COMPOUNDS AND USES THEREOF FOR THE MODULATION OF HEMOGLOBIN

FIELD OF THE INVENTION

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

STATE OF THE ART

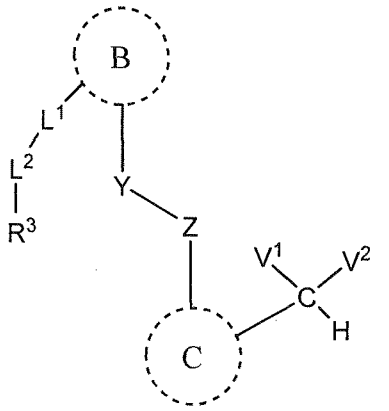
[0002] Sickle cell disease is a disorder of the red blood cells, found particularly among those of African and Mediterranean descent. The basis for sickle cell disease is found in sickle hemoglobin (HbS), which contains a point mutation relative to the prevalent peptide sequence of hemoglobin (Hb).

[0003] Hemoglobin (Hb) transports oxygen molecules from the lungs to various tissues and organs throughout the body. Hemoglobin binds and releases oxygen through conformational changes. Sickle hemoglobin (HbS) contains a point mutation where glutamic acid is replaced with valine, allowing HbS to become susceptible to polymerization to give the HbS containing red blood cells their characteristic sickle shape. The sickled cells are also more rigid than normal red blood cells, and their lack of flexibility can lead to blockage of blood vessels. US 7,160,910 discloses compounds that are allosteric modulators of hemoglobin. However, a need exists for additional therapeutics that can treat disorders that are mediated by Hb or by abnormal Hb such as HbS.

SUMMARY ~~OF THE INVENTION~~

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

[0004a] In one aspect, there is provided a compound of Formula (I)



(A)

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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, or $-NR^1R^2$;

each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-10 membered heterocycle or 5-10 membered heteroaryl, each 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 each alkyl, cycloalkyl, heterocycle, aryl or heteroaryl is optionally substituted, or R^1 and R^2 together with the nitrogen atom they are attached to form an optionally substituted 4-7 membered heterocycle; or

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

L^2 is C=O or SO_2;

ring B is a optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, 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; or

ring B is a 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;

each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{10}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O, provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and Y and Z are both not heteroatoms or oxidized forms thereof;

wherein Y is α or β substituted relative to the $-L^1L^2R^3$;

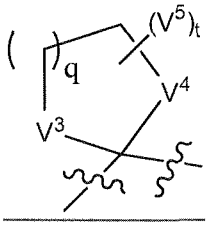
wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

ring C is a optionally substituted C_6-C_{10} aryl or optionally substituted 5-10 membered heteroaryl containing 1-3 nitrogen atoms, or an oxidized form of N; or

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl 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 of which is optionally substituted with 1-4: halo, oxo, $-OR^{19}$, 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, C_1-C_6 alkoxy and/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; and

R^{19} is hydrogen or a prodrug moiety R;

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 CV1V2 is C=V, wherein V is O, NOR^{80}, or $NNR^{81}R^{82}$;

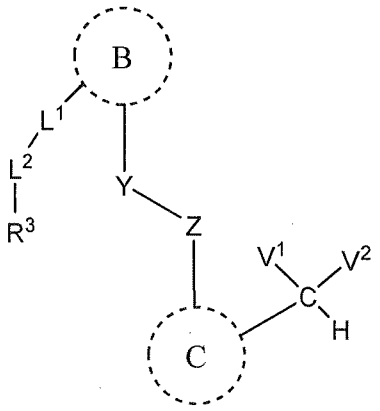
R^{80} is optionally substituted C_1-C_6 alkyl;

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

R^{83} is hydrogen or optionally substituted C1-C6 alkyl; and

R^{84} is optionally substituted C1-C6 alkyl.

[0005] In certain ~~aspects~~ embodiments of the ~~invention~~disclosure, a compound of Formula (A) is provided:



(A)

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

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})_d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

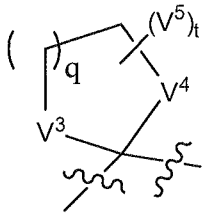
L^2 is C=O or SO_2;

each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{10}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O, provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and Y and Z are both not heteroatoms or oxidized forms thereof;

wherein Y is α or β substituted relative to the $-L^1L^2R^3$;

wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

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:



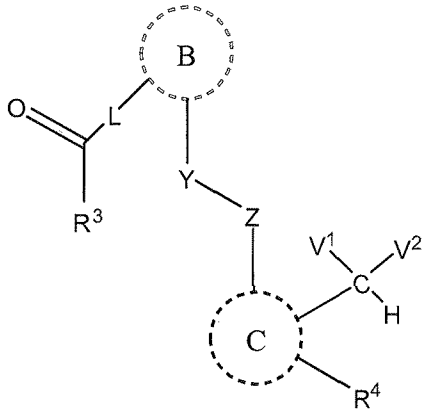
wherein each V^3 and V^4 are independently O, S, or NH, provided that when one of V^3 and V^4 is S, the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60}, where each R^{60}

ring B is a 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;

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl 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 of which is optionally substituted with 1-4: halo, oxo, -OR^{19}, 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, C_1-C_6 alkoxy and/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 certain preferred substituents include OH, halo, C_1-C_6 alkoxy, C_3-C_6 cycloalkoxy or O-R, where R is a prodrug moiety, wherein the C_1-C_6 alkoxy is optionally substituted with 1-5 halo;; and

R^{19} is hydrogen or a prodrug moiety R.

[0008] In one aspect~~certain aspects of the invention~~, there is provided a compound of Formula (II) is provided:



(II)

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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, or $-NR^1R^2$;

each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-10 membered heterocycle or 5-10 membered heteroaryl, each 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 each alkyl,

~~R^4 is OH, halo, C_1-C_6 alkoxy, C_3-C_6 cycloalkoxy or O-R, where R is a prodrug moiety, wherein the C_1-C_6 alkoxy is optionally substituted with 1-5 halo;~~

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

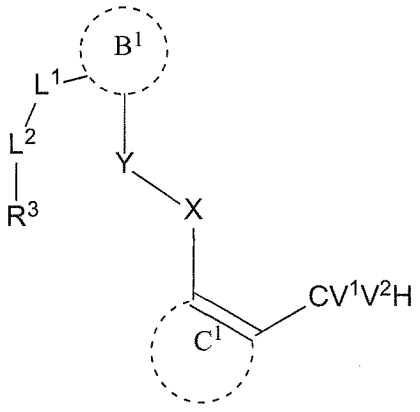
R^{81} and R^{82} independently are selected from the group consisting of hydrogen; optionally substituted C_1-C_6 alkyl, COR^{83} and CO_2R^{84};

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

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

R^4 is OH, halo, C_1-C_6 alkoxy, C_3-C_6 cycloalkoxy or O-R, where R is a prodrug moiety, wherein the C_1-C_6 alkoxy is optionally substituted with 1-5 halo.

[0009] In certain ~~aspects~~ embodiments of the ~~invention~~disclosure, a compound of formula (IV) is provided:



(IV)

wherein

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4: C_1-C_6 alkyl;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})_d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

L^2 is C=O or SO_2;

ring B is a 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;

each Y and Z is independently $(CR^{10}R^{11})_e$, O, S, SO, SO_2, or NR^{10}; e is 1 to 4, preferably 1; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O, provided

[0011] ~~In further aspects of the invention~~In one aspect, there is provided a composition ~~is provided~~ comprising any of the compounds as described herein, and at least ~~a~~ one pharmaceutically acceptable excipient.

[0012] In still further ~~aspects~~ embodiments of the ~~invention~~disclosure, 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.

[0012a] In one aspect, there is provided the use of a compound as defined herein or the composition as defined herein in the manufacture of a medicament for increasing oxygen affinity of hemoglobin S in a subject.

[0013] In further ~~aspects~~ embodiments of the ~~invention~~disclosure, 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.

[0013a] In one aspect, there is provided the use of a compound as defined herein or the composition as defined herein in the manufacture of a medicament for treating oxygen deficiency in a subject in need thereof.

[0013b] In one aspect, there is provided the use of a compound as defined herein or the composition as defined herein in the manufacture of a medicament for the treatment of sickle cell disease, a cancer, a pulmonary disorder, acute respiratory distress syndrome, a stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, or a wound.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0014] 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.

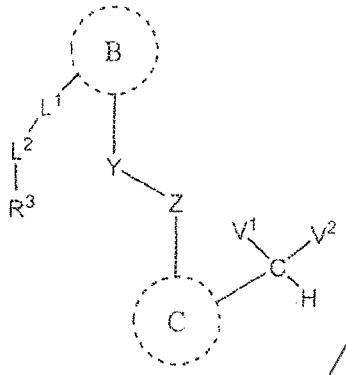
[0015] As used herein, the term "comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean

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.

[0016] 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.

CLAIMS

1. A compound of Formula (I)



(A)

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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, or $-NR^1R^2$;

each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-10 membered heterocycle or 5-10 membered heteroaryl, each 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 each alkyl, cycloalkyl, heterocycle, aryl or heteroaryl is optionally substituted, or R^1 and R^2 together with the nitrogen atom they are attached to form an optionally substituted 4-7 membered heterocycle; or

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

L^2 is C=O or SO_2;

ring B is a optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, 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; or

ring B is a 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;

each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{10}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O, provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and Y and Z are both not heteroatoms or oxidized forms thereof;

wherein Y is α or β substituted relative to the $-L^1L^2R^3$;

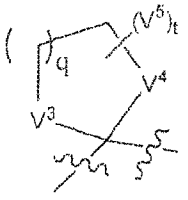
wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

ring C is a optionally substituted C_6-C_{10} aryl or optionally substituted 5-10 membered heteroaryl containing 1-3 nitrogen atoms, or an oxidized form of N; or

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl 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 of which is optionally substituted with 1-4: halo, oxo, $-OR^{19}$, 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, C_1-C_6 alkoxy and/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; and

R^{19} is hydrogen or a prodrug moiety R;

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 CV1V2 is C=V, wherein V is O, NOR^{80}, or $NNR^{81}R^{82}$;

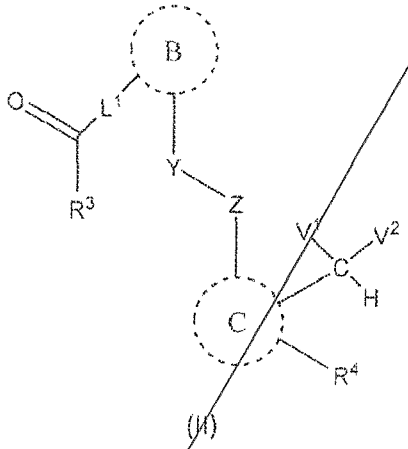
R^{80} is optionally substituted C_1-C_6 alkyl;

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

R^{83} is hydrogen or optionally substituted C1-C6 alkyl; and

R^{84} is optionally substituted C1-C6 alkyl.

2. A compound of Formula (II)



(II)

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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, or $-NR^1R^2$;

each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-10 membered heterocycle or 5-10 membered heteroaryl, each 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 each alkyl, cycloalkyl, heterocycle, aryl or heteroaryl is optionally substituted, or R^1 and R^2 together with the nitrogen atom they are attached to form an optionally substituted 4-7 membered heterocycle;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})_d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

ring B is a optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, 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;

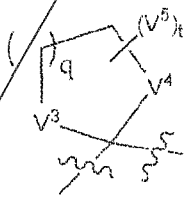
each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{10}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O, provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and Y and Z are both not heteroatoms or oxidized forms thereof;

wherein Y is α or β substituted relative to the $-LCOR^3$;

ring C is a optionally substituted C_6-C_{10} aryl or optionally substituted 5-10 membered heteroaryl containing 1-3 nitrogen atoms, or an oxidized form of N;

wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

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;

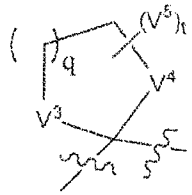
R^{81} and R^{82} independently are selected from the group consisting of hydrogen; optionally substituted C_1-C_6 alkyl, COR^{83} and CO_2R^{84};

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

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

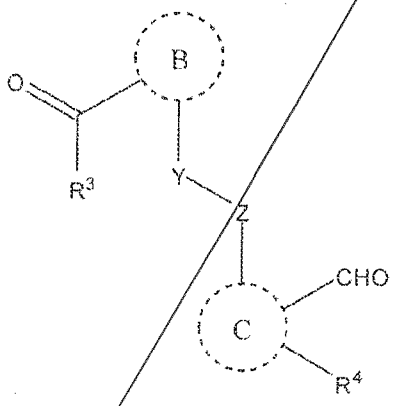
R^4 is OH, halo, C_1-C_6 alkoxy, C_3-C_6 cycloalkoxy or O-R, where R is a prodrug moiety, wherein the C_1-C_6 alkoxy is optionally substituted with 1-5 halo.

3. The compound of claim 2, wherein V^1 and V^7 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.

4. A compound of claim 2 of Formula (III):

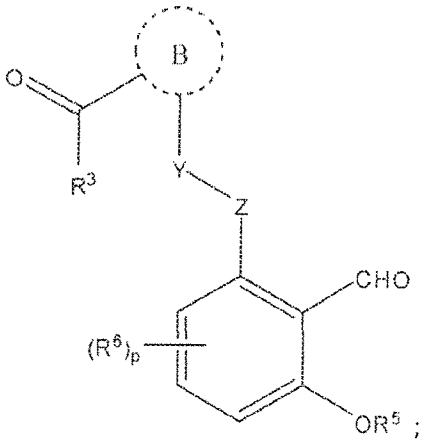


(III)

wherein Y-Z is $-CH_2O-$ or $-CH_2CH_2-$ and the remaining substituents are defined as in claim 2.

5. The compound of claim 4, wherein and R^4 and –CHO are joined to adjacent atoms on ring C.

6. The compound of any one of claims 3-5, of Formula IIIA:



IIIA

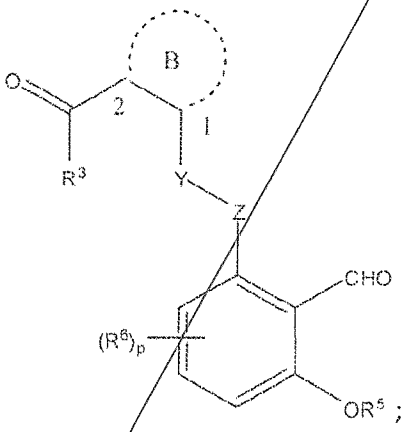
wherein ring B is a optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N;

R^5 is hydrogen, C_1-C_6 alkyl or a prodrug moiety R;

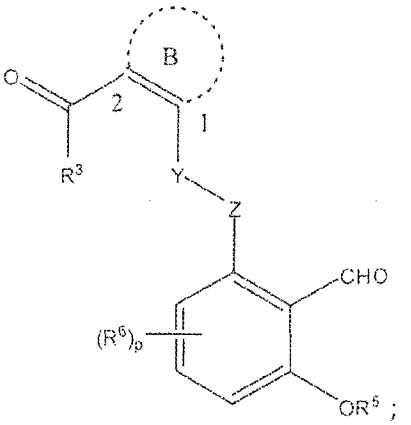
R^6 is halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo; and

p is 0, 1, 2 or 3.

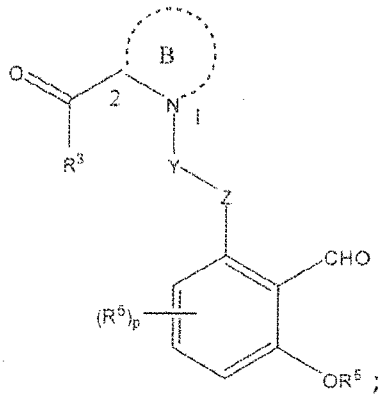
7. The compound of any one of claims 3-5, wherein the compound is of Formula IIIB, IIIC, or IIID:



IIIB

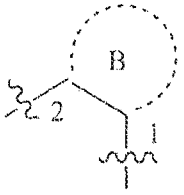
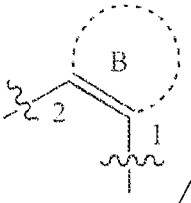
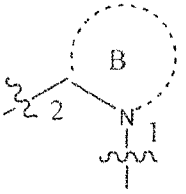


IIIC



IIID

wherein


, 
, and 

are optionally substituted 4-10 membered heterocycle as defined in claim 1;

R^5 is hydrogen, C_1-C_6 alkyl or a prodrug moiety;

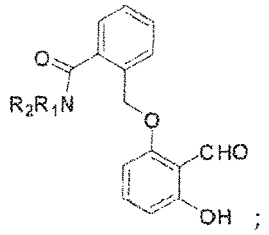
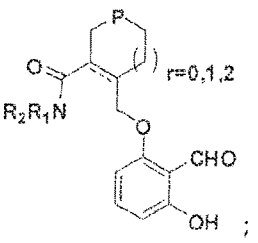
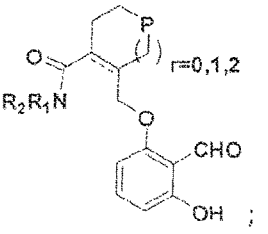
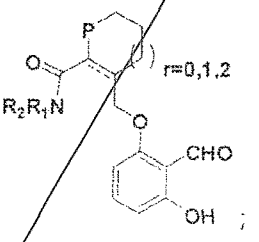
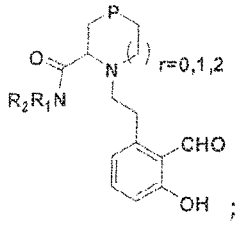
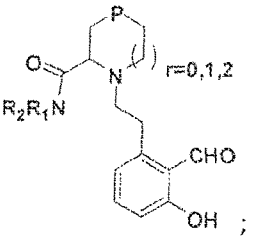
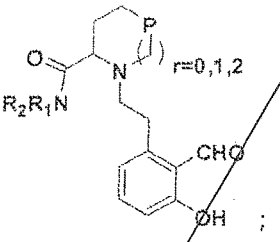
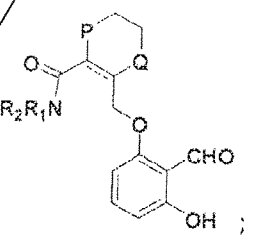
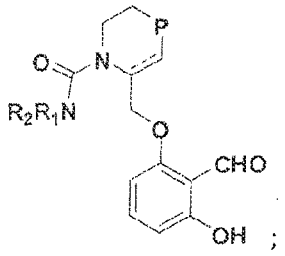
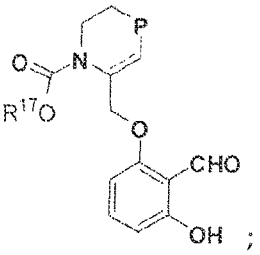
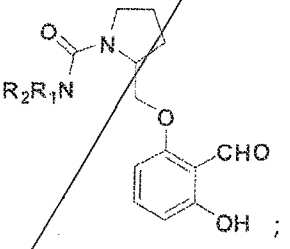
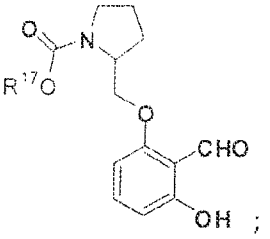
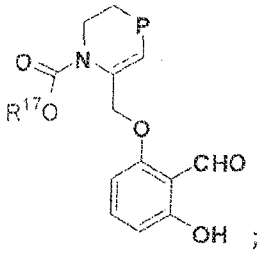
R^6 is halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo;

p is 0, 1, 2 or 3.

8. The compound of any one of claims 3-7, wherein ring B is substituted with 1-3: halo, C_1-C_6 alkyl, COR^{15}, 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.

9. The compound of claim 3, wherein the compound is selected from the group consisting of

or an N oxide thereof, wherein

 is a single or a double bond;

each P and Q is independently selected from CHR^{17}, $NCOR^{15}$, NCO_2R^{15}; N-O, O, S, SO, and SO_2;

each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, a 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;

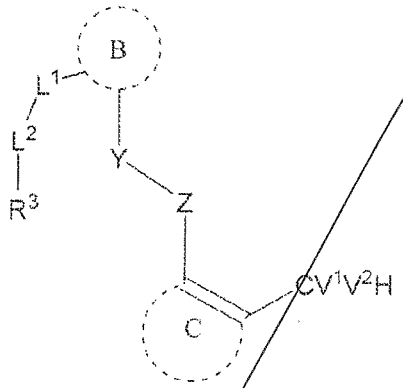
R^{15} is C_1-C_6 alkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl or a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is

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;

R^{17} 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;

and r is 0, 1, or 2.

10. The compound of claim 1 of Formula (IV)



(IV)

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

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})_d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

L^2 is C=O or SO_2;

ring B is a 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;

each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{10}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with 1-3 halo,

OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O, provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and Y and Z are both not heteroatoms or oxidized forms thereof;

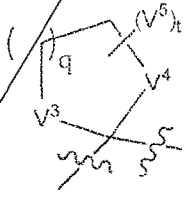
wherein Y is α or β substituted relative to the $-L^1L^2R^1$;

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl 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 of which is optionally substituted with 1-4: halo, oxo, $-OR^{19}$, 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, C_1-C_6 alkoxy and/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;

R^{19} is hydrogen or a prodrug moiety R; and

wherein Z and $-CV^1V^2H$ are attached to adjacent atoms on ring C;

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 $NNR^{81}R^{82}$;

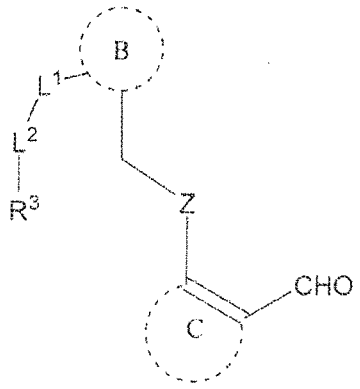
R^{80} is optionally substituted C_1-C_6 alkyl;

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

11. A compound of claim 10 of Formula (V):



(V)

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

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})_d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

L^2 is C=O or SO_2;

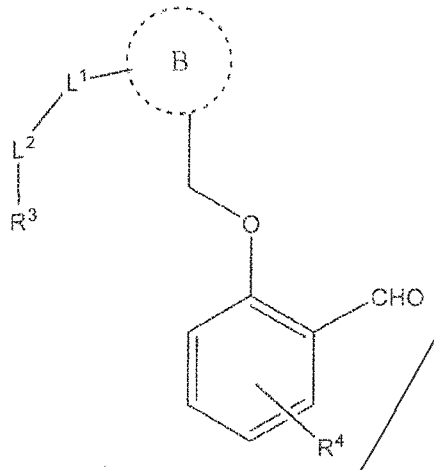
ring B is a optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

Z is O, S, SO or SO_2;

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl 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 of which is optionally substituted with 1-4: halo, oxo, $-OR^{19}$, 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, C_1-C_6 alkoxy and/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; and

R^{19} is hydrogen or a prodrug moiety R.

12. A compound of claim 10 of Formula (VI):



(VI)

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

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})_d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

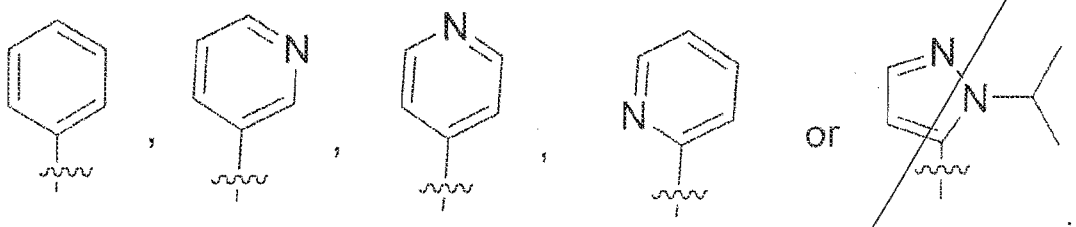
L^2 is C=O or SO_2;

ring B is a 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;

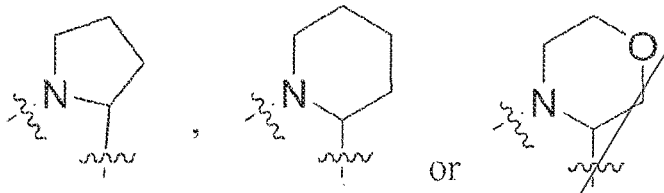
R^4 is $-OR^{19}$ or C_1-C_6 alkoxy; and

R^{19} is hydrogen or a prodrug moiety R.

13. The compound of any one of claims 10-12, wherein R^3 is selected from the group consisting of:

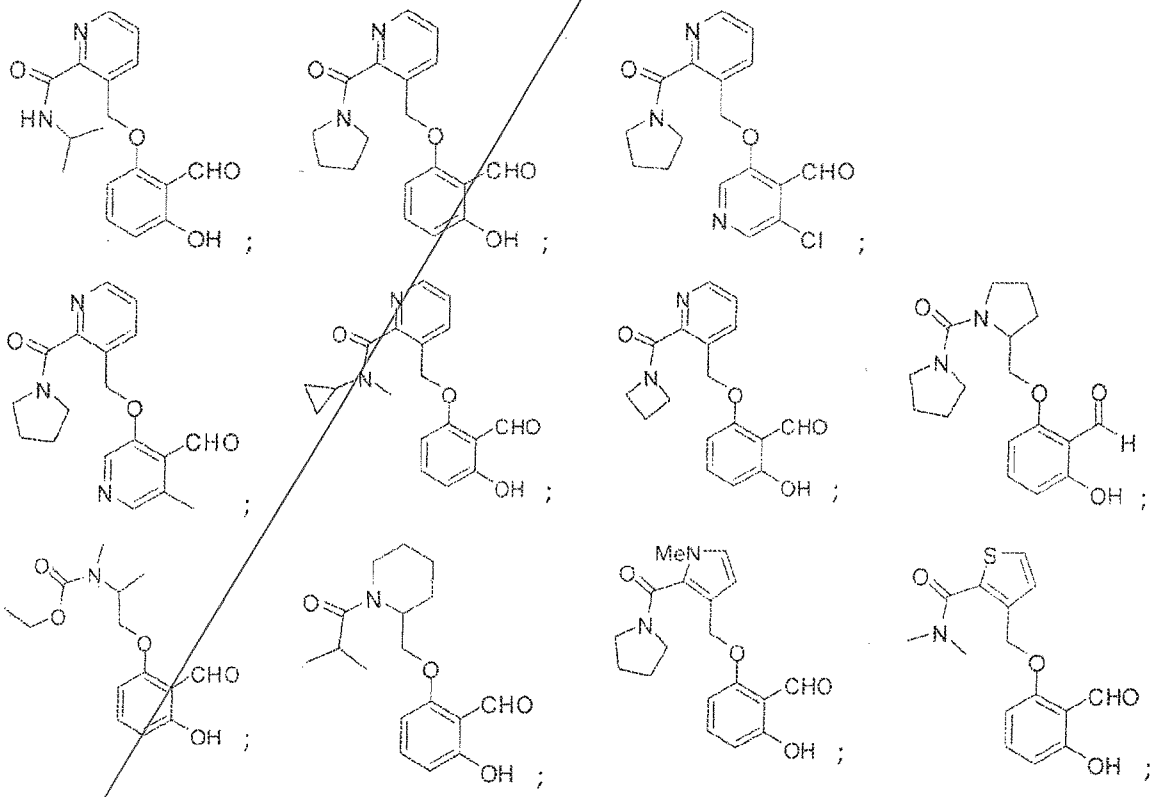


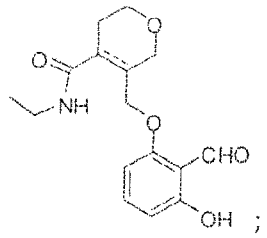
14. The compound of any one of claims 10-13, wherein ring B is selected from the group consisting of

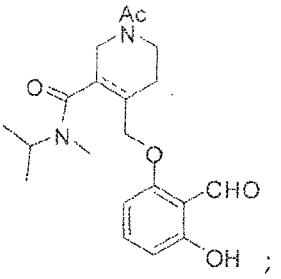


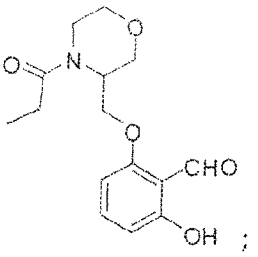
14. The compound of any one of claims 10-14, wherein L^1 is a bond and L^2 is C=O or SO_2.

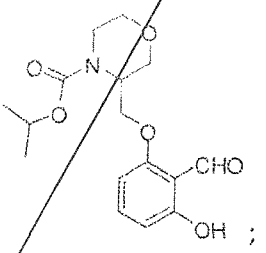
15. The compound of claim 1 of formula:

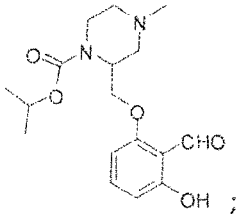


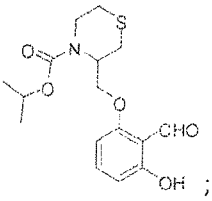

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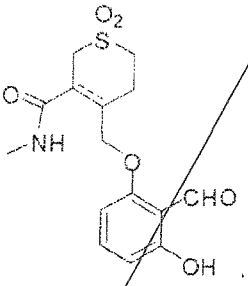

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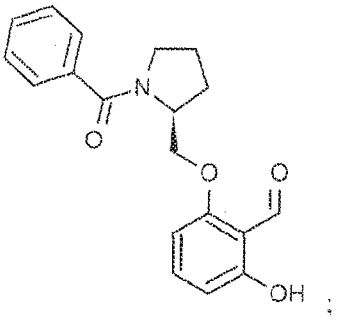

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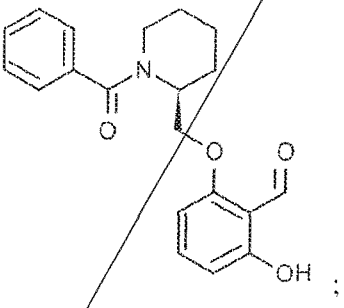

; and

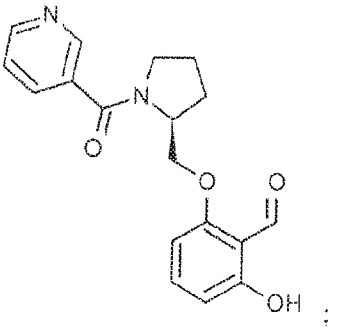

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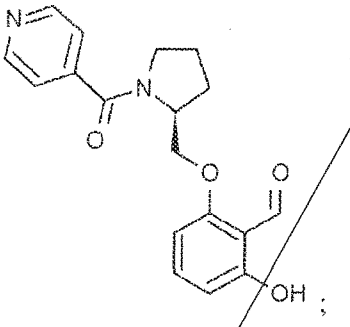
or an N oxide thereof, or a pharmaceutically acceptable salt of each thereof.

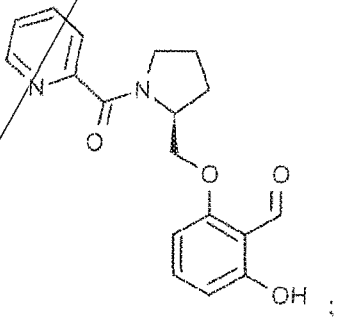
16. The compound of claim 1 of formula:

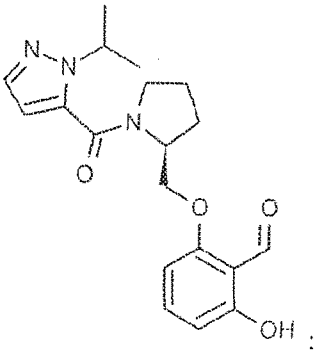

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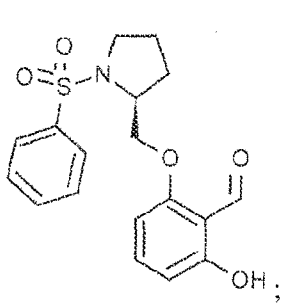
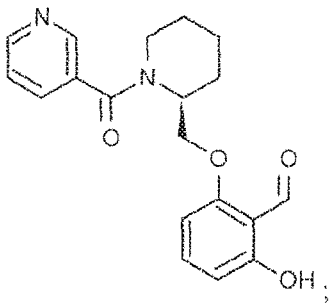
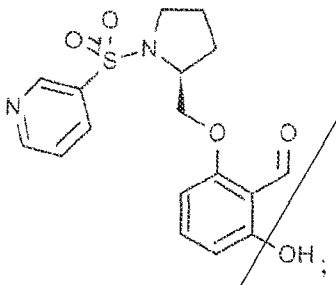
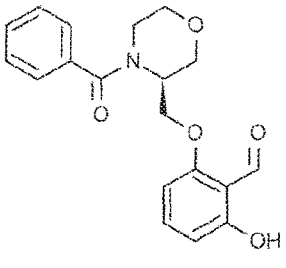
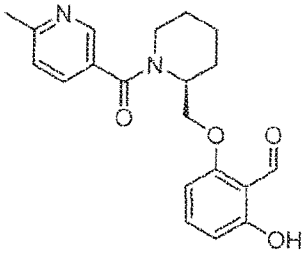
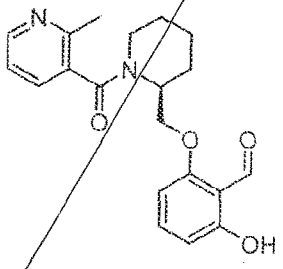

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and


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

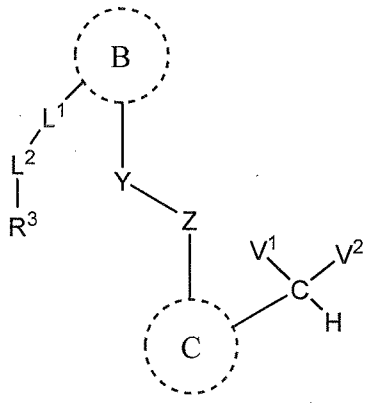
17. A composition comprising a compound of any one of claims 3-9 and 11-16 and at least one pharmaceutically acceptable excipient.

18. 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 3-9 and 11-16 or the composition of claim 17.

19. 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 3-9 and 11-16 or the composition of claim 17.

CLAIMS

1. A compound of Formula (I)



(A)

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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, or $-NR^1R^2$;

each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-10 membered heterocycle or 5-10 membered heteroaryl, each 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 each alkyl, cycloalkyl, heterocycle, aryl or heteroaryl is optionally substituted, or R^1 and R^2 together with the nitrogen atom they are attached to form an optionally substituted 4-7 membered heterocycle; or

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

L^2 is C=O or SO_2;

ring B is a optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, 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; or

ring B is a 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;

each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{10}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O, provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and Y and Z are both not heteroatoms or oxidized forms thereof;

wherein Y is α or β substituted relative to the $-L^1L^2R^3$;

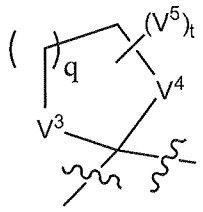
wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

ring C is a optionally substituted C_6-C_{10} aryl or optionally substituted 5-10 membered heteroaryl containing 1-3 nitrogen atoms, or an oxidized form of N; or

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl 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 of which is optionally substituted with 1-4: halo, oxo, $-OR^{19}$, 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, C_1-C_6 alkoxy and/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; and

R^{19} is hydrogen or a prodrug moiety R;

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 $NNR^{81}R^{82}$;

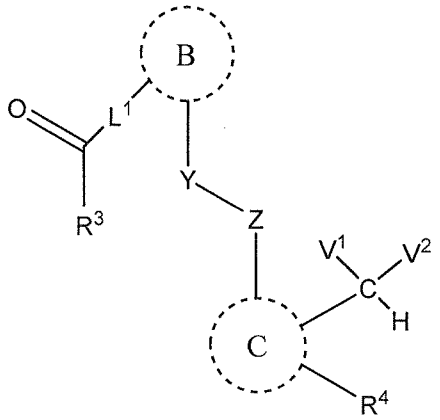
R^{80} is optionally substituted C_1-C_6 alkyl;

R^{81} and R^{82} independently are selected from the group consisting of hydrogen; optionally substituted C_1-C_6 alkyl, COR^{83} and 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. A compound of Formula (II)



(II)

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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkoxy, or $-NR^1R^2$;

each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4-10 membered heterocycle or 5-10 membered heteroaryl, each 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 each alkyl, cycloalkyl, heterocycle, aryl or heteroaryl is optionally substituted, or R^1 and R^2 together with the nitrogen atom they are attached to form an optionally substituted 4-7 membered heterocycle;

L^1 is a bond or is NR^{70}, O, S, or $(CR^{71}R^{72})_d$; wherein each R^{70}, R^{71}, and R^{72} independently are hydrogen or C_1-C_6 alkyl;

d is 1, 2, or 3;

ring B is a optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, 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;

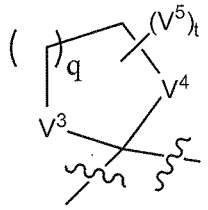
each Y and Z is independently $CR^{10}R^{11}$, O, S, SO, SO_2, or NR^{10}; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1-C_6 alkoxy, or $CR^{10}R^{11}$ is C=O, provided that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and Y and Z are both not heteroatoms or oxidized forms thereof;

wherein Y is α or β substituted relative to the $-LCOR^3$;

ring C is a optionally substituted C_6-C_{10} aryl or optionally substituted 5-10 membered heteroaryl containing 1-3 nitrogen atoms, or an oxidized form of N;

wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

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;

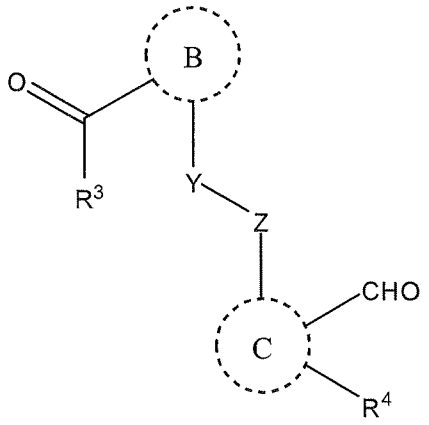
R^{81} and R^{82} independently are selected from the group consisting of hydrogen; optionally substituted C_1-C_6 alkyl, COR^{83} and CO_2R^{84};

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

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

R^4 is OH, halo, C_1-C_6 alkoxy, C_3-C_6 cycloalkoxy or O-R, where R is a prodrug moiety, wherein the C_1-C_6 alkoxy is optionally substituted with 1-5 halo.

3. The compound of claim 2 having a structure of Formula (III):

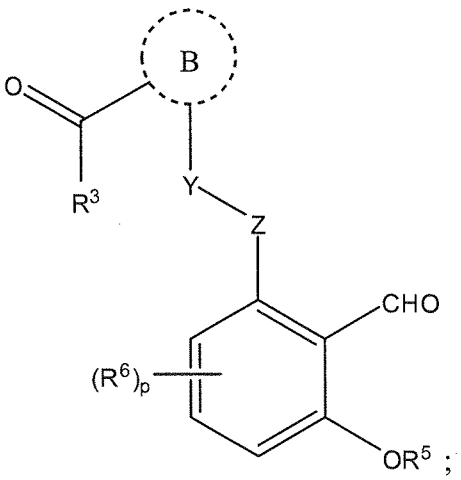


(III)

or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein Y-Z is $-CH_2O-$ or $-CH_2CH_2-$ and the remaining substituents are defined as in claim 2.

4. The compound of claim 3 or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein R^4 and –CHO are joined to adjacent atoms on ring C.

5. The compound of claim 3 or 4 having a structure of Formula IIIA:



IIIA

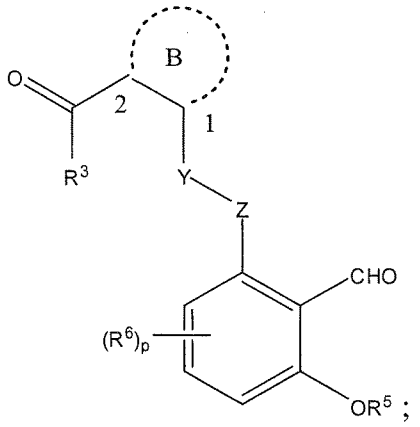
or a tautomer thereof, or pharmaceutically acceptable salt of each thereof wherein ring B is a optionally substituted C_6-C_{10} aryl, optionally substituted 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N;

R^5 is hydrogen, C_1-C_6 alkyl or a prodrug moiety R;

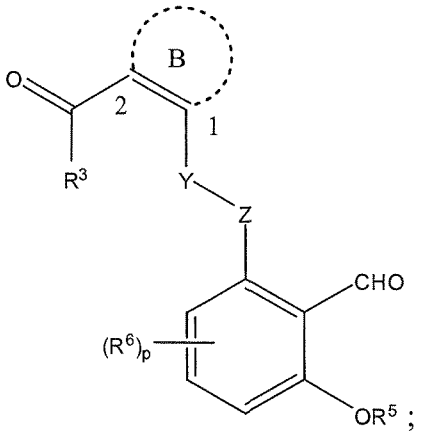
R^6 is halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo; and

p is 0, 1, 2 or 3.

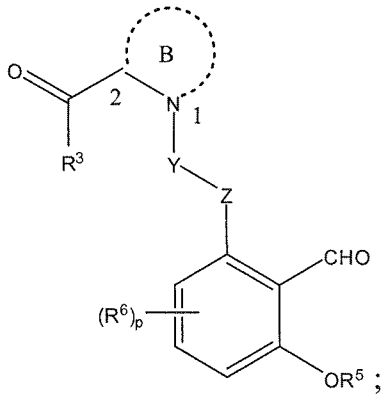
6. The compound of claim 3 or 4 or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein the compound is of Formula IIIB, IIIC, or IIID:



IIIB

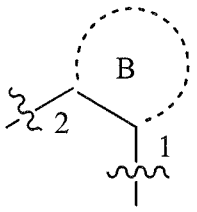


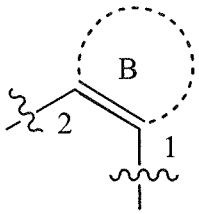
IIIC

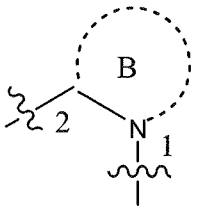


IIID

wherein



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, and


are optionally substituted 4-10 membered heterocycle as defined in claim 1;

R^5 is hydrogen, C_1-C_6 alkyl or a prodrug moiety;

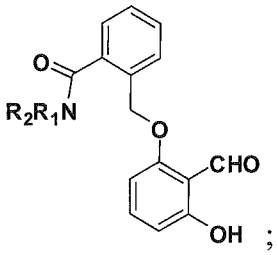
R^6 is halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo;

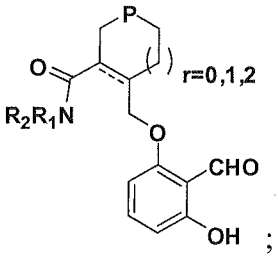
p is 0, 1, 2 or 3.

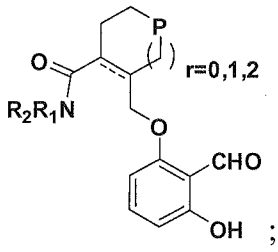
7. The compound of any one of claims 3-6 or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein ring B is substituted with 1-3: halo, C_1-C_6 alkyl, COR^{15}, or $COOR^{15}$; and

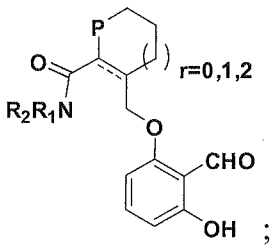
R^{15} is C_1-C_6 alkyl.

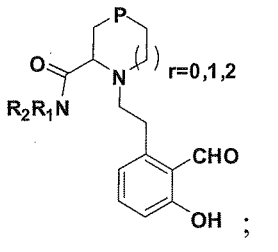
8. The compound of claim 3 or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein the compound is selected from the group consisting of

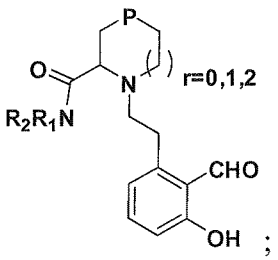


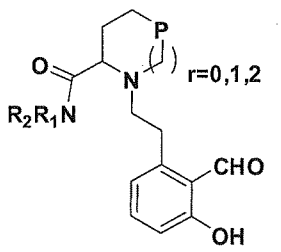
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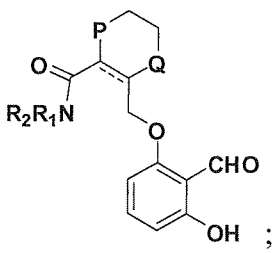
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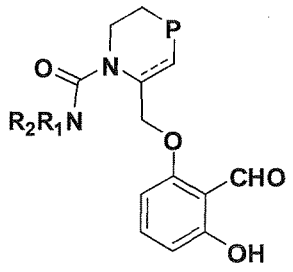
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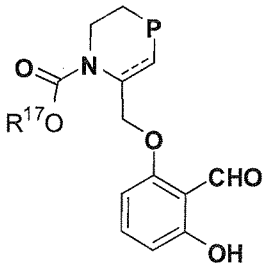
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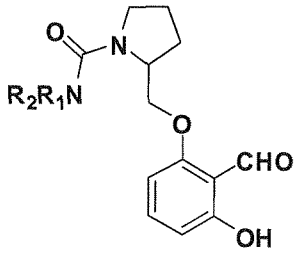
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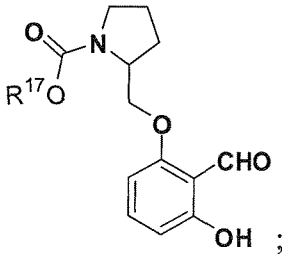
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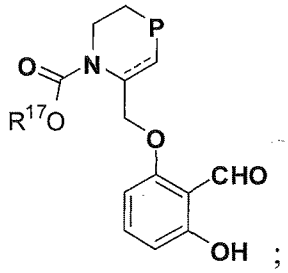
;



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and


;

or an N oxide thereof, wherein

 is a single or a double bond;

each P and Q is independently selected from CHR^{17}, $NCOR^{15}$, NCO_2R^{15}; N-O, O, S, SO, and SO_2;

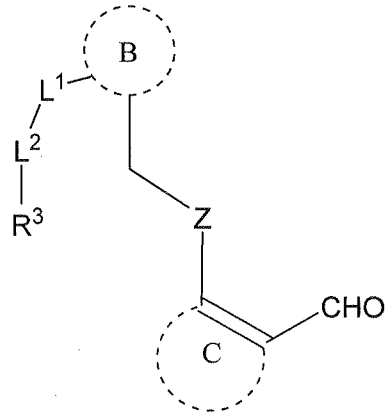
each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, a C_6-C_{10} aryl, 5-10 membered heteroaryl or a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein the alkyl, aryl, heteroaryl or heterocyclyl is optionally substituted;

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;

R^{17} 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;

and r is 0, 1, or 2.

9. A compound of claim 1 having a structure of Formula (V):



(V)

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

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond;

L^2 is C=O or SO_2;

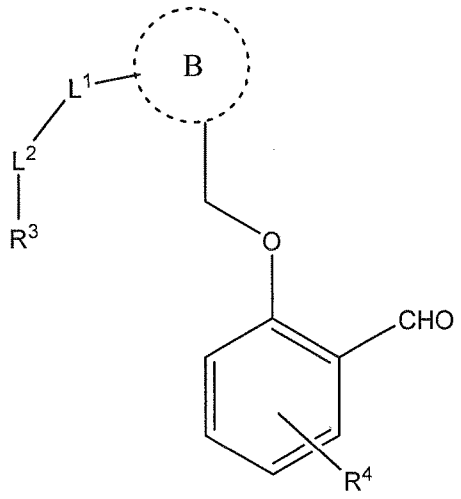
ring B is a optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

Z is O;

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl 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 of which is optionally substituted with 1-4: halo, oxo, $-OR^{19}$, 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, C_1-C_6 alkoxy and/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; and

R^{19} is hydrogen.

10. A compound of claim 1 having a structure of Formula (VI):



(VI)

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

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond;

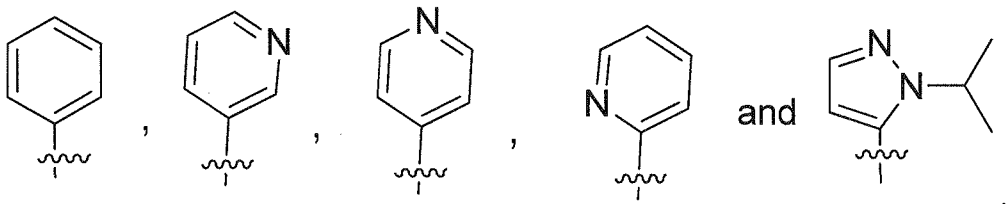
L^2 is C=O or SO_2;

ring B is a 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;

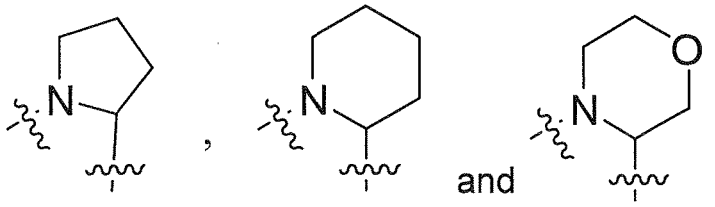
R^4 is $-OR^{19}$ or C_1-C_6 alkoxy and is located on a carbon adjacent to a carbon substituted with -CHO; and

R^{19} is hydrogen.

11. The compound of any one of claims 8-10 or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein R^3 is selected from the group consisting of:



12. The compound of any one of claims 8-10 or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein ring B is selected from the group consisting of



13. The compound of claim 1 or a tautomer thereof, or pharmaceutically acceptable salt of each of thereof or a pharmaceutically acceptable salt of each thereof, wherein

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkoxy, or $-NR^1R^2$;

each R^1 and R^2 independently is hydrogen, C_1-C_6 alkyl, or C_3-C_8 cycloalkyl, or R^1 and R^2 together with the nitrogen atom they are attached to form an optionally substituted 4-7 membered heterocycle; or

R^3 is C_6-C_{10} aryl, or a 5-10 membered heteroaryl, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond;

L^2 is C=O or SO_2;

ring B is a 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, 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; or

Y is $CR^{10}R^{11}$,and Z is O; each R^{10} and R^{11} independently is hydrogen or C_1-C_3 alkyl;

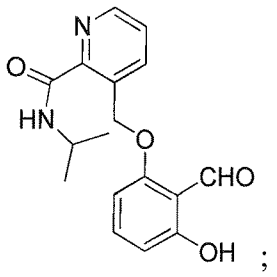
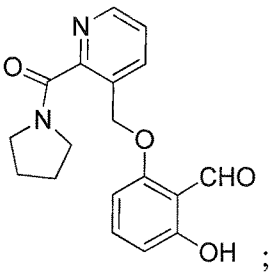
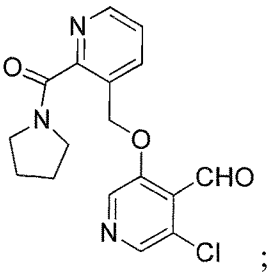
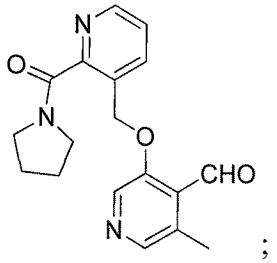
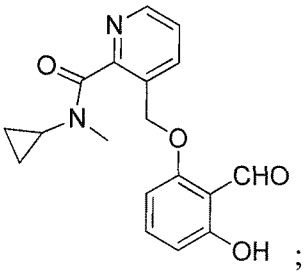
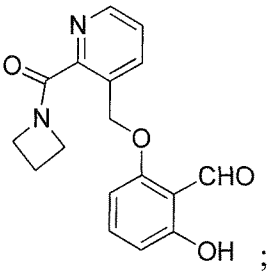
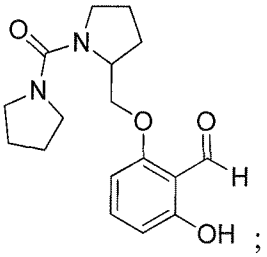
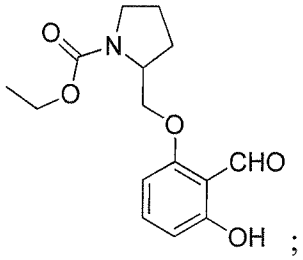
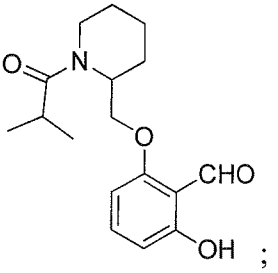
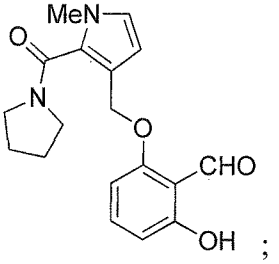
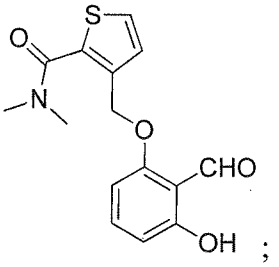
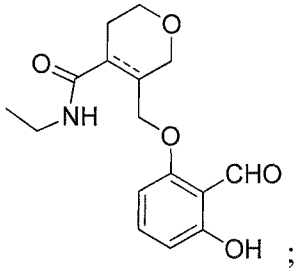
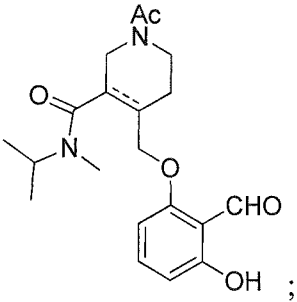
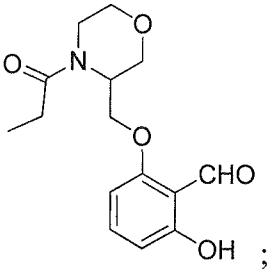
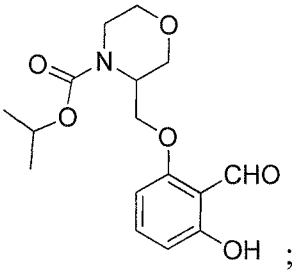
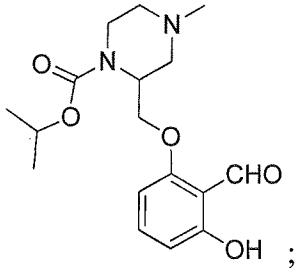
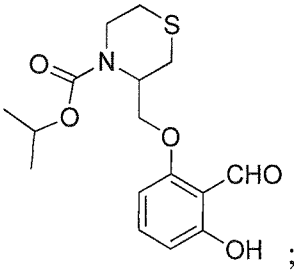
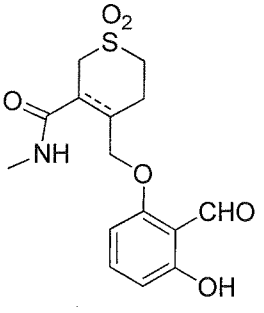
wherein Y is α substituted relative to the $-L^1L^2R^3$;

wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl 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 of which is optionally substituted with 1-4: halo, oxo, $-OR^{19}$, 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, C_1-C_6 alkoxy; where R^{19} is hydrogen; and

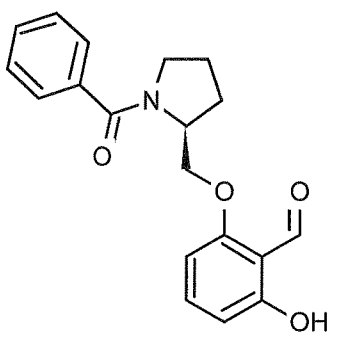
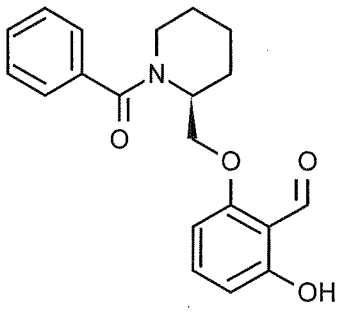
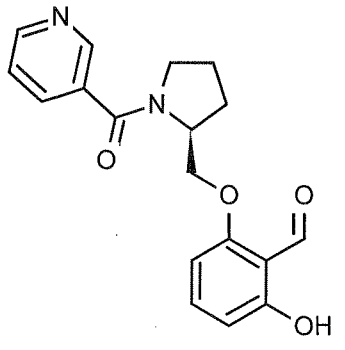
CV^1V^2 is –CHO.

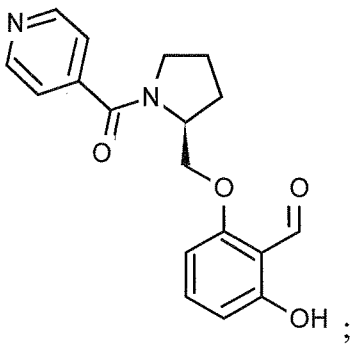
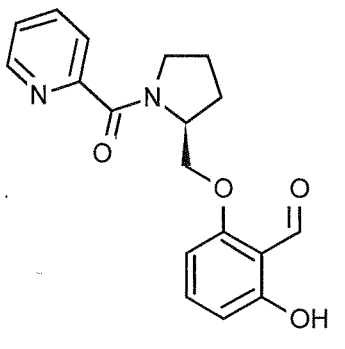
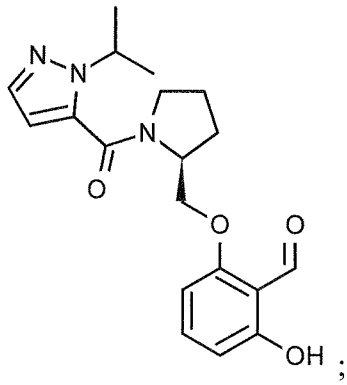
14. The compound of claim 1 of formula:

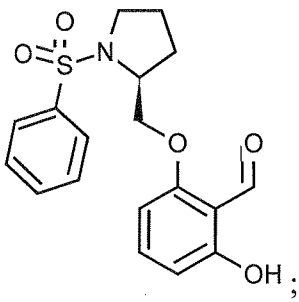
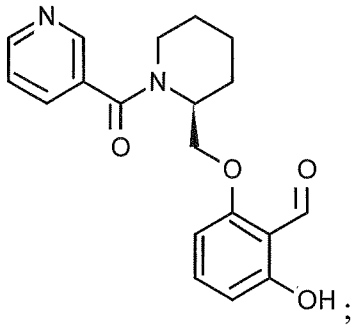
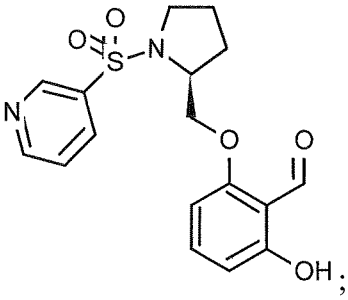

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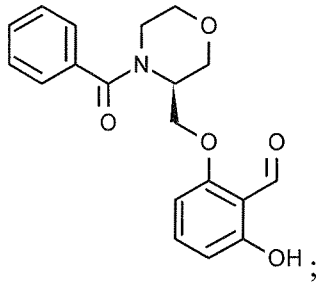
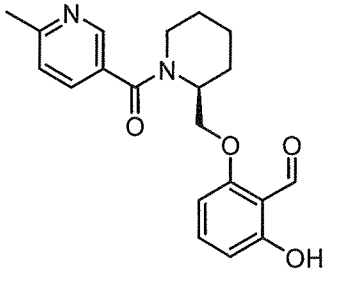
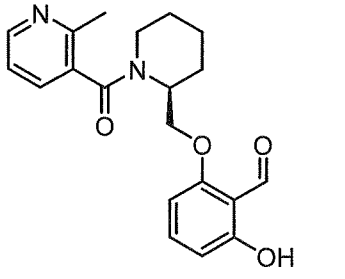
or an N oxide thereof, or a pharmaceutically acceptable salt of each thereof.

15. The compound of claim 1 of formula:


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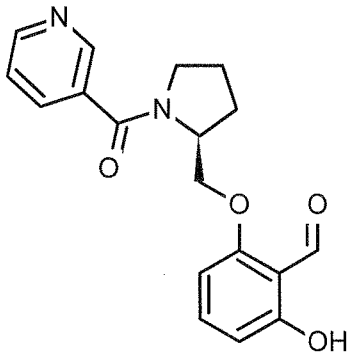

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and


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

16. The compound of claim 1 having the structure:



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

17. A composition comprising a compound of any one of claims 1-16 and at least one pharmaceutically acceptable excipient.

18. Use of a compound of any one of claims 1-16 or the composition of claim 17 in the manufacture of a medicament for increasing oxygen affinity of hemoglobin S in a subject.

19. Use of a compound of any one of claims 1-16 or the composition of claim 17 in the manufacture of a medicament for the treatment of oxygen deficiency in a subject in need thereof.

20. Use of a compound of any one of claims 1-16 or the composition of claim 17 in the manufacture of a medicament for the treatment of sickle cell disease, a cancer, a pulmonary disorder, acute respiratory distress syndrome, a stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, or a wound.