COMPOUNDS AND USES THEREOF FOR THE MODULATION OF HEMOGLOBIN

FIELD OF THE INVENTION

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

STATE OF THE ART

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

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

SUMMARY

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

[0004a] Disclosed is a compound of Formula (I)

that if one of Y and Z is O, S, SO, SO_2, then the other is not CO, and Y and Z are both not heteroatoms or oxidized forms thereof;

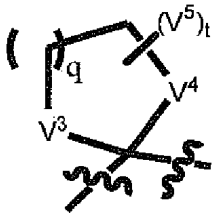
wherein Y is α or β substituted relative to the $-L^1L^2R^3$;

ring C is C_6-C_{10} aryl or a 5-10 membered heteroaryl containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S, each of which is optionally substituted with 1-4: halo, oxo, $-OR^2$, C_1-C_6 alkyl, and/or C_1-C_6 alkoxy, wherein the C_1-C_6 alkyl is optionally substituted with 1-5 halo, C_1-C_6 alkoxy and/or a 4-10 membered heterocycle containing up to 5 ring heteroatoms, wherein the heteroatom is selected from the group consisting of O, N, S, and oxidized forms of N and S;

R^2 is hydrogen or a prodrug moiety R; and

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

V^1 and V^2 independently are C_1-C_6 alkoxy; or V^1 and V^2 together with the carbon atom they are attached to form a ring of formula:



wherein each V^3 and V^4 are independently O, S, or NH, provided that when one of V^3 and V^4 is S, the other is NH, and provided that V^3 and V^4 are both not NH; q is 1 or 2; each V^5 is independently C_1-C_6 alkyl or CO_2R^{60}, where each R^{60} independently is C_1-C_6 alkyl or hydrogen; t is 0, 1, 2, or 4; or CV^1V^2 is C=V, wherein V is O, NOR^{80}, or $NNR^{81}R^{82}$;

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

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

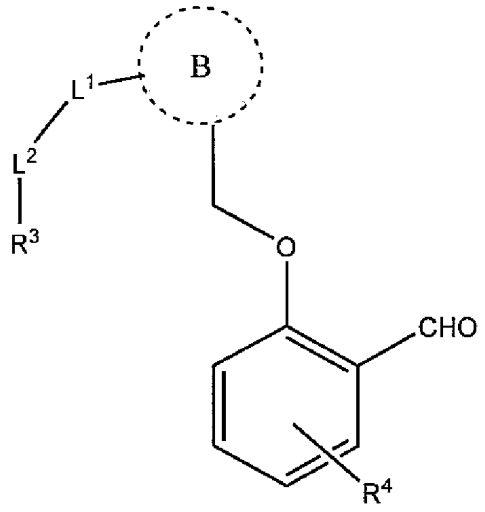
R^{83} is hydrogen or optionally substituted C_1-C_6 alkyl; and

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

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

[0010a] Disclosed is a compound or a tautomer thereof, or pharmaceutically acceptable salt of each thereof, wherein the compound is selected from the group consisting of

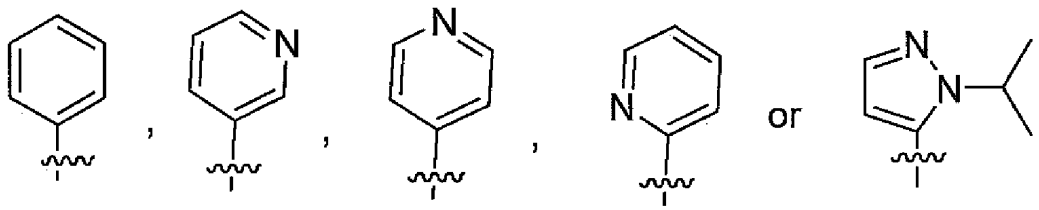
[0010b] In one aspect, there is provided a compound of Formula (VI):



(VI)

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

R^3 is

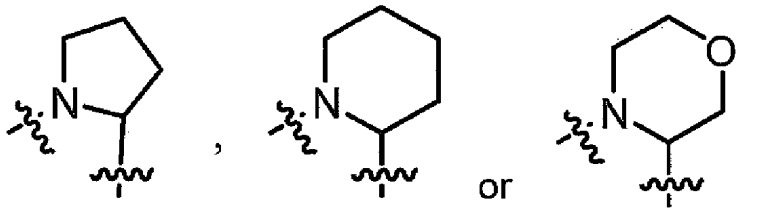


each of which is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond;

L^2 is C=O or SO_2;

ring B is

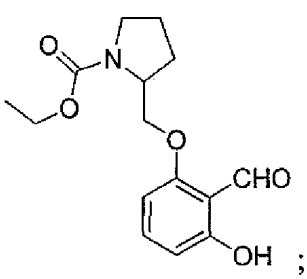


each of which is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$;

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

R^{19} is hydrogen.

[0010c] In one aspect, there is provided a compound of formula: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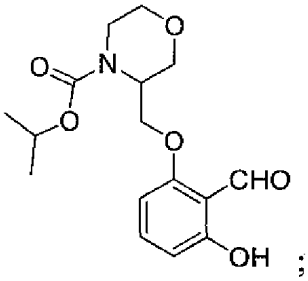
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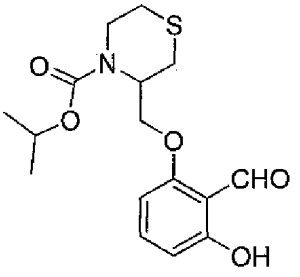
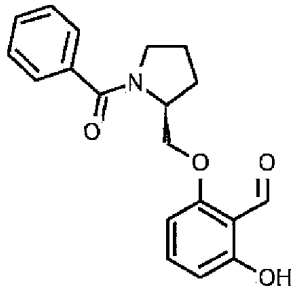


or a pharmaceutically acceptable salt of each thereof.

[0010d] In one aspect, there is provided a compound of formula: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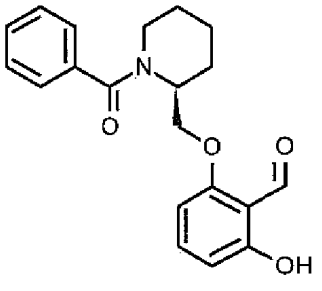
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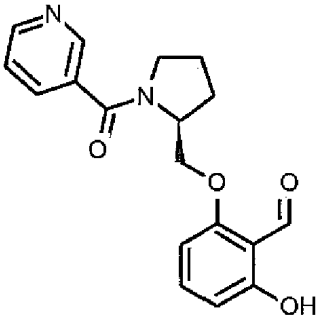
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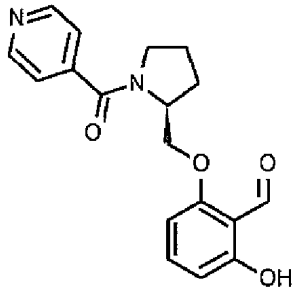
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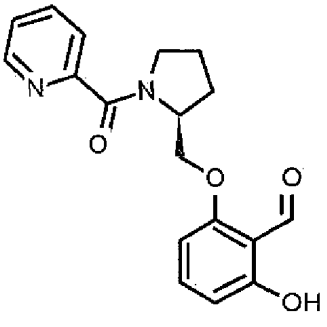
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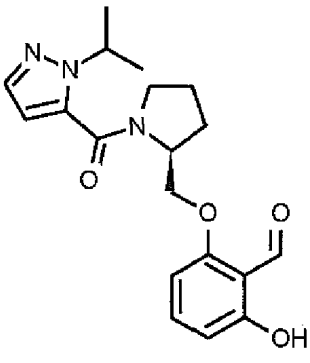
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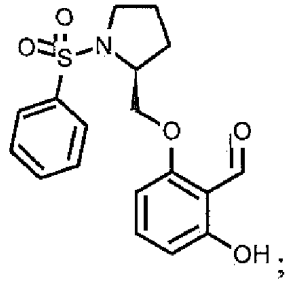
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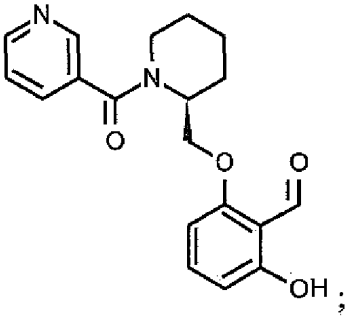
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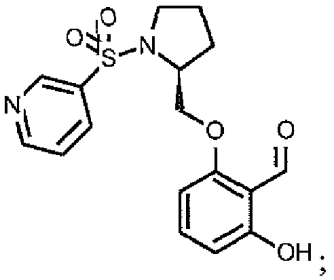
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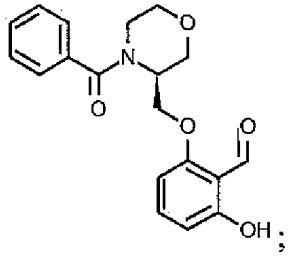
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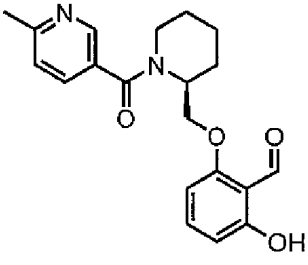
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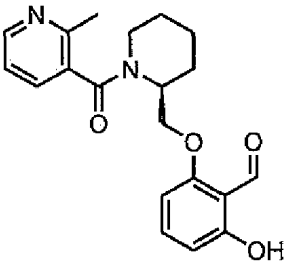
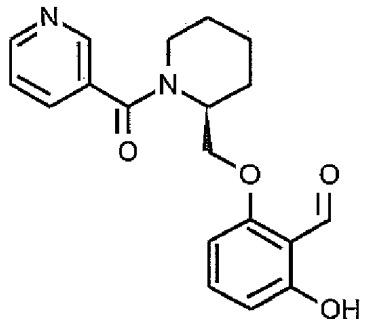


or a pharmaceutically acceptable salt of each thereof.

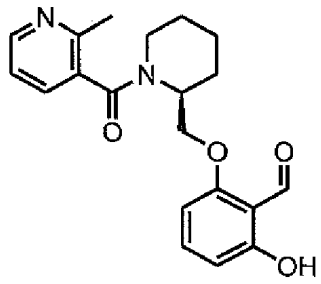
[0010e] In one aspect, there is provided a

[0010f] In one aspect, there is provided a compound of formula:



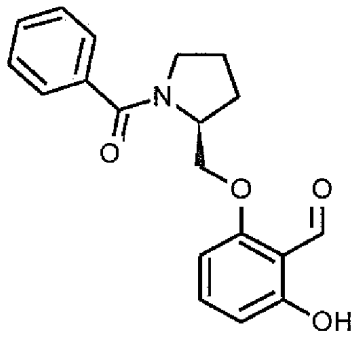
or a pharmaceutically acceptable salt thereof.

[0010g] In one aspect, there is provided a compound of formula:



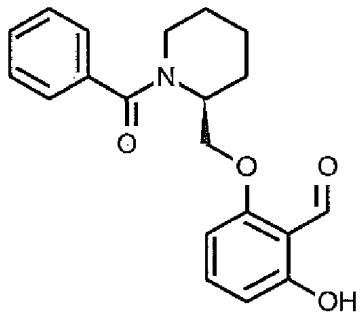
or a pharmaceutically acceptable salt thereof.

[0010h] In one aspect, there is provided a compound of formula:



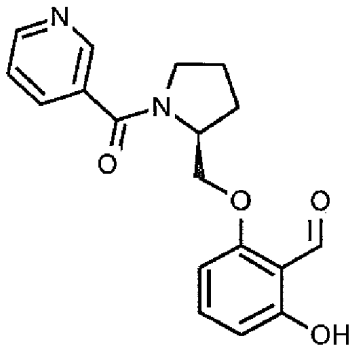
or a pharmaceutically acceptable salt thereof.

[0010i] In one aspect, there is provided a compound of formula:



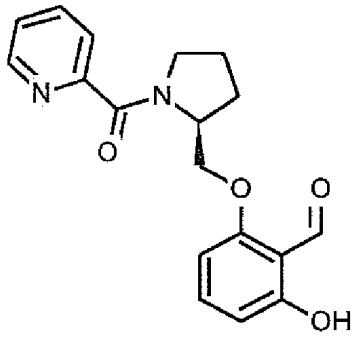
or a pharmaceutically acceptable salt thereof.

[0010j] In one aspect, there is provided a compound of formula:



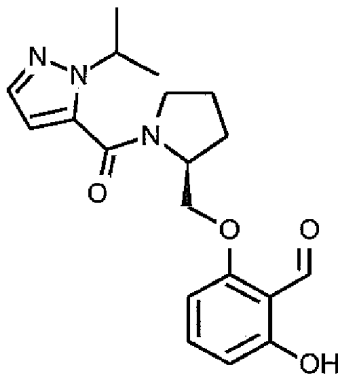
or a pharmaceutically acceptable salt thereof.

[0010k] In one aspect, there is provided a compound of formula:



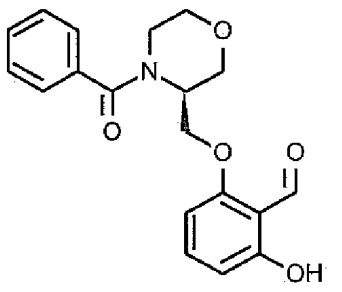
or a pharmaceutically acceptable salt thereof.

[0010l] In one aspect, there is provided a compound of formula:



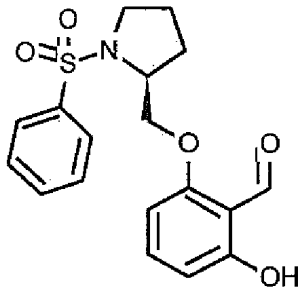
or a pharmaceutically acceptable salt thereof.

[0010m] In one aspect, there is provided a compound of formula:



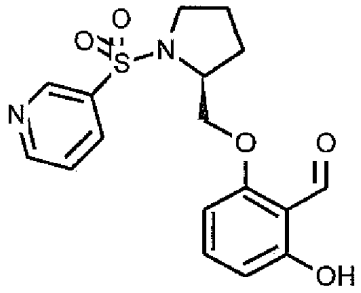
or a pharmaceutically acceptable salt thereof.

[0010n] In one aspect, there is provided a compound of formula:



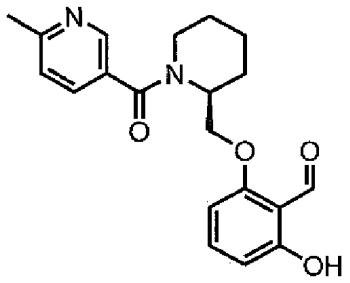
or a pharmaceutically acceptable salt thereof.

[0010o] In one aspect, there is provided a compound of formula:



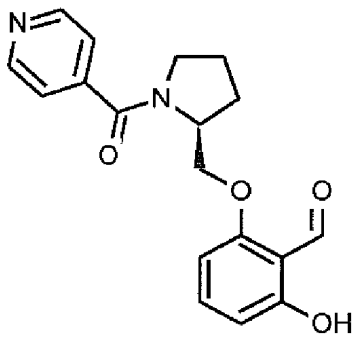
or a pharmaceutically acceptable salt thereof.

[0010p] In one aspect, there is provided a compound of formula:



or a pharmaceutically acceptable salt thereof.

[0010q] In one aspect, there is provided a compound of formula:



or a pharmaceutically acceptable salt thereof.

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

[0012] In still further embodiments of the disclosure, a method is provided for increasing oxygen affinity of hemoglobin S in a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

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

[0013] In further embodiments of the disclosure, a method is provided for treating oxygen deficiency associated with sickle cell anemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of any of the compounds or compositions described herein.

[0013a] In one aspect, there is provided the use of a compound as defined herein or the composition as defined herein in the manufacture of a medicament for treating a condition associated with oxygen deficiency in a subject in need thereof, wherein the condition is sickle cell disease or a cancer.

[0013b] In one aspect, there is provided the use of a compound as defined herein or the composition as defined herein in the manufacture of a medicament for the treatment of sickle cell disease.

DETAILED DESCRIPTION OF THE INVENTION

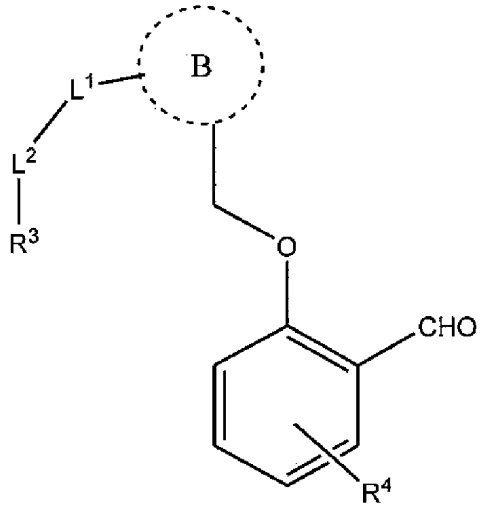
Definitions

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

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

CLAIMS

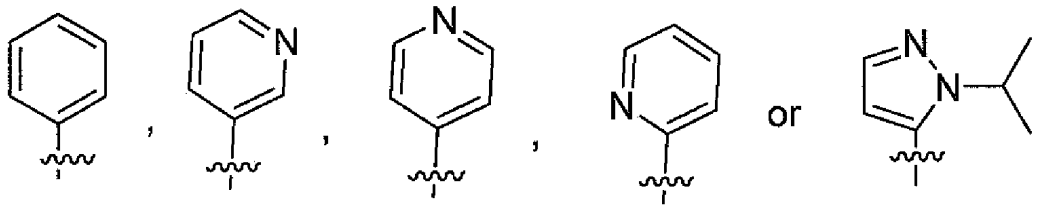
1. A compound of Formula (VI):



(VI)

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

R^3 is

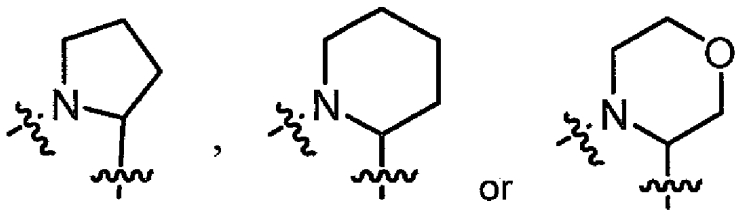


each of which is optionally substituted with 1-4 C_1-C_6 alkyl;

L^1 is a bond;

L^2 is C=O or SO_2;

ring B is

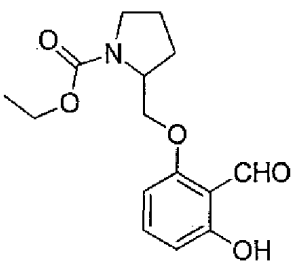


each of which is optionally substituted with 1-3 halo, C_1-C_6 alkyl optionally substituted with 1-5 halo, C_1-C_6 alkoxy, hydroxyl, oxo, COR^{15}, or $COOR^{15}$;

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

R^{19} is hydrogen.

2. A compound of formula: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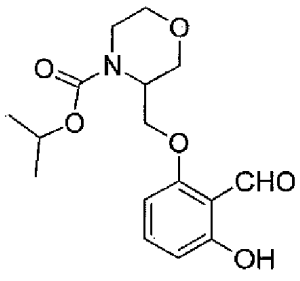
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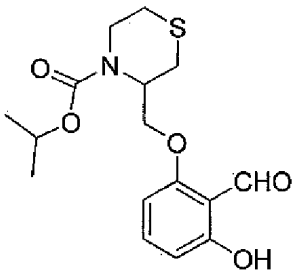
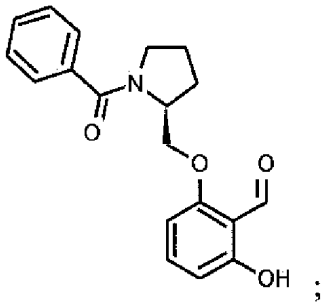


or a pharmaceutically acceptable salt of each thereof.

3. A compound of formula: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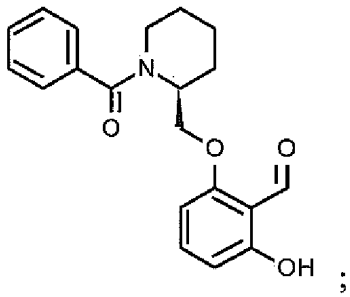
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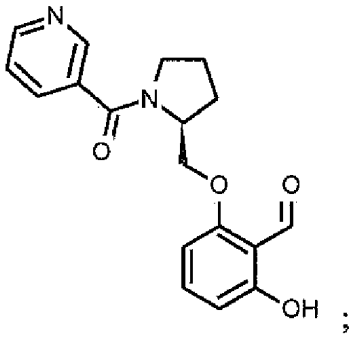
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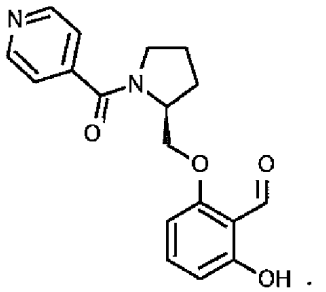
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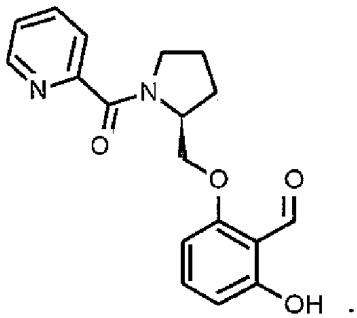
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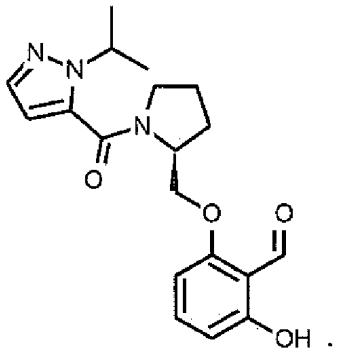
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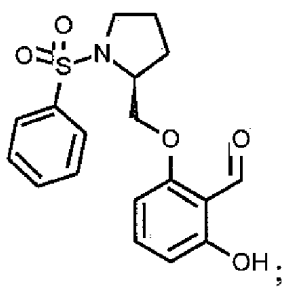
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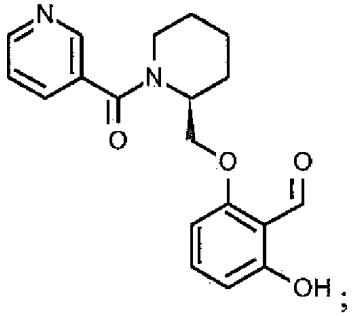
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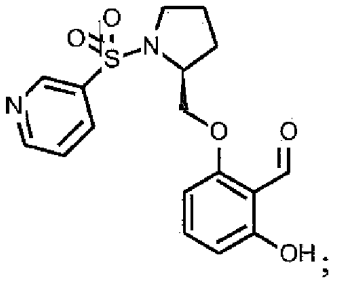
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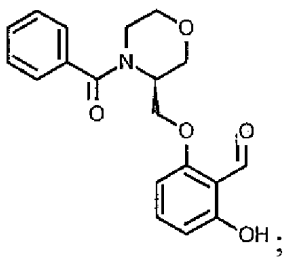
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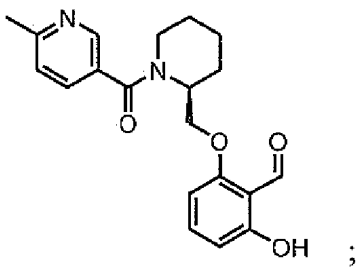
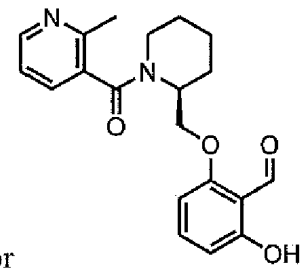
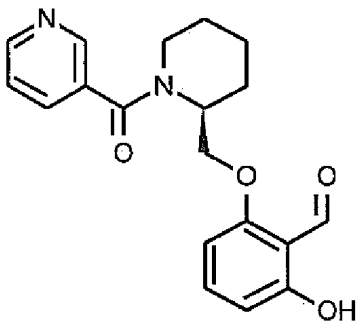

; or



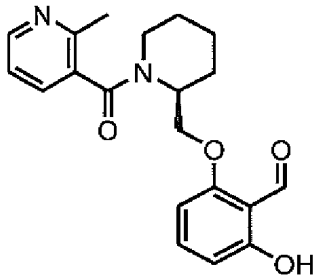
or a pharmaceutically acceptable salt of each thereof.

4. A compound of formula:



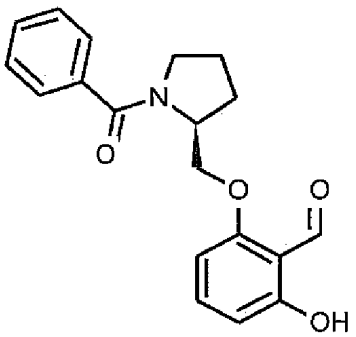
or a pharmaceutically acceptable salt thereof.

5. A compound of formula:



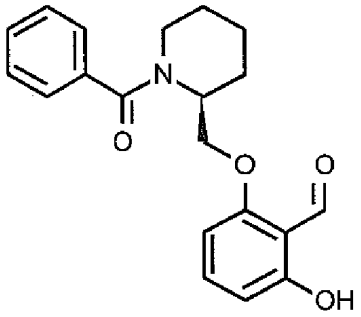
or a pharmaceutically acceptable salt thereof.

6. A compound of formula:



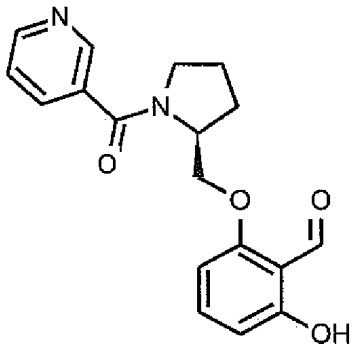
or a pharmaceutically acceptable salt thereof.

7. A compound of formula:



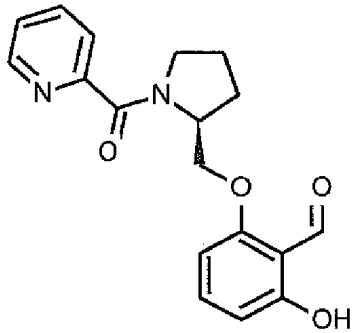
or a pharmaceutically acceptable salt thereof.

8. A compound of formula:



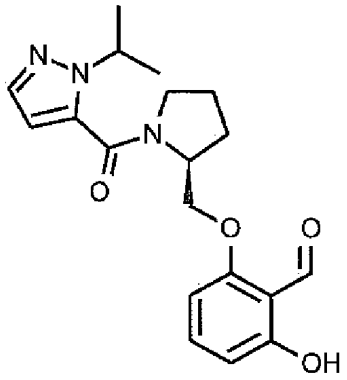
or a pharmaceutically acceptable salt thereof.

9. A compound of formula:



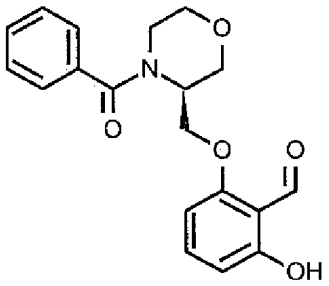
or a pharmaceutically acceptable salt thereof.

10. A compound of formula:



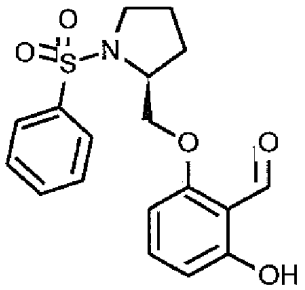
or a pharmaceutically acceptable salt thereof.

11. A compound of formula:



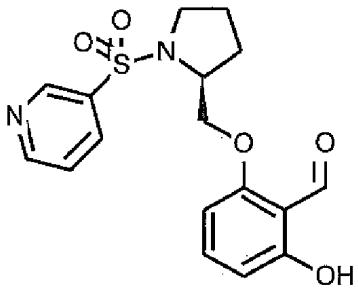
or a pharmaceutically acceptable salt thereof.

12. A compound of formula:



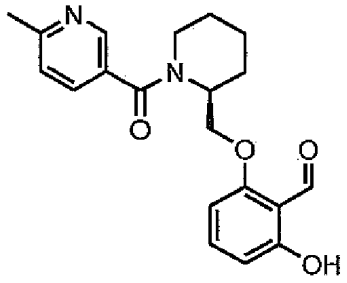
or a pharmaceutically acceptable salt thereof.

13. A compound of formula:



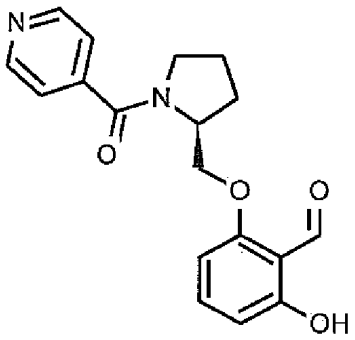
or a pharmaceutically acceptable salt thereof.

14. A compound of formula:



or a pharmaceutically acceptable salt thereof.

15. A compound of formula:



or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound of any one of claims 1-15 and at least one pharmaceutically acceptable excipient.

17. Use of a compound of any one of claims 1-15 or the composition of claim 16 in the manufacture of a medicament for increasing oxygen affinity of hemoglobin S in a subject.

18. Use of a compound of any one of claims 1-15 or the composition of claim 16 in the manufacture of a medicament for the treatment of a condition associated with oxygen deficiency in a subject in need thereof, wherein the condition is sickle cell disease or a cancer.

19. Use of a compound of any one of claims 1-15 or the composition of claim 16 in the manufacture of a medicament for the treatment of sickle cell disease.