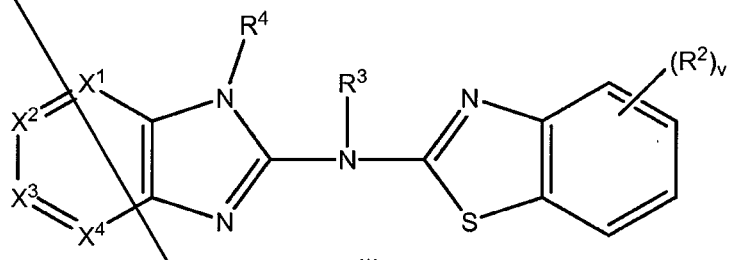
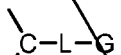
CLAIMS

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein

one of X^1, X^2, X^3, and X^4 is , and the remaining members of X^1, X^2, X^3, and X^4 are independently N or ;

G is hydrogen, -C_{1-8} alkyl, -C_{3-10} cycloalkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, heterocyclyl, -C_{1-6} alkylene-C_{3-10} heterocyclyl, or NR^hR^k, where the alkyl, alkylene, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^c;

L is -C(O)N(R^6)-, -C(O)-O-, -SO_2-, or -C(O)-;

R^1 is hydrogen or R^a;

R^2 is R^b;

R^3 is hydrogen, -C_{1-6} alkyl, or -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^z;

R^4 is -C_{1-6} alkyl or -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^y;

R^6 is hydrogen, -C_{1-6} alkyl, -C_{1-6} alkylene-C_{3-10} cycloaklyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^a is

a) -halogen,
b) -C_{1-6} alkyl,
c) -C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -cyano,
f) -CF_3,
g) -OCF_3,
h) -O-R^d,
i) -$S(O)_w$-R^d,
j) -$S(O)_2O$-R^d,
k) -NR^dR^e,
l) -C(O)-R^d,
m) -C(O)-O-R^d,
n) -OC(O)-R^d,
o) -$C(O)NR^d$ R^e,
p) -C(O)-heterocyclyl,
q) -NR^d $C(O)R^e$,
r) -$OC(O)NR^d$ R^e,
s) -NR^d $C(O)OR^d$, or
t) -NR^d $C(O)NR^d$ R^e,

where the alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^y;

R^b is

a) -halogen,
b) -C_{1-6} alkyl,
c) -C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -phenyl,
f) -heteroaryl,
g) -cyano,
h) -CF_3,
i) -OCF_3,
j) -O-R^f,

k) $-S(O)_w-R^f$,
l) $-S(O)_2O-R^f$,
m) $-NR^fR^g$,
n) $-C(O)-R^f$,
o) $-C(O)-O-R^f$,
p) $-OC(O)-R^f$,
q) $-C(O)NR^fR^g$,
r) -C(O)-heterocyclyl,
s) $-NR^fC(O)R^g$,
t) $-OC(O)NR^fR^g$,
u) $-NR^fC(O)OR^f$, or
v) $-NR^fC(O)NR^fR^g$,

where the alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^z;

R^c is

a) -halogen,
b) $-C_{1-6}$ alkyl,
c) $-C_{3-10}$ cycloalkyl,
d) -heterocyclyl,
e) -cyano,
f) $-CF_3$,
g) $-OCF_3$,
h) $-O-R^h$,
i) $-S(O)_w-R^h$,
j) $-S(O)_2O-R^h$,
k) $-NR^hR^k$,
l) $-C(O)-R^h$,
m) $-C(O)-O-R^h$,
n) $-OC(O)-R^h$,
o) $-C(O)NR^hR^k$,
p) -C(O)-heterocyclyl,
q) $-NR^hC(O)R^k$,
r) $-OC(O)NR^hR^k$,

s) $-NR^h C(O)OR^k$,

t) $-NR^h C(O)NR^h R^k$,

u) $-NR^h S(O)_wR^k$, or

v) $-O-(C_{1-4}$ alkylene)$-O-(C_{1-4}$ alkylene)$-N(R^h)C(O)-OR^k$,

where the alkylene, alkyl, cycloalkyl, or heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^d and R^e are independently selected from hydrogen, C_{1-6} alkyl, and C_{3-10} cycloalkyl, where the alkyl and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^y; or, if R^d and R^e are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^y;

R^f and R^g are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl, or heteroaryl, where the alkyl, cycloalkyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^z; or, if R^f and R^g are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^z;

R^h and R^k are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, or heterocyclyl, where the alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^x; or, if R^h and R^k are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^x;

R^y is

a) -halogen,
b) $-NH_2$,
c) -cyano,
d) -carboxy,
e) -hydroxy,
f) -thiol,
g) $-CF_3$,
h) $-OCF_3$,
i) $-C(O)-NH_2$,
j) $-S(O)_2-NH_2$,
k) oxo,
l) $-C_{1-6}$ alkyl, optionally substituted one or more times with substituetnts selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}$ alkyl$)_2$,
m) -heterocyclyl optionally substituted one or more times with one or more times with substituetnts selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}$ alkyl$)_2$,
n) $-C_{3-10}$ cycloalkyl optionally substituted one or more times with one or more times with substituetnts selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}$ alkyl$)_2$,
o) $-O-C_{1-6}$ alkyl optionally substituted one or more times with one or more times with substituetnts selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}$ alkyl$)_2$,
p) $-O-C_{3-10}$ cycloalkyl optionally substituted one or more times with one or more times with substituetnts selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}$ alkyl$)_2$,
q) $-NH-C_{1-6}$ alkyl optionally substituted one or more times with one or more times with substituetnts selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}$ alkyl$)_2$,
r) $-N(C_{1-6}$ alkyl$)_2$ optionally substituted one or more times with one or more times with substituetnts selected independently from the group consisting of halogen, -OH, $-O-C_{1-6}$ alkyl, $-NH_2$, $-NH-C_{1-6}$ alkyl, and $-N(C_{1-6}$ alkyl$)_2$,

s) -C(O)-C_{1-6} alkyl, optionally substituted one or more times with one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

t) -C(O)-O-C_{1-6} alkyl, optionally substituted one or more times one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

u) -S-C_{1-6} alkyl, optionally substituted one or more times with one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

v) -$S(O)_2$-C_{1-6} alkyl, optionally substituted one or more times one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

w) -C(O)-NH-C_{1-6} alkyl, optionally substituted one or more times one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

x) -C(O)-N(C_{1-6} alkyl)$_2$, optionally substituted one or more times one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

y) -$S(O)_2$-NH-C_{1-6} alkyl, optionally substituted one or more times one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

z) -$S(O)_2$-N(C_{1-6} alkyl)$_2$, optionally substituted one or more times one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$,

aa) -NH-C(O)-C_{1-6} alkyl, optionally substituted one or more times one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$, or

bb) -NH-$S(O)_2$-C_{1-6} alkyl, optionally substituted one or more times one or more times with substituetnts selected independently from the group consisting of halogen, -OH, -O-C_{1-6} alkyl, -NH_2, -NH-C_{1-6} alkyl, and -N(C_{1-6} alkyl)$_2$;

R^x is R^y;

R^z is

a) -R^y

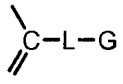
b) -phenyl,

c) -heteroaryl;
d) -O-phenyl,
e) -O-heteroaryl,
f) -C(O)-phenyl,
g) -C(O)-heteroaryl,
h) -C(O)-O-phenyl, or
i) -C(O)-O-heteroaryl;

v is an integer from 0 to 4, and

w is an integer from 0 to 2.

2. The compound of claim 1, wherein R^3 is hydrogen.

3. The compound of claim 1, wherein X^3 is  and X^1, X^2, and X^4 are each .

4. The compound of claim 1, wherein v is 1 and R^2 is attached at the 6-position of the benzothiazole ring.

5. The compound of claim 1, wherein R^2 is fluoro, chloro, $-CF_3$, or $-OCF_3$.

6. The compound of claim 1, wherein R^1 is hydrogen.

7. The compound of claim 1, wherein R^4 is methyl.

8. The compound of claim 1, wherein L is -C(O)NH-.

9. The compound of claim 1, wherein G is C_{1-8} alkyl optionally substituted one or more times with substituents independently selected from R^c.

10. The compound of claim 9, wherein G is C_{1-8} alkyl optionally substituted once by $-C(O)NR^hR^k$.

11. The compound of claim 10, wherein G is $-CH_2-C(O)NR^hR^k$.

12. The compound of claim 9, wherein G is C_{1-8} alkyl optionally substituted once by $-O-R^h$.

13. The compound of claim 12, wherein G is $-(CH_2)_2-OR^h$.

14. The compound of claim 1, wherein G is C_{3-10} cycloalkyl optionally substituted one or more times with substituents independently selected from R^c.

15. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier or diluent.

16. The pharmaceutical composition of claim 15, where the pharmaceutical composition further comprises a medically effective active ingredient selected from the group consisting of an Nrf2 activator, an antioxidant, a detoxification agent, and an anti-inflammatory agent.

17. Use of a compound of claim 1 or a pharmaceutical composition of claim 15 in medicine.

18. The use of claim 17, where the use comprises increasing the activity or the amount of HMOX-1 in a human subject.

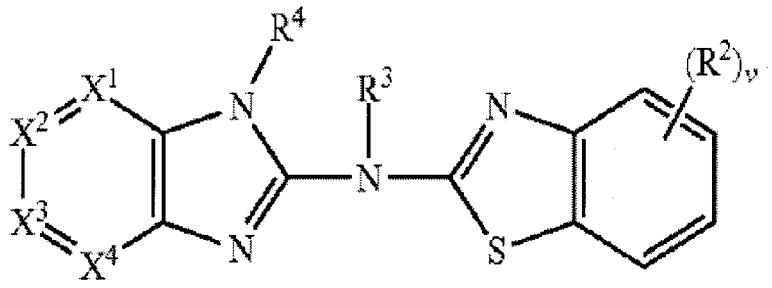
19. The use of claim 17, where the use comprises treating a disease, disorder, or condition selected from the group consisting of: (i) a cardiovascular disease, including arteriosclerosis and hypertension; (ii) diabetes and diabetic-related complications, including glomerular nephropathy; (iii) a cerebral nerve degenerative disease, including Alzheimers disease, Parkinsons disease, ALS (amyotrophic lateral sclerosis), and multiple sclerosis; (iv) asthma; (v) chronic obstructive pulmonary disease; (vi) a skin disease; (vii) an eye disease, including macular degeneration, cataracts, light retinopathy, and retinopathy of prematurity; and (viii) cancer.

20. Use of a compound of claim 1 or a pharmaceutical composition of claim 15 for the preparation of a medicament for use in treating a disease, disorder, or condition selected from the group consisting of: (i) a cardiovascular disease, including arteriosclerosis and hypertension; (ii) diabetes and diabetic-related complications, including glomerular nephropathy; (iii) a cerebral nerve degenerative disease, including Alzheimers disease, Parkinsons disease, ALS (amyotrophic lateral sclerosis), and multiple sclerosis; (iv) asthma; (v) chronic obstructive pulmonary disease; (vi) a skin disease; (vii) an eye disease, including macular degeneration, cataracts, light retinopathy, and retinopathy of prematurity; and (viii) cancer.

CLAIMS

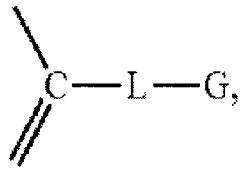
1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof,

(I)

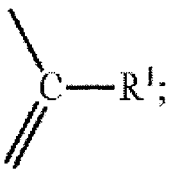


wherein

one of X^1, X^2, X^3, and X^4 is



and the remaining members of X^1, X^2, X^3, and X^4 are independently N or



G is hydrogen, —C_{1-8} alkyl, —C_{3-10} cycloalkyl, —C_{1-6} alkylene-C_{3-10} cycloalkyl, heterocyclyl, —C_{1-6} alkylene-C_{3-10} heterocyclyl, phenyl, heteroaryl, or $NR^h R^k$, where the alkyl, alkylene, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^c;

L is —CH_2—C(O)N(R^6)—, —C(O)N(R^6)—, —C(O)—O—, —SO_2—, —C(O)—, heteroarylene optionally substituted one or more times with substituents independently selected from R^x, or heterocyclylene optionally substituted one or more times with substituents independently selected from R^x; or the group -L-G is -cyano;

R^1 is hydrogen, R^a, phenyl, or heteroaryl, where the phenyl and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^2 is R^b;

R^3 is hydrogen, —C_{1-6} alkyl, or —C_{1-6} alkylene-C_{3-10} cycloalkyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^z;

R^4 is —C_{1-6} alkyl or —C_{1-6} alkylene-C_{3-10} cycloalkyl, where the alkyl, alkylene, and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^y;

R^6 is hydrogen, —C_{1-6} alkyl, —C_{1-6} alkylene-C_{3-10} cycloalkyl, where the alkyl, alkylene, and cycloalkyl

groups are optionally substituted one or more times with substituents independently selected from R^x;

R^a is

a) -halogen,

b) —C_{1-6} alkyl,

c) —C_{3-10} cycloalkyl,

d) -heterocyclyl,

e) -cyano,

f) —CF_3,

g) —OCF_3,

h) —O—R^d,

i) —$S(O)_w$—R^d,

j) —$S(O)_2O$—R^d,

k) —NR^dR^e,

l) —C(O)—R^d,

m) —C(O)—O—R^d,

n) —OC(O)—R^d,

o) —$C(O)NR^d R^e$,

p) —C(O)-heterocyclyl,

q) —$NR^d C(O)R^e$,

r) —$OC(O)NR^d R^e$,

s) —$NR^d C(O)OR^d$, or

t) —$NR^d C(O)NR^d R^e$,

where the alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^y;

R^b is

a) -halogen,
b) —C_{1-6} alkyl,
c) —C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -phenyl,
f) -heteroaryl,
g) -cyano,
h) —CF_3,
i) —OCF_3,
j) —O—R^f,
k) —$S(O)_w$—R^f,
l) —$S(O)_2O$—R^f,
m) —NR^fR^g,
n) —C(O)—R^f,
o) —C(O)—O—R^f,
p) —OC(O)—R^f,
q) —$C(O)NR^fR^g$,
r) —C(O)-heterocyclyl,
s) —$NR^fC(O)R^g$,
t) —$OC(O)NR^fR^g$,
u) —$NR^fC(O)OR^f$, or
v) —$NR^fC(O)NR^fR^g$,

where the alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^z;

R^c is

a) -halogen,
b) —C_{1-6} alkyl,
c) —C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -cyano,
f) —CF_3,
g) —OCF_3,
h) —O—R^h,
i) —$S(O)_w$—R^h,
j) —$S(O)_2O$—R^h,
k) —NR^hR^k,
l) —C(O)—R^h,
m) —C(O)—O—R^h,
n) —OC(O)—R^h,
o) —$C(O)NR^hR^k$,
p) —C(O)-heterocyclyl,
q) —NR^h $C(O)R^k$,
r) —$OC(O)NR^h$ R^k,
s) —NR^h $C(O)OR^k$,
t) —NR^h $C(O)NR^h$ R^k,
u) —NR^h $S(O)_wR^k$,
v) -phenyl,
w) -heteroaryl, or
x) —O—(C_{1-4} alkylene)-O—(C_{1-4} alkylene)-$N(R^h)C$(O)—OR^k,

where the alkylene, alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^d and R^e are independently hydrogen, C_{1-6} alkyl, or C_{3-10} cycloalkyl, where the alkyl and cycloalkyl groups are optionally substituted one or more times with substituents independently selected from R^y; or, if R^d and R^e are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^y;

R^f and R^g are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, phenyl, or heteroaryl, where the alkyl, cycloalkyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^z; or, if R^f and R^g are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^z;

R^h and R^k are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, heterocyclyl, phenyl, or heteroaryl, where the alkyl, cycloalkyl, heterocyclyl, phenyl, and heteroaryl groups are optionally substituted one or more times with substituents independently selected from R^x; or, if R^h and R^k are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from the group consisting of azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^x;

R^y is

a) -halogen,
b) —NH_2,
c) -cyano,
d) -carboxy,
e) -hydroxy,
f) -thiol,
g) —CF_3,
h) —OCF_3,
i) —C(O)—NH_2,
j) —$S(O)_2$—NH_2,
k) oxo,
l) —C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the

group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

m) -heterocyclyl optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

n) —C_{3-10} cycloalkyl optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

o) —O—C_{1-6} alkyl optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

p) —O—C_{3-10} cycloalkyl optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

q) —NH—C_{1-6} alkyl optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

r) —N(C_{1-6} alkyl)$_2$ optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

s) —C(O)—C_{1-6} alkyl, optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

t) —C(O)—O—C_{1-6} alkyl, optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

u) —S—C_{1-6} alkyl, optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

v) —S(O)$_2$—C_{1-6} alkyl, optionally substituted one or more times with substituents
selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

w) —C(O)—NH—C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

x) —C(O)—N(C_{1-6} alkyl)$_2$, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

y) —$S(O)_2$—NH-C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

z) —$S(O)_2$—N(C_{1-6} alkyl)$_2$, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

aa) —NH—C(O)—C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$, or

bb) —NH—$S(O)_2$—C_{1-6} alkyl, optionally substituted one or more times with substituents selected independently from the group consisting of

halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$;

R^x is

a) —R^y

b) -phenyl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

c) -heteroaryl, optionally substituted one or more times with substituents selected independently from the group consisting of halogen, —OH, —O—C_{1-6} alkyl, —NH_2, —NH—C_{1-6} alkyl, and —N(C_{1-6} alkyl)$_2$,

d) —O-phenyl,

e) —O-heteroaryl,

f) —C(O)-phenyl,

g) —C(O)-heteroaryl,

h) —C(O)—O-phenyl, or

i) —C(O)—O-heteroaryl;

v is an integer from 0 to 4, and

w is an integer from 0 to 2.

2. The compound of claim **1**, wherein: G is hydrogen, —C_{1-8} alkyl, —C_{3-10} cycloalkyl, —C_{1-6} alkylene-C_{3-10} cycloalkyl, heterocyclyl, —C_{1-6} alkylene-C_{3-10} heterocyclyl, or —NR^h R^k, where the alkyl, alkylene, cycloalkyl, and het-

erocyclyl groups are optionally substituted one or more times with substituents independently selected from R^c;

L is —C(O)N(R^6)—, —C(O)—O—, —SO_2—, or —C(O)—;

R^1 is hydrogen or R^a;

R^c is

a) -halogen,
b) —C_{1-6} alkyl,
c) —C_{3-10} cycloalkyl,
d) -heterocyclyl,
e) -cyano,
f) —CF_3,
g) —OCF_3,
h) —O—R^h,
i) —$S(O)_w$—R^h,
j) —$S(O)_2O$—R^h,
k) —NR^hR^k,
l) —C(O)—R^h,
m) —C(O)—O—R^h,
n) —OC(O)—R^h,
o) —C(O)NR^h R^k,
p) —C(O)-heterocyclyl,
q) —NR^h C(O)R^k,
r) —OC(O)NR^h R^k,
s) —NR^h C(O)OR^k,
t) —NR^h C(O)NR^h R^k,
u) —NR^h $S(O)_wR^k$, or
v) —O—(C_{1-4} alkylene)—O—(C_{1-4} alkylene)—N(R^h) C(O)—OR^k,

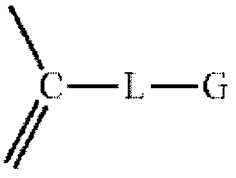
where the alkylene, alkyl, cycloalkyl, or heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^x;

R^h and R^k are independently hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, or heterocyclyl, where the alkyl, cycloalkyl, and heterocyclyl groups are optionally substituted one or more times with substituents independently selected from R^x; or, if R^h and R^k are both attached to the same nitrogen atom, together with that nitrogen atom may optionally form a heterocyclic ring selected from azetidino, pyrrolidino, pyrazolidino, imidazolidino, oxazolidino, isoxazolidino, thiazolidino, isothiazolidino, piperidino, piperazino, morpholino, thiomorpholino, and azepano, where each ring is optionally substituted one or more times with substituents independently selected from R^x;

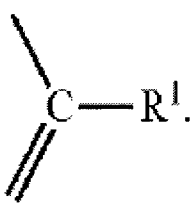
R^x is R^y.

3. The compound of claim **2**, wherein R^3 is hydrogen.

4. The compound of claim **3**, wherein X^3 is



and X^1, X^2, and X^4 are each



5. The compound of claim **4**, wherein v is 1 and R^2 is attached at the 6-position of the benzothiazole ring.

6. The compound of claim **4**, wherein R^2 is fluoro, chloro, $—CF_3$, or $—OCF_3$.

7. The compound of claim **4**, wherein R^1 is hydrogen.

8. The compound of claim **4**, wherein R^4 is methyl.

9. The compound of claim **4**, wherein L is —C(O)NH—.

10. The compound of claim **4**, wherein G is C_{1-8} alkyl optionally substituted one or more times with substituents independently selected from R^c.

11. The compound of claim **10**, wherein G is C_{1-8} alkyl optionally substituted once by $—C(O)NR^hR^k$.

12. The compound of claim **11**, wherein G is $—CH_2—C(O)NR^hR^k$.

13. The compound of claim **10**, wherein G is C_{1-8} alkyl optionally substituted once by $—O—R^h$.

14. The compound of claim **13**, wherein G is $—(CH_2)_2—OR^h$.

15. The compound of claim **4**, wherein G is C_{3-10} cycloalkyl optionally substituted one or more times with substituents independently selected from R^c.

16. A pharmaceutical composition comprising a compound of claim **1** and a pharmaceutically acceptable carrier or diluent.

17. The pharmaceutical composition of claim **16**, where the pharmaceutical composition further comprises a medically effective active ingredient selected from the group consisting of an Nrf2 activator, an antioxidant, a detoxification agent, an anti-inflammatory agent, and an antidiabetic agent, where the antidiabetic agent is optionally metformin.

18. A compound of claim **1** for use in increasing the activity of or the amount of HMOX-1 in a human subject.

19. A compound of claim **1** for use in increasing Nrf2 dependent gene transcription in a human subject.

20. A compound of claim **1** for use in reducing the amount of ROS in a human subject.

21. A compound of claim **1**, wherein the compound is selected from the group consisting of:

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethyl)-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-2-methyl-propyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-hydroxy-ethyl)-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide;

6-Fluoro-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ethylamide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-fluoro-ethoxy)-ethyl]-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-2-hydroxy-propyl)-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-2-hydroxy-propyl)-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide;

1-Ethyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide;

1-(2-Methoxy-ethyl)-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-ethoxy-ethyl)-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-ethyl-1H-benzoimidazole-5-carboxylic acid (2-fluoro-ethyl)-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-ethyl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-2-hydroxy-propyl)-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-methoxy-ethoxy)-ethyl]-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-methoxy-ethoxy)-ethyl]-amide; and

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-dimethylamino-ethoxy)-ethyl]-amide;

or a pharmaceutically acceptable salt thereof.

22. A compound of claim **1**, wherein the compound is selected from the group consisting of:

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (3-morpholin-4-yl-3-oxo-propyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-methoxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-methoxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-methoxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-dimethylamino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-dimethylamino-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-2-oxo-ethyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((R)-3-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-((S)-3-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid [2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-amide; and

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [(R)-1-methyl-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-amide;

or a pharmaceutically acceptable salt thereof.

23. A compound of claim **1**, wherein the compound is selected from the group consisting of:

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzimidazole-5-carboxylic acid (2-dimethylcarbamoyl-ethyl)-amide;

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-1-dimethylcarbamoyl-ethyl)amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (2-dimethylcarbamoyl-ethyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-dimethylcarbamoyl-ethyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid methylcarbamoylmethyl-amide;

2-(6-Chloro-benzothiazol-2-ylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid ((S)-1-dimethylcarbamoyl-ethyl)-amide;

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((S)-1-dimethylcarbamoyl-ethyl)amide; and

1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid ((R)-1-dimethylcarbamoyl-ethyl)-amide;

or a pharmaceutically acceptable salt thereof.

24. A compound of claim **1**, wherein the compound is selected from the group consisting of:

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzimidazole-5-carboxylic acid (2-ethanesulfonyl-ethyl)-amide; and

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzimidazole-5-carboxylic acid (3-methanesulfonyl-propyl)-amide;

or a pharmaceutically acceptable salt thereof.

25. A compound, wherein the compound is

3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid dimethylcarbamoylmethyl-amide or a pharmaceutically acceptable salt thereof.

26. The compound of claim **25**, wherein the compound is 3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid dimethylcarbamoylmethyl-amide.

27. A compound, wherein the compound is

1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide or a pharmaceutically acceptable salt thereof.

28. The compound of claim **27**, wherein the compound is 1-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-amide.

29. A compound, wherein the compound is

3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-methoxy-ethyl)-amide or a pharmaceutically acceptable salt thereof.

30. The compound of claim **29**, wherein the compound is 3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-

3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-methoxy-ethyl)-amide.

31. A compound, wherein the compound is 1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide or a pharmaceutically acceptable salt thereof.

32. The compound of claim **31**, wherein the compound is 1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid [2-(2-hydroxy-ethoxy)-ethyl]-amide.

33. A compound, wherein the compound is
6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide or a pharmaceutically acceptable salt thereof.

34. The compound of claim **33**, wherein the compound is 6-Methoxy-1-methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-1H-benzoimidazole-5-carboxylic acid (2-morpholin-4-yl-ethyl)-amide.

35. A compound, wherein the compound is
3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-morpholin-4-yl-ethyl)-amide or a pharmaceutically acceptable salt thereof.

36. The compound of claim **35**, wherein the compound is 3-Methyl-2-(6-trifluoromethoxy-benzothiazol-2-ylamino)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (2-morpholin-4-yl-ethyl)-amide.

37. A compound, wherein the compound is 1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide or a pharmaceutically acceptable salt thereof.

38. The compound of claim **37**, wherein the compound is 1-Methyl-2-(6-trifluoromethyl-benzothiazol-2-ylamino)-1H-benzimidazole-5-carboxylic acid dimethylcarbamoylmethyl-amide.

39. A pharmaceutical composition comprising a compound of claim **21** and a pharmaceutically acceptable carrier.

40. A pharmaceutical composition comprising a compound of claim **22** and a pharmaceutically acceptable carrier.

41. A pharmaceutical composition comprising a compound of claim **23** and a pharmaceutically acceptable carrier.

42. A pharmaceutical composition comprising a compound of claim **24** and a pharmaceutically acceptable carrier.

43. A pharmaceutical composition comprising a compound of claim **25** and a pharmaceutically acceptable carrier.

44. A pharmaceutical composition comprising a compound of claim **27** and a pharmaceutically acceptable carrier.

45. A pharmaceutical composition comprising a compound of claim **29** and a pharmaceutically acceptable carrier.

46. A pharmaceutical composition comprising a compound of claim **31** and a pharmaceutically acceptable carrier.

47. A pharmaceutical composition comprising a compound of claim **33** and a pharmaceutically acceptable carrier.

48. A pharmaceutical composition comprising a compound of claim **35** and a pharmaceutically acceptable carrier.

49. A pharmaceutical composition comprising a compound of claim **37** and a pharmaceutically acceptable carrier.