the polymer forming T state to the non-polymer forming R state (Nnamani et al. Chemistry & Biodiversity Vol. 5, 2008 pp. 1762-1769) by acting as allosteric modulators to stabilize the R state through formation of a Schiff base with an amino group on hemoglobin.

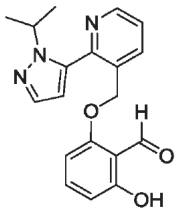
[0005] US 7,160,910 discloses 2-furfuraldehydes and related compounds that are also allosteric modulators of hemoglobin. One particular compound 5-hydroxymethyl-2-furfuraldehyde (5HMF) was found to be a potent hemoglobin modulator both *in vitro* and *in vivo*. Transgenic mice producing human HbS that were treated with 5HMF were found to have significantly improved survival times when exposed to extreme hypoxia (5% oxygen). Under these hypoxic conditions, the 5HMF treated mice were also found to have reduced amounts of hypoxia-induced sickled red blood cells as compared to the non-treated mice.

[0006] A need exists for therapeutics that can shift the equilibrium between the deoxygenated and oxygenated states of Hb to treat disorders that are mediated by Hb or by abnormal Hb such as HbS. A need also exists for therapeutics to treat disorders that would benefit from having Hb in the R state with an increased affinity for oxygen. Such therapeutics would have applications ranging, for example, from sensitizing hypoxic tumor cells that are resistant to standard radiotherapy or chemotherapy due to the low levels of oxygen in the cell, to treating pulmonary and hypertensive disorders, and to promoting wound healing.

BRIEF SUMMARY

[0007] The present disclosure provides, in one example, allosteric modulators of hemoglobin. In another example, provided are pharmaceutical compositions comprising the allosteric modulators disclosed herein. In other examples, provided are methods for treating disorders mediated by hemoglobin and methods for increasing tissue oxygenation for treating disorders that would benefit from increased oxygenation, such methods comprising administering the allosteric modulators disclosed herein to a subject in need thereof. In still other examples, provided are methods for preparing the allosteric modulators disclosed herein. These and other examples of the disclosure are more fully described in the description that follows.

In one aspect, the present disclosure refers to a compound which is



or a tautomer or pharmaceutically acceptable salt thereof.

In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein or a tautomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In a further aspect, the present disclosure refers to use of a compound disclosed herein, or a tautomer or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing tissue oxygenation.

In yet a further aspect, the present disclosure refers to use of a compound disclosed herein, or a tautomer or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition associated with oxygen deficiency.

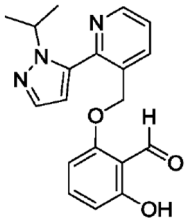
DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[0008] As used herein, the below terms have the following meanings unless specified otherwise.

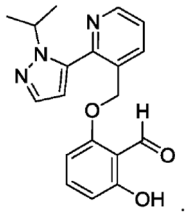
WHAT IS CLAIMED IS:

1. A compound which is



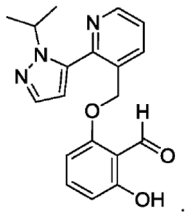
or a tautomer or pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein the compound is:



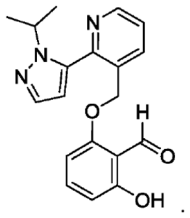
3. A pharmaceutical composition comprising a compound of claim 1 or claim 2 or a tautomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

4. The pharmaceutical composition of claim 3 wherein the compound is:



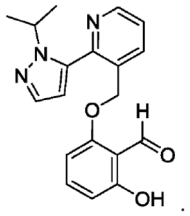
5. Use of a compound of claim 1 or claim 2, or a tautomer or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for increasing tissue oxygenation.

6. The use of claim 5, wherein the compound is:



7. Use of a compound of claim 1 or claim 2, or a tautomer or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a condition associated with oxygen deficiency.

8. The use of claim 7, wherein the compound is:



9. The use of claim 7 or claim 8, wherein the condition is selected from the group consisting of sickle cell disease, cancer, a pulmonary disorder, stroke, high altitude sickness, an ulcer, a pressure sore, Alzheimer's disease, acute respiratory disease syndrome, and a wound.

10. The use of claim 9, wherein the condition is sickle cell disease.

11. The use of claim 9, wherein the condition is a pulmonary disorder.

12. The use of claim 9 wherein the condition is acute respiratory disease syndrome.