However, compounds of the formula (I) described therein are not substituted with at least one carboxyl, carboxyl ester, acylamino or sulfonylamino group and compounds of the formula (II) or (III) described therein are not substituted with at least one carbonylamino or sulfonylamino group.

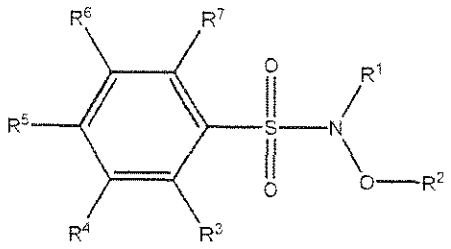
Significant Medical Need

[0019] 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

[0020] 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.

[0020a] In one aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound has formula (I):



(I)

wherein:

R^1 is H;

R^2 is H;

R^3 is H;

R^4 is $-C(O)NR_aR_b$, where R_a is H or alkyl, and R_b is alkyl or substituted alkyl, or R_a and R_b are taken together to form a heterocyclic ring or substituted heterocyclic ring;

R^5 is H;

R^6 is H; and

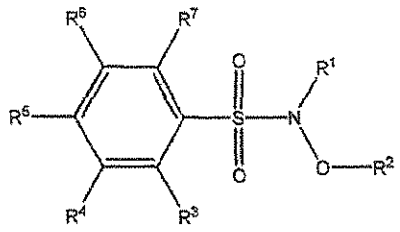
R^7 is H or halo.

[0020b] In one aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutically acceptable carrier.

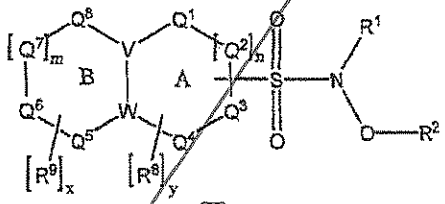
[0021] In one embodiment, the present invention provides a method of administering to a subject in need thereof, a therapeutically effective amount of a derivative of PA wherein the derivative donates nitroxyl under physiological conditions. In one embodiment,

CLAIMS

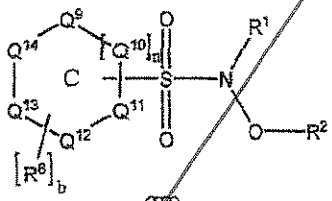
Claim 1. A compound of the formula (I), (II) or (III):



(I)



(II)



(III)

wherein:

R^1 is H;

R^2 is H, aralkyl or heterocyclyl;

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

x is an integer from 0 to 4 and y is an integer from 0 to 3, provided that at least one of x and y is greater than 0;

b is an integer from 1-4;

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, arylsulfinyl, carboxyl, carboxyl ester, acylamino and sulfonylamino, provided that at least one of R^3, R^4, R^5, R^6 and R^7 is carboxyl, carboxyl ester, acylamino or sulfonylamino;

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, arylsulfinyl, carbonylamino and sulfonylamino, provided that: (1) at least one R^8 is carbonylamino or sulfonylamino when the compound is of the formula (III) and (2) at least one of R^8 and R^9 is carbonylamino or sulfonylamino when the compound is of the formula (II);

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;

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, and

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 x and y are both 1.

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 at least one of R^3, R^4, R^5, R^6 and R^7 is carboxyl, –COO-alkyl, -C(O)NH_2, -C(O) NR_aR_b where R_a is hydrogen and R_b is alkyl, -C(O)NR_aR_b where R_a and R_b are independently alkyl, -C(O)NR_aR_b where R_a and R_b are taken together with the nitrogen to which they are attached to form a heterocyclic or substituted heterocyclic ring, -SO_2NH_2, -SO_2NR-alkyl where R is hydrogen, -SO_2NR-alkyl where R is alkyl, -SO_2NR_2, where the two R groups are taken together with the nitrogen to which they are attached to form a heterocyclic or substituted heterocyclic ring.

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. 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 of claim 1 or a pharmaceutically acceptable salt thereof.

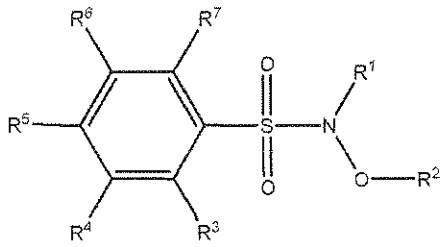
Claim 11. A method of treating, preventing or delaying the onset or development of a disease or condition that is responsive to nitroxyl therapy, comprising administering to an individual in need thereof a compound of claim 1 or a pharmaceutically acceptable salt thereof.

Claim 12. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

Claim 13. 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.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein the compound has formula (I):



(I)

wherein:

R^1 is H;

R^2 is H;

R^3 is H;

R^4 is $-C(O)NR_aR_b$, where R_a is H or alkyl, and R_b is alkyl or substituted alkyl, or R_a and R_b are taken together to form a heterocyclic ring or substituted heterocyclic ring;

R^5 is H;

R^6 is H; and

R^7 is H or halo.

2. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein R^4 is $-C(O)NR_aR_b$, where R_a and R_b are taken together to form a heterocyclic ring or substituted heterocyclic ring.

3. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 2, wherein R_a and R_b form a heterocyclic ring selected from the group consisting of piperazinyl, azetidinyl, pyrrolidinyl, piperidinyl, thiomorpholinyl and morpholinyl; and wherein the heterocyclic ring is unsubstituted or substituted.

4. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 3, wherein R_a and R_b form a piperidinyl ring.

5. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 4, wherein the piperidinyl ring is unsubstituted.

6. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 4, wherein the piperidinyl ring is substituted.

7. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 6, wherein the piperidinyl ring is substituted with one or two substituents selected from the group consisting of lower alkyl, carboxylester, acyl, halo, amino, hydroxyl, substituted lower alkyl, oxo and alkoxy.

8. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 7, wherein the piperidinyl ring is substituted with one or two halo groups.

9. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 8, wherein the piperidinyl ring is substituted with one or two F groups.

10. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 9, wherein the piperidinyl ring is substituted at position 4 of the piperidinyl ring.

11. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein R^4 is $-C(O)NR_aR_b$, where R_a is H and R_b is alkyl or substituted alkyl.

12. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 11, wherein R_b is a substituted alkyl.

13. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 12, wherein R_b is a substituted lower alkyl.

14. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 12, wherein R_b is a substituted branched lower alkyl.

15. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 13, wherein R_b is a lower alkyl substituted with a substituent selected from the group consisting of hydroxyl, carboxyl, amino and alkoxy.

16. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 15, wherein R_b is a lower alkyl substituted with carboxyl.

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

18. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein R^4 is $-C(O)NR_aR_b$, where R_a is alkyl and R_b is alkyl.

19. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein R^4 is $-C(O)NR_aR_b$, where R_a is alkyl and R_b is substituted alkyl.