first and rate-limiting step is the production of biliverdin and carbon monoxide from heme by HMOX1. The second step is the production of bilirubin from biliverdin by biliverdin reductase. Both bilirubin and carbon monoxide have been shown to scavenge ROS and to have potent anti-oxidant and anti-inflammatory activities.

Agents that induce production of HMOX1 have been shown to have beneficial activity in models of diabetes, cardiovascular disease, hypertension, and pulmonary function. Heme, heavy metal ions (*e.g.*, arsenite, cadmium, iron, lead, chromium and mercury), and electrophiles (*e.g.*, natural products such as sulforaphane and curcumin) can all induce production of HMOX1. Induction of HMOX1 and other phase II genes are controlled by a number of transcription factors that are responsive to heavy metals, heme, and electrophiles. The transcription factors Nrf2, Bach1, and small Maf proteins are particularly important in this process. For example, a common sequence called antioxidant responsive element (ARE) is present in a promoter of each gene of the phase II enzymes, and its expression is induced by the transcription factor Nrf2 (NF-E2 related factor 2).

HMOX1 is also induced as part of a generalized stress response to stimuli such as thermal shock, oxidative stress and cytokines such as interleukin-1 (IL-1), tumor necrosis factor and interleukin-6 (IL-6).This stress response is seen as beneficial in that it results in protection of vulnerable cells from multiple insults.

It has been reported that HMOX1 can be induced by small molecules that bind to the transcription factor Bach1. Heme binding to Bach1 has been shown to reduce DNA binding activity of Bach1 and induce gene transcription. *See* Ogawa K *et al.* EMBO J (2001) 20:2835-284. Additionally, a small molecule has been reported to induce HMOX1 through binding to Bach1. See Attucks OC *et al.* PLOS ONE (2014) 9(7): e101044, WO2011/103018 and WO2012/094580.

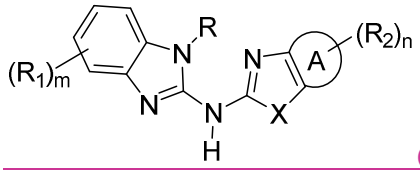
As such, there is a need for new HMOX1 inducers and/or Bach 1 binders/ inhibitors for the above referenced therapeutic indications.

SUMMARY ~~OF THE INVENTION~~

The applicant has discovered novel compounds which are effective HMOX1 inducers (*see* Examples 1-142). In particular, it has been demonstrated that certain compounds of the present ~~invention~~disclosure effectively induced production of HMOX1 (*see* Example 143). Also, certain compounds of the ~~invention~~present disclosure have a combination of desirable properties, including potent HMOX1 induction activity (Example 143), significantly reduced hERG inhibition

compared to certain comparator compounds (*see* Example 145), good solubility (Example 144) and a strong impact on HMOX1 protein expression *in vivo* (Example 151). Moreover, the applicant has also discovered that the compounds disclosed herein bind to Bach 1 (*see* Example 146).

In one aspect of the present disclosure, there is provided a compound represented by structural formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is 5-7 membered monocyclic cycloalkyl

X is -S-, -O-, or -NR^b-;

R is -H, -(C_1-C_4)alkyl, or -$(CH_2)_i$3-7 membered monocyclic heterocyclyl, wherein the -(C_1-C_4)alkyl or 3-7 membered monocyclic heterocyclyl represented by R is optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, -SO_2R^a, and -NR^aR^a;

each R_1 is independently -H, halogen, -$(CH_2)_k$COOH, -$(CH_2)_k$CO(C_1-C_4)alkyl, -$(CH_2)_k$COO(C_1-C_4)alkyl, -$(CH_2)_p$C(=O)NR^aR_3, -$CH(CF_3)NR^aR_3$, -C(=NOH)CF_3, or -$CH(CF_3)OR_3$, wherein the (C_1-C_4)alkyl in the group represented by R_1 is optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, and -NR^aR^a;

each R_2 is independently -H, halo, CN, -(C_1-C_4)alkyl, -OH, -(C_1-C_4)alkoxy, -COOH, -C(=O)(C_1-C_4)alkyl, -C(=O)O(C_1-C_4)alkyl, -C(=O)NR^a(C_1-C_4)alkyl, -NR^aR^a, 3-6 membered monocyclic cycloalkyl, –$O(CH_2)_i$3-7 membered monocyclic heterocyclyl, 3-7 membered monocyclic heterocyclyl, or 5-6 membered heteroaryl, wherein the -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, heterocyclyl, or heteroaryl represented by R_2 or in the group represented by R_2 is optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkyl,
-(C_1-C_4)hydroxyalkyl, -(C_1-C_4)haloalkoxy, and -NR^aR^a;

each R_3 is independently H, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $-(CH_2)_{p1}$3-7 membered monocyclic heterocyclyl, $-(CH_2)_{p1}$NH3-7 membered monocyclic heterocyclyl, 5-6 membered heteroaryl, $-O(CH_2)_{p2}NR^aC(=O)(C_1$-$C_4)$alkyl, $-(CH_2)_{p2}O(CH_2)_{p2}O(C=O)(C_1$-$C_4)$alkyl, or $(CH_2)_{p2}NR^aC(=O)(C_1$-$C_4)$alkyl, wherein the alkyl, alkoxy, heteroaryl, or heterocyclyl represented by R_3 or in the group represented by R_3 is optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, $-(C_1$-$C_4)$alkyl, $-(C_1$-$C_4)$haloalkyl, $-(C_1$-$C_4)$alkoxy, $-(C_1$-$C_4)$hydroxyalkyl, $-(C_1$-$C_4)$haloalkoxy, $-(C_1$-$C_4)$carboxyalkoxy, $-S(O)_2(C_1$-$C_4)$alkyl, $-(C_1$-$C_4)$hydroxyalkoxy, and $-NR^aR^a$;

each R^a is independently -H or $-(C_1$-$C_4)$alkyl;

each R^b is independently -H or $-(C_1$-$C_4)$alkyl; wherein the $-(C_1$-$C_4)$alkyl represented by R^b is optionally substituted with one or more groups selected from halo, -CN, -OH, $-(C_3$-$C_6)$cycloalkyl, phenyl, 3-7 membered monocyclic heterocyclyl, and 5-6 membered heteroaryl;

i is 0 or 1;

k is 0, 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

p_1 is 0, 1, 2, 3, or 4; and

p_2 is 2, 3, or 4.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a use of the compound or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for increasing the activity of or the amount of HMOX-1, activating transcription factor Nrf2, or reducing the amount of ROS in a human subject.

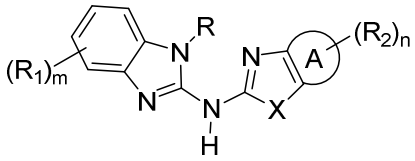
In another aspect of the present disclosure, there is provided a use of the compound or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disease, disorder, or condition, wherein the disease, disorder, or condition is: (i) a fibrotic disease, including a fibrotic disease of the lung, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, sarcoidosis, a fibrotic disease of the liver including those caused by alcoholic cirrhosis, steatosis, cholestasis, drug side effect, and viral infection, a fibrotic diseases of the skin, scleroderma, or psoriasis; (ii) a neurodegenerative disease, including Friedreich's ataxia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, cerebral nerve degenerative disease, or Charcot-Marie-Tooth syndrome; (iii) a cardiovascular disease, including hypertension, hypercholesterolaemia, atherosclerosis, arteriosclerosis, thrombosis, acute coronary thrombosis, deep vein thrombosis, peripheral vascular disease, congestive heart failure, acute coronary syndrome, failure of arterial fistula for dialysis, ischemia-reperfusion injury, primary pulmonary hypertension, primary pulmonary arterial hypertension, or secondary pulmonary arterial hypertension; (iv) a renal disease, including acute kidney injury, polycystic kidney disease, Alport syndrome, diabetic nephropathy, glomerular nephritis, lupus nephritis, sickle cell nephropathy, and acute tubular necrosis; (v) an inflammatory disease, including asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, inflammatory bowel syndrome, Crohn's disease, celiac disease, ulcerative colitis, chronic inflammatory bowel disease, scleroderma, dermatitis, systemic lupus erythematosus, esophagitis, vasculitis, pancreatitis, tendonitis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or chronic inflammation of the brain; (vi) a liver disease, including drug induced liver toxicity, nonalcoholic steatohepatitis, hepatitis B infection, or hepatitis C infection; (vii) an eye disease, including conjunctivitis, glaucoma, uveitis, an eye wound, eye trauma, corneal grafts, Fuchs' endothelial corneal dystrophy, macular degeneration, cataracts, light retinopathy, retinitis pigmentosa, diabetic retinopathy, and retinopathy of prematurity; (viii) a thyroid disease, including Graves' disease, follicular adenoma, or papillary and follicular carcinomas; (ix) a viral infection, including infections from human immunodeficiency virus, hepatitis B, hepatitis C, or herpesvirus; (x) osteoporosis; (xi) a pregnancy disorder; (xii) endometriosis; (xiii) diabetes, including type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, pre-diabetes, hyperglycemia, metabolic syndrome, or a secondary condition resulting from a diabetic condition; (xiv) cancer; (xv) a skin disease, including dermatitis, scleroderma, or psoriasis; (xvi) a mitochondrial diseases such as mitochondrial myopathies, Leber's hereditary optic neuropathy (LHON), myoclonic

epilepsy with ragged red fibers (MERFF), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) or Leigh's Syndrome; (xvii) a hematological disorder such as Diamond Blackfan anemia, myelodysplasic syndrome, sickle cell disease and beta-thalessemia; or (xviii) a muscle diseases, such as Duchenne muscular dystrophy, limb girdle muscular dystrophy, Becker muscular dystrophy, myotonic dystrophy and rhabdomyolysis.

In a further aspect of the present disclosure, there is provided a use of the compound or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating sickle cell disease.

In another aspect of the present disclosure, there is provided a compound or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein, for use in therapy.

In one ~~embodiment~~example, provided herein is a compound represented by the following structural Formula (I):



(I);

or a pharmaceutically acceptable salt thereof, the definition of each variable is provided below.

Pharmaceutical compositions of the compounds of the ~~invention~~present disclosure are also disclosed herein. Particular ~~embodiment~~examples comprise a pharmaceutically acceptable carrier or diluent and one or more of the compounds of the ~~invention~~present disclosure, or a pharmaceutically acceptable salt thereof.

The compounds of Formula (I) and pharmaceutically acceptable salts thereof are useful as agents that induce the production of and/or increase the activity of HMOX1, and thus may be useful to treat various chronic diseases that are associated, at least in part, with oxidative stress including, but not limited to: fibrotic diseases, neurodegenerative disease, cardiovascular disease, renal disease, inflammatory disease, liver disease, eye disease, thyroid disease, viral infection, osteoporosis, pregnancy disorders, endometriosis, diabetes, cancers, skin diseases, mitochondrial diseases, hematological disorders, and muscle diseases.

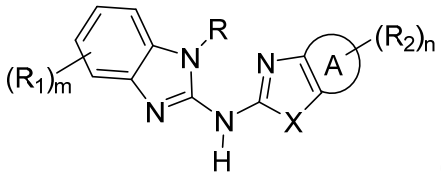
Another ~~embodiment~~example of the present ~~invention~~disclosure comprises treating the above-referenced diseases or conditions in a subject by administering to the subject an effective amount of one or more compounds of the ~~invention~~present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the disclosed compound(s).

Also provided herein is the use of one or more compounds of the ~~invention~~present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or more compounds of the ~~invention~~present disclosure, for the preparation of a medicament for the treatment of the above-referenced diseases or conditions.

In another ~~embodiment~~example, provided herein is the compounds of the ~~invention~~present disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising one or

CLAIMS

1. A compound represented by structural formula (I):



(I);

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is 5-7 membered monocyclic cycloalkyl~~, 5-7 membered monocyclic heterocyclyl, 5-6 membered heteroaryl, or phenyl;~~

X is -S-, -O-, or -NR^b-;

~~when X is -S- and ring A is phenyl, then R is 3-7 membered monocyclic heterocyclyl optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, and -NR^aR^a;~~

~~when X is -S- and ring A is 5-7 membered monocyclic cycloalkyl, 5-7 membered monocyclic heterocyclyl, or 5-6 membered heteroaryl; or when X is -O- or -NR^b-; then~~ R is -H, -(C_1-C_4)alkyl, or -(CH_2)$_i$3-7 membered monocyclic heterocyclyl, wherein the -(C_1-C_4)alkyl or 3-7 membered monocyclic heterocyclyl represented by R is optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, -SO_2R^a, and -NR^aR^a;

each R_1 is independently -H, halogen, -(CH_2)$_k$COOH, -(CH_2)$_k$CO(C_1-C_4)alkyl, -(CH_2)$_k$COO(C_1-C_4)alkyl, -(CH_2)$_p$C(=O)NR^aR_3, -$CH(CF_3)NR^aR_3$, -C(=NOH)CF_3, or -$CH(CF_3)OR_3$, wherein the (C_1-C_4)alkyl in the group represented by R_1 is optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, and -NR^aR^a;

each R_2 is independently -H, halo, CN, -(C_1-C_4)alkyl, -OH, -(C_1-C_4)alkoxy, -COOH, -C(=O)(C_1-C_4)alkyl, -C(=O)O(C_1-C_4)alkyl, -C(=O)NR^a(C_1-C_4)alkyl, -NR^aR^a, 3-6 membered monocyclic cycloalkyl, –O(CH_2)$_i$3-7 membered monocyclic heterocyclyl, 3-7 membered monocyclic heterocyclyl, or 5-6 membered heteroaryl, wherein the -(C_1-

C_4)alkyl, -(C_1-C_4)alkoxy, heterocyclyl, or heteroaryl represented by R_2 or in the group represented by R_2 is optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkyl, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)haloalkoxy, and -NR^aR^a;

each R_3 is independently H, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, -$(CH_2)_{p1}$3-7 membered monocyclic heterocyclyl, -$(CH_2)_{p1}$NH3-7 membered monocyclic heterocyclyl, 5-6 membered heteroaryl, -$O(CH_2)_{p2}NR^aC(=O)$(C_1-C_4)alkyl, -$(CH_2)_{p2}O(CH_2)_{p2}O(C=O)$($C_1$-$C_4$)alkyl, or $(CH_2)_{p2}NR^aC(=O)$(C_1-C_4)alkyl, wherein the alkyl, alkoxy, heteroaryl, or heterocyclyl represented by R_3 or in the group represented by R_3 is optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)haloalkoxy, -(C_1-C_4)carboxyalkoxy, -$S(O)_2$(C_1-C_4)alkyl, -(C_1-C_4)hydroxyalkoxy, and -NR^aR^a;

each R^a is independently -H or -(C_1-C_4)alkyl;

each R^b is independently -H or -(C_1-C_4)alkyl; wherein the -(C_1-C_4)alkyl represented by R^b is optionally substituted with one or more groups selected from halo, -CN, -OH, -(C_3-C_6)cycloalkyl, phenyl, 3-7 membered monocyclic heterocyclyl, and 5-6 membered heteroaryl;

i is 0 or 1;

k is 0, 1, 2, 3, or 4;

m is 0, 1, 2, 3, or 4;

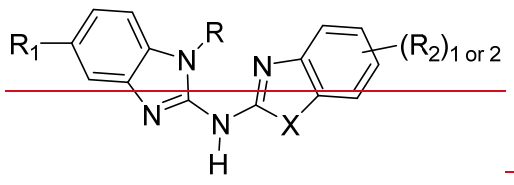
n is 0, 1, 2, 3, or 4;

p is 0, 1, 2, 3, or 4;

p_1 is 0, 1, 2, 3, or 4; and

p_2 is 2, 3, or 4.

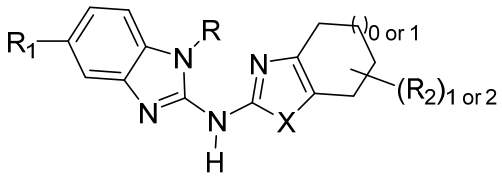
~~2. The compound of claim 1, wherein the compound is represented by structural formula (II):~~



~~(II);~~

~~or a pharmaceutically acceptable salt thereof.~~

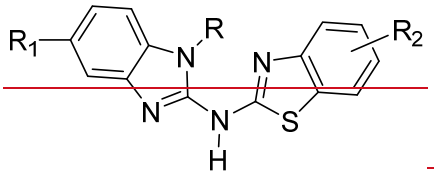
~~3~~2. The compound of claim 1, wherein the compound is represented by structural formula (II'):



(II');

or a pharmaceutically acceptable salt thereof.

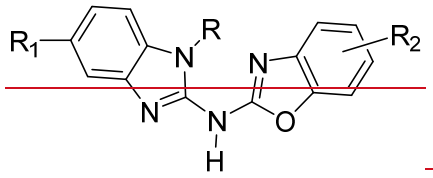
~~4. The compound of claim 1 or 2, wherein the compound is represented by structural formula (II-A):~~



~~(II-A);~~

~~or a pharmaceutically acceptable salt thereof.~~

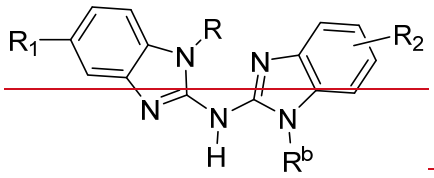
~~5. The compound of claim 1 or 2, wherein the compound is represented by structural formula (II-B):~~



~~(II-B);~~

~~or a pharmaceutically acceptable salt thereof.~~

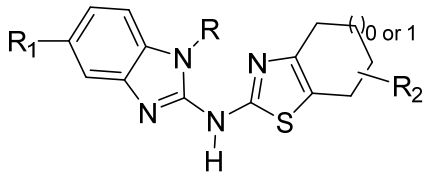
~~6. The compound of claim 1 or 2, wherein the compound is represented by structural formula (II-C):~~



~~(II-C);~~

~~or a pharmaceutically acceptable salt thereof.~~

~~7~~3. The compound of claim 1 or ~~3~~2, wherein the compound is represented by structural formula (II'-A):



(II'-A);

or a pharmaceutically acceptable salt thereof.

~~8. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^b is H or -(C_1-C_4)alkyl, wherein the -(C_1-C_4)alkyl represented by R^b is optionally substituted with one or more groups selected from halo, -CN, and -OH.~~

~~9~~4. The compound of any one of claims 1-3~~ or 5-8~~, or a pharmaceutically acceptable salt thereof, wherein R is -(C_1-C_4)alkyl optionally substituted with -(C_1-C_4)alkoxy; or –$(CH_2)_i$3-6 membered monocyclic heterocyclyl optionally substituted with one or more groups selected from the group consisting of halo, -CN, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, and -NR^aR^a.

~~10~~5. The compound of any one of claims 1-~~8~~3, or a pharmaceutically acceptable salt thereof, wherein R is azetidinyl, azepanyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl, each of which is optionally substituted with one or more groups selected from the group consisting of halo, -OH, -(C_1-C_4)alkyl, and -NH_2.

~~11~~6. The compound of any one of claims 1-~~10~~5, or a pharmaceutically acceptable salt thereof, wherein R_1 is -$(CH_2)_k$COOH, -$(CH_2)_k$CO(C_1-C_4)alkyl optionally substituted with halo, -$(CH_2)_p$C(=O)NR^aR_3, -C(=NOH)CF_3, or -CH(CF_3)NR^aR_3.

~~12~~7. The compound of any one of claims 1-~~11~~6, or a pharmaceutically acceptable salt thereof, wherein R_2 is H; halogen; CN; -(C_1-C_4)alkyl optionally substituted with halo; -(C_1-C_4)alkoxy optionally substituted with halo, hydroxy, methoxy, or ethoxy; -C(=O)(C_1-C_4)alkyl; 3-4 membered monocyclic cycloalkyl; –$O(CH_2)_i$3-7 membered monocyclic heterocyclyl, 3-7 membered monocyclic heterocyclyl, or 5-6 membered

heteroaryl, wherein the heterocyclyl, or heteroaryl represented by R_2 or in the group represented by R_2 is optionally substituted with halo, hydroxy, or -(C_1-C_4)alkoxy.

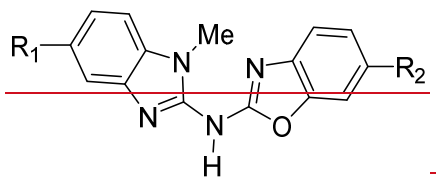
~~13~~8. The compound of any one of claims 1-~~3~~4, ~~5-9, 11~~6, or ~~12~~7, or a pharmaceutically acceptable salt thereof, wherein R is -(C_1-C_4)alkyl optionally substituted with methoxy or -SO_2CH_3; -(CH_2)tetrohydrofuranyl; -(CH_2)oxetanyl optionally substituted with hydroxy; pyrrolidinyl; piperidinyl; or tetrahydropyranyl; wherein the pyrrolidinyl or piperidinyl is optionally substituted with -(C_1-C_4)alkyl.

~~14~~9. The compound of any one of claims 1-~~13~~8, or a pharmaceutically acceptable salt thereof, wherein R_1 is -COOH, -C(=O)CF_3, -CH(CF_3)(NH_2), -C(=NOH)CF_3, or -C(=O)NHR_3.

~~15~~10. The compound of any one of claims 1-~~14~~9, or a pharmaceutically acceptable salt thereof, wherein R_3 is (C_1-C_4)alkyl, (C_1-C_4)alkoxy, $(CH_2)_{p1}$3-6 membered monocyclic heterocyclyl, or $(CH_2)_{p2}$NHC(=O)(C_1-C_4)alkyl, wherein the alkyl, alkoxy, or heterocyclyl represented by R_3 or in the group represented by R_3 is optionally substituted with one or more groups selected from the group consisting of halo, -OH, -(C_1-C_4)alkyl, -(C_1-C_4)haloalkyl, -(C_1-C_4)hydroxyalkyl, -(C_1-C_4)alkoxy, -(C_1-C_4)haloalkoxy, -$S(O)_2$(C_1-C_4)alkyl, -(C_1-C_4)hydroxyalkoxy, and -NR^aR^a.

~~16~~11. The compound of any one of claims 1-~~15~~10, or a pharmaceutically acceptable salt thereof, wherein R_2 is H; halogen; CN; -(C_1-C_4)alkyl optionally substituted with halo; -(C_1-C_4)alkoxy optionally substituted with halo, hydroxy, methoxy, or ethoxy; -C(=O)(C_1-C_4)alkyl; cyclopropyl; O-tetrahydropyranyl; N-pyrolidinyl; or thiazolyl.

~~17. The compound of claim 5, wherein the compound is represented by structural formula (III-B):~~



~~(III-B);~~

~~or a pharmaceutically acceptable salt thereof.~~

~~18~~12. The compound of any one of claims 1-~~17~~11, or a pharmaceutically acceptable salt thereof, wherein

R_1 is -COOH or -C(=O)NHR_3,

R_3 is -(C_1-C_4)alkyl, -hydroxy(C_1-C_4)alkyl, -methoxy(C_1-C_4)alkyl, -amino(C_1-C_4)alkyl, -(C_1-C_4)hydroxyalkoxy(C_1-C_4)alkyl, or -$(CH_2)_{p2}$NHC(=O)(dimethylamino(C_1-C_4)alkyl).

~~19~~13. The compound of any one of claims 1-~~18~~12, or a pharmaceutically acceptable salt thereof, wherein R_2 is H, halo, -(C_1-C_4)haloalkyl, -(C_1-C_4)haloalkoxy, -(C_1-C_4)alkoxy optionally substituted with methoxy, or -N-pyrrolidinyl.

~~20~~14. The compound of any one of claims 1-~~19~~13, or a pharmaceutically acceptable salt thereof, wherein R_2 is H, F, CF_3, $OCHF_2$, OCF_3, $OCH_2CH_2OCH_3$, or -N-pyrrolidinyl.

~~21~~15. The compound of any one of claims 1-~~20~~14, or a pharmaceutically acceptable salt thereof, wherein

R_2 is H, R_1 is -C(=O)NH(C_1-C_4)alkyl optionally substituted with –OH, NH_2, ~~oxetanyl,~~ or -(C_1-C_4)hydroxyalkoxy; or -C(=O)NH$(CH_2)_{p2}$NHC(=O)(dimethylamino(C_1-C_4)alkyl); or

R_2 is F, R_1 is -C(=O)NH(methoxy(C_1-C_4)alkyl); or

R_2 is -N-pyrrolidinyl, R_1 is -C(=O)NH((C_1-C_4)hydroxyalkoxy(C_1-C_4)alkyl),

R_2 is CF_3, $OCHF_2$, or OCF_3, R_1 is -COOH; or

R_2 is $OCH_2CH_2OCH_3$, R_1 is -C(=O)NH((C_1-C_4)hydroxyalkoxy(C_1-C_4)alkyl), -C(=O)NH(hydroxy(C_1-C_4)alkyl), -C(=O)NH(methoxy(C_1-C_4)alkyl), or -C(=O)NH(hydroxy(C_1-C_4)alkoxy).

~~22. The compound of 17, or a pharmaceutically acceptable salt thereof, wherein~~

~~R_1 is -C(=O)NH(C_1-C_4)alkyl optionally substituted with –OH, NH_2, -(C_1-C_4)alkoxy, or -(C_1-C_4)hydroxyalkoxy, and~~

~~R_2 is H, or $OCH_2CH_2OCH_3$.~~

~~23. The compound of 22, or a pharmaceutically acceptable salt thereof, wherein~~

~~R_2 is H.~~

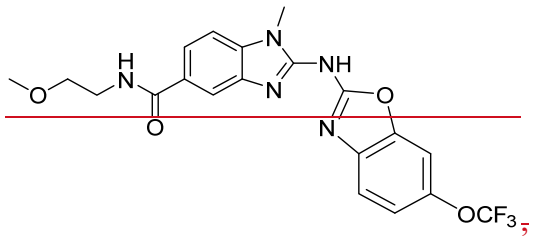
~~24. The compound of 23, or a pharmaceutically acceptable salt thereof, wherein R_1 is -C(=O)NH(C_1-C_4)alkyl substituted with -(C_1-C_4)hydroxyalkoxy.~~

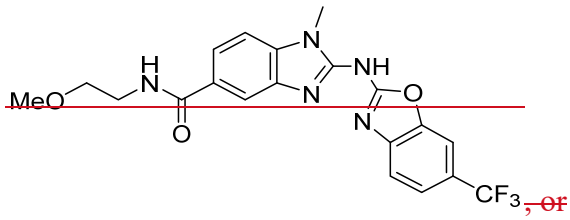
~~25. The compound of 24, wherein the compound is: 2-(benzo[*d*]oxazol-2-ylamino)-*N*-(2-(2-hydroxyethoxy)ethyl)-1-methyl-1*H*-benzo[*d*]imidazole-5-carboxamide or a pharmaceutically acceptable salt thereof.~~

~~26. The compound of 22, or a pharmaceutically acceptable salt thereof, wherein R_1 is -C(=O)NH(C_1-C_4)alkyl substituted with -(C_1-C_4)alkoxy, and R_2 is $OCH_2CH_2OCH_3$.~~

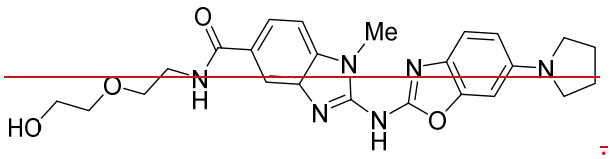
~~27. The compound of 26, wherein the compound is: 2-((6-(2-methoxyethoxy)benzo[*d*]oxazol-2-yl)amino)-*N*-(2-methoxyethyl)-1-methyl-1*H*-benzo[*d*]imidazole-5-carboxamide or a pharmaceutically acceptable salt thereof.~~

~~28. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is~~





~~, or~~



~~.~~

~~29~~16. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of any one of claims 1-~~28~~15, or a pharmaceutically acceptable salt thereof.

~~30~~17. ~~A method~~Use of the compound of any one of claims 1-15, or the pharmaceutical composition of claim 16, in the manufacture of a medicament for increasing the activity of or the amount of HMOX-1, activating transcription factor Nrf2, or reducing the amount of ROS in a human subject ~~comprising: administering to a human subject an effective amount of the compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or an effective amount of the pharmaceutical composition of claim 29~~.

~~31. A method of activating transcription factor Nrf2 in a human subject comprising: administering to a human subject an effective amount of the compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or an effective amount of the pharmaceutical composition of claim 29.~~

~~32. A method of reducing the amount of ROS in a human subject comprising: administering to a human subject an effective amount of the compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or an effective amount of the pharmaceutical composition of claim 29.~~

~~33~~18. ~~A method~~Use of the compound of any one of claims 1-15, or the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating a disease, disorder, or condition ~~comprising administering to a human subject an effective amount of the compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or an effective amount of the pharmaceutical composition of claim 29~~, wherein the disease, disorder, or condition is: (i) a fibrotic disease, including a fibrotic disease of the lung, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, sarcoidosis, a fibrotic disease of the liver including those caused by alcoholic cirrhosis, steatosis, cholestasis, drug side effect, and viral infection, a fibrotic diseases of the skin, scleroderma, or psoriasis; (ii) a neurodegenerative disease, including Friedreich's ataxia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, cerebral nerve degenerative disease, or Charcot-Marie-Tooth syndrome; (iii) a cardiovascular disease, including hypertension, hypercholesterolaemia, atherosclerosis,

arteriosclerosis, thrombosis, acute coronary thrombosis, deep vein thrombosis, peripheral vascular disease, congestive heart failure, acute coronary syndrome, failure of arterial fistula for dialysis, ischemia-reperfusion injury, primary pulmonary hypertension, primary pulmonary arterial hypertension, or secondary pulmonary arterial hypertension; (iv) a renal disease, including acute kidney injury, polycystic kidney disease, Alport syndrome, diabetic nephropathy, glomerular nephritis, lupus nephritis, sickle cell nephropathy, and acute tubular necrosis; (v) an inflammatory disease, including asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, inflammatory bowel syndrome, Crohn's disease, celiac disease, ulcerative colitis, chronic inflammatory bowel disease, scleroderma, dermatitis, systemic lupus erythematosus, esophagitis, vasculitis, pancreatitis, tendonitis, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, or chronic inflammation of the brain; (vi) a liver disease, including drug induced liver toxicity, nonalcoholic steatohepatitis, hepatitis B infection, or hepatitis C infection; (vii) an eye disease, including conjunctivitis, glaucoma, uveitis, an eye wound, eye trauma, corneal grafts, Fuchs' endothelial corneal dystrophy, macular degeneration, cataracts, light retinopathy, retinitis pigmentosa, diabetic retinopathy, and retinopathy of prematurity; (viii) a thyroid disease, including Graves' disease, follicular adenoma, or papillary and follicular carcinomas; (ix) a viral infection, including infections from human immunodeficiency virus, hepatitis B, hepatitis C, or herpesvirus; (x) osteoporosis; (xi) a pregnancy disorder; (xii) endometriosis; (xiii) diabetes, including type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, pre-diabetes, hyperglycemia, metabolic syndrome, or a secondary condition resulting from a diabetic condition; (xiv) cancer; (xv) a skin disease, including dermatitis, scleroderma, or psoriasis; (xvi) a mitochondrial diseases such as mitochondrial myopathies, Leber's hereditary optic neuropathy (LHON), myoclonic epilepsy with ragged red fibers (MERFF), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) or Leigh's Syndrome; (xvii) a hematological disorder such as Diamond Blackfan anemia, myelodysplasic syndrome, sickle cell disease and beta-thalessemia; or (xviii) a muscle diseases, such as Duchenne muscular dystrophy, limb girdle muscular dystrophy, Becker muscular dystrophy, myotonic dystrophy and rhabdomyolysis.

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

~~34. A compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 29 for treating a disease, disorder, or condition of claim 33 in a human subject, comprising administering to the subject in need thereof.~~

~~35. Use of a compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 29, for the manufacture of a medicament for treating a disease, disorder, or condition of claim 33 in a human subject, comprising administering to the subject in need thereof.~~

20. A compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 16, for use in therapy.

~~36. Use of a compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 29, for treating a disease, disorder, or condition of claim 33 in a human subject, comprising administering to the subject in need thereof.~~