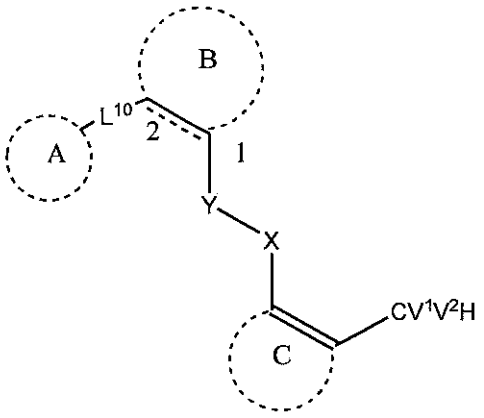
[0004a] Provided is a compound of formula (I):



(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

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

R^1 is hydrogen or a prodrug moiety;

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

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

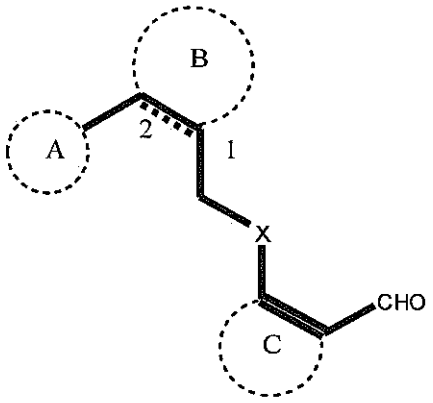
then ring A excludes optionally substituted 5-10 membered heteroaryl;

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.

[0007a] In one aspect, there is provided a compound of formula (II):



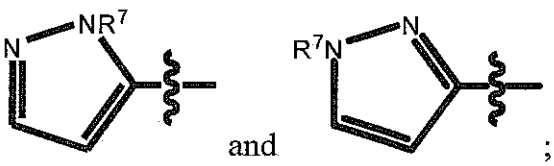
(II)

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

ring A is phenyl optionally substituted with 1-3 substituents independently selected from halo and C_1-C_6 alkoxy, 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, optionally substituted, or is

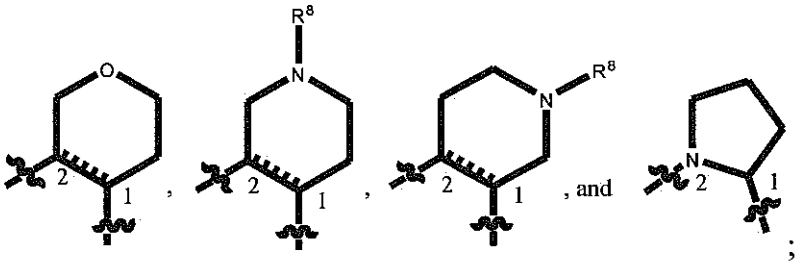
a ring selected from:



and ;

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



, , , and ;

wherein R^8 is C_1-C_6 alkyl or –CO-C_1-C_6 alkyl;

is a single or a double bond;

X is O, S, SO, or SO_2;

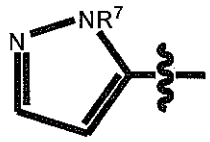
ring C is phenyl or a 6 membered nitrogen-containing heteroaryl, each of which is optionally substituted with 1-4 substituents independently selected from: halo, oxo, -OR^1, C_1-C_6 alkyl, -$COOR^1$ and C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy is optionally substituted with 1-5 substituents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

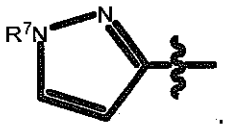
R^1 is hydrogen;

provided that:

(i) when ring C is phenyl,

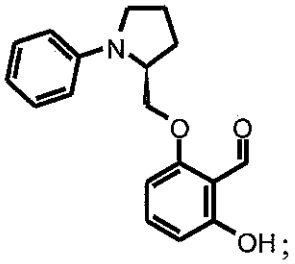
then ring A is not

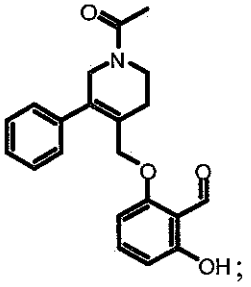


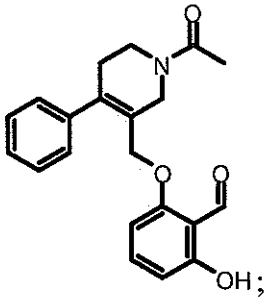
or


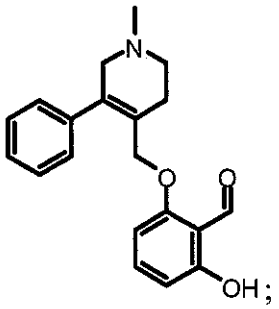
.

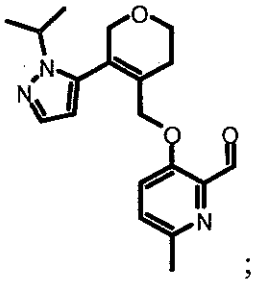
[0007b] In one aspect, there is provided a compound selected from the group consisting of:

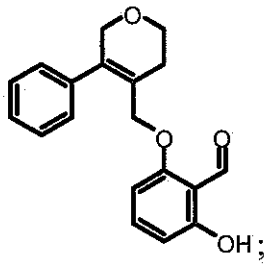


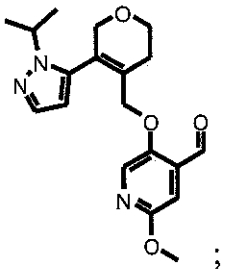








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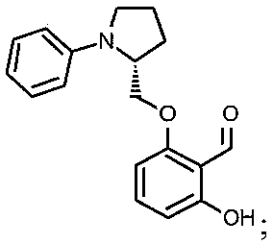
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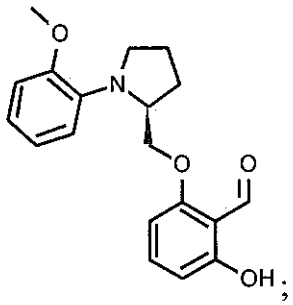
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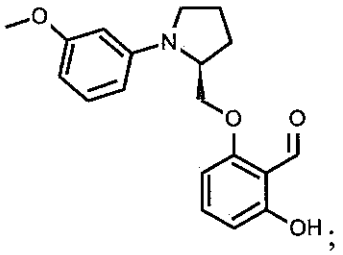
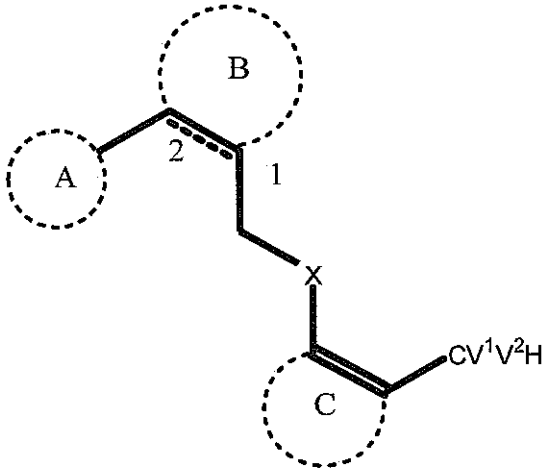

;

and

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

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



(X-I)

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

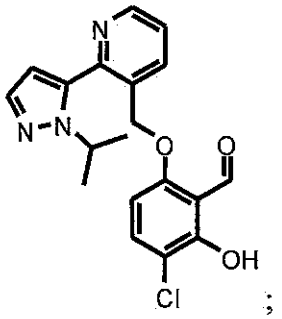
ring A is phenyl optionally substituted with 1-3 halo and/or C_1-C_6 alkoxy, or is a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, optionally substituted, or is

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.

[0013a] Provided is a compound selected from: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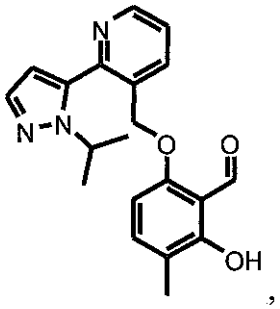
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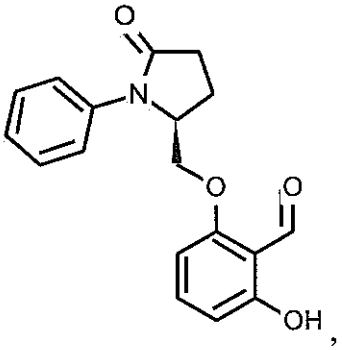
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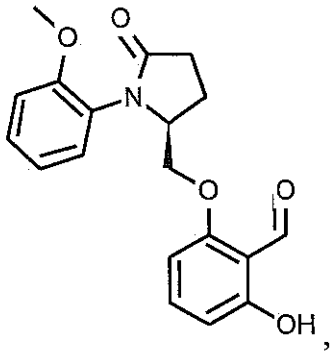
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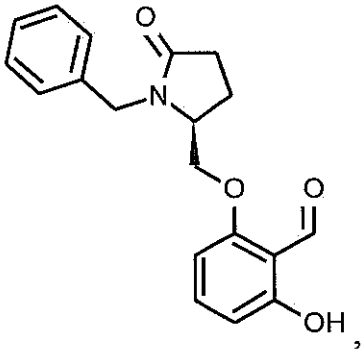
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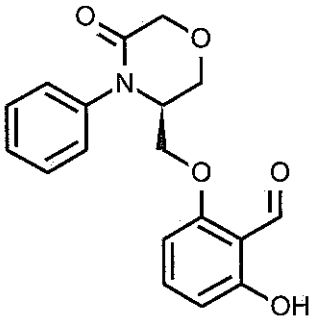
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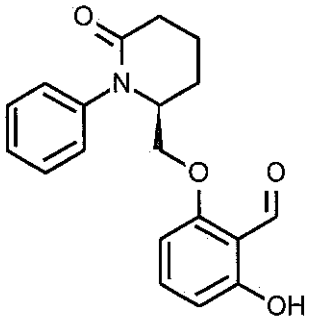


or N oxides thereof, or a pharmaceutically acceptable salt of each thereof.

[0014] In one aspect, there is provided a composition comprising a compound as described herein, and at least a pharmaceutically acceptable excipient.

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

[0015] In still further embodiments of the disclosure, a method is provided for increasing oxygen affinity of hemoglobin S in a subject, the method comprising

administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

[0015a] In one aspect, there is provided use of a compound as defined herein or a composition as defined herein in the manufacture of a medicament for the treatment of sickle cell disease in a subject in need thereof.

[0016] In further embodiments of the disclosure, a method is provided for treating oxygen deficiency associated with sickle cell anemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

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.

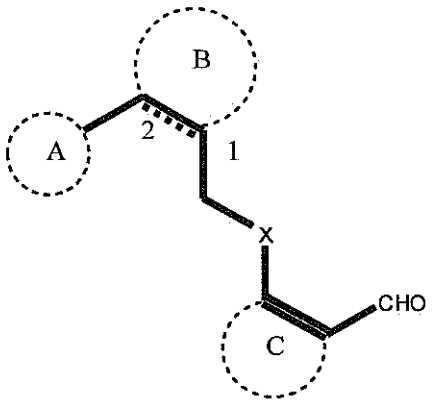
[0018] As used herein, the term "comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance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



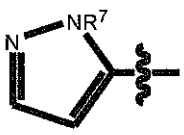
(II)

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

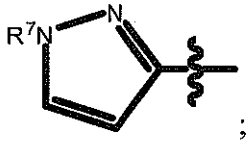
ring A is phenyl optionally substituted with 1-3 substituents independently selected from halo and C_1-C_6 alkoxy, or

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, optionally substituted, or

a ring selected from:



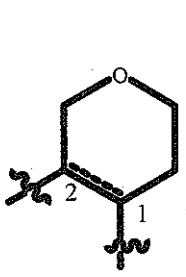
and



;

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



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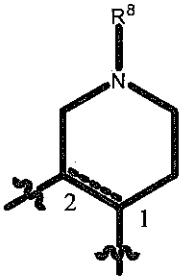

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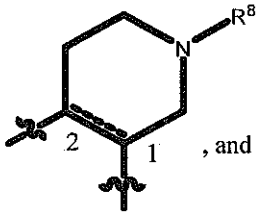
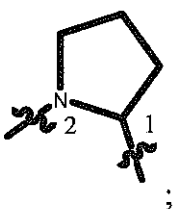


, and



;

wherein R^8 is C_1-C_6 alkyl or –CO-C_1-C_6 alkyl;

is a single or a double bond;

X is O, S, SO, or SO_2;

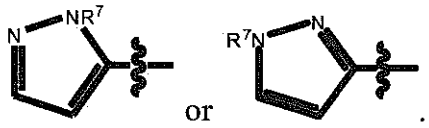
ring C is phenyl or a 6 membered nitrogen-containing heteroaryl, each of which is optionally substituted with 1-4 substituents independently selected from: halo, oxo, -OR^1, C_1-C_6 alkyl, -$COOR^1$ and C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl or C_1-C_6 alkoxy is optionally substituted with 1-5 substituents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

R^1 is hydrogen;

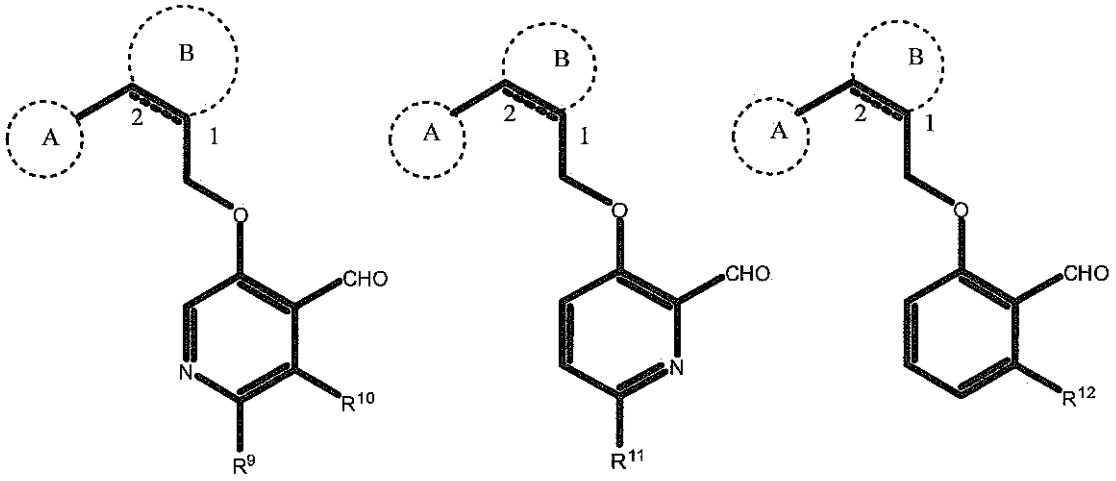
provided that:

(i) when ring C is phenyl,

then ring A is not



2. A compound of claim 1 selected from formulas (IIA), (IIB) and (IIC):



IIA IIB IIC

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

R^9 is hydrogen, hydroxy, 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;

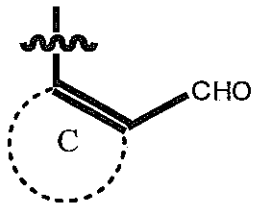
R^{10} is hydrogen, halo, hydroxy, or C_1-C_6 alkoxy;

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

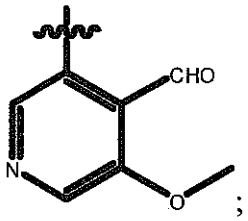
R^{12} is hydroxy.

3. The compound of claim 1 or 2, wherein ring A is
phenyl substituted with 1-3 halo or C_1-C_6 alkoxy, or
C_3-C_8 heterocycle containing 1-3 heteroatoms, wherein the heterocycle is optionally substituted with 1-3 halo.

4. The compound of any one of claims 1 to 3, wherein



is selected from the group consisting of:



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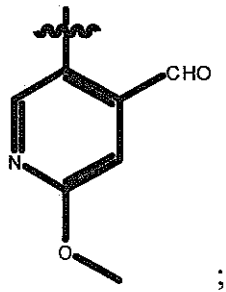

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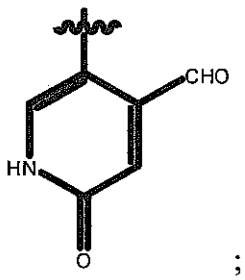

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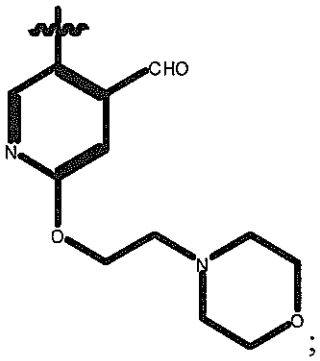

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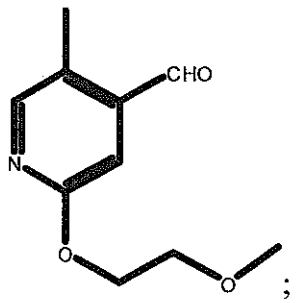

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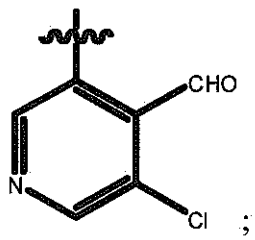

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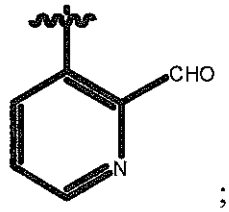

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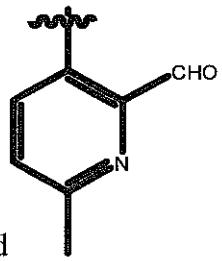
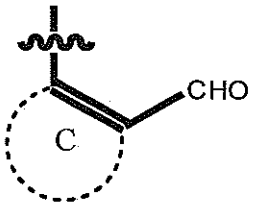
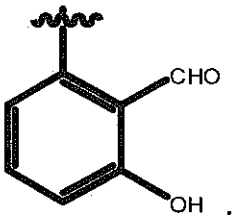


and .

5. The compound of any one of claims 1 to 3, wherein

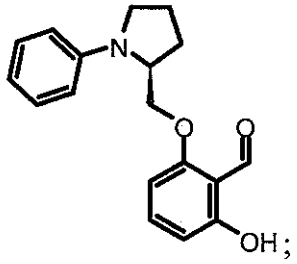


is



.

6. A compound selected from the group consisting of:



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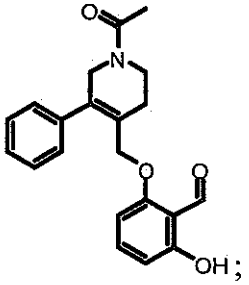

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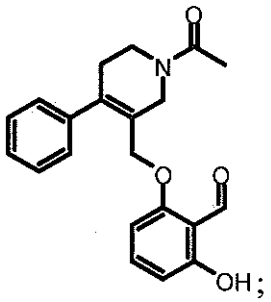

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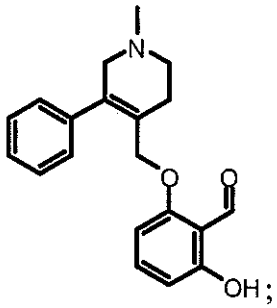

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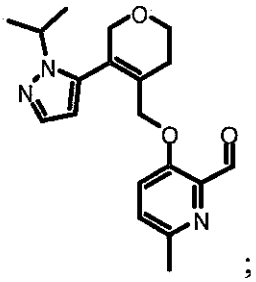

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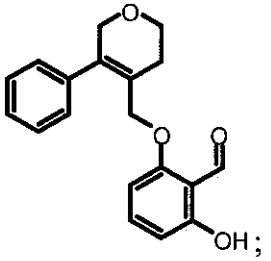

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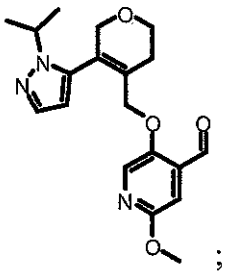

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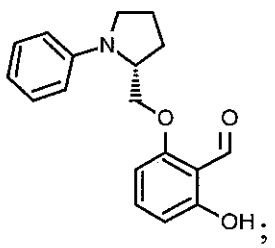

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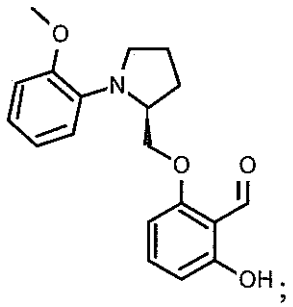

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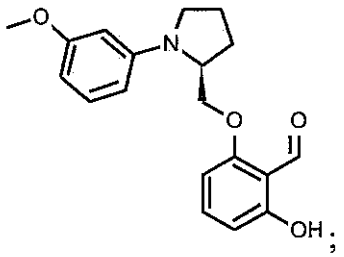
and  ;

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

7. A composition comprising a compound of any one of claims 1 to 6, and at least one pharmaceutically acceptable excipient.

8. Use of a compound of any one of claims 1 to 6 or the composition of claim 7 in the manufacture of a medicament for increasing oxygen affinity of hemoglobin S in a subject.

9. Use of a compound of any one of claims 1 to 6 or the composition of claim 7 in the manufacture of a medicament for the treatment of sickle cell disease in a subject in need thereof.