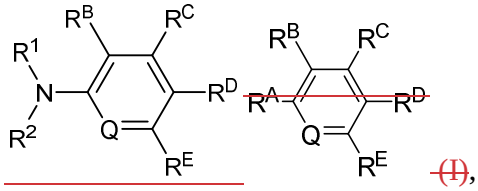
We claim:

1. A compound ~~according to formula I~~, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, according to the formula



~~(I)~~,

wherein:

~~R^A is $-N(R^1)R^2$ and~~ R^B is H, aliphatic, -O-aliphatic, -S-aliphatic, -O-C(O)-aliphatic, or halogen~~, ;~~ ~~or R^A is $N(R^1)$ or $CH_2N(R^1)$ and R^A together with R^B forms a 5- or 6-membered heteroaliphatic or heteroaryl ring;~~

R^C is H~~,~~ or aliphatic~~;, -S-aliphatic, or -O-C(O)-aliphatic, and~~

R^D is ~~substituted aliphatic or~~ ~~$-Y-(CR^7_2)_n$~~-X-$(CR^7_2)_m$-$N(R^4)R^5$,

$-(CH_2)_qSO_3M$, $-(CH_2)_qNH_2$, or $-(CH_2)_qOH$;

~~or R^C and R^D together form a 5- or 6-membered heteroaliphatic or heteroaryl ring, wherein the 5- or 6-membered heteroaliphatic or heteroaryl ring is substituted with $-X-(CR^7_2)_m-N(R^4)R^5$~~;

R^E is H, -O-aliphatic, aliphatic, -S-aliphatic, -O-C(O)-aliphatic, or halogen;

Q is C-R^3;

X is $N(R^6)$~~, O, C(O), $S(O_2)O$, $OS(O_2)$, $P(O)(OH)O$, $OP(O)OH$, $N(H)C(H)(CF_3)$, or $C(H)(CF_3)N(H)$, or X is absent~~;

~~Y is $-(CR^7_2)_n-$ or a divalent azole ring;~~

R^1 and R^2 independently are H or aliphatic;

R^3 is H, aliphatic, -O-aliphatic, or -S-aliphatic;

R^4 and R^5 independently are H, aliphatic, aryl or heteroaryl, or R^4 and R^5 together with N form a heterocycloaliphatic or heteroaryl ring;

R^6 is H or aliphatic;

each R^7 independently is H, halogen, or aliphatic;

M is a monatomic cation; and

m, *n*, and *q* ~~*m* and *n*~~ independently are integers from 1 to 10,

wherein if R^D is $–(CR^7_2)_n$-X-$(CR^7_2)_m$-$N(R^4)R^5$, then at least one of the following conditions applies

(i) at least one of R^1 and R^2 is other than H, or

(ii) at least one of R^C and R^E is other than H, or

(iii) X is other than N(H), or

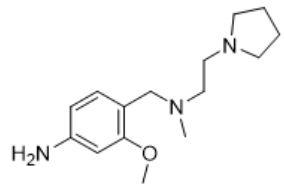
(iv) *m* is not 2, or

(v) *n* is not 1, or

(vi) if Q is CH then R^B is not –O-aliphatic, or

(vii) if R^B is H then Q is not C-R^3 where R^3 is -O-aliphatic, and

wherein the compound is not



~~wherein at least one of the following conditions applies~~

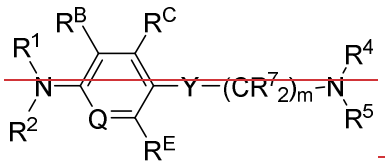
~~(i) at least one of R^B, R^C, R^E, and R^3 is other than H, or~~

~~(ii) the compound includes –Y-X-$(CR^7_2)_m$-$N(R^4)R^5$ or –X-$(CR^7_2)_m$-$N(R^4)R^5$, where X is present, or~~

~~(iii) if Y is a divalent azole ring, then X is absent, or~~

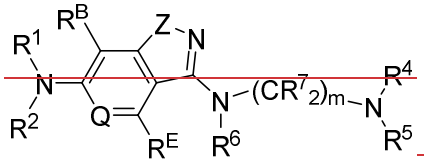
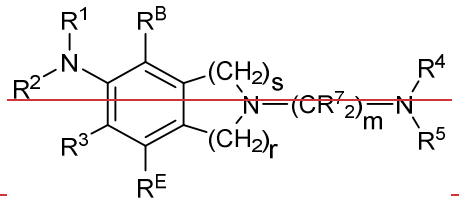
~~(iv) if R^4 and R^5 together with N form a heterocycloaliphatic or heteroaryl ring, then at least of one of R^B, R^C, R^E, and R^3 is other than H, or at least one of R^1 and R^2 is other than H or $–CH_3$; or~~

~~(v) if X is absent, then the compound has a structure according to formula III~~

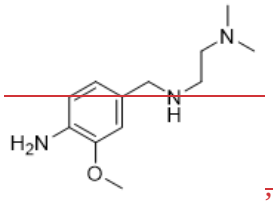
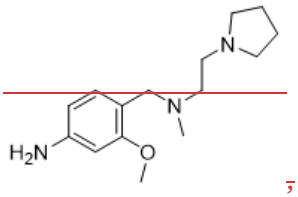
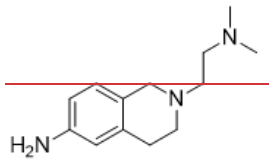


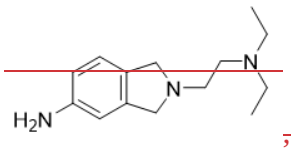
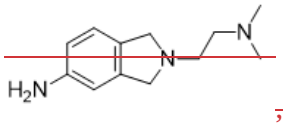
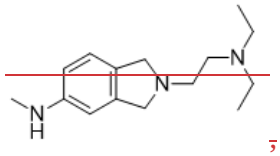
~~(III) where Y is a divalent azole ring; or~~

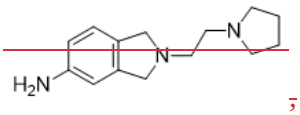
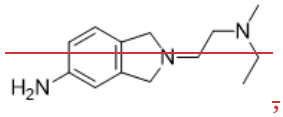
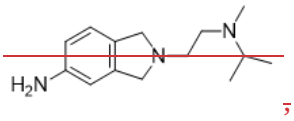
~~(vi) if R^C and R^D together form a 5- or 6-membered heteroaliphatic or heteroaryl ring, then the compound has a structure according to formula IV or formula VI~~

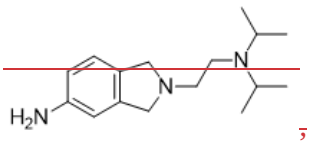
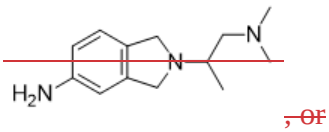
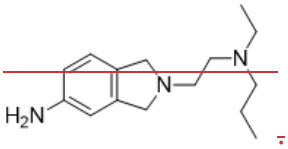
~~~~ ~~(IV) or~~ ~~~~ ~~(VI)~~

~~where (a) Z is O, N(H), or CH_2, and (b) *r* is 1 or 2, *s* is 1 or 2, and *r*+*s* = 2 or 3, and wherein the compound is not~~

~~~~ ~~;~~ ~~~~ ~~;~~ ~~~~ ~~;~~

~~~~ ~~;~~ ~~~~ ~~;~~ ~~~~ ~~;~~

~~~~ ~~;~~ ~~~~ ~~;~~ ~~~~ ~~;~~

~~~~ ~~;~~ ~~~~ ~~, or~~ ~~~~ ~~;~~

2. The compound according to claim 1, wherein R^B is H, aliphatic, -O-aliphatic, -S-aliphatic, or halogen.

3. The compound according to claim ~~1~~2, wherein:

R^D is ~~–~~$(CR^7_2)_n$ ~~Y~~-X-$(CR^7_2)_m$-$N(R^4)R^5$; and

X is $N(R^6)$ where R^6 is aliphatic.

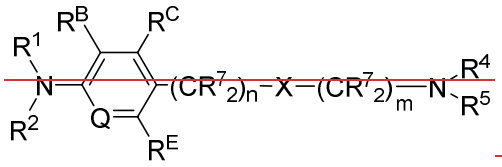
~~3~~4. The compound according to claim 1, wherein:

(i) R^4 and R^5 are alkyl; or

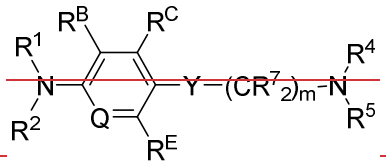
(ii) *m* is 2, or *n* is 1, or *m* is 2 and *n* is 1; or

(iii) R^6 is H, or each R^7 is H, or R^6 is H and each R^7 is H; or

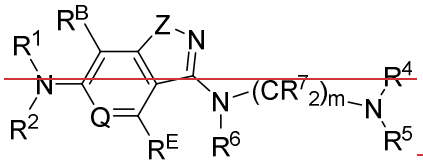
(iv) any combination thereof.~~The compound according to claim 1, wherein the compound has a structure according to one of formulas II, III, IV, V, VI, or VII~~



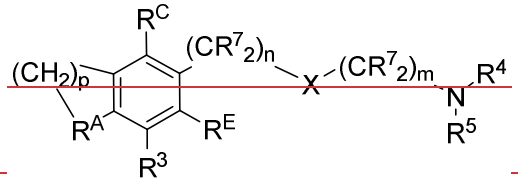
~~(II),~~



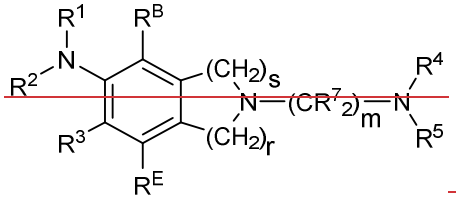
~~(III),~~



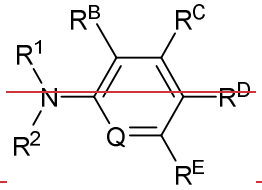
~~(IV),~~



~~(V),~~



~~(VI), or~~



~~(VII),~~

~~wherein:~~

~~R^A is $N(R^1)$ or $-CH_2N(R^1)-$;~~

~~R^B is H, aliphatic, -O-aliphatic, -S-aliphatic, or halogen;~~

~~R^C is H or aliphatic;~~

~~R^D is $-(CH_2)_qSO_3M$, $-(CH_2)_qNH_2$, or $-(CH_2)_qOH$, where *q* is an integer from 1 to 10 and M is a monatomic cation;~~

~~X is $N(R^6)$, O, C(O), $-S(O_2)O-$, $-OS(O_2)-$, $-P(O)(OH)O-$, $-OP(O)(OH)-$, $-N(H)-C(H)(CF_3)-$ or $-C(H)(CF_3)-N(H)-$;~~

~~Y is a divalent azole ring;~~

~~Z is O, N(H), or CH_2;~~

~~*p* is 1, 2, or 3 when R^A is $N(R^1)$, or *p* is 1 or 2 when R^A is $-CH_2N(R^1)-$;~~

~~*q* is an integer from 1 to 10; and~~

~~*r* is 1 or 2, *s* is 1 or 2, and *r*+*s* = 2 or 3,~~

~~wherein if the compound has a structure according to formula II, then at least one of the following conditions applies~~

~~(i) at least one of R^1 and R^2 is other than H, or~~

(ii) at least one of R^C and R^E is other than H, or

(iii) X is other than N(H), or

(iv) *m* is not 2, or

(v) *n* is not 1, or

(vi) if Q is CH then R^B is not -O-aliphatic, or

(vii) if R^B is H then Q is not C-R^3 where R^3 is -O-aliphatic.

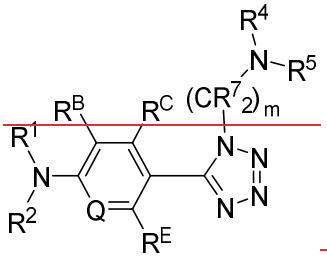
4. The compound according to claim 3, wherein the compound has a structure according to Formula II, and X is N(R^6) where R^6 is aliphatic.

5. The compound according to claim 3, wherein the compound has a structure according to formula III, and Y is an imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, furazanyl, thiazolyl, isothiazolyl, or thiadiazolyl group.

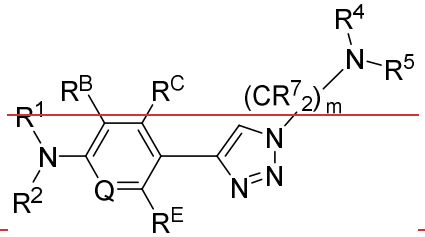
6. The compound according to claim 5, wherein Y is a triazolyl, tetrazolyl, or oxadiazolyl group.

7. The compound according to claim 5, wherein Y is a tetrazolyl or oxadiazolyl group.

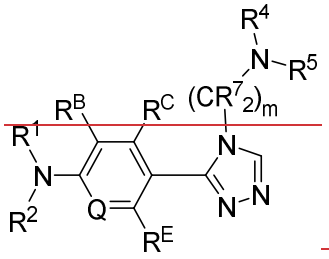
8. The compound according to claim 3, wherein the compound has a structure according to one of formulas IIIA, IIIB, IIIC, or IIID



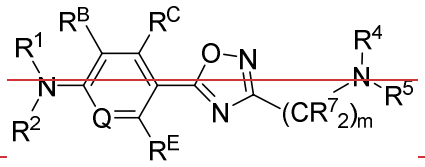
(IIIA),



(IIIB),



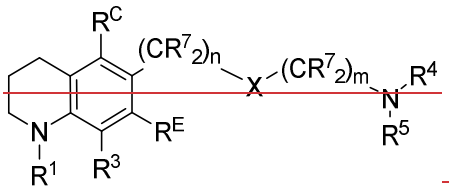
(IIIC), or



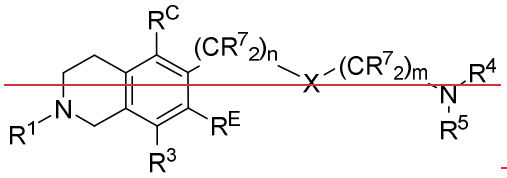
(IIID),

wherein if the compound has a structure according to formula IIIA, then at least one of R^1 and R^2 is other than H, or at least one of R^B, R^C, and R^E is other than H, or Q is other than CH.

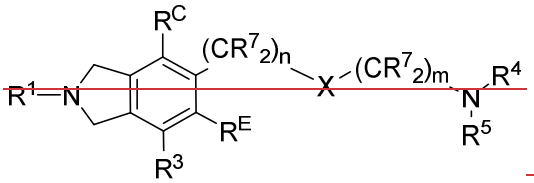
9. The compound of claim 3, wherein the compound has a structure according to one of formulas VA, VB, or VC



(VA),



(VB), or



(VC).

10. The compound according to claim 9, wherein:

R^1 is H or alkyl;

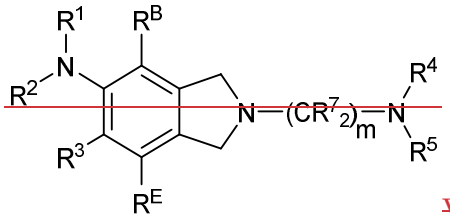
each R^7 independently is H or halogen; and

(i) R^4 and R^5 are H, or

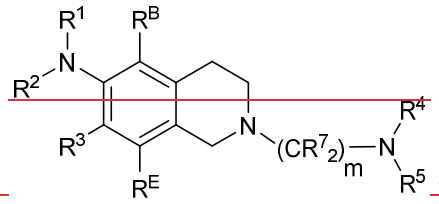
(ii) R^4 is H and R^5 is alkyl, or

(iii) R^4 and R^5 are alkyl.

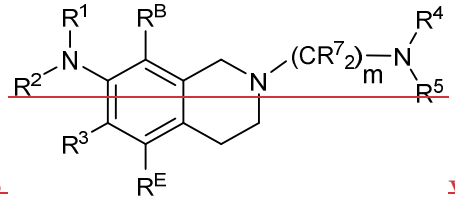
11. The compound according to claim 3, wherein the compound has a structure according to one of formulas VIA, VIB, or VIC



VIA,



VIB,



or VIC,

wherein:

if the compound has a structure according formula VIA, then at least one of R^B, R^E, or R^3 is other than H, or *m* is not 2, or if one of R^1 and R^2 is H, then the other of R^1 and R^2 is other than H or CH_3, or

if the compound has a structure according to formula VIB, then at least one of R^B, R^E, or R^3 is other than H, or *m* is not 2, or at least one of R^1 and R^2 is other than H, or at least one of R^4 and R^5 is other than CH_3.

12. The compound according to any one of claims 1-9 or 11, wherein R^4 and R^5 are alkyl.

13. The compound of any one of claims 3-12, wherein R^C is H.

14. The compound according to any one of claims 1-13, wherein *m* is 2, or *n* is 1, or *m* is 2 and *n* is 1.

15. The compound according to any one of claims 1-14, wherein R^6 is H, or each R^7 is H, or R^6 is H and each R^7 is H.

~~16. The compound according to any one of claims 2-7, 9, 10, or 12-15, wherein X is N(H), O, C(O), -S(O$_2$)O-, -OS(O$_2$)-, -P(O)(OH)O-, -OP(O)(OH)-, -N(H)-C(H)(CF$_3$)-, or -C(H)(CF$_3$)-N(H)-.~~

~~17. The compound according to any one of claims 2-7, 9, 10, or 12-15, wherein X is N(H), O, C(O), -S(O$_2$)O-, or -P(O)(OH)O-.~~

~~18. The compound according to any one of claims 2-7, 9, 10, or 12-15, wherein X is N(H), O, or -S(O$_2$)O-.~~

~~19. The compound according to claim 1, wherein:~~

~~R^A is -N(R^1)R^2 where R^1 is H or aliphatic and R^2 is H or aliphatic;~~

~~R^B is H, aliphatic, -O-aliphatic, -S-aliphatic, -O-C(O)-aliphatic, or halogen;~~

~~R^C is H, aliphatic, -S-aliphatic, or -O-C(O)-aliphatic; and~~

~~R^D is substituted aliphatic.~~

~~20~~5. The compound according to claim 1~~9~~, wherein R^D is -$(CH_2)_qNH_2$, -$(CH_2)_qOH$, or -$(CH_2)_qSO_3M$ where *q* is an integer from 1 to 10 and M is a monatomic cation.

~~21. The compound according to claim 19, wherein R^D is -CH$_2$SO$_3$M, -CH$_2$NH$_2$, or -CH$_2$OH.~~

~~22. The compound according to any one of claims 1-21, wherein at least one H atom is replaced by a deuterium atom.~~

~~23~~6. The compound according to claim 1, wherein the compound is:

N^1-(4-amino-2-methoxybenzyl)-*N*^{2},*N*^{2}-diethylethane-1,2-diamine;

3-methoxy-4-(((2-(pyrrolidin-1-yl)ethyl)amino)methyl)aniline;

sodium (4-amino-2-methoxyphenyl)methanesulfonate;

~~*N*-butyl-2-(2-(diethylamino)ethyl)isoindolin-5-amine;~~

~~*N*-butyl-2-(2-(pyrrolidin-1-yl)ethyl)isoindolin-5-amine;~~

sodium (4-(dibutylamino)-3-methoxyphenyl)methanesulfonate;

sodium (4-amino-3-methoxyphenyl)methanesulfonate;

4-((2-(diethylamino)ethoxy)methyl)-2,3-dimethoxyaniline; or

~~*N*-butyl-4-(3-((diethylamino)methyl)-1,2,4-oxadiazol-5-yl)-3-methoxyaniline;~~

~~*N*-butyl-4-(3-((dimethylamino)methyl)-1,2,4-oxadiazol-5-yl)-3-methoxyaniline;~~

~~*N*-butyl-4-(3-((dibutylamino)methyl)-1,2,4-oxadiazol-5-yl)-3-methoxyaniline;~~

~~*N*-butyl-4-(3-((dibutylamino)methyl)-1,2,4-oxadiazol-5-yl)-2-methylaniline;~~

~~N^1-((1-butyl-1,2,3,4-tetrahydroquinolin-6-yl)methyl)-N^2,N^2-dimethylethane-1,2-diamine;~~

~~*N*-butyl-4-(1-(2-(dibutylamino)ethyl)-1H-tetrazol-5-yl)-2-methylaniline;~~

~~2-(2-(diethylamino)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-amine;~~

~~N^3-(2-(diethylamino)ethyl)-1H-indazole-3,6-diamine;~~

~~N^6,N^6-dibutyl-N^3-(2-(diethylamino)ethyl)-1H-indazole-3,6-diamine;~~

~~N^1-((1-butyl-1,2,3,4-tetrahydroquinolin-6-yl)methyl)-N^2,N^2-diethylethane-1,2-diamine;~~

N^1-(4-amino-3-methylbenzyl)-N^2,N^2-diethylethane-1,2-diamine~~;~~

~~*N*-butyl-2-(2-(diethylamino)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-amine; or~~

~~*N*-butyl-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-amine~~.

~~24~~7. A pharmaceutical composition, comprising:

a therapeutically effective amount of at least one compound according to ~~any one of~~ claim~~s~~ 1~~-23~~, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof; and

at least one pharmaceutically acceptable additive.

~~25. A method, comprising:~~

~~for modulating activity of a calcium ion channel by contacting the calcium ion channel with an effective amount of a compound according to any one of claims 1-23, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof.~~

~~26. The method of claim 25, wherein contacting the calcium ion channel with the compound inhibits activity of the calcium ion channel.~~

27. The method of claim 25 or claim 26, wherein the calcium ion channel is a ryanodine receptor.

28. The method of claim 27, wherein the ryanodine receptor is RyR2.

29. The method of any one of claims 25-28, wherein contacting the calcium ion channel comprises administering the effective amount of the compound, or stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, to a subject.

30. The method of claim 29, wherein the subject is a subject identified as having, or being at risk of having, a cardiac arrhythmia or heart failure.

31. The method of claim 30, wherein administering the effective amount of the compound, or stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, comprises administering an amount of a pharmaceutical composition comprising the effective amount of the compound to the subject.

32. The method of any one of claims 25-31, wherein the compound is:

N^1-(4-amino-2-methoxybenzyl)-N^2,N^2-diethylethane-1,2-diamine;

3-methoxy-4-(((2-(pyrrolidin-1-yl)ethyl)amino)methyl)aniline;

sodium (4-amino-2-methoxyphenyl)methanesulfonate;

N-butyl-2-(2-(diethylamino)ethyl)isoindolin-5-amine;

N-butyl-2-(2-(pyrrolidin-1-yl)ethyl)isoindolin-5-amine; or

any combination thereof.

33. A method for ameliorating at least one sign or symptom of a cardiac arrhythmia or heart failure, the method comprising:

administering one or more therapeutically effective doses of a compound according to any one of claims 1-23, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, over an effective period of time to a subject identified as having, or being at risk

~~of having, a cardiac arrhythmia or heart failure, thereby ameliorating at least one sign or symptom of the cardiac arrhythmia or heart failure.~~

~~34. The method of claim 33, wherein administering the therapeutically effective dose of the compound, or stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, comprises administering an amount of a pharmaceutical composition comprising the therapeutically effective dose of the compound, or stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, to the subject.~~

~~35. The method of claim 33 or claim 34, wherein administering is performed by an oral, parenteral, transmucosal, or transdermal route.~~

~~36. The method of any one of claims 33-35, wherein administering is performed by an oral, intramuscular, subcutaneous, intravenous, or intra-arterial route.~~

8. Use of a compound according to claim 1, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, in the manufacture of a medicament for inhibiting activity of a ryanodine receptor, wherein an effective amount of the compound, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof is to be contacted with the ryanodine receptor.

9. The use of claim 8, wherein the effective amount of the compound, or stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, is to be administered to a subject to be contacted with the ryanodine receptor.

10. The use of claim 9, wherein the subject is a subject identified as having, or being at risk of having, a cardiac arrhythmia or heart failure.

11. The use of claim 8, wherein the compound is:

N^1-(4-amino-2-methoxybenzyl)-N^2,N^2-diethylethane-1,2-diamine;

3-methoxy-4-(((2-(pyrrolidin-1-yl)ethyl)amino)methyl)aniline;

sodium (4-amino-2-methoxyphenyl)methanesulfonate; or

any combination thereof.

12. Use of the compound according to claim 1, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof in the manufacture of a medicament for ameliorating at least one sign or symptom of a cardiac arrhythmia or heart failure, wherein one or more therapeutically effective doses of the compound, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, are to be administered over an effective period of time to a subject identified as having, or being at risk of having, a cardiac arrhythmia or heart failure.

~~37~~11~~3~~3. The ~~method~~ use of ~~any one of~~ claim~~s~~ ~~33-36~~102, wherein the compound is:

N^1-(4-amino-2-methoxybenzyl)-N^2,N^2-diethylethane-1,2-diamine;

3-methoxy-4-(((2-(pyrrolidin-1-yl)ethyl)amino)methyl)aniline;

sodium (4-amino-2-methoxyphenyl)methanesulfonate;

~~*N*-butyl-2-(2-(diethylamino)ethyl)isoindolin-5-amine;~~

~~*N*-butyl-2-(2-(pyrrolidin-1-yl)ethyl)isoindolin-5-amine;~~ or

any combination thereof.

~~38~~12~~4~~4. The ~~method~~ use of ~~any one of~~ claim~~s~~ ~~25-37~~8, wherein the compound has a calcium spark response IC_{50} value within a range of from 20 nM to 500 nM as determined in cells from a catecholaminergic polymorphic ventricular tachycardic (CPVT) mouse model.

1~~3~~5. The compound according to claim 1, or a stereoisomer, tautomer, pharmaceutically acceptable salt, hydrate, or solvate thereof for use in therapy.