with CHF; the incidence of such diagnosis is approaching 10 per 1000 after 65 years of age. Hospitalization for CHF is usually the result of inadequate outpatient therapy. Hospital discharges for CHF rose from 377,000 (in 1979) to 970,000 (in 2002) making CHF the most common discharge diagnosis in people age 65 and over. The five-year mortality from CHF approaches 50%. Hence, while therapies for heart disease have greatly improved and life expectancies have extended over the last several years, new and better therapies continue to be sought, particularly for CHF.

[0010] "Acute" congestive heart failure (also known as acute "decompensated" heart failure) involves a precipitous drop in cardiac function resulting from a variety of causes. For example in a patient who already has congestive heart failure, a new myocardial infarction, discontinuation of medications, and dietary indiscretions may all lead to accumulation of edema fluid and metabolic insufficiency even in the resting state. A therapeutic agent that increases cardiac function during such an acute episode could assist in relieving this metabolic insufficiency and speeding the removal of edema, facilitating the return to the more stable "compensated" congestive heart failure state. Patients with very advanced congestive heart failure particularly those at the end stage of the disease also could benefit from a therapeutic agent that increases cardiac function, for example, for stabilization while waiting for a heart transplant. Other potential benefits could be provided to patients coming off a bypass pump, for example, by administration of an agent that assists the stopped or slowed heart in resuming normal function. Patients who have diastolic dysfunction (insufficient relaxation of the heart muscle) could benefit from a therapeutic agent that modulates relaxation.

[0011] Inotropes are drugs that increase the contractile ability of the heart. As a group, all current inotropes have failed to meet the gold standard for heart failure therapy, i.e., to prolong patient survival. In addition, current agents are poorly selective for cardiac tissue, in part leading to recognized adverse effects that limit their use. Despite this fact, intravenous inotropes continue to be widely used in acute heart failure (e.g., to allow for reinstitution of oral medications or to bridge patients to heart transplantation) whereas in chronic heart failure, orally given digoxin is used as an inotrope to relieve patient symptoms, improve the quality of life, and reduce hospital admissions.

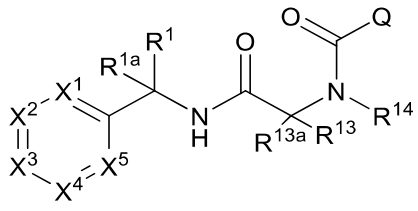
[0012] Current inotropic therapies improve contractility by increasing the calcium transient via the adenylyl cyclase pathway, or by delaying cAMP degradation through inhibition of phosphodiesterase (PDE), which can be detrimental to patients with heart failure.

[0013] New approaches are needed to improve cardiac function in congestive heart failure. There remains a need for agents that exploit different mechanisms of action and may have better outcomes in terms of relief of symptoms, safety, and patient mortality, both short-term and long-term.

Summary

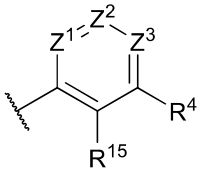
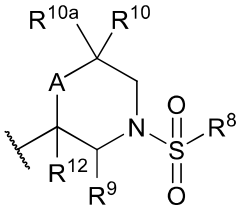
[0014] The present disclosure provides new compounds which activate the cardiac sarcomere. In particular, compounds of the disclosure may bind to the Troponin C/Troponin I interface to increase activity of the cardiac sarcomere.

[0014a] In one aspect, the present disclosure refers to a compound or pharmaceutically acceptable salt thereof, according to Formula (I):



(I)

wherein

Q is  or  or a 5-member heteroaryl having 1 or 2 ring heteroatoms independently selected from N, O, and S which is optionally substituted with 1 or 2 groups selected from C_1-C_6alkyl and halo C_1-C_6alkyl;

A is absent, oxygen, N(H), N(C_1-C_6alkyl) or $CR^{11}R^{11a}$;

X^1 is N or CR^2;

X^2, X^3, X^4 and X^5 are each independently selected from N and CR^3 provided that 0, 1, or 2 of X^1, X^2, X^3, X^4 and X^5 are N and the remainder are CR^2 or CR^3;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6alkyl and halogen;

R^1 is selected from the group consisting of hydrogen, C_1-C_6alkyl, halo C_1-C_6alkyl, hydroxy C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl optionally substituted with 1 or 2 groups selected from hydroxy, halogen, and C_1-C_4alkyl, hydroxy C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, hydroxy C_3-C_7cycloalkylC_1-C_4alkyl,and 4 to 7 member heterocycloalkyl having 1 or 2 ring heteroatoms independently selected from N, O and S, which heterocycloalkyl is optionally substituted with 1 or 2 groups selected from oxo, hydroxy, halogen and C_1-C_4alkyl;

R^2 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy and SF_5;

or

R^1 and R^2, taken in combination, form a divalent group selected from -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -OCH_2-, -CH_2OCH_2-, -OCH_2CH_2, -$CH_2N(H)CH_2$- and -$CH_2N(C_1$-C_4alkyl$)CH_2$-, each of which is optionally substituted with C_1-C_4alkyl or hydroxyC_1-C_4alkyl and wherein the oxygen of –OCH_2CH_2- or –OCH_2- is attached to the CR^2 carbon;

R^3 is independently selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy and SF_5;

Z^1 is N or CR^5;

Z^2 is N or CR^6;

Z^3 is N or CR^7, wherein 0, 1, or 2 of Z^1, Z^2 and Z^3 can be N;

R^4 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, C_3-C_7cycloalkyl, cyano, benzoyl, SO_2-R^8 or 4 to 7 member heterocycloalkyl having a ring heteroatom selected from N, O and S which heterocycloalkyl is substituted with 0, 1 or 2 groups independently selected from the group consisting of halogen, oxo, C_1-C_6alkyl, C(O)C_1-C_6alkyl, and SO_2-R^8, and wherein when R^4 is C_1-C_6alkyl, haloC_1-C_6alkyl, or C_3-C_7cycloalkyl, it is optionally substituted with one or two groups independently selected from hydroxy, cyano, CO_2H, CO_2C_1-C_6alkyl and $C(O)NH_2$;

R^5 is hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxy, amino, mono- or di-C_1-C_6alkylamino, C_3-C_7cycloalkylamino or -N(H)C(O)C_1-C_4alkyl, where each alkyl or cycloalkyl is optionally substituted with hydroxy;

R^6 is hydrogen, C_1-C_6alkyl, haloC_1-C_6alkyl or halogen; or

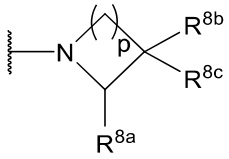
R^5 and R^6, taken in combination with the interposed atoms, form a 5- or 6- membered heteroaryl having 1 or 2 ring heteroatoms selected from N, O, and S;

R^7 and R^8 taken in combination form a divalent group selected from –CH_2CH_2- and –$CH_2CH_2CH_2$-; or

R^7 is hydrogen, C_1-C_6alkyl, or SO_2C_1-C_6alkyl;

R^8 is C_1-C_6alkyl, $NR^{8d}R^{8e}$, C_3-C_7cycloalkyl, haloC_1-C_6alkyl or benzyl, wherein each alkyl, cycloalkyl or haloalkyl is optionally substituted with hydroxy, CO_2H, CO_2C_1-C_6alkyl or $C(O)NH_2$; or

R^8 is a group of the formula:



wherein

p is 1 or 2;

R^{8a} is hydrogen, C_1-C_6alkyl, benzyl, or phenyl optionally substituted with C_1-C_6alkyl or halogen;

R^{8b} is hydrogen, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxyC_1-C_4alkyl, C_3-C_7cycloalkyl, cyano, amino, N(H)C(O)C_1-C_6alkyl, N(H)C(O)C_3-C_7cycloalkyl, N(H)C(O)haloC_1-C_6alkyl, CO_2H, $C(O)NH_2$, C(O)NH(C_1-C_6alkyl), C(O)N(C_1-C_6alkyl)$_2$, C(O)C_1-C_6alkyl, C(O)haloC_1-C_6alkyl, SO_2C_1-C_6alkyl, phenyl optionally substituted with halogen, C_1-C_4alkyl or haloC_1-C_4alkyl, benzyl optionally substituted withhalogen, phenoxy optionally substituted with halogen, 4 to 7 member heterocycloalkyl having 1 or 2 ring heteroatoms selected from N, O and S, or 5 or 6 member heteroaryl having 1 ring heteroatom selected from N, O or S and 0, 1 or 2 additional ring nitrogen atoms, which heteroaryl is optionally substituted with 1 or 2 C_1-C_6alkyl, and wherein the alkoxy is optionally substituted with halogen, phenyl or halogen-substituted phenyl;

R^{8c} is hydrogen, halogen, hydroxy or C_1-C_6alkyl; or

$CR^{8b}R^{8c}$, taken in combination, forms a spirocyclic 3 to 6 member carboxycle or a 4 to 6

member heterocycle having a ring heteratom selected from N, O and S, which spirocycle is optionally substituted with hydroxy, C_1-C_4alkyl, haloC_1-C_4alkyl or C_1-C_4alkoxy;

R^{8d} is hydrogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_3-C_7cycloalkyl, or 4 to 7 member heterocycloalkyl having 1 ring heteroatoms selected from N, O and S and 0 or 1 additional ring nitrogen atoms, which heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from hydroxy, halogen, oxo, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{8e} is hydrogen or C_1-C_6alkyl; or

$NR^{8d}R^{8e}$, taken in combination, forms a 4 to 7 member heterocycloalkyl optionally comprising an additional ring heteroatom selected from N, O and S, which heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from hydroxy, halogen, oxo, C_1-C_6alkyl, C_1-C_6alkoxy and heteroaryl, which heteroaryl has 5 or 6 ring atoms and has one ring heteroatom selected from N, O and S and 0 or 1 additional ring nitrogen atom, or

$NR^{8d}R^{8e}$, taken in combination, forms a 5 or 6 member heteroaryl optionally comprising 1 additional ring heteroatom selected from N, O and S;

R^9 is hydrogen or C_1-C_6alkyl;

R^{10} and R^{10a} are each independently selected from the group consisting of hydrogen, halogen and C_1-C_6alkyl; or

R^9 and R^{10} taken in combination form a divalent bridge selected from O, CH_2, and CH_2CH_2 and R^{10a} is hydrogen;

R^{11a} is hydrogen or halogen;

R^{12} is hydrogen or halogen;

R^{11} is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, N(H)C_1-C_6alkyl and N(H)C_3-C_7cycloalkyl; or

R^{11} and R^{12}, taken in combination, form a double bond;

R^{13a} is hydrogen or C_1-C_6alkyl;

R^{13} is C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkyl;

R^{14} is C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkyl; or

R^{13} and R^{14}, taken in combination with the interposed C and N atoms, form a saturated or partially unsaturated 4 to 7 member heterocycle which heterocycle further comprises 0 or 1 additional ring heteroatoms selected from N, O and S, which heterocycle is optionally fused to a benzo ring or to a saturated carbocycle having 3 to 7 ring atoms, or which heterocycle is optionally taken together with a saturated carbocyle having 3 to 7 ring atoms to form a spirocyclic ring, and wherein the heterocycle is optionally substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxy, oxo, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_7cycloalkyl, O-C(O)pyridine substituted with C_1-C_4alkyl and haloC_1-C_4alkyl; and

R^{15} is hydrogen or halogen;

with the proviso that

(1) when R^4 is SO_2CH_3, then at least one occurrence of R^1, R^2 or R^3 is not hydrogen,

(2) when R^4 is halogen, trifluoromethyl or cyano and R^6 is hydrogen or halogen, then at least one occurrence of R^1 or R^2 is not hydrogen or R^1 is not methyl,

(3) when R^5 is C_1-C_6alkoxy, then R^4 is not hydrogen or halogen, and

(4) when R^4 is C_1-C_6alkoxy or C_1-C_6alkyl, then R^2 is not hydrogen.

[0014b] In another aspect, the present disclosure refers to a compound, which is recited in Table A, or a pharmaceutically acceptable salt thereof. In another aspect, the present disclosure refers to a compound, which is recited in Table B, or a pharmaceutically acceptable salt thereof. In another aspect, the present disclosure refers to a compound, which is recited in Table C, or a pharmaceutically acceptable salt thereof.

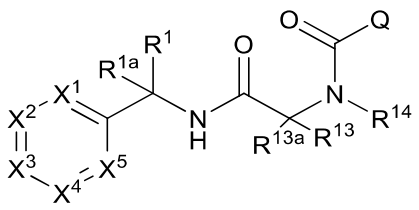
[0014c] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a pharmaceutically acceptable excipient, carrier or adjuvant and at least one compound as described herein. In yet another aspect, the present disclosure refers to a packaged pharmaceutical composition, comprising a pharmaceutical composition as described herein and instructions for using the composition to treat a patient suffering from a heart disease.

[0014d] In another aspect, the present disclosure refers to the use of at least one compound as described herein, or a pharmaceutical salt thereof or a pharmaceutical composition thereof in the manufacture of a medicament for treating heart disease in a mammal. In yet another aspect, the present disclosure refers to the use of at least one compound as described herein or a pharmaceutical salt thereof or a pharmaceutical composition thereof in the manufacture of a medicament for modulating the cardiac sarcomere in a mammal. In yet another aspect, the present disclosure refers to the use of at least one compound as described herein or a pharmaceutical salt thereof or a pharmaceutical composition thereof in the manufacture of a medicament for potentiating cardiac myosin in a mammal.

[0014e] In a further aspect, the present disclosure refers to a compound as described herein for use as a medicament. In another aspect, the present disclosure refers to the use of the compound as described herein in the manufacture of a medicament for treating heart failure.

[0015] The disclosure provides, in one example, bis-amide compounds which modulate the activity of cardiac sarcomere. Preferably, the bis-amide compounds of the disclosure are troponin activators interface to increase activity of the cardiac sarcomere. In some examples, the bis-amide compounds of the disclosure are troponin activators that activate the cardiac sarcomere. In some examples, the bis-amide compounds of the disclosure are troponin activators that increase the activity of the cardiac sarcomere. In certain preferred applications, the bis-amide compounds of the disclosure are compounds that activate the cardiac sarcomere by binding to the Troponin C and Troponin I interface.

[0016] The bis-amide compounds of the disclosure are compounds and salts according Formula (I):



(I)

[0017] Also provided is a pharmaceutical composition comprising a pharmaceutically acceptable excipient, carrier or adjuvant and at least one compound of formula (I) or subformulae thereof.

[0018] Also provided is a packaged pharmaceutical composition, comprising a pharmaceutical composition comprising a pharmaceutically acceptable excipient, carrier or adjuvant and at least one compound of formula (I) or subformulae thereof, and instructions for using the composition to treat a patient suffering from a heart disease.

[0019] Also provided is a method of treating heart disease in a mammal which method comprises administering to a mammal in need thereof a therapeutically effective amount of at least one compound of formula (I) or subformulae thereof or a pharmaceutical composition comprising a pharmaceutically acceptable excipient, carrier or adjuvant and at least one compound of formula (I) or subformulae thereof.

[0020] Also provided is a method for modulating the cardiac sarcomere in a mammal which method comprises administering to a mammal in need thereof a therapeutically effective amount of at least one compound of formula (I) or subformulae thereof or a pharmaceutical composition comprising a pharmaceutically acceptable excipient, carrier or adjuvant and at least one compound of formula (I) or subformulae thereof.

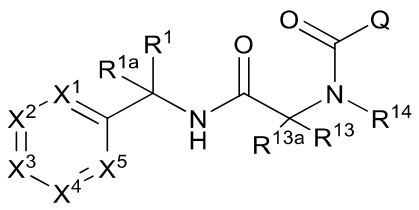
[0021] Also provided is a method for potentiating Troponin C, Troponin I or the interface of Troponin C and Troponin I to increase activity of the cardiac sarcomere in a mammal which method comprises administering to a mammal in need thereof a therapeutically effective amount of at least one compound of formula (I) or subformulae thereof or a pharmaceutical composition comprising a pharmaceutically acceptable excipient, carrier or adjuvant and at least one compound of formula (I) or subformulae thereof.

[0022] Also provided is the use, in the manufacture of a medicament for treating heart disease, of at least one compound of formula I or subformulae thereof.

[0023] Other aspects and examples will be apparent to those skilled in the art form the following detailed description.

Detailed Description of the Invention

[0024] The invention related generally to compounds of Formula I and salts and tautomers thereof which activate the cardiac sarcomere. Compounds and salts thereof according to Formula I are generally represented by the structure:



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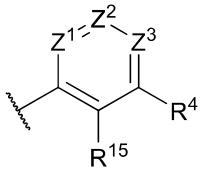
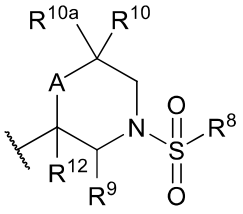
wherein

Q is  or  or a 5-member heteroaryl having 1 or 2 ring heteroatoms independently selected from N, O, and S which is optionally substituted with 1 or 2 groups selected from C_1-C_6alkyl and halo C_1-C_6alkyl;

A is absent, oxygen, N(H), N(C_1-C_6alkyl) or $CR^{11}R^{11a}$;

X^1 is N or CR^2;

X^2, X^3, X^4 and X^5 are each independently selected from N and CR^3 provided that 0, 1, or 2 of X^1, X^2, X^3, X^4 and X^5 are N and the remainder are CR^2 or CR^3;

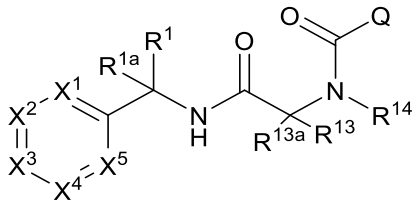
R^1 is selected from the group consisting of hydrogen, C_1-C_6alkyl, halo C_1-C_6alkyl, hydroxy C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl optionally substituted with 1 or 2 groups selected from hydroxy, halogen, and C_1-C_4alkyl, hydroxy C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, hydroxy C_3-C_7cycloalkylC_1-C_4alkyl,and 4 to 7 member heterocycloalkyl having 1 or 2 ring heteroatoms independently selected from N, O and S, which heterocycloalkyl is optionally substituted with 1 or 2 groups selected from oxo, hydroxy, halogen and C_1-C_4alkyl;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6alkyl and halogen;

R^2 is iselected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy and SF_5; or

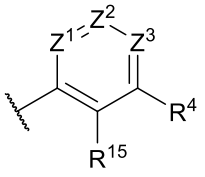
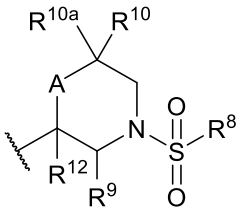
What is Claimed:

1. A compound or pharmaceutically acceptable salt thereof, according to Formula (I):



(I)

wherein

Q is  or  or a 5-member heteroaryl having 1 or 2 ring heteroatoms independently selected from N, O, and S which is optionally substituted with 1 or 2 groups selected from C_1-C_6alkyl and halo C_1-C_6alkyl;

A is absent, oxygen, N(H), N(C_1-C_6alkyl) or $CR^{11}R^{11a}$;

X^1 is N or CR^2;

X^2, X^3, X^4 and X^5 are each independently selected from N and CR^3 provided that 0, 1, or 2 of X^1, X^2, X^3, X^4 and X^5 are N and the remainder are CR^2 or CR^3;

R^{1a} is selected from the group consisting of hydrogen, C_1-C_6alkyl and halogen;

R^1 is selected from the group consisting of hydrogen, C_1-C_6alkyl, halo C_1-C_6alkyl, hydroxy C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl optionally substituted with 1 or 2 groups selected from hydroxy, halogen, and C_1-C_4alkyl, hydroxy C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, hydroxy C_3-C_7cycloalkylC_1-C_4alkyl,and 4 to 7 member heterocycloalkyl having 1 or 2 ring heteroatoms independently selected from N, O and S, which heterocycloalkyl is optionally substituted with 1 or 2 groups selected from oxo, hydroxy, halogen and C_1-C_4alkyl;

R^2 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy and SF_5;

or

R^1 and R^2, taken in combination, form a divalent group selected from -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -OCH_2-, -CH_2OCH_2-, -OCH_2CH_2, -$CH_2N(H)CH_2$- and -$CH_2N(C_1$-C_4alkyl)CH_2-, each of which is optionally substituted with C_1-C_4alkyl or hydroxyC_1-C_4alkyl and wherein the oxygen of –OCH_2CH_2- or –OCH_2- is attached to the CR^2 carbon;

R^3 is independently selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy and SF_5;

Z^1 is N or CR^5;

Z^2 is N or CR^6;

Z^3 is N or CR^7, wherein 0, 1, or 2 of Z^1, Z^2 and Z^3 can be N;

R^4 is hydrogen, halogen, C_1-C_6alkyl, C_1-C_6alkoxy, haloC_1-C_6alkyl, C_3-C_7cycloalkyl, cyano, benzoyl, SO_2-R^8 or 4 to 7 member heterocycloalkyl having a ring heteroatom selected from N, O and S which heterocycloalkyl is substituted with 0, 1 or 2 groups independently selected from the group consisting of halogen, oxo, C_1-C_6alkyl, C(O)C_1-C_6alkyl, and SO_2-R^8, and wherein when R^4 is C_1-C_6alkyl, haloC_1-C_6alkyl, or C_3-C_7cycloalkyl, it is optionally substituted with one or two groups independently selected from hydroxy, cyano, CO_2H, CO_2C_1-C_6alkyl and $C(O)NH_2$;

R^5 is hydrogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxy, amino, mono- or di-C_1-C_6alkylamino, C_3-C_7cycloalkylamino or -N(H)C(O)C_1-C_4alkyl, where each alkyl or cycloalkyl is optionally substituted with hydroxy;

R^6 is hydrogen, C_1-C_6alkyl, haloC_1-C_6alkyl or halogen; or

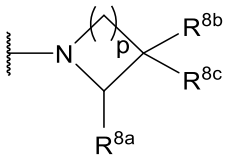
R^5 and R^6, taken in combination with the interposed atoms, form a 5- or 6- membered heteroaryl having 1 or 2 ring heteroatoms selected from N, O, and S;

R^7 and R^8 taken in combination form a divalent group selected from $–CH_2CH_2$- and $–CH_2CH_2CH_2$-; or

R^7 is hydrogen, C_1-C_6alkyl, or SO_2C_1-C_6alkyl;

R^8 is C_1-C_6alkyl, $NR^{8d}R^{8e}$, C_3-C_7cycloalkyl, haloC_1-C_6alkyl or benzyl, wherein each alkyl, cycloalkyl or haloalkyl is optionally substituted with hydroxy, CO_2H, CO_2C_1-C_6alkyl or $C(O)NH_2$; or

R^8 is a group of the formula:



wherein

p is 1 or 2;

R^{8a} is hydrogen, C_1-C_6alkyl, benzyl, or phenyl optionally substituted with C_1-C_6alkyl or halogen;

R^{8b} is hydrogen, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6alkoxyC_1-C_4alkyl, C_3-C_7cycloalkyl, cyano, amino, N(H)C(O)C_1-C_6alkyl, N(H)C(O)C_3-C_7cycloalkyl, N(H)C(O)haloC_1-C_6alkyl, CO_2H, $C(O)NH_2$, C(O)NH(C_1-C_6alkyl), C(O)N(C_1-C_6alkyl)$_2$, C(O)C_1-C_6alkyl, C(O)haloC_1-C_6alkyl, SO_2C_1-C_6alkyl, phenyl optionally substituted with halogen, C_1-C_4alkyl or haloC_1-C_4alkyl, benzyl optionally substituted withhalogen, phenoxy optionally substituted with halogen, 4 to 7 member heterocycloalkyl having 1 or 2 ring heteroatoms selected from N, O and S, or 5 or 6 member heteroaryl having 1 ring heteroatom selected from N, O or S and 0, 1 or 2 additional ring nitrogen atoms, which heteroaryl is optionally substituted with 1 or 2 C_1-C_6alkyl, and wherein the alkoxy is optionally substituted with halogen, phenyl or halogen-substituted phenyl;

R^{8c} is hydrogen, halogen, hydroxy or C_1-C_6alkyl; or

$CR^{8b}R^{8c}$, taken in combination, forms a spirocyclic 3 to 6 member carboxycle or a 4 to 6 member heterocycle having a ring heteratom selected from N, O and S, which spirocycle is optionally

substituted with hydroxy, C_1-C_4alkyl, haloC_1-C_4alkyl or C_1-C_4alkoxy;

R^{8d} is hydrogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_3-C_7cycloalkyl, or 4 to 7 member heterocycloalkyl having 1 ring heteroatoms selected from N, O and S and 0 or 1 additional ring nitrogen atoms, which heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from hydroxy, halogen, oxo, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{8e} is hydrogen or C_1-C_6alkyl; or

$NR^{8d}R^{8e}$, taken in combination, forms a 4 to 7 member heterocycloalkyl optionally comprising an additional ring heteroatom selected from N, O and S, which heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from hydroxy, halogen, oxo, C_1-C_6alkyl, C_1-C_6alkoxy and heteroaryl, which heteroaryl has 5 or 6 ring atoms and has one ring heteroatom selected from N, O and S and 0 or 1 additional ring nitrogen atom, or

$NR^{8d}R^{8e}$, taken in combination, forms a 5 or 6 member heteroaryl optionally comprising 1 additional ring heteroatom selected from N, O and S;

R^9 is hydrogen or C_1-C_6alkyl;

R^{10} and R^{10a} are each independently selected from the group consisting of hydrogen, halogen and C_1-C_6alkyl; or

R^9 and R^{10} taken in combination form a divalent bridge selected from O, CH_2, and CH_2CH_2 and R^{10a} is hydrogen;

R^{11a} is hydrogen or halogen;

R^{12} is hydrogen or halogen;

R^{11} is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, N(H)C_1-C_6alkyl and N(H)C_3-C_7cycloalkyl; or

R^{11} and R^{12}, taken in combination, form a double bond;

R^{13a} is hydrogen or C_1-C_6alkyl;

R^{13} is C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkyl;

R^{14} is C_1-C_6alkyl, C_3-C_7cycloalkyl or C_3-C_7cycloalkylC_1-C_6alkyl; or

R^{13} and R^{14}, taken in combination with the interposed C and N atoms, form a saturated or partially unsaturated 4 to 7 member heterocycle which heterocycle further comprises 0 or 1 additional ring heteroatoms selected from N, O and S, which heterocycle is optionally fused to a benzo ring or to a saturated carbocycle having 3 to 7 ring atoms, or which heterocycle is optionally taken together with a saturated carbocyle having 3 to 7 ring atoms to form a spirocyclic ring, and wherein the heterocycle is optionally substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxy, oxo, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloC_1-C_6alkyl, C_1-C_6alkoxy, C_3-C_7cycloalkyl, O-C(O)pyridine substituted with C_1-C_4alkyl and haloC_1-C_4alkyl; and

R^{15} is hydrogen or halogen;

with the proviso that

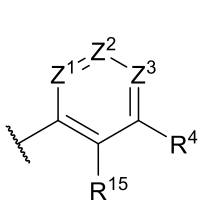
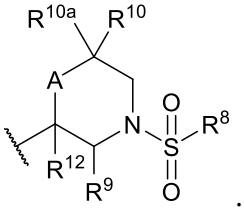
(1) when R^4 is SO_2CH_3, then at least one occurrence of R^1, R^2 or R^3 is not hydrogen,

(2) when R^4 is halogen, trifluoromethyl or cyano and R^6 is hydrogen or halogen, then at least

one occurrence of R^1 or R^2 is not hydrogen or R^1 is not methyl,

(3) when R^5 is C_1-C_6alkoxy, then R^4 is not hydrogen or halogen, and

(4) when R^4 is C_1-C_6alkoxy or C_1-C_6alkyl, then R^2 is not hydrogen.

2. The compound of claim 1, wherein Q is  or .

3. The compound of claim 1 or claim 2, wherein

X^1 is CR^2, X^2 is N or CR^3, X^3 is CR^{3a}, X^4 is N or CR^3 and X^5 is CR^3;

R^2 is hydrogen, halogen, C_1-C_4alkyl, cyclopropyl, haloC_1-C_4alkyl, C_1-C_4alkoxy or haloC_1-C_4alkoxy;

R^3 is independently selected at each occurrence from the group consisting of hydrogen, halogen, C_1-C_4alkyl, cyclopropyl, haloC_1-C_4alkyl, C_1-C_4alkoxy and haloC_1-C_4alkoxy; and

R^{3a} is halogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylC_1-C_4alkyl, C_1-C_6alkoxy, haloC_1-C_6alkoxy or SF_5.

4. The compound of any one of claims 1 to 3, wherein

X^1 is CR^2;

R^2 is hydrogen, halogen, C_1-C_4alkyl or C_1-C_4alkoxy;

X^2 is CH or N;

X^3 is CR^{3a};

R^{3a} is halogen, C_1-C_4alkyl, haloC_1-C_4alkyl, haloC_1-C_6alkoxy or SF_5;

X^4 is CR^3 or N;

R^3 is hydrogen or halogen; and

X^5 is CH.

5. The compound of any one of claims 1 to 4, wherein

X^1 is CR^2;

R^2 is hydrogen, halogen, methyl, ethyl, methoxy or ethoxy;

X^2 and X^5 are each CH;

X^3 is CR^{3a};

R^{3a} is halogen, methyl, ethyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, or SF_5;

X^4 is CR^3; and

R^3 is hydrogen or halogen.

6. The compound of any one of claims 1 to 5, wherein R^1 is selected from the group consisting of hydrogen, C_1-C_6alkyl, halo C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylmethyl, and 4 to 6 member heterocycloalkyl having a ring heteroatom selected from N and O, which heterocycloalkyl is

optionally substituted with 1 or 2 groups selected from oxo, halogen, and hydroxy, and wherein the alkyl or cycloalkyl is optionally substituted with hydroxy.

7. The compound of any one of claims 1 to 6, wherein R^1 is C_1-C_4alkyl, trifluoromethyl, C_3-C_5cycloalkyl, C_3-C_5cycloalkylmethyl, oxetanyl, tetrahydrofuryl, or azetidinyl, wherein each alkyl, cycloalkyl, oxetanyl or azetidinyl is optionally substituted with hydroxy or halogen.

8. The compound of any one of claims 1 to 7, wherein R^1 is methyl, isopropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, oxetanyl, difluoromethyl, 1-hydroxycyclopropyl, 3-hydroxycyclobutyl, 3-hydroxy-3-methylcyclobutyl, 3-fluorooxetanyl or oxopyrrolidinyl.

9. The compound of any one of claims 1 to 8, wherein

R^{13} and R^{14} are each independently selected from the group consisting of C_1-C_4alkyl, C_3-C_5cycloalkyl and C_3-C_5cycloalkylmethyl; and

R^{13a} is hydrogen.

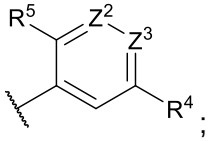
10. The compound of any one of claims 1 to 9, wherein R^{13} and R^{14} are each methyl and R^{13a} is hydrogen.

11. The compound of any one of claims 1 to 8, wherein R^{13a} is hydrogen; and R^{13} and R^{14}, taken in combination with the interposed C and N atoms, form a saturated or partially unsaturated 4 to 6 member heterocycle, which heterocycle further comprises 0 or 1 additional ring heteroatoms selected from N, O and S, wherein the heterocycle is optionally fused to a saturated carbocycle having 3 to 7 ring atoms, or which heterocycle is optionally taken together with a saturated carbocyle having 3 to 7 ring atoms to form a spirocyclic ring, and wherein the heterocycle is optionally substituted with 0, 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxy, C_1-C_6alkyl, haloC_1-C_6alkyl, C_1-C_6alkoxy and C_3-C_7cycloalkyl.

12. The compound of any one of claims 1 to 8 and 11, wherein R^{13a} is hydrogen; and R^{13} and R^{14}, taken in combination with the interposed C and N atoms, form a heterocyclic ring selected from the group consisting of azetidine, pyrrolidine, thiazolidine, piperidine and morpholine, wherein the heterocyclic ring is optionally fused to a cyclopropyl ring and the heterocyclic ring is further optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxy, methyl, hydroxymethyl, methoxy and cyclopropyl.

13. The compound of any one of claims 1 to 8, 11 and 12, wherein R^{13a} is hydrogen; and R^{13} and R^{14}, taken in combination with the interposed C and N atoms, form a pyrrolidine ring, wherein the pyrrolidine ring is optionally fused to a cyclopropyl ring and the pyrrolidine ring is further optionally substituted with 1 or 2 substituents independently selected from the group consisting of halogen, hydroxy, methyl, hydroxymethyl and cyclopropyl.

14. The compound of any one of claims 1 to 13, wherein

Q is ;

Z^2 is N or CR^6; Z^3 is N or CR^7, wherein 0 or 1 of Z^2 and Z^3 can be N;

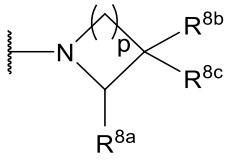
R^4 is C_1-C_4alkyl, C_1-C_4alkoxy, cyano, SO_2-R^8, or 4 to 7 member heterocycloalkyl having a ring heteroatom selected from N, O and S which heterocycloalkyl is substituted with 0, 1 or 2 groups independently selected from the group consisting of halogen, oxo, C_1-C_6alkyl, $C(O)C_1$-C_6alkyl, and SO_2R^8 and wherein each alkyl or cycloalkyl is optionally substituted with hydroxy, cyano, CO_2H or $C(O)NH_2$;

R^5 is hydrogen, C_1-C_4alkyl, amino, mono- or di-C_1-C_4alkylamino, C_3-C_6cycloalkylamino or -$N(H)C(O)C_1$-C_4alkyl, where each alkyl or cycloalkyl is optionally substituted with hydroxy;

R^6 is hydrogen, C_1-C_4alkyl, haloC_1-C_6alkyl or halogen;

R^7 is hydrogen or C_1-C_4alkyl; and

R^8 is C_1-C_6alkyl, $NR^{8d}R^{8e}$, C_3-C_7cycloalkyl or haloC_1-C_6alkyl, wherein each alkyl, cycloalkyl or haloalkyl is optionally substituted with hydroxy, CO_2H, CO_2C_1-C_6alkyl or $C(O)NH_2$; or

R^8 is a group of the formula: 

p is 1 or 2;

R^{8a} is hydrogen, C_1-C_6alkyl or phenyl substituted with halogen;

R^{8b} is hydrogen, halogen, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_5cycloalkyl, cyano, amino or SO_2C_1-C_6alkyl;

R^{8c} is hydrogen, halogen, hydroxy or C_1-C_6alkyl; or

$CR^{8b}R^{8c}$, taken in combination, forms a spirocyclic 3 to 6 member carboxycle or a 4 to 6 member heterocycle having a ring heteratom selected from N, O and S, which spirocycle is optionally substituted with hydroxy, C_1-C_4alkyl, haloC_1-C_4alkyl or C_1-C_4alkoxy;

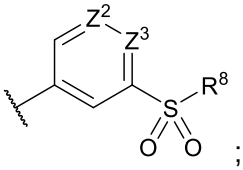
R^{8d} is hydrogen, C_1-C_6alkyl, haloC_1-C_6alkyl, C_3-C_7cycloalkyl, or 4 to 7 member heterocycloalkyl having a ring heteroatoms selected from N, O and S and 0 or 1 additional ring nitrogen atoms, which heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from hydroxy, halogen, oxo, C_1-C_6alkyl, and C_1-C_6alkoxy;

R^{8e} is hydrogen or C_1-C_6alkyl; or

$NR^{8d}R^{8e}$, taken in combination, forms a 4 to 7 member heterocycloalkyl optionally comprising 1 additional ring heteroatom selected from N, O and S, which heterocycloalkyl is optionally substituted with 1 or 2 substituents independently selected from hydroxy, halogen, oxo, C_1-C_6alkyl, C_1-C_6alkoxy and heteroaryl, which heteroaryl has 5 or 6 ring atoms and has one ring heteroatom selected from N, O and S and 0 or 1 additional ring nitrogen atom, or

$NR^{8d}R^{8e}$, taken in combination, forms a 5 or 6 member heteroaryl, which heteroaryl optionally comprises 1 additional ring heteroatom selected from N, O and S.

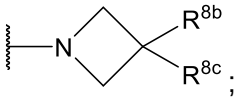
15. The compound of any one of claims 1 to 14, wherein

Q is  ;

Z^2 is CH or N;

Z^3 is CH or N; and

R^8 is C_1-C_6alkyl, C_3-C_7cycloalkyl or haloC_1-C_6alkyl; or

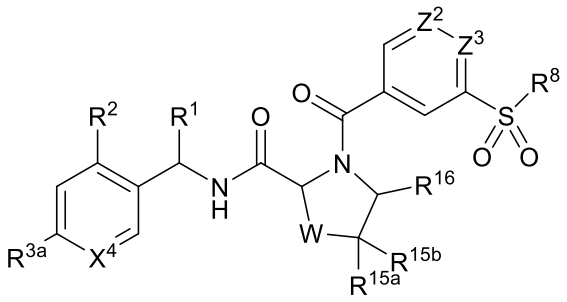
R^8 is a group of the formula:  ;

R^{8b} is halogen, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_5cycloalkyl, cyano, or amino;

R^{8c} is hydrogen, halogen, hydroxy or C_1-C_6alkyl; or

$CR^{8b}R^{8c}$, taken in combination, forms a spirocyclic 3 to 4 member carboxycle or a 4 or 5 member heterocycle having a ring heteratom selected from N, O and S, which spirocycle is optionally substituted with hydroxy, C_1-C_4alkyl, haloC_1-C_4alkyl or C_1-C_4alkoxy.

16. The compound of any one of claims 1 to 4, according to the formula:



wherein

R^1 is selected from the group consisting of hydrogen, C_1-C_6alkyl, halo C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylmethyl, and 4 to 6 member heterocycloalkyl having a ring heteroatom selected from N and O, which heterocycloalkyl is optionally substituted with 1 or 2 groups selected from oxo or hydroxy, and wherein the alkyl or cycloalkyl is optionally substituted with hydroxy;

R^2 is hydrogen, halogen, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{3a} is halogen, C_1-C_4alkyl, haloC_1-C_4alkyl or SF_5;

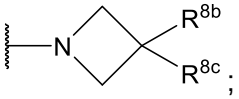
X^4 is CR^3 or N;

R^3 is hydrogen or halogen;

Z^2 is CH or N;

Z^3 is CH or N;

R^8 is C_1-C_6alkyl, C_3-C_7cycloalkyl or haloC_1-C_6alkyl; or

R^8 is a group of the formula: ;

R^{8b} is halogen, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_5cycloalkyl, cyano, or amino;

R^{8c} is hydrogen, halogen, hydroxy or C_1-C_6alkyl; or

$CR^{8b}R^{8c}$, taken in combination, forms a spirocyclic 3 to 4 member carboxycle or a 4 or 5 member heterocycle having a ring heteratom selected from N, O and S, which spirocycle is optionally substituted with hydroxy, C_1-C_4alkyl, haloC_1-C_4alkyl or C_1-C_4alkoxy;

W is a bond, CH_2, CH_2CH_2 or CH_2O, where the oxygen is adjacent to $CR^{15a}R^{15b}$; and

R^{15a} and R^{15b} are independently selected from the group consisting of hydrogen, halogen, hydroxy, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxy and C_3-C_6cycloalkyl; or

R^{15a} and R^{15b}, taken in combination with the carbon atom to which they are attached, form a spirocyclic cyclopropyl ring; and

R^{16} is hydrogen; or

R^{15a} and R^{16}, taken in combination with the carbon atoms to which they are attached, form a fused cyclopropyl ring.

17. The compound of claim 16, wherein

X^4 is CR^3;

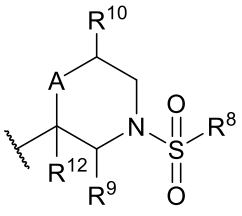
R^3 is hydrogen or halogen;

W is CH_2;

Z^2 is N; and

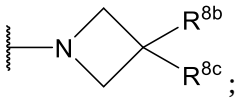
Z^3 is CH.

18. The compound of any one of claims 1 to 13, wherein

Q is ;

A is oxygen, N(H), or CHR^{11};

R^8 is C_1-C_6alkyl, $NR^{8d}R^{8e}$, C_3-C_7cycloalkyl, haloC_1-C_6alkyl or benzyl, and wherein each alkyl, cycloalkyl or haloalkyl is optionally substituted with hydroxy, CO_2H, CO_2C_1-C_6alkyl or $C(O)NH_2$; or

R^8 is a group of the formula: ;

R^{8b} is hydrogen, C_1-C_4alkyl, halo C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_6cycloalkyl, cyano, or amino;

R^{8c} is hydrogen, hydroxy or C_1-C_6alkyl;

R^{8d} is hydrogen, C_1-C_6alkyl, haloC_1-C_6alkyl, or C_3-C_7cycloalkyl;

R^{8e} is hydrogen or C_1-C_6alkyl;

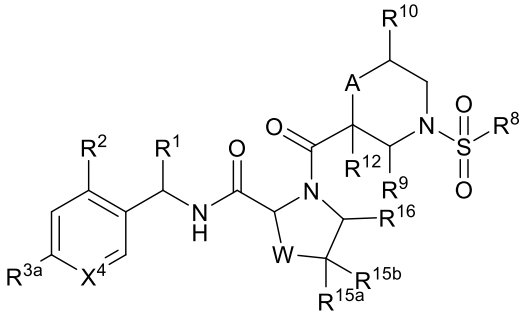
R^9 is hydrogen;

R^{10} is hydrogen; or

R^9 and R^{10}, taken in combination, form a divalent methylene bridge; and

R^{11} is hydrogen or C_1-C_6alkyl.

19. The compound of any one of claims 1 to 4, according to the formula:



wherein

R^1 is selected from the group consisting of hydrogen, C_1-C_6alkyl, halo C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_7cycloalkylmethyl, and 4 to 6 member heterocycloalkyl having a ring heteroatom selected from N and O, which heterocycloalkyl is optionally substituted with 1 or 2 groups selected from oxo and hydroxy, and wherein the alkyl or cycloalkyl is optionally substituted with hydroxy;

R^2 is hydrogen, halogen, C_1-C_4alkyl or C_1-C_4alkoxy;

R^{3a} is halogen, C_1-C_4alkyl, haloC_1-C_4alkyl or SF_5;

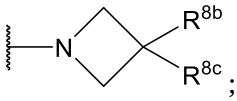
X^4 is CR^3 or N;

R^3 is hydrogen or halogen;

Z^2 is CH or N;

Z^3 is CH or N;

R^8 is C_1-C_6alkyl, C_3-C_7cycloalkyl or haloC_1-C_6alkyl; or

R^8 is a group of the formula: 

;

R^{8b} is halogen, C_1-C_4alkyl, haloC_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_5cycloalkyl, cyano, or amino;

R^{8c} is hydrogen, halogen, hydroxy or C_1-C_6alkyl; or

$CR^{8b}R^{8c}$, taken in combination, forms a spirocyclic 3 to 4 member carboxycle or a 4 or 5 member heterocycle having a ring heteratom selected from N, O and S, which spirocycle is optionally substituted with hydroxy, C_1-C_4alkyl, haloC_1-C_4alkyl or C_1-C_4alkoxy;

W is a bond, CH_2, CH_2CH_2 or CH_2O, where the oxygen is adjacent to $CR^{15a}R^{15b}$; and

R^{15a} and R^{15b} are independently selected from the group consisting of hydrogen, halogen, hydroxy, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxy and C_3-C_6cycloalkyl; or

R^{15a} and R^{15b}, taken in combination with the carbon to which they are attached, form a spirocyclic cyclopropyl ring; and

R^{16} is hydrogen; or

R^{15a} and R^{16}, taken in combination with the carbon atoms to which they are attached, form a

fused cyclopropyl ring, and R^{15b} is selected from the group consisting of hydrogen, halogen, hydroxy, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkoxy and C_3-C_6cycloalkyl.

20. A compound, which is recited in Table A, or a pharmaceutically acceptable salt thereof.

21. A compound, which is recited in Table B, or a pharmaceutically acceptable salt thereof.

22. A compound, which is recited in Table C, or a pharmaceutically acceptable salt thereof.

23. The compound of any one of claims 1 to 22 in the form of a pharmaceutically acceptable salt.

24. A pharmaceutical composition comprising a pharmaceutically acceptable excipient, carrier or adjuvant and at least one compound of any one of claims 1 to 23.

25. The pharmaceutical composition of claim 24, wherein the composition is formulated in a form selected from the group consisting of an injectable fluid, an aerosol, a tablet, a pill, a capsule, a syrup, a cream, a gel and a transdermal patch.

26. A packaged pharmaceutical composition, comprising a pharmaceutical composition of claim 24 or 25 and instructions for using the composition to treat a patient suffering from a heart disease.

27. The packaged pharmaceutical composition of claim 26, wherein the heart disease is heart failure.

28. Use of at least one compound of any one of claims 1 to 23, or a pharmaceutical salt thereof or a pharmaceutical composition thereof in the manufacture of a medicament for treating heart disease in a mammal.

29. The use of claim 28, wherein the heart disease is heart failure.

30. The use of claim 29, wherein the heart failure is congestive heart failure.

31. The use of claim 29, wherein the heart failure is systolic heart failure.

32. Use of at least one compound of any one of claims 1 to 23 or a pharmaceutical salt thereof or a pharmaceutical composition thereof in the manufacture of a medicament for modulating the cardiac sarcomere in a mammal.

33. Use of at least one compound of any one of claims 1 to 23 or a pharmaceutical salt thereof or a pharmaceutical composition thereof in the manufacture of a medicament for potentiating cardiac myosin in a mammal.

34. A compound of any one of claims 1 to 23 for use as a medicament.

35. Use of the compound of any one of claims 1 to 23 in the manufacture of a medicament for treating heart failure.