholine according to a modified scheme 5, reaction steps 1, 3 and 4.



[0161] Step 1a: To a solution of ethyl 2-fluoronicotinate (0.40 g, 2.6 mmol) in DMF (0.3 mL) was added diisopropylethyl amine (1.8 mL, 10 mmol), and morpholine (0.45 g, 5.2 mmol). The resulting mixture was irradiated with microwaves (100 °C) for 1h and loaded directly onto a silica column. Eluting the column with EtOAc/hexanes (0-100%) Methyl 2-morpholinonicotinate as a clear oil (0.36 g, 62% yield). MS (ES) for $C_{12}H_{16}N_2O_3$: 237 (MH^+).

[0162] Step 1b: To a cooled (0 °C) solution of Methyl 2-morpholinonicotinate (0.36 g, 1.6 mmol) in THF (5 mL) was added a solution of lithium aluminum hydride (4.9 mL, 1M in THF). The reaction mixture was stirred for 1h and then 180 µL of H2O was added followed by 180 µL of 15% NaOH (aq) and then 540 µL of additional water. The slurry was stirred for 1h and filtered and the resulting residue was washed with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromotography (EtOAc/hexanes,0-100%) provided (2-morpholinopyridin-3-yl)methanol (0.224 g, 71% yield). MS (ES) for $C_{10}H_{14}N_2O_2$: 195 (MH^+).

[0163] **Step 3:** To a cooled (0 °C) solution of provided (2-morpholinopyridin-3-yl)methanol (0.100 g, 0.51 mmol) in dichloromethane was added $SOCl_2$ (0.50 mL, 6.9 mmol) and the reaction mixture was allowed to warm to ambient temperature. After 1 h, the reaction mixture was concentrated and azeotroped with toluene to provide 4-(3-(chloromethyl)pyridin-2-yl)morpholine (0.11 g, 96%) as a clear oil. MS (ES) for $C_{10}H_{13}ClN_2O$: 213 (MH^+).

[0164] **Step 4:** To a solution of 4-(3-(chloromethyl)pyridin-2-yl)morpholine (0.11 g, 0.50 mmol) and 2-hydroxy-6-(methoxymethoxy)benzaldehyde (0.09 g, 0.50 mmol) in DMF was added potassium carbonate (0.210 g, 1.5 mmol) and the reaction mixture was heated (60 °C). After 30 minutes, the reaction mixture was partitioned between EtOAc and saturated $NaHCO_3$ and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to yield 2-(methoxymethoxy)-6-((2-morpholinopyridin-3-yl)methoxy)benzaldehyde (0.145 mg, 80% yield) as a white powder. MS (ES) for $C_{19}H_{22}N_2O_5$: 359 (MH^+).

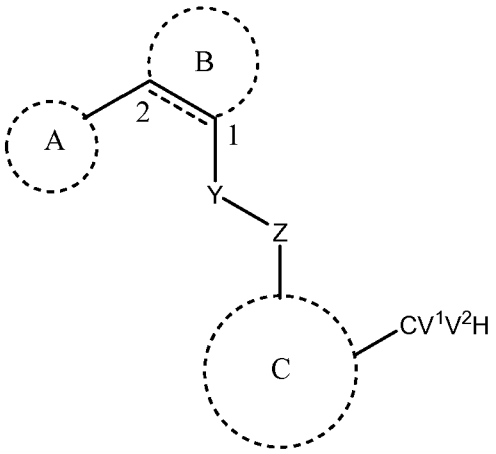
[0165] **Step 5:** To a solution of 2-(methoxymethoxy)-6-((2-morpholinopyridin-3-yl)methoxy)benzaldehyde (0.120 g, 0.33 mmol) in THF (5 mL) was added concentrated HCl (0.5 mL, 6 mmol). After stirring at ambient temperature for 3 hours, the mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$ and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Purification, reaction silica gel chromatography provided 2-hydroxy-6-((2-morpholinopyridin-3-yl)methoxy)benzaldehyde (0.074 g, 0.24 mmol) as a white powder. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.95 (s, 1H), 10.40 (s, 1H), 8.34 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.77 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.40 (t, *J* = 8.4 Hz, 1H), 7.04 (dd, *J* = 7.5, 4.9 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.40 (d, *J* = 8.3 Hz, 1H), 5.15 (s, 2H), 3.90 – 3.83 (m, 3H), 3.22 – 3.15 (m, 4H). MS (ES) for $C_{17}H_{18}N_2O_4$: 315 (MH^+).

[0166] From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

[0167] Throughout the description of this invention, reference is made to various patent applications and publications, each of which are herein incorporated by reference in their entirety.

CLAIMS

1. In certain aspects of the invention, a compound of formula (I) is provided:



(I)

or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein

ring A is an optionally substituted 4-10 membered cycloalkyl or 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

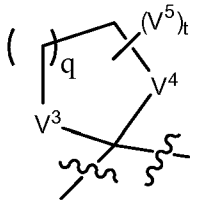
ring B is a C_6-C_{10} aryl or 5-10 membered heteroaryl having 1-3 nitrogen atoms, preferably 1-2 nitrogen atoms and more preferably 1 nitrogen atom, or oxidized versions thereof, wherein the aryl or heteroaryl is optionally substituted;

 is a single or a double bond;

each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{12}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O; R^{12} is hydrogen or C_1-C_6 alkyl; provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and provided that Y and Z are both not heteroatoms or oxidized forms thereof;

ring C is C_6-C_{10} aryl, optionally substituted;

V^1 and V^2 independently are C_1-C_6 alkoxy; or V^1 and V^2 together with the carbon atom they are attached to form a ring of formula:



wherein each V^3 and V^4 are independently O, S, or NH, provided that when one of V^3 and V^4 is S, the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60}, where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 0, 1, 2, or 4; or CV^1V^2 is C=V, wherein V is O, NOR^{80}, or $NNR^{81}R^{82}$;

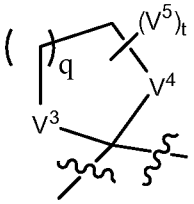
R^{80} is optionally substituted C_1-C_6 alkyl;

R^{81} and R^{82} independently are selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, COR^{83}, or CO_2R^{84};

R^{83} is hydrogen or optionally substituted C_1-C_6 alkyl; and

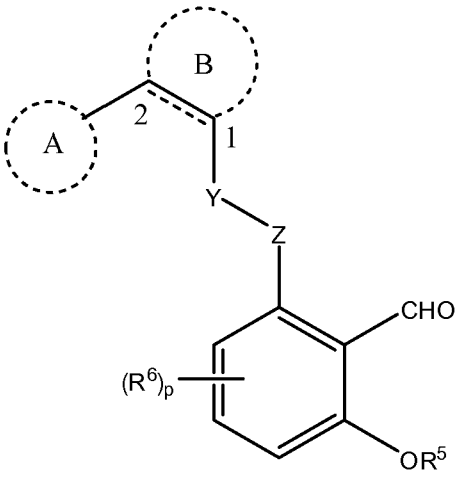
R^{84} is optionally substituted C_1-C_6 alkyl.

2. The compound of claim 1, wherein V^1 and V^2 independently are C_1-C_6 alkoxy; or V^1 and V^2 together with the carbon atom they are attached to form a ring of formula:



wherein each V^3 and V^4 are independently O, S, or NH, provided that when one of V^3 and V^4 is S the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60}, where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 0, 1, 2, or 4; or CV^1V^2 is C=V, wherein V is O, and wherein the remaining variables are defined as in claim 1.

3. The compound of claim 2 of formula (II):



(II)

wherein R^5 is hydrogen, C_1-C_6 alkyl or a prodrug moiety R, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo;

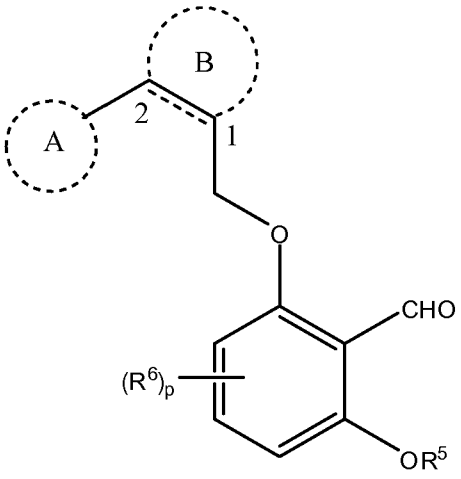
R^6 is halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 S(O)-, C_1-C_6 $S(O)_2$-,wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo; or

R^6 is 4-10 membered cycloalkyl or heterocycle substituted with an R'R'N- moiety wherein each R' is independently C_1-C_6 alkyl or hydrogen;

p is 0, 1, 2 or 3; and

the remaining variables are defined as in claim 2.

4. A compound of claim 2 or 3 of Formula (IIA):



(II)

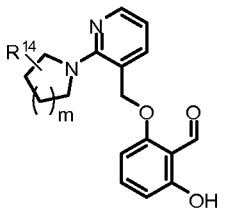
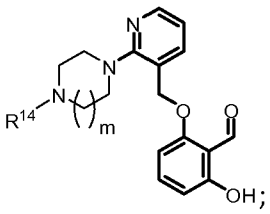
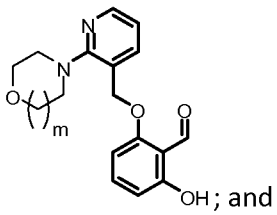
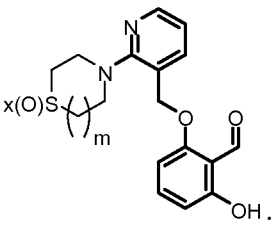
wherein

the variables are defined as in claims 2 and 3.

5. The compound of claim 2, wherein ring A is optionally substituted with 1-3: halo, C_1-C_6 alkyl, COR^{15} and/or $COOR^{15}$; wherein R^{15} is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl containing up to 5 ring heteroatoms, or optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S.

6. The compound of claim 4 or 5, wherein ring B is optinally substituted with 1-3: halo, C_1-C_6 alkyl COR^{15} and/or $COOR^{15}$; wherein R^{15} is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl containing up to 5 ring heteroatoms, or optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S.

7. The compound of claim 2, wherein the compound is selected from the group consisting of



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; and

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or an N oxide thereof, wherein

R^{14} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, COR^{15} or $COOR^{15}$;

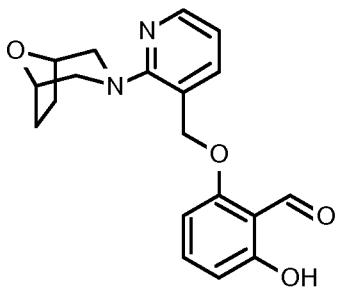
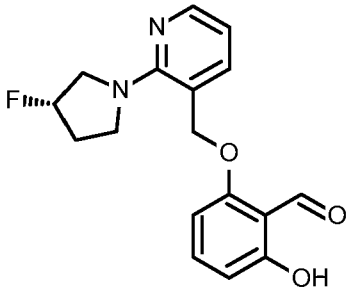
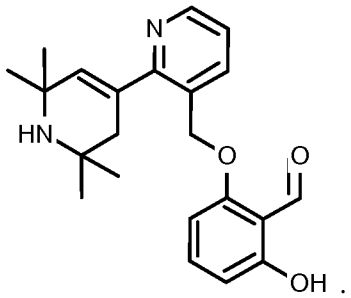
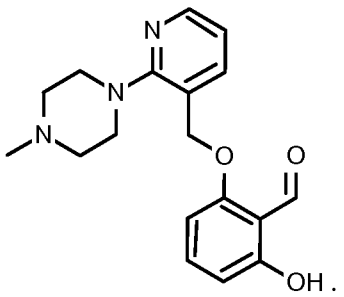
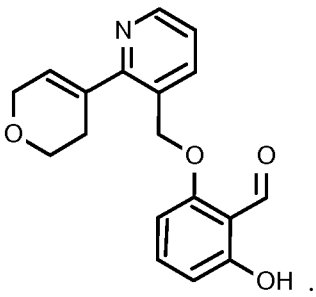
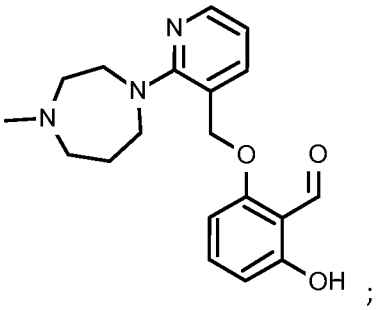
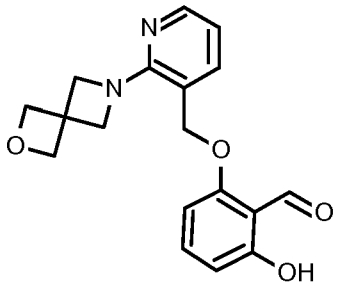
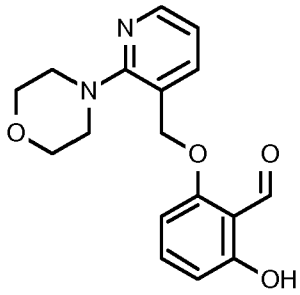
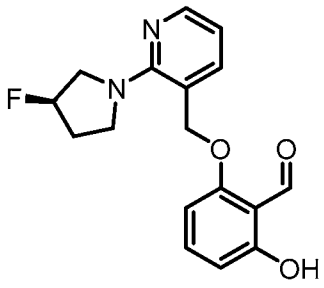
R^{15} is optionally substituted C_1-C_6 alkyl, optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl containing up to 5 ring heteroatoms, or optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

x is 0, 1, or 2;

p is 0, 1, and 2; and

m is 0, 1 or 2.

8. A compound of claim 1 selected from the group consisting of:


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; and


or a prodrug thereof, or a pharmaceuticlaly acceptable salt of each thereof.

9. A composition comprising a compound of any one of claims 2-8 and at least one pharmaceutically acceptable excipient.

10. A method for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 2-8 or the composition of claim 9.

11. A method for treating oxygen deficiency associated with sickle cell anemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 2-8 or the composition of claim 9.