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.

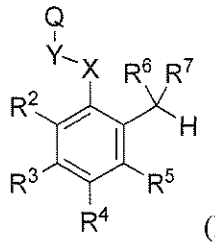
[0005] US 7,160,910 discloses 2-furfuraldehydes and related compounds that are also allosteric modulators of hemoglobin. One particular compound 5-hydroxymethyl-2-furfuraldehyde (5HMF) was found to be a potent hemoglobin modulator both *in vitro* and *in vivo*. Transgenic mice producing human HbS that 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 embodiment, allosteric modulators of hemoglobin. In another embodiment, provided are pharmaceutical compositions comprising the allosteric modulators disclosed herein. In other embodiments, 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 embodiments, provided are methods for preparing the allosteric modulators disclosed herein. These and other embodiments of the invention are more fully described in the description that follows.

In one aspect, there is provided a compound of Formula (I):

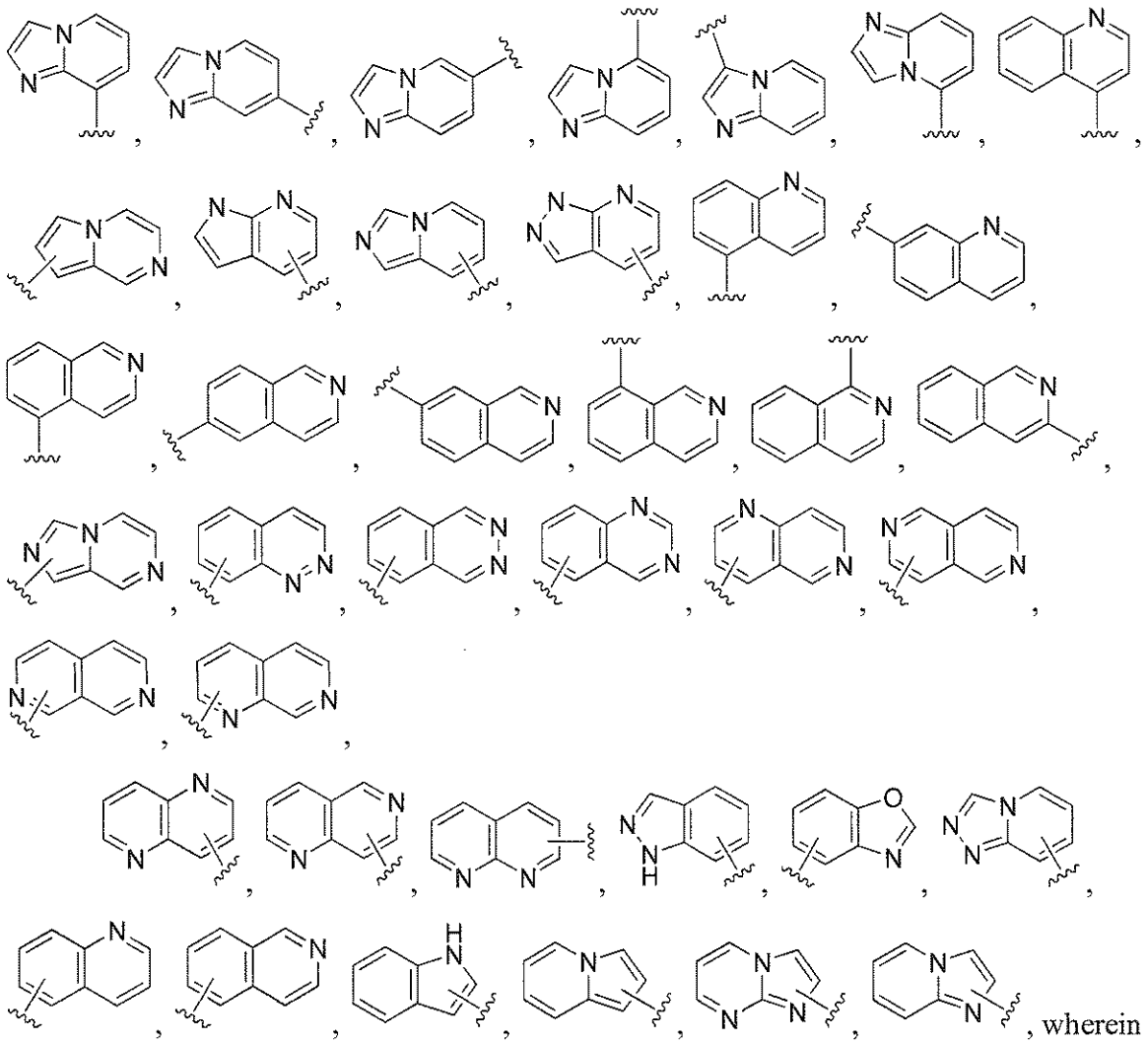


(I)

or a tautomer or pharmaceutically acceptable salt thereof,

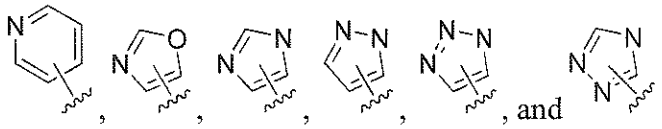
wherein Q is selected from the group consisting of:

(a)(i) heteroaryl selected from:



each of the above rings in (a)(i) is substituted with one to three R^a; or

(a)(ii) heteroaryl selected from



above rings in (a)(ii) is substituted with one to three R^a wherein at least one R^a is $-(CH_2)_k$heteroaryl optionally substituted with one to three R^c,

Y is CH_2;

X is O;

R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, halo, R^b, OR^d, $-O(CH_2)_zOR^d$, $-O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, CO_2R^d, $CONR^dR^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3, where z is 0, 1, 2, 3, 4, 5, or 6;

R^6 and R^7 together form oxo;

each R^a is independently selected from the group consisting of halo, oxo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, $-(CH_2)_kOC(O)R^e$, $-(CH_2)_kSR^d$, CN, $(CH_2)_kCO_2(C_{1-8}alkyl)OH$, $-(CH_2)_kCO_2(C_{1-8}alkyl)(heteroaryl)C(O)(C_{1-8}alkyl)$, $-(CH_2)_kCO_2R^d$, $-(CH_2)_kCONR^dR^d$, $-(CH2)_kNR^dC(O)R^e$, $-(CH_2)_kNR^dC(O)_2R^e$, $-(CH_2)_kC(O)R^d$, $-(CH_2)_kOC(O)NR^dR^d$, $-NR^d(CH_2)_uOR^d$, $-NR^d(CH_2)_uNR^dR^d$, $-NR^d(CH_2)_uNR^dC(O)R^e$, $-NR^d(CH_2)_uNR^dC(O)_2R^e$, $-NR^d(CH_2)_uNR^dS(O)_2R^e$, $-(CH_2)_kNR^dC(O)R^e$, $-(CH_2)_kNR^dC(O)_2R^d$, $-(CH_2)_kNR^dC(O)NR^dR^d$, $-(CH_2)_kS(O)R^e$, $-(CH_2)_kS(O)_2R^e$, $-(CH_2)_kNR^dS(O)_2R^e$, $-(CH_2)_kS(O)_2NR^dR^d$, N_3, $-(CH_2)_k$aryl optionally substituted with one to three R^c, $-NR^d(CH_2)_k$aryl optionally substituted with one to three R^c, $-(CH_2)_k$heteroaryl optionally substituted with one to three R^c, $-NR^d(CH_2)_k$heteroaryl optionally substituted with one to three R^c, $-(CH_2)_k$heterocycloalkyl optionally substituted with one to three R^c, and $-NR^d(CH_2)_k$heterocycloalkyl optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6;

each R^b is independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and C_{2-8}alkynyl, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

each R^c is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, C_{2-8}alkynyl, haloC_{2-8}alkynyl, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, CO_2R^f, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR_fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, N_3, heteroaryl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

each R^h is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, OR^j, $OC(O)R$, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, $C(O)R^j$, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^t$, $NR^jC(O)_2R^t$, $NR^jC(O)NR^jR^j$, $S(O)R^t$, $S(O)_2R^t$, $NR^jS(O)_2R^t$, and $S(O)_2NR^jR^j$;

R^d, R^f, and R^j are each independently selected from the group consisting of hydrogen, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, C_{2-8}alkynyl, and haloC_{2-8}alkynyl; and

R^e, R^g, and R^t are each independently selected from the group consisting of C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, C_{2-8}alkynyl, and haloC_{2-8}alkynyl;

and provided that the compound is not one of the following:

5-hydroxy-2-[7-chloroquinolin-2-yl]methoxybenzaldehyde;

2-((2-aminoquinolin-3-yl)methoxy)benzaldehyde;

2-((2-chloroquinolin-3-yl)methoxy)benzaldehyde; or

2-((5'-methyl-[2,2'-bipyridin]-5-yl)methoxy)benzaldehyde.

In another aspect, there is provided a compound that is: 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde; or a tautomer or a pharmaceutically acceptable salt thereof.

In yet another aspect, there is provided a pharmaceutical composition comprising a compound disclosed herein or a tautomer or pharmaceutically acceptable salt thereof.

In a further aspect, there is provided use of a compound disclosed herein or a tautomer or pharmaceutically acceptable salt thereof in the preparation of a medicament for increasing tissue oxygenation in a subject.

In yet a further aspect, there is provided use of a compound disclosed herein or a tautomer or pharmaceutically acceptable salt thereof in the preparation of a medicament for treating condition associated with oxygen deficiency 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.

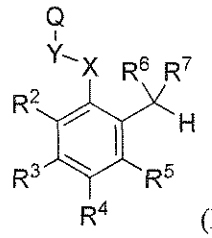
DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

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

WHAT IS CLAIMED IS:

1. A compound of Formula (I):

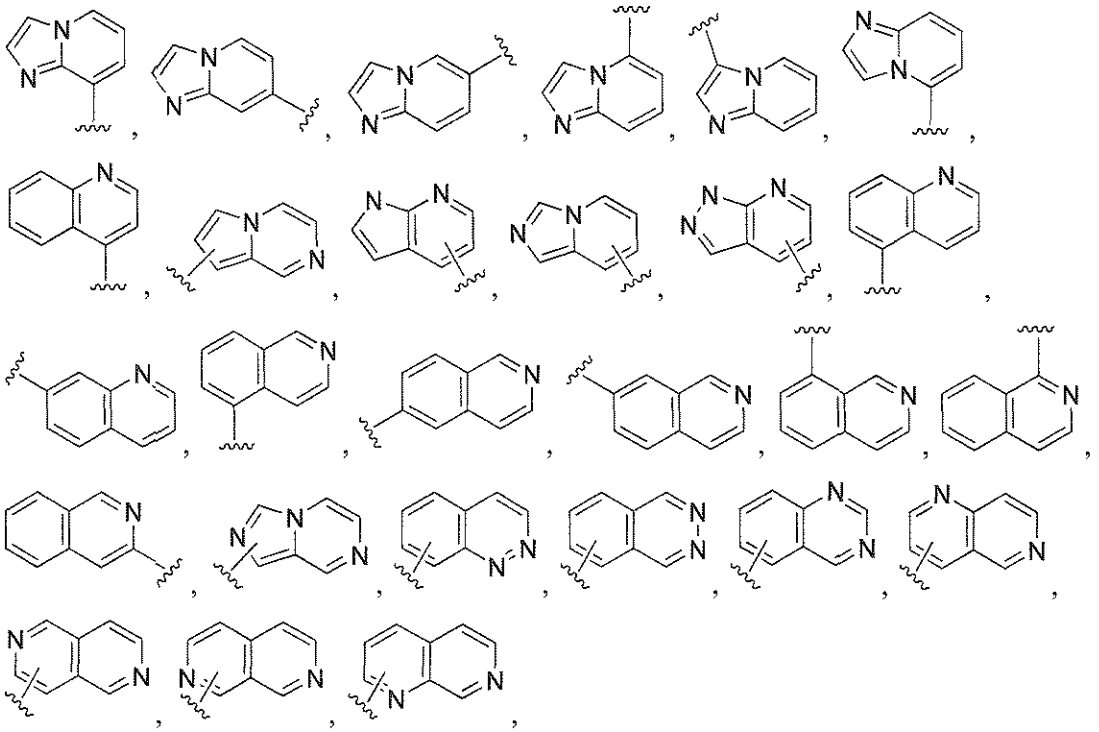


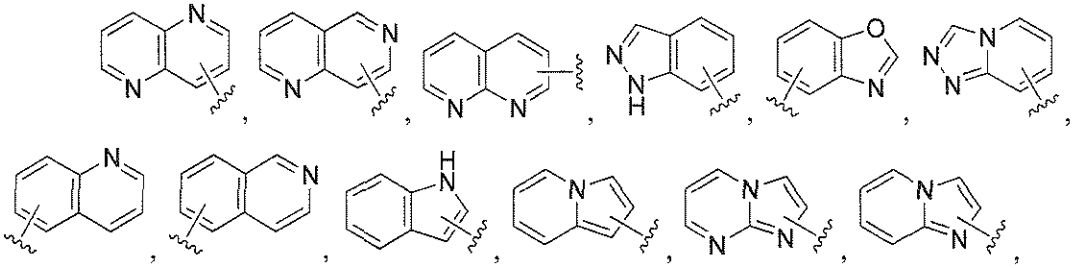
(I)

or a tautomer or pharmaceutically acceptable salt thereof,

wherein Q is selected from the group consisting of:

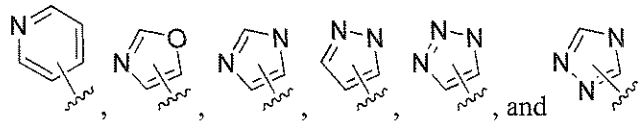
(a)(i) heteroaryl selected from:





wherein each of the above rings in (a)(i) is substituted with one to three R^a; or

(a)(ii) heteroaryl selected from



, wherein each of the above rings in (a)(ii) is substituted with one to three R^a wherein at least one R^a is -$(CH_2)_k$heteroaryl optionally substituted with one to three R^c,

Y is CH_2;

X is O;

R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, halo, R^b, OR^d, -$O(CH_2)_zOR^d$, -$O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, CO_2R^d, $CONR^dR^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3, where z is 0, 1, 2, 3, 4, 5, or 6;

R^6 and R^7 together form oxo;

each R^a is independently selected from the group consisting of halo, oxo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, -$(CH_2)_kOC(O)R^e$, -$(CH_2)_kSR^d$, CN, $(CH_2)_kCO_2(C_{1\text{-}8}alkyl)OH$, -$(CH_2)_kCO_2(C_{1\text{-}8}alkyl)$(heteroaryl)$C(O)(C_{1\text{-}8}alkyl)$, -$(CH_2)_kCO_2R^d$, -$(CH_2)_kCONR^dR^d$, -$(CH2)_kNR^dC(O)R^e$, -$(CH_2)_kNR^dC(O)_2R^e$, -$(CH_2)_kC(O)R^d$, -$(CH_2)_kOC(O)NR^dR^d$, -$NR^d(CH_2)_uOR^d$, -$NR^d(CH_2)_uNR^dR^d$, -$NR^d(CH_2)_uNR^dC(O)R^e$, -$NR^d(CH_2)_uNR^dC(O)_2R^e$, -$NR^d(CH_2)_uNR^dS(O)_2R^e$, -$(CH_2)_kNR^dC(O)R^e$, -$(CH_2)_kNR^dC(O)_2R^d$, -$(CH_2)_kNR^dC(O)NR^dR^d$, -$(CH_2)_kS(O)R^e$, -$(CH_2)_kS(O)_2R^e$, -$(CH_2)_kNR^dS(O)_2R^e$, -$(CH_2)_kS(O)_2NR^dR^d$, N_3, -$(CH_2)_k$aryl optionally substituted with one to three R^c, -$NR^d(CH_2)_k$aryl optionally substituted with one to three R^c, -$(CH_2)_k$heteroaryl optionally substituted with one to three R^c, -$NR^d(CH_2)_k$heteroaryl optionally substituted with one to three R^c, -$(CH_2)_k$heterocycloalkyl optionally substituted with one to three

R^c, and $-NR^d(CH_2)_k$heterocycloalkyl optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6;

each R^b is independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and C_{2-8}alkynyl, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

each R^c is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, C_{2-8}alkynyl, haloC_{2-8}alkynyl, $(CH_2)_mOR^f$, $OC(O)R^g$, SR^f, CN, CO_2R^f, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR_fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, N_3, heteroaryl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

each R^h is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, OR^j, OC(O)R, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, $C(O)R^j$, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^t$, $NR^jC(O)_2R^t$, $NR^jC(O)NR^jR^j$, $S(O)R^t$, $S(O)_2R^t$, $NR^jS(O)_2R^t$, and $S(O)_2NR^jR^j$;

R^d, R^f, and R^j are each independently selected from the group consisting of hydrogen, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, C_{2-8}alkynyl, and haloC_{2-8}alkynyl; and

R^e, R^g, and R^t are each independently selected from the group consisting of C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, C_{2-8}alkynyl, and haloC_{2-8}alkynyl;

and provided that the compound is not one of the following:

5-hydroxy-2-[7-chloroquinolin-2-yl]methoxybenzaldehyde;

2-((2-aminoquinolin-3-yl)methoxy)benzaldehyde;

2-((2-chloroquinolin-3-yl)methoxy)benzaldehyde; or

2-((5'-methyl-[2,2'-bipyridin]-5-yl)methoxy)benzaldehyde.

2. The compound according to claim 1, or a tautomer or pharmaceutically acceptable salt thereof, wherein:

Q is selected from the group consisting of:

i) imidazo[1,5-a]pyridin-8-yl, imidazo[1,5-a]pyridin-6-yl, imidazo[1,5-a]pyridin-5-yl, imidazo[1,2-a]pyridin-8-yl, imidazo[1,2-a]pyridin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyridin-5-yl, imidazo[1,2-a]pyridin-3-yl, 8-methylimidazo[1,2-a]pyridin-2-yl, indazol-4-yl, pyrrolo[2,3-b]pyridin-4-yl, pyrrolo[1,2-

a]pyrazin-6-yl, pyrrolo[1,2-a]pyrazin-4-yl, pyrazolo[3,4-b]pyridin-4-yl, and quinolin-5-yl, each of which is substituted with one to three R^a; wherein

R^2, R^3, R^4, and R^5, are independently selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, CO_2R^d, $CONR^dR^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3; and

ii) pyridinyl which is substituted with one to three R^a provided that at least one R^a is $-(CH_2)_k$heteroaryl optionally substituted with one to three R^c; wherein

R^2, R^3, and R^4 are independently selected from the group consisting of hydrogen, halo, R^b, OR^d, $O(CH_2)_zOR^d$, $O(CH_2)_zNR^dR^d$, $OC(O)R^e$, SR^d, CN, CO_2R^d, $CONR^dR^d$, $OC(O)NR^dR^d$, NR^dR^d, $NR^dC(O)R^e$, $NR^dC(O)_2R^e$, $NR^dC(O)NR^dR^d$, $S(O)R^e$, $S(O)_2R^e$, $NR^dS(O)_2R^e$, $S(O)_2NR^dR^d$, and N_3 where z is 1, 2, or 3; and

R^5 is selected from the group consisting of halo and OR^d;

each R^a is independently selected from the group consisting of halo, oxo, R^b, OR^d, $O(CH_2)_uOR^d$, $O(CH_2)_uNR^dR^d$, $O(CH_2)_uNR^dC(O)R^e$, $O(CH_2)_uNR^dC(O)_2R^e$, $O(CH_2)_uNR^dS(O)_2R^e$, NH_2, $-(CH_2)_kOC(O)R^e$, $-(CH_2)_kSR^d$, CN, $-(CH_2)_kCO_2(C_{1-8}$alkyl)OH, $-(CH_2)_kCO_2(C_{1-8}$alkyl)(heteroaryl)C(O)(C_{1-8}alkyl), $-(CH_2)_kCO_2R^d$, $-(CH_2)_kCONR^dR^d$, $-(CH_2)_kNR^dC(O)R^e$, $-(CH_2)_kNR^dC(O)_2R^e$, $-(CH_2)_kC(O)R^d$, $-(CH_2)_kOC(O)NR^dR^d$, $-NR^d(CH_2)_uOR^d$, $-NR^d(CH_2)_uNR^dR^d$, $-NR^d(CH_2)_uNR^dC(O)R^e$, $-NR^d(CH_2)_uNR^dC(O)_2R^e$, $-NR^d(CH_2)_uNR^dS(O)_2R^e$, $-(CH_2)_kNR^dC(O)R^e$, $-(CH_2)_kNR^dC(O)_2R^d$, $-(CH_2)_kNR^dC(O)NR^dR^d$, $-(CH_2)_kS(O)R^e$, $-(CH_2)_kS(O)_2R^e$, $-(CH_2)_kNR^dS(O)_2R^e$, $-C(O)(CH_2)_kNR^dS(O)_2R^e$, $-(CH_2)_kC(O)NR^dS(O)_2R^e$, $-(CH_2)_kS(O)_2NR^dR^d$, N_3, $-(CH_2)_k$aryl optionally substituted with one to three R^c, $-NR^d(CH_2)_k$aryl optionally substituted with one to three R^c, $-(CH_2)_k$heteroaryl optionally substituted with one to three R^c, $-NR^d(CH_2)_k$heteroaryl optionally substituted with one to three R^c, $-(CH_2)_k$heterocycloalkyl optionally substituted with one to three R^c, and $-NR^d(CH_2)_k$heterocycloalkyl optionally substituted with one to three R^c where k is 0, 1, 2, 3, 4, 5, or 6 and u is 1, 2, 3, 4, 5, or 6;

each R^b is independently selected from the group consisting of C_{1-8}alkyl, C_{2-8}alkenyl, and C_{2-8}alkynyl, each optionally independently substituted with one to three halo, OR^d, or NR^dR^d;

each R^c is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8}alkenyl, haloC_{2-8}alkenyl, C_{2-8}alkynyl, haloC_{2-8}alkynyl, $(CH_2)_mOR^f$, $OC(O)R^g$,

SR^f, CN, $(CH_2)_mCO_2R^f$, $CONR^fR^f$, $C(O)R^f$, $OC(O)NR^fR^f$, $(CH_2)_mNR^fR^f$, $NR^fC(O)R^g$, $NR^fC(O)_2R^g$, $NR^fC(O)NR^fR^f$, $S(O)R^g$, $S(O)_2R^g$, $NR^fS(O)_2R^g$, $S(O)_2NR^fR^f$, N_3, heteroaryl optionally substituted with one to three R^h, cycloalkyl optionally substituted with one to three R^h, and heterocycloalkyl optionally substituted with one to three R^h where m is selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

each R^h is independently selected from the group consisting of halo, C_{1-8}alkyl, haloC_{1-8}alkyl, OR^j, OC(O)R, SR^j, NO_2, CO_2R^j, $CONR^jR^j$, $C(O)R^j$, $OC(O)NR^jR^j$, NR^jR^j, $NR^jC(O)R^t$, $NR^jC(O)_2R^t$, $NR^jC(O)NR^jR^j$, $S(O)R^t$, $S(O)_2R^t$, $NR^jS(O)_2R^t$, and $S(O)_2NR^jR^j$;

R^d, R^f, and R^j are each independently selected from the group consisting of hydrogen, C_{1-8} alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl; and

R^e, R^g, and R^t are each independently selected from the group consisting of C_{1-8}alkyl, haloC_{1-8}alkyl, C_{2-8} alkenyl, haloC_{2-8}alkenyl, C_{2-8} alkynyl, and haloC_{2-8}alkynyl.

3. The compound according to claim 2, or a tautomer or pharmaceutically acceptable salt thereof, wherein Q is selected from the group consisting of imidazo[1,5-a]pyridin-8-yl, imidazo[1,5-a]pyridin-6-yl, imidazo[1,5-a]pyridin-5-yl, imidazo[1,2-a]pyridin-8-yl, imidazo[1,2-a]pyridin-7-yl, imidazo[1,2-a]pyridin-6-yl, imidazo[1,2-a]pyridin-5-yl, imidazo[1,2-a]pyridin-3-yl, 8-methylimidazo[1,2-a]pyridin-2-yl, indazol-4-yl, pyrrolo[2,3-b]pyridin-4-yl, pyrrolo[1,2-a]pyrazin-6-yl, pyrrolo[1,2-a]pyrazin-4-yl, pyrazolo[3,4-b]pyridin-4-yl, and quinolin-5-yl, each of which is optionally substituted with one to three R^a;

R^2 is selected from the group consisting of H and OR^d;

R^3 is selected from the group consisting of H, CN, halo, and OR^d;

R^4 is selected from the group consisting of H, CN, and OR^d: and

R^5 is H.

4. The compound according to claim 1 selected from the group consisting of:

5-methoxy-2-((1-methyl-1H-indazol-4-yl)methoxy)benzaldehyde,

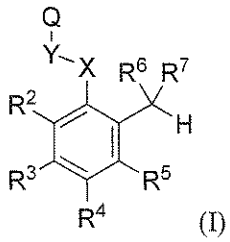
5-methoxy-2-((8-methylimidazo[1,2-a]pyridin-2-yl)methoxy)benzaldehyde,

6-((2-formyl-4-methoxyphenoxy)methyl)pyrrolo[1,2-a]pyrazine-7-carbonitrile, and

6-((2-formyl-4-methoxyphenoxy)methyl)pyrrolo[1,2-a]pyrazine-7-carboxamide;

or a tautomer or pharmaceutically acceptable salt thereof.

5. The compound according to claim 1 having the formula:



(I)

or a tautomer or pharmaceutically acceptable salt thereof,

wherein Q is pyridin-3-yl or pyridin-4-yl substituted with one to three R^a where at least one R^a is heteroaryl optionally substituted with one to three R^c wherein the heteroaryl is attached to the carbon atom on the pyridyl ring that is ortho to the pyridyl carbon atom attached to the -Y-X- group;

Y is CH_2;

X is O;

R^2, R^3, R^4, and R^5 are independently selected from the group consisting of hydrogen, halo, R^b, OR^d, or CN;

each R^b is independently C_{1-8}alkyl;

each R^c is independently selected from the group consisting of C_{1-8}alkyl or haloC_{1-8}alkyl; and

each R^d is selected from the group consisting of hydrogen or C_{1-8} alkyl.

6. The compound according to claim 5 selected from the group consisting of:

2-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-5-methoxybenzaldehyde,

2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde,

2-hydroxy-6-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde,

2-hydroxy-6-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde,

2-fluoro-6-((2-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde,

2-fluoro-6-((2-(1-(3,3,3-trifluoropropyl)-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde, and

2-fluoro-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde;
or a tautomer or pharmaceutically acceptable salt thereof.

7. A compound that is:

2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde; or a tautomer or a pharmaceutically acceptable salt thereof.

8. The compound of claim 6, wherein the compound is 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde.

9. The compound of claim 8 wherein the compound is a pharmaceutically acceptable salt of 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde.

10. A pharmaceutical composition comprising a compound of any one of the preceding claims or a tautomer or pharmaceutically acceptable salt thereof.

11. The pharmaceutical composition of claim 10, wherein the compound is 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde; or a tautomer or a pharmaceutically acceptable salt thereof.

12. The pharmaceutical composition of claim 11, wherein the compound is 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde.

13. Use of a compound according to any one of the preceding claims or a tautomer or pharmaceutically acceptable salt thereof in the preparation of a medicament for increasing tissue oxygenation in a subject.

14. Use of a compound according to any one of the preceding claims or a tautomer or pharmaceutically acceptable salt thereof in the preparation of a medicament for treating condition associated with oxygen deficiency 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.

15. The use of claim 14, wherein the condition is sickle cell disease.

16. The use of claim 14, wherein the condition is a-pulmonary disorder.

17. The use of any one of claims 14-16, wherein the compound is 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)benzaldehyde; or a tautomer; or a pharmaceutically acceptable salt thereof.

18. The use of any one of claims 14-16, wherein the compound is 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl)pyridin-3-yl)methoxy)-benzaldehyde.