QUINAZOLINES AS POTASSIUM ION CHANNEL INHIBITORS

RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/239,452, filed on September 3, 2009~~, incorporated herein by reference in its entirety~~.

FIELD OF THE INVENTION

[0002] The present invention provides for quinazolines useful as inhibitors of potassium channel function (especially inhibitors of the K_v1 subfamily of voltage gated K^+ channels, more especially inhibitors of $K_v1.5$ (which have been linked to the ultra-rapidly activating delayed rectifier K^+ current I_{Kur}), and/or $K_v1.3$ channels, and/or $K_v1.1$ channels) and to pharmaceutical compositions containing such compounds. The present invention further provides for the use of such compounds in the treatment and prevention of arrhythmia, I_{Kur}-associated disorders, and other disorders mediated by ion channel function.

BACKGROUND OF THE INVENTION

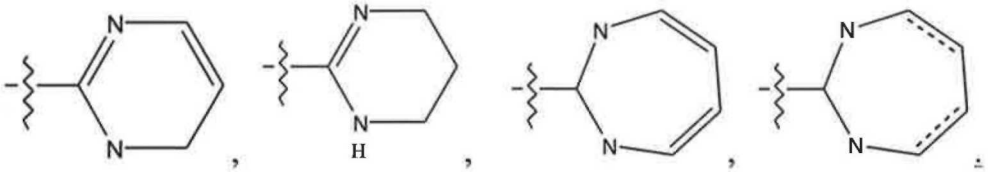
[0003] The ultra-rapidly activating delayed rectifier K^+ current (I_{Kur}) is believed to represent the native counterpart to a cloned potassium channel designated $K_v1.5$ and, while present in human atrium, it appears to be absent in human ventricle. Furthermore, because of its rapidity of activation and limited slow inactivation, I_{Kur} is believed to contribute significantly to repolarization in human atrium. Consequently, a specific blocker of I_{Kur}, that is a compound which blocks $K_v1.5$, would overcome the short coming of other compounds by prolonging refractoriness by retarding repolarization in the human atrium without causing the delays in ventricular repolarization that underlie arrhythmogenic after depolarizations and acquired long QT syndrome observed during treatment with current Class III antiarrhythmic agents. (Antiarrhythmic agents of Class III are drugs that cause a selective prolongation of the duration of the action potential without significant cardiac depression.)

[0004] Immunoregulatory abnormalities have been shown to exist in a wide variety of autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I and II diabetes mellitus,

[0020] The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

[0021] The terms "heterocycle", "heterocyclic", "heterocyclic group" or "heterocyclo" refer to fully saturated or partially or completely unsaturated, including aromatic ("heteroaryl") or nonaromatic cyclic groups (for example, 3 to 13 ring member monocyclic, 7 to 17 ring member bicyclic, or 10 to 20 ring member tricyclic ring systems, such as, in certain embodiments, a monocyclic or bicyclic ring containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro unions.

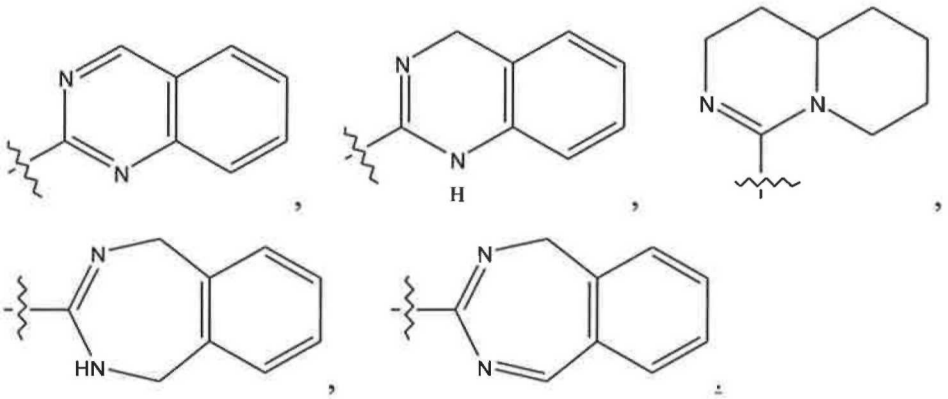
[0022] Exemplary monocyclic heterocyclic groups include azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, tetrahydropyranyl, tetrazoyl, triazolyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl,



~~and the like.~~

[0023] Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofuranyl,

dihydrobenzofuranyl, chromonyl, coumarinyl, benzodioxolyl, dihydrobenzodioxolyl, benzodioxinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl, azabicycloalkyls (such as 6-azabicyclo[3.2.1]octane), azaspiroalkyls (such as 1,4 dioxa-8-azaspiro[4.5]decane), imidazopyridinyl (such as imidazo[1,5-a]pyridin-3-yl), triazolopyridinyl (such as 1,2,4-triazolo[4,3-a]pyridin-3-yl), and hexahydroimidazopyridinyl (such as 1,5,6,7,8,8a-hexahydroimidazo[1,5-a]pyridin-3-yl),



~~and the like.~~

[0024] Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl ~~and the like~~.

[0025] The terms "substituted heterocycle", "substituted heterocyclic", "substituted heterocyclic group" and "substituted heterocyclo" refer to heterocycle, heterocyclic and heterocyclo groups substituted with one or more groups (such as by groups described above in the definition of R^{10}), such as selected from alkyl, substituted alkyl, alkenyl, oxo, aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo (optionally substituted), halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkanoyl (optionally substituted), aroyl (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), cyano, nitro, amido, amino, substituted amino, lactam, urea, urethane, sulfonyl, , or any subset of the foregoing, where optionally one or more pair of substituents together with the atoms to which they are bonded form a 3 to 7 member ring.

those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates~~, and the like~~.

[0029] The compounds described herein which contain an acidic moiety may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, *t*-butyl amines, and salts with amino acids such as arginine, lysine~~ and the like~~.

[0030] Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.*, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others.

[0031] The term "prodrugs" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates~~, and the like~~.

[0032] Various forms of prodrugs are well known in the art and are described in:

a) Wermuth, C.G. et al., *The Practice of Medicinal Chemistry*, Chapter 31, Academic Press (1996);

b) *Design of Prodrugs*, H. Bundgaard, ed., Elsevier (1985);

c) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs," *A Textbook of Drug Design and Development*, pp. 113-191, P. Krosgaard-Larsen et al., eds., Harwood Academic Publishers (1991); and

d) Testa, B. et al., *Hydrolysis in Drug and Prodrug Metabolism*, Wiley-VCH (2003).

[0033] In addition, compounds described herein are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% of the compound described herein ("substantially pure" compound), which is then used or formulated as described herein. Such "substantially pure" compounds described herein are also contemplated herein as part of the present invention.

[0034] To the extent that compounds described herein, and salts thereof, may exist in their tautomeric form, all such tautomeric forms are contemplated herein as part of the present invention.

[0035] All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons) and diastereomeric forms are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers.

[0036] The terms "including", "such as", "for example" ~~and the like~~ are intended to refer to exemplary embodiments and not to limit the scope of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

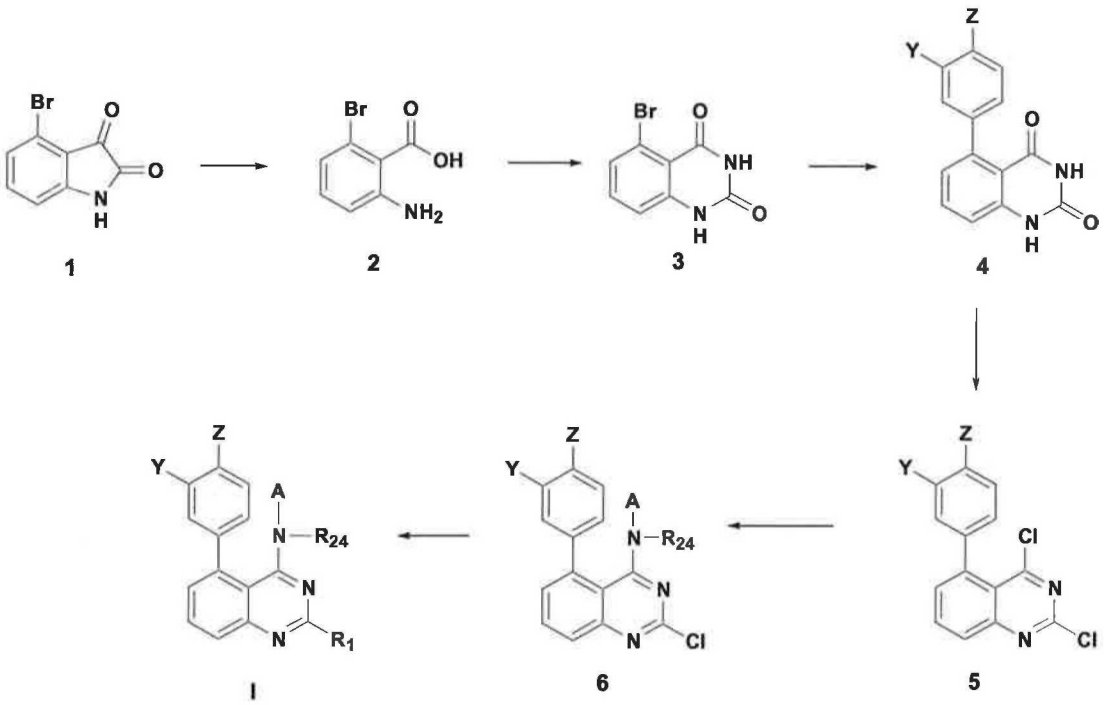
[0037] In accordance with the present invention, compounds of formula I are provided

SYNTHESIS

[0079] The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include~~, but are not limited to,~~ those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

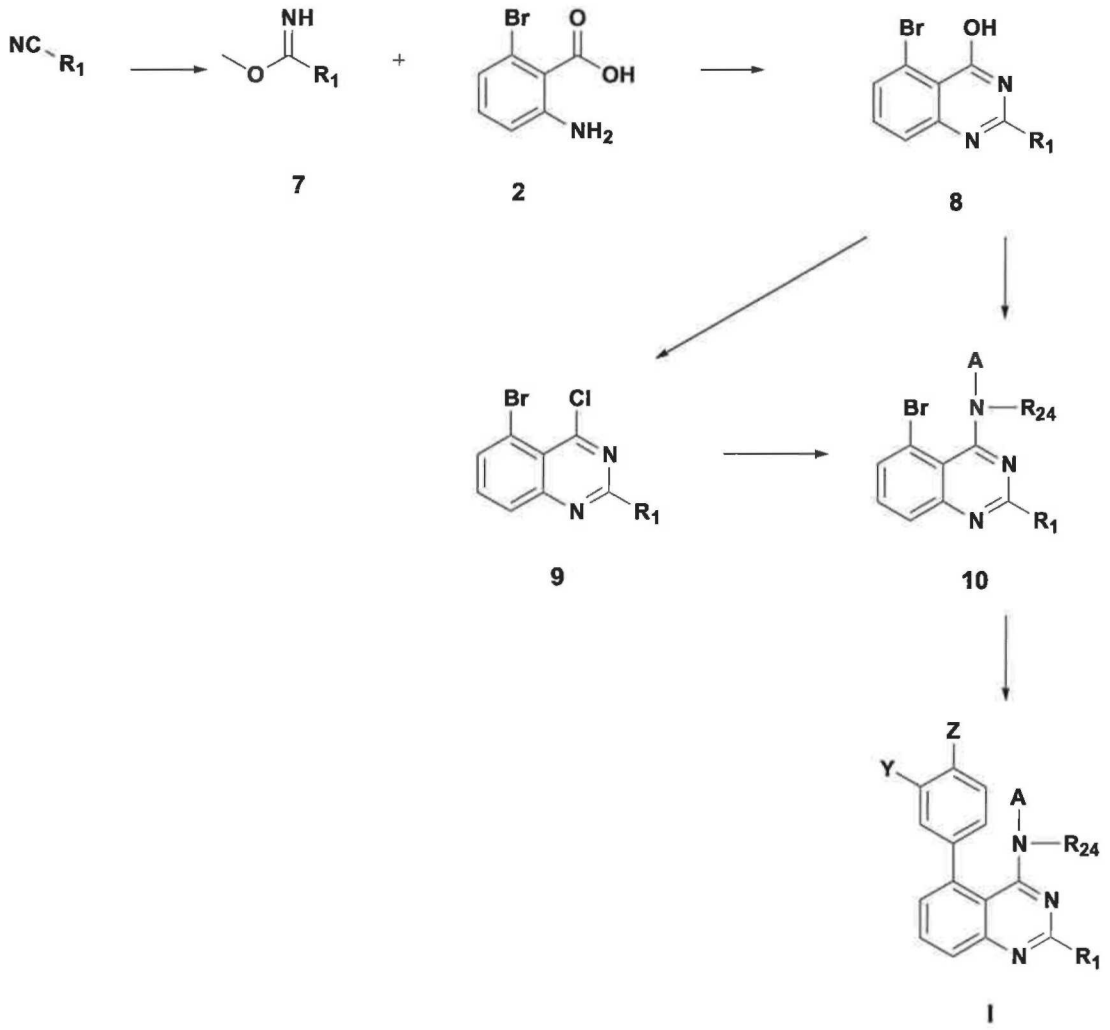
[0080] The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

[0081] The compounds of the present invention may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples. Protection and de-protection of functional groups in the processes below may be carried out by procedures generally known in the art (see, for example, Greene, T.W. et al., *Protecting Groups in Organic Synthesis*, 3rd Ed., Wiley (1999). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. et al., eds., *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*, Pergamon Press, New York, NY (1991);



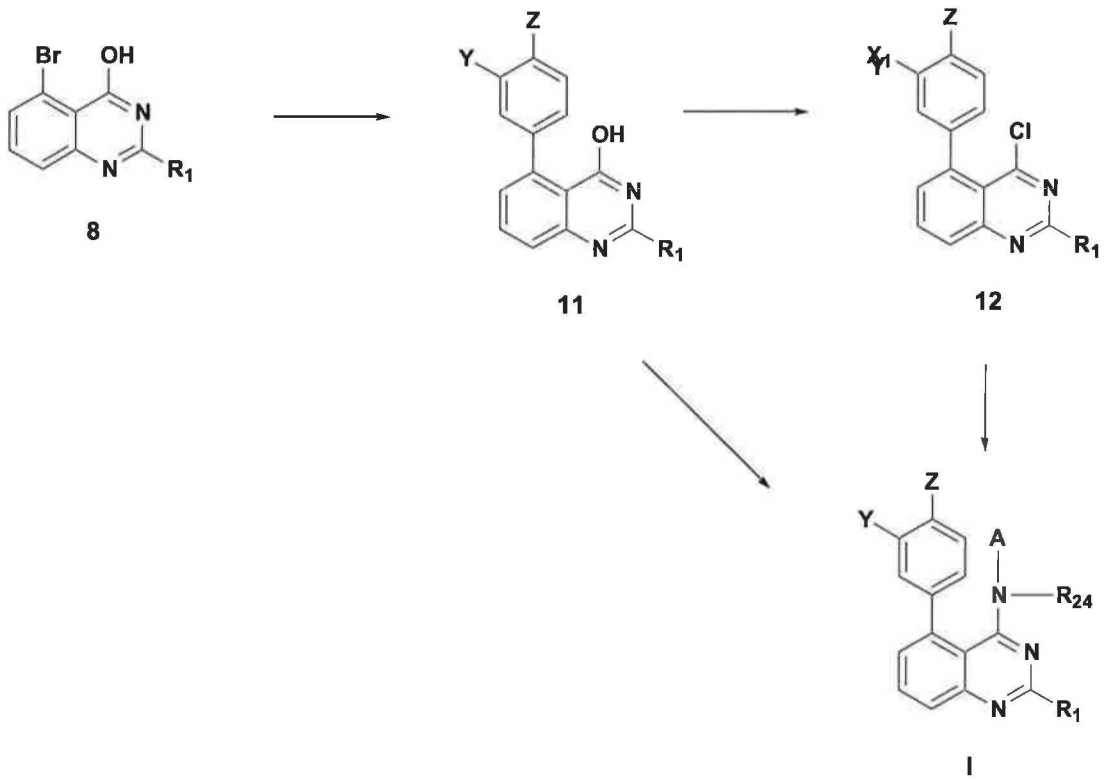
[0084] Compounds of formula I may be synthesized according to Scheme 1. Commercially available 4-bromoindoline-2,3-dione may be hydrolyzed to 2-amino-6-bromobenzamide followed by condensation with sodium isocyanate to form 5-bromoquinazoline-2,4(1H,3H)-dione. The protocols include~~, but are not limited to,~~ palladium mediated cross coupling between 5-bromoquinazoline-2,4(1H,3H)-dione and the aryl boronic acid or ester to form the intermediate 5-substituted quinazoline-2,4(1H, 3H)-dione. Conversion to the corresponding dichloro quinazoline and sequential displacement at the 4- position followed by transition metal mediated cross coupling or displacement of the C_2 chloride forms compounds I as described.

Scheme 2



[0085] Alternatively, compounds of formula I may also be synthesized according to Scheme 2. Formation of the methyl-carbimidate from the corresponding nitrile and subsequent condensation with 2-amino-6-bromobenzamide provides compounds of formula **8**. Subsequent conversion of **8** to 4-chloroquinazoline intermediate **9** and displacement of the chloride provides 5-bromoquinazoline **10.** Compounds of formula **10** may be obtained directly from **8** utilizing coupling reagents, for example ~~but not limited to~~, PyBOP in suitable solvents. The protocols include ~~but are not limited to~~ palladium mediated cross coupling between quinazoline **10** and a suitable aryl boronic acid or ester to obtain compounds of formula I.

Scheme 3



[0086] Alternatively, compounds of formula **I** may also be synthesized according to Scheme 3. Compounds of formula **8** may be subjected to cross coupling conditions, for example, ~~but not limited to~~ palladium mediated cross coupling of aryl boronic acids or esters, followed by subsequent conversion to the quinazoline intermediate **12** and displacement of the C_4 chloro group to obtain compounds of Formula **I**.

[0087] It should be recognized that the above schemes are only illustrations of some general synthetic routes to prepare compounds of the present invention. The experimental details for the synthesis of various specific examples of the present invention will be further described in the examples set forth below. Additional functional group manipulations of compounds obtained in the above schemes using methods known in the art should provide additional compounds of this invention.

EXAMPLES

[0088] The following examples are offered to illustrate, but not limit, some of the preferred embodiments of the present invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the

or salts thereof capable of preventing or treating one or more of the aforementioned disorders in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may contain other therapeutic agents as described below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors~~, etc.~~) according to techniques such as those well known in the art of pharmaceutical formulation.

[00322] The compounds of the formula I, Ia, Ib, and/or Ic, preferably compounds exemplified in the examples, more preferably, Examples 7, 22, 29, 31, 32, 38, 40, 42, 46, 50, 97, 105, 107, 108, 110, 111, 130, 134 and 137, even more preferably, Examples 7, 32, and 101, still even more preferably, Examples 7 and 101, may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (*e.g.*, as sterile injectable aqueous or non aqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non toxic, pharmaceutically acceptable vehicles or diluents. The present compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. In the case where the compounds of formula I, Ia, Ib, and/or Ic, preferably compounds exemplified in the examples, more preferably, Examples 7, 22, 29, 31, 32, 38, 40, 42, 46, 50, 97, 105, 107, 108, 110, 111, 130, 134 and 137, even more preferably, Examples 7, 32, and 101, still even more preferably, Examples 7 and 101, are being administered to prevent or treat arrhythmias, the compounds may be administered to achieve chemical conversion to normal sinus rhythm, or may optionally be used in conjunction with electrical cardioconversion.

a 4- to 12-membered heterocyclyl, wherein the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl may be optionally substituted with one or more R_{13}'s and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R_{13}, at each occurrence, is independently H, -OH, F, Cl, Br, I, C_{1-10} alkyl, C_{1-10} alkoxy, haloC_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, C_{6-10}aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C_{1-10} alkyl, -CN, $-NO_2$, $-(CH_2)_m-SO_2R_{14}$, $-NR_{14}SO_2R_{14}$, =O, $-CONR_{14}R_{14}$, $-(CH_2)_m-SO_2NR_{14}R_{14}$, $-(CH_2)_m-NR_{14}SO_2R_{14}$, $-(CH_2)_n-NR_{14}SO_2NR_{14}R_{14}$, $-NR_{14}SO_2NR_{14}R_{14}$, $-CO_2NR_{14}R_{14}$, $-NR_{14}CO_2NR_{14}R_{14}$, $-NR_{14}COR_{14}$, $-SO_2NR_{14}COR_{14}$, $-SO_2NR_{14}CONR_{14}R_{14}$, $-NR_{14}CO_2R_{14}$, $-CO_2R_{14}$, $-NR_{14}R_{14}$, $-NR_{14}CONR_{14}R_{14}$, $-C(=NOR_{14})NR_{14}R_{14}$, $-CONR_{14}OR_{14}$ or $-NCOR_{14}$, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be optionally substituted with one or more R_{14a}'s and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O; provided that when R_{13} is alkyl substituted with one R_{14a}, R_{14a} is not –OH;

R_{13a} is independently H, -OH, F, Cl, Br, I, C_{1-10} alkyl, C_{2-10} alkoxy, haloC_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-12} alkenyl, C_{6-10}aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C_{1-10} alkyl, -CN, $-(CH_2)_m-SO_2R_{14}$, $-NR_{14}SO_2R_{14}$, $-CONR_{14}R_{14}$, $-(CH_2)_m-NR_{14}SO_2R_{14}$, $-(CH_2)_n-NR_{14}SO_2NR_{14}R_{14}$, $-NR_{14}SO_2NR_{14}R_{14}$, $-CO_2NR_{14}R_{14}$, $-NR_{14}CO_2NR_{14}R_{14}$, $-NR_{14}COR_{14}$, $-SO_2NR_{14}COR_{14}$, $-SO_2NR_{14}CONR_{14}R_{14}$, $-NR_{14}CO_2R_{14}$, $-CO_2R_{14}$ or $-NR_{14}R_{14}$, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be optionally substituted with one or more R_{14a}'s and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R_{13a-2} is independently H, -OH, F, Br, I, C_{1-10} alkyl, C_{1-10} alkoxy, haloC_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-12} alkenyl, C_{6-10}aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C_{1-10} alkyl, $-(CH_2)_m-SO_2R_{14}$, $-NR_{14}SO_2R_{14}$, $-CONR_{14}R_{14}$, $-(CH_2)_m-SO_2NR_{14}R_{14}$, $-(CH_2)_m-NR_{14}SO_2R_{14}$, $-(CH_2)_n-NR_{14}SO_2NR_{14}R_{14}$, $-NR_{14}SO_2NR_{14}R_{14}$, $-CO_2NR_{14}R_{14}$, $-NR_{14}CO_2NR_{14}R_{14}$, $-NR_{14}COR_{14}$, $-SO_2NR_{14}COR_{14}$, $-SO_2NR_{14}CONR_{14}R_{14}$, $-NR_{14}CO_2R_{14}$, $-CO_2R_{14}$ or $-NR_{14}R_{14}$, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be optionally substituted with one or more R_{14a}'s and the heteroaryl and heterocyclyl consist of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, S, or O;

R_{13b} is independently H, F, Cl, Br, I, C_{1-10} alkyl, C_{1-10} alkoxy, haloC_{1-10} alkyl, C_{3-10} cycloalkyl, C_{2-12} alkenyl, C_{6-10}aryl, a 4- to 12-membered heteroaryl, a 4- to 12-membered heterocyclyl, a 4- to 12-membered heteroaryl-C_{1-10} alkyl, -CN, $-(CH_2)_m-SO_2R_{14}$, $-NR_{14}SO_2R_{14}$, $-(CH_2)_m-NR_{14}SO_2R_{14}$, $-(CH_2)_n-NR_{14}SO_2NR_{14}R_{14}$, $-NR_{14}SO_2NR_{14}R_{14}$, $-CO_2NR_{14}R_{14}$, $-CONR_{14}R_{14}$, $-NR_{14}CO_2NR_{14}R_{14}$, $-NR_{14}COR_{14}$, $-SO_2NR_{14}COR_{14}$, $-SO_2NR_{14}CONR_{14}R_{14}$, $-NR_{14}CO_2R_{14}$, $-CO_2R_{14}$, $-NR_{14}R_{14}$ or $-NR_{14}CONR_{14}R_{14}$, wherein the alkyl, cycloalkyl, alkenyl, alkoxy, aryl, heteroaryl and heterocyclyl may be optionally substituted with one or more R_{14a}'s and the heteroaryl

7. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of any of claims 1 to 6, and optionally further comprising at least one other therapeutic agent.

~~8. A compound according to any one of claims 1 to 6, or an enantiomer, diastereomer, tautomer or salt thereof, for use in therapy~~.

~~9~~8. A compound according to one of claims 1 to 6 for use in treating or preventing arrhythmia.

~~10~~9. A compound according to any one of claims 1 to 6 for use in controlling heart rate.