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

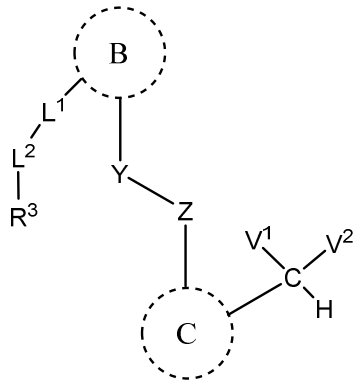
[0002] Sickle cell disease is a disorder of the red blood cells, found particularly among those of African and Mediterranean descent. The basis for sickle cell disease is found in sickle hemoglobin (HbS), which contains a point mutation relative to the prevalent peptide sequence of hemoglobin (Hb).

[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

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

[0005] In certain examples of the 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;

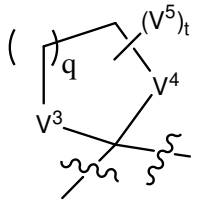
L^2 is C=O or SO_2;

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:



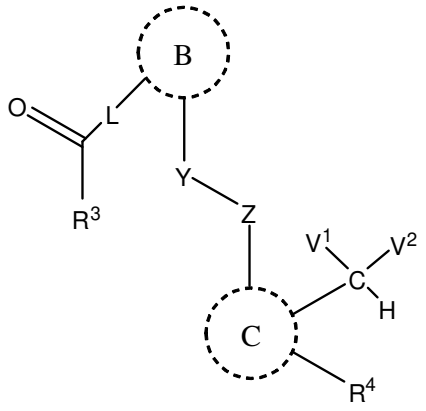
wherein each V^3 and V^4 are independently O, S, or NH, provided that when one of V^3 and V^4 is S, the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60}, where each R^{60}

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 certain examples of the disclosure, 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;

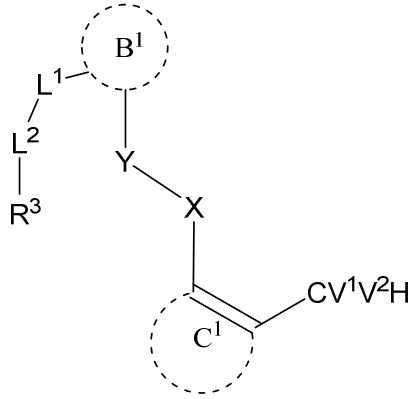
R^{80} is optionally substituted C_1-C_6 alkyl;

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.

[0009] In certain examples of the 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

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;

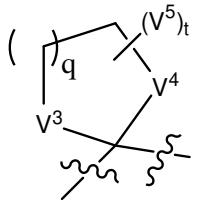
wherein Y is α or β substituted relative to the $–L^1L^2R^3$;

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;

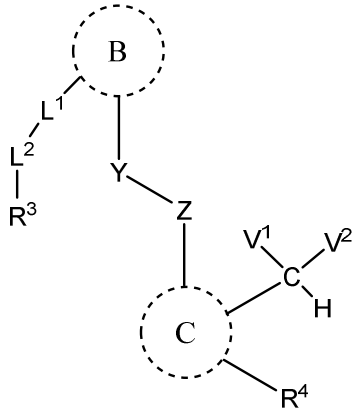
R^{81} and R^{82} independently are selected from the group consisting of hydrogen; optionally substituted C_1-C_6 alkyl, COR^{83} and CO_2R^{84};

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 example, ring b is joined to L^1 or L^2 via a nitrogen atom. In another example, R^3 is joined to L^2 via a nitrogen atom.

[0010a] In one aspect, the present disclosure provides a compound of Formula (I)



(I)

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

wherein:

R^3 is pyridine optionally substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of oxo, halo, -CN, NO_2, $-N_2+$, $-CO_2R^{100}$, $-OR^{100}$, $-SR^{100}$, $-SOR^{100}$, $-SO_2R^{100}$, $-NR^{101}R^{102}$, $-CONR^{101}R^{102}$, $-SO_2NR^{101}R^{102}$, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CR^{100}=C(R^{100})_2$, $-CCR^{100}$, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, and C_2-C_{12} heteroaryl;

L^1 is a bond, 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 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 of 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 C=O, and Y and Z are not both heteroatoms or oxidized forms thereof;

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

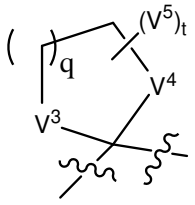
wherein Z and $–CV^1V^2H$ are joined to adjacent atoms on ring C;

ring C is 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, wherein ring C 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;

R^{19} is hydrogen;

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;

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 C_1-C_6 alkyl;

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

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

R^{84} is C_1-C_6 alkyl;

each R^{100} independently is hydrogen, C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, or C_2-C_{12} heteroaryl; wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 substituents selected from halo, 1-3 C_1-C_6 alkyl, 1-3 C_1-C_6 haloalkyl, and 1-3 C_1-C_6 alkoxy;

R^{101} and R^{102} independently is hydrogen, C_1-C_8 alkyl, optionally substituted with -CO_2H or an ester thereof, C_1-C_6 alkoxy, oxo, $-CR^{103}=C(R^{103})_2$, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, or C_2-C_{12} heteroaryl, or

R^{101} and R^{102} together with the nitrogen atom they are attached to form a 5-7 membered heterocycle; and

each R^{103} independently is hydrogen, C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, or C_2-C_{12} heteroaryl; wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl or 1-3 halo.

[0011] In further examples of the disclosure, a composition is provided comprising any of the compounds described herein, and at least a pharmaceutically acceptable excipient. In one aspect, the present disclosure provides a composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt of each thereof, and at least one pharmaceutically acceptable excipient.

[0012] In still further examples 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. In one aspect, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for increasing oxygen affinity of hemoglobin S.

[0013] In further examples 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. In one aspect, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for treating sickle cell

disease. In another aspect, the present disclosure provides use of a compound disclosed herein in the manufacture of a medicament for treating cancer, a pulmonary disorder, stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, acute respiratory disease syndrome, or a wound. In one aspect, the present disclosure provides use of a composition disclosed herein in the manufacture of a medicament for treating sickle cell disease in a subject in need thereof. In another aspect, the present disclosure provides use of a composition disclosed herein in the manufacture of a medicament for treating cancer, a pulmonary disorder, stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, acute respiratory disease syndrome, or a wound in a subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

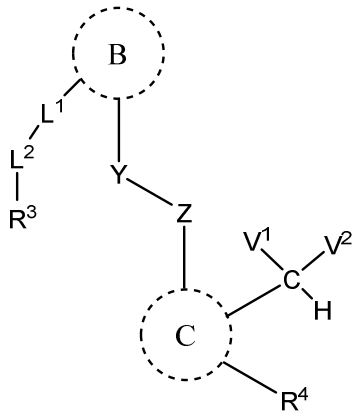
[0014] It must be noted that as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a solvent” includes a plurality of such solvents.

[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)



(I)

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

R^3 is pyridine optionally substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of oxo, halo, -CN, NO_2, $-N_2+$, $-CO_2R^{100}$, $-OR^{100}$, $-SR^{100}$, $-SOR^{100}$, $-SO_2R^{100}$, $-NR^{101}R^{102}$, $-CONR^{101}R^{102}$, $-SO_2NR^{101}R^{102}$, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CR^{100}=C(R^{100})_2$, $-CCR^{100}$, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, and C_2-C_{12} heteroaryl;

L^1 is a bond, 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 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 of 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 C=O, and Y and Z are not both heteroatoms or oxidized forms thereof;

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

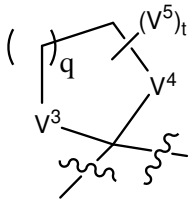
wherein Z and $-CV^1V^2H$ are joined to adjacent atoms on ring C;

ring C is 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, wherein ring C 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;

R^{19} is hydrogen;

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;

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 C_1-C_6 alkyl;

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

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

R^{84} is C_1-C_6 alkyl;

each R^{100} independently is hydrogen, C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, or C_2-C_{12} heteroaryl; wherein each alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 substituents selected from halo, 1-3 C_1-C_6 alkyl, 1-3 C_1-C_6 haloalkyl, and 1-3 C_1-C_6 alkoxy;

R^{101} and R^{102} independently is hydrogen, C_1-C_8 alkyl, optionally substituted with -CO_2H or an ester thereof, C_1-C_6 alkoxy, oxo, $-CR^{103}=C(R^{103})_2$, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, or C_2-C_{12} heteroaryl, or

R^{101} and R^{102} together with the nitrogen atom they are attached to form a 5-7 membered heterocycle; and

each R^{103} independently is hydrogen, C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, or C_2-C_{12} heteroaryl; wherein each cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1-3 alkyl or 1-3 halo.

2. The compound of claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein L^1 is a bond.

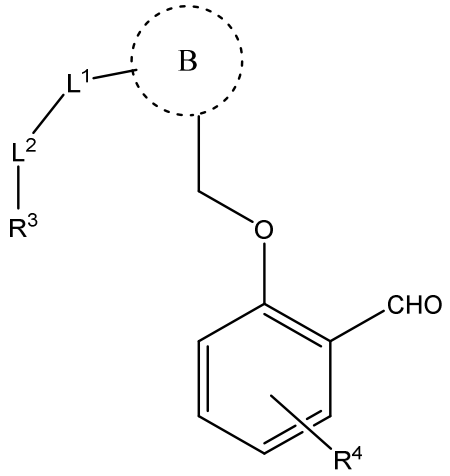
3. The compound of claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein L^2 is C=O.

4. The compound of claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein L^2 is SO_2.

5. The compound of any one of claims 1-4, or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein ring C is phenyl optionally substituted with 1-4 members independently selected from halo, $-OR^{19}$, C_1-C_6 alkyl, and C_1-C_6 alkoxy, wherein R^{19} is hydrogen.

6. The compound of any one of claims 1-5, or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein CV^1V^2 is C=V, and V is O.

7. The compound of claim 1 of Formula (VI):



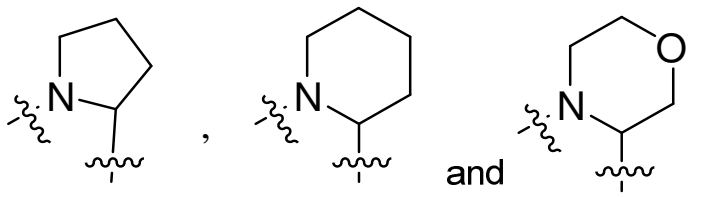
(VI)

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

wherein:

R^4 is OH or C_1-C_6 alkoxy.

8. The compound of claim 7, or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein ring B is selected from the group consisting of



9. The compound of any one of claims 7 or 8, or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein L^1 is a bond and L^2 is C=O or SO_2.

10. The compound of any one of claims 7-9, or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein R^4 is OH.

11. The compound of claim 1, wherein R^3 is a pyridine optionally substituted with 1, 2, or 3 substituents selected from the group consisting of oxo, halo, -CN, NO_2, $-N_2+$, $-CO_2R^{100}$, $-OR^{100}$, $-SR^{100}$, $-SOR^{100}$, $-SO_2R^{100}$, $-NR^{101}R^{102}$, $-CONR^{101}R^{102}$, $-SO_2NR^{101}R^{102}$, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-CR^{100}=C(R^{100})_2$, $-CCR^{100}$, C_3-C_{10} cycloalkyl, C_3-C_{10} heterocyclyl, C_6-C_{12} aryl, and C_2-C_{12} heteroaryl.

12. The compound of claim 1, wherein R^3 is a pyridine optionally substituted with 1-4 C_1-C_6 alkyl.

13. A composition comprising a compound of any one of claims 1-12, or a pharmaceutically acceptable salt of each thereof, and at least one pharmaceutically acceptable excipient.

14. Use of a compound of any one of claims 1-12 in the manufacture of a medicament for increasing oxygen affinity of hemoglobin S.

15. Use of a compound of any one of claims 1-12 in the manufacture of a medicament for treating sickle cell disease.

16. Use of a compound of any one of claims 1-12 in the manufacture of a medicament for treating cancer, a pulmonary disorder, stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, acute respiratory disease syndrome, or a wound.

17. Use of a composition of claim 13 in the manufacture of a medicament for treating sickle cell disease in a subject in need thereof.

18. Use of a composition of claim 13 in the manufacture of a medicament for treating cancer, a pulmonary disorder, stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, acute respiratory disease syndrome, or a wound in a subject in need thereof.