Significant Medical Need

[0018] Despite efforts towards the development of new therapies for the treatment of diseases and conditions such as heart failure and ischemia/reperfusion injury, there remains a significant interest in and need for additional or alternative compounds that treat or prevent the onset or severity of these and related diseases or conditions. In particular, there remains a significant medical need for alternative or additional therapies for the treatment of diseases or conditions that are responsive to nitroxyl therapy. New compounds that donate nitroxyl under physiological conditions and methods of using compounds that donate nitroxyl under physiological conditions may thus find use as therapies for treating, preventing and/or delaying the onset and/or development of diseases or conditions responsive to nitroxyl therapy, including heart disease and ischemia/reperfusion injury. Preferably, the therapeutic agents can improve the quality of life and/or prolong the survival time for patients with the disease or condition.

BRIEF SUMMARY OF THE ~~INVENTION~~DISCLOSURE

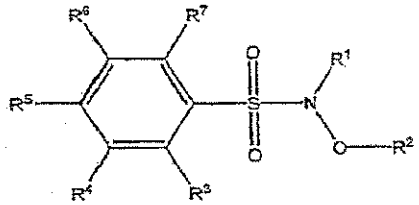
[0019] Methods, compounds and compositions for treating and/or preventing the onset or development of diseases or conditions that are responsive to nitroxyl therapy are described. Aromatic and non-aromatic *N*-hydroxylsulfonamide derivatives that donate nitroxyl under physiological conditions are described. By modifying PA with appropriate substituents, such as electron-withdrawing groups or groups that sterically hinder the sulfonyl moiety, the HNO producing capacity of these derivatives is substantially enhanced under physiological conditions. Significantly, when compared to AS, PA has the capacity for broad substituent modification, enabling optimization of physicochemical and pharmacological properties. Such optimization is reported herein.

[0020] In one embodiment, the present disclosure~~invention~~ provides a method of administering to a subject in need thereof, a therapeutically effective amount of a derivative of PA wherein the derivative donates nitroxyl under physiological conditions. In one embodiment, the disclosure~~invention~~ embraces a method of treating or preventing the onset and/or development of a disease or condition that is responsive to nitroxyl therapy, the method comprising administering to an individual in need thereof an *N*-hydroxylsulfonamide that donates an effective amount of nitroxyl under physiological conditions. Also embraced are methods of treating heart failure or

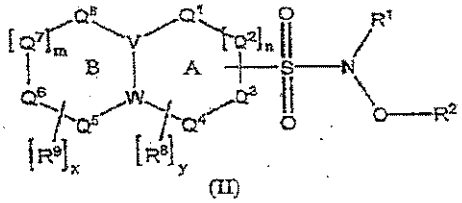
ischemia/reperfusion injury by administering to an individual in need thereof an *N*-hydroxysulfonamide that donates an effective amount of nitroxyl under physiological conditions.

[0021] Kits comprising the compounds are also described, which may optionally contain a second therapeutic agent such as a positive inotropic compound, which may be, *e.g.*, a beta-adrenergic receptor agonist.

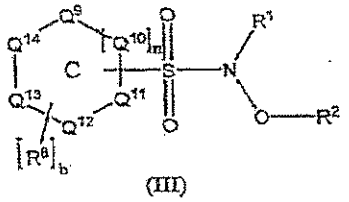
[0022] Novel compounds that find use in the disclosure~~invention~~ described herein include compounds of the formula (I), (II), (III) or (IV):



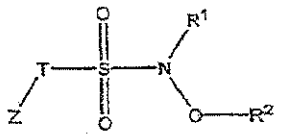
(I)



(II)



(III)

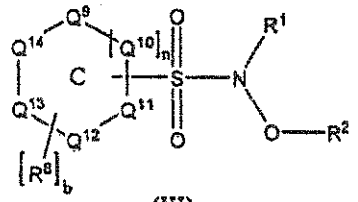


(IV)

[0023] where R^1 is H; R^2 is H, aralkyl or heterocyclyl; m and n are independently an integer from 0 to 2; x and b are independently an integer from 0 to 4; y is an integer from 0 to 3; T is an alkyl or substituted alkyl; Z is an electron withdrawing group; R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, halo, alkylsulfonyl, *N*-hydroxylsulfonamidyl, perhaloalkyl, nitro, aryl, cyano, alkoxy, perhaloalkoxy, alkyl, substituted aryloxy, alkylsulfanyl, alkylsulfinyl, heterocycloalkyl, substituted heterocycloalkyl, dialkylamino, cycloalkoxy, cycloalkylsulfanyl, arylsulfanyl and arylsulfinyl, provided that: (1) at least one of R^3, R^4, R^5, R^6 and R^7 is other than H; (2) at least one of R^3, R^4, R^5, R^6 and R^7 is other than halo; (3) when R^3, R^4, R^6 and R^7 are H, R^5 is other than halo, nitro, cyano, alkyl or alkoxy; (4) when one of R^3 or R^7 is halo and the R^3 or R^7 that is not halo is H and one of R^4 or R^6 is halo and the R^4 or R^6 that is not halo is H, R^5 is other than halo; (5) when R^3, R^7 and R^5 are H and one of R^4 and R^6 is H, the R^4 or R^6 that is not H is other than N-hydroxysulfonamidyl, perhaloalkyl

aromatic or heteroaromatic ring containing ring moieties Q^5, Q^6, Q^7 and Q^8, which are taken together with V and W to form ring B; V and W are independently C, CH, N or NR^{10}; Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, $Q^7$and Q^8 are independently selected from the group consisting of C, CH_2, CH, N, NR^{10}, O and S; C is a heteroaromatic ring containing ring moieties Q^9, Q^{10}, Q^{11}, Q^{12}, $Q^{13}$and Q^{14} that are independently selected from the group consisting of C, CH_2, CH, N, NR^{10}, O and S; and R^{10} is H, alkyl, acyl or sulfonyl.

In one embodiment, there is provided a compound of the formula (III)



(III)

or pharmaceutically acceptable salt thereof, wherein:

R^1 is H;

R^2 is H, aralkyl or heterocyclyl;

n is an integer from 0 to 2;

b is an integer from 0 to 4;

each R^8 is independently selected from halo, alkylsulfonyl, N-hydroxylsulfonamidyl, perhaloalkyl, nitro, aryl,

cyano, alkoxy, perhaloalkoxy, alkyl, substituted aryloxy, alkylsulfanyl, alkylsulfinyl, heterocycloalkyl, substituted heterocycloalkyl, dialkylamino, NH2, OH, C(O)OH, C(O)Oalkyl, NHC(O)alkylC(O)OH, $C(O)NH_2$, NHC(O)alkylC(O)alkyl, NHC(O)alkenylC(O)OH, $NHC(O)NH_2$, OalkylC(O)Oalkyl, NHC(O)alkyl, $C(=N\text{-}OH)NH_2$, cycloalkoxy, cycloalkylsulfanyl, arylsulfanyl, and arylsulfinyl,

wherein said substituted aryloxy is an aryl group connected to the parent structure through an oxygen atom, which aryl group is substituted with 1 to 3 groups selected from halo, nitro, cyano, oxo, aryl, alkoxy, alkyl, acyl, acylamino, amino, hydroxyl, carboxyl, carboxylalkyl, thiol, thioalkyl, heterocyclyl and -OS(O)2-alkyl, and wherein said substituted heterocycloalkyl is a heterocyclyl group substituted with 1 to 5 groups selected from halo, nitro, cyano, oxo, aryl, alkoxy, alkyl, acyl, acylamino, amino, hydroxyl, carboxyl, carboxylalkyl, thiol,thioalkyl, heterocyclyl and $-OS(O)_2$-alkyl;

C is a heteroaromatic ring containing ring moieties Q^9, Q^{10}, Q^{11}, Q^{12}, Q^{13} and Q^{14} that are independently selected from the group consisting of C, CH, N, NR^{10}, O and S, provided that at least one of Q^9, Q^{10}, Q^{11}, Q^{12}, Q^{13} and Q^{14} is N, NR^{10}, O or S; and

R^{10} is H, alkyl, acyl or sulfonyl; for use in a method of modulating *in vivo* nitroxyl levels, treating a disease or condition that is responsive to nitroxyl therapy, treating a cardiovascular disease or condition, or treating heart failure.

In one embodiment, there is provided the use of a compound or pharmaceutically acceptable salt as defined herein in the preparation of a medicament for modulating *in vivo* nitroxyl levels, treating a disease or condition that is responsive to nitroxyl therapy, treating a cardiovascular disease or condition, or treating heart failure.

In one embodiment, there is provided a pharmaceutical composition comprising a compound as defined herein, and a pharmaceutically acceptable carrier.

[0026] Pharmaceutical compositions comprising a compound of the disclosure~~invention~~ are disclosed, such as pharmaceutical compositions that are amenable to intravenous injection. Kits comprising a compound of the disclosure~~invention~~ and instructions for use are also described.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] FIG. 1 depicts the nitrous oxide headspace analysis of compounds tested as nitroxyl donors as compared to the nitrous oxide headspace analysis of the nitroxyl donor Angeli's Salt (AS). Nitrous oxide (N_2O) is the product of nitroxyl (HNO) dimerization and is thus indicative of whether a compound is a nitroxyl donor under the test conditions.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0028] Unless clearly indicated otherwise, the following terms as used herein have the meanings indicated below.

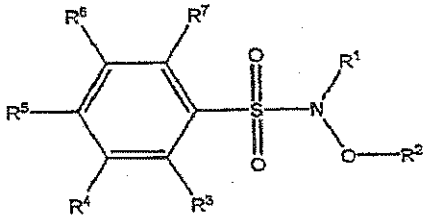
[0029] Use of the terms "a", "an" and the like refers to one or more.

[0030] "Aralkyl" refers to a residue in which an aryl moiety is attached to the parent structure via an alkyl residue. Examples include benzyl ($-CH_2-Ph$), phenethyl ($-CH_2CH_2Ph$), phenylvinyl (-CH=CH-Ph), phenylallyl and the like.

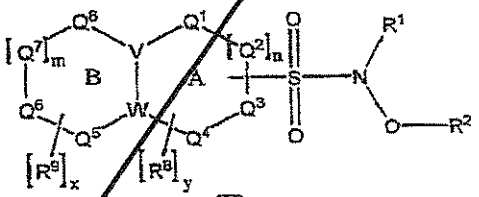
[0031] "Acyl" refers to and includes the groups –C(O)H, -C(O)alkyl, -C(O)substituted alkyl, -C(O)alkenyl, -C(O)substituted alkenyl, -C(O)alkynyl, -C(O)substituted alkynyl, -C(O)cycloalkyl, -C(O)substituted cycloalkyl, -C(O)aryl, -C(O)substituted aryl, -C(O)heteroaryl, -C(O)substituted heteroaryl, -C(O)heterocyclic, and -C(O)substituted heterocyclic wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted

CLAIMS

Claim 1. A compound of the formula (I), (II), (III) or (IV):



(I)



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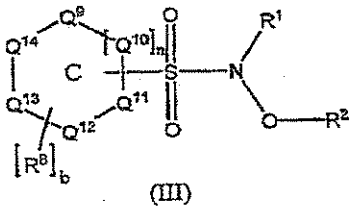

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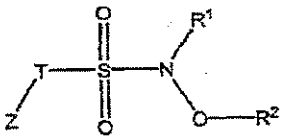


(IV)

wherein:

R^1 is H;

R^2 is H, aralkyl or heterocyclyl;

m and n are independently an integer from 0 to 2;

x and b are independently an integer from 0 to 4;

y is an integer from 0 to 3;

T is an alkyl or substituted alkyl;

Z is an electron withdrawing group;

R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, halo, alkylsulfonyl, *N*-hydroxylsulfonamidyl, perhaloalkyl, nitro, aryl, cyano, alkoxy, perhaloalkoxy, alkyl, substituted aryloxy, alkylsulfanyl, alkylsulfinyl, heterocycloalkyl, substituted heterocycloalkyl, dialkylamino, cycloalkoxy, cycloalkylsulfanyl, arylsulfanyl and arylsulfinyl, provided that:

(1) at least one of R^3, R^4, R^5, R^6 and R^7 is other than H;

(2) at least one of R^3, R^4, R^5, R^6 and R^7 is other than halo;

(3) when R^3, R^4, R^6 and R^7 are H, R^5 is other than halo, nitro, cyano, alkyl or alkoxy;

(4) when one of R^3 or R^7 is halo and the R^3 or R^7 that is not halo is H and one of R^4 or R^6 is halo and the R^4 or R^6 that is not halo is H, R^5 is other than halo;

(5) when R^3, R^7 and R^5 are H and one of R^4 and R^6 is H, the R^4 or R^6 that is not H is other than N-hydroxysulfonamidyl, perhaloalkyl or nitro;

(6) when R^4, R^5 and R^6 are H and one of R^3 and R^7 is H, the R^3 or R^7 that is not H is other than nitro or alkyl;

(7) when R^3 and R^7 are H, R^5 is nitro and one of R^4 and R^6 is H, the R^4 or R^6 that is not H is other than halo;

(8) when R^4 and R^6 are nitro and R^3 and R^7 are H, R^5 is other than dialkylamino;

(9) when R^4 and R^6 are H and R^3 and R^7 are alkyl, R^5 is other than alkyl; and

(10) when R^3 and R^7 are H and R^4 and R^6 are nitro, R^5 is other than dialkylamino;

each R^8 and R^9 is independently selected from the group consisting of halo, alkylsulfonyl, N-hydroxylsulfonamidyl, perhaloalkyl, nitro, aryl, cyano, alkoxy, perhaloalkoxy, alkyl, substituted aryloxy, alkylsulfanyl, alkylsulfinyl, heterocycloalkyl, substituted heterocycloalkyl, dialkylamino, NH_2, OH, C(O)OH, C(O)Oalkyl, NHC(O)alkylC(O)OH, $C(O)NH_2$, NHC(O)alkylC(O)alkyl, NHC(O)alkenylC(O)OH, $NHC(O)NH_2$, OalkylC(O)Oalkyl, NHC(O)alkyl, $C(=N\text{-}OH)NH_2$, cycloalkoxy, cycloalkylsulfanyl, arylsulfanyl, and arylsulfinyl;

A is a cycloalkyl, heterocycloalkyl, aromatic or heteroaromatic ring containing ring moieties Q^1, Q^2, Q^3 and Q^4, which are taken together with V and W to form ring A;

B is a cycloalkyl, heterocycloalkyl, aromatic or heteroaromatic ring containing ring moieties Q^5, Q^6, Q^7 and Q^8, which are taken together with the V and W to form ring B;

V and W are independently C, CH, N or NR^{10};

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, $Q^7$and Q^8 are independently selected from the group consisting of C, CH_2, CH, N, NR^{10}, O and S, provided that either (1) when rings A and B form naphthalene, x is an integer from 1 to 3 or y is an integer from 2 to 4 or R^8 is other than Cl or (2) at least one of Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, $Q^7$and Q^8 is N, NR^{10}, O or S;

C is a heteroaromatic ring containing ring moieties Q^9, Q^{10}, Q^{11}, Q^{12}, $Q^{13}$and Q^{14} that are independently selected from the group consisting of C, CH_2, CH, N, NR^{10}, O and S, provided that at least one of Q^9, Q^{10}, Q^{11}, Q^{12}, $Q^{13}$and Q^{14} is N, NR^{10}, O or S;

R^{10} is H, alkyl, acyl or sulfonyl,

or a pharmaceutically acceptable salt thereof.

Claim 2. The compound of claim 1, wherein R^2 is H.

Claim 3. The compound of claim 1, wherein each R^8 and R^9 is independently selected from the group consisting of Cl, F, I, Br, SO_2CH_3, SO_2NHOH, CF_3, CH_3, NO_2, phenyl, CN, OCH_3, OCF_3, *t*-Bu, O-*i*Pr, 4-nitrophenyloxy (OPh4-NO_2), propane-2-thiyl ($SCH(CH_3)_2$), propane-2-sulfinyl ($S(O)CH(CH_3)_2$), morpholino, *N*-methyl-piperazino, dimethylamino, piperidino, cyclohexyloxy, cyclopentylsulfanyl, phenylsulfanyl and phenylsulfinyl.

Claim 4. The compound of claim 1, wherein the compound is of the formula (I).

Claim 5. The compound of claim 4 wherein the compound is of the formula (I) and at least one of R^3 and R^7 is other than H.

Claim 6. The compound of claim 4, wherein the compound is of the formula (I) and at least one of R^3 and R^7 is an electron withdrawing group.

Claim 7. The compound of claim 4, wherein the compound is of the formula (I) and R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, halo, alkylsulfonyl, *N*-hydroxylsulfonamidyl, perhaloalkyl, nitro, aryl, cyano, alkoxy, perhaloalkoxy, alkyl, substituted aryloxy, alkylsulfanyl, alkylsulfinyl, heterocycloalkyl, substituted heterocycloalkyl, dialkylamino, cycloalkoxy, cycloalkylsulfanyl, arylsulfanyl, and arylsulfinyl,

provided that (1) at least one of R^3, R^4, R^5, R^6 and R^7 is other than H; (2) at least one of R^3, R^4, R^5, R^6 and R^7 is other than F; (3) when R^3, R^4, R^6 and R^7 are H, R^5 is other than F, Cl, Br, I, NO_2, CN, CH_3 or OCH_3; (4) when one of R^3 or R^7 is Cl and the R^3 or R^7 that is not Cl is H and one of R^4 or R^6 is Cl and the R^4 or R^6 that is not Cl is H, R^5 is other than Cl; (5) when R^3, R^7 and R^5 are H and one of R^4 and R^6 is H, the R^4 or R^6 that is not H is other than SO_2NHOH, CF_3 or NO_2; (6) when R^4, R^5 and R^6 are H and one of R^3 and R^7 is H, the R^3 or R^7 that is not H is other than NO_2 or CH_3; (7) when R^3 and R^7 are H, R^5 is NO_2 and one of R^4 and R^6 is H, the R^4 or R^6 that is not H is other than Cl; (8) when R^4 and R^6 are nitro and R^3 and R^7 are H, R^5 is other than a C_1-C_5 dialkylamino; (9) when R^4 and R^6 are H and R^3 and R^7 are alkyl, R^5 is other than CH_3; and (10) when R^3 and R^7 are H and R^4 and R^6 are nitro, R^5 is other than a C_1-C_5 dialkylamino.

Claim 8. The compound of claim 1, wherein the compound is of the formula (II).

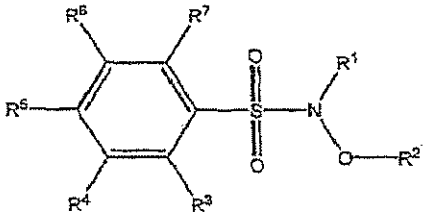
Claim 9. The compound of claim 1, wherein the compound is of the formula (III).

Claim 10. The compound of claim 1, wherein the compound is of the formula (IV).

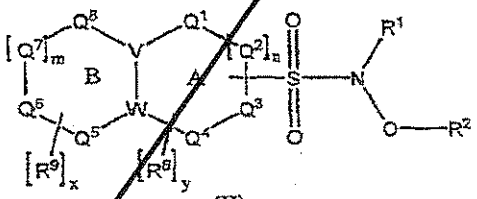
Claim 11. A method of modulating the *in vivo* nitroxyl levels in an individual in need thereof, the method comprising administering to the individual an *N*-hydroxysulfonamide that donates nitroxyl under physiological conditions or a pharmaceutically acceptable salt thereof.

Claim 12. A method of treating, preventing or delaying the onset or development of a disease or condition that is responsive to nitroxyl therapy, comprising administering to an individual in need thereof an *N*-hydroxysulfonamide that donates nitroxyl under physiological conditions or a pharmaceutically acceptable salt thereof.

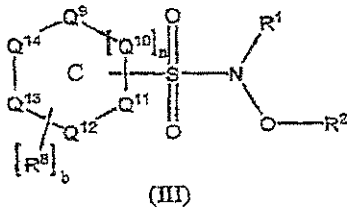
Claim 13. The method of claim 12 wherein the method comprises administering to the individual a compound of the formula:



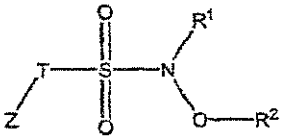
(I)



(II)



(III)



(IV)

wherein:

R^1 is H;

R^2 is H;

m and n are independently an integer from 0 to 2;

x and b are independently an integer from 0 to 4;

y is an integer from 0 to 3;

T is an alkyl or substituted alkyl;

Z is an electron withdrawing group;

R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, halo, alkylsulfonyl, *N*-hydroxylsulfonamidyl, perhaloalkyl, nitro, aryl, cyano, alkoxy, perhaloalkoxy, alkyl, substituted aryloxy, alkylsulfanyl, alkylsulfinyl, heterocycloalkyl, substituted heterocycloalkyl, dialkylamino, cycloalkoxy, cycloalkylsulfanyl, arylsulfanyl and arylsulfinyl, provided that at least one of R^3, R^4, R^5, R^6 and R^7 is other than H;

each R^8 and R^9 is independently a substituent;

A is a cycloalkyl, heterocycloalkyl, aromatic or heteroaromatic ring containing ring moieties Q^1, Q^2, Q^3 and Q^4, which are taken together with V and W to form ring A;

B is a cycloalkyl, heterocycloalkyl, aromatic or heteroaromatic ring containing ring moieties Q^5, Q^6, Q^7 and Q^8, which are taken together with the V and W to form ring B;

V and W are independently C, CH, N or NR^{10};

Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, $Q^7$and Q^8 are independently selected from the group consisting of C, CH_2, CH, N, NR^{10}, O and S, provided that either (1) when rings A and B form naphthalene, x is an integer from 1 to 3 or y is an integer from 2 to 4 or R^8 is other than Cl or (2) at least one of Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, $Q^7$and Q^8 is N, NR^{10}, O or S;

C is a heteroaromatic ring containing ring moieties Q^9, Q^{10}, Q^{11}, Q^{12}, $Q^{13}$and Q^{14} that are independently selected from the group consisting of C, CH_2, CH, N, NR^{10}, O and S, provided that at least one of Q^9, Q^{10}, Q^{11}, Q^{12}, $Q^{13}$and Q^{14} is N, NR^{10}, O or S;

R^{10} is H, alkyl, acyl or sulfonyl,

or a pharmaceutically acceptable salt thereof.

Claim 14. The method of claim 13, wherein each R^8 and R^9 is independently selected from the group consisting of halo, alkylsulfonyl, *N*-hydroxylsulfonamidyl, perhaloalkyl, nitro, aryl, cyano, alkoxy, perhaloalkoxy, alkyl, substituted aryloxy, alkylsulfanyl, alkylsulfinyl, heterocycloalkyl, substituted heterocycloalkyl, dialkylamino, NH_2, OH, C(O)OH, C(O)Oalkyl, NHC(O)alkylC(O)OH, $C(O)NH_2$, NHC(O)alkylC(O)alkyl, NHC(O)alkenylC(O)OH, $NHC(O)NH_2$, OalkylC(O)Oalkyl, NHC(O)alkyl, $C(=N\text{-}OH)NH_2$, cycloalkoxy, cycloalkylsulfanyl, arylsulfanyl, and arylsulfinyl.

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

Claim 16. The method of claim 13, wherein the disease or condition is a cardiovascular disease or condition.

Claim 17. The method of claim 16, wherein the disease or condition is acute heart failure.

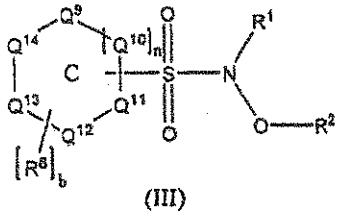
Claim 18. The method of claim 13, wherein the disease or condition implicates ischemia/reperfusion injury.

Claim 19. A kit comprising a compound of the claim 1 and instructions for use in the treatment of a disease or condition that is responsive to nitroxyl therapy.

Claim 20. A method of treating heart failure comprising administering to an individual in need thereof a compound selected from the group consisting of: 2-fluoro-*N*-hydroxybenzenesulfonamide; 2-chloro-*N*-hydroxybenzenesulfonamide; 2-bromo-*N*-hydroxybenzenesulfonamide; 2-(trifluoromethyl)-*N*-hydroxybenzenesulfonamide; 5-chlorathiophene-2-sulfohydroxainic acid; 2,5-dichlorothiophene-3-sulfohydroxamic acid; 4-fluoro-*N*-hydroxybenzenesulfonamide; 4-(trifluoromethyl)-*N*-hydroxybenzenesulfonamide; 4-cyano-*N*-hydroxybenzenesulfonamide; and 4-nitro-*N*-hydroxybenzenesulfonamide, or a pharmaceutically acceptable salt thereof.

CLAIMS

1. A compound of the formula (III)



(III)

or pharmaceutically acceptable salt thereof, wherein:

R^1 is H;

R^2 is H, aralkyl or heterocyclyl;

n is an integer from 0 to 2;

b is an integer from 0 to 4;

each R^8 is independently selected from halo, alkylsulfonyl, N-hydroxylsulfonamidyl, perhaloalkyl, nitro, aryl,

cyano, alkoxy, perhaloalkoxy, alkyl, substituted aryloxy, alkylsulfanyl, alkylsulfinyl, heterocycloalkyl, substituted heterocycloalkyl, dialkylamino, NH2, OH, C(O)OH, C(O)Oalkyl, NHC(O)alkylC(O)OH, $C(O)NH_2$, NHC(O)alkylC(O)alkyl, NHC(O)alkenylC(O)OH, $NHC(O)NH_2$, OalkylC(O)Oalkyl, NHC(O)alkyl, C(=N-OH)NH_2, cycloalkoxy, cycloalkylsulfanyl, arylsulfanyl, and arylsulfinyl,

wherein said substituted aryloxy is an aryl group connected to the parent structure through an oxygen atom, which aryl group is substituted with 1 to 3 groups selected from halo, nitro, cyano, oxo, aryl, alkoxy, alkyl, acyl, acylamino, amino, hydroxyl, carboxyl, carboxylalkyl, thiol, thioalkyl, heterocyclyl and -OS(O)2-alkyl, and wherein said substituted heterocycloalkyl is a heterocyclyl group substituted with 1 to 5 groups selected from halo, nitro, cyano, oxo, aryl, alkoxy, alkyl, acyl, acylamino, amino, hydroxyl, carboxyl, carboxylalkyl, thiol,thioalkyl, heterocyclyl and $-OS(O)_2$-alkyl;

C is a heteroaromatic ring containing ring moieties Q^9, Q^{10}, Q^{11}, Q^{12}, Q^{13} and Q^{14} that are independently selected from the group consisting of C, CH, N, NR^{10}, O and S, provided that at least one of Q^9, Q^{10}, Q^{11}, Q^{12}, Q^{13} and Q^{14} is N, NR^{10}, O or S; and

R^{10} is H, alkyl, acyl or sulfonyl; for use in a method of modulating *in vivo* nitroxyl levels, treating a disease or condition that is responsive to nitroxyl therapy, treating a cardiovascular disease or condition, or treating heart failure.

2. The compound or pharmaceutically acceptable salt of claim 1, for use in a method as defined in claim 1, wherein R^2 is H, benzyl or tetrahydropyran-2-yl.

3. The compound or pharmaceutically acceptable salt of claim 1, for use in a method as defined in claim 1, wherein R^2 is H.

4. The compound or pharmaceutically acceptable salt of any one of claims 1 to 3, for use in a method as defined in claim 1, wherein each R^8 is independently selected from Cl, F, I, Br, SO_2CH_3, SO_2NHOH CF_3, CH_3, NO_2, phenyl, CN, OCH_3, OCF_3, *t*-Bu, O-*i*Pr, 4-nitrophenyloxy (OPh_4-NO_2), propane-2-thiyl ($SCH(CH_3)_2$), propane-2-sulfinyl ($S(O)CH(CH_3)_2$), morpholino, *N*-methyl-piperazino, dimethylamino, piperidino, cyclohexyloxy, cyclopentylsulfanyl, phenylsulfanyl and phenylsulfinyl.

5. The compound or pharmaceutically acceptable salt of any one of claims 1 to 3, for use in a method as defined in claim 1, wherein each R^8 is independently selected from F, Br, Cl, CF_3, phenyl, methyl, SO_2NHOH, morpholino, piperidino, 4-methyl-piperazino.

6. The compound or pharmaceutically acceptable salt of any one of claims 1 to 5, for use in a method as defined in claim 1, wherein:

n is 0; and

C is isoxazole or pyrazole.

7. The compound or pharmaceutically acceptable salt of any one of claims 1 to 3, for use in a method as defined in claim 1, wherein:

n is 0;

C is isoxazole, pyrazole, or furan;

b is 1; and

R^8 is halo, nitro, alkyl or cyano.

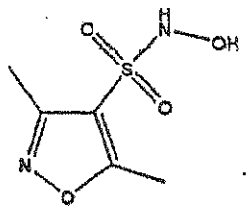
8. The compound or pharmaceutically acceptable salt of claim 7, for use in a method as defined in claim 1, wherein:

R^8 is Cl, Br, nitro, methyl or cyano.

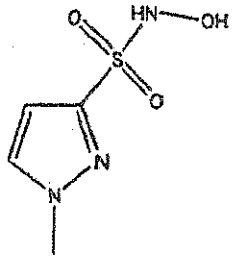
9. The compound or pharmaceutically acceptable salt of any one of claims 1 to 5, for use in a method as defined in claim 1, wherein:

C is thiophene;
b is 1; and
R^8 is halo.

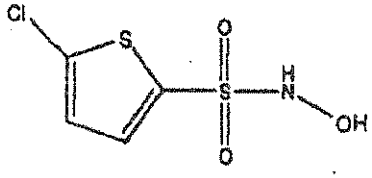
10. The compound or pharmaceutically acceptable salt of claim 1, for use in a method as defined in claim 1, wherein the compound or pharmaceutically acceptable salt is selected from:



or a pharmaceutically acceptable salt thereof,



or a pharmaceutically acceptable salt thereof, and



or a pharmaceutically acceptable salt thereof.

11. The compound or pharmaceutically acceptable salt of any one of claims 1 to 3, for use in a method as defined in claim 1, wherein:

n is 0;

C is thiophene, isoxazole, pyrazole, pyrrole, imidazole, furan, thiazole, triazole, N-methylimidazole or thiadiazole;

b is 1; and

R^8 is alkyl.

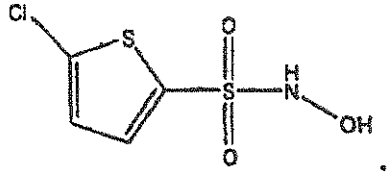
12. The compound or pharmaceutically acceptable salt of claim 11, for use in a method as defined in claim 1, wherein:

R^8 is methyl.

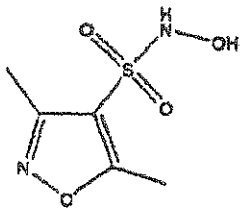
13. Use of a compound or pharmaceutically acceptable salt as defined in any one of claims 1 to 12 in the preparation of a medicament for modulating *in vivo* nitroxyl levels, treating a disease or condition that is responsive to nitroxyl therapy, treating a cardiovascular disease or condition, or treating heart failure.

14. A compound or pharmaceutically acceptable salt as defined in any one of claims 6 to 12.

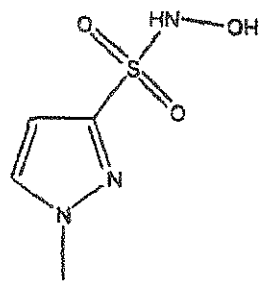
15. A compound or pharmaceutically acceptable salt according to claim 14, which is the compound



16. A compound or pharmaceutically acceptable salt according to claim 14, which is the compound



17. A compound or pharmaceutically acceptable salt according to claim 14, which is the compound



18. A compound or pharmaceutically acceptable salt according to claim 14, which is a compound as defined in claim 12 or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a compound of any one of claims 6 to 12 or 14 to 18, and a pharmaceutically acceptable carrier.