

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

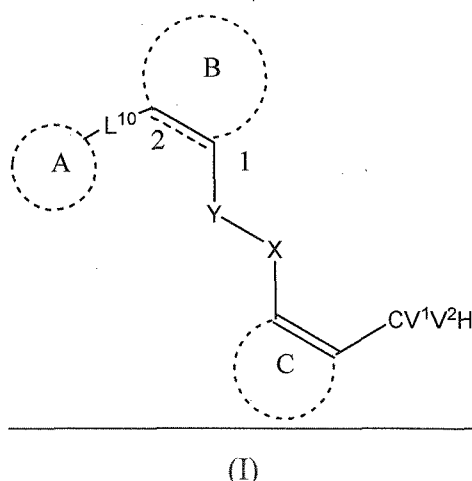
[0002] Sickle cell disease is a disorder of the red blood cells, found particularly among those of African and Mediterranean descent. The basis for sickle cell disease is found in sickle hemoglobin (HbS), which contains a point mutation relative to the prevalent peptide sequence of hemoglobin (Hb).

[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. U.S. 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):



or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein L^{10} is optionally substituted methylene or, preferably, a bond;

ring A is C_6 - C_{10} aryl, a C_3 - C_8 cycloalkyl, a 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 each of the aryl, heteroaryl, cycloalkyl, or heterocycle is optionally substituted with 1-4: halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and/or C_3 - C_{10} cycloalkyl, wherein the C_1 - C_6 alkyl is optionally substituted with 1-5 halo, C_1 - C_6 alkoxy, and/or C_3 - C_{10} cycloalkyl;

ring B is a 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 each of the heteroaryl and the heterocycle is optionally substituted with 1-4: halo, C_1 - C_6 alkyl and/or $-CO$ - C_1 - C_6 alkyl,

 is a single or a double bond;

each X and Y is independently $(CR^{20}R^{21})_e$, O, S, SO, SO_2 , or NR^{20} ; e is 1 to 4, preferably 1; each R^{20} and R^{21} independently is hydrogen or C_1 - C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1 - C_6 alkoxy, or $CR^{20}R^{21}$ is $C=O$, provided that if one of X and Y is O, S, SO, SO_2 , then the other is not CO, and X and Y are both not heteroatoms or oxidized forms thereof;

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

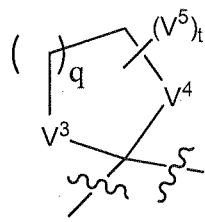
substituted with 1-4: halo, oxo, $-OR^1$, C_1-C_6 alkyl, $-COOR^1$, NR^5R^6 , and/or C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo, C_1-C_6 alkoxy and/or a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

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

R^5 and R^6 are each independently hydrogen, optionally substituted C_1-C_6 alkyl or $-COOR^3$;

R^3 is hydrogen or optionally substituted C_1-C_6 alkyl;

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 optionally substituted with 1-3 OH groups, or V^5 is CO_2R^{60} , where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 0, 1, 2, or 4; or CV^1V^2 is $C=V$, wherein V is O, NOR^{80} , or $NNR^{81}R^{82}$;

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

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

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

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

with the proviso that:

(i) when ring C is C₆-C₁₀ aryl optionally substituted with 1-4: halo, oxo, -OR¹, C₁-C₆ alkyl, -COOR¹, NR⁵R⁶, and/or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ 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 ring B is 4-10 membered heterocyclyl 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 heterocycle is optionally

substituted with 1-4: halo, C₁-C₆ alkyl and/or -CO-C₁-C₆alkyl;

then ring A is not 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 and optionally substituted with 1-4: halo, C₁-

C₆alkyl, C₁-C₆ alkoxy, and/or C₃-C₁₀ cycloalkyl, wherein the C₁-C₆ alkyl is

optionally substituted with 1-5 halo, C₁-C₆ alkoxy, and/or C₃-C₁₀cycloalkyl;

(ii) when ring C is C₆-C₁₀ aryl optionally substituted with 1-4: halo, oxo, -OR¹,

C₁-C₆ alkyl, -COOR¹, NR⁵R⁶, and/or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl is

optionally substituted with 1-5 halo, C₁-C₆ 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 ring B is 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 and optionally substituted with 1-4: halo, C₁-C₆ alkyl and/or

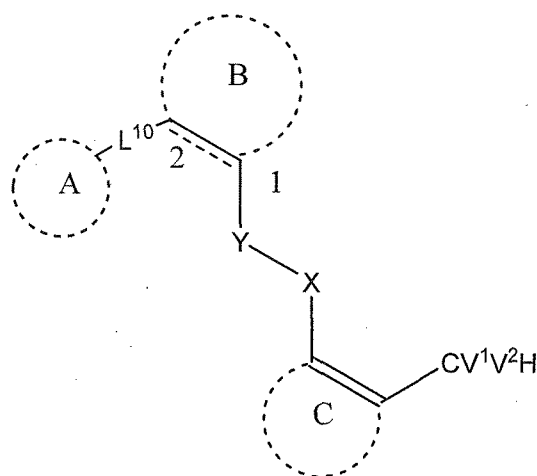
-CO-C₁-C₆ alkyl;

then ring A is not 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 heterocycle is optionally substituted
with 1-4: halo, C₁-C₆ alkyl C₁-C₆ alkoxy, and/or C₃-C₁₀ cycloalkyl, wherein
the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ alkoxy, and/or
C₃-C₁₀ cycloalkyl; and

(iii) when ring B is 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 and optionally substituted with 1-4:
halo, C₁-C₆ alkyl and/or -CO-C₁-C₆ alkyl;

then ring A is not 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 and optionally substituted with 1-4: halo, C₁-C₆alkyl, C₁-C₆ alkoxy, and/or C₃-C₁₀
cycloalkyl, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ alkoxy,
and/or C₃-C₁₀cycloalkyl.

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



(I)

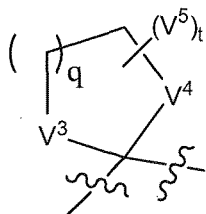
or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein L^{10} is optionally substituted methylene or, preferably, a bond;



is a single or a double bond;

each X and Y is independently $(CR^{20}R^{21})_e$, O, S, SO, SO_2 , or NR^{20} ; e is 1 to 4, preferably 1; each R^{20} and R^{21} independently is hydrogen or C_1 - C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1 - C_6 alkoxy, or $CR^{20}R^{21}$ is $C=O$, provided that if one of X and Y is O, S, SO, SO_2 , then the other is not CO, and X and Y are both not heteroatoms or oxidized forms thereof;

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 optionally substituted with 1-3 OH groups, or V^5 is 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 $NNR^{81}R^{82}$;

ring C is C₆-C₁₀ 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, preferably with 1-4: halo, oxo, -OR¹, C₁-C₆ alkyl, -COOR¹, and/or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ 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

R¹ is hydrogen or a prodrug moiety;

provided that when ring C is C₆-C₁₀ aryl;

and ring B is optionally substituted 4-10 membered heterocyclyl;

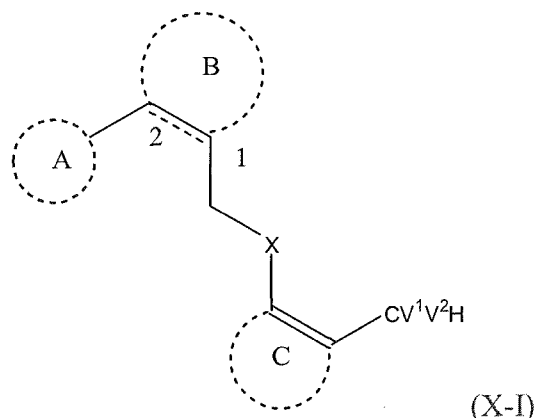
then ring A excludes optionally substituted 5-10 membered heteroaryl;

and provided that when ring C is C₆-C₁₀ aryl;

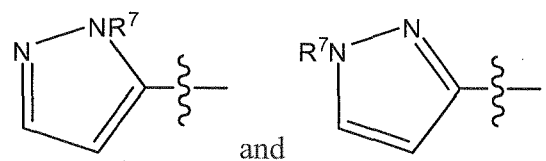
and ring B is optionally substituted 5-10 membered heteroaryl;

then ring A is not optionally substituted 4-10 membered heterocycle.

[0007a] In another aspect, there is provided a compound of formula (X-I):

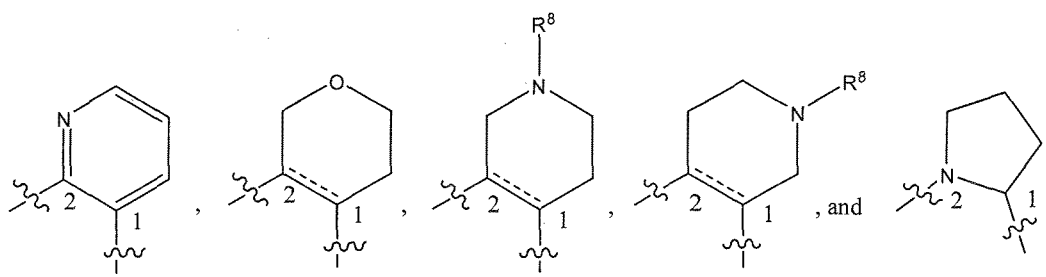


or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein ring A is phenyl optionally substituted with 1-3 halo and/or C₁-C₆ alkoxy, or is a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, optionally substituted, or is



wherein R^7 is C_1 - C_6 alkyl, optionally substituted with 3-5 fluoro groups, or is C_3 - C_6 cycloalkyl;

ring B is selected from the group consisting of



wherein R^8 is C_1 - C_6 alkyl, $-\text{CO}-C_1$ - C_6 alkyl or a prodrug moiety;

X is O, S, SO, or SO_2 ;

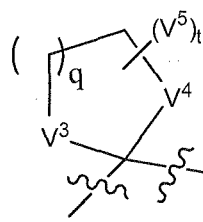
 is a single or a double bond;

ring C is phenyl or a 6 membered nitrogen-containing heteroaryl, each of which is

optionally substituted with 1-4: halo, oxo, $-\text{OR}^1$, 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 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

each R^1 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 1, 2, or 4; or CV^1V^2 is $\text{C}=\text{V}$, wherein V is O, NOR^{80} , or $\text{NNR}^{81}\text{R}^{82}$;

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

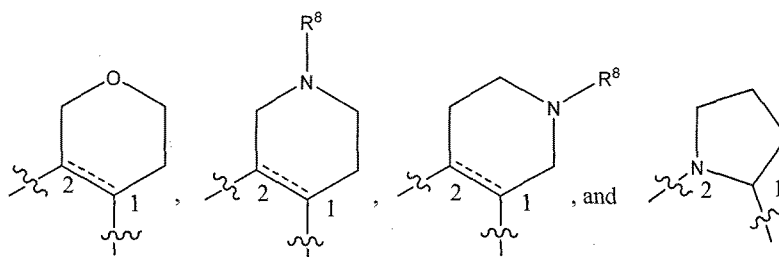
R^{81} and R^{82} independently are selected from the group consisting of hydrogen, optionally substituted C_1 - C_6 alkyl, COR^{83} , or CO_2R^{84} ;

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

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

provided that:

- (i) when ring C is phenyl optionally substituted with 1-4: halo, oxo, $-OR^1$, 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 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;

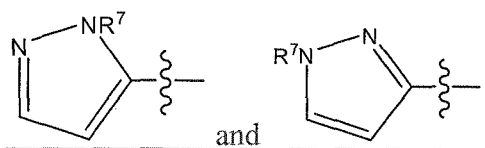


and ring B is

wherein R^8

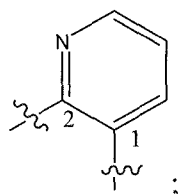
is C_1-C_6 alkyl, $-CO-C_1-C_6$ alkyl or a prodrug moiety;

then ring A is not



wherein R^7 is C_1-C_6 alkyl, optionally substituted with 3-5 fluoro groups, or is C_3-C_6 cycloalkyl;

- (ii) when ring C is phenyl optionally substituted with 1-4: halo, oxo, $-OR^1$, 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 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;

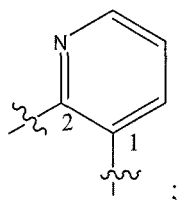


and ring B is

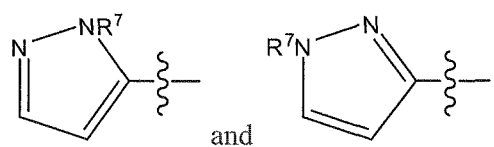
then ring A is not optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, optionally substituted;
and

(iii) when ring C is phenyl or a 6 membered nitrogen-containing heteroaryl, each of which is optionally substituted with 1-4: halo, oxo, $-OR^1$, 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 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 ring B is

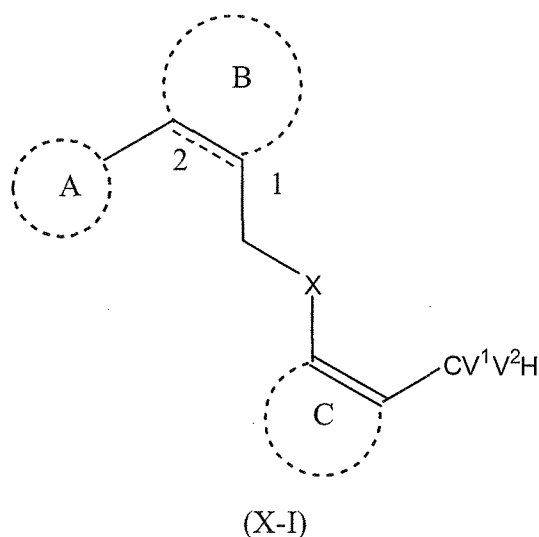


then ring A is not



wherein R^7 is C_1-C_6 alkyl, optionally substituted with 3-5 fluoro groups, or is C_3-C_6 cycloalkyl.

[0008] In certain aspects ~~embodiments of the invention~~disclosure, a compound of formula (X-I) is provided:



an N-oxide thereof, or a tautomer or each thereof, or a pharmaceutically acceptable salt of each of the preceding, wherein

ring A is phenyl optionally substituted with 1-3 halo and/or C_1-C_6 alkoxy, or 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, optionally substituted, or is

R^{10} is hydrogen, hydroxy, halo or C_1 - C_6 alkoxy;

R^{11} is hydrogen or C_1 - C_6 alkyl; and

R^{12} is $-OR^1$;

wherein R^1 is hydrogen or the prodrug moiety R.

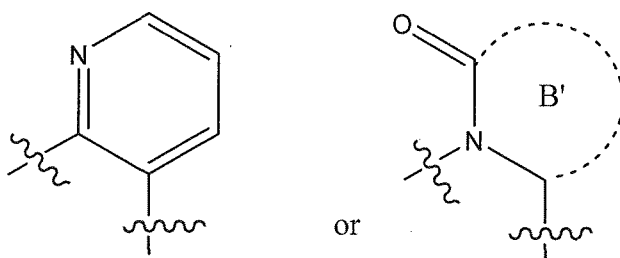
[0013] In certain aspects ~~embodiments~~ of the invention ~~disclosure~~, a compound of formula (I) is provided:

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

L^{10} is optionally substituted methylene or, preferably, a bond;

ring A 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 and/or C_1 - C_6 alkoxy groups;

ring B is:



wherein ring B' including the $-N-CO-$ moiety is a 5-6 membered heterocycle containing up to 3 heteroatoms selected from nitrogen, oxygen, and sulfur and oxidized forms of N and S, wherein each of the heteroaryl and the heterocycle is optionally substituted with 1-4 C_1 - C_6 alkyl groups;

each X and Y is independently $(CR^{20}R^{21})_e$, O, S, SO, SO_2 , or NR^{20} ; e is 1 to 4, preferably 1; each R^{20} and R^{21} independently is hydrogen or C_1 - C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1 - C_6 alkoxy, or $CR^{20}R^{21}$ is $C=O$, provided that if one of X and Y is O, S, SO, SO_2 , then the other is not CO, and X and Y are both not heteroatoms or oxidized forms thereof;

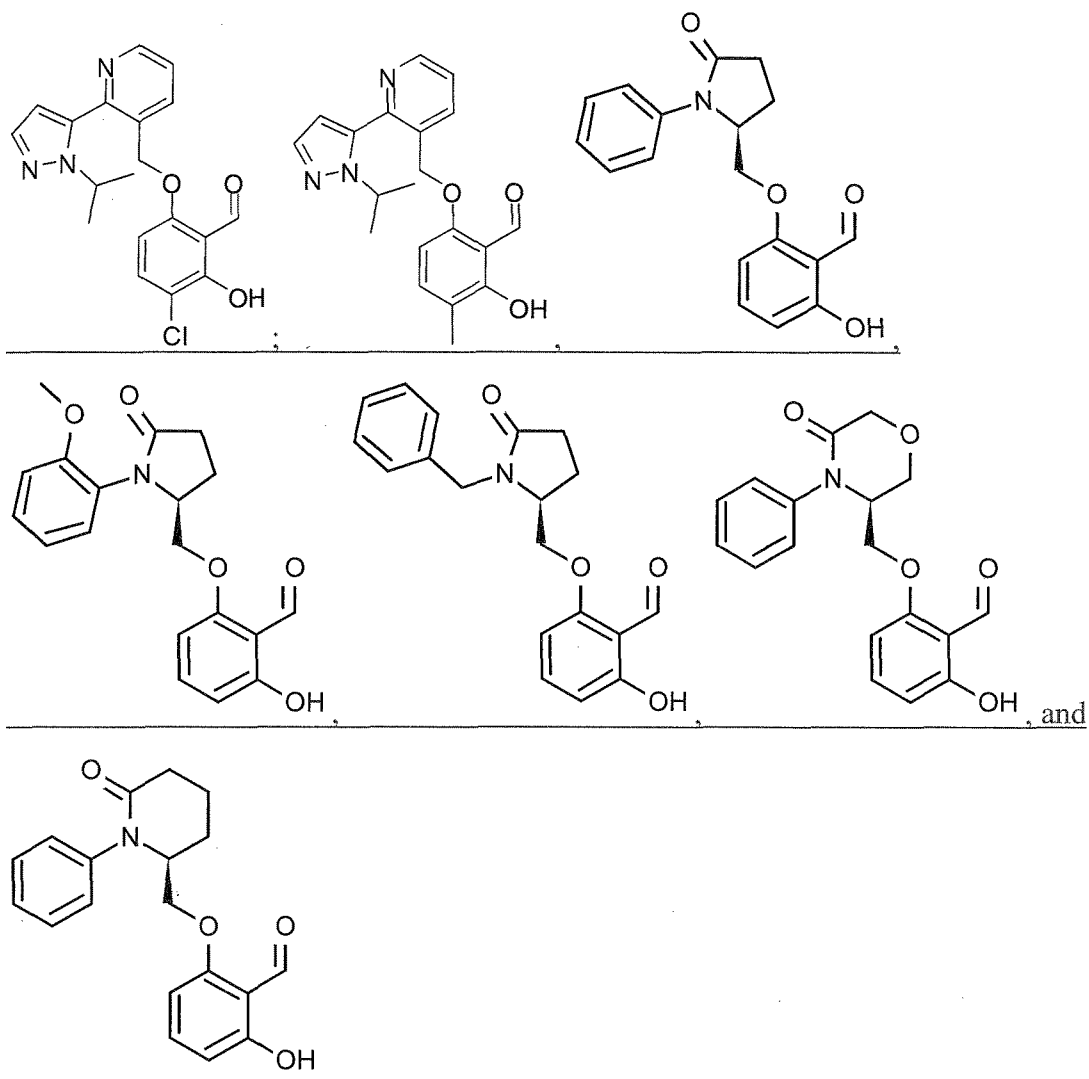
ring C is C_6 - C_{10} aryl or a 5-10 membered heteroaryl containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, each of which is optionally substituted with 1-4: halo, oxo, $-OR^1$, C_1 - C_6 alkyl, $-COOR^5$, NR^5R^6 ,

and provided that when ring C is C₆-C₁₀ aryl;

and ring B is optionally substituted 5-10 membered heteroaryl;

then ring A is not optionally substituted 4-10 membered heterocycle.

[0013a] In one aspect, there is provided a compound selected from:



or N oxides thereof, or a pharmaceutically acceptable salt of each thereof.

[0014] In further aspects of the invention one aspect, there is provided a composition is provided comprising any of the a compounds as described herein, and at least a pharmaceutically acceptable excipient.

[0014a] In one aspect, there is provided use of a compound as defined herein in the manufacture of a medicament for increasing oxygen affinity of hemoglobin S in a subject.

[0015] 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.

[0015a] In one aspect, there is provided use of a compound as defined herein in the manufacture of a medicament for the treatment of oxygen deficiency associated with sickle cell anemia in a subject in need thereof.

[0016] 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.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0017] 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.

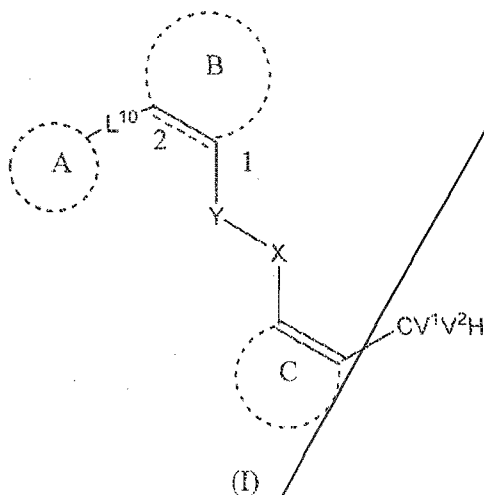
[0018] As used herein, the term “comprising” or “comprises” is intended to mean that the compositions and methods include the recited elements, but not excluding others. “Consisting essentially of” when used to define compositions and methods, shall mean excluding other elements of any essential significance 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.

[0019] 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

What is claimed is:

1. A compound of formula (I):



or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein L^{10} is optionally substituted methylene or, preferably, a bond;

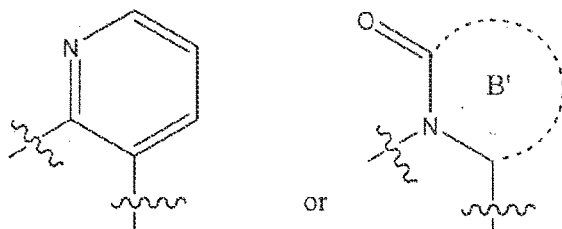
ring A is C_6 - C_{10} aryl, a C_3 - C_8 cycloalkyl, a 5-10 membered heteroaryl or a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl, heteroaryl, cycloalkyl, or heterocycle is optionally substituted with 1-4: halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and/or C_3 - C_{10} cycloalkyl, wherein the C_1 - C_6 alkyl is optionally substituted with 1-5 halo, C_1 - C_6 alkoxy, and/or C_3 - C_{10} cycloalkyl; or

ring A 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 and/or C_1 - C_6 alkoxy groups;

ring B is a 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 each of the

heteroaryl and the heterocycle is optionally substituted with 1-4: halo, C₁-C₆ alkyl and/or -CO-C₁-C₆ alkyl, or

ring B is:



wherein ring B' including the -N-CO- moiety is a 5-6 membered heterocycle containing up to 3 heteroatoms selected from nitrogen, oxygen, and sulfur and oxidized forms of N and S, wherein each of the heteroaryl and the heterocycle is optionally substituted with 1-4 C₁-C₆ alkyl groups;

is a single or a double bond;

each X and Y is independently (CR²⁰R²¹)_e, O, S, SO, SO₂, or NR²⁰; e is 1 to 4, preferably 1; each R²⁰ and R²¹ independently is hydrogen or C₁-C₃ alkyl optionally substituted with 1-3 halo, OH, or C₁-C₆ alkoxy, or CR²⁰R²¹ is C=O, provided that if one of X and Y is O, S, SO, SO₂, then the other is not CO, and X and Y are both not heteroatoms or oxidized forms thereof;

ring C is C₆-C₁₀ 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, -OR¹, C₁-C₆ alkyl, -COOR¹, and/or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ 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; or

ring C is C₆-C₁₀ 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, -OR¹, C₁-C₆ alkyl, -COOR¹, NR⁵R⁶,

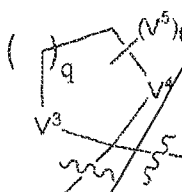
R¹ is a hydrogen, C₁-C₆ alkyl or a prodrug moiety; wherein the alkyl is optionally substituted with a 5-10 membered heteroaryl containing up to 5 ring

heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, which is optionally substituted with 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 the heteroaryl is optionally substituted with C₁-C₆ alkyl;

R⁵ and R⁶ are each independently hydrogen, optionally substituted C₁-C₆ alkyl or -COOR³;

R³ is hydrogen or optionally substituted C₁-C₆ alkyl;

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



wherein each V³ and V⁴ are independently O, S, or NH, provided that when one of V³ and V⁴ is S, the other is NH, and provided that V³ and V⁴ are both not NH; q is 1 or 2; each V⁵ is independently C₁-C₆ alkyl optionally substituted with 1-3 OH groups, or V⁵ is CO₂R⁶⁰, where each R⁶⁰ independently is C₁-C₆ alkyl or hydrogen; t is 0, 1, 2, or 4; or CV¹V² is C=V, wherein V is O, NOR⁸⁰, or NNR⁸¹R⁸²;

R⁸⁰ is optionally substituted C₁-C₆ alkyl;

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

R⁸³ is hydrogen or optionally substituted C₁-C₆ alkyl; and

R⁸⁴ is optionally substituted C₁-C₆ alkyl;

with the proviso that when ring C is C₆-C₁₀ aryl;

and ring B is optionally substituted 4-10 membered heterocyclyl;

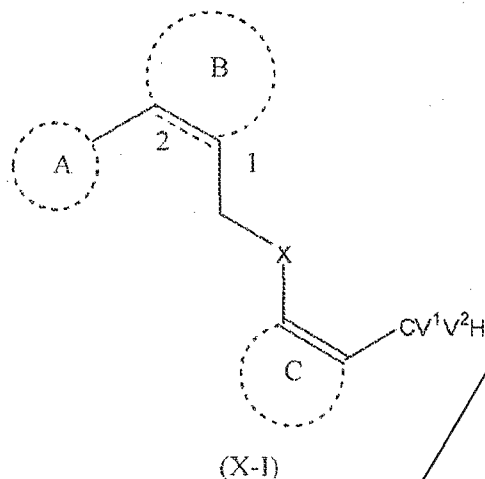
then ring A excludes optionally substituted 5-10 membered heteroaryl;

and provided that when ring C is C₆-C₁₀ aryl;

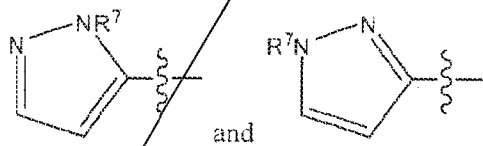
and ring B is optionally substituted 5-10 membered heteroaryl;

then ring A is not optionally substituted 4-10 membered heterocycle.

2. A compound of formula (X-I):

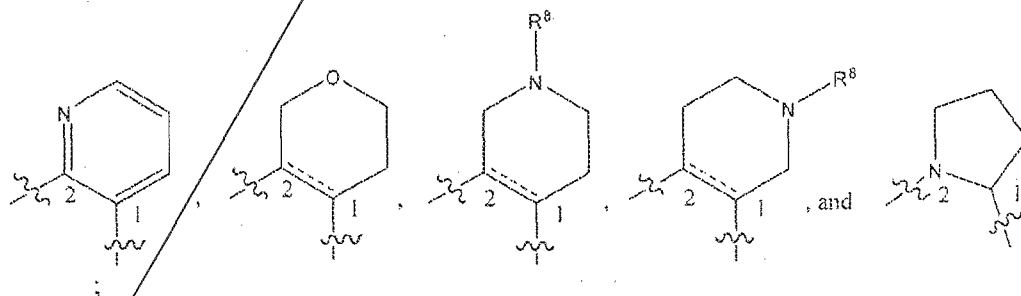


or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein ring A is phenyl optionally substituted with 1-3 halo and/or C₁-C₆ alkoxy, or is a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, optionally substituted, or is



wherein R⁷ is C₁-C₆ alkyl, optionally substituted with 3-5 fluoro groups, or is C₃-C₆ cycloalkyl;

ring B is selected from the group consisting of



wherein R⁸ is C₁-C₆ alkyl, -CO-C₁-C₆ alkyl or a prodrug moiety and wherein the pyridyl ring is optionally substituted with a halo or an NR²⁵(CH₂)₂N(R²⁵)₂ group where each R²⁵ is independently hydrogen or C₁-C₆ alkyl;

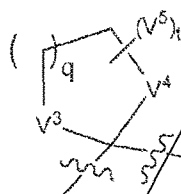
X is O, S, SO, or SO₂;

 is a single or a double bond;

ring C is phenyl or a 6 membered nitrogen-containing heteroaryl, each of which is optionally substituted with 1-4: halo, oxo, $-OR^1$, C_1-C_6 alkyl, $-COOR^1$, 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 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

each R^1 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 1, 2, or 4; or CV^1V^2 is $C=V$, wherein V is O, NOR^{80} , or $NNR^{81}R^{82}$;

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

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

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

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

provided that when ring C is C_6-C_{10} aryl;

and ring B is optionally substituted 4-10 membered heterocyclyl;

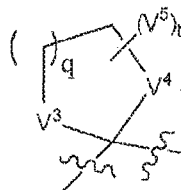
then ring A excludes optionally substituted 5-10 membered heteroaryl;

and provided that when ring C is C_6-C_{10} aryl;

and ring B is optionally substituted 5-10 membered heteroaryl;

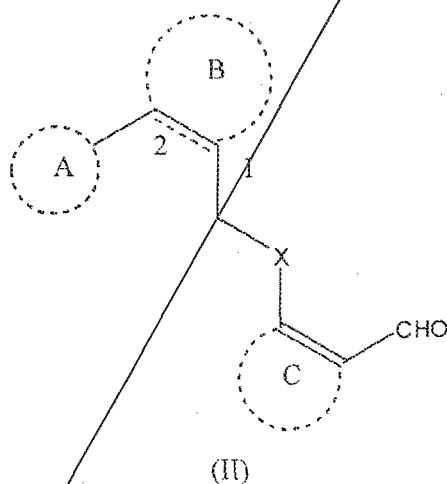
then ring A is not optionally substituted 4-10 membered heterocycle.

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



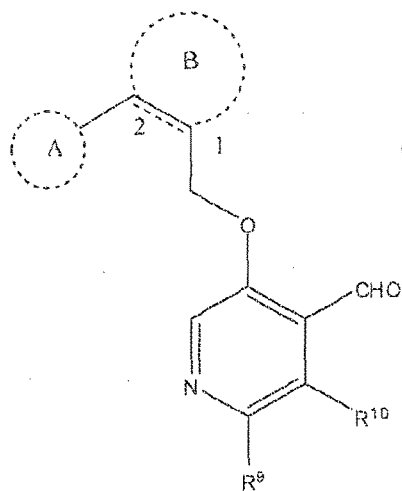
wherein each V^3 and V^4 are independently O, S, or NH, provided that when one or V^3 and V^4 is S the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1 - C_6 alkyl or CO_2R^{60} , where each R^{60} independently is C_1 - C_6 alkyl or hydrogen; t is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

4. The compound of claim 3, of formula:

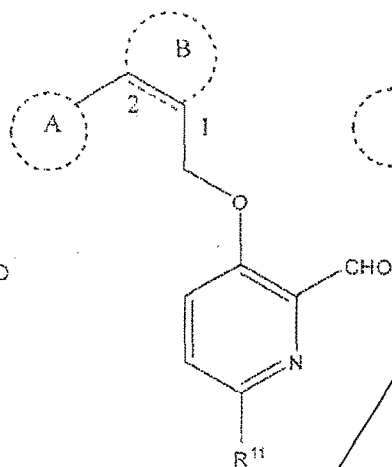


wherein the remaining variables are defined as in claim 2.

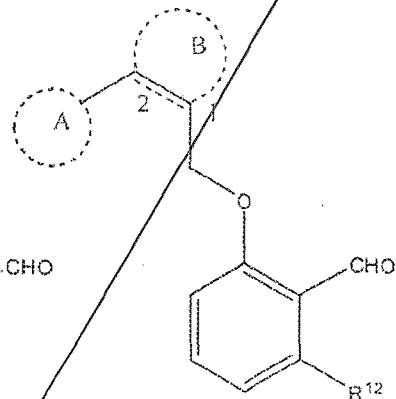
5. A compound of claim 3 or 4 selected from formulas (IIA), (IIB) and (IIC):



IIA



IIB



IIC

wherein

R^9 is hydrogen, $-OR^1$, C_1-C_6 alkoxy optionally substituted with 1-3 C_1-C_6 alkoxy or 4-10 membered heterocycle containing up to 5 ring heteroatoms selected from N, O, S or oxidized forms thereof;

R^{10} is hydrogen, halo, hydroxy, or C_1-C_6 alkoxy;

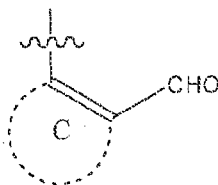
R^{11} is hydrogen or C_1-C_6 alkyl; and

R^{12} is $-OR^1$;

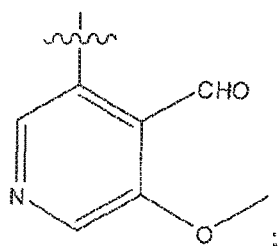
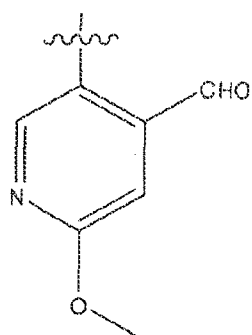
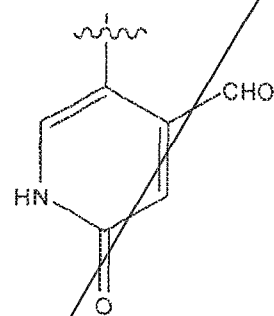
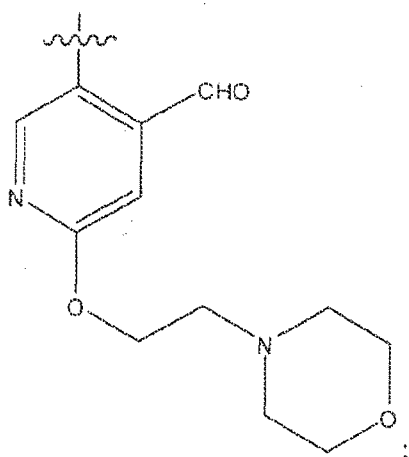
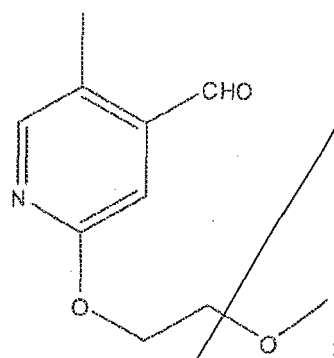
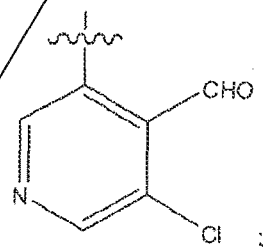
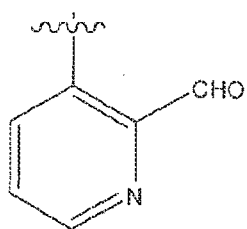
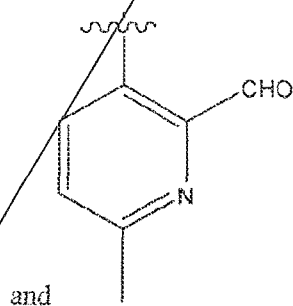
wherein R^1 is hydrogen or the prodrug moiety R.

6. The compound of claim 4, wherein ring A is phenyl substituted with 1-3 halo or C_1-C_6 alkoxy, or C_3-C_8 heterocyclyl containing 1-3 heteroatoms, wherein the heterocycle is optionally substituted with 1-3 halo.

7. The compound of any one of claims 3-6, wherein

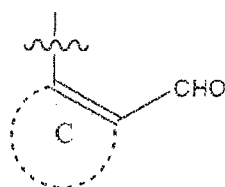


is selected from the group consisting of:

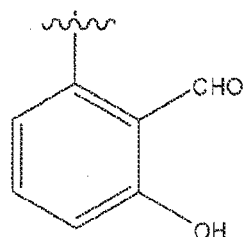


and

8. The compound of any one of claims 3-6, wherein

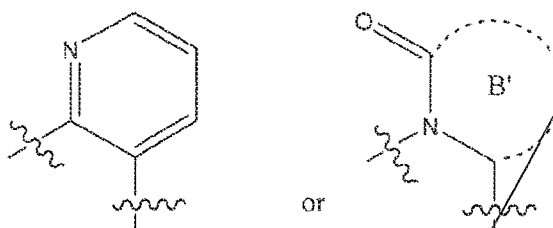


is



9. A compound of claim 1 wherein:
 ring A is C₆-C₁₀ 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: C₁-C₆ alkyl and/or C₁-C₆ alkoxy;

ring B is:



wherein ring B' including the -N-CO- moiety is a 5-6 membered heterocycle containing up to 3 heteroatoms selected from nitrogen, oxygen, and sulfur and oxidized forms of N and S, wherein each of the heteroaryl and the heterocycle is optionally substituted with 1-4 C₁-C₆ alkyl groups;

each X and Y is independently CR²⁰R²¹, O, S, SO, SO₂, or NR²⁰; each R²⁰ and R²¹ independently is hydrogen or C₁-C₃ alkyl optionally substituted with 1-3 halo, OH, or C₁-C₆ alkoxy, or CR²⁰R²¹ is C=O, provided that if one of X and Y is O, S, SO, SO₂, then the other is not CO, and X and Y are both not heteroatoms or oxidized forms thereof;

ring C is C₆-C₁₀ 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, -OR¹, C₁-C₆ alkyl, -COOR⁵, NR⁵R⁶,

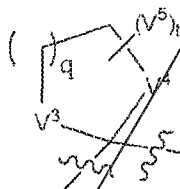
R¹ is a hydrogen, C₁-C₆ alkyl or a prodrug moiety; wherein the alkyl is optionally substituted with a 5-10 membered heteroaryl containing up to 5 ring

heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, which is optionally substituted with 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 the heteroaryl is optionally substituted with C₁-C₆ alkyl;

R⁵ and R⁶ are each independently hydrogen, optionally substituted C₁-C₆ alkyl or -COOR³;

R³ is hydrogen or optionally substituted C₁-C₆ alkyl;

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



wherein each V³ and V⁴ are independently O, S, or NH, provided that when one of V³ and V⁴ is S, the other is NH, and provided that V³ and V⁴ are both not NH; q is 1 or 2; each V⁵ is independently C₁-C₆ alkyl optionally substituted with 1-3 OH groups, or V⁵ is CO₂R⁶⁰, where each R⁶⁰ independently is C₁-C₆ alkyl or hydrogen; t is 0, 1, 2, or 4; or CV¹V² is C=V, wherein V is O, NOR⁸⁰, or NNR⁸¹R⁸²;

R⁸⁰ is optionally substituted C₁-C₆ alkyl;

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

R⁸³ is hydrogen or optionally substituted C₁-C₆ alkyl; and

R⁸⁴ is optionally substituted C₁-C₆ alkyl;

with the proviso that when ring C is C₆-C₁₀ aryl;

and ring B is optionally substituted 4-10 membered heterocyclyl;

then ring A excludes optionally substituted 5-10 membered heteroaryl;

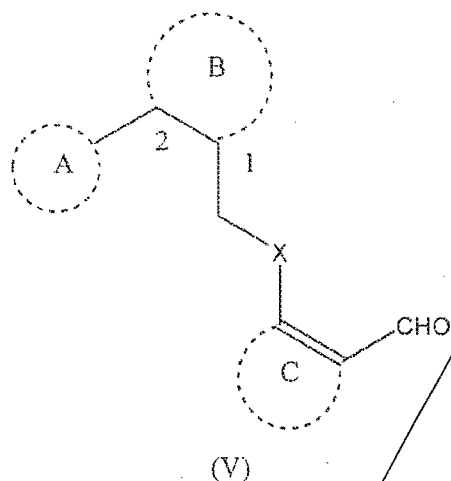
and provided that when ring C is C₆-C₁₀ aryl;

and ring B is optionally substituted 5-10 membered heteroaryl;

then ring A is not optionally substituted 4-10 membered heterocycle.

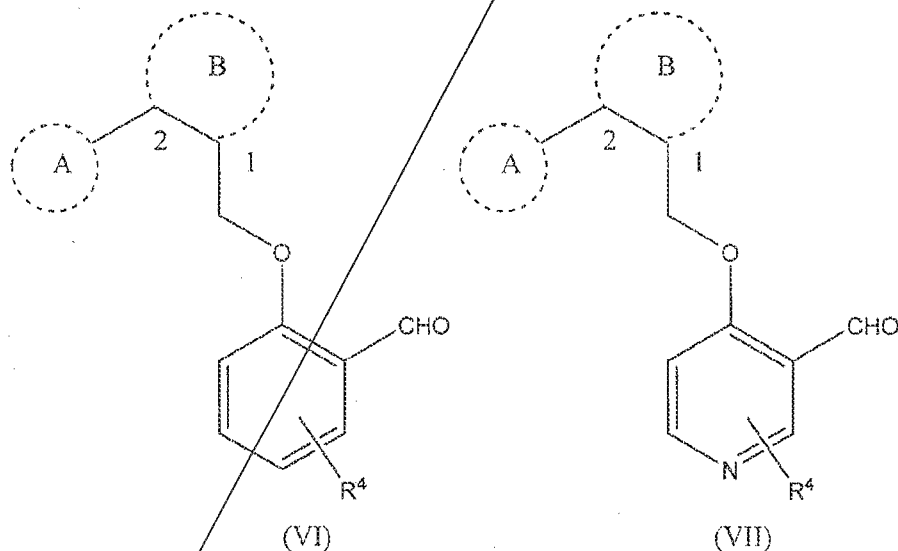
10. The compound of claim 9, wherein CV^1V^2 is $C=V$, wherein V is O, and wherein the remaining variables are defined as in claim 10.

11. The compound of claim 10, of formula:



or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein the remaining variables are defined as in claim 9.

12. A compound of claim 10 or 11 of formula (VI) or (VII):



or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein ring A 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 C₁-C₆ alkyl;

ring B is C₆-C₁₀ aryl, C₃-C₈ cycloalkyl, a 5-10 membered heteroaryl containing up to 5 ring heteroatoms 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 each of the aryl, heteroaryl, cycloalkyl or heterocycle is optionally substituted with 1-4: halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ alkoxy, and/or C₃-C₁₀ cycloalkyl;

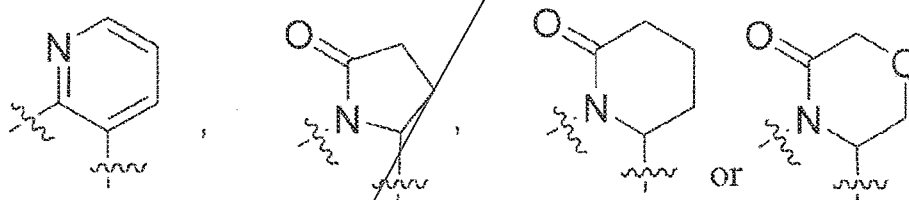
R⁴ is halo, oxo, -OR¹⁸, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOR⁵, and/or NR⁵R⁶;

R¹⁸ is hydrogen, substituted C₁-C₆ alkyl, or a prodrug moiety R;

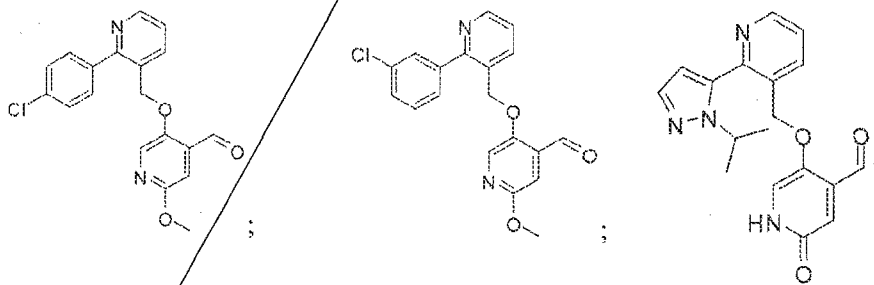
R⁵ and R⁶ are each independently hydrogen, optionally substituted C₁-C₆ alkyl or -COOR³; and

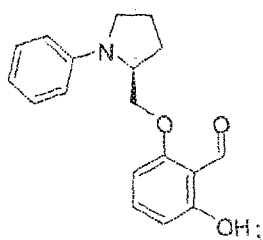
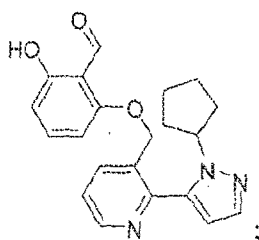
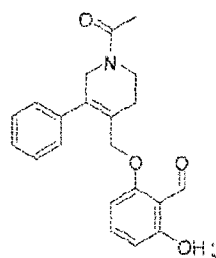
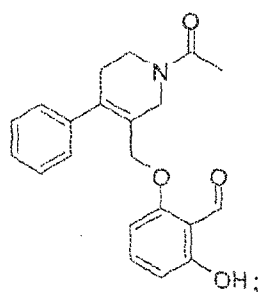
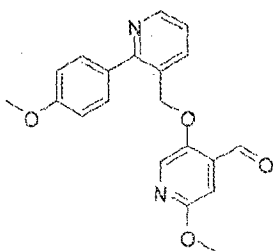
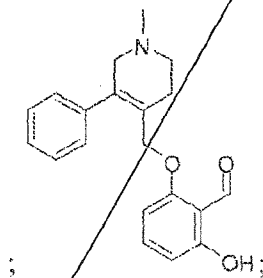
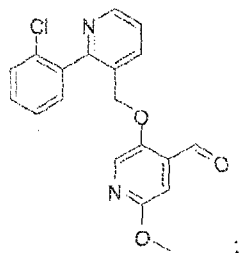
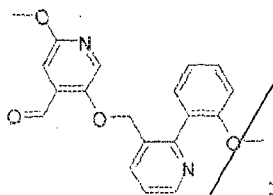
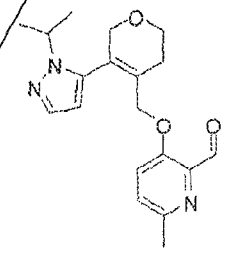
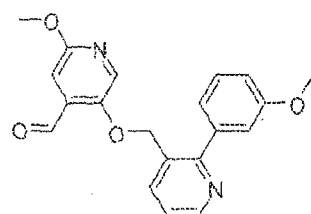
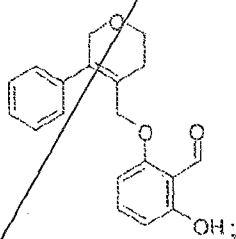
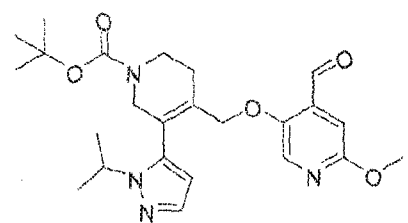
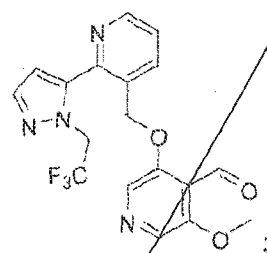
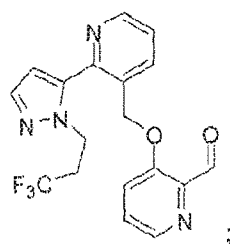
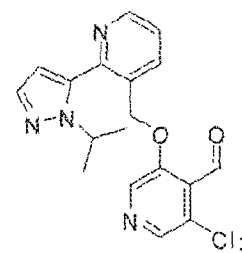
R³ is hydrogen, provided that the COOR³ is not joined to a nitrogen atom, or optionally substituted C₁-C₆ alkyl.

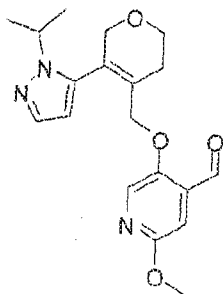
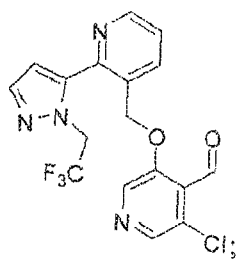
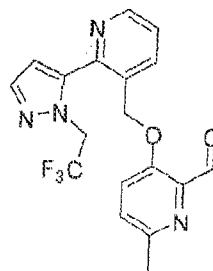
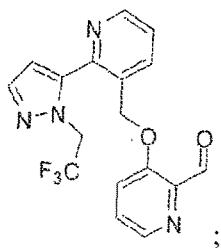
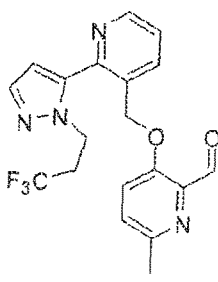
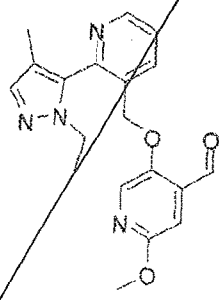
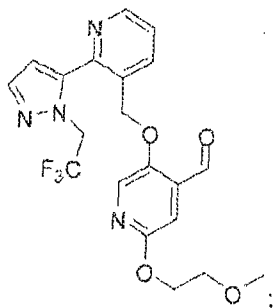
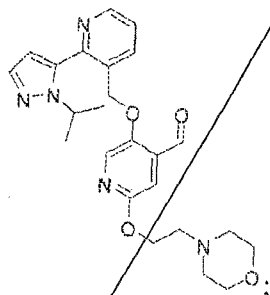
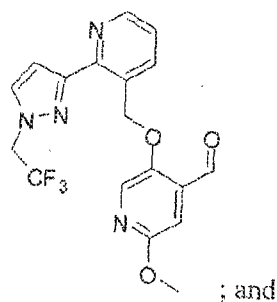
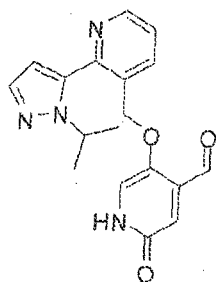
13. The compound of claim 12, wherein ring B is selected from the group consisting of:

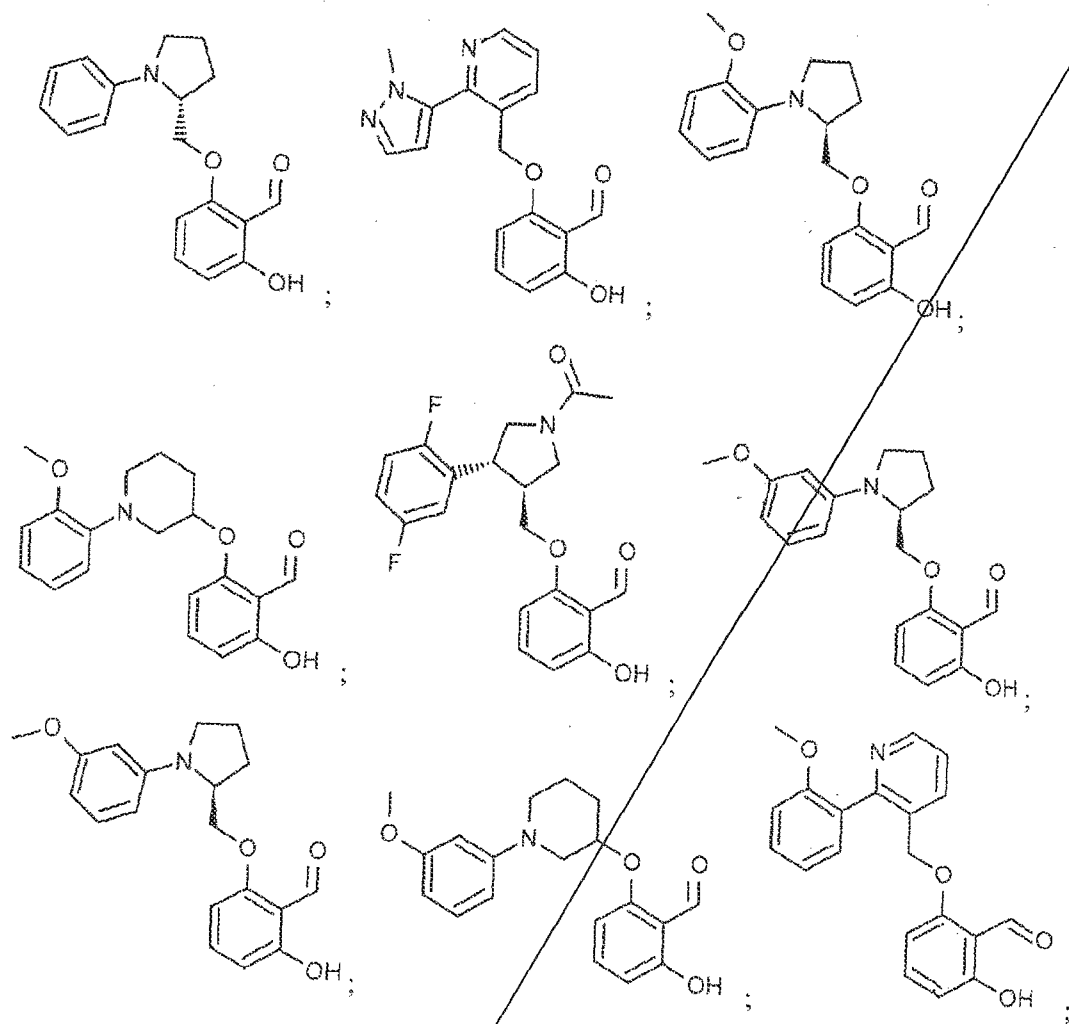


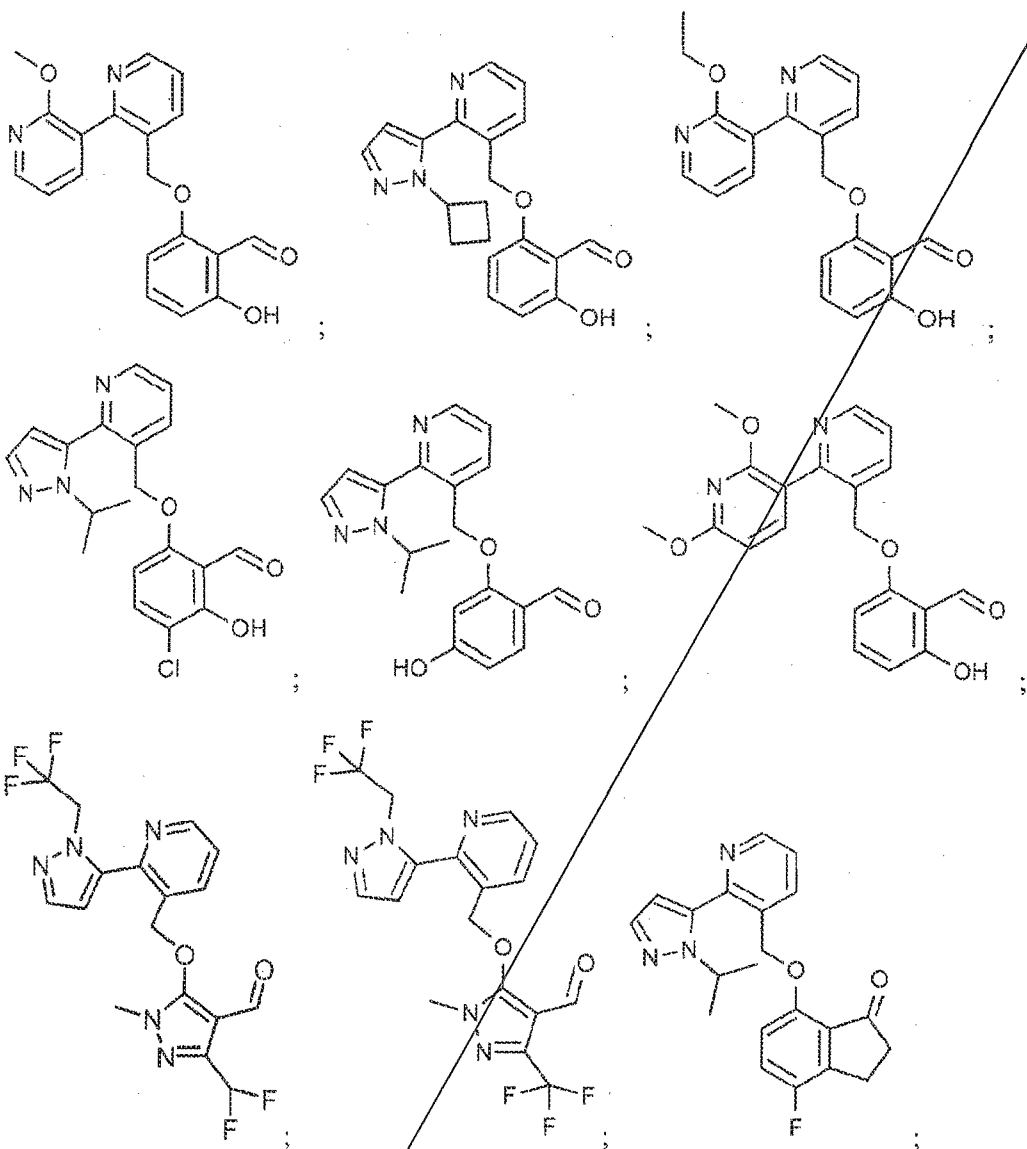
14. A compound of claim 1 selected from the group consisting of:

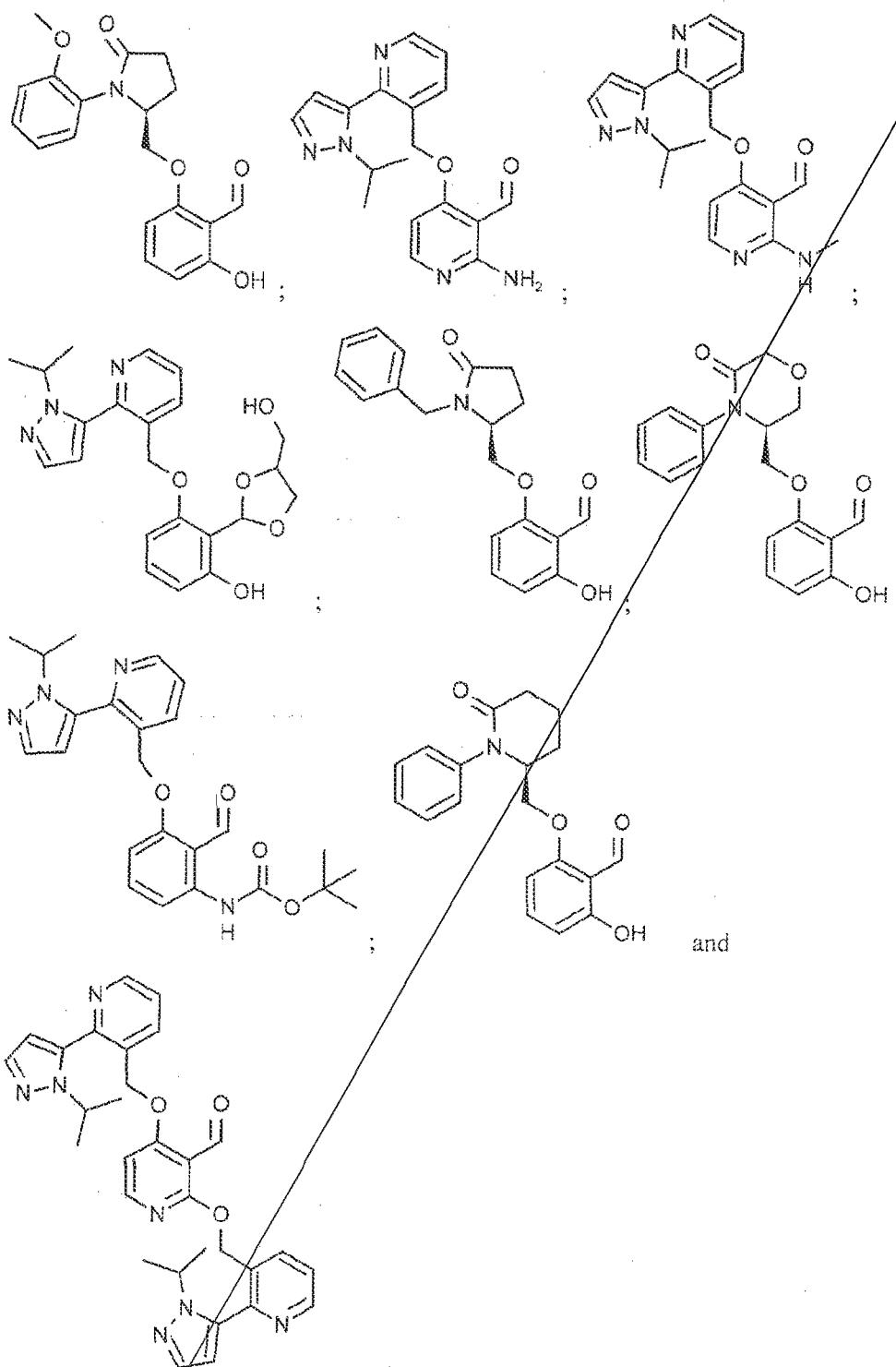












or N oxides thereof, or a pharmaceutically acceptable salt of each thereof.

16. A composition comprising a compound of any one of claims 3-8 and 10-15, and at least one pharmaceutically acceptable excipient.

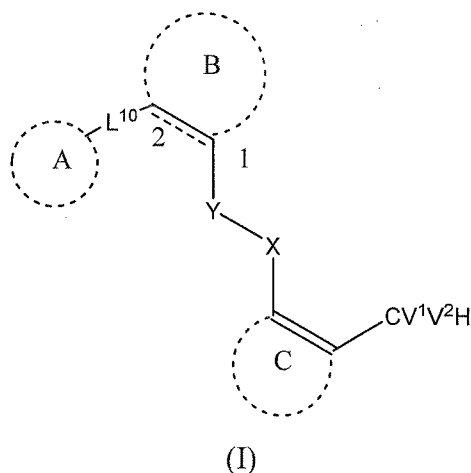
17. A method for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 3-8 and 10-15 or the composition of claim 16.

18. 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 3-8 and 10-15 or the composition of claim 16.

CLAIMS

What is claimed is:

1. A compound of formula (I):



or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein L^{10} is optionally substituted methylene or, preferably, a bond;

ring A is C_6 - C_{10} aryl, a C_3 - C_8 cycloalkyl, a 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 each of the aryl, heteroaryl, cycloalkyl, or heterocycle is optionally substituted with 1-4: halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and/or C_3 - C_{10} cycloalkyl, wherein the C_1 - C_6 alkyl is optionally substituted with 1-5 halo, C_1 - C_6 alkoxy, and/or C_3 - C_{10} cycloalkyl;

ring B is a 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 each of the heteroaryl and the heterocycle is optionally substituted with 1-4: halo, C_1 - C_6 alkyl and/or $-CO$ - C_1 - C_6 alkyl,

 is a single or a double bond;

each X and Y is independently $(CR^{20}R^{21})_e$, O, S, SO, SO₂, or NR²⁰; e is 1 to 4, preferably 1; each R²⁰ and R²¹ independently is hydrogen or C_1 - C_3 alkyl optionally substituted with 1-3 halo, OH, or C_1 - C_6 alkoxy, or $CR^{20}R^{21}$ is C=O, provided that if one of X and Y is O, S, SO, SO₂, then the other is not CO, and X and Y are both not heteroatoms or oxidized forms thereof;

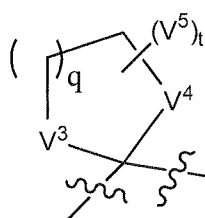
ring C is C₆-C₁₀ aryl or a 5-10 membered heteroaryl containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, each of which is optionally substituted with 1-4: halo, oxo, -OR¹, C₁-C₆ alkyl, -COOR¹, NR⁵R⁶, and/or C₁-C₆ alkoxy, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ 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;

R¹ is a hydrogen, C₁-C₆ alkyl or a prodrug moiety; wherein the alkyl is optionally substituted with 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, which is optionally substituted with with 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 the heteroaryl is optionally substituted with C₁-C₆ alkyl;

R⁵ and R⁶ are each independently hydrogen, optionally substituted C₁-C₆ alkyl or -COOR³;

R³ is hydrogen or optionally substituted C₁-C₆ alkyl;

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



wherein each V³ and V⁴ are independently O, S, or NH, provided that when one of V³ and V⁴ is S, the other is NH, and provided that V³ and V⁴ are both not NH; q is 1 or 2; each V⁵ is independently C₁-C₆ alkyl optionally substituted with 1-3 OH groups, or V⁵ is CO₂R⁶⁰, where each R⁶⁰ independently is C₁-C₆ alkyl or hydrogen; t is 0, 1, 2, or 4; or CV¹V² is C=V, wherein V is O, NOR⁸⁰, or NNR⁸¹R⁸²;

R⁸⁰ is optionally substituted C₁-C₆ alkyl;

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

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

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

with the proviso that:

- (i) when ring C is C_6 - C_{10} aryl optionally substituted with 1-4: halo, oxo, $-OR^1$, C_1 - C_6 alkyl, $-COOR^1$, NR^5R^6 , 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 ring B is 4-10 membered heterocyclyl 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 heterocycle is optionally

substituted with 1-4: halo, C_1 - C_6 alkyl and/or $-CO-C_1$ - C_6 alkyl;

then ring A is not 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 and optionally substituted with 1-4: halo, C_1 -

C_6 alkyl, C_1 - C_6 alkoxy, and/or C_3 - C_{10} cycloalkyl, wherein the C_1 - C_6 alkyl is

optionally substituted with 1-5 halo, C_1 - C_6 alkoxy, and/or C_3 - C_{10} cycloalkyl;

- (ii) when ring C is C_6 - C_{10} aryl optionally substituted with 1-4: halo, oxo, $-OR^1$, C_1 - C_6 alkyl, $-COOR^1$, NR^5R^6 , 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 ring B is 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

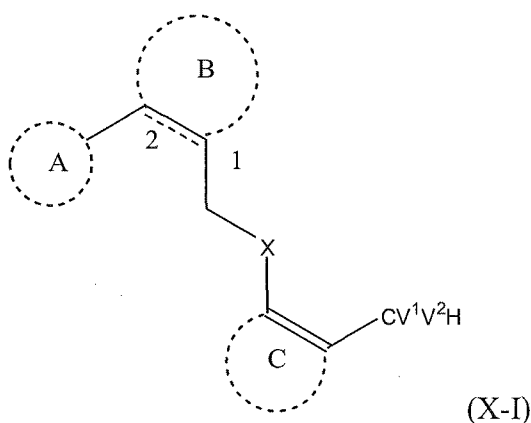
forms of N and S and optionally substituted with 1-4: halo, C_1 - C_6 alkyl and/or

$-CO-C_1$ - C_6 alkyl;

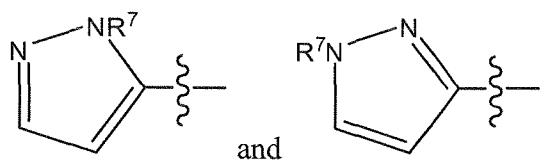
then ring A is not 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein the heterocycle is optionally substituted with 1-4: halo, C₁-C₆ alkyl C₁-C₆ alkoxy, and/or C₃-C₁₀ cycloalkyl, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ alkoxy, and/or C₃-C₁₀ cycloalkyl; and

- (iii) when ring B is 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 and optionally substituted with 1-4: halo, C₁-C₆ alkyl and/or -CO-C₁-C₆ alkyl;
then ring A is not 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 and optionally substituted with 1-4: halo, C₁-C₆alkyl, C₁-C₆ alkoxy, and/or C₃-C₁₀ cycloalkyl, wherein the C₁-C₆ alkyl is optionally substituted with 1-5 halo, C₁-C₆ alkoxy, and/or C₃-C₁₀cycloalkyl.

2. A compound of formula (X-I):

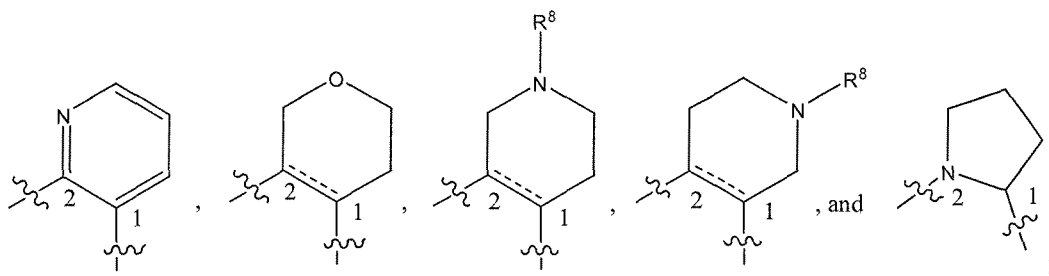


or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein ring A is phenyl optionally substituted with 1-3 halo and/or C₁-C₆ alkoxy, or is a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, optionally substituted, or is



wherein R^7 is C_1 - C_6 alkyl, optionally substituted with 3-5 fluoro groups, or is C_3 - C_6 cycloalkyl;

ring B is selected from the group consisting of



wherein R^8 is C_1 - C_6 alkyl, $-\text{CO}-C_1$ - C_6 alkyl or a prodrug moiety;

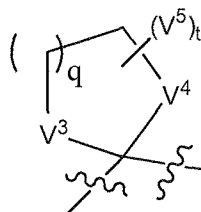
X is O, S, SO, or SO_2 ;

 is a single or a double bond;

ring C is phenyl or a 6 membered nitrogen-containing heteroaryl, each of which is optionally substituted with 1-4: halo, oxo, $-\text{OR}^1$, 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 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

each R^1 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 1, 2, or 4; or CV^1V^2 is $\text{C}=\text{V}$, wherein V is O, NOR^{80} , or $\text{NNR}^{81}\text{R}^{82}$;

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

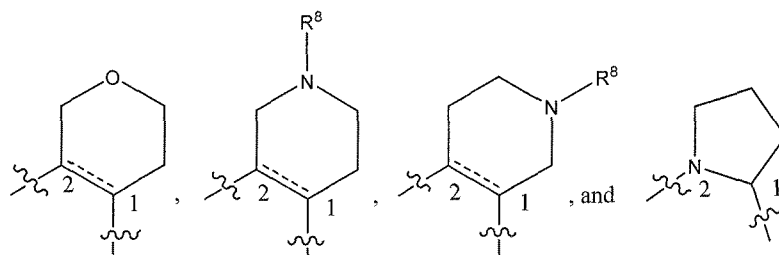
R^{81} and R^{82} independently are selected from the group consisting of hydrogen, optionally substituted C_1 - C_6 alkyl, COR^{83} , or CO_2R^{84} ;

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

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

provided that:

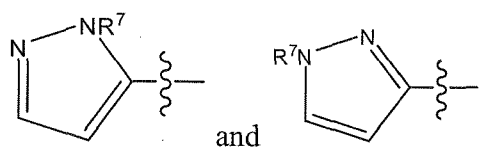
- (i) when ring C is phenyl optionally substituted with 1-4: halo, oxo, $-OR^1$, C_1 - C_6 alkyl, and/or C_1 - C_6 alkoxy, wherein the C_1 - C_6 alkyl is optionally substituted with 1-5 halo, C_1 - C_6 alkoxy and/or 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;



and ring B is

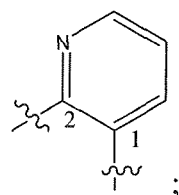
is C_1 - C_6 alkyl, $-CO$ - C_1 - C_6 alkyl or a prodrug moiety;

then ring A is not



wherein R^7 is C_1 - C_6 alkyl, optionally substituted with 3-5 fluoro groups, or is C_3 - C_6 cycloalkyl;

- (ii) when ring C is phenyl optionally substituted with 1-4: halo, oxo, $-OR^1$, 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 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;



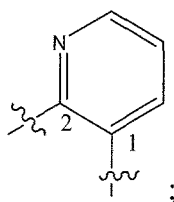
and ring B is

then ring A is not optionally substituted 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group

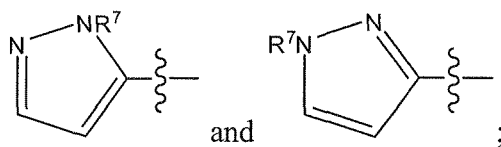
consisting of O, N, S, and oxidized forms of N and S, optionally substituted;
and

- (iii) when ring C is phenyl or a 6 membered nitrogen-containing heteroaryl, each of which is optionally substituted with 1-4: halo, oxo, $-OR^1$, 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 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 ring B is

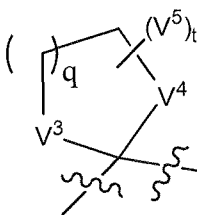


then ring A is not



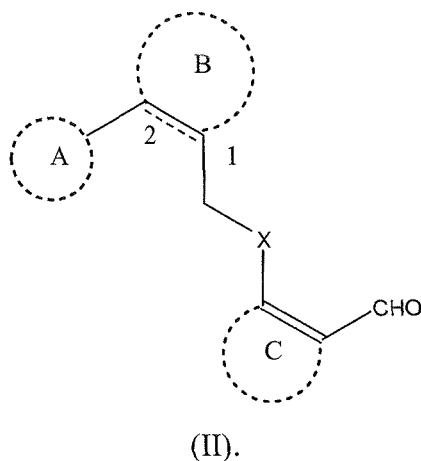
wherein R^7 is C_1-C_6 alkyl, optionally substituted with 3-5 fluoro groups, or is C_3-C_6 cycloalkyl.

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

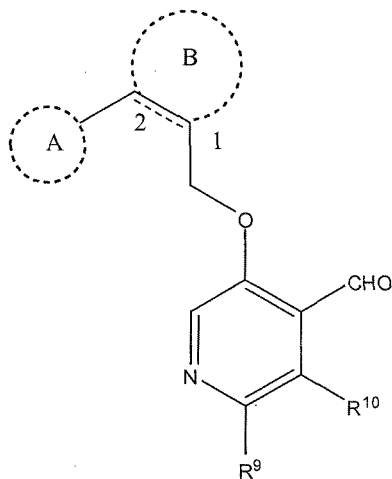
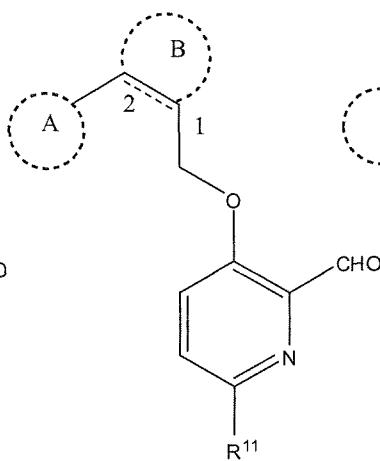
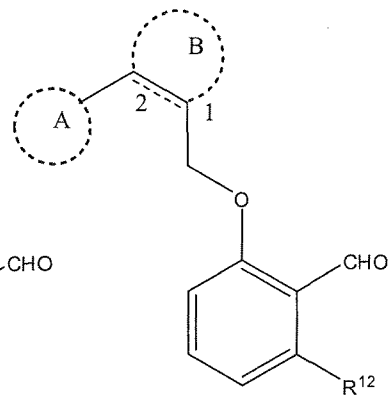


wherein each V^3 and V^4 are independently O, S, or NH, provided that when one or V^3 and V^4 is S the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60} , where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 1,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

4. The compound of claim 3, of formula:



5. A compound of claim 3 or 4 selected from formulas (IIA), (IIB) and (IIC):



wherein

R^9 is hydrogen, $-OR^1$, C_1-C_6 alkoxy optionally substituted with 1-3 C_1-C_6 alkoxy or 4-10 membered heterocycle containing up to 5 ring heteroatoms selected from N, O, S or oxidized forms thereof;

R^{10} is hydrogen, halo, or C_1-C_6 alkoxy;

R^{11} is hydrogen or C_1-C_6 alkyl; and

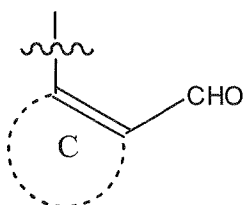
R^{12} is $-OR^1$;

wherein R^1 is hydrogen or the prodrug moiety R.

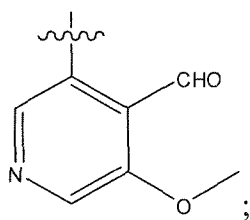
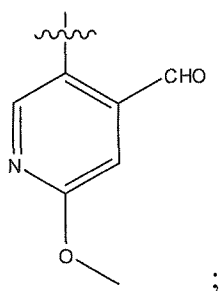
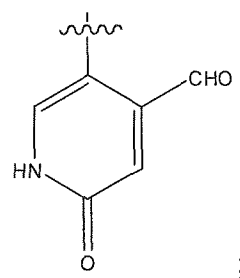
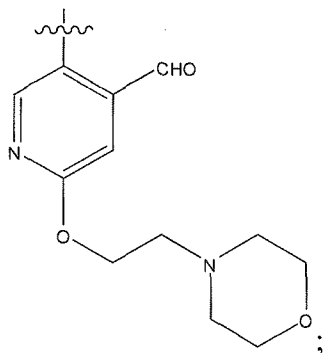
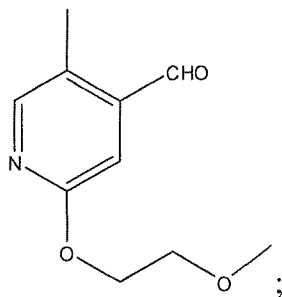
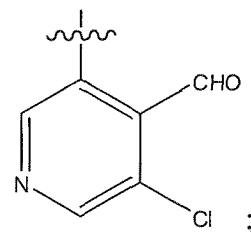
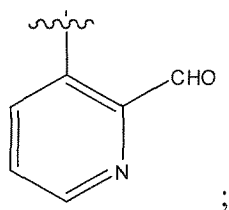
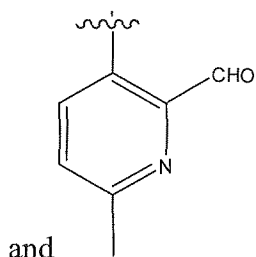
6. The compound of claim 4, wherein ring A is phenyl substituted with 1-3 halo or C_1-C_6 alkoxy, or

C₃-C₈ heterocyclyl containing 1-3 heteroatoms, wherein the heterocycle is optionally substituted with 1-3 halo.

7. The compound of any one of claims 3-6, wherein

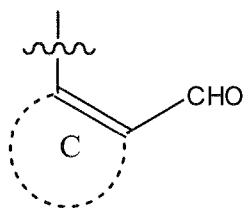


is selected from the group consisting of:

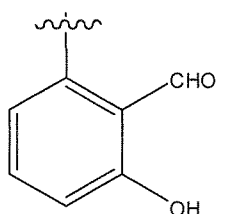


and

8. The compound of any one of claims 3-6, wherein



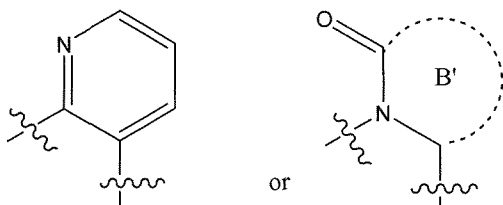
is



9. A compound of claim 1 wherein:

ring A is C₆-C₁₀ 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 each of the aryl, or heteroaryl is optionally substituted with 1-4: C₁-C₆ alkyl and/or C₁-C₆ alkoxy;

ring B is:



wherein ring B' including the -N-CO- moiety is a 5-6 membered heterocycle containing up to 3 heteroatoms selected from nitrogen, oxygen, and sulfur and oxidized forms of N and S, wherein each of the pyridyl and ring B' is optionally substituted with 1-4 C₁-C₆ alkyl groups;

each X and Y is independently CR²⁰R²¹, O, S, SO, SO₂, or NR²⁰; each R²⁰ and R²¹ independently is hydrogen or C₁-C₃ alkyl optionally substituted with 1-3 halo, OH, or C₁-C₆ alkoxy, or CR²⁰R²¹ is C=O, provided that if one of X and Y is O, S, SO, SO₂, then the other is not CO, and X and Y are both not heteroatoms or oxidized forms thereof;

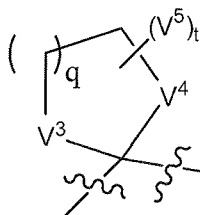
ring C is C₆-C₁₀ aryl or a 5-10 membered heteroaryl containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of

O, N, S, and oxidized forms of N and S, each of which is optionally substituted with 1-4: halo, oxo, $-OR^1$, C_1-C_6 alkyl, $-COOR^5$, NR^5R^6 , R^1 is a hydrogen, C_1-C_6 alkyl or a prodrug moiety; wherein the alkyl is optionally substituted with 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, which is optionally substituted with 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 the heteroaryl is optionally substituted with C_1-C_6 alkyl;

R^5 and R^6 are each independently hydrogen, optionally substituted C_1-C_6 alkyl or $-COOR^3$;

R^3 is hydrogen or optionally substituted C_1-C_6 alkyl;

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 optionally substituted with 1-3 OH groups, or V^5 is CO_2R^{60} , where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 0, 1, 2, or 4; or CV^1V^2 is $C=V$, wherein V is O, NOR^{80} , or $NNR^{81}R^{82}$;

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

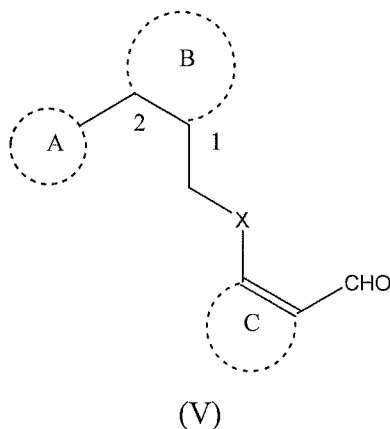
R^{81} and R^{82} independently are selected from the group consisting of hydrogen, optionally substituted C_1-C_6 alkyl, COR^{83} , or CO_2R^{84} ;

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

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

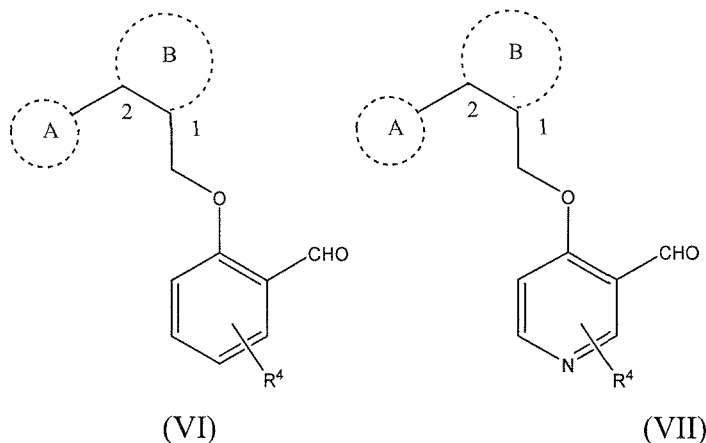
10. The compound of claim 9, wherein CV^1V^2 is $C=V$, wherein V is O.

11. The compound of claim 10, of formula:



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

12. A compound of claim 10 or 11 of formula (VI) or (VII):



or a tautomer thereof, or a pharmaceutically acceptable salt of each thereof, wherein ring A is C₆-C₁₀ aryl, or a 5-10 membered heteroaryl containing up to 5 ring

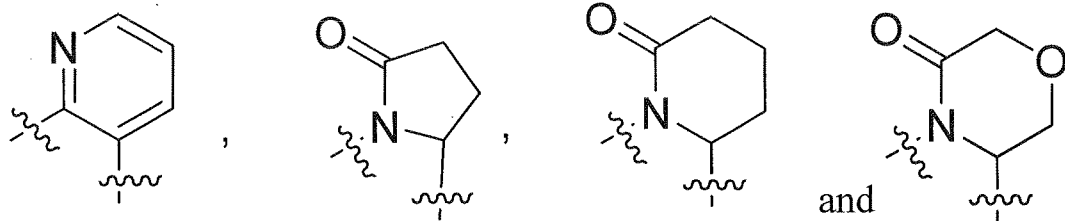
heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, wherein each of the aryl or heteroaryl is optionally substituted with 1-4 C₁-C₆ alkyl;

R⁴ is halo, oxo, -OR¹, C₁-C₆ alkyl, -COOR⁵, and/or NR⁵R⁶;

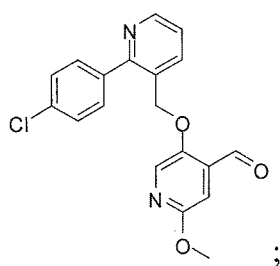
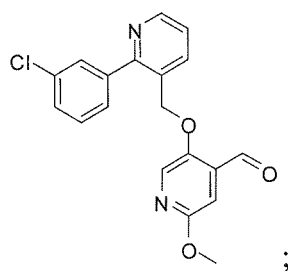
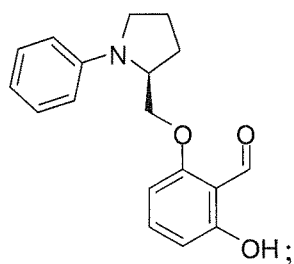
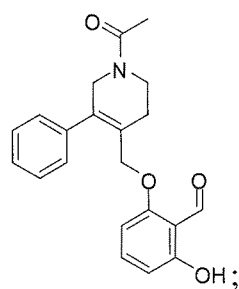
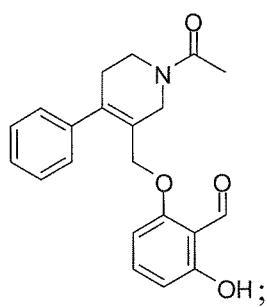
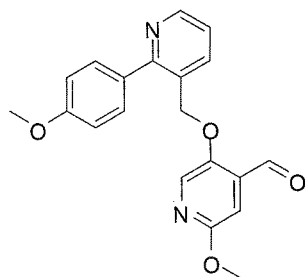
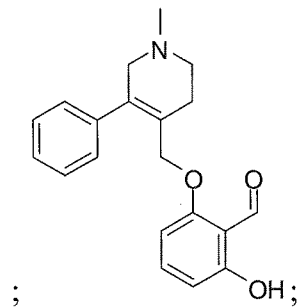
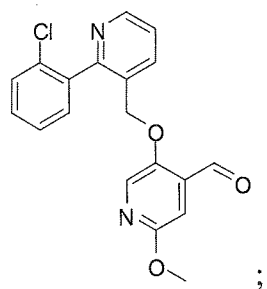
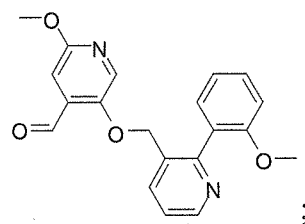
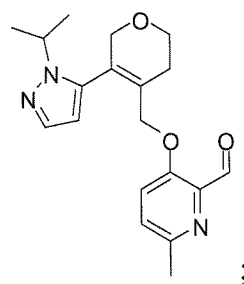
R⁵ and R⁶ are each independently hydrogen, optionally substituted C₁-C₆ alkyl or -COOR³; and

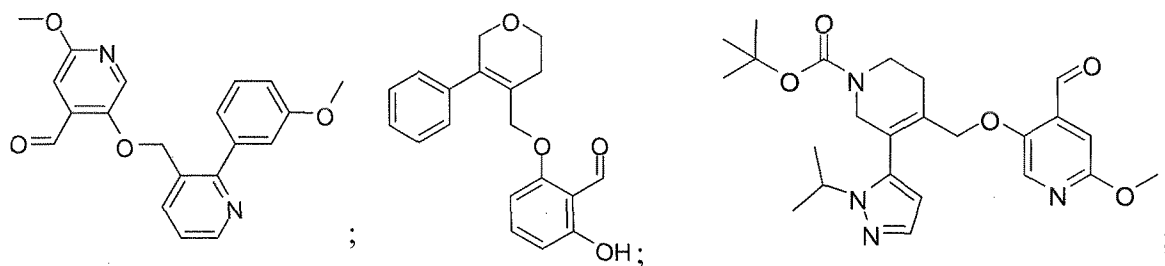
R³ is hydrogen.

13. The compound of claim 12, wherein ring B is selected from the group consisting of:

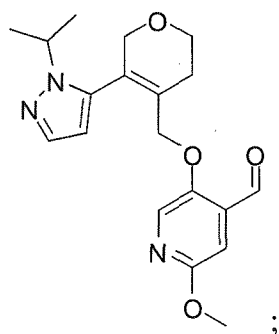


14. A compound of claim 2 selected from the group consisting of:



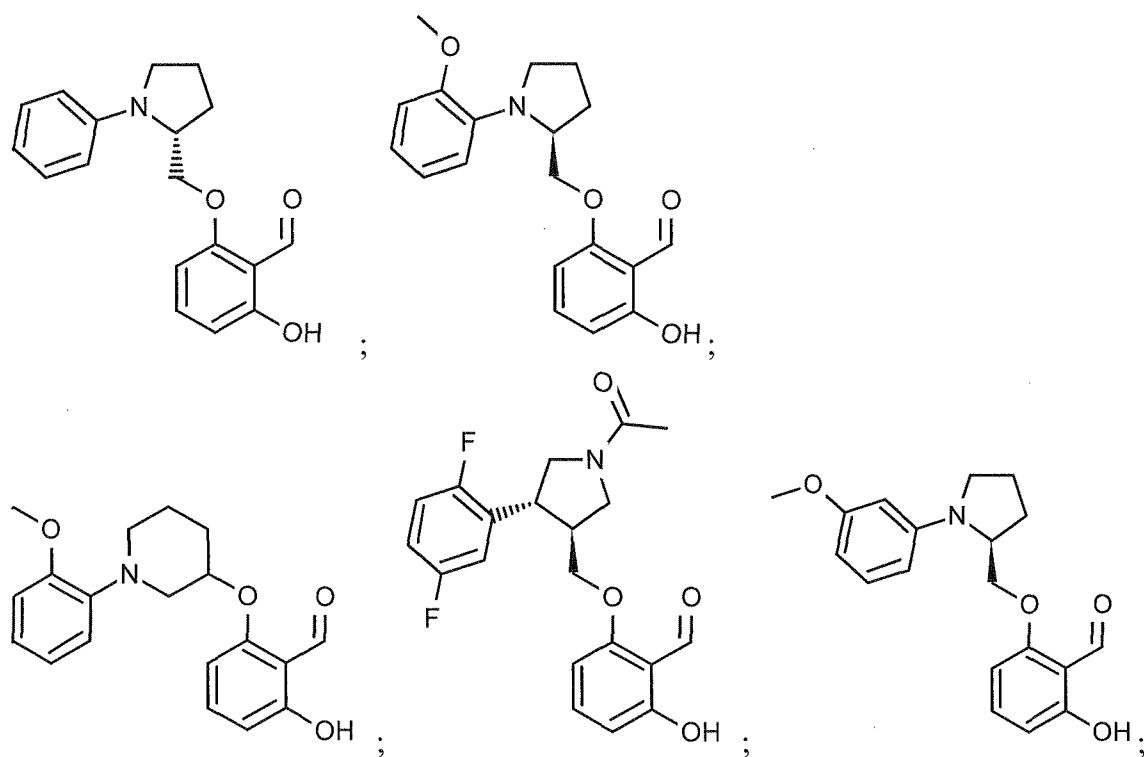


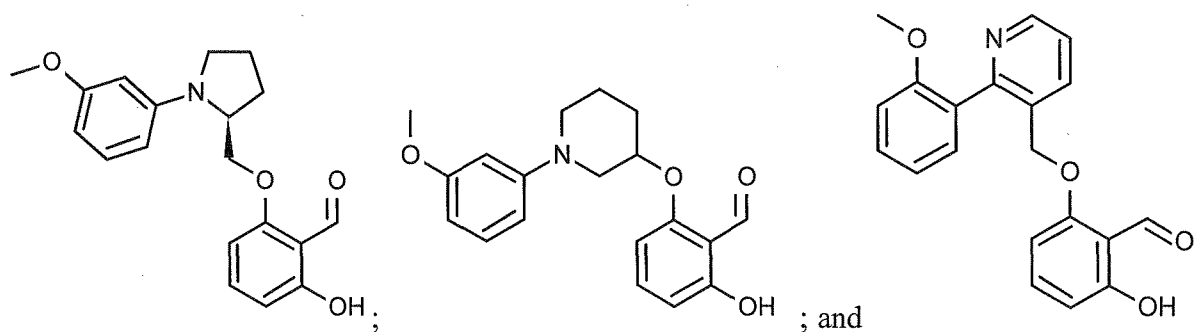
and



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

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

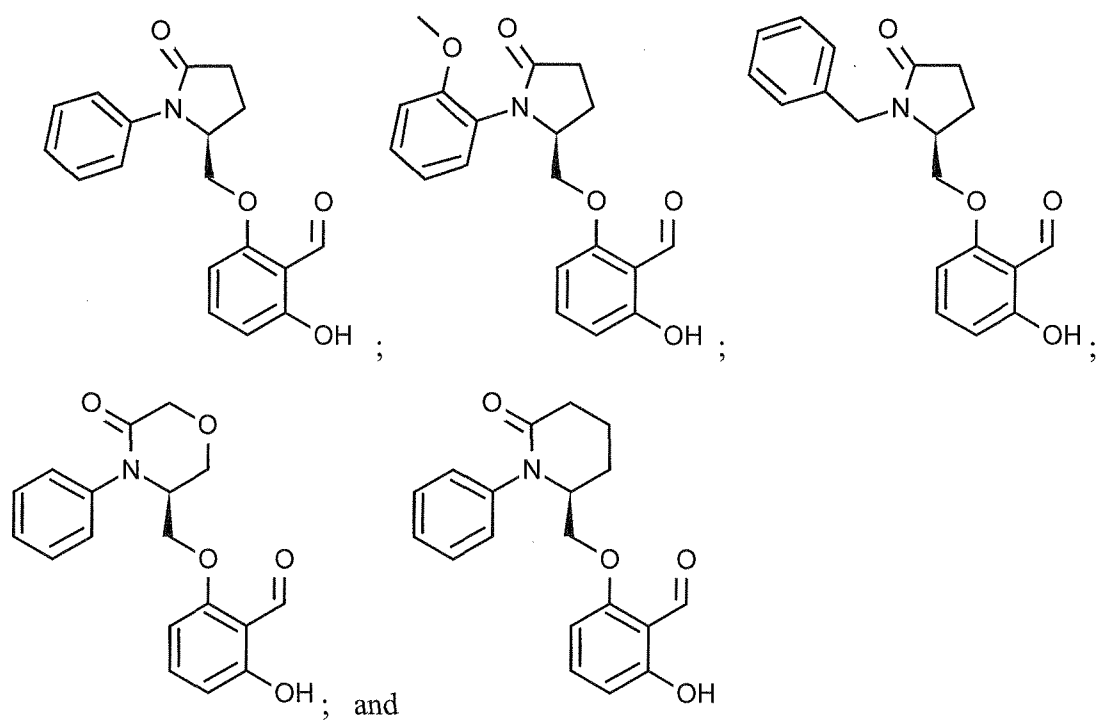




;

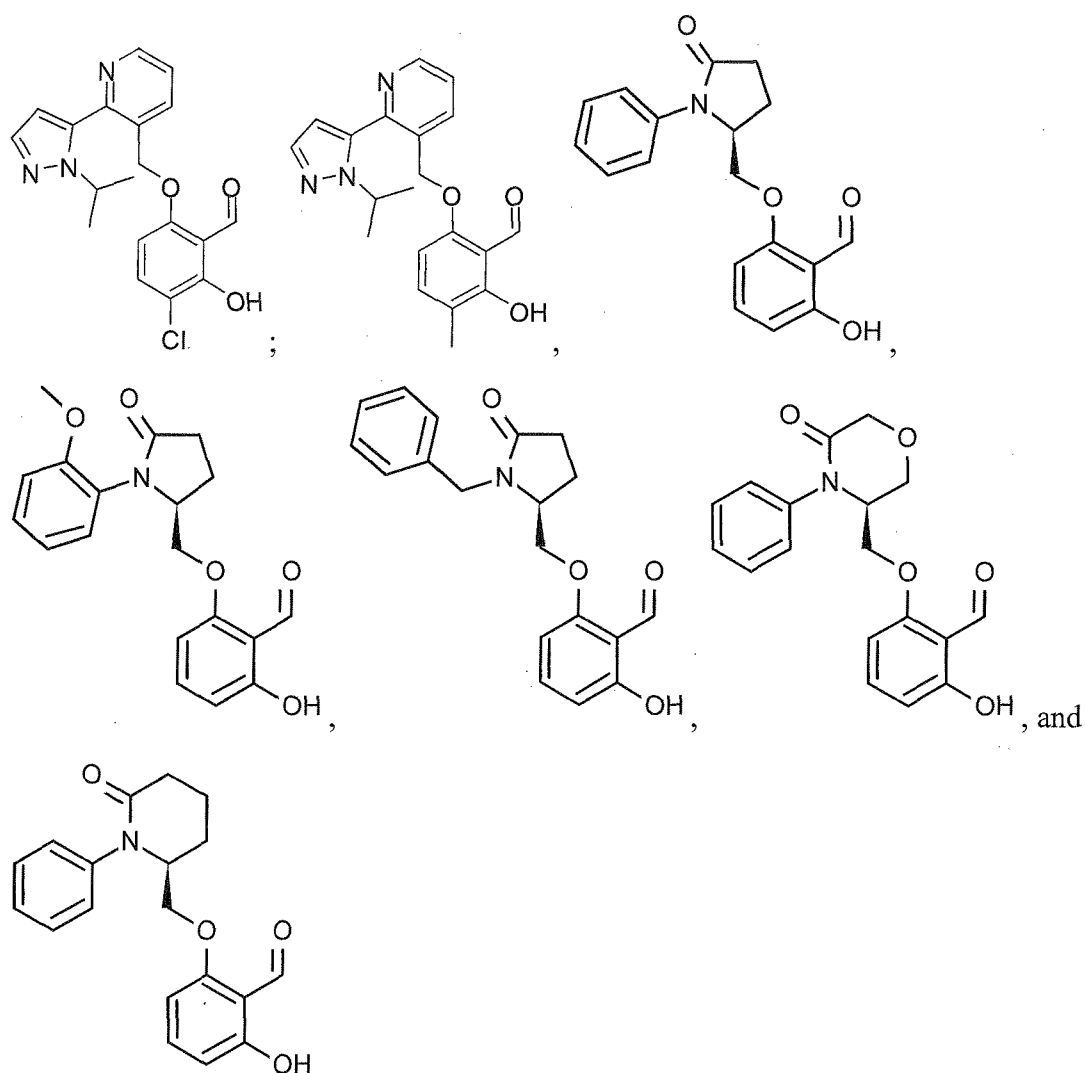
or a prodrug thereof, or a pharmaceutically acceptable salt of each thereof.

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



or N oxides thereof, or a pharmaceutically acceptable salt of each thereof.

17. A compound selected from:



or N oxides thereof, or a pharmaceutically acceptable salt of each thereof.

18. A composition comprising a compound of any one of claims 3-8 and 10-17, and at least one pharmaceutically acceptable excipient.

19. Use of a compound of any one of claims 3-8 and 10-16 or the composition of claim 18 in the manufacture of a medicament for increasing oxygen affinity of hemoglobin S in a subject.

20. Use of a compound of any one of claims 3-8 and 10-16 or the composition of claim 18 in the manufacture of a medicament for the treatment of oxygen deficiency associated with sickle cell anemia in a subject in need thereof.