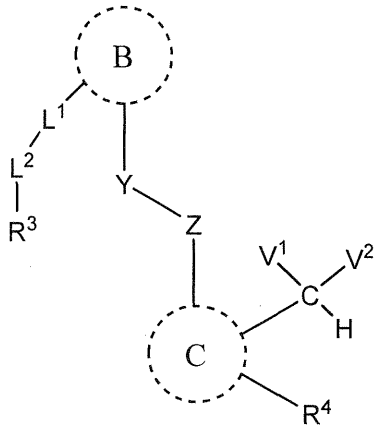


(I)

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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 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 the aryl or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond or is O, S, or $(CR^{71}R^{72})d$; wherein each 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 C_6-C_{10} aryl, 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, 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, and wherein the C_6-C_{10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycle is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$; or

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 heterocycle is optionally substituted;

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, or SO_2, then the other is not CO, and Y and Z are not both heteroatoms or oxidized forms thereof;

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

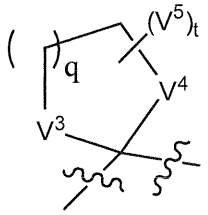
wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

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 members independently selected from halo, oxo, $-OR^{19}$, C_1-C_6 alkyl, and C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 members independently selected from halo, C_1-C_6 alkoxy and 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;

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 not both 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;

R^4 is OH, halo, C_1-C_6 alkoxy, or C_3-C_6 cycloalkoxy, wherein the C_1-C_6 alkoxy is optionally substituted with 1-5 halo;

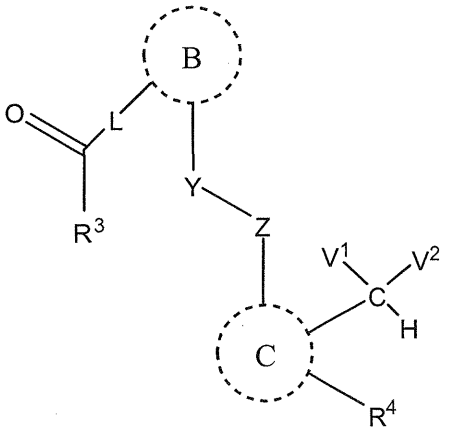
wherein R^4 and $-CV^1V^2H$ are joined to adjacent atoms on ring C.

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 embodiment, 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,

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;

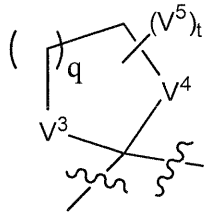
wherein Y is α or β substituted relative to the $-L^1L^2R^3$;

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, $-OR^2$, 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^2 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;

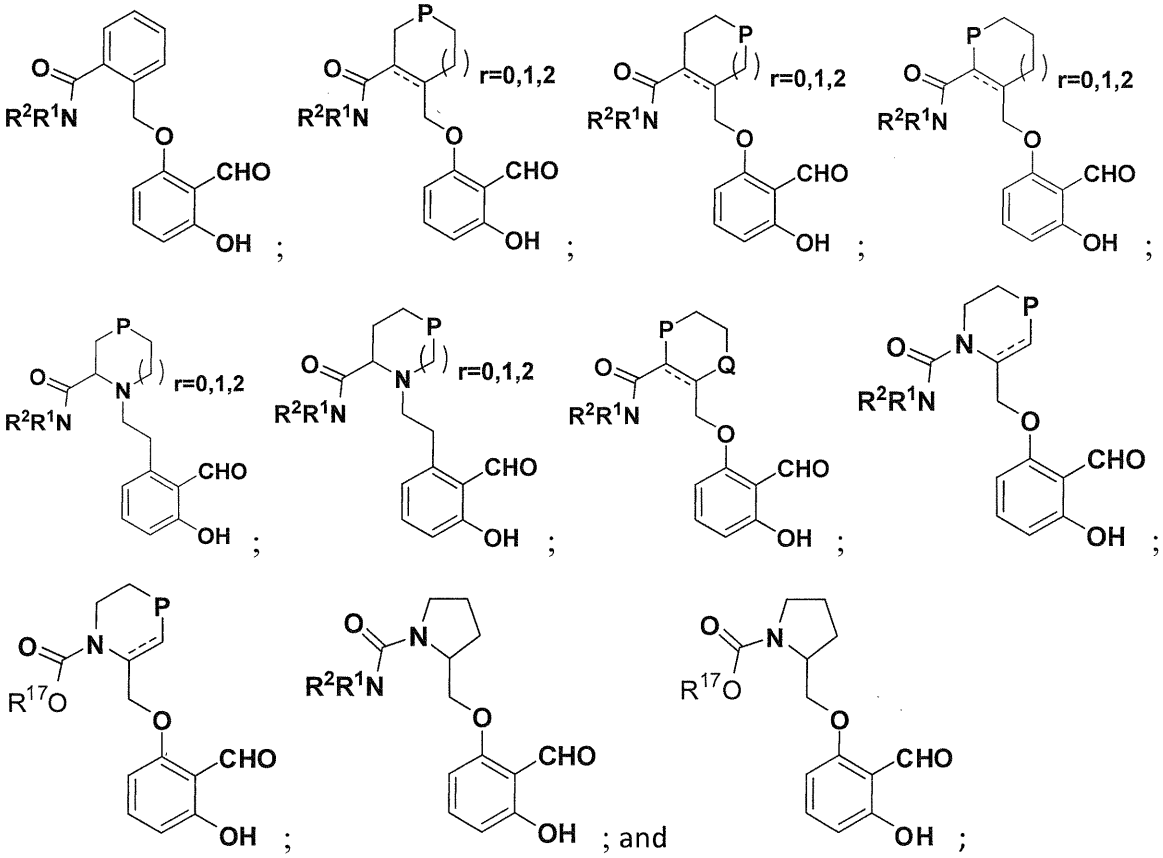
R^{81} and R^{82} independently are selected from the group consisting of hydrogen; optionally substituted C_1-C_6 alkyl, COR^{83} and CO_2R^{84};

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

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

[0010] In one embodiment, ring b is joined to L^1 or L^2 via a nitrogen atom. In another embodiment, R^3 is joined to L^2 via a nitrogen atom.

[0010a] In one aspect, there is provided a compound or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, 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.

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

[0012] In still further embodiments of the 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 embodiments of the 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 a condition associated with oxygen deficiency in a subject in need thereof, wherein the condition is 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.

[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.

DETAILED DESCRIPTION OF THE INVENTION

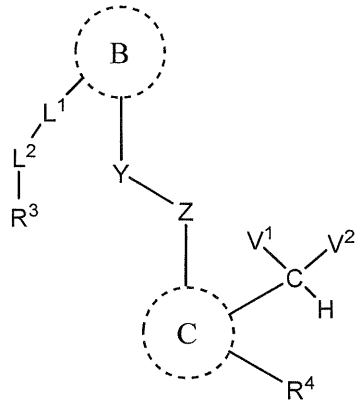
Definitions

[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

CLAIMS

1. A compound of Formula (I)



(I)

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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 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 the aryl or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond or is O, S, or $(CR^{71}R^{72})d$; wherein each 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 C_6-C_{10} aryl, 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, 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, and wherein the C_6-C_{10} aryl, 5-10 membered heteroaryl, or 4-10 membered heterocycle is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$;

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 heterocycle is optionally substituted;

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, or SO_2, then the other is not CO, and Y and Z are not both heteroatoms or oxidized forms thereof;

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

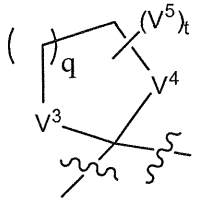
wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

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 members independently selected from halo, oxo, $-OR^{19}$, C_1-C_6 alkyl, and C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 members independently selected from halo, C_1-C_6 alkoxy and 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;

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 not both 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};

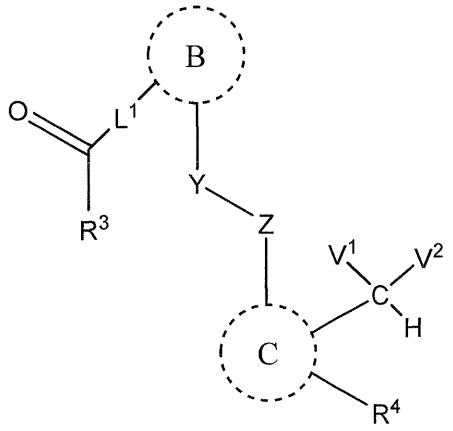
R^{83} is hydrogen or optionally substituted C_1-C_6 alkyl; and

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

R^4 is OH, halo, C_1-C_6 alkoxy, or C_3-C_6 cycloalkoxy, wherein the C_1-C_6 alkoxy is optionally substituted with 1-5 halo;

wherein R^4 and $-CV^1V^2H$ are joined to adjacent atoms on ring C.

2. The compound of claim 1 having Formula (II)



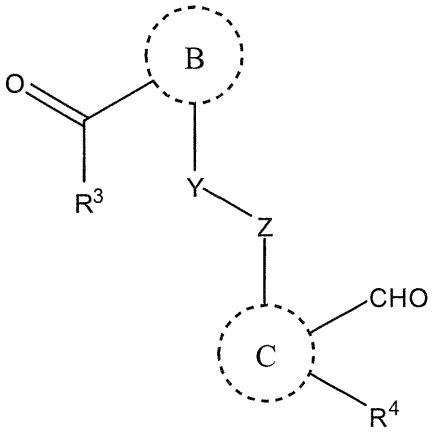
(II)

or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkoxy, or $-NR^1R^2$;

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

ring C is an 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.

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

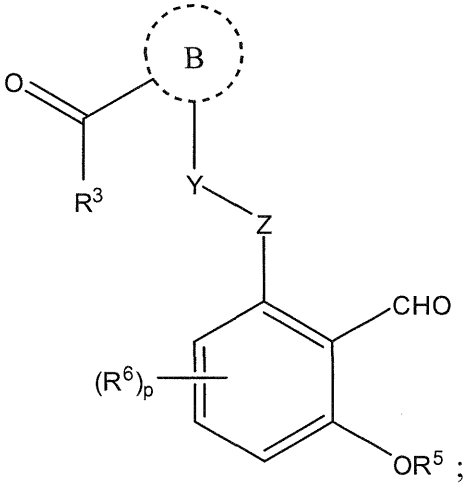


(III)

or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein Y-Z is $-CH_2O-$ or $-CH_2CH_2-$; and

R^4 and –CHO are joined to adjacent atoms on ring C.

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



IIIA

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

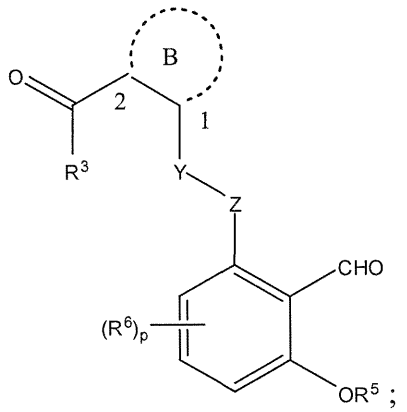
ring B is C_6-C_{10} aryl or 5-10 membered heteroaryl having 1-3 nitrogen atoms or oxidized forms of N, wherein the C_6-C_{10} aryl or 5-10 membered heteroaryl is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$;

R^5 is hydrogen or C_1-C_6 alkyl;

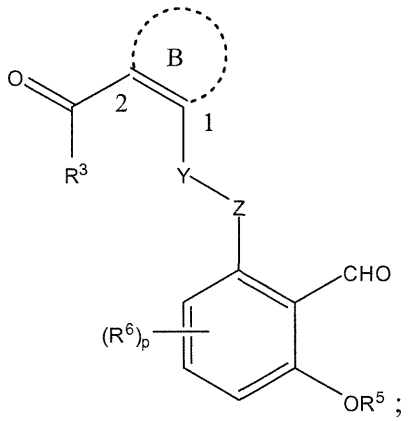
R^6 is halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-3 halo; and

p is 0, 1, 2 or 3.

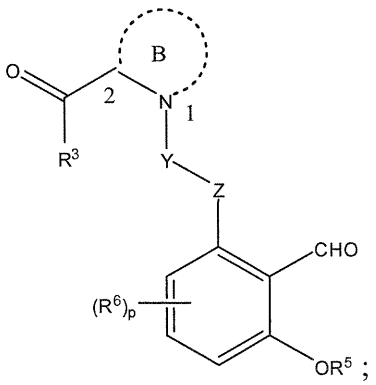
5. The compound of claim 3 or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein the compound is of Formula IIIB, IIIC, or IIID:



IIIB

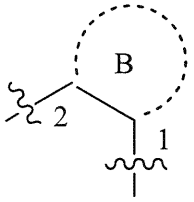


IIIC



IIID

wherein



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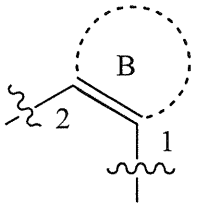

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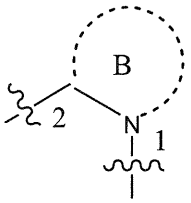


are a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, and wherein the 4-10 membered heterocycle is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$;

R^5 is hydrogen or C_1-C_6 alkyl;

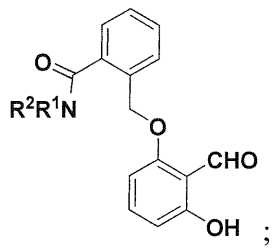
R^6 is halo, C_1-C_6 alkyl, or C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-3 halo; and

p is 0, 1, 2 or 3.

6. The compound of any one of claims 3-5 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.

7. A compound 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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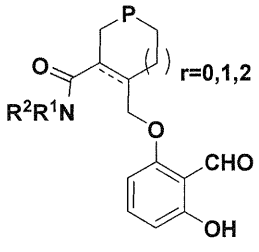

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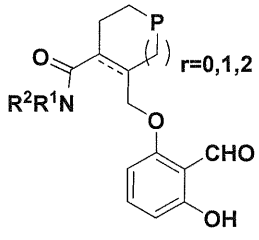

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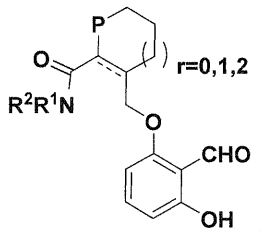

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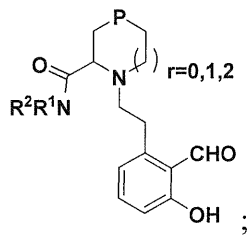

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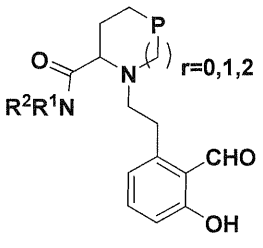

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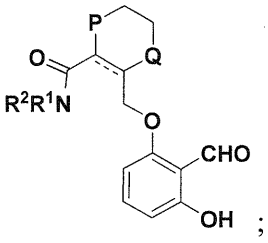

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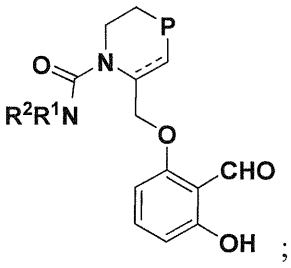

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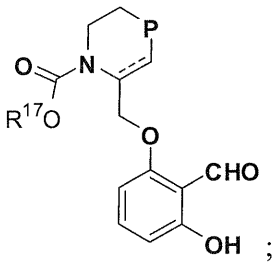

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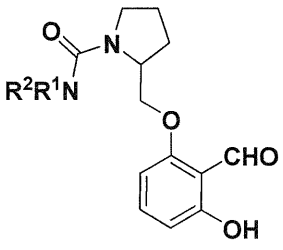

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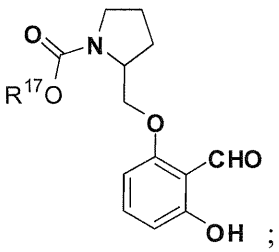


;

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.

8. The compound of claim 1 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 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;

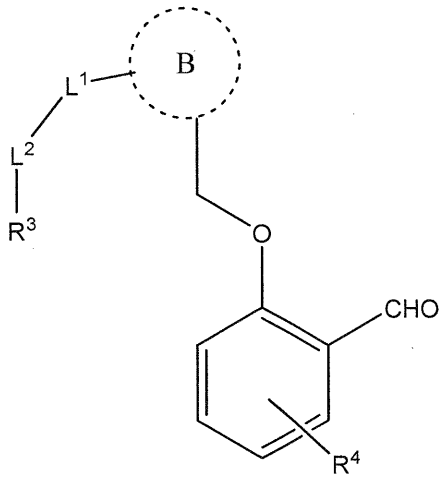
ring B is 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, and wherein the 4-10 membered heterocycle is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$;

Y is CH_2;

Z is O;

CV^1V^2 is C=V, wherein V is O.

9. The 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 the aryl or heteroaryl is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond;

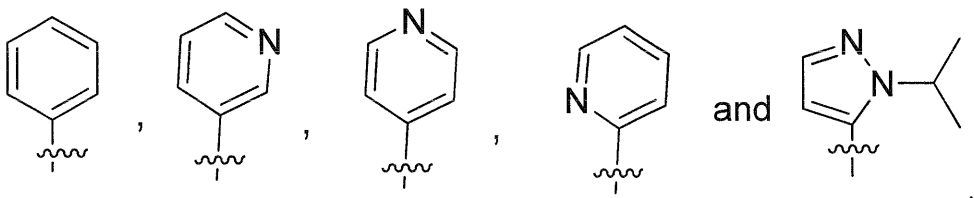
L^2 is C=O or SO_2;

ring B is 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 wherein the 4-10 membered heterocycle is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$;

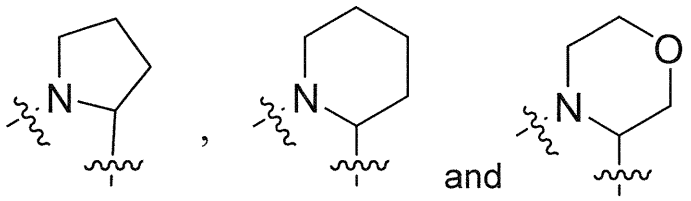
R^4 is $-OR^{19}$ or C_1-C_6 alkoxy and is located on a carbon adjacent to a carbon substituted with -CHO; and

R^{19} is hydrogen.

10. The compound of any one of claims 8-9 or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein R^3 is selected from the group consisting of:



11. The compound of any one of claims 8-9 or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein ring B is selected from the group consisting of



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

R^3 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, 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 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 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 wherein the 4-10 membered heterocycle is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$;

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;

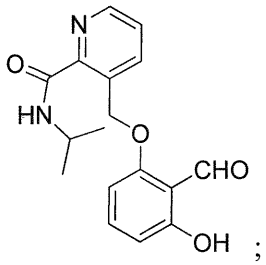
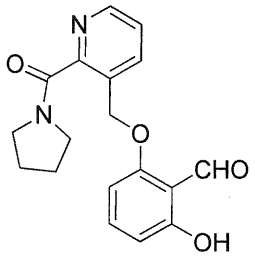
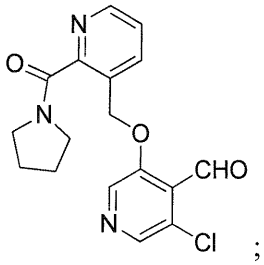
wherein Y is α substituted relative to the $-L^1L^2R^3$;

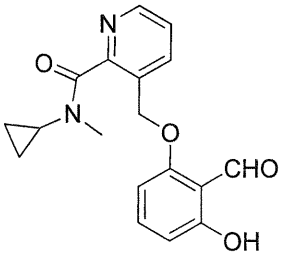
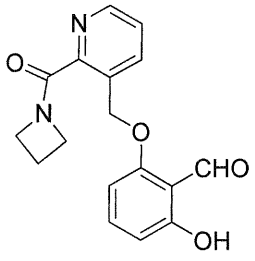
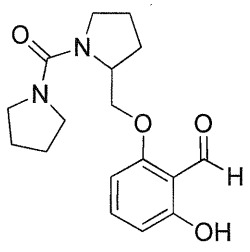
wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

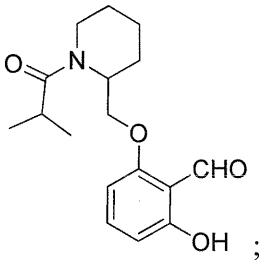
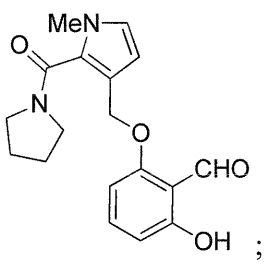
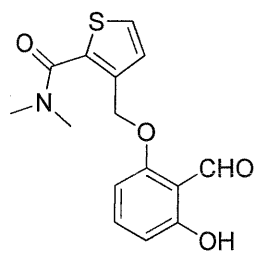
ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, each of which is optionally substituted with 1-4 members independently selected from halo, oxo, $-OR^{19}$, C_1-C_6 alkyl, and C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 members independently selected from halo and C_1-C_6 alkoxy; where R^{19} is hydrogen; and

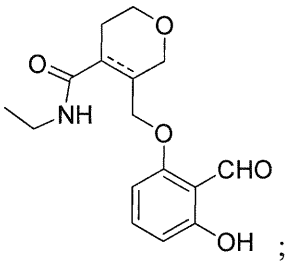
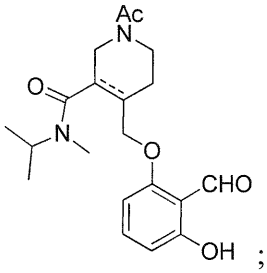
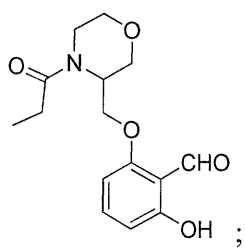
CV^1V^2H is –CHO.

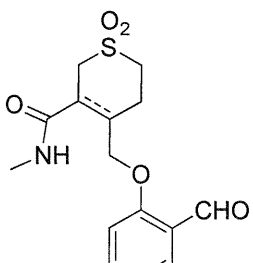
13. The compound of claim 1 of formula:

 ;  ;  ;

 ;  ;  ;

 ;  ;  ;

 ;  ;  ;

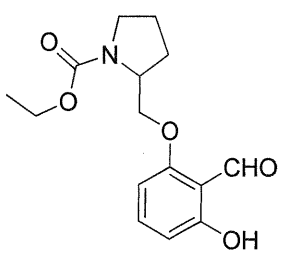
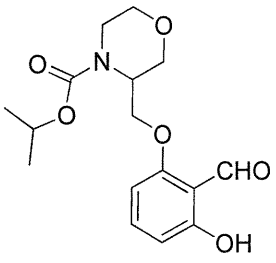
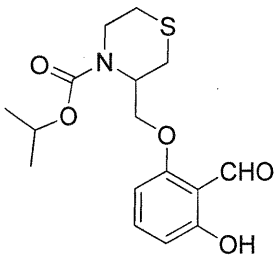


or

wherein  is a single or a double bond;

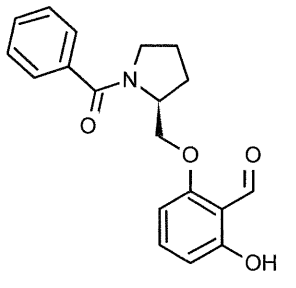
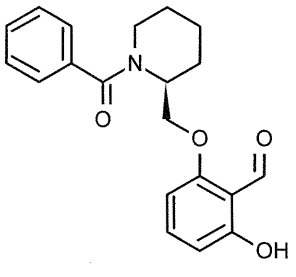
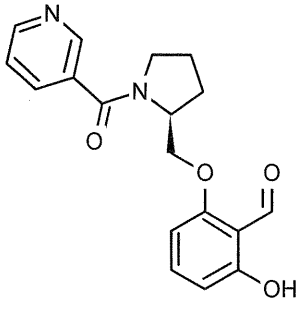
or an N oxide thereof, or a pharmaceutically acceptable salt of each thereof.

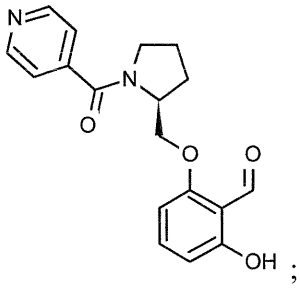
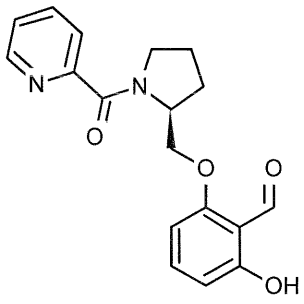
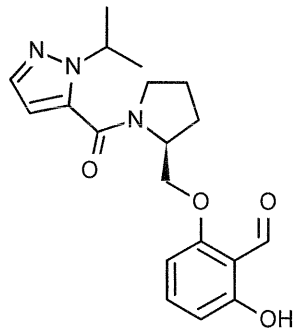
14. The compound of claim 7 of formula:

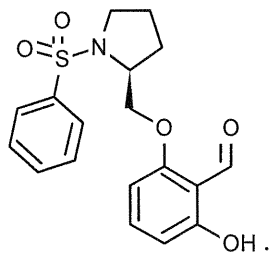
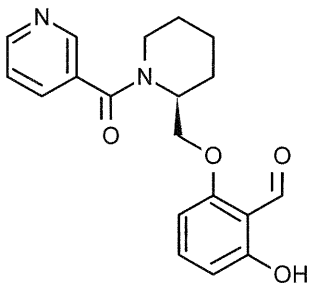
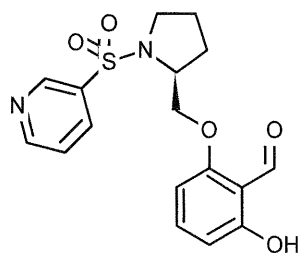
 ;  ; or 

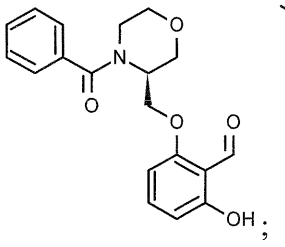
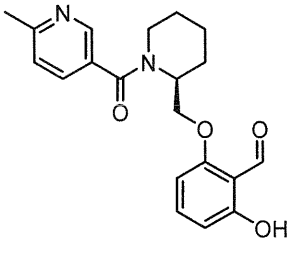
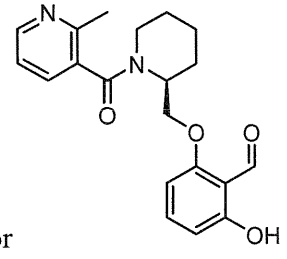
or an N oxide thereof, or a pharmaceutically acceptable salt of each thereof.

15. The compound of claim 1 of formula:

 ;  ;  ;

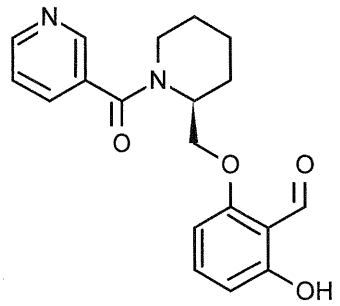
 ;  ;  ;

 ;  ;  ;

 ;  ; or 

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 pharmaceutical 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 a condition associated with oxygen deficiency in a subject in need thereof, wherein the condition is 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.

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.