

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number

WO 2014/150289 A1

(43) International Publication Date
25 September 2014 (25.09.2014)

(51) International Patent Classification:
C07D 487/12 (2006.01) A61K 31/4375 (2006.01)
C07D 471/12 (2006.01) A61K 31/437 (2006.01)
C07D 487/04 (2006.01) A61P 7/00 (2006.01)
C07D 471/04 (2006.01)

(21) International Application Number:
PCT/US2014/022846

(22) International Filing Date:
10 March 2014 (10.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
13/815,776 15 March 2013 (15.03.2013) US
61/905,802 18 November 2013 (18.11.2013) US

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,
SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii))

Published:

— with international search report (Art. 21(3))
— before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments (Rule 48.2(h))

(54) Title: COMPOUNDS AND USES THEREOF FOR THE MODULATION OF HEMOGLOBIN

(55) Abstract: Provide herein are compounds and pharmaceutical compositions suitable as 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.

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COMPOUNDS AND USES THEREOF FOR THE MODULATION OF HEMOGLOBIN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/905,802 entitled “COMPOUNDS AND USES THEREOF FOR THE MODULATION OF HEMOGLOBIN” filed November 18, 2013; and U.S. Patent Application No. 13/815,776 entitled “COMPOUNDS AND USES THEREOF FOR THE MODULATION OF HEMOGLOBIN” filed March 15, 2013, and assigned to the assignee hereof and hereby expressly incorporated by reference herein.

FIELD OF THE INVENTION

[0002] 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

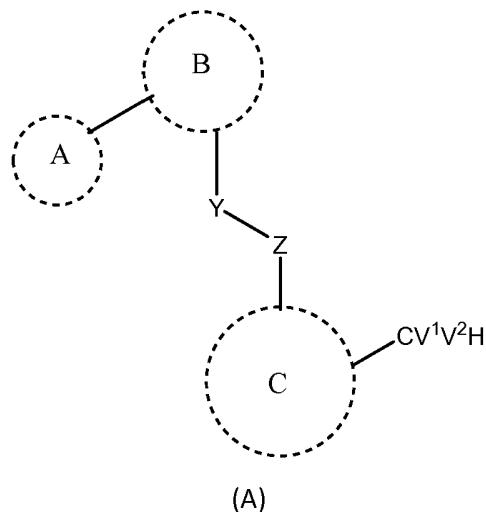
[0003] Sickle cell disease is a disorder of the red blood cells, found particularly among those of African and Mediterranean descent. The basis for sickle cell disease is found in sickle hemoglobin (HbS), which contains a point mutation relative to the prevalent peptide sequence of hemoglobin (Hb).

[0004] 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

[0005] 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.

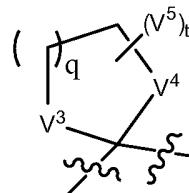
[0006] In certain aspects of the invention, a compound of Formula (A) is provided:



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

ring A is an optionally substituted 5-10 membered heteroaryl containing up to 3 ring N, O, and/or S atoms, and oxidized forms of N and/or S atoms;
wherein ring A is α or β substituted relative to the Y substituent;
ring B is an optionally substituted C_6 - C_{10} aryl 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;
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 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 $NNR^{81}R^{82}$;

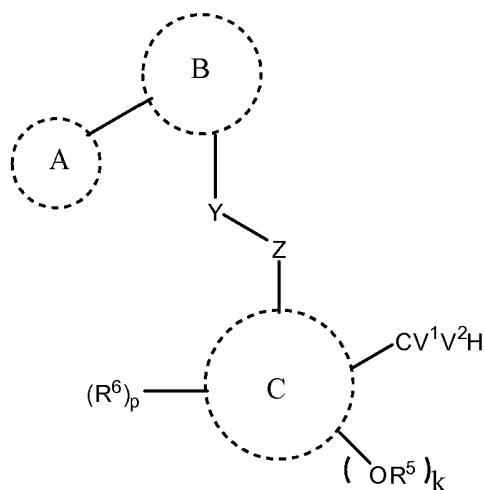
R^{80} is optionally substituted C_1 - C_6 alkyl;

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.

[0007] In one embodiment, the compound provided is of formula (I):



(I)

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 a substituent that is halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ S(O)-, C₁-C₆ S(O)₂-, wherein the C₁-C₆ 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 C₁-C₆ alkyl or hydrogen;
k is 0 or 1; and
p is 0, 1, 2, or 3.
and the remaining variables are defined as above.

[0008] In further aspects of the invention, a composition is provided comprising any of the compounds described herein, and at least a pharmaceutically acceptable excipient.

[0009] 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.

[0010] 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

[0011] 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.

[0012] 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.

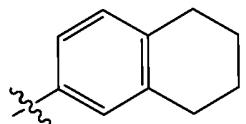
[0013] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters 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 %.

[0014] 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.

[0015] The term "alkoxy" refers to $-O$ -alkyl. The term alkylthio refers to $-S$ -alkyl.

[0016] 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 ($(CH_3)_3CCH_2-$).

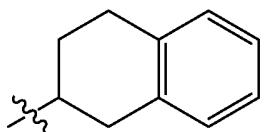
[0017] The term "aryl" refers to a monovalent, aromatic mono- or bicyclic ring having 6-10 ring carbon atoms. Examples of aryl include phenyl and naphthyl. The condensed ring may or may not be aromatic provided that the point of attachment is at an aromatic carbon atom. For example, and without limitation, the following is an aryl group:



[0018] The term “-CO₂H ester” refers to an ester formed between the -CO₂H group and an alcohol, preferably an aliphatic alcohol. A preferred example included -CO₂R^E, wherein R^E is alkyl or aryl group optionally substituted with an amino group.

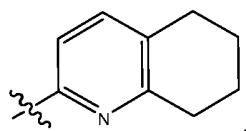
[0019] The term “chiral moiety” refers to a moiety that is chiral. Such a moiety can possess one or more asymmetric centers. Preferably, the chiral moiety is enantiomerically enriched, and more preferably a single enantiomer. Non limiting examples of chiral moieties include chiral carboxylic acids, chiral amines, chiral amino acids, such as the naturally occurring amino acids, chiral alcohols including chiral steroids, and the likes.

[0020] 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, adamantyl, 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:

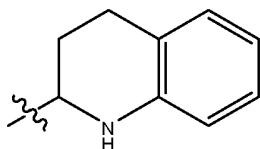


[0021] The term “halo” refers to F, Cl, Br, and/or I.

[0022] 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:



[0023] 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 tetrahydropyran. 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:



[0024] The term “hydrolyzing” refers to breaking an R^H -O-CO-, R^H -O-CS-, or an R^H -O-SO₂- 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.

[0025] The term “oxo” refers to a C=O group, and to a substitution of 2 geminal hydrogen atoms with a C=O group.

[0026] 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, NO₂, -N₂+, -CO₂R¹⁰⁰, -OR¹⁰⁰, -SR¹⁰⁰, -SOR¹⁰⁰, -SO₂R¹⁰⁰, -NR¹⁰¹R¹⁰², -CONR¹⁰¹R¹⁰², -SO₂NR¹⁰¹R¹⁰², C₁-C₆ alkyl, C₁-C₆ alkoxy, -CR¹⁰⁰=C(R¹⁰⁰)₂, -CCR¹⁰⁰, C₃-C₁₀ cycloalkyl, C₃-C₁₀ heterocyclyl, C₆-C₁₂ aryl and C₂-C₁₂ heteroaryl, wherein each R¹⁰⁰ independently is hydrogen or C₁-C₈ alkyl; C₃-C₁₂ cycloalkyl; C₃-C₁₀ heterocyclyl; C₆-C₁₂ aryl; or C₂-C₁₂ heteroaryl; wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 halo, 1-3 C₁-C₆ alkyl, 1-3 C₁-C₆ haloalkyl or 1-3 C₁-C₆ alkoxy groups. Preferably, the substituents are selected from the group consisting of chloro, fluoro, -OCH₃, methyl, ethyl, *iso*-propyl, cyclopropyl, vinyl, ethynyl, -CO₂H, -CO₂CH₃, -OCF₃, -CF₃ and -OCHF₂.

[0027] R¹⁰¹ and R¹⁰² independently is hydrogen; C₁-C₈ alkyl, optionally substituted with -CO₂H or an ester thereof, C₁-C₆ alkoxy, oxo, -CR¹⁰³=C(R¹⁰³)₂, -CCR, C₃-C₁₀ cycloalkyl, C₃-C₁₀ heterocyclyl, C₆-C₁₂ aryl, or C₂-C₁₂ heteroaryl, wherein each R¹⁰³ independently is hydrogen or C₁-C₈ alkyl; C₃-C₁₂ cycloalkyl; C₃-C₁₀ heterocyclyl; C₆-C₁₂ aryl; or C₂-C₁₂ heteroaryl; wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl groups or 1-3 halo groups, or R¹⁰¹ and R¹⁰² together with the nitrogen atom they are attached to form a 5-7 membered heterocycle.

[0028] The term “pharmaceutically acceptable” refers to safe and non-toxic for *in vivo*, preferably, human administration.

[0029] The term “pharmaceutically acceptable salt” refers to a salt that is pharmaceutically acceptable.

[0030] 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, NH₄, 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, bisulfate, mono-, di-, and tribasic phosphate, mesylate, tosylate, and the likes.

[0031] 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.

[0032] 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.

[0033] 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.

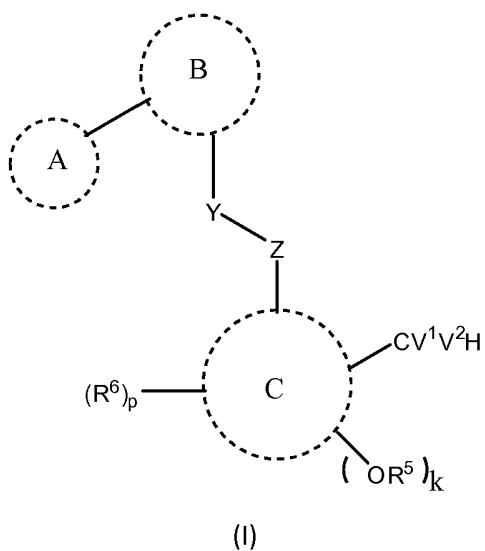
[0034] The term “carrier” as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells, *e.g.*, red blood cells, or tissues.

[0035] 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 Nogradi, 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

[0036] In certain aspects of the invention, a compound of Formula (I) is provided:

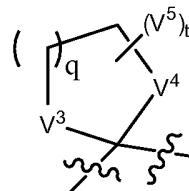


or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof,
wherein

ring A is an optionally substituted 5-10 membered heteroaryl containing up to 3 ring N, O, and/or S atoms, and oxidized forms of N and/or S atoms;
wherein ring A is α or β substituted relative to the Y substituent;
ring B is an optionally substituted C_6 - C_{10} aryl 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;
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 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 C₆-C₁₀ aryl;

V¹ and V² independently are C₁-C₆ alkoxy; or V¹ and V² together with the carbon atom they are attached to form a ring of formula:



wherein each V³ and V⁴ are independently O, S, or NH, provided that when one of V³ and V⁴ is S, the other is NH, and provided that V³ and V⁴ are both not NH; q is 1 or 2; each V⁵ is independently C₁-C₆ alkyl or CO₂R⁶⁰, where each R⁶⁰ independently is C₁-C₆ alkyl or hydrogen; t is 0, 1, 2, or 4; or CV¹V² is C=V, wherein V is O, NOR⁸⁰, or NNR⁸¹R⁸²;

R⁵ is hydrogen, C₁-C₆ alkyl or a prodrug moiety R, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo;

R⁶ is a substituent that is halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ S(O)-, C₁-C₆ S(O)₂-, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo; or

R⁶ is 4-10 membered cycloalkyl or heterocycle substituted with an R'R'N- moiety wherein each R' is independently C₁-C₆ alkyl or hydrogen;

R⁸⁰ is optionally substituted C₁-C₆ alkyl;

R⁸¹ and R⁸² independently are selected from the group consisting of hydrogen, optionally substituted C₁-C₆ alkyl, COR⁸³, or CO₂R⁸⁴;

R⁸³ is hydrogen or optionally substituted C₁-C₆ alkyl;

R⁸⁴ is optionally substituted C₁-C₆ alkyl;

k is 0 or 1; and

p is 0, 1, 2, or 3.

[0037] In certain embodiments, t is 0. In certain embodiments, t is 1. In certain embodiments, t is 2. In certain embodiments, t is 3.

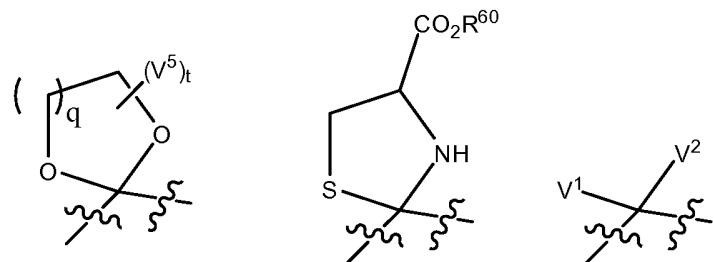
[0038] As used herein, R⁶⁰ can be hydrogen, provided that the CO₂R⁶⁰ is not joined to a nitrogen atom.

[0039] In certain embodiments, Y and Z are both not a heteroatom or a heteroatom containing moiety. In some preferred embodiments, one of Y and Z is a methylene or

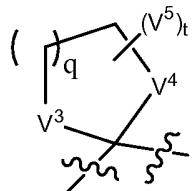
substituted methylene and the other is a heteroatom or a heteroatom containing moiety.

More preferably, Y is an alkylene, and Z is a heteroatom or a heteroatom containing moiety, which, yet more preferably is oxygen.

[0040] In certain embodiments, V¹ and V² together with the carbon atom they are attached to form a ring of formula:



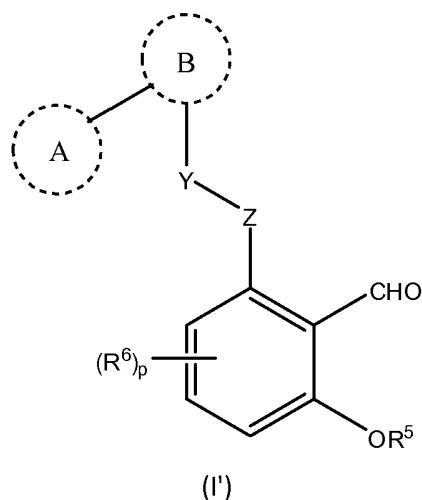
[0041] In certain embodiments, V¹ and V² independently are C₁-C₆ alkoxy; or V¹ and V² together with the carbon atom they are attached to form a ring of formula:



wherein each V³ and V⁴ are independently O, S, or NH, provided that when one or V³ and V⁴ is S the other is NH, and provided that V³ and V⁴ are both not NH; q is 1 or 2; each V⁵ is independently C₁-C₆ alkyl or CO₂R⁶⁰, where each R⁶⁰ independently is C₁-C₆ alkyl or hydrogen; t is 0, 1, 2, or 4; or CV¹V² is C=V, wherein V is O, and wherein the remaining variables are defined herein.

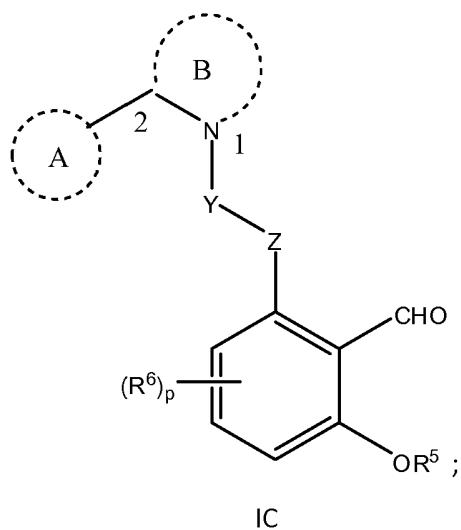
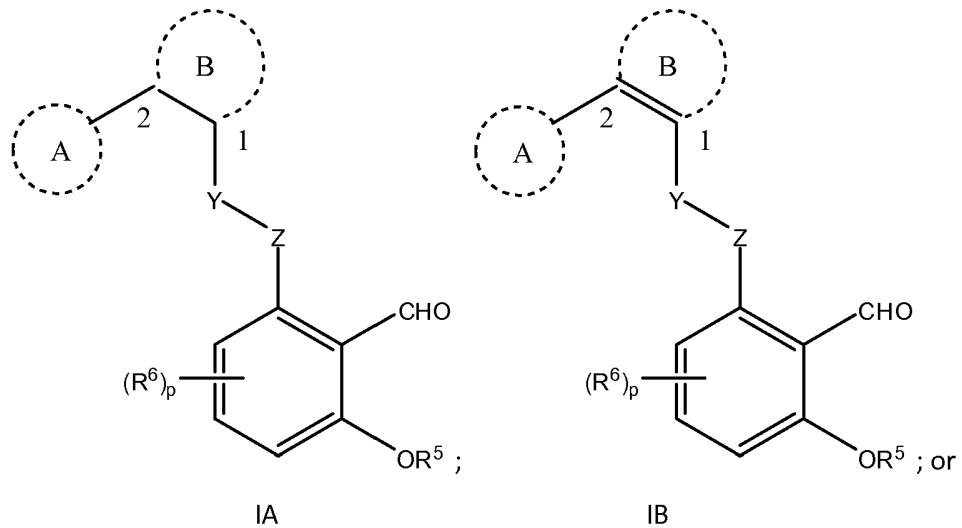
[0042] In certain embodiments, ring B contains a double bond. In some other embodiments, ring B contains no double bonds.

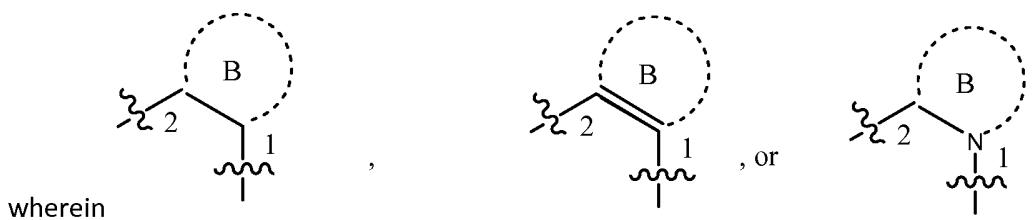
[0043] In certain embodiments, the compound is of Formula (I'):



wherein the remaining variables are defined herein.

[0044] In certain embodiments, the compound is of Formula IA, IB or IC:





is an optionally substituted 4-10 membered heterocycle as defined herein, and the remaining variables are defined herein.

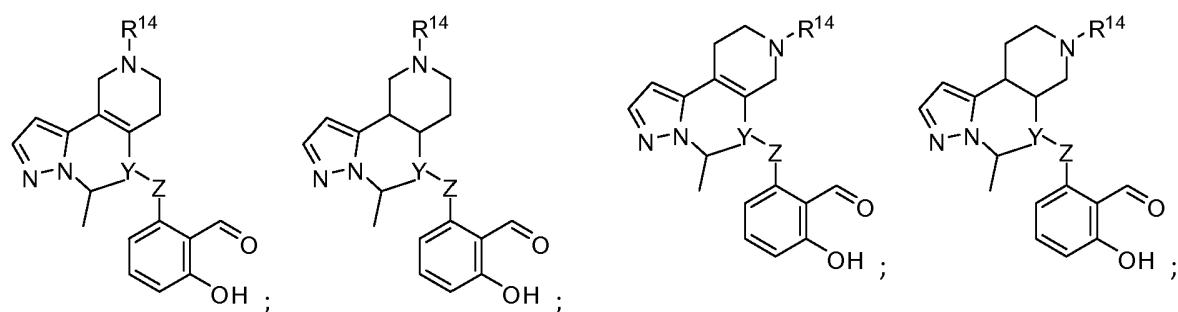
[0045] In certain embodiments, ring A is substituted with 1-3: halo, OH, C₁-C₆ alkyl, and/or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo.

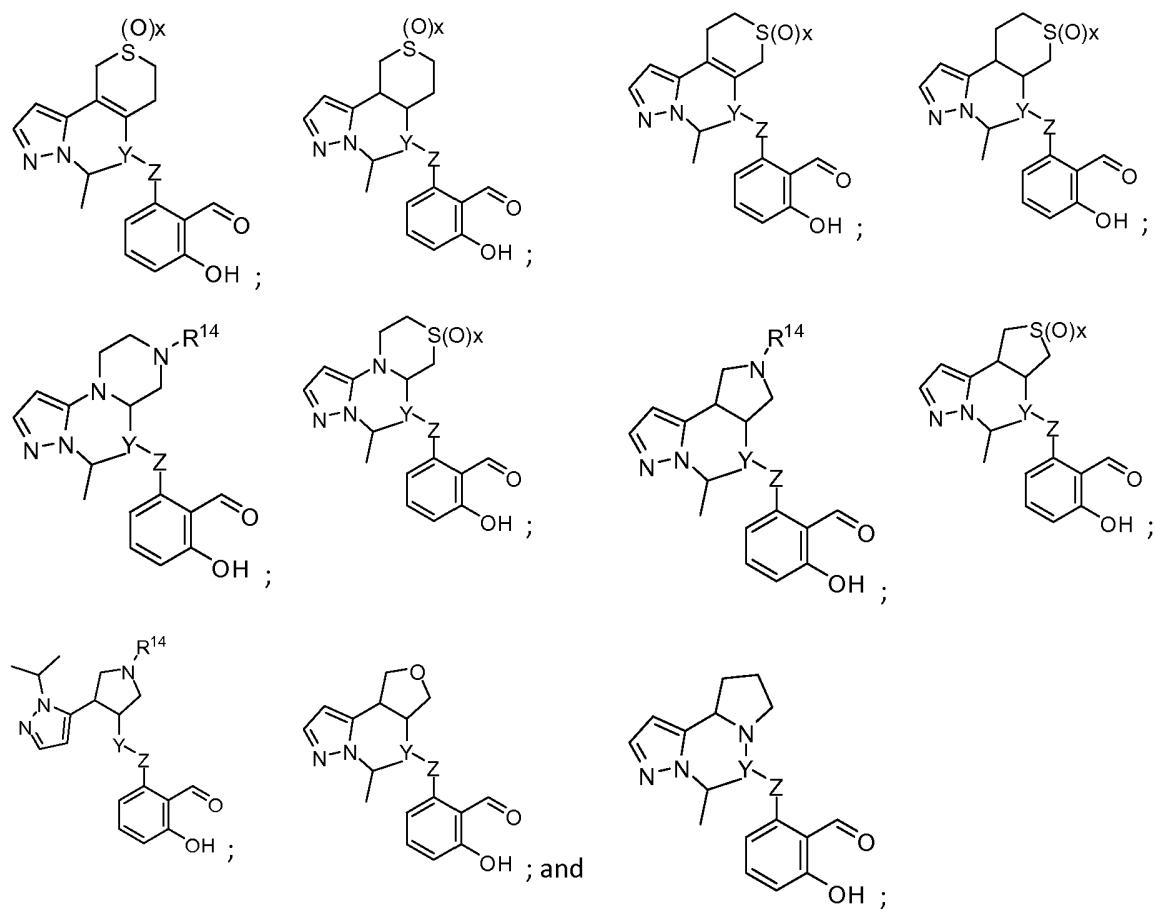
[0046] In certain embodiments, ring B is substituted with 1-3: halo, OH, C₁-C₆ alkyl, COR¹⁵, and/or COOR¹⁵; and

R¹⁵ is C₁-C₆ alkyl, C₆-C₁₀ aryl, 5-10 membered heteroaryl or a 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, wherein the alkyl, aryl, heteroaryl or heterocyclyl is optionally substituted.

[0047] In certain embodiments, Y-Z is -CH₂O-, -CH₂CH₂-, -CONH- or -NHCO-, wherein the right hand side of the substituent is joined with the substituted aryl or substituted phenyl ring.

[0048] In certain embodiments, the compound is selected from the group consisting of





or an N oxide thereof wherein

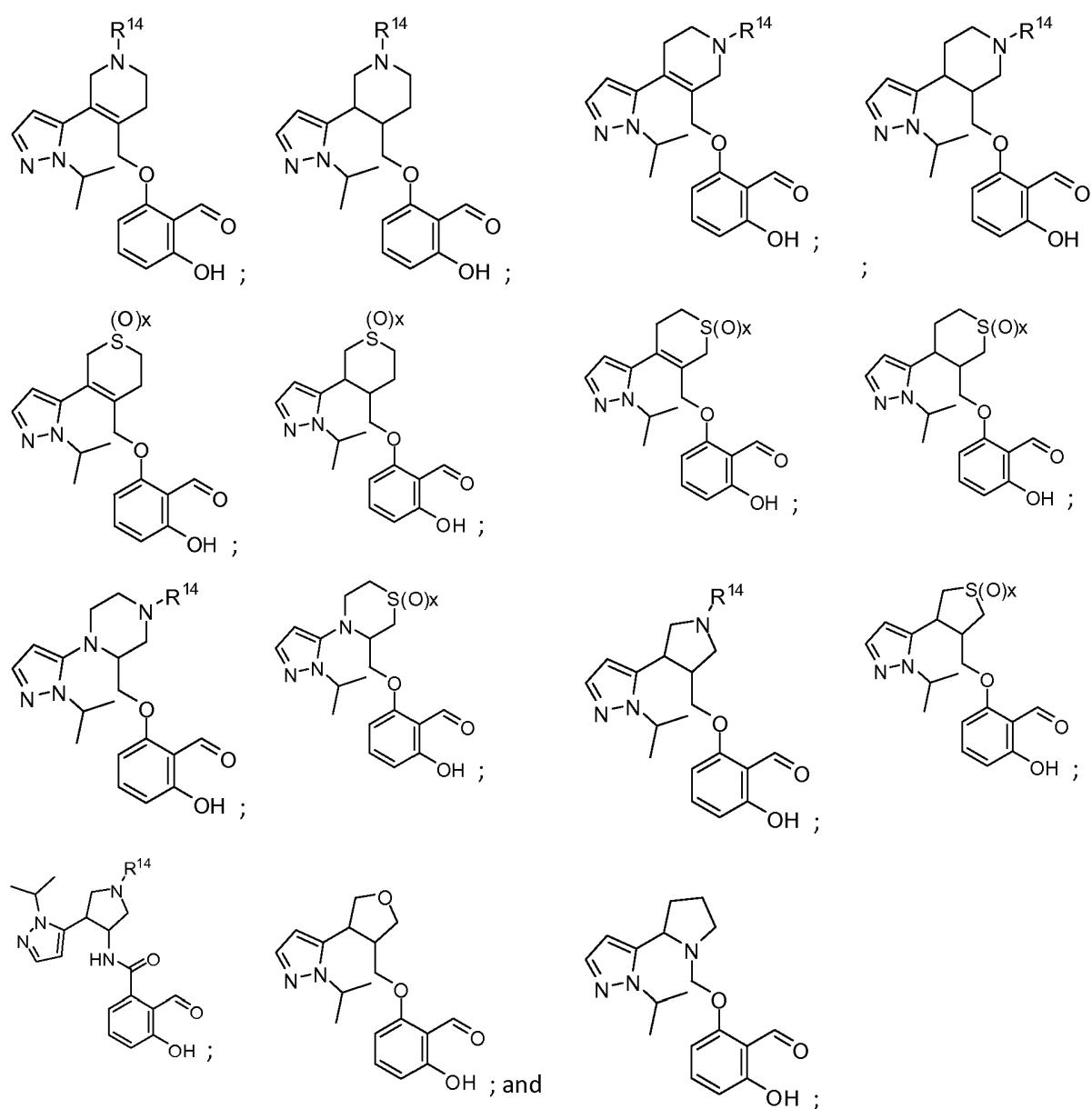
Y and Z are as defined herein;

x is 0, 1, or 2;

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

and R^{15} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_6 - C_{10} aryl, optionally substituted 5-10 membered heteroaryl 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.

[0049] In certain embodiments, the compound is selected from the group consisting of



or an N oxide thereof wherein

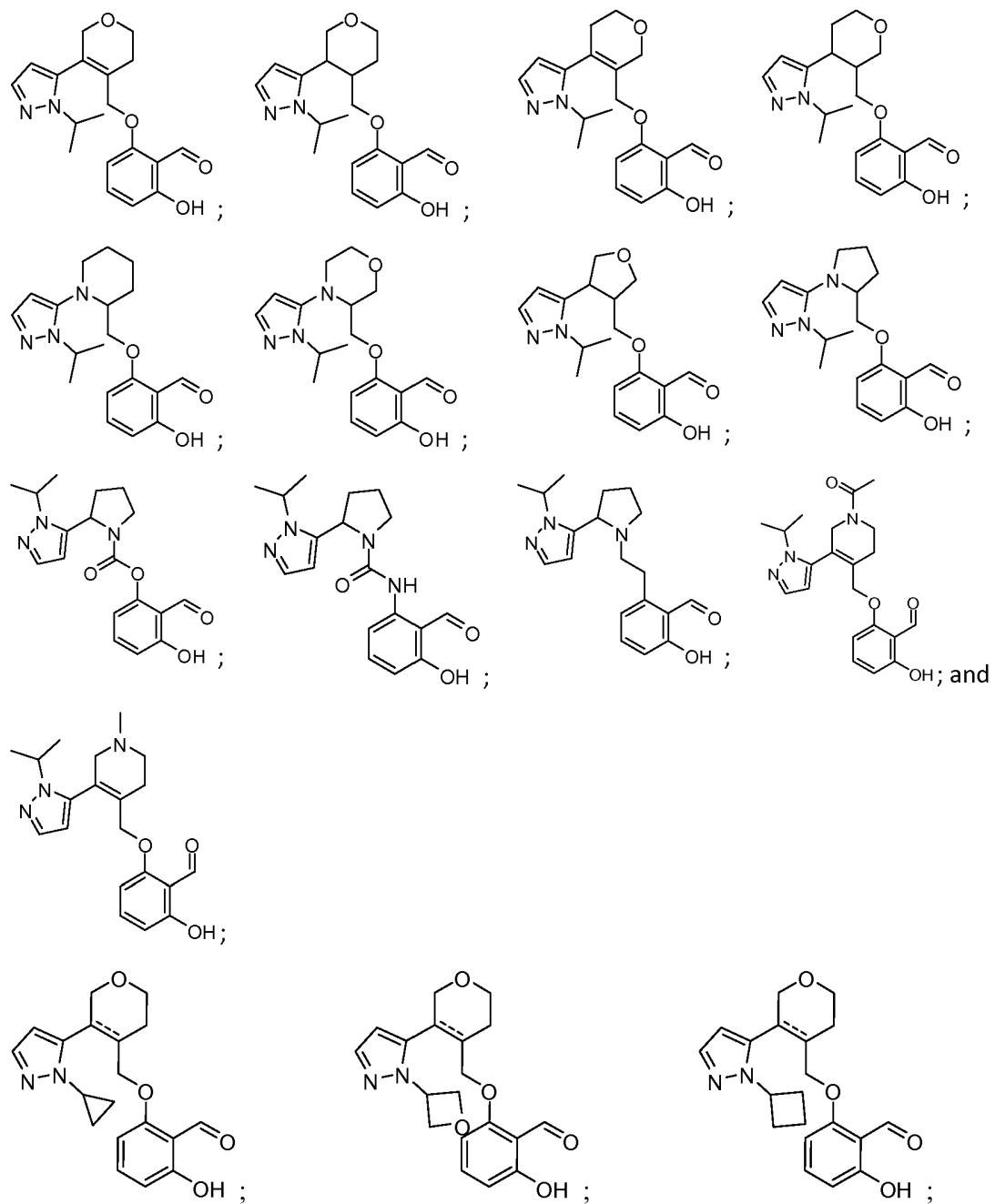
x is 0, 1, or 2;

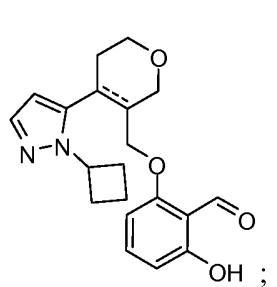
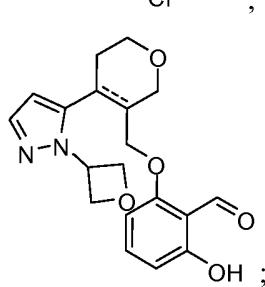
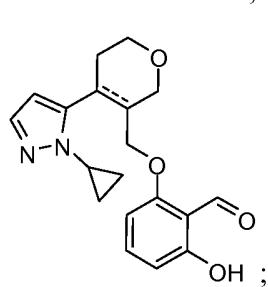
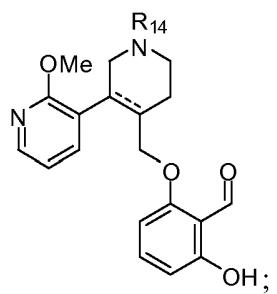
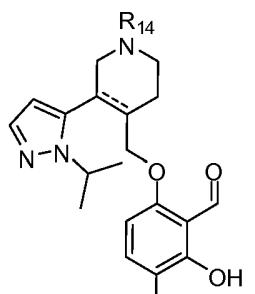
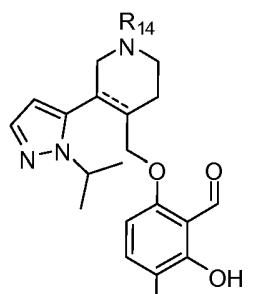
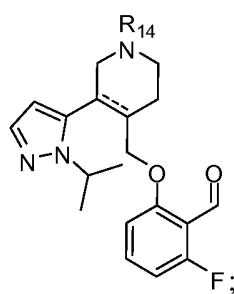
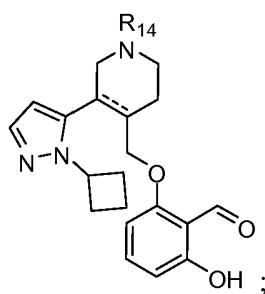
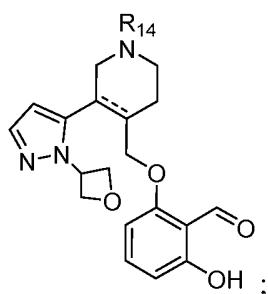
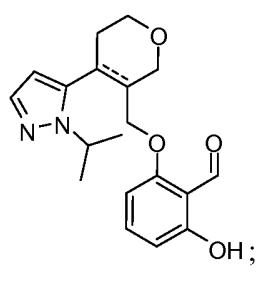
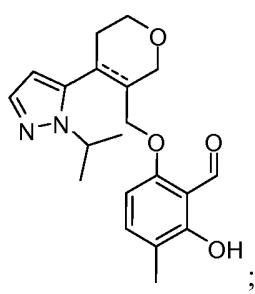
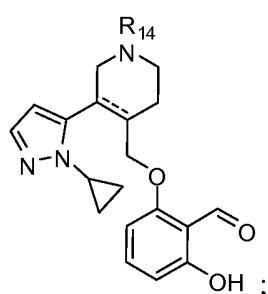
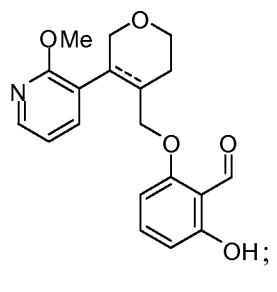
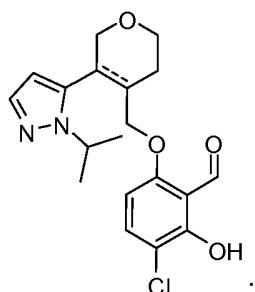
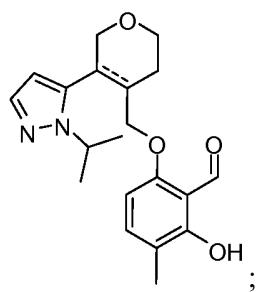
R¹⁴ is C₁-C₆ alkyl and C₃-C₈ cycloalkyl, COR¹⁵, CNR¹⁵, R¹⁵ or COOR¹⁵;

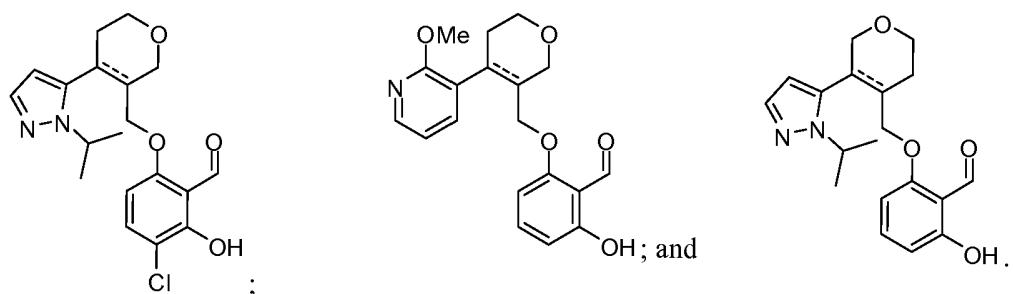
and R¹⁵ is optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl,

optionally substituted 5-10 membered heteroaryl 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.

[0050] In certain aspects of the invention, a compound is provided, wherein the compound is selected from the group consisting of:



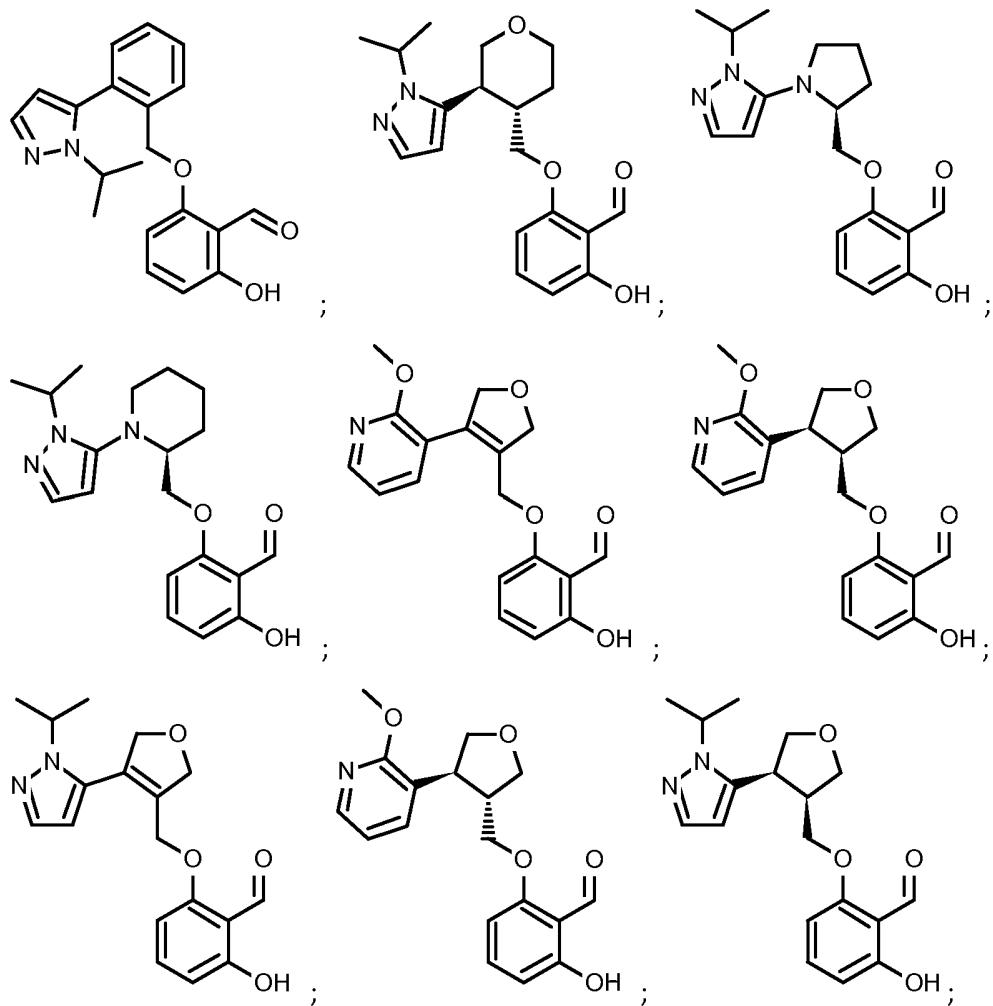


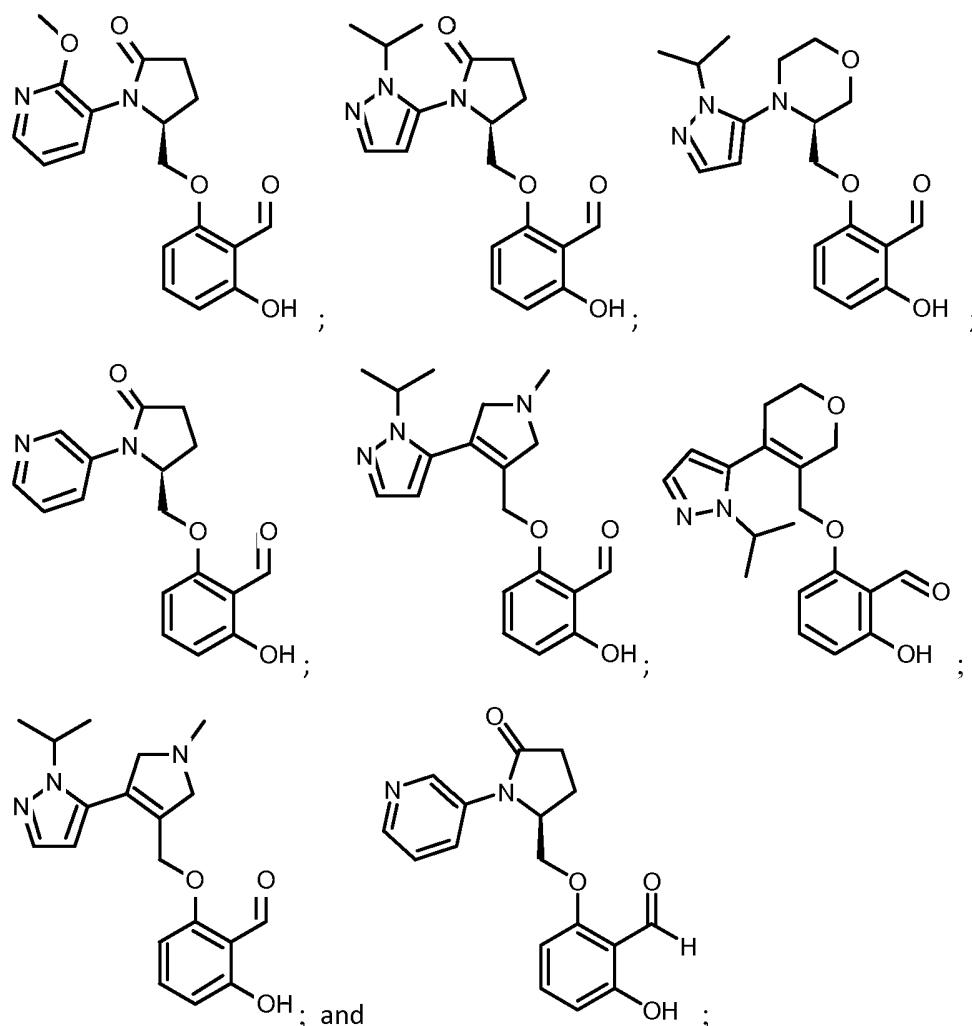


 is a double or a single bond.

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

[0051] In certain aspects of the invention, a compound is provided, wherein the compound is selected from the group consisting of:





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

[0052] Other compounds provided herein are included in the Examples section.

Prodrug Moiety

[0053] 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.

[0054] In one embodiments, **R** is $-\text{COR}^{90}$, CO_2R^{91} , or $\text{CONR}^{92}\text{R}^{93}$ 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.

[0055] 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} moieties 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.

[0056] 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.

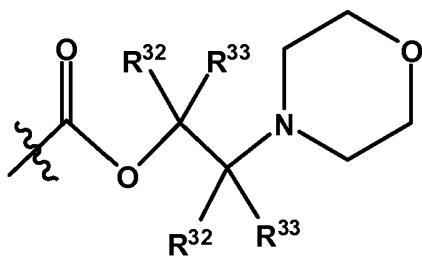
[0057] In one embodiment, R^{31} is a group of the formula $(CR^{32}R^{33})_eNR^{34}R^{35}$, wherein each R^{32} and R^{33} is independently H, a C_1 - C_8 alkyl, C_3 - C_9 heterocyclyl, C_3 - C_8 cycloalkyl, C_6 - C_{10} aryl, C_3 - C_9 heteroaryl or R^{32} and R^{33} together with the carbon atom they 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.

[0058] In some less preferred embodiments R^{34} and R^{35} can be hydrogen.

[0059] In one embodiment, the subscript e is preferably 2 and each R³² and R³³ is preferably independently selected from the group, H, CH₃, and a member in which R³² and R³³ are joined together to form a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or 1,1-dioxo-hexahydro-1*λ*⁶-thiopyran-4-yl or tetrahydropyran-4-yl group.

[0060] With regard to the prodrug group, preferred embodiments are compounds wherein NR³⁴R³⁵ is morpholino.

[0061] In one embodiment, R is:



wherein

each R³² and R³³ is independently H, C₁-C₈ alkyl, or optionally, if both present on the same substituent, may be joined together to form a C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, C₃-C₉ heterocyclyl or C₃-C₉ heteroaryl ring system.

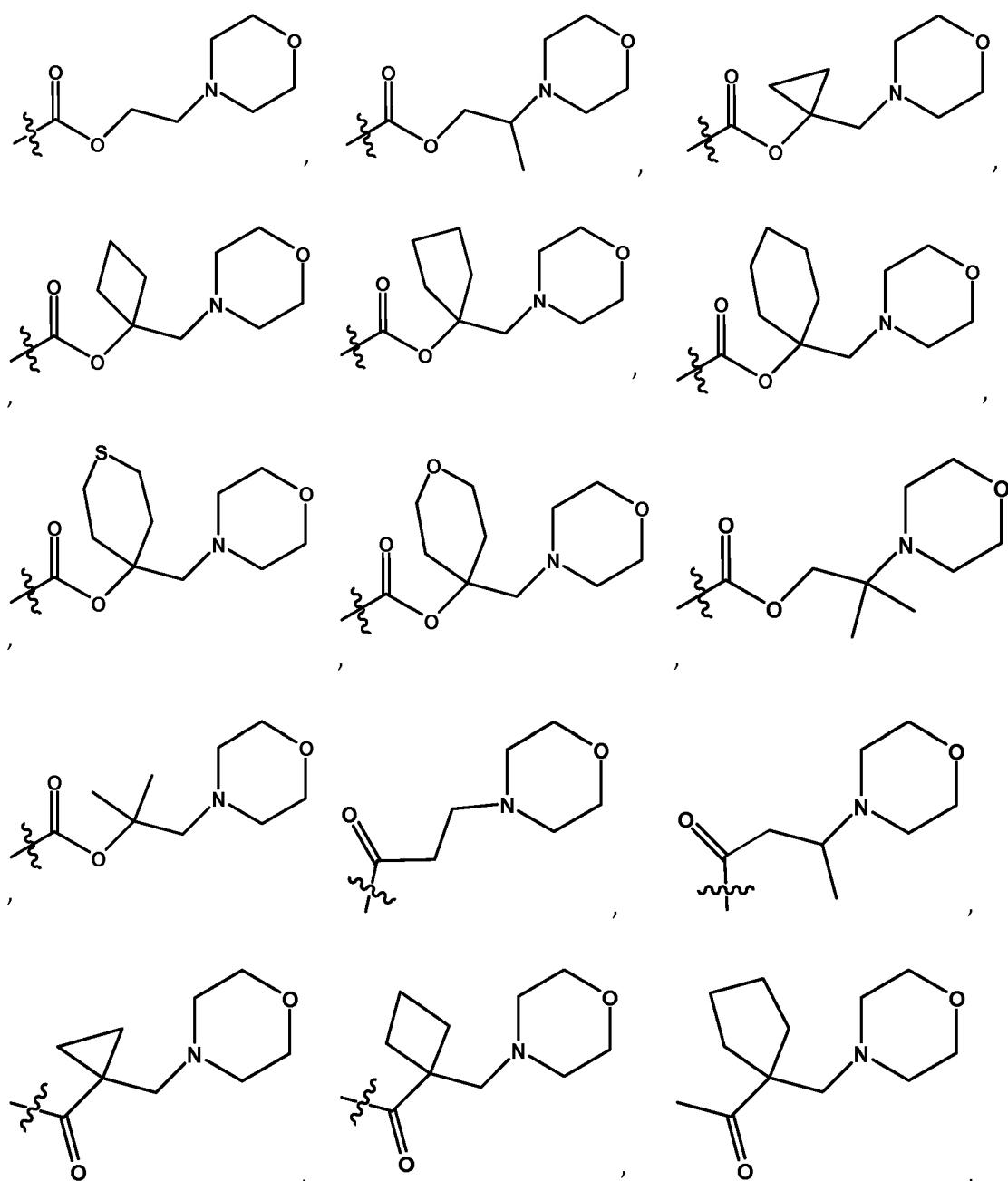
[0062] Within this embodiment, each R³² and R³³ is independently, H, CH₃, or are joined together to form a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1,1-dioxo- hexahydro-1*λ*⁶-thiopyran-4-yl or tetrahydropyran-4-yl group.

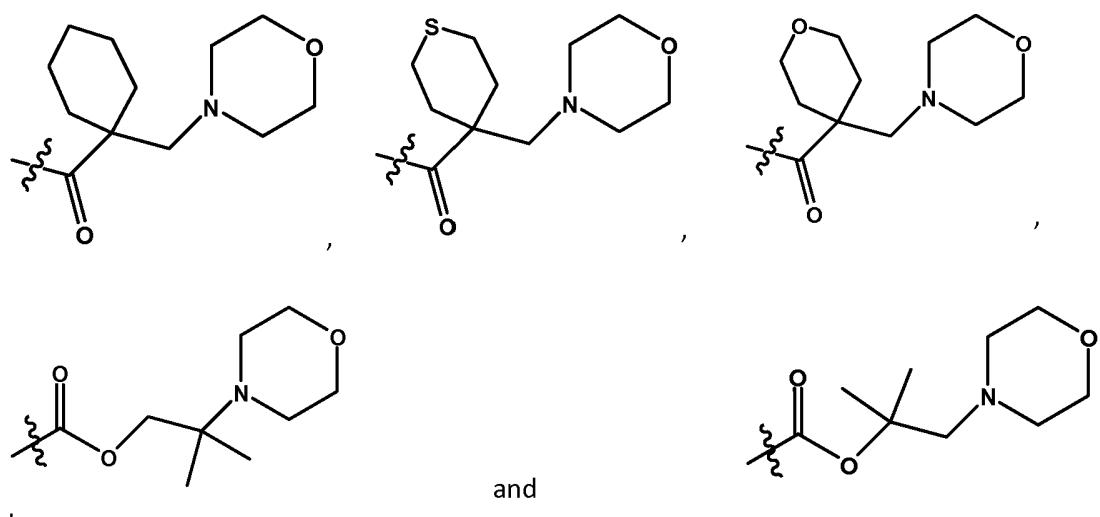
[0063] In a preferred embodiment, linkage of the prodrug moiety to the rest of the active molecule is stable enough so that the serum half life of the prodrug is from about 8 to about 24 hours.

[0064] 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.

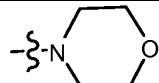
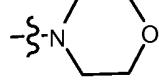
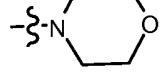
[0065] Examples of R include, without limitation:





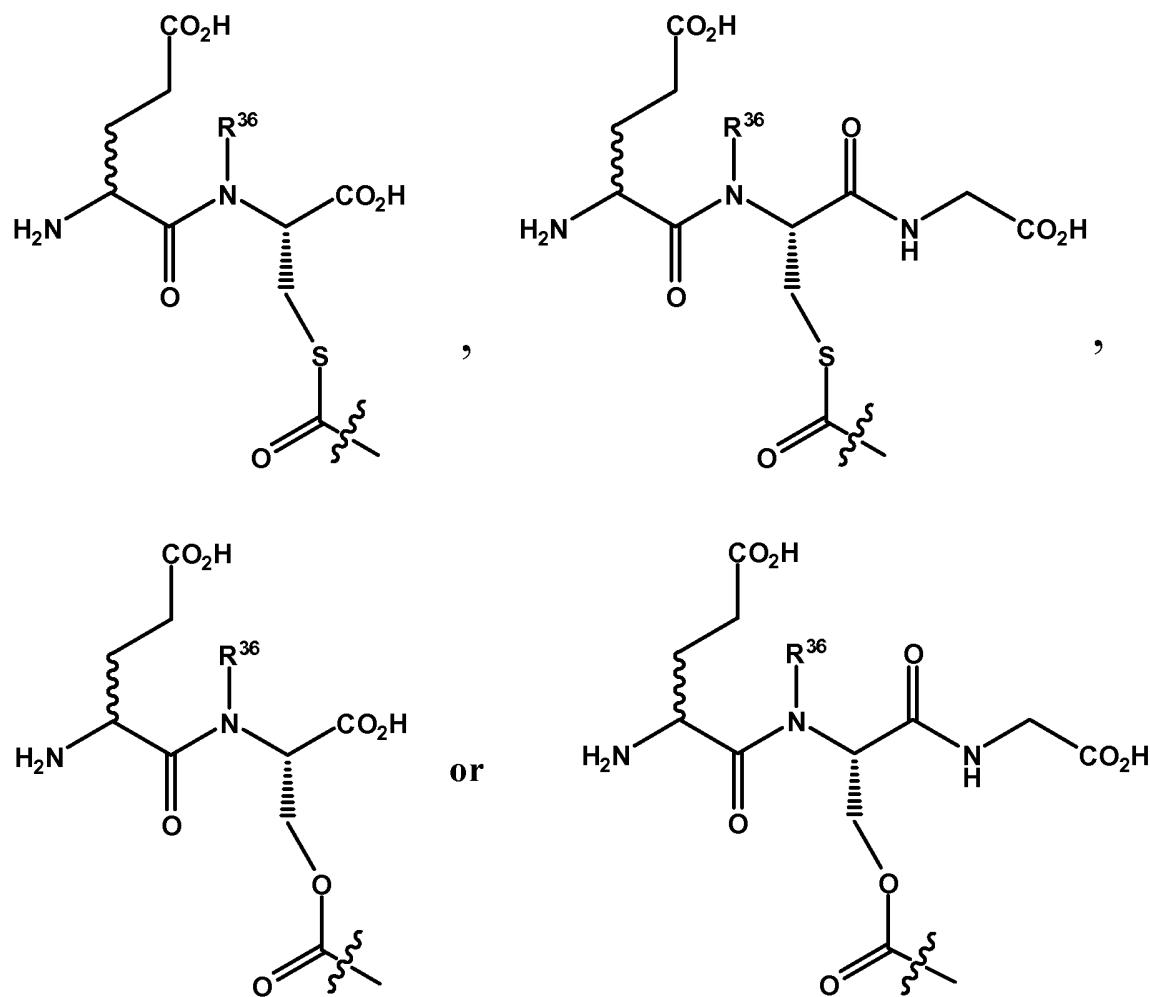
[0001] In another embodiment, R is as tabulated below:

R	m	R ³⁴	R ³⁵	NR ³⁴ R ³⁵
C(O)(CH ₂) _m NR ³⁴ R ³⁵	1	Me	Me	
C(O)(CH ₂) _m NR ³⁴ R ³⁵	2	Me	Me	
C(O)(CH ₂) _m NR ³⁴ R ³⁵	3	Me	Me	
C(O)(CH ₂) _m NR ³⁴ R ³⁵	4	Me	Me	
C(O)(CH ₂) _m NR ³⁴ R ³⁵	1			- ξ -N(piperazine)
C(O)(CH ₂) _m NR ³⁴ R ³⁵	2			- ξ -N(piperazine)
C(O)(CH ₂) _m NR ³⁴ R ³⁵	3			- ξ -N(piperazine)
C(O)(CH ₂) _m NR ³⁴ R ³⁵	4			- ξ -N(piperazine)
C(O)O(CH ₂) _m NR ³⁴ R ³⁵	2	Me	Me	
C(O)O(CH ₂) _m NR ³⁴ R ³⁵	3	Me	Me	
C(O)O(CH ₂) _m NR 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.

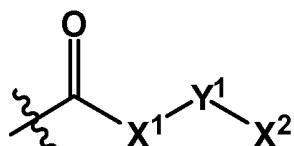
[0066] In another aspect, R is,



wherein

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

[0067] In yet another aspect, R is:



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

[0068] 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 heterocyclyl, 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, heterocyclyl, 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:

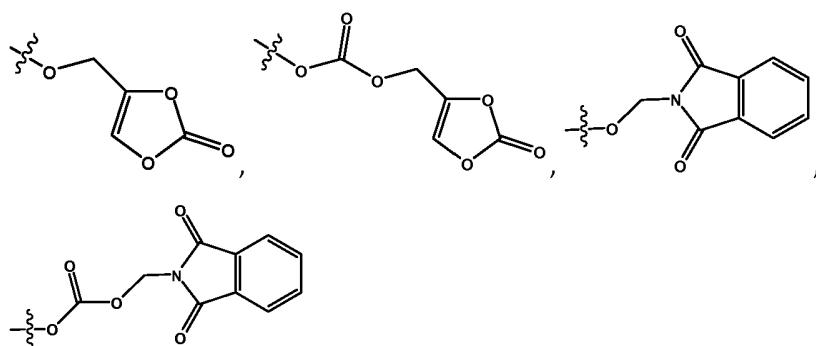
X^4 is selected from the group consisting of O, S, $S=O$, and SO_2 ; and

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.

[0069] Each heterocyclic and heteroaryl ring system is optionally substituted with C₁-C₃ alkyl, -OH, amino and carboxyl groups.

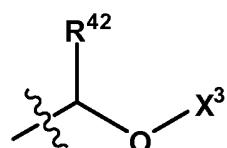
[0070] In one embodiment, the present invention utilizes the following Y¹ groups: CH₂, CHMe, CH(isopropyl), CH(tertiarybutyl), C(Me)₂, C(Et)₂, C(isopropyl)₂, and C(propyl)₂.

[0071] In another embodiment, the present invention utilizes the following X² 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)-NMe₂, -O-C(=O)-NHMe, -O-C(=O)-NH₂, -O-C(=O)-N(H)-CH(R⁴¹)-CO₂Et wherein R⁴¹ is a side chain C₁-C₆ alkyl, or C₃-C₉ heterocyclyl group selected from the side chain groups present in essential amino acids; -O-P(=O)(OMe)₂, -O-P(=O)(O-isopropyl)₂, and -O-P(=O)(O-isobutyl)₂. Each heterocyclic is optionally substituted with one or more, preferably, 1-3, C₁-C₃ alkyl, -OH, amino and/or carboxyl groups.

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



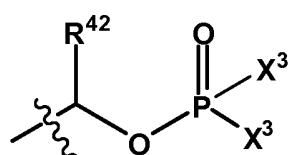
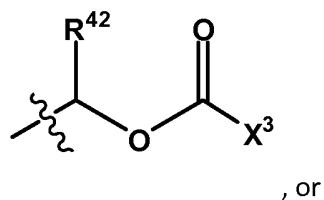
wherein

X³ is independently C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₉ heterocyclyl, C₆-C₁₀ aryl, or C₃-C₉ heteroaryl; and

R⁴² is independently hydrogen or C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₉ heterocyclyl, C₆-C₁₀ aryl, or C₃-C₉ heteroaryl.

[0073] Each heterocyclic is optionally substituted with one or more, preferably, 1-3, C₁-C₃ alkyl, -OH, amino and/or carboxyl groups.

[0074] In one embodiment, **R** is:



wherein

each X³ is independently amino, hydroxyl, mercapto, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₉ heterocyclyl, C₆-C₁₀ aryl, or C₃-C₉ heteroaryl, C₁-C₆ alkoxy, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ alkylthio, a bile acid based alkoxy group, a sugar moiety, a PEG moiety, and -O-CH₂-CH(OR⁴⁰)CH₂X⁴R⁴⁰,

wherein:

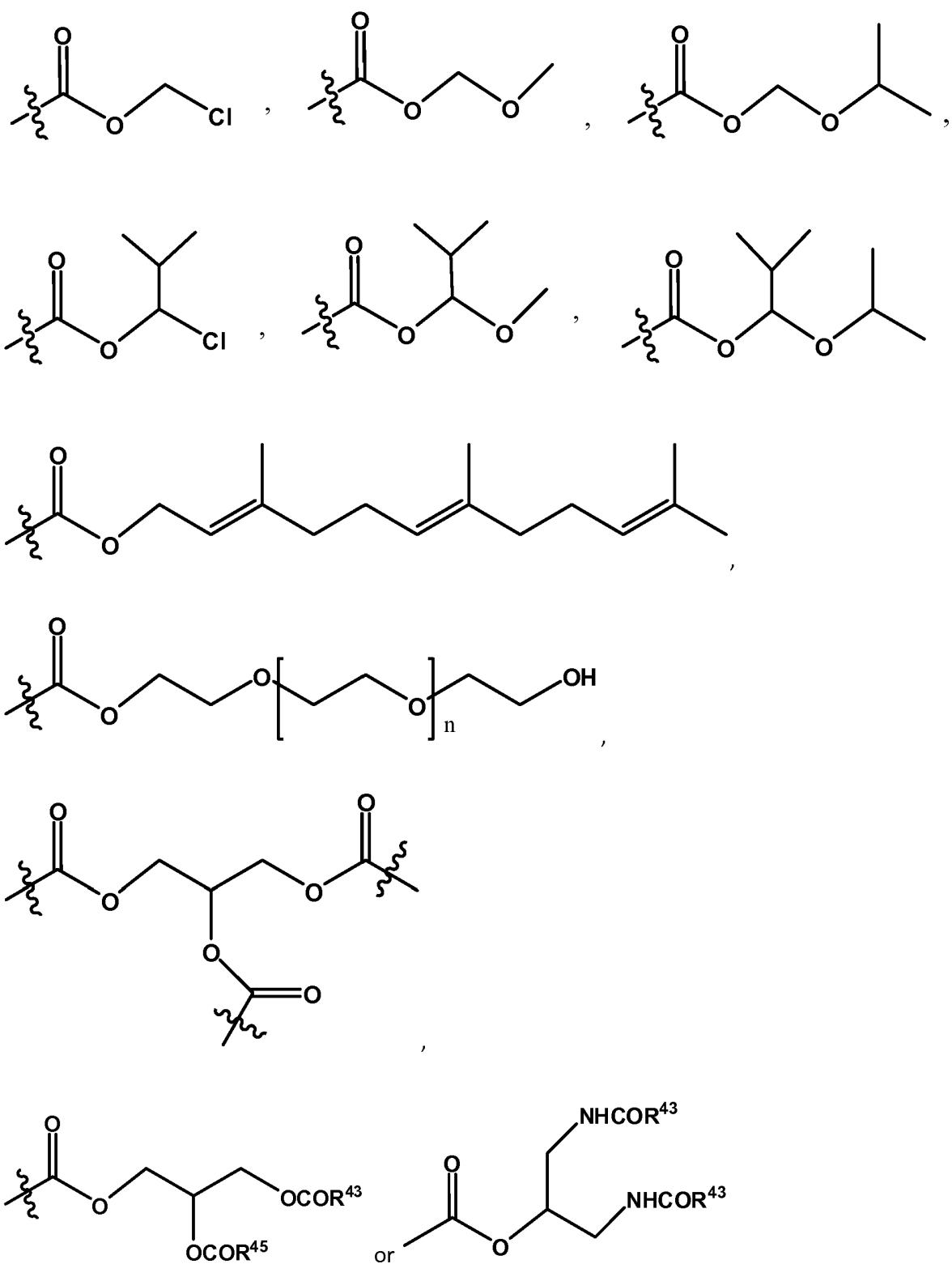
X⁴ is selected from the group consisting of O, S, S=O, and SO₂; and

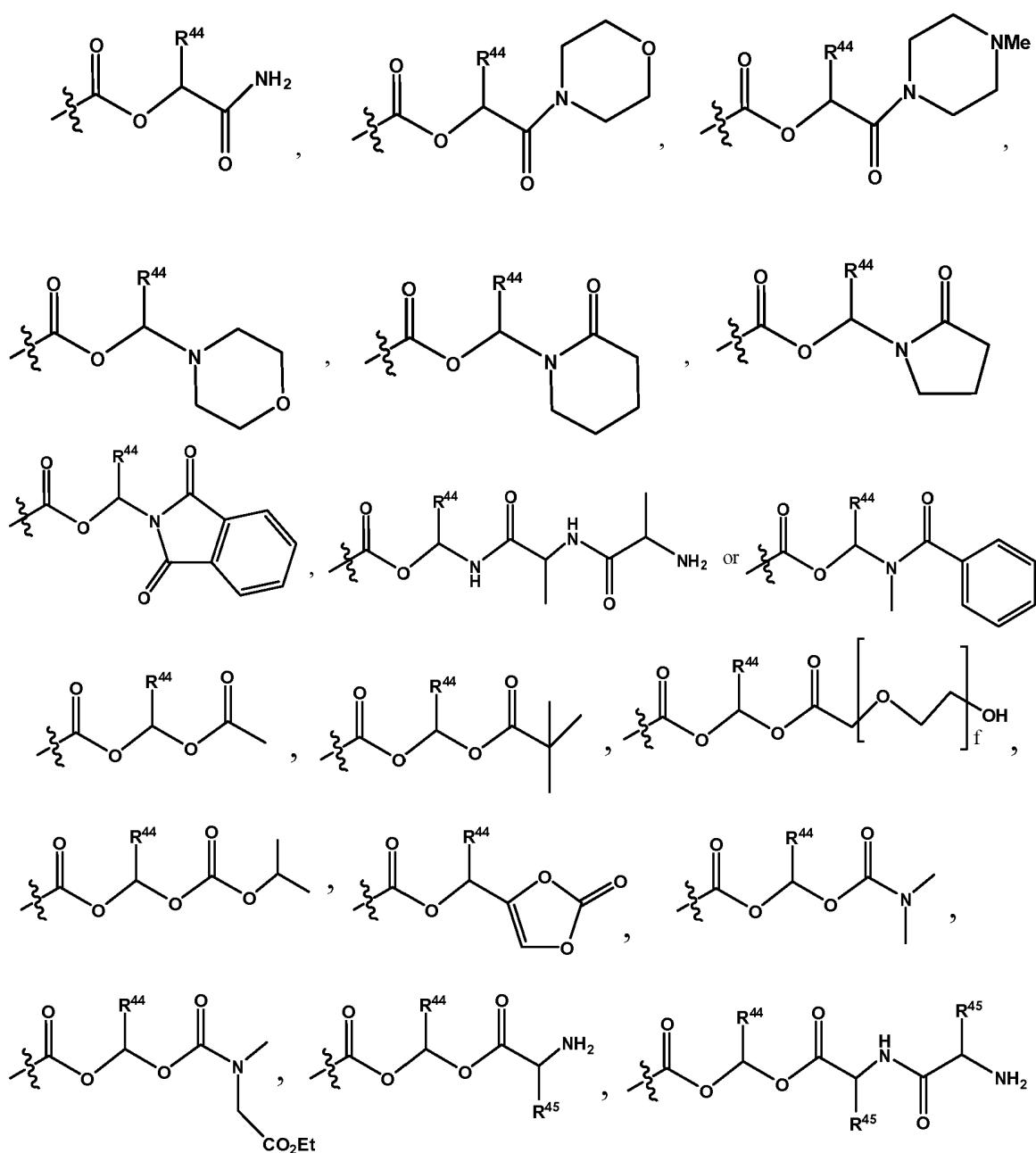
each R⁴⁰ is independently C₁₀-C₂₂ alkyl, C₃-C₈ cycloalkyl, C₃-C₉ heterocyclyl, C₆-C₁₀ aryl, C₃-C₉ heteroaryl, C₁-C₈ alkylene, or C₁-C₈ heteroalkylene; and

R⁴² is independently hydrogen or C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₉ heterocyclyl, C₆-C₁₀ aryl, or C₃-C₉ heteroaryl.

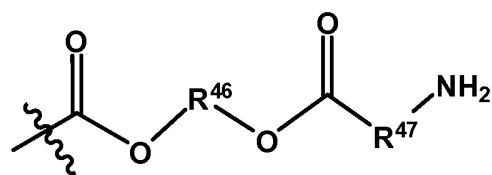
[0075] In some embodiments, R⁴² is independently hydrogen or C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₉ heterocyclyl, C₆-C₁₀ aryl, or C₃-C₉ heteroaryl; and each X³ independently is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₉ heterocyclyl, C₆-C₁₀ aryl, or C₃-C₉ heteroaryl, C₁-C₆ alkoxy, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, or C₁-C₆ alkylthio.

[0076] In some embodiments, **R** is represented by the following structures:

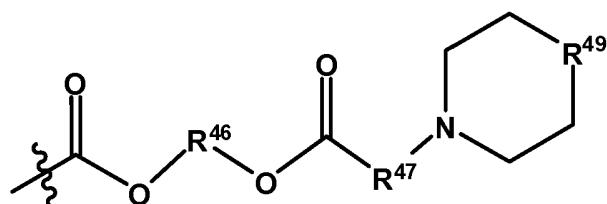




wherein, in the above examples, R⁴³ is C₁₀-C₂₂ alkyl or alkylene, R⁴⁴ is H or C₁-C₆ alkyl and R⁴⁵ represents side chain alkyl groups present in naturally occurring alpha amino acids;

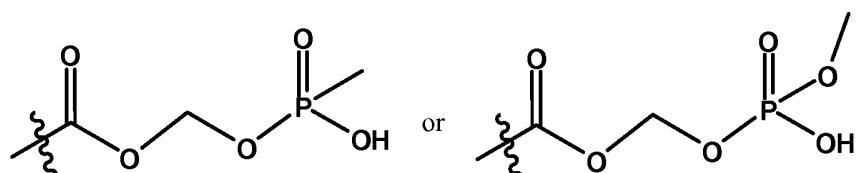


wherein R⁴⁶ is (CH₂)_n, f=2-4, and CO-R⁴⁷-NH₂ represents an aminoacyl group; or



wherein R⁴⁶ is (CH₂)_n, n=2-4, R⁴⁷ is (CH₂)_n, n=1-3 and R⁴⁹ is O or NMe.

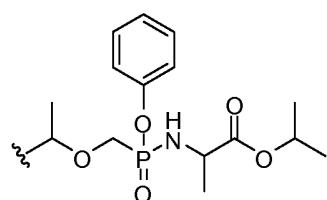
[0077] In one embodiment, R is:



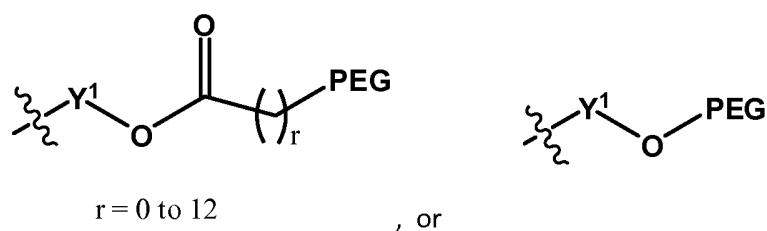
[0078] In one aspect, R is -C(R²⁰⁰R²⁰¹)O(R²⁰²R²⁰³)P(O)OR²⁰⁴NR²⁰⁵R²⁰⁶, wherein each R²⁰⁰, R²⁰¹, R²⁰², R²⁰³, R²⁰⁴, R²⁰⁵ and R²⁰⁶ is independently H, a C₁-C₈ alkyl, C₃-C₉ heterocyclyl, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, C₃-C₉ heteroaryl, wherein each alkyl, heterocyclyl, cycloalkyl, aryl, and heteroaryl is optionally substituted.

[0079] In some embodiments, R is -CH(R²⁰¹)OCH₂P(O)OR²⁰⁴NHR²⁰⁶, wherein R²⁰¹ is C₁-C₈ alkyl, R²⁰⁴ is phenyl, optionally substituted. In one embodiment, R²⁰⁶ is -CHR²⁰⁷C(O)OR²⁰⁸ wherein R²⁰⁷ is selected from the group consisting of the naturally occurring amino acid side chains and CO₂H esters thereof and R²⁰⁸ is C₁-C₈ alkyl. In one embodiment, R²⁰⁶ is C₁-C₆ alkyl, optionally substituted with 1-3, CO₂H, SH, NH₂, C₆-C₁₀ aryl, and C₂-C₁₀ heteroaryl.

[0080] In some embodiments, R is:



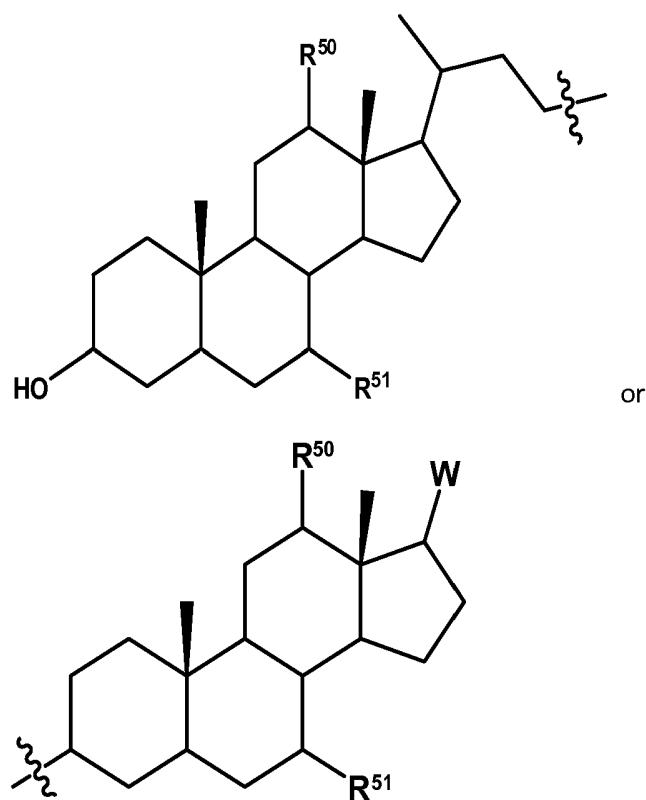
[0081] In one embodiment, R is:



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.

[0082] 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.

[0083] In one embodiment, R is



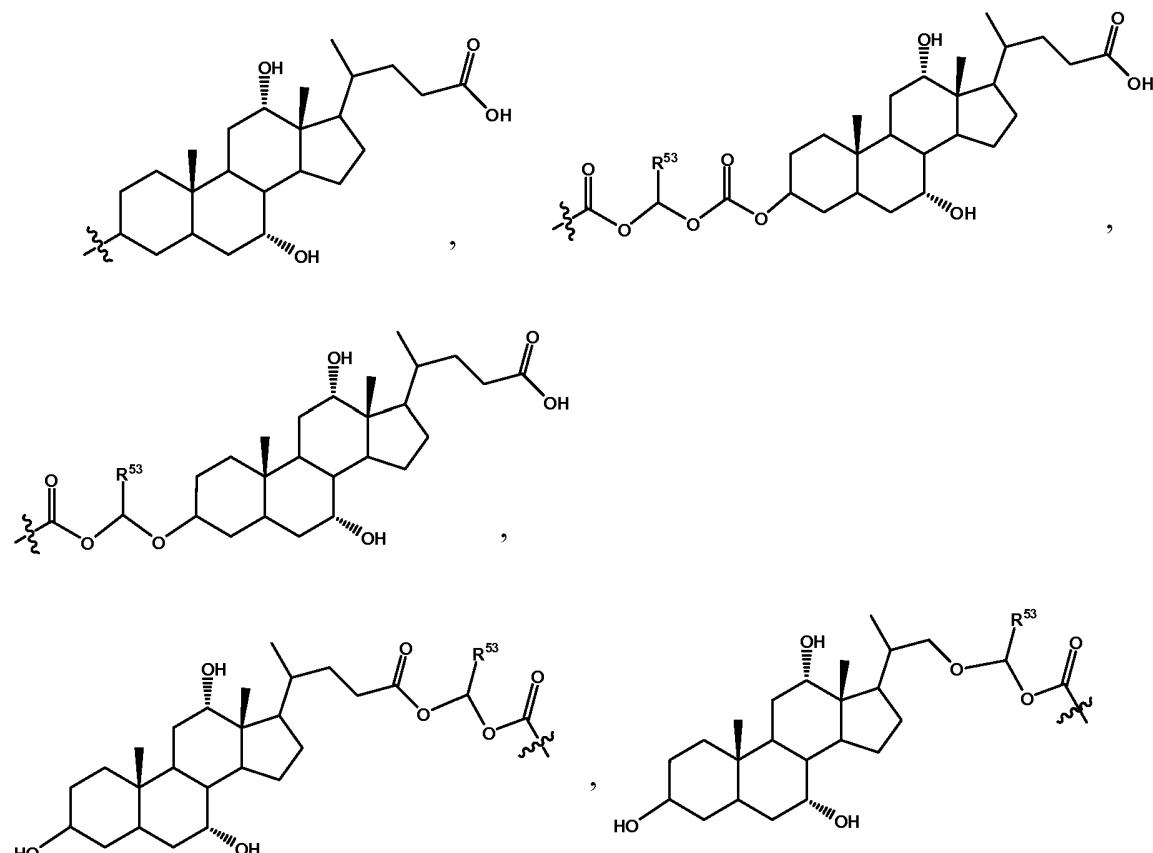
wherein

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.

[0084] Each heterocyclic and heteroaryl ring system is optionally substituted with one or more, preferably 1-3, C₁-C₃ alkyl, -OH, amino and/or carboxyl groups.

[0085] In one embodiment, R is:



wherein R⁵³ is H or C₁-C₆ alkyl.

[0086] In another aspect, **R** is SO_3H .

[0087] 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.

[0088] 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

[0089] In further aspects of the invention, a composition is provided comprising any of the compounds described herein, and at least a pharmaceutically acceptable excipient.

[0090] In another aspect, this invention provides a composition comprising any of the compounds described herein, and a pharmaceutically acceptable excipient.

[0091] 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).

[0092] 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.

[0093] 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.

[0094] 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.

[0095] 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.

[0096] 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

[0097] 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.

[0098] 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.

[0099] 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.

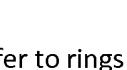
[0100] In further aspects of the invention, a method is provided for treating oxygen deficiency associated with sickle cell anemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

[0101] 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

[0102] 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, $^1\text{H-NMR}$, 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.

[0103] An illustrative and non-limiting method for synthesizing a compound of formula (I), is schematically shown below.

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

A^5 and B^5 are independently NR^{70} , O , S , S(O)x , NBoC , CH_2 , CHR^{70} , $\text{C(R}^{70})_2$ provided that when only one of A^5 or B^5 is present, then A^5 or B^5 is not CH_2 , CHR^{70} , $\text{C(R}^{70})_2$, and when both A^5 and B^5 are present in a ring, both are not CH_2 , CHR^{70} , $\text{C(R}^{70})_2$;

wherein R^{70} is $\text{C}_1\text{-C}_6$ alkyl or defined as R^{14} as defined herein;

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

R^{71} is $\text{C}_1\text{-C}_6$ alkyl;

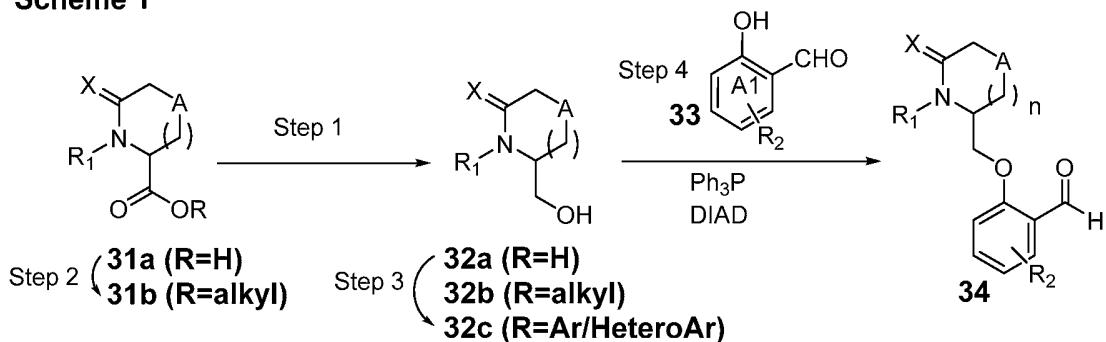
R^{72} is C_1 - C_6 alkyl;

n is 0, 1, or 2; and

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

General Synthetic Schemes

Scheme 1



[0104] Compounds of structure **34** can be synthesized via general synthetic scheme 1.

Reduction of carboxylic acid derivative **31** gives hydroxymethyl analog **32**, which can be N-derivatitized at via copper-mediated N-arylation reaction (CuI , $Ar-I$, base such as N,N -dimethylethylenediamine and potassium phosphate, heat) to give key hydroxymethyl intermediate **32**. Coupling of **32** with phenol aldehyde **33** produces the desired aldehyde analog **34** via typical Mistunobu conditions using either triphenylphosphine or polymer supported triphenylphosphine.

[0105] General method step 1 – reduction of carboxylic acid derivative 1 to methyl alcohol 2: To a suspension of carboxylic acid **1** (1-10mmol) in MeOH or EtOH (2-10 mL) at 0 °C was added $SOCl_2$ (1.5eq). After stirred at room temperature for 1-12h, it was concentrated to remove all solvents, dried under high vacuum to give corresponding methyl or ethyl ester. The ester was dissolved in MeOH or EtOH (5-30 mL), to this solution, was added $NaBH_4$ (1-4eq) at 0 °C, the mixture was warmed up to room temperature and stirred for additional 1-24 h. The mixture was quenched with Sat. NH_4Cl , filtered off the insolubles and the filtrate was concentrated to give crude product, which was purified by flash silica gel chromatography to give the corresponding hydroxymethylene compound **32**.

[0106] General method step 2 – N-alkylation (1a to 1b): The carboxylate **31a** ($R_1=H$) can be first alkylated and then reduced to give N-alkyl hydroxymethylene analog **31b** ($R_1=alkyl$).

In a typical procedure, the carboxylate **31a** (1-10mmol) is first dissolved in DMF (2-20 mL); to this was then added a base such as NaH or Cs₂CO₃ (1-1.2eq), followed by the addition of alkyl halide (eg, BnBr) (0.9-1.5eq). The reaction allowed to proceed at room temperature or heat at 40 to 115 °C for 0.5 to 24 h. 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 NH₄Cl was added at 0 °C 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, reaction appropriate solvents mixture (e.g., ethyl acetate/hexanes).

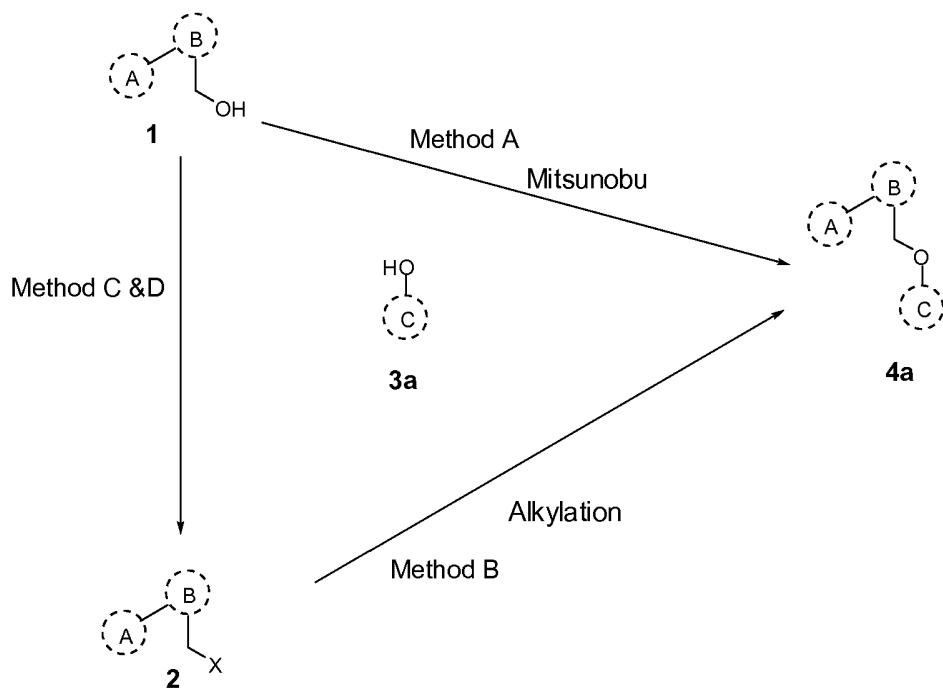
[0107] General method step 3 – Copper-mediated N-arylation from 32a to 32c: For cyclic amines (X=H, H), to a solution of hydroxymethylene compound **32a** (1-10 mmol) and aryl/hetero iodide (1-1.5eq) in iPrOH (0.5-10 mL) was added ethylene diol (1.3eq) and CuI (6.7mol%), followed by K₃PO₄ (1.3eq), then it was degassed and heated at 88 °C for 6-24 h. Alternatively, for lactams (X=O), to a solution of hydroxymethylene compound **32a** (1-10mmol) and aryl/hetero iodide (1-1.5eq) in Dioxane (2-20 mL) was added CuI (0.17eq), N,N-dimethylethylenediamine (0.17eq), K₃PO₄ (1.7eq), then it was degassed and heated at 100 °C for 6-48 h.

[0108] Workup for both procedures: the reaction mixture was cooled to room temperature the mixture was diluted with EtOAc and water, organic layer was separated and the aqueous layer was extracted with EtOAc, organic layer was combined, washed with brine, dried and concentrated to give crude product, which was purified by flash silica gel chromatography to give N-aryl/heteroaryl compound **32c**.

[0109] General method C –Mitsunobu conditions A hydroxyl (hetero)arylaldehyde derivatives (**34**) (0.1-2 mmol) mixture with substituted methylene alcohol (**33**) (0.8 to 1.2eq) and (polymer-supported) PPh₃ (1-1.5eq) in anhydrous THF (1-10mL) was stirred under nitrogen until complete dissolution. The solution was cooled to 0 °C 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 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.



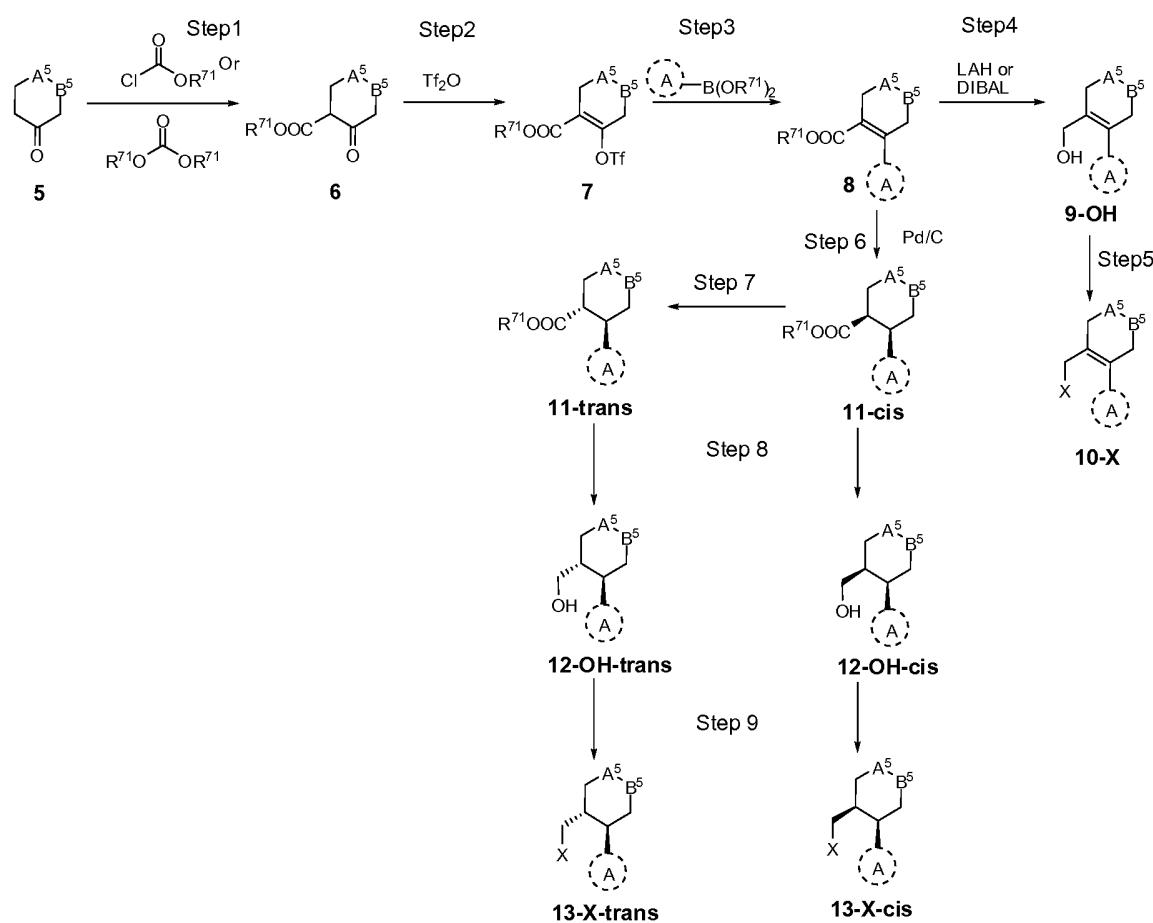
[0110] General method A for preparing aryoxy ether analogs (4a) from substituted methylene alcohol (1) and hydroxyl aryl aldehyde derivatives (3a). A hydroxyl (hetero)arylaldehyde derivatives (3a) (0.1-2 mmol) mixture with substituted methylene alcohol (1) (0.8 to 1.2eq) and PPh_3 (1-1.5eq) in anhydrous THF (1-10mL) was stirred under nitrogen until complete dissolution. The solution was cooled to 0 °C 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.

[0111] General method B for preparing aryoxyether analogs (4a) from substituted methylene halide (2) and hydroxyl aryl aldehyde derivatives (3a). A mixture of hydroxyl (hetero)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 °C 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 NH₄Cl was added at 0 °C 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).

[0112] 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 SOCl₂ dropwise (2eq to 5eq) at 0 °C 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 Na₂CO₃ 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).

[0113] 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 Ph₃P Br₂ dropwise (2eq to 5eq) at 0 °C 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**.

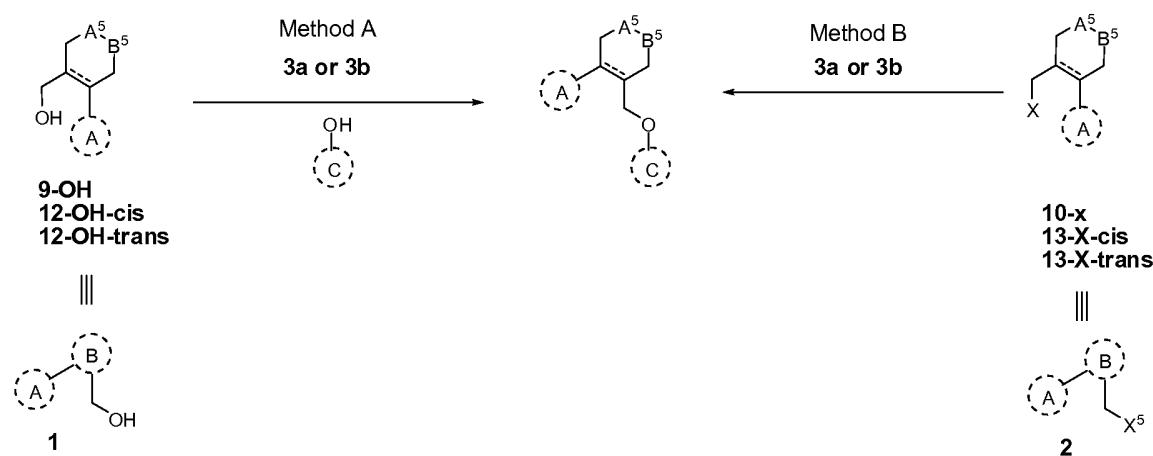


[0114] General method E for preparing heterocyclic methylene derivatives 9, 10, 12 and 13.

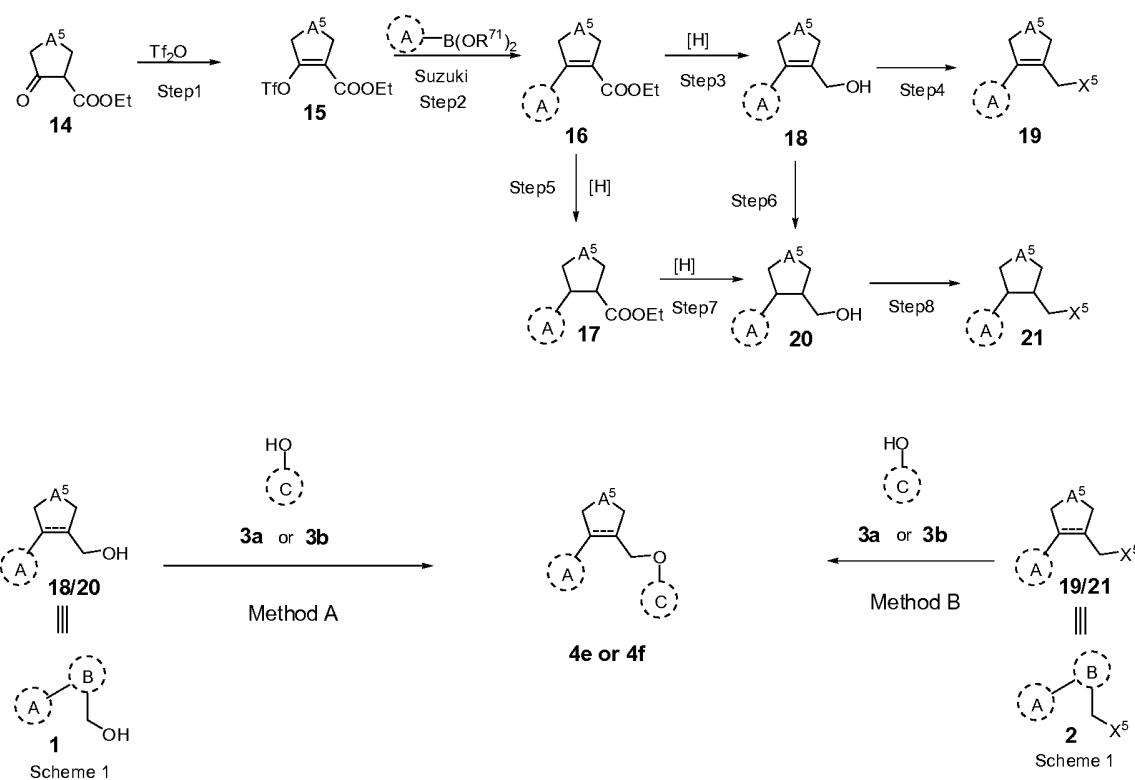
Condensation of heterocyclic ketone analog 5 with chlorformate or dialkyl carbonate gives (hetero)cyclic beta-ketone ester 6 (Step 1). The ketone ester 6 is converted to the triflate intermediate 7 by treating with a triflating agent (e.g, triflic anhydride) in the presence of an organic base such as 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 $\text{CBr}_4-\text{Ph}_3\text{P}$ or PBr_3), or alkyl/aryl sulfonyl chloride produces the corresponding 10-X chloride, bromide or sulfonate (Step 5).

[0115] 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 sulfonyl 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 Step 9 similar to these for the corresponding *cis*-isomers.



[0116] Coupling of the (hetero)cyclic methylene derivatives **9**, **10**, **12** and **13** with hydroxyl (hetero)arylaldehyde derivatives (**3a/3b**) by general method A or B affords the corresponding aryloxy/heteroarylether analogs (**4c** and **4d**).



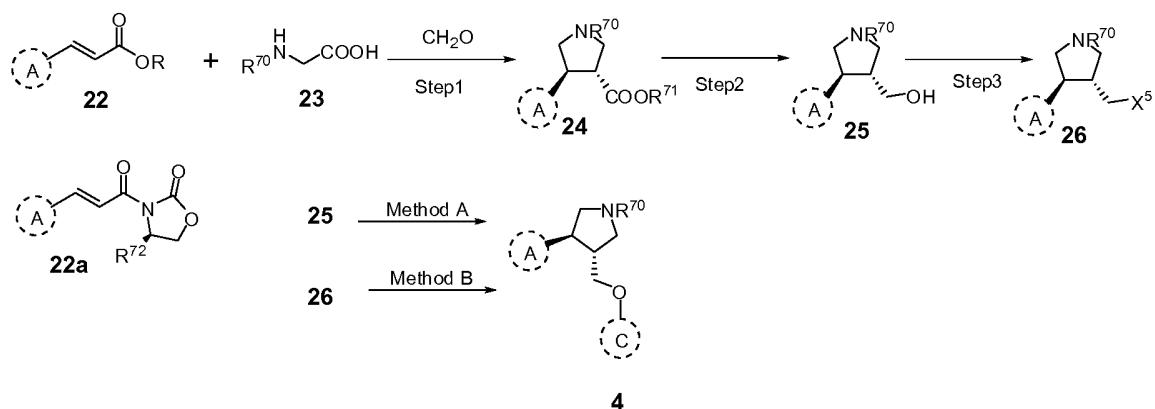
[0117] General method F Scheme 2 for preparing heterocyclic methylene derivatives 18, 19, 20 and 21.

The ketone ester **14** is converted to the triflate intermediate **15** by treating with a triflating agent (e.g, triflic anhydride) in the presence of an organic base such as Hunig's base (Step 1). Suzuki coupling of the triflate **15** with a boronic acid or ester affords heterocyclo carboxylate **16** (Step 2). Subsequent reduction of the ester group by LAH or DIBAL gives the corresponding alcohol **18** (Step 3). Further reaction of the alcohol **18** with thionyl chloride, Ph_3PBr_2 (or $\text{CBr}_4\text{-Ph}_3\text{P}$ or PBr_3), or alkyl/aryl sulfonyl chloride produces the corresponding **19** chloride, bromide or sulfonate (Step 4).

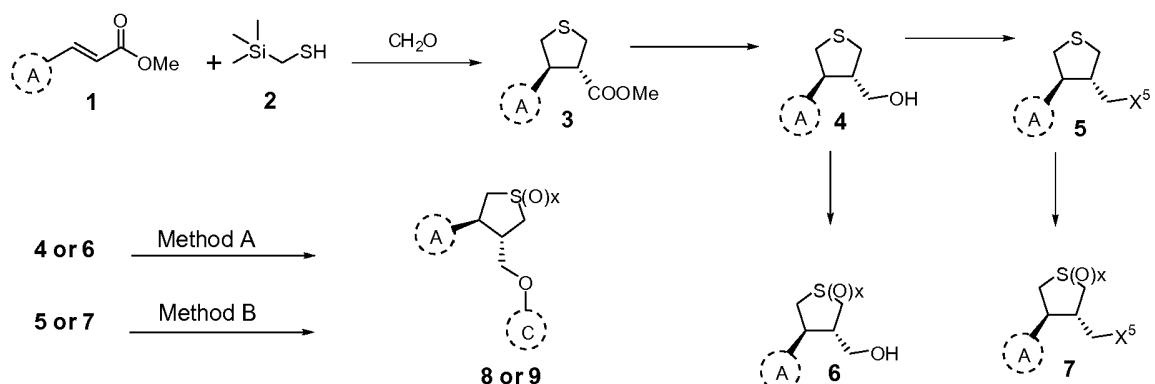
[0118] Alternatively, the double bond of **16** is reduced to give the saturated heterocyclic analog **17** under palladium catalyzed hydrogenation conditions (Step 5). Reduction of the ester group of **17** by LAH or DIBAL yields alcohol **20** (Step 7). Conversion of the alcohol **20** to its chloride, bromide or sulfonate (such as mesylate, tosylate) **21** can be achieved by reacting with thionyl chloride, or Ph_3PBr_2 , or sulfonyl chloride (such as mesyl chloride or tosyl chloride) (Step 8).

[0119] Coupling of the (hetero)cyclic methylene derivatives **18**, **19**, **20** and **21** with hydroxyl (hetero)arylaldehyde derivatives (**3a**/**3b**) by general method A or B affords the corresponding aryloxy/heteroaryloxyether analogs (**4e** and **4f**).

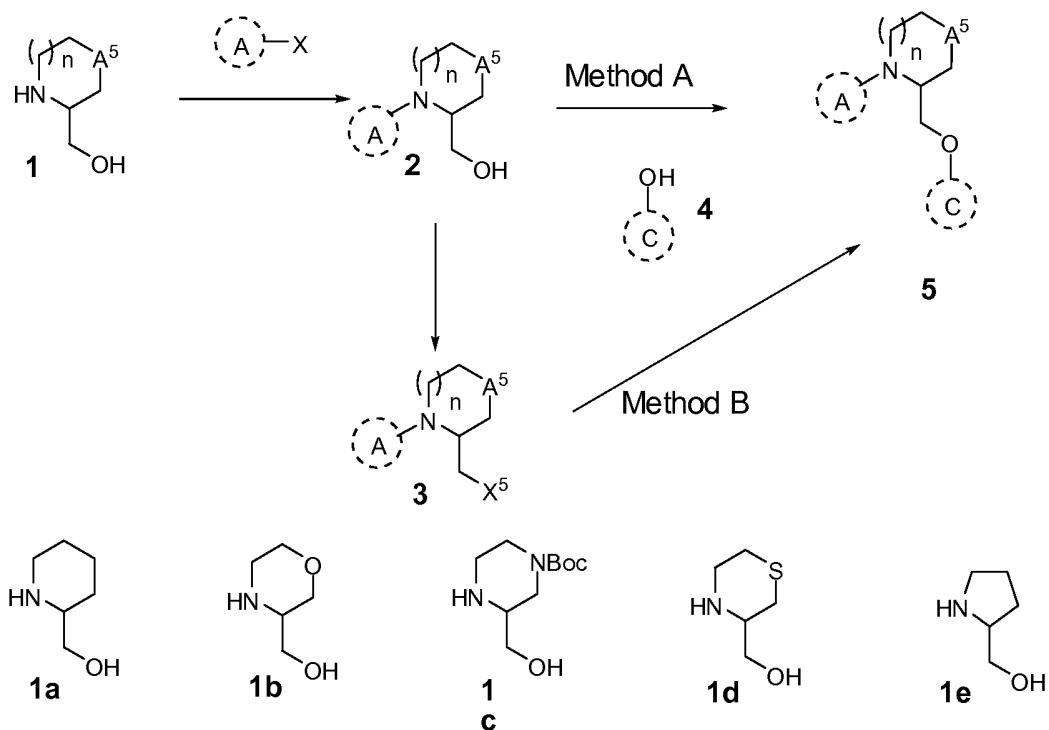
[0120] Chiral pyrrolidine methylene derivatives **25** and **26** can be prepared according to reaction sequence depicted herein. The pyrrolidine ester **24** is produced via a 1,3-dipolar cycloaddition of alkene **22** with azomethine-ylide generated in situ from formaldehyde and amino acid **23** alkene (Step1). Subsequent reduction of the ester to alcohol **24** and further conversion **25** are accomplished by analogous methods described herein. If a chiral auxiliary group such as chiral oxazolidinone derivative **22a** is used, optically active pyrrolidine derivatives **25** and **26** can also be obtained. Coupling of **25** and **26** with hydroxyl (hetero)arylaldehyde derivatives (**3a**/**3b**) by general method A or B affords the corresponding aryloxy/heteroaryloxyether analogs (**4**).



[0121] Separate from the general synthesis of tetrahydrothiophenes (i.e., **20** and **21**, $\text{A}^5=\text{S}$) described herein, also described is a different synthetic approach to this class of analogs.



[0122] Other heterocyclic analogs (compound **5**) with C-N linkage are synthesized by applying Buchwald/Hartwig amination conditions. Many of the cyclic amines (**1**) are available commercially (e.g., **1a**, **1b**, **1c**, **1d**, and **1e**).



[0123] Protected amides of formula $-\text{CONHR}^{95}$ and $-\text{CONHOR}^{95}$ can be converted e.g., hydrolyzed to the corresponding amides according to methods known to the skilled artisan.

Prodrug Synthesis

[0124] 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

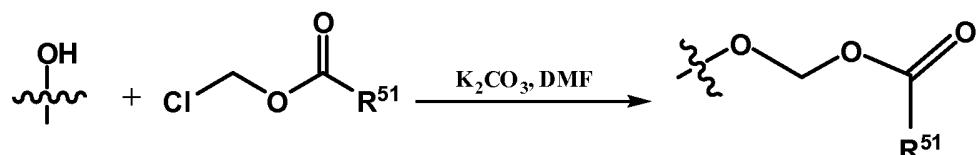
(benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate, and the like (see Nagy et al., 1993, Proc. Natl. Acad. Sci. USA 90:6373-6376) followed by reaction with the free alcohol. Isolation of the ester products can be affected by extraction with an organic solvent, such as ethyl acetate 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 chloride; evaporation of the organic solvent layer; and recrystallization 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.

[0125] 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.

[0126] 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.

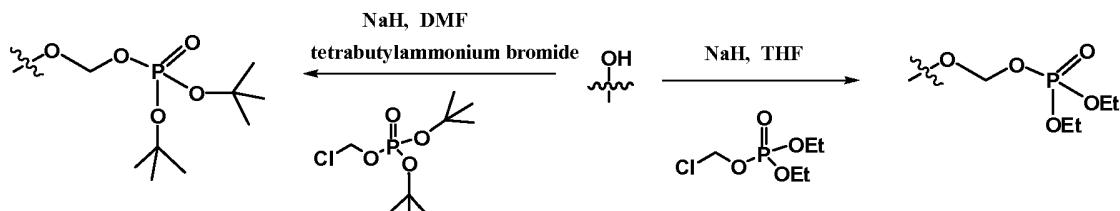
[0127] Various protecting groups and synthetic methods related to them that can be used or adapted to make compounds of the invention can be adapted from the references Testa et al., Hydrolysis in Drug and Prodrug Metabolism, June 2003, Wiley- VCH, Zurich, 419-534 and Beaumont et al., Curr. Drug Metab. 2003, 4:461-85.

[0128] 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.

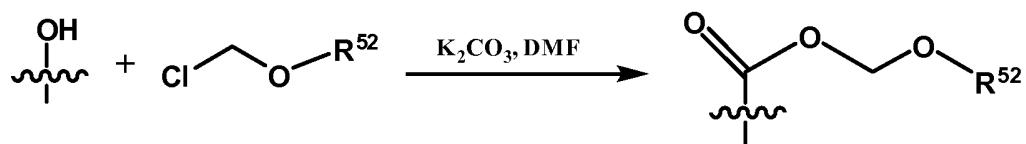


R^{51} is C₁-C₆ alkyl.

[0129] 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.



[0130] Provided herein is a method of synthesizing an alkyloxymethyl version of a prodrug



R^{52} is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, C₃-C₉ heterocyclyl, C₆-C₁₀ aryl, or C₃-C₉ heteroaryl.

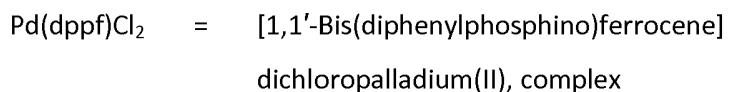
Examples

[0131] 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.

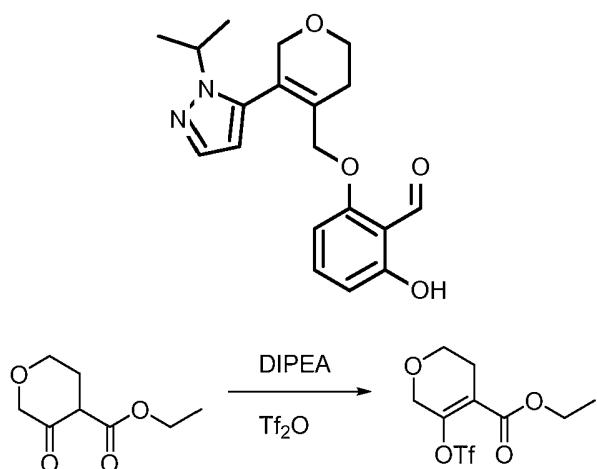
[0132] In the examples below as well as throughout the application, the following abbreviations have the following meanings. If not defined, the terms have their generally accepted meanings.

$^{\circ}\text{C}$	=	degrees Celsius
RT	=	Room temperature
min	=	minute(s)
h	=	hour(s)
μL	=	Microliter

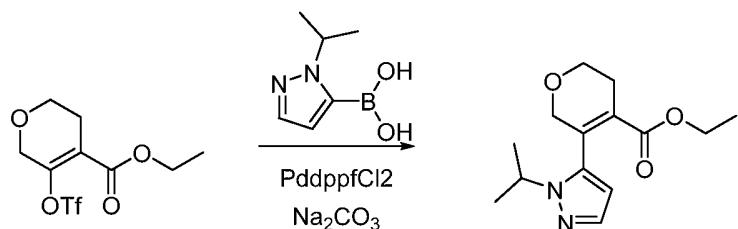
mL	=	Milliliter
mmol	=	Millimole
eq	=	Equivalent
mg	=	Milligram
ppm	=	Parts per million
atm	=	Atmospheric pressure
MS	=	Mass spectrometry
LC-MS	=	Liquid chromatography–mass spectrometry
HPLC	=	High performance liquid chromatography
NMR	=	Nuclear magnetic resonance
Sat.	=	Saturated
MeOH	=	Methanol
EtOH	=	Ethanol
EtOAc	=	Ethyl acetate
Et ₃ N	=	Triethylamine
ACN	=	Acetonitrile
Ac ₂ O	=	Acetic anhydride
Na(OAc) ₃ BH	=	Sodium triacetoxy borohydride
PBr ₃	=	phosphorus tribromide
Ph ₃ P	=	Triphenylphosphine
Ph ₃ PBr ₂	=	Triphenylphosphine dibromide
CBr ₄	=	Tetrabromomethane
DMF	=	N, N-Dimethylformamide
DCM	=	Dichloromethane
LAH/ LiAlH ₄	=	Lithium aluminum hydride
THF	=	Tetrahydrofuran
DIBAL	=	Diisobutylaluminium hydride
DIAD	=	Diisopropyl azodicarboxylate
DEAD	=	Diethyl azodicarboxylate
DIPEA	=	N,N-Diisopropylethylamine
Tf ₂ O	=	Trifluoromethanesulfonic (triflic) anhydride



[0133] Preparation of 2-hydroxy-6-((5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydro-2H-pyran-4-yl)methoxy)benzaldehyde

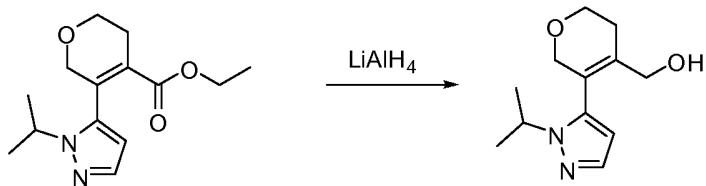


[0134] Step 1: To a solution of ethyl 3-oxotetrahydro-2H-pyran-4-carboxylate (1.0 g, 5.81 mmol) in DCM (30 mL) was added DIPEA (1.22 mL, 6.97 mmol) and Tf_2O (1.08 mL, 6.39 mmol) at -78 °C, then it was warmed up to room temperature and stirred at room temperature for 2 h, the solution was diluted with DCM, washed with Sat. NaHCO_3 , brine, dried and concentrated to give ethyl 5-((trifluoromethyl)sulfonyl)oxy)-3,6-dihydro-2H-pyran-4-carboxylate as crude product (2 g).

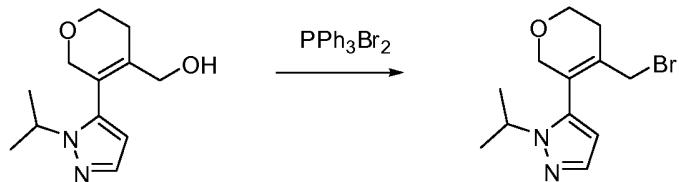


[0135] Step 2: To a solution of ethyl 5-((trifluoromethyl)sulfonyl)oxy)-3,6-dihydro-2H-pyran-4-carboxylate (crude from step 1) and 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.37 g, 5.82 mmol) in dioxane (20 ml) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (430 mg, 0.58 mmol) and Na_2CO_3 (1.85 g, 17.46 mmol) in water (6 mL), the mixture was degassed with N2 for 5 min, and was heated at 100 °C for 15 h, after cooling to room temperature the mixture was diluted with EtOAc and washed with Sat. NaHCO_3 and

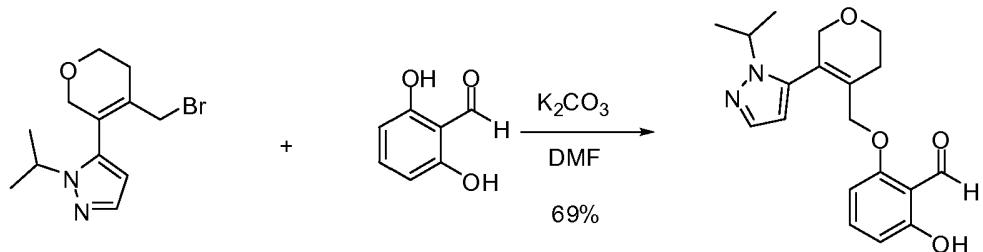
brine, organic layer was combined, dried and concentrated to give crude product, which was purified by column chromatography (Hexanes/EtOAc=3:1) to give ethyl 5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydro-2H-pyran-4-carboxylate (850 mg).



[0136] Step 3: To a solution of ethyl 5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydro-2H-pyran-4-carboxylate (600 mg, 2.27 mmol) in THF (10 mL) was added LiAlH₄ (1M in THF, 2.72 mL, 2.72 mmol) at -20 °C, the reaction was stirred at -20 °C for 30 min, and was quenched with Sat. NH₄Cl, the aqueous layer was extracted with EtOAc, the combined organics were washed with brine, dried and concentrated to give crude oil, which was purified by column (Hexanes/EtOAc= 100:0 to 20:80) to give (5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydro-2H-pyran-4-yl)methanol (500 mg).

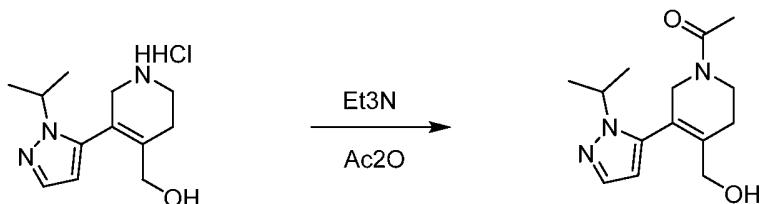
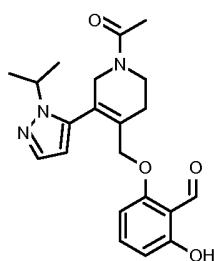


[0137] Step 4: To a solution of (5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydro-2H-pyran-4-yl)methanol (300 mg, 1.35 mmol) in DCM (5 mL) was added dibromotriphenylphosphorane (630 mg, 1.35 mmol) at room temperature, after stirring for 30 min, it was diluted with DCM, organic layer was washed with Sat. NaHCO₃, brine, dried and concentrated to give crude product, which was purified by column(Hexanes/EtOAc= 4:1) to give 5-(4-(bromomethyl)-5,6-dihydro-2H-pyran-3-yl)-1-isopropyl-1H-pyrazole (360 mg).



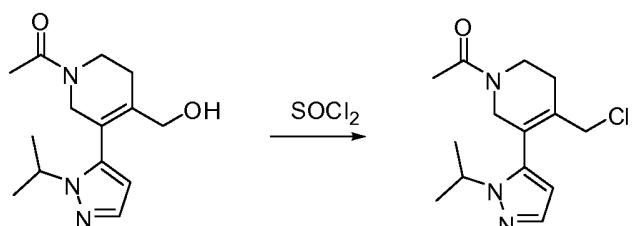
[0138] Step 5: To a solution of 5-(4-(bromomethyl)-5,6-dihydro-2H-pyran-3-yl)-1-isopropyl-1H-pyrazole (110 mg, 0.38 mmol) and 2,6-dihydroxybenzaldehyde (100 mg, 0.76 mmol) in DMF (6 mL) was added K_2CO_3 (110 mg, 0.76 mmol). After stirred at room temperature for 1 h, it was diluted with water and EtOAc, organic layer was separated, and the aqueous layer was extracted with EtOAc. Organic layer was combined, washed with brine, dried and concentrated to give crude product, which was purified by column (Hexanes/EtOAc=1:1) to give 2-hydroxy-6-((5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydro-2H-pyran-4-yl)methoxy)benzaldehyde (90 mg). 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 11.89 (s, 1H), 10.33 (s, 1H), 7.53 (d, J =1.6 Hz, 1H), 7.33 (t, J =8.8 Hz, 1H), 6.51 (d, J =8.8 Hz, 1H), 6.16 (d, J =8.0 Hz, 1H), 6.08 (d, J =2.0 Hz, 1H), 4.40 (dd, J =12.8, 6.4 Hz, 1H), 4.35 (s, 2H), 4.18 (s, 2H), 3.97 (t, J =5.2 Hz, 2H), 2.44 (s, 2H), 1.40 (d, J =6.4 Hz, 6H); MS (ESI) m/z 343.3 $[M+H]^+$.

[0139] Preparation of 2-[[1-acetyl-5-(2-propan-2-ylpyrazol-3-yl)-3,6-dihydro-2H-pyridin-4-yl]methoxy]-6-hydroxybenzaldehyde

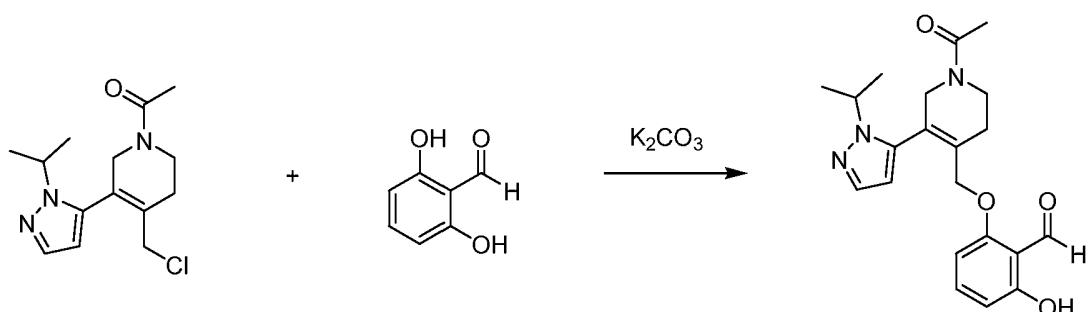


[0140] Step 1: To a solution of (5-(1-isopropyl-1H-pyrazol-5-yl)-1,2,3,6-tetrahydropyridin-4-yl)methanol hydrochloride (110 mg, 0.41 mmol) in DCM (2 mL) at 0 °C was added Et_3N (0.12 mL, 0.82 mmol) and a solution of Ac_2O (0.04 mL, 0.41 mmol) in DCM (0.4 mL), after stirred for 15 min, it was diluted with Sat. NH_4Cl and EtOAc, organic layer was separated and the aqueous layer was further extracted with EtOAc, organic layers were combined, washed with Sat. $NaHCO_3$, brine, dried over Na_2SO_4 , and was concentrated to give 1-(4-

(hydroxymethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihdropyridin-1(2H)-yl)ethan-1-one as crude product.

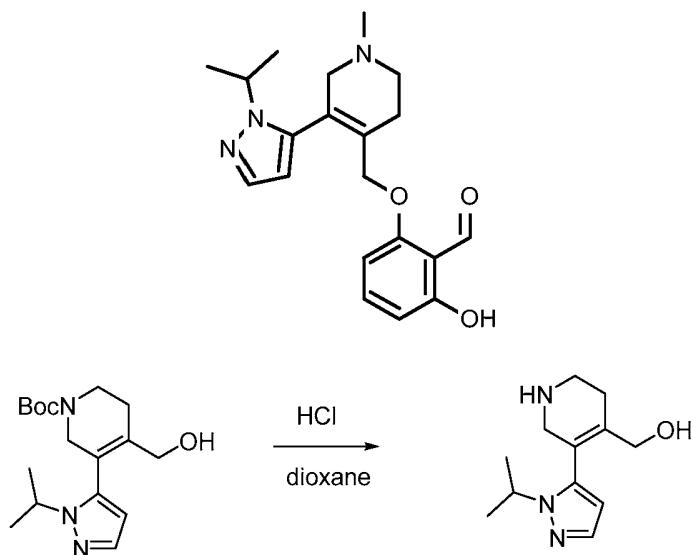


[0141] Step 2: To a solution of 1-(4-(hydroxymethyl)-3-phenyl-5,6-dihdropyridin-1(2H)-yl)ethanone (88 mg, 0.41 mmol) in DCM (2 mL) was added SOCl_2 (0.58 mL, 8.25 mmol). After stirred at RT for 15 min, the mixture was concentrated and dried under high vacuum to give 1-(4-(chloromethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihdropyridin-1(2H)-yl)ethan-1-one as crude product (80 mg).

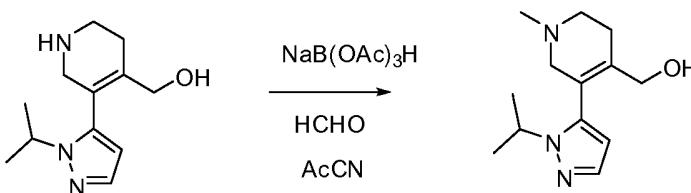


[0142] Step 3: To a suspension of K_2CO_3 (80 mg, 0.56 mmol) and 2,6-dihydroxybenzaldehyde (80 mg, 0.56 mmol) in DMF (2 ml) was added a solution of 1-(4-(chloromethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihdropyridin-1(2H)-yl)ethan-1-one (80 mg, 0.28 mmol) in DMF (2 mL), the mixture was heated at 50 °C for 3 h, cooled to room temperature, and was diluted with EtOAc , organic layer was separated and aqueous layer was extracted with EtOAc . EtOAc layers were combined, washed with Sat. NaHCO_3 , brine, dried over Na_2SO_4 , and was concentrated to give crude oil, which was purified by preparative HPLC (eluted with $\text{ACN}/\text{H}_2\text{O}$) to give 2-((1-acetyl-5-(1-isopropyl-1H-pyrazol-5-yl)-1,2,3,6-tetrahydropyridin-4-yl)methoxy)-6-hydroxybenzaldehyde (9 mg). ^1H NMR (400 MHz, CDCl_3 , NMR shows rotamer exist, only one set of signal was reported) δ (ppm) 11.87 (s, 1H), 10.34 (s, 1H), 7.54 (d, J = 1.6 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.15 (d, J = 8.4 Hz, 1H), 6.11 (d, J = 1.6 Hz, 1H), 4.36 (s, 2H), 4.34 (m, 1H), 4.21 (s, 2H), 3.71 (t, J = 6.0 Hz, 2H), 2.51 (m, 2H), 2.19 (s, 3H), 1.42 (d, J = 6.8 Hz, 6H); MS (ESI) m/z 384.3 $[\text{M}+\text{H}]^+$

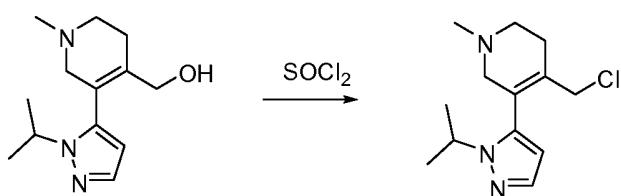
[0143] Preparation of 2-hydroxy-6-[[1-methyl-5-(2-propan-2-ylpyrazol-3-yl)-3,6-dihydro-2H-pyridin-4-yl]methoxy]benzaldehyde



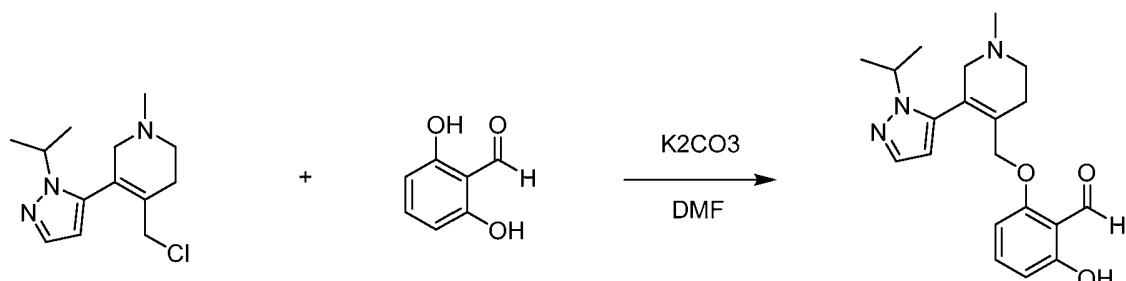
[0144] Step 1: To a solid of tert-butyl 4-(hydroxymethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (150 mg, 0.47 mmol) in round bottom flask was added 4N HCl in dioxane (3 mL) at room temperature, and was stirred for 1 h, then the mixture was concentrated and dried under high vacuum to give (5-(1-isopropyl-1H-pyrazol-5-yl)-1,2,3,6-tetrahydropyridin-4-yl)methanol as HCl salt (120 mg).



[0145] Step 2: To a solution of (5-(1-isopropyl-1H-pyrazol-5-yl)-1,2,3,6-tetrahydropyridin-4-yl)methanol hydrochloride in ACN (3 mL) was added Et₃N followed by formalin. After stirred at room temperature for 10 min, it was added Na(OAc)₃BH and after another 30 min, the mixture was concentrated and pass through a short silica gel column, the column was washed with 10% MeOH in CHCl₃, and then the filtrated was collected and concentrated to give crude product, which was further diluted with EtOAc, filtered to get rid of triethylamine HCl salt, the filtrate was concentrated again to give (5-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)methanol (100 mg).



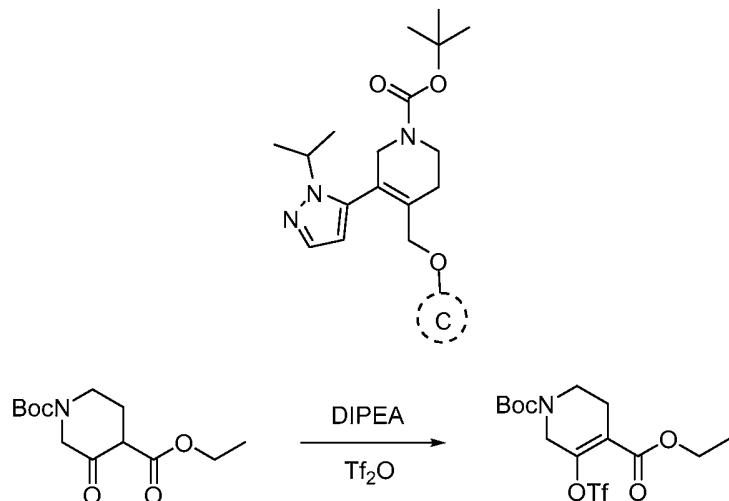
[0146] Step 3: To a solution of (5-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)methanol (100 mg, 0.42 mmol) in DCM (2.5 mL) was added SOCl_2 (0.76 mL, 10.5 mmol) at room temperature and then was stirred at room temperature for 30 min, the mixture was concentrated and diluted with toluene and concentrated, dried under high vacuum to give 4-(chloromethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine as crude product.



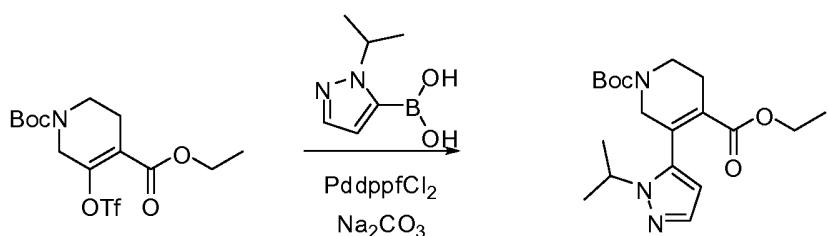
[0147] Step 4: To a suspension of K_2CO_3 (230 mg, 1.68 mmol) and 2,6-dihydroxybenzaldehyde (120 mg, 0.84 mmol) in DMF (2 ml) was added a solution of 4-(chloromethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridine (110 mg, 0.42 mmol) in DMF (3 mL), the mixture was heated at 50 °C for 4 h, cooled to room temperature, and was diluted with EtOAc , organic layer was separated and aqueous layer was extracted with EtOAc . EtOAc layer was combined, washed with Sat. NaHCO_3 , brine, dried over Na_2SO_4 , and was concentrated to give crude oil, which was purified by column (Hexane/ EtOAc = 65:35 followed by DCM/MeOH= 95:5) to give 2-hydroxy-6-((5-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)methoxy)benzaldehyde (44 mg). ^1H NMR (400 MHz, CDCl_3) δ (ppm) 11.89 (s, 1H), 10.34 (s, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.31 (dd, J = 8.4, 7.2 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.16 (d, J = 7.2 Hz, 1H), 6.07 (d, J = 1.6 Hz, 1H), 4.36 (m, 1H), 4.34 (s, 2H), 3.07 (s, 2H), 2.71 (s, 2H), 2.52 (s, 2H), 2.43 (s, 3H), 1.41 (d, J = 6.4 Hz, 6H); MS (ESI) m/z 356.3 $[\text{M}+\text{H}]^+$.

[0148] The following exemplary A-ring and B-ring intermediates may also be incorporated into the compounds of the invention.

[0149] Preparation of:

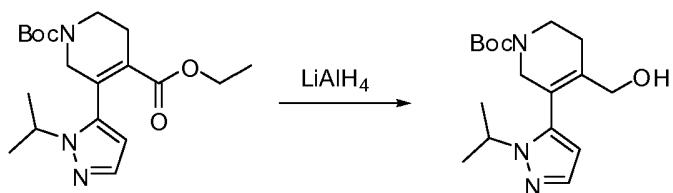


[0150] **Step 1:** To a solution of 1-tert-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (2.0g, 7.37 mmol) in DCM (45 mL) was added DIPEA (1.54 ml, 8.84 mmol) and Tf_2O (1.36 mL, 8.11 mmol) at -78 °C, then the temperature was warmed up to room temperature and the solution was stirred at RT for 1.5 h, the mixture was diluted with DCM (100 mL), organic layer was washed with Sat. NaHCO_3 , brine, dried and concentrated to give 1-(tert-butyl) 4-ethyl 5-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1,4(2H)-dicarboxylate, which was used for next step without purification.

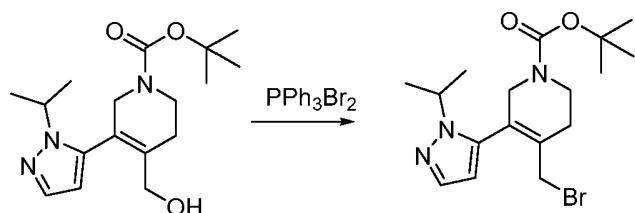


[0151] **Step 2:** To a solution of 1-tert-butyl 4-ethyl 3-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1,4(2H)-dicarboxylate (1.49 g, 3.7 mmol) and (1-isopropyl-1H-pyrazol-5-yl)boronic acid (0.57 g, 3.7 mmol) in dioxane (10 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.27 g, 0.37 mmol) and a solution of sodium carbonate (1.18 g, 11.10) in water (3 ml), the mixture was degassed with N_2 for 5 min, and was heated at 100 °C for 15 h, after cooling to room temperature the mixture was diluted with EtOAc and washed with Sat. NaHCO_3 and brine,

organic layer was combined, dried and concentrated to give crude product, which was purified by column chromatography (Hexanes/EtOAc=3:1) to give desired product 830 mg (62%).

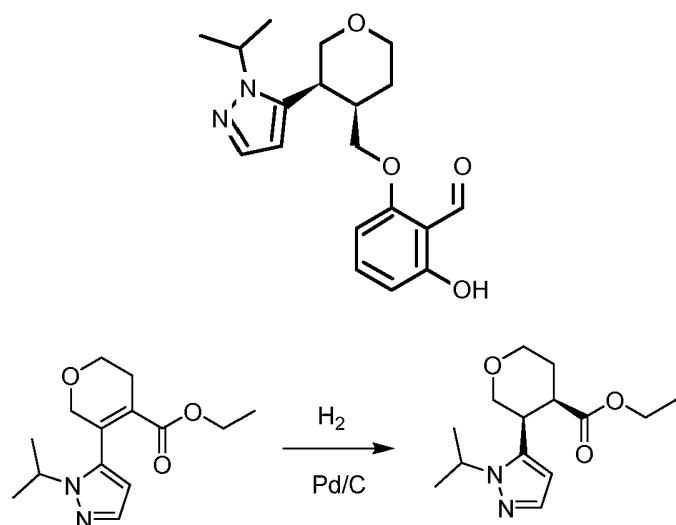


[0152] Step 3: To a solution of 1-(tert-butyl) 4-ethyl 5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydropyridine-1,4(2H)-dicarboxylate (450 mg, 1.24 mmol) in THF (6 mL) was added LiAlH₄ (1M in THF, 1.49 mL, 1.49 mmol) at -20 °C, the reaction was stirred at -20 °C for 30 min, and was quenched with Sat. NH₄Cl, the aqueous layer was extracted with EtOAc, the combined organics were washed with brine, dried and concentrated to give crude oil, which was purified by column (Hexanes/EtOAc= 100:0 to 40:60) to give tert-butyl 4-(hydroxymethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (370 mg, 91%).

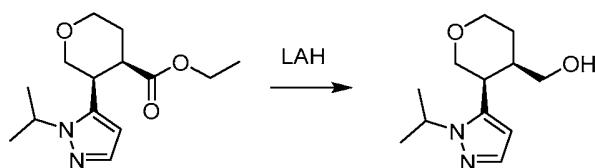


[0153] Step 4: To a solution of give tert-butyl 4-(hydroxymethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (25 mg, 0.08 mmol) in DCM (1 mL) was added triphenylphosphine bromine adduct (40 mg, 0.09 mmol) at room temperature, after stirring for 30 min, it was diluted with DCM, washed with Sat. NaHCO₃, brine, dried and concentrated to give crude product, which was purified by column to give tert-butyl 4-(bromomethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydropyridine-1(2H)-carboxylate (18 mg).

[0154] Preparation of 2-hydroxy-6-[[cis-3-(2-propan-2-ylpyrazol-3-yl)oxan-4-yl]methoxy]benzaldehyde

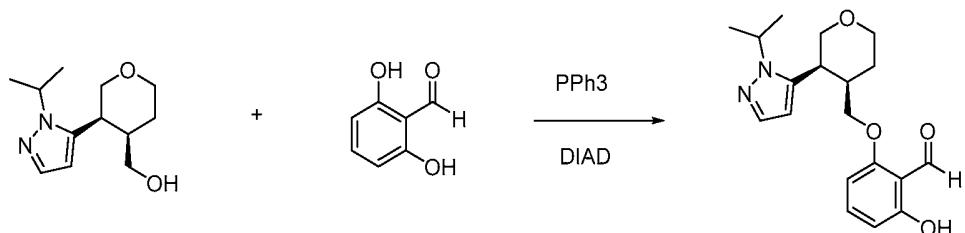


[0155] Step 1: To a solution of ethyl 5-(1-isopropyl-1H-pyrazol-5-yl)-3,6-dihydro-2H-pyran-4-carboxylate (100 mg, 0.38 mmol) in EtOH (2 mL) was added Pd/C (50 mg), then it was charged with H₂ (1atm) and stirred at room temperature for 3 days, Mass spec shows about 50% conversion. The mixture was then added a solution of NH₄CO₂H (200 mg) in water (2 ml) and additional Pd/C, and the mixture was further heated at 75 °C for 1.5 h, after cooled to room temperature, the reaction was diluted with EtOH, Pd/C was filtered off, and the filtrate was concentrated to give crude oil, which was diluted with CHCl₃, organic layer was washed with Sat. NaHCO₃, dried and concentrated to give crude product, which was purified by column (Hexanes/EtOAc=65:35) to give (±) ethyl (3S,4R)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-carboxylate (70 mg).



[0156] Step 2: To a solution of (±) (3S,4R)-ethyl 3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-carboxylate (70 mg, 0.26 mmol) in THF (1.5 mL) at -15 °C was added 1M LiAlH₄ solution in THF (0.34 mL, 0.34 mmol) slowly. After stirred for 30 min, it was quenched with Sat. NH₄Cl; the mixture was extracted with EtOAc. Organic layers were combined, dried and

concentrated to give (\pm) (3S,4R)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-yl)methanol as crude product (60 mg).

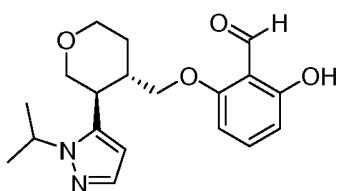


[0157] Step 3: To a solution of (\pm) ((3S, 4R)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-yl)methanol (50 mg, 0.22 mmol) and 2,6-dihydroxybenzaldehyde (60 mg, 0.44 mmol) in THF (1 mL) was added PPh_3 (120 mg, 0.44 mmol) and DIAD (0.09 mL, 0.44 mmol) at 0 °C. After stirred for 30 min, the solution was concentrated and the residue was purified by column (Hexanes/EtOAc=60:40) to give impure product, which was further purified by prep HPLC (eluted with ACN/H₂O) to give (\pm) 2-hydroxy-6-(((3S,4R)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-yl)methoxy)benzaldehyde (6 mg). ¹H NMR (400 MHz, CDCl_3) δ (ppm) 11.90 (s, 1H), 10.36 (s, 1H), 7.79 (s, 1H), 7.50 (d, J =2.0 Hz, 1H), 7.32 (t, J = 8.8 Hz, 1H), 6.52 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 1.6 Hz, 1H), 6.16 (d, J = 8.0 Hz, 1H), 4.46 (m, 1H), 4.13 (dt, J = 11.2, 4.0 Hz, 1H), 3.95 (dd, J = 11.2, 3.2 Hz, 1H), 3.81 (dd, J = 11.6, 3.2 Hz, 1H), 3.73 (dd, J = 9.2, 5.6 Hz, 1H), 3.65 (dt, J = 11.6, 3.2 Hz, 1H), 3.57 (t, J = 8.8 Hz, 1H), 3.28 (d, J = 4.0 Hz, 1H), 2.56 (m, 1H), 1.87 (m, 1H), 1.58 (m, 1H), 1.31 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 7.6 Hz, 3H); MS (ESI) m/z 334.3 [M+H]⁺.

[0158] Step 5: To a solution of tert-butyl 4-(bromomethyl)-5-(1-isopropyl-1H-pyrazol-5-yl)-

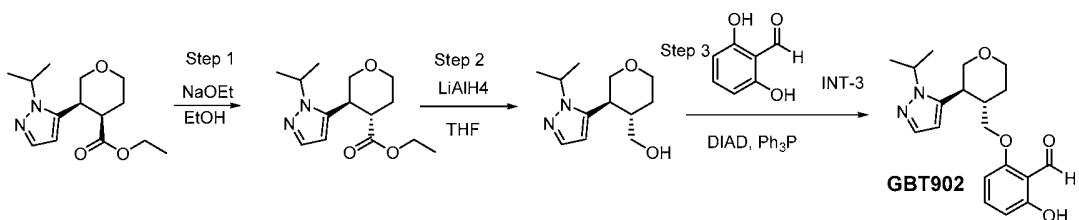
3,6-dihydropyridine-1(2H)-carboxylate (18 mg, 0.05 mmol) and 10 mg, 0.06 mmol) in DMF (1 mL) is added K_2CO_3 (14 mg, 0.1 mmol). After stirring at room temperature for 1 h, it is diluted with water and EtOAc, organic layer is separated, and the aqueous layer is extracted with EtOAc, organic layer is combined, washed with brine, dried and concentrated to give crude product, which is purified by column (Hexanes/EtOAc=2:1).

GBT902



2-hydroxy-6-(((3S,4S)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-yl)methoxy)benzaldehyde

[0159] **GBT902- (\pm) 2-hydroxy-6-(((3S, 4S)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-yl)methoxy)benzaldehyde.** The compound was synthesized in three steps starting from (\pm) (3S,4R)-ethyl 3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-carboxylate.



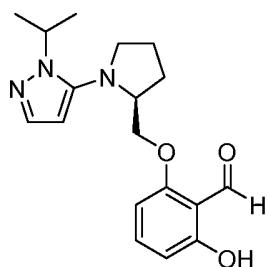
[0160] Step 1: To EtOH (2 mL) in round bottom flask was added NaH (65% dispersion in mineral oil, 60 mg, 1.36 mmol), after stirring for 5 min, the mixture was added a solution of (\pm) (3S,4R)-ethyl 3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-carboxylate (297 mg, 1.13 mmol) in EtOH. The mixture was heated at 80 °C for 3 h, cooled and diluted with EtOAc and Sat. NH4Cl, organic layer was separated and the aqueous layer was extracted with EtOAc, organic layer was combined, dried and concentrated to give crude product, which was purified by column (Hexanes/EtOAc=2:1) to give ethyl (3S,4S)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-carboxylate 190 mg.

[0161] Step 2: To a solution of (3S,4S)-ethyl 3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-carboxylate (190 mg, 0.71 mmol) in THF (3 mL) at -20 °C was added LiAlH4 (1M in THF, 0.89 mL, 0.89 mmol). After stirring at -20 °C for 15 min, the reaction was quenched with Sat. NH4Cl, extracted with EtOAc, organic layer was combined, washed with brine, dried and concentrated to give ((3S,4S)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-yl)methanol as crude product (160 mg).

[0162] Step 3: To a solution of ((3S,4S)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-yl)methanol (160 mg, 0.71 mmol) in THF (2 mL) was added 2,6-dihydroxybenzaldehyde (0.15 g, 1.06 mmol) at room temperature, then it was cooled to 0 °C and added DIAD (0.20 mL, 1.06 mmol). After stirring for 1 h, the mixture was

concentrated and subjected to column chromatography to (\pm) 2-hydroxy-6-((3S, 4S)-3-(1-isopropyl-1H-pyrazol-5-yl)tetrahydro-2H-pyran-4-yl)methoxy)benzaldehyde 104 mg (Hexanes/EtOAc=100:0 to 65:35 to 55:45) to give ^1H NMR (400 MHz, Chloroform-*d*) δ 11.90 (d, *J* = 0.4 Hz, 1H), 10.35 (d, *J* = 0.6 Hz, 1H), 7.51 (dt, *J* = 2.0, 0.6 Hz, 1H), 7.30 (t, *J* = 8.5 Hz, 1H), 6.51 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.16 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.06 (dd, *J* = 1.9, 0.4 Hz, 1H), 4.47 (p, *J* = 6.6 Hz, 1H), 4.21 – 4.07 (m, 1H), 3.99 – 3.84 (m, 2H), 3.80 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.65 – 3.53 (m, 1H), 3.36 (t, *J* = 11.3 Hz, 1H), 3.09 (td, *J* = 11.0, 4.4 Hz, 1H), 2.29 – 2.21 (m, 1H), 1.95 – 1.85 (m, 2H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.33 – 1.21 (m, 3H). MS (M+H)⁺ found for C₁₉H₂₄N₂O₄: 345.3.

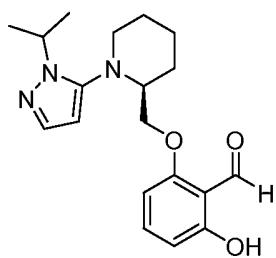
GBT906



(*S*)-2-hydroxy-6-((1-(1-isopropyl-1H-pyrazol-5-yl)pyrrolidin-2-yl)methoxy)benzaldehyde

[0163] GBT906 - Preparation of (*S*)-2-hydroxy-6-((1-(1-isopropyl-1H-pyrazol-5-yl)pyrrolidin-2-yl)methoxy)benzaldehyde. The compound was prepared from (*S*)-pyrrolidin-2-ylmethanol and 5-iodo-1-isopropyl-1H-pyrazole according to scheme 1, reaction steps 3 and 4. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.92 (s, 1H), 10.07 (d, *J* = 0.6 Hz, 1H), 7.45 (dd, *J* = 2.0, 0.5 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 6.49 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.24 (dd, *J* = 8.3, 0.8 Hz, 1H), 5.91 – 5.81 (m, 1H), 4.70 – 4.55 (m, 1H), 3.97 (dd, *J* = 9.3, 4.8 Hz, 1H), 3.88 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.75 (dd, *J* = 7.6, 6.6, 5.5, 4.8 Hz, 1H), 3.48 – 3.37 (m, 1H), 2.94 (dt, *J* = 9.2, 7.2 Hz, 1H), 2.31 – 2.15 (m, 1H), 2.09 – 1.81 (m, 3H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H). MS (M+H)⁺ found for C₁₈H₂₃N₃O₃: 330.3.

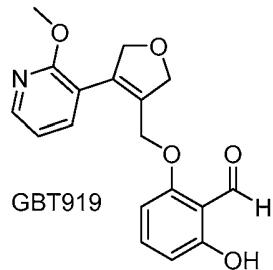
GBT918



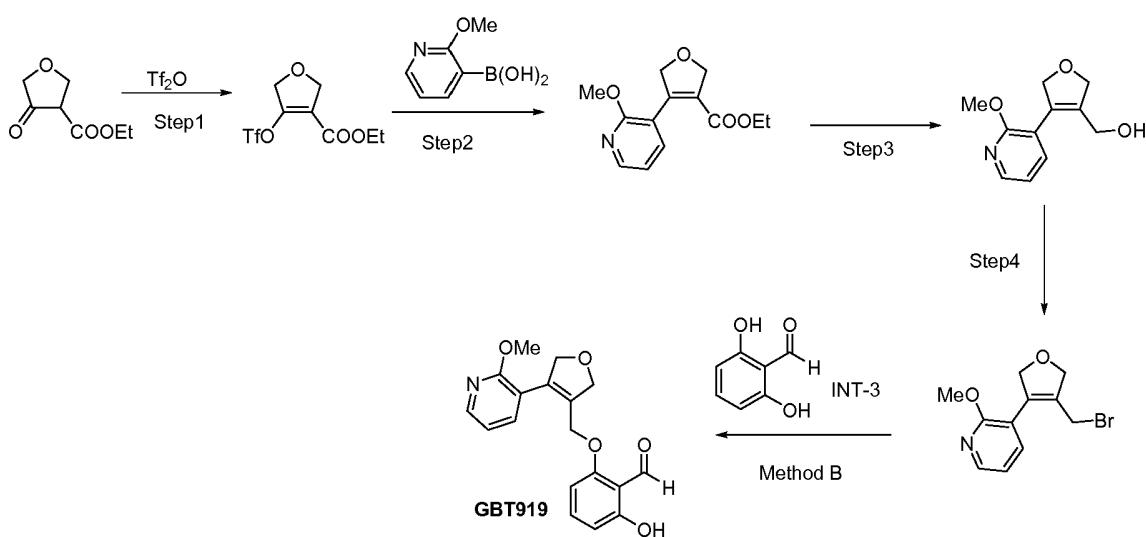
(S)-2-hydroxy-6-((1-(1-isopropyl-1H-pyrazol-5-yl)piperidin-2-yl)methoxy)benzaldehyde

[0164] GBT918 - Preparation of (S)-2-hydroxy-6-((1-(1-isopropyl-1H-pyrazol-5-yl)piperidin-2-yl)methoxy)benzaldehyde. The compound was prepared from (S)-piperidin-2-ylmethanol hydrochloride and 5-iodo-1-isopropyl-1H-pyrazole according to scheme 1, reaction steps 3 and 4. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.88 (d, *J* = 0.4 Hz, 1H), 10.31 (d, *J* = 0.6 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.36 – 7.28 (m, 1H), 6.49 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.09 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.06 (d, *J* = 2.1 Hz, 1H), 4.84 (hept, *J* = 6.7 Hz, 1H), 3.87 – 3.75 (m, 2H), 3.17 (dq, *J* = 8.4, 3.8 Hz, 1H), 3.02 (dt, *J* = 11.8, 3.8 Hz, 1H), 2.75 (td, *J* = 11.2, 3.4 Hz, 1H), 2.03 – 1.86 (m, 2H), 1.71 (dd, *J* = 16.8, 15.4, 11.8, 7.2 Hz, 3H), 1.59 – 1.45 (m, 1H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.32 (d, *J* = 6.7 Hz, 3H). MS (M+H)⁺ found for C₁₉H₂₅N₃O₃: 344.4.

GBT919



[0165] GBT919- 2-hydroxy-6-((4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-yl)methoxy)benzaldehyde. The compound was synthesized according to scheme 2 in five steps starting from ethyl 4-oxotetrahydrofuran-3-carboxylate using reaction steps 1, 2, 3, 4 and method B.



[0166] Step 1: To a solution of ethyl 4-oxotetrahydrofuran-3-carboxylate (1.13 g, 7.15 mmol) in DCM (20 ml) was added DIPEA (1.38 mL, 7.87 mmol) and Tf_2O (1.20 mL, 7.15 mmol) at -78°C , then it was warmed up to room temperature and was further stirred for 15 h, the mixture was diluted with DCM, washed with Sat. NaHCO_3 , brine, dried and concentrated to give ethyl 4-((trifluoromethyl)sulfonyl)oxy)-2,5-dihydrofuran-3-carboxylate as crude product, which was used for next step without purification (2.3 g).

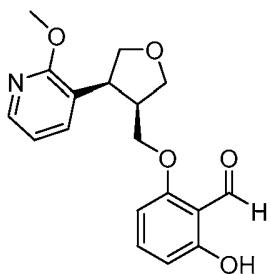
[0167] Step 2: To a solution of ethyl 4-((trifluoromethyl)sulfonyl)oxy)-2,5-dihydrofuran-3-carboxylate (2.3 g) and (2-methoxypyridin-3-yl)boronic acid (1.09 g, 7.15 mmol) in Dioxane (20 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (530 mg, 0.72 mmol) and a solution of Na_2CO_3 (2.27 g, 21.45 mmol) in water (10 mL), the mixture was degassed and heated at 100°C for 15 h, the solution was diluted with EtOAc, organic layer was washed with water, brine, dried over MgSO_4 and was concentrated to give crude product, which was purified by column chromatography to give ethyl 4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-carboxylate (1.1 g).

[0168] Step 3: To a solution of ethyl 4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-carboxylate (146 mg, 0.60 mmol) in THF (2 ml) at -20°C was added 1M LiAlH_4 in THF (0.72 mL, 0.72 mmol). After stirred for 20 min, it was quenched with Sat. NH_4Cl , the mixture was extracted with EtOAc (3X), organic layers were combined, dried over MgSO_4 and was concentrated to give (4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-yl)methanol as crude product (120 mg), which was used without purification in next step.

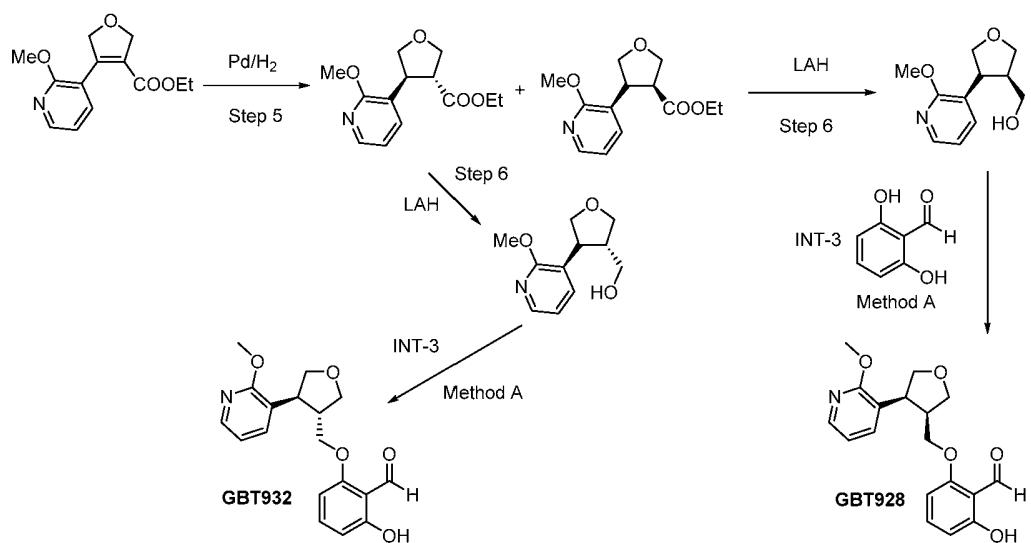
[0169] Step 4: To a solution of (4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-yl)methanol (120 mg, 0.58 mmol) in DCM (2 mL) was added PPh_3Br_2 (300 mg, 0.72 mmol). After stirred at room temperature for 30 min, it was diluted with DCM and washed with Sat. NaHCO_3 , brine, dried over MgSO_4 and concentrated to give crude product, which was purified by column chromatography to give 3-(4-(bromomethyl)-2,5-dihydrofuran-3-yl)-2-methoxypyridine (62 mg).

[0170] Method B: To a solution of 3-(4-(bromomethyl)-2,5-dihydrofuran-3-yl)-2-methoxypyridine (62 mg, 0.22 mmol) and 2,6-dihydroxybenzaldehyde (60 mg, 0.44 mmol) in DMF (1 mL) was added K_2CO_3 (90 mg, 0.66 mmol). After stirred at room temperature for 30 min, the mixture was added water, extracted with EtOAc (3X), organic layers were combined, washed with brine, dried and concentrated to give crude product, which was purified by column chromatography to give 2-hydroxy-6-((4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-yl)methoxy)benzaldehyde (47 mg). ^1H NMR (400 MHz, Chloroform-*d*) δ 11.93 (s, 1H), 10.20 (d, *J* = 0.6 Hz, 1H), 8.16 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.42 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 6.96 – 6.87 (m, 1H), 6.52 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.24 (dd, *J* = 8.3, 0.8 Hz, 1H), 5.00 (ddq, *J* = 4.9, 2.2, 1.2 Hz, 2H), 4.97 – 4.90 (m, 2H), 4.73 – 4.67 (m, 2H), 3.94 (s, 3H). MS(M-H) found for C₁₈H₁₇NO₅: 326.2.

GBT928



[0171] **GBT928- 2-hydroxy-6-((3S,4S)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-yl)methoxybenzaldehyde.** The compound was synthesized in three steps according to scheme 2 starting from ethyl 4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-carboxylate using reaction steps 5, 6 and method A.



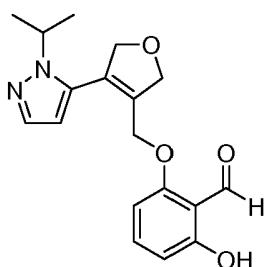
[0172] Step 5: To a solution of ethyl 4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-carboxylate (500 mg, 1 mmol) in EtOH (3 mL) was added Pd/C (50 mg), charged with H₂ (1 atm). After stirred for 24 h, Pd/C was filtered off and the filtrate was concentrated to give crude product, which was purified by column chromatography to give (\pm) ethyl (3*S*,4*S*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-carboxylate (140 mg) and (\pm) ethyl (3*R*,4*S*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-carboxylate (100 mg).

[0173] Step 6: To a solution of (3*S*,4*S*)-ethyl 4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-carboxylate (140 mg) in THF (2 mL) was added LiAlH₄ in THF at -20 °C, then after 30 min, it was quenched with Sat. NH₄Cl, extracted with EtOAc, organic layers were combined, washed with brine, dried and concentrated to give ((3*R*,4*S*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-yl)methanol as crude oil 120 mg.

[0174] Method A: To a solution of ((3*R*,4*S*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-yl)methanol (120 mg, 0.57 mmol) and 2,6-dihydroxybenzaldehyde (0.10 g, 0.71 mmol) in THF (1mL) was added PPh₃ (0.22 g, 0.85 mmol) and DIAD (0.17 mL, 0.85 mmol) at room temperature, after stirred for 1 h, it was concentrated to give drude oil, which was purified by column chromatography followed by preparative HPLC to give 2-hydroxy-6-(((3*S*,4*S*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-yl)methoxy)benzaldehyde 6 mg. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.90 (s, 1H), 10.12 (t, *J* = 0.5 Hz, 1H), 8.04 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.52 (ddd, *J* = 7.3, 1.8, 0.6 Hz, 1H), 7.29 (t, *J* = 8.4 Hz, 1H), 6.85 (ddd, *J* = 7.4, 5.0, 0.5 Hz, 1H), 6.46 (dq, *J* = 8.5, 0.6 Hz, 1H), 6.06 (dd, *J* = 8.3, 0.8 Hz, 1H), 4.23 – 4.12 (m, 3H), 3.92 (d, *J* = 0.4 Hz,

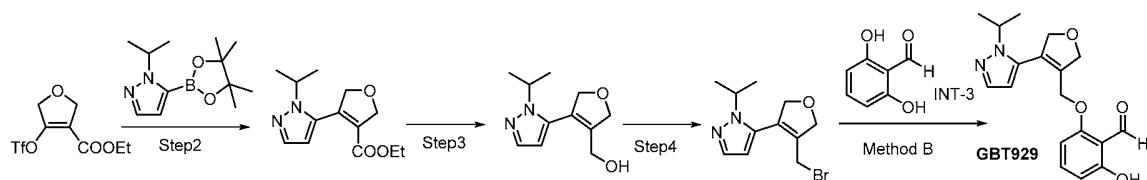
3H), 3.90 – 3.77 (m, 3H), 3.65 (dd, J = 9.3, 7.7 Hz, 1H), 3.20 (qt, J = 7.6, 6.2 Hz, 1H). MS found for C₁₈H₁₉NO₅: 330.3.

GBT929



2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydrofuran-3-yl)methoxy)benzaldehyde

[0175] GBT929- 2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydrofuran-3-yl)methoxy)benzaldehyde. The compound was synthesized according to scheme 2 in four steps starting from ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydrofuran-3-carboxylate using reaction steps 2, 3, 4 and method B



[0176] Step 2: To a solution of ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydrofuran-3-carboxylate (2.76 g, 9.5 mmol) and 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.24 g, 9.50 mmol) in Dioxane (20 mL) was added Pd(dppf)Cl₂ (700 mg, 0.95 mmol) and a solution of Na₂CO₃ (3.02 g, 28.50 mmol) in water (10 mL), the mixture was degassed and heated at 100 °C for 15 h, the solution was diluted with EtOAc, organic layer was washed with water, brine, dried over MgSO₄ and was concentrated to give crude product, which was purified by column chromatography (hexanes/EtOAc=3:1) to give ethyl 4-(2-methoxypyridin-3-yl)-2,5-dihydrofuran-3-carboxylate (900 mg).

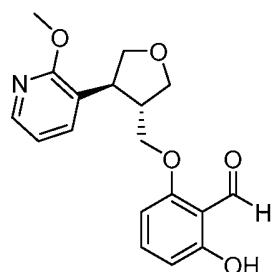
[0177] Step 3: To a solution of ethyl 4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydrofuran-3-carboxylate (250 mg, 1 mmol) in THF (3 mL) at -20 °C was added LiAlH₄ (1M in THF, 1.2 mL, 1.2 mmol). After stirred for 20 min, it was quenched with Sat. NH₄Cl and was extracted with EtOAc, organic layers were combined, washed with brine, dried over MgSO₄ and was

concentrated to give (4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydrofuran-3-yl)methanol as crude product (210 mg).

[0178] Step 4: To a solution of (4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydrofuran-3-yl)methanol (210 mg, 1 mmol) in DCM (3 mL) was added PPh_3Br_2 (420 mg, 1 mmol) at room temperature, after stirred for 20 min, it was diluted with DCM, organic layer was washed with Sat. NaHCO_3 , brine, dried over MgSO_4 and was concentrated to give crude product, which was purified by column chromatography (Hexanes/EtOAc=3:1) to give 5-(4-(bromomethyl)-2,5-dihydrofuran-3-yl)-1-isopropyl-1H-pyrazole (110 mg).

[0179] Method B: To a solution of 5-(4-(bromomethyl)-2,5-dihydrofuran-3-yl)-1-isopropyl-1H-pyrazole (110 mg, 0.41 mmol) in DMF (2 mL) was added K_2CO_3 (170 mg, 1.23 mmol) and 2,6-dihydroxybenzaldehyde (0.11 g, 0.82 mmol) at room temperature, after stirred for 30 min, it was diluted with water and EtOAc, EtOAc layer was separated and the aqueous layer was extracted with EtOAc, organic layers were combined, washed with brine, dried and concentrated to give crude product, which was purified by column (Hexanes/EtOAc=2:1) to give 2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydrofuran-3-yl)methoxy)benzaldehyde (101 mg). ^1H NMR (400 MHz, Chloroform-*d*) δ 11.93 (d, *J* = 0.4 Hz, 1H), 10.23 (d, *J* = 0.6 Hz, 1H), 7.57 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.35 (t, *J* = 8.5, 1H), 6.55 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.23 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.14 (d, *J* = 1.8 Hz, 1H), 4.97 (dt, *J* = 4.9, 3.3 Hz, 2H), 4.93 – 4.86 (m, 2H), 4.70 – 4.65 (m, 2H), 4.44 – 4.32 (m, 1H), 1.67 – 1.41 (m, 6H). MS found for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$: 329.3.

GBT932

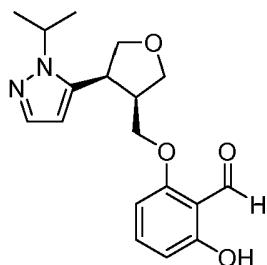


[0180] GBT932- 2-hydroxy-6-((3*S*,4*R*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-yl)methoxy)benzaldehyde. The compound was synthesized in two steps starting from (3*S*,4*S*)-ethyl 4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-carboxylate using reaction steps 6 and method A.

[0181] Step 6: To a solution of (3*S*,4*S*)-ethyl 4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-carboxylate (100 mg, 0.40 mmol) in THF (2 mL) was added LiAlH₄ (1M in THF, 0.48 mL, 0.48 mmol) at -20 °C, after stirred for 30 min, it was quenched with Sat. NH₄Cl, extracted with EtOAc, organic layers were combined, washed with brine, dried over MgSO₄, and was concentrated to give ((3*S*,4*S*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-yl)methanol as crude oil 80 mg.

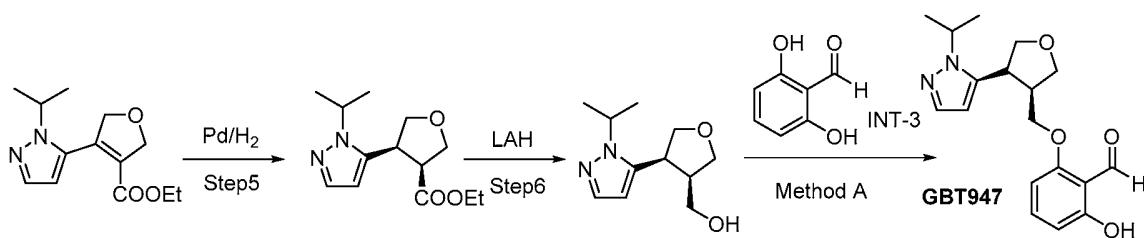
[0182] Method A: To a solution of ((3*R*,4*S*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-yl)methanol (80 mg, 0.40 mmol) and 2,6-dihydroxybenzaldehyde (0.07 g, 0.52 mmol) in THF (1mL) was added PPh₃ (0.16 g, 0.60 mmol) and DIAD (0.12 mL, 0.60 mmol) at room temperature, after stirred for 1 h, it was concentrated to give crude oil, which was purified by column chromatography to give 2-hydroxy-6-((3*S*,4*R*)-4-(2-methoxypyridin-3-yl)tetrahydrofuran-3-yl)methoxy)benzaldehyde 20 mg. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.93 (d, *J* = 0.3 Hz, 1H), 10.13 (d, *J* = 0.6 Hz, 1H), 8.08 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.3, 1.8, 0.5 Hz, 1H), 7.43 – 7.32 (m, 1H), 6.93 – 6.83 (m, 1H), 6.52 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.33 (dd, *J* = 8.3, 0.8 Hz, 1H), 4.20 (ddd, *J* = 8.7, 7.6, 5.2 Hz, 2H), 4.14 – 4.03 (m, 2H), 3.94 (s, 3H), 3.92 – 3.80 (m, 2H), 3.52 (q, *J* = 7.1 Hz, 1H), 2.93 (dq, *J* = 7.4, 6.6 Hz, 1H). MS found for C₁₈H₁₉NO₅: 330.3.

GBT947



2-hydroxy-6-((3*S*,4*S*)-4-(1-isopropyl-1*H*-pyrazol-5-yl)tetrahydrofuran-3-yl)methoxy)benzaldehyde

[0183] **GBT947- 2-hydroxy-6-((3*S*,4*S*)-4-(1-isopropyl-1*H*-pyrazol-5-yl)tetrahydrofuran-3-yl)methoxy)benzaldehyde.** The compound was synthesized according scheme 2 in three steps starting from ethyl 4-(1-isopropyl-1*H*-pyrazol-5-yl)-2,5-dihydrofuran-3-carboxylate using reaction steps 5, 6 and method A.

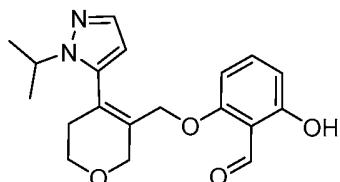


[0184] Step 5: To a solution of ethyl 4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydrofuran-3-carboxylate (325 mg, 1.32 mmol) in EtOH (4 mL) was added Pd/C (150 mg), then it was charged with H₂ (1atm) and then stirred at room temperature for 3 h, H₂ balloon was removed and the mixture was added NH₄CO₂H in water (1 mL) and was heated at 75 °C for 3 h, the mixture was cooled and diluted with EtOAc and water, aqueous layer was separated and extracted with EtOAc, organic layers were combined, washed with brine, dried over MgSO₄ and concentrated to give crude oil, which was purified by column (Hexanes/EtOAc=60:40) to give ethyl (3S,4S)-4-(1-isopropyl-1H-pyrazol-5-yl)tetrahydrofuran-3-carboxylate (216 mg).

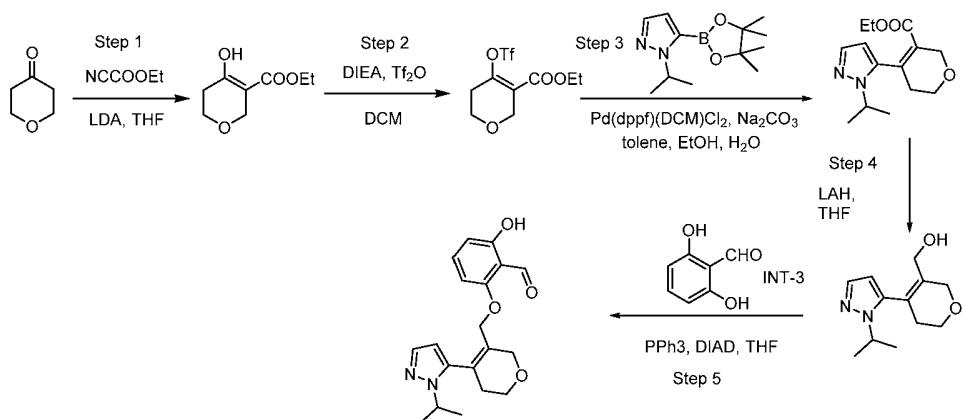
[0185] Step 6: To a solution of (4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydrofuran-3-yl)methanol (216 mg, 0.87 mmol) in THF (4 mL) at -20 °C was added LiAlH₄ (1M in THF, 1.04 mL, 1.04 mmol). After stirred for 20 min, it was quenched with Sat. NH₄Cl, aqueous layer was extracted with EtOAc, organic layers were combined, washed with brine, dried and concentrated to give ((3R,4S)-4-(1-isopropyl-1H-pyrazol-5-yl)tetrahydrofuran-3-yl)methanol as crude oil (180 mg).

[0186] Method A; To a solution of ((3R,4S)-4-(1-isopropyl-1H-pyrazol-5-yl)tetrahydrofuran-3-yl)methanol (180 mg, 0.86 mmol) and 2,6-dihydroxybenzaldehyde (150 mg, 1.12 mmol) in THF (1.6 mL) was added PPh₃ (340 mg, 1.29 mmol) and DIAD (0.25 mL, 1.29 mmol) at 0 °C, then it was stirred at room temperature for 1 h, and was concentrated and purified by column (Hexanes/EtOAc = 60:40) to give 2-hydroxy-6-(((3S,4S)-4-(1-isopropyl-1H-pyrazol-5-yl)tetrahydrofuran-3-yl)methoxy)benzaldehyde 82 mg. ¹H NMR (400 MHz, Chloroform-d) δ 11.88 (d, *J* = 0.4 Hz, 1H), 10.27 (t, *J* = 0.5 Hz, 1H), 7.50 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.35 (t, *J* = 8.5, 1H), 6.51 (dq, *J* = 8.5, 0.6 Hz, 1H), 6.10 (ddt, *J* = 5.4, 3.5, 0.6 Hz, 1H), 4.53 (h, *J* = 6.5 Hz, 1H), 4.29 – 4.22 (m, 1H), 4.19 (dd, *J* = 8.9, 7.1 Hz, 1H), 4.04 (dd, *J* = 8.6, 6.5 Hz, 1H), 3.94 (dd, *J* = 8.9, 5.9 Hz, 1H), 3.79 – 3.69 (m, 2H), 3.60 (dd, *J* = 9.3, 6.2 Hz, 1H), 3.02 (dtd, *J* = 13.6, 7.7, 6.1 Hz, 2H), 1.46 (dd, *J* = 14.1, 6.6 Hz, 6H). MS found for C₁₈H₂₂N₂O₄: 331.3.

GBT966



[0187] **GBT966- 2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)-5,6-dihydro-2H-pyran-3-yl)methoxy)benzaldehyde.** The compound was synthesized in five steps starting from oxan-4-one.



[0188] **Step 1:** Into a 250-mL round-bottom flask, was placed a solution of oxan-4-one (5.0 g, 49.94 mmol, 1.00 equiv) in tetrahydrofuran (60 mL). This was followed by the addition of LDA (newly prepared from diisopropylamine and BuLi) (1.20 equiv) dropwise with stirring at -78 °C. The mixture was stirred for 1 h at 0 °C. HMPA (9.8 g, 54.69 mmol, 1.10 equiv) was then added to the reaction dropwise at -78 °C. The mixture was stirred for another 15 min at the same temperature. 2-Ethoxy-2-oxoacetonitrile (5 g, 50.46 mmol, 1.01 equiv) was then added to the reaction dropwise at -78 °C. The resulting solution was stirred for 2 h at 0 °C, and then it was quenched with 50 mL of water. The resulting mixture was concentrated under vacuum, and then it was extracted with EA (50 mL x 3). The combined organic layers were washed with 2x80 mL of water and 1x80 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:30) as eluent to yield 1.82 g (21%) of ethyl 4-oxooxane-3-carboxylate as a colorless oil.

[0189] Step 2: Into a 50-mL round-bottom flask, was placed a solution of ethyl 4-hydroxy-5,6-dihydro-2H-pyran-3-carboxylate (570 mg, 3.31 mmol, 1.00 equiv) and DIEA (2.5 mL, 5.00 equiv) in dichloromethane (20 mL). Tf₂O (1.0 mL, 2.00 equiv) was added to the reaction dropwise at 0 °C. The resulting solution was stirred for 1 h at 0 °C and for another 2 h at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 2x40 mL of ethyl acetate, and the combined organic layers were washed with 3x20 mL of water and 1x20 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:25) as eluent to yield 0.67 g (67%) of ethyl 4-[(trifluoromethane)sulfonyloxy]-5,6-dihydro-2H-pyran-3-carboxylate as a light yellow oil.

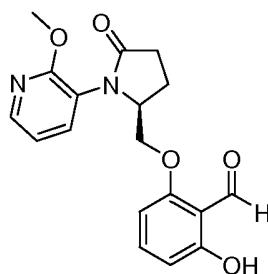
[0190] Step 3: Into a 50-mL round-bottom flask, was placed a solution of ethyl 4-[(trifluoromethane)sulfonyloxy]-5,6-dihydro-2H-pyran-3-carboxylate (540 mg, 1.77 mmol, 1.00 equiv), 1-(propan-2-yl)-5-(tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (543 mg, 2.30 mmol, 1.30 equiv) in a solvent mixture of toluene (15.0 mL), aqueous solution of sodium carbonate (2M) (5.0 mL) and ethanol (5.0 mL). This was followed by the addition of Pd(dppf)Cl₂CH₂Cl₂ (115 mg, 0.08 equiv). The resulting solution was stirred for 4 h at 100 °C under N₂. The reaction was then quenched with 15 mL of water. The resulting solution was extracted with 3x30 mL of ethyl acetate. The combined organic layers were washed with 2x50 mL of water and 1x50 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:15-1:6) as eluent to yield 372 mg (79%) of ethyl 4-[1-(propan-2-yl)-1H-pyrazol-5-yl]-5,6-dihydro-2H-pyran-3-carboxylate as a light yellow oil.

[0191] Step 4: Into a 50-mL round-bottom flask, was placed a solution of ethyl 4-[1-(propan-2-yl)-1H-pyrazol-5-yl]-5,6-dihydro-2H-pyran-3-carboxylate (234 mg, 0.89 mmol, 1.00 equiv) in tetrahydrofuran (15 mL). This was followed by the addition of LAH (51 mg, 1.34 mmol, 1.52 equiv) at 0 °C. The resulting solution was stirred for 1 h at 0 °C. The reaction was then quenched by the addition of 10 mL of 2.5 M sodium hydroxide aq. The resulting solution was extracted with 3x30 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1x20 mL of water and 1x20 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (2:3) as eluent to

furnish 124 mg (63%) of [4-[1-(propan-2-yl)-1H-pyrazol-5-yl]-5,6-dihydro-2H-pyran-3-yl]methanol as a colorless oil.

[0192] Step 5: Into a 25-mL round-bottom flask, was placed a solution of [4-[1-(propan-2-yl)-1H-pyrazol-5-yl]-5,6-dihydro-2H-pyran-3-yl]methanol (124 mg, 0.56 mmol, 1.00 equiv), 2,6-dihydroxybenzaldehyde (116 mg, 0.84 mmol, 1.50 equiv), and PPh_3 (220 mg, 0.84 mmol, 1.50 equiv), in tetrahydrofuran (10 mL). This was followed by the addition of DIAD (170 mg, 0.84 mmol, 1.50 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 30 min at 0 °C and for an additional 1 h at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x25 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2x60 mL of water and 1x40 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10-1:7) as eluent. The crude product was further 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 (42.0% MeCN up to 55.0% in 8 min, up to 95.0% in 2 min, down to 42.0% in 2 min); Detector, Waters2545 UvDector 254&220nm. This provided 68 mg (36%) of 2-hydroxy-6-([4-[1-(propan-2-yl)-1H-pyrazol-5-yl]-5,6-dihydro-2H-pyran-3-yl]methoxy)benzaldehyde as a light yellow solid. ^1H NMR (400MHz, CDCl_3 , ppm): 11.90 (s, 1H), 10.32 (s, 1H), 7.56 (s, 1H), 7.33 (t, J = 8.4 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.16 (d, J = 8.4 Hz, 1H), 6.07 (s, 1H), 4.44-4.40 (m, 5H), 3.96 (t, J = 5.6 Hz, 2H), 2.19 (s, 2H), 1.43 (d, J = 6.4 Hz, 6H); MS (ES, m/z :) 343.2 [M+1]⁺

GBT999

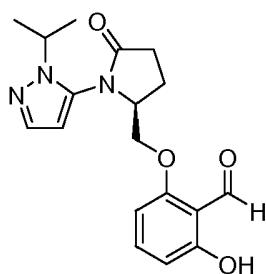


(S)-2-hydroxy-6-((1-(2-methoxypyridin-3-yl)-5-oxopyrrolidin-2-yl)methoxy)benzaldehyde

[0193] GBT999- Preparation of (S)-2-hydroxy-6-((1-(2-methoxypyridin-3-yl)-5-oxopyrrolidin-2-yl)methoxy)benzaldehyde

[0194] The compound was prepared from (S)-5-(hydroxymethyl)pyrrolidin-2-one and 3-iodo-2-methoxypyridine according to scheme 1, reaction steps 3 and 4. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.91 (d, *J* = 0.4 Hz, 1H), 9.85 (d, *J* = 0.6 Hz, 1H), 8.16 – 8.09 (m, 1H), 7.56 – 7.49 (m, 1H), 7.35 (ddd, *J* = 8.8, 8.1, 0.4 Hz, 1H), 6.99 – 6.90 (m, 1H), 6.53 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.21 (dd, *J* = 8.3, 0.8 Hz, 1H), 4.67 (dtd, *J* = 8.5, 4.9, 3.7 Hz, 1H), 4.07 – 3.95 (m, 2H), 3.93 (d, *J* = 0.5 Hz, 3H), 2.76 – 2.56 (m, 2H), 2.50 (dddd, *J* = 13.0, 9.5, 8.4, 7.4 Hz, 1H), 2.20 – 2.04 (m, 1H). MS found for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_5$: 343.3.

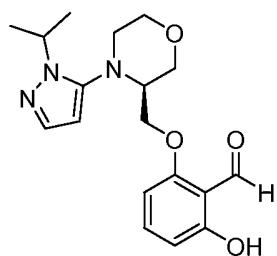
GBT1000



(S)-2-hydroxy-6-((1-(1-isopropyl-1H-pyrazol-5-yl)-5-oxopyrrolidin-2-yl)methoxy)benzaldehyde

[0195] GBT1000 - Preparation of (S)-2-hydroxy-6-((1-(1-isopropyl-1H-pyrazol-5-yl)-5-oxopyrrolidin-2-yl)methoxy)benzaldehyde. The compound was prepared from (S)-5-(hydroxymethyl)pyrrolidin-2-one and 5-iodo-1-isopropyl-1H-pyrazole according to scheme 1, reaction steps 3 and 4. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.92 (s, 1H), 10.13 (d, *J* = 0.6 Hz, 1H), 7.56 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 6.57 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.25 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.02 (d, *J* = 1.9 Hz, 1H), 4.34 – 4.19 (m, 2H), 4.08 (dd, *J* = 10.0, 3.4 Hz, 1H), 4.02 (dd, *J* = 10.0, 3.6 Hz, 1H), 2.79 – 2.60 (m, 2H), 2.52 (dddd, *J* = 13.3, 9.7, 8.4, 7.0 Hz, 1H), 2.28 (dddd, *J* = 13.3, 9.9, 6.8, 5.4 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 3H). MS found for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_4$: 344.3.

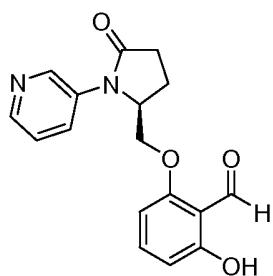
GBT1042



(S)-2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)morpholin-3-yl)methoxy)benzaldehyde

[0196] GBT1042 - Preparation of (S)-2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)morpholin-3-yl)methoxy)benzaldehyde. The compound was prepared from (*R*)-tert-butyl 3-(hydroxymethyl)morpholine-4-carboxylate and 3-iodo-2-methoxypyridine according to scheme 1, reaction steps 1, 3 and 4. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.88 (s, 1H), 10.26 (d, J = 0.6 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.40 – 7.28 (m, 1H), 6.51 (dt, J = 8.5, 0.7 Hz, 1H), 6.11 (dd, J = 8.4, 0.8 Hz, 1H), 6.07 (d, J = 2.0 Hz, 1H), 4.79 (hept, J = 6.6 Hz, 1H), 4.10 (ddd, J = 11.4, 3.4, 0.7 Hz, 1H), 3.98 – 3.86 (m, 3H), 3.86 – 3.73 (m, 2H), 3.42 – 3.32 (m, 1H), 3.04 – 2.91 (m, 2H), 1.52 – 1.37 (m, 3H), 1.33 (d, J = 6.7 Hz, 3H). MS found for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_4$: 346.3.

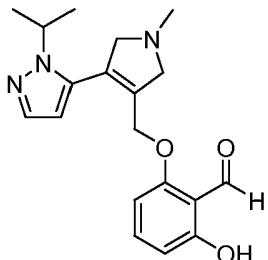
GBT1059



(S)-2-hydroxy-6-((5-oxo-1-(pyridin-3-yl)pyrrolidin-2-yl)methoxy)benzaldehyde

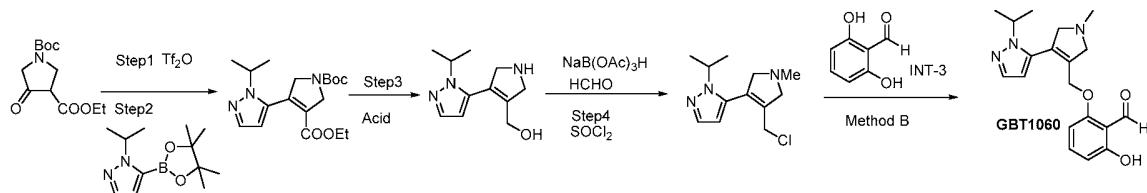
[0197] GBT1059- Preparation of (S)-2-hydroxy-6-((5-oxo-1-(pyridin-3-yl)pyrrolidin-2-yl)methoxy)benzaldehyde. The compound was prepared from (S)-5-(hydroxymethyl)pyrrolidin-2-one and 3-iodopyridine according to scheme 1, reaction steps 3 and 4. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.88 (s, 1H), 10.05 (s, 1H), 8.64 (dd, J = 2.7, 0.7 Hz, 1H), 8.48 (dd, J = 4.8, 1.5 Hz, 1H), 7.90 (ddd, J = 8.3, 2.6, 1.5 Hz, 1H), 7.39 – 7.28 (m, 2H), 6.55 (dd, J = 8.5, 0.8 Hz, 1H), 6.22 (dt, J = 8.3, 1.0 Hz, 1H), 4.72 (dq, J = 8.3, 4.1 Hz, 1H), 4.19 – 4.05 (m, 2H), 2.84 – 2.61 (m, 2H), 2.54 (ddt, J = 13.2, 10.0, 8.3 Hz, 1H), 2.22 (dddd, J = 13.5, 9.9, 4.9, 3.7 Hz, 1H). MS found for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_4$: 313.3.

GBT1060



2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)methoxy)benzaldehyde

[0198] GBT1060- 2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)methoxy)benzaldehyde. The compound was synthesized in 7 steps according to a modified scheme 2 starting from 1-tert-butyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate.



[0199] Steps 1&2: To a solution of 1-tert-butyl 3-ethyl 4-oxopyrrolidine-1,3-dicarboxylate (1.49 g, 5.81 mmol) in DCM (15 mL) at -78 °C was added DIPEA (1.22 mL) and Tf₂O (1.08 mL), then it was warmed to room temperature and was further stirred for 2 h, mixture was diluted with more DCM, DCM layer was washed with Sat. NaHCO₃, brine, dried over MgSO₄ and concentrated to give crude triflate. To a solution of this crude triflate in Dioxane (15 mL) was added 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.37 g, 5.81 mmol) and Pd(dppf)Cl₂ (0.42 g, 0.58 mmol) and a solution of Na₂CO₃ (1.23 g, 11.62 mmol) in water (5 mL). After heated at 100 °C for 15 h the solution was diluted with EtOAc, organic layer was washed with water, brine, dried over MgSO₄ and was concentrated to give crude product, which was purified by column chromatography to give ethyl 1-tert-butyl 3-ethyl 4-(1-isopropyl-1H-pyrazol-5-yl)-1H-pyrrole-1,3(2H,5H)-dicarboxylate (0.59 g).

[0200] Step 3: To a solution of 1-tert-butyl 3-ethyl 4-(1-isopropyl-1H-pyrazol-5-yl)-1H-pyrrole-1,3(2H,5H)-dicarboxylate (590 mg, 1.69 mmol) in THF (6 ml) at -20 °C was added 1M LiAlH₄ in THF (2.03 mL, 2.03 mmol). After stirred for 20 min, it was quenched with Sat. NH₄Cl, the mixture was extracted with EtOAc (3X), organic layers were combined, dried over

MgSO_4 and was concentrated to give tert-butyl 3-(hydroxymethyl)-4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate as crude product, which was used without purification in next step.

[0201] Steps 4a&4: To a suspension of (4-(1-isopropyl-1H-pyrazol-5-yl)-2,5-dihydro-1H-pyrrol-3-yl)methanol (200 mg, 0.96 mmol) in AcCN (2 mL) was added TEA (0.14 mL, 0.96 mmol) and HCHO aqueous solution (0.24 g). After stirred for 30 min, it was added $\text{NaB}(\text{OAc})_3\text{H}$ (0.41 g, 1.92 mmol). Another 15 min later, it was filtered and the filtrate was concentrated to give crude product, which was purified by column (DCM/MeOH=100:0 to 80:20) to give (4-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)methanol (170 mg). To a solution of 4-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)methanol in DCM (3mL) was added SOCl_2 (0.2 mL) at 0 °C, after stirred for 30 min, it was then concentrated to give 5-(4-(chloromethyl)-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-1-isopropyl-1H-pyrazole as crude HCl salt (140 mg).

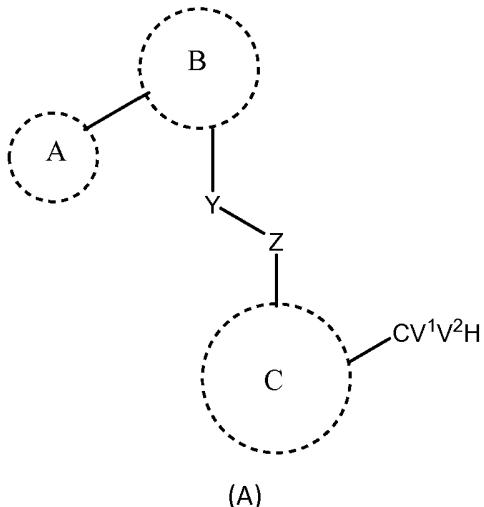
[0202] Method B: To a solution of 5-(4-(chloromethyl)-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)-1-isopropyl-1H-pyrazole (140 mg, 0.60 mmol) and 2,6-dihydroxybenzaldehyde (170 mg, 1.20 mmol) in DMF (3 mL) was added K_2CO_3 (330 mg, 2.4 mmol). After stirred at 50 °C for 30 min, the mixture was added water, extracted with EtOAc (3X), organic layers were combined, washed with brine, dried and concentrated to give crude product, which was purified by preparative HPLC to give 2-hydroxy-6-((4-(1-isopropyl-1H-pyrazol-5-yl)-1-methyl-2,5-dihydro-1H-pyrrol-3-yl)methoxy)benzaldehyde (6 mg). ^1H NMR (400 MHz, Chloroform-*d*) δ 10.26 (d, *J* = 0.6 Hz, 1H), 8.26 (s, 1H), 7.55 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 6.54 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.21 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.11 (d, *J* = 1.8 Hz, 1H), 4.62 (d, *J* = 1.4 Hz, 2H), 4.47 – 4.33 (m, 1H), 3.98 – 3.88 (m, 4H), 2.67 (s, 3H), 1.44 (d, *J* = 6.7 Hz, 6H). MS (M+H) found for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_3$: 342.2.

[0203] 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.

[0204] 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. A compound of Formula (A):



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

wherein

ring A is an optionally substituted 5-10 membered heteroaryl containing up to 3 ring

N, O, and/or S atoms, and oxidized forms of N and/or S atoms;

wherein ring A is α or β substituted relative to the Y substituent;

ring B is an optionally substituted C₆-C₁₀ aryl 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;

each Y and Z is independently CR¹⁰R¹¹, O, S, SO, SO₂, or NR¹²; each R¹⁰ and R¹¹

independently is hydrogen or C₁-C₃ alkyl, optionally substituted with halo,

OH, or alkoxy, or CR¹⁰R¹¹ is C=O; R¹² is hydrogen or C₁-C₆ alkyl; provided that

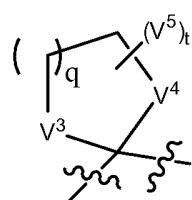
if one of Y and Z is O, S, SO, SO₂, then the other is not CO, and provided that Y

and Z are both not heteroatoms or oxidized forms thereof;

ring C is C₆-C₁₀ aryl, optionally substituted;

V¹ and V² independently are C₁-C₆ alkoxy; or V¹ and V² 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;

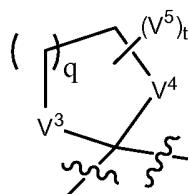
R^{81} and R^{82} independently are selected from the group consisting of hydrogen,

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

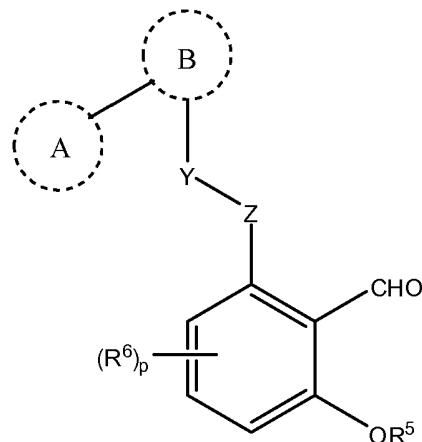
R^{84} is optionally substituted C_1 - C_6 alkyl.

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 or 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 (I'):



(1')

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 a substituent that 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

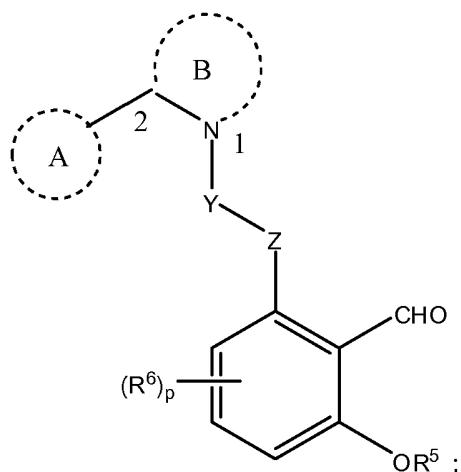
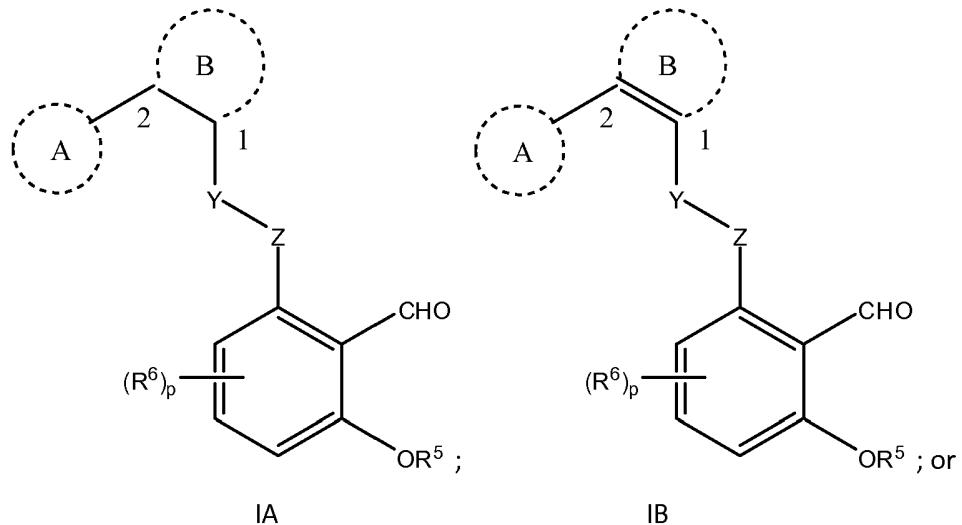
R^6 is 4-10 membered cycloalkyl or heterocycle substituted with an $R'R'N-$ moiety

wherein each R' is independently C₁-C₆ alkyl or hydrogen; and

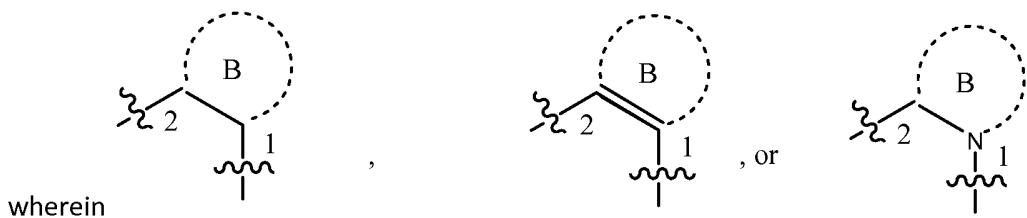
p is 0, 1, 2, or 3.

and the remaining variables are defined as in claim 2.

4. The compound of claim 2 or 3, wherein the compound is of Formula IA, IB or IC:



IC



is an optionally substituted 4-10 membered heterocycle as defined in claim 2,

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;

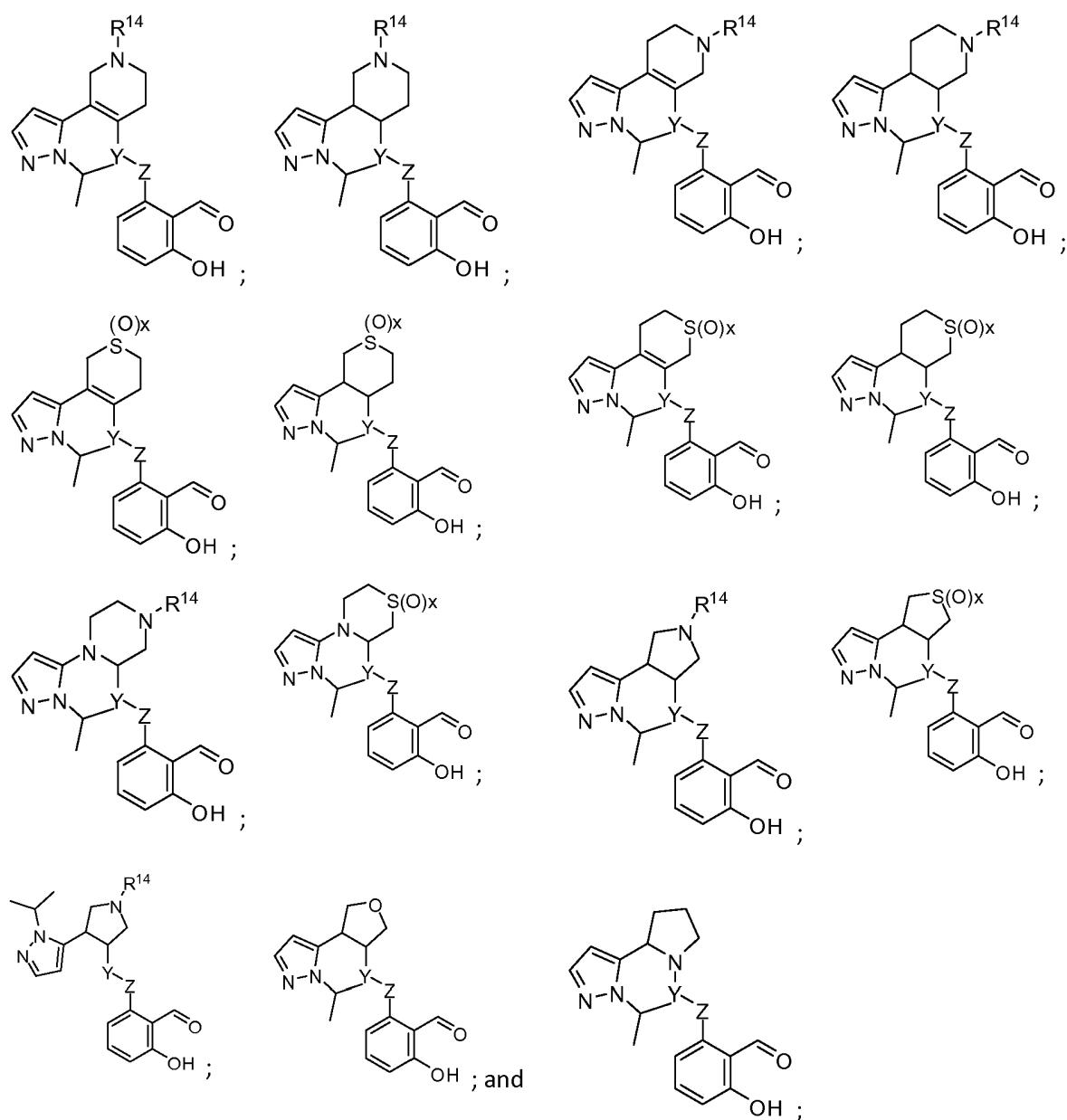
R^6 is a substituent that is halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylthio, C_1 - C_6 $S(O)$ -, C_1 - C_6 $S(O)_2$ -, wherein the C_1 - C_6 alkyl is optionally substituted with 1-5 halo; or

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; and

p is 0, 1, 2, or 3; and

the remaining variables are defined as in claim 2.

5. The compound of claim 2 or 3, wherein ring A is substituted with 1-3: halo, C_1 - C_6 alkyl, and/or C_1 - C_6 alkoxy, wherein the C_1 - C_6 alkyl is optionally substituted with 1-5 halo.
6. The compound of claim 2 or 3, wherein ring B is substituted with 1-3: halo, C_1 - C_6 alkyl, COR^{15} , and/or $COOR^{15}$; and
 R^{15} is C_1 - C_6 alkyl, C_6 - C_{10} aryl, 5-10 membered heteroaryl or a 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, wherein the alkyl, aryl, heteroaryl or heterocyclyl is optionally substituted.
7. The compound of any one of claim 1-4, wherein Y-Z is $-CH_2O$ -, $-CH_2CH_2$ -, $-CONH$ -, $-NHCO$ -, wherein the right hand side of the substituent is joined with the substituted aryl or substituted phenyl ring.
8. The compound of claim 2, wherein the compound is selected from the group consisting of



or an N oxide thereof wherein

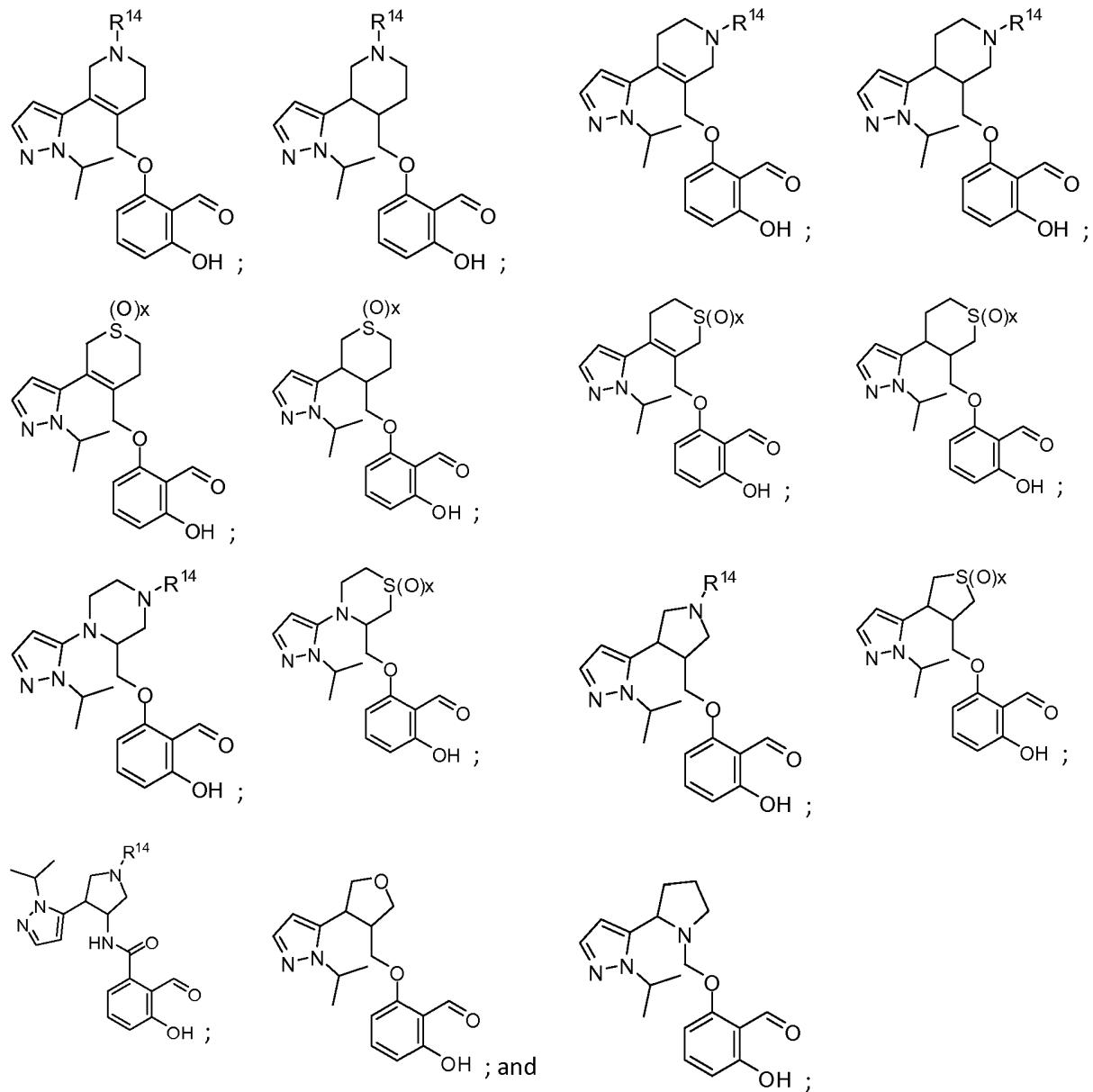
Y and Z are defined as in claim 2;

x is 0, 1, or 2;

R^{14} is C_1 - C_6 alkyl, COR^{15} , or $COOR^{15}$.

and R^{15} is optionally substituted C_1 - C_6 alkyl, optionally substituted C_6 - C_{10} aryl, optionally substituted 5-10 membered heteroaryl 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 and/or S and/or oxidized forms of N and S.

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



or an N oxide thereof wherein

x is 0, 1, or 2;

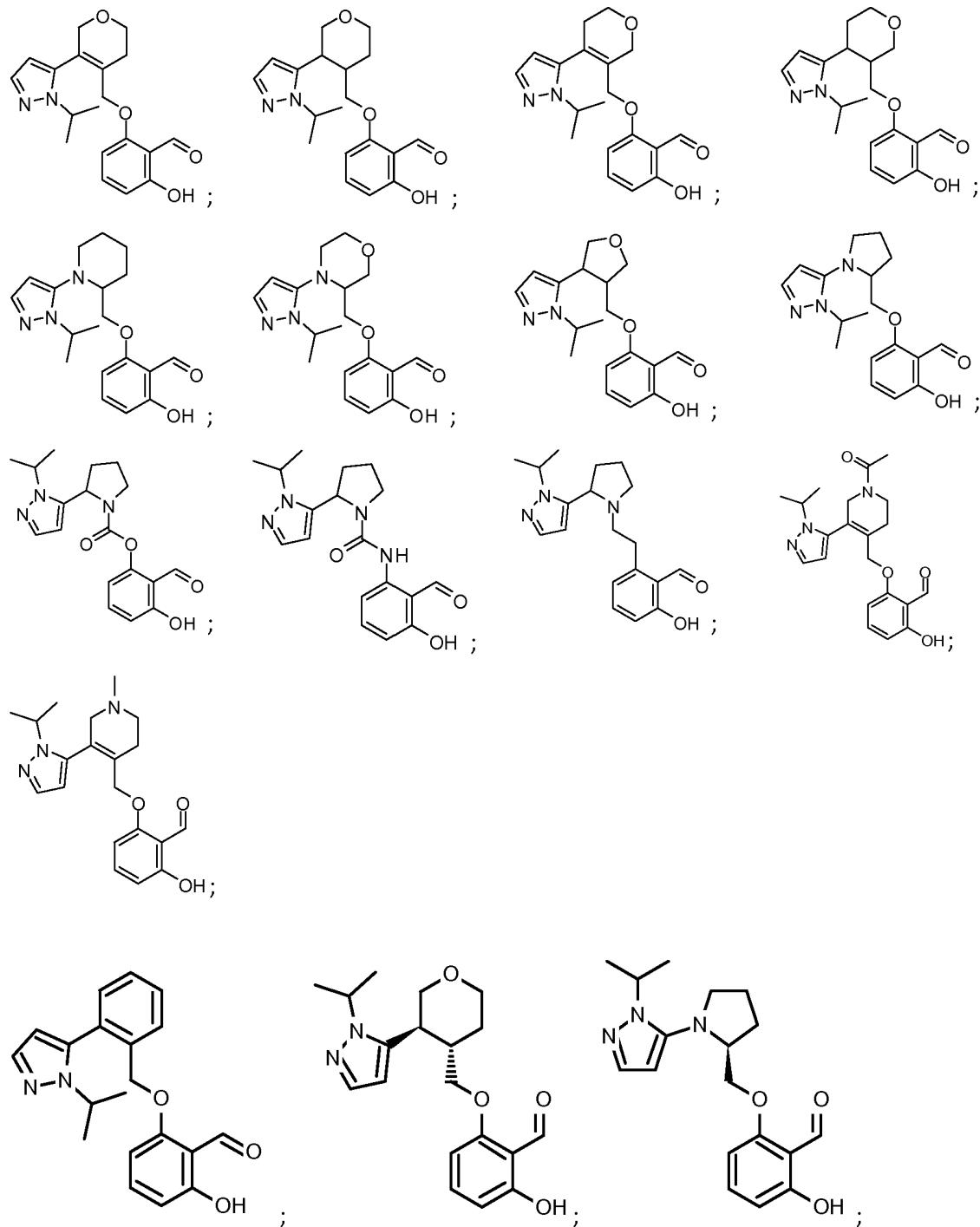
R^{14} is C_1 - C_6 alkyl, COR^{15} , or $COOR^{15}$;

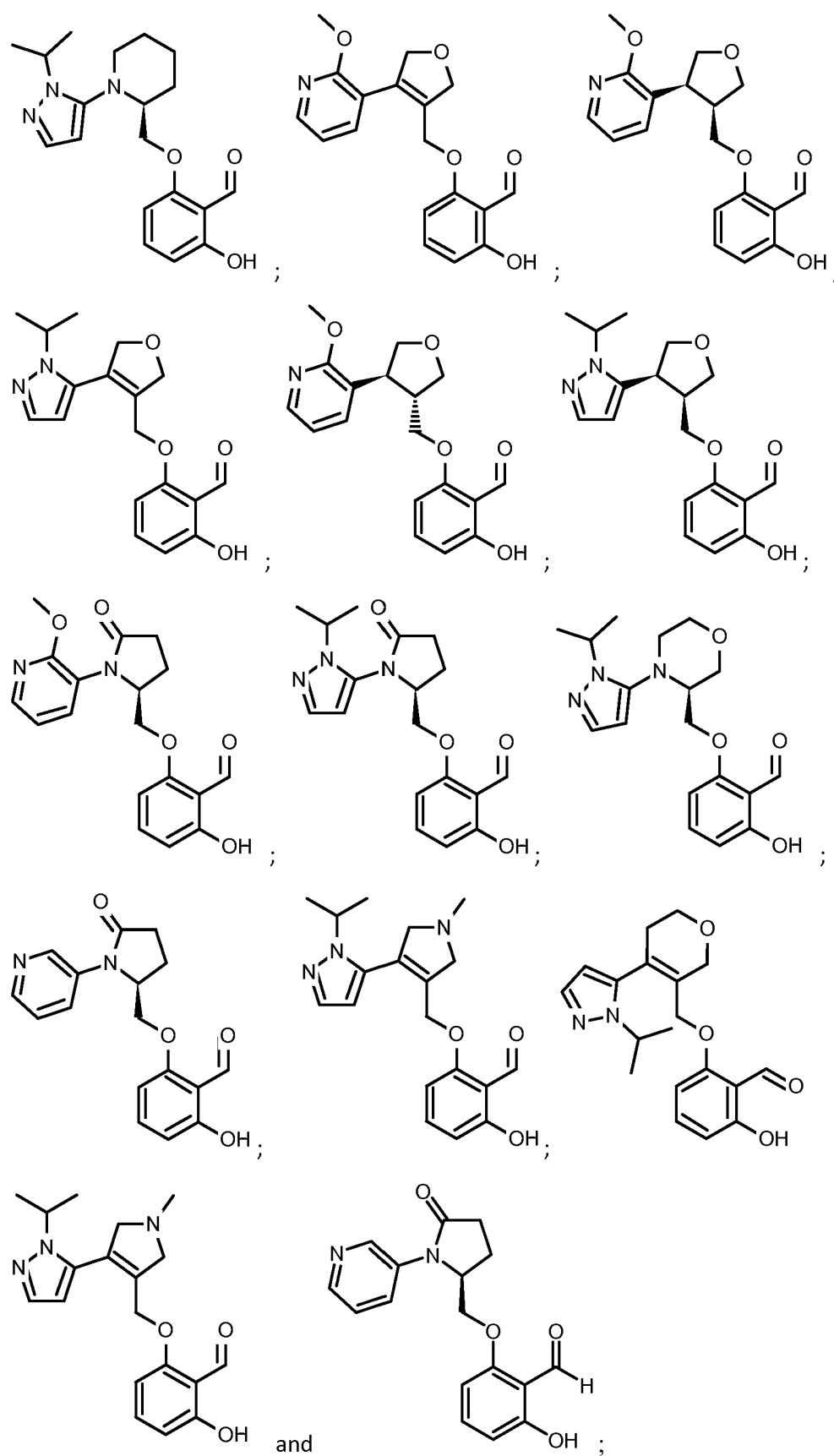
and R¹⁵ is optionally substituted C₁-C₆ alkyl, optionally substituted C₆-C₁₀ aryl,

optionally substituted 5-10 membered heteroaryl 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.

10. A compound selected from the group consisting of:





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

11. A composition comprising a compound of any one of claims 2-10 and at least one pharmaceutically acceptable excipient.
12. 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 2-10 or the composition of claim 11.
13. 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 2-10 or the composition of claim 11.