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- (71) Applicant (for all designated States except US): **NOVARTIS VACCINES AND DIAGNOSTICS INC.** [US/US]; 4560 Horton Street, Emeryville, CA 94662-8097 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **CROSS, Maurice, Robert** [GB/GB]; C/O NOVARTIS VACCINES AND DIAGNOSTICS INC., P.o. Box 8097, Emeryville, CA 94662-8097 (US). **TERRAR, Derek, Anthony** [US/US]; NOVARTIS VACCINES AND DIAGNOSTICS INC., P.o. Box 8097, Emeryville, CA 94662-8097 (US).
- (74) Agents: **SUH, Young, J.** et al.; NOVARTIS VACCINES AND DIAGNOSTICS INC., CORPORATE INTELLECTUAL PROPERTY R-338, P.o. Box 8097, Emeryville, CA 94662-8097 (US).
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(54) Title: AGENTS FOR THE TREATMENT OF CARDIAC ARRHYTHMIAS

(57) Abstract: The present invention provides a method of treating a subject suffering from a cardiac arrhythmia comprising contacting an effective amount of dexrazoxane or a pharmaceutically acceptable salt, analog, tautomer, or stereoisomer thereof with a cell.

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AGENTS FOR THE TREATMENT OF CARDIAC ARRHYTHMIAS

FIELD OF THE INVENTION

[0001] This invention relates to methods of treating cardiac arrhythmias while minimizing undesirable side effects, comprising administration of dexrazoxane, analogs thereof, prodrugs thereof, metabolites thereof, or therapeutic dosage forms thereof.

BACKGROUND

[0002] Dexrazoxane is known to prevent cardiomyopathy in cancer patients receiving high doses of the anthracycline agent, doxorubicin. To date, the mechanism by which dexrazoxane exerts its cardioprotective effect is not fully understood; however, it is suggested that an active metabolite, ADR-925, chelates iron accumulated in the heart from doxorubicin administration. Although safe and useful in protection against damage from doxorubicin, there has yet to have been exploration into the use of dexrazoxane as a therapeutic agent or for use in preventing/treating myocardial conditions outside of anthracycline-associated toxicities.

[0003] Approximately 50% of post-myocardial infarction (MI) fatalities are sudden cardiac deaths resulting mostly from ventricular tachycardia (VT) or ventricular fibrillation (VF). It is believed that these arrhythmias arise from mechanical dysfunction and ischemic events interacting within a disordered electrophysiologic milieu. This has prompted the active search for safe and effective treatment modalities and their ultimate evaluation in clinical trials. A variety of anti-arrhythmic drug therapies are presently available. These compounds, however, have significant limitations. Digoxin, for example, has a delayed onset of action (about 30 min) and its peak effects are not observed for 3 to 4 hours after administration. Other examples are β -blockers and calcium-channel blockers, which are widely used to treat arrhythmias, can cause hypotension and have negative inotropic effects. Currently, beta blockers (class II agents) are recommended for post-MI patients with frequent premature ventricular

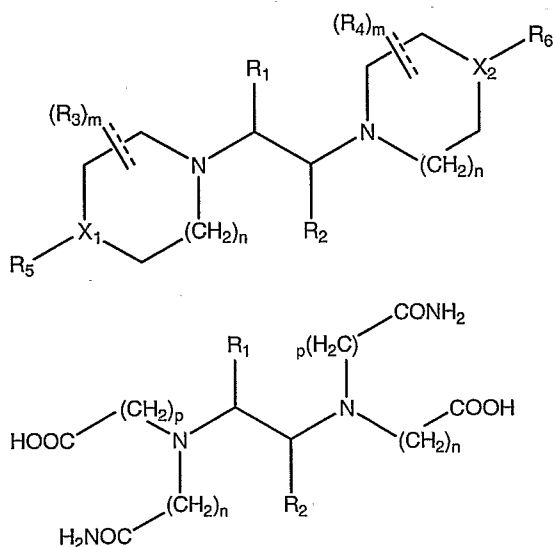
contractions (PVCs), whereas calcium antagonists (class IV agents) are not helpful, and class I agents are actually harmful. Selective adenosine A₁ receptor modulators with a significant half-life are also being considered for amelioration of arrhythmias. US Patent No. 6,537,974. The benefit of class III drugs, which affect action potential duration (APD) is presently of great interest and being evaluated further in large clinical trials. One drug in particular, amiodarone, has shown positive responses, however, toxicity and even proarrhythmic effects have limited its use.

[0004] The diversity and complexity of cardiac associated disorders, particularly arrhythmias, has called into need a number of different treatments. As such, it is an object of the present invention to provide a safe and effective treatment for patients suffering from cardiac arrhythmias.

SUMMARY

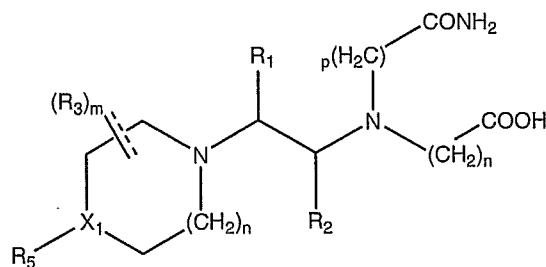
[0005] It is an object of this invention to provide an effective method of treating cardiac arrhythmias in a subject while minimizing undesirable side effects. Accordingly, in a first aspect, the invention relates to a method of treating cardiac arrhythmias in a mammal comprising administration of a therapeutically effective dose of dexrazoxane, and novel derivatives of dexrazoxane and their prodrugs.

[0006] In one embodiment, the invention provides a method of treating a subject suffering from a cardiac arrhythmia comprising administering a compound of Formula (IA), (IB), (IC), or a pharmaceutically acceptable salt, tautomer, stereoisomer, or prodrug thereof:



IA

IB



IC

wherein,

X_1 and X_2 are independently selected from CH, N, S, or O;

each R_1 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl; each R_2 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl; or R_1 and R_2 are taken together to form a 3-7 membered substituted or unsubstituted carbocyclyl or heterocyclyl group;

each R_3 and R_4 group is independently selected from =O, =S, =NH; H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl, wherein the dotted line represents the optional placement of a double bond;

R_5 and R_6 are independently selected from H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{1-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl, with the proviso that if X_1 is O or S, R_5 is absent, or if X_2 is O or S, R_6 is absent;

each m is independently 1, 2, or 3;

each n is independently 0, 1, or 2; and

each p is independently 0, 1, or 2;

wherein the cardiac arrhythmia is treated in the subject after administration of the compound of Formula (IA), (IB), (IC), or a pharmaceutically acceptable salt, tautomer, stereoisomer, or prodrug thereof.

[0007] In a more particular embodiment, the compound has the Formula (IA). In a more particular embodiment, R₅ and R₆ are both H.

[0008] In a more particular embodiment, X₁ and X₂ are N and each n is 1.

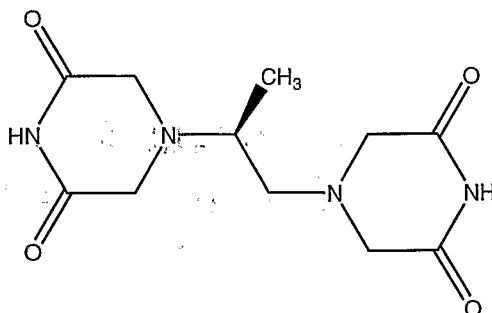
In a more particular embodiment, R₃ and R₄ are both =O, m is 2, and n is 1. In another embodiment, each of R₃ and R₄ are appended to the adjacent (alpha) carbon to X₁ and X₂.

[0009] In a more particular embodiment, R₁ is unsubstituted C₁₋₆ alkyl and R₂ is H.

[0010] In a more particular embodiment, the compound has the Formula (IC), R₂ is unsubstituted C₁₋₆ alkyl and R₁ is H.

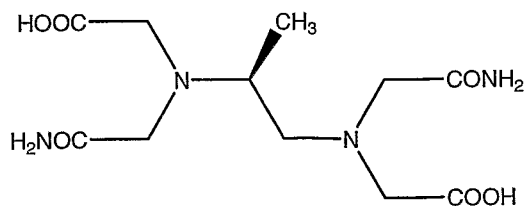
[0011] In another embodiment, the compound has the Formula (IB) or (IC) and each n and p is 1.

[0012] In another embodiment, the compound is:

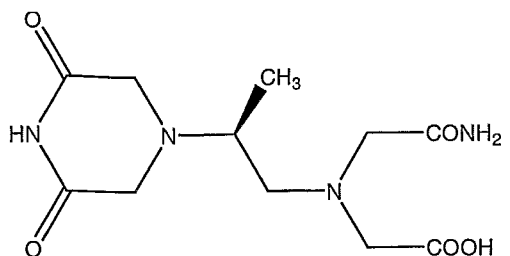


or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

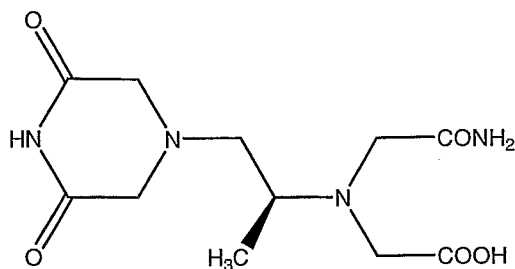
[0013] In another embodiment, the compound is:



[0014] In another embodiment, the compound is:

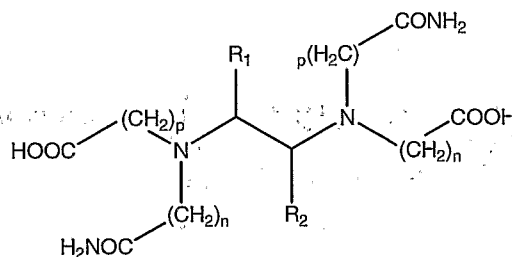


[0015] In another embodiment, the compound is:



[0016] In another embodiment, the prodrug of Formula (IA), (IB) or (IC) is administered to the subject.

[0017] Another embodiment of the invention provides a method of treating a subject suffering from a cardiac arrhythmia comprising administering a prodrug of a compound of Formula (IB):



IB

wherein,

X_1 and X_2 are independently selected from CH, N, S, or O;

each R_1 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl,

substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl;

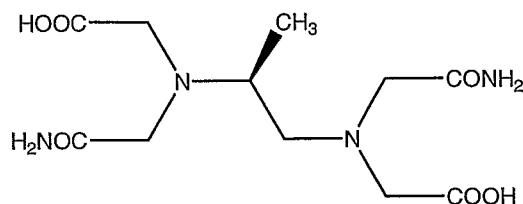
each R_2 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl,

substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl,

substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl; or

R_1 and R_2 are taken together to form a 3-7 membered substituted or unsubstituted carbocyclyl or heterocyclyl group;
 each n is independently 0, 1, or 2; and
 each p is independently 0, 1, or 2;
 wherein the cardiac arrhythmia is treated in the subject after contacting the compound of Formula (IB) with a cell and/or tissue in the subject.

[0018] In a more particular embodiment, the compound of Formula IB is:



[0019] In another more particular embodiment, the prodrug has the Formula (IA) or (IC).

[0020] In another embodiment, the prodrug that is administered to the subject is a compound listed in Table 1.

[0021] In another embodiment, the myocardial action potential duration (APD) decreases in the subject.

[0022] In another embodiment, the QT interval is maintained or decreased in the subject.

[0023] In another embodiment, the compound or a pharmaceutically acceptable salt, tautomer, stereoisomer, or prodrug thereof, does not decrease contractility in the subject.

[0024] In another embodiment, the compound is not co-administered nor used in conjunction with an anthracycline compound.

[0025] In another embodiment, the compound is not co-administered nor used in conjunction with doxorubicin.

[0026] In another embodiment, the subject has minimal myelosuppression after administration of the compound, tautomer, stereoisomer or prodrug thereof.

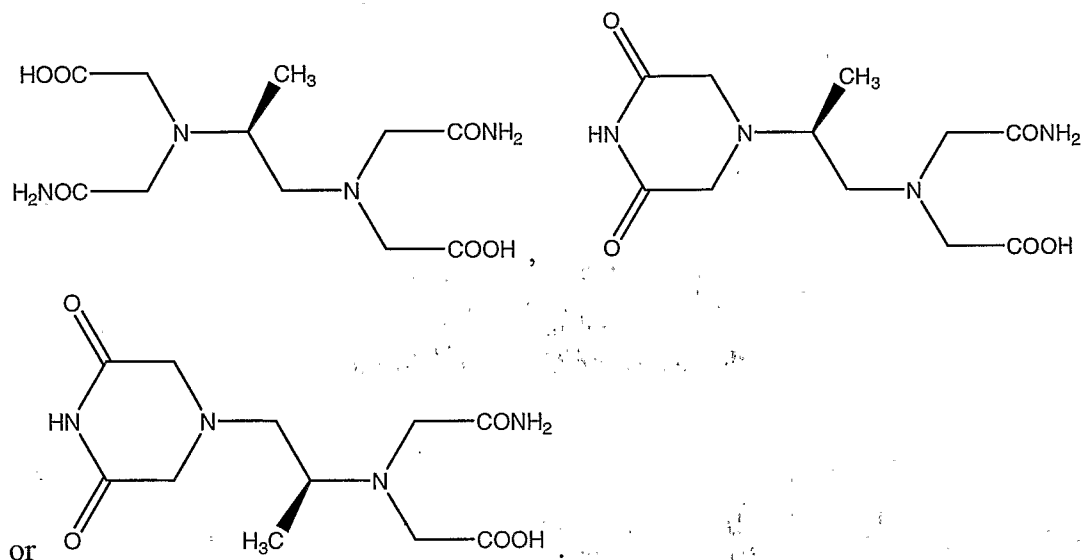
[0027] In another embodiment, the cardiac arrhythmia is a ventricular or supraventricular arrhythmia.

[0028] In another embodiment, the cardiac arrhythmia is a ventricular tachyarrhythmia.

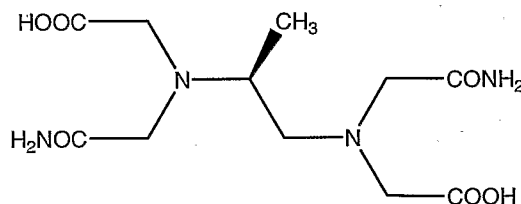
[0029] In another embodiment, the cardiac arrhythmia is re-entrant tachyarrhythmia.

[0030] In another embodiment, the subject is suffering from congestive heart failure (CHF).

[0031] In another embodiment, the compound is administered after an ischemic insult. In another embodiment, the compound contacts a cell or tissue in the subject's heart. In a more particular embodiment, the compound of Formula (IA) is administered to the subject and a compound of Formula (IB) or (IC) contacts the cell or tissue in the subject's heart. In an even more particular embodiment, the compound that contacts the cell is:

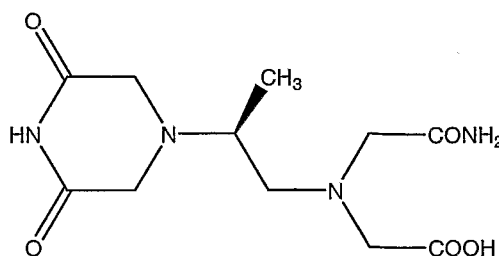


[0032] Another embodiment provides, a pharmaceutical composition, comprising:



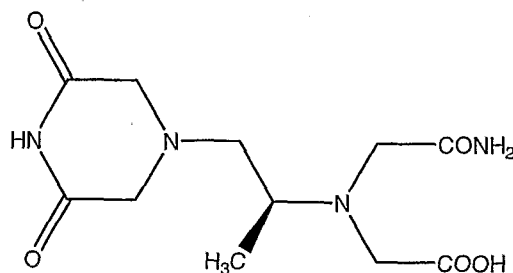
the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0033] Another embodiment provides, a pharmaceutical composition, comprising:



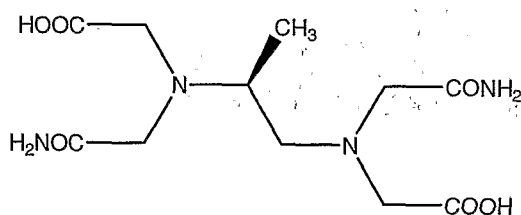
the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0034] Another embodiment provides, a pharmaceutical composition, comprising:



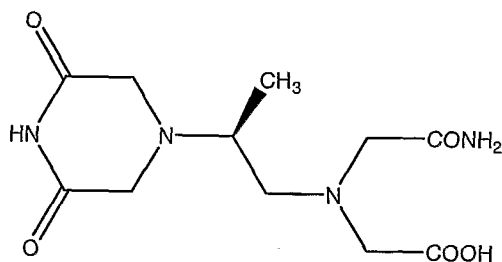
the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

[0035] Another embodiment provides, a compound, comprising:



the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and further, wherein the compound is isolated, the pharmaceutically acceptable salt of the compound is isolated, or the pharmaceutically acceptable salt of the tautomer is isolated.

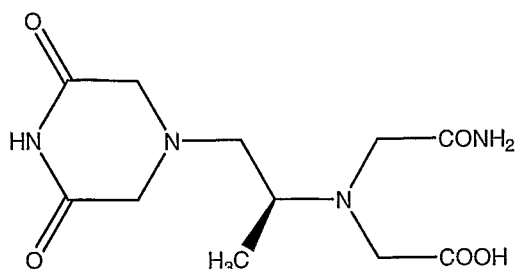
[0036] Another embodiment provides, a compound, comprising:



the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and further, wherein the compound is isolated, the pharmaceutically acceptable salt of the

compound is isolated, or the pharmaceutically acceptable salt of the tautomer is isolated.

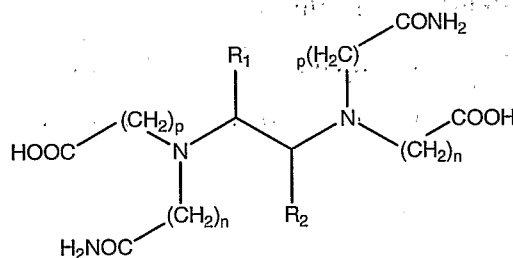
[0037] Another embodiment provides, a compound, comprising:



the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and further, wherein the compound is isolated, the pharmaceutically acceptable salt of the compound is isolated, or the pharmaceutically acceptable salt of the tautomer is isolated.

[0038] Another embodiment provides, a method of treating a subject suffering from cardiac arrhythmia comprising: administering to the subject an effective amount of the compound or pharmaceutical composition of any one of preceding compounds.

[0039] Another embodiment provides, a prodrug of a compound of Formula (IB):



IB

wherein,

X_1 and X_2 are independently selected from CH, N, S, or O;

each R_1 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl; each R_2 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl,

substituted or unsubstituted C₁₋₆ alkoxy, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₆₋₁₀ aryl, or substituted or unsubstituted heterocyclyl; or R₁ and R₂ are taken together to form a 3-7 membered substituted or unsubstituted carbocyclyl or heterocyclyl group;

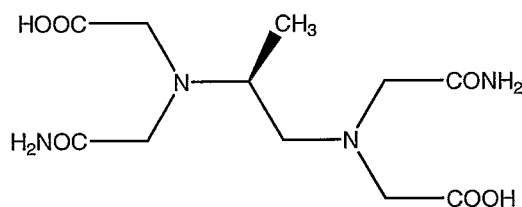
each n is independently 0, 1, or 2; and

each p is independently 0, 1, or 2;

wherein the cardiac arrhythmia is treated in the subject after contacting the compound of Formula (IB) with a cell and/or tissue in the subject;

wherein the prodrug is not dexrazoxane.

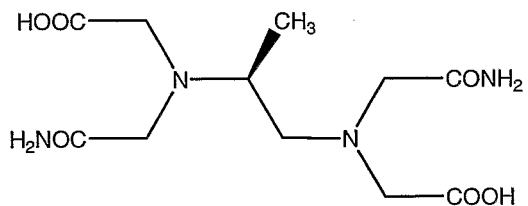
[0040] In a more particular embodiment thereof, the compound is:



[0041] Another embodiment provides, a method of preventing or treating cardiomyopathy comprising: administering to the subject an effective amount of any one of the preceding compounds or a prodrug of any one of the preceding compounds. In a more particular embodiment, the cardiomyopathy is from administration of an anticancer agent, particularly anthracycline, more particularly doxorubicin.

[0042] In another embodiment, the prodrug is listed in Table 1, excluding Example 1.

[0043] Another embodiment of the invention provides a composition comprising human serum from a patient suffering from a cardiac arrhythmia and a compound having the following structure:



[0044] The present invention also encompasses pharmaceutical compositions of each of the compounds described herein.

[0045] The compositions of the present invention may be administered or used in conjunction with an adjuvant.

[0046] Methods of manufacturing the compositions described herein are provided and contemplated to fall within the scope of the invention, as is the use of the compositions in methods for manufacturing medicaments for use in the methods of the invention.

[0047] Further embodiments of the invention include those described in the detailed description.

DESCRIPTION OF THE FIGURES

[0048] **Figure 1.** Effects of Dexrazoxane on developed tension in guinea pig whole hearts.

[0049] **Figure 2.** Effects of Dexrazoxane on unloaded cell shortening in single ventricular myocytes.

[0050] **Figure 3.** Mean data showing the effect of dexrazoxane (10 μ M) on action potential duration (APD₉₀) is shown. The data shows that perfusion with dexrazoxane (27 minutes) caused an 18 ± 3 % shortening of APD₉₀ from 212 ± 9 ms to 168 ± 12 ms ($n=4$, $P<0.005$).

[0051] **Figure 4.** The addition of dexrazoxane to the superfusion solution caused an 18 ± 4 % a decrease in APD₄₀ from 175 ± 8 ms to 136 ± 15 ms ($n=3$, $P<0.005$).

[0052] **Figure 5.** Superfusion of dexrazoxane did not significantly alter the APD₉₀₋₄₀ duration which is taken as an index of triangulation. Accordingly, time control data show that under control condition there was no change in either APD₉₀ (Figure 3), APD₄₀ (Figure 4), or in APD₉₀₋₄₀ (Figure 5).

[0053] **Figure 6.** Mean data for the peak amplitude of action potential driven unloaded cell shortening (UCS) measured in single ventricular myocytes is shown. Application of dexrazoxane (10 μ M, 27 minutes) did not significantly alter the amplitude of UCS expressed as absolute cell shortening (control, 9.4 ± 3.4 μ m; dexrazoxane 10.7 ± 3.2 μ m, $n=3$, $P=ns$; the left panel of Figure 6 shows contraction in μ m while the right panel shows percentage change from control).

[0054] **Figure 7.** Similar findings to Figure 6 were made when shortening was expressed as percentage of resting cell length as in Figure 7 (control, 8.5 ± 2.7 % RCL; dexrazoxane 8.0 ± 2.0 % RCL, $n=3$, $P=ns$; the left panel of Figure 7 shows shortening as percentage of cell length while the right panel shows percentage change from control).

[0055] **Figure 8.** Effects of Dexrazoxane on APD₉₀ in single ventricular myocytes. Figure 8 shows typical action potential records taken from a single ventricular

myocytes under control conditions and in the presence of dexrazoxane ($10\mu\text{M}$) superfused for 10 minutes, 20 minutes and 30 minutes. Dexrazoxane (under these conditions) shortened action potential duration.

[0056] **Figure 9.** Effects of Dexrazoxane on APD_{90} and QT interval.

[0057] **Figure 10.** Effects of Dexrazoxane on heart rate variability in stable Langendorff heart preparations

[0058] **Figure 11.** Effects of Dexrazoxane on heart rate variability in unstable Langendorff heart preparations

[0059] **Figure 12.** Effects of total flow occlusion on heart rate variability in stable Langendorff heart preparations. In the presence of dexrazoxane ($10\mu\text{M}$, 30 min) the coefficient of variation was increased by only 77% during reperfusion following a 15 min period of total flow ischemia (from control, 2.9 ± 0.2 to reperfusion 3.3 ± 1.1 $n=3$, $P=\text{ns}$).

[0060] **Figure 13.** (a) Metabolites formed from dexrazoxane (**B**, **C**, and ADR-925); (b) catalyzed by dihydroorotase (DHOase); (c) which is inhibited by furosemide.

DETAILED DESCRIPTION

[0061] The present invention provides compositions with equivalent efficacy and desired pharmacological properties of amiodarone, yet without the associated toxicities and without decreased contractility.

[0062] The successful application of dexrazoxane or a pharmaceutically acceptable salt, derivative, tautomer, stereoisomer, or metabolite thereof to the treatment of cardiac arrhythmias is evidenced by the evaluation of the thermodynamic properties of the compound, e.g., measuring its partition coefficient between water and octanol, evaluation of its kinetics of elimination by measuring its stability in buffer and in human plasma, and evaluation of its safety and physiological properties in humans and animal preparations. More specifically, dexrazoxane can be used for treating life-threatening ventricular tachyarrhythmias, especially in patients with congestive heart failure. This product can provide effective management of not only ventricular tachyarrhythmias and less severe ventricular arrhythmias, but also atrial fibrillation and re-entrant tachyarrhythmias involving accessory pathways. Compositions comprising dexrazoxane have many advantages over the currently available antiarrhythmic agents such as amiodarone. These advantages include: proven safety profiles, rapid onset of action, increased

efficacy, decreased toxicities, new dosing regimens permitting long term exposure and greater propensity for adherence, lower potential for drug interactions, and simultaneous reduction in potential metal ion/topoisomerase associated toxicities.

[0063] The subject compounds have properties similar to those of amiodarone, but provide further advantages. More specifically, the subject compounds are Class III agents with efficacy comparable or surpassing amiodarone, having a structure such that the drug can be readily metabolized to a polar, water-soluble composition which can be eliminated by the kidneys. This is a definite advantage over amiodarone, which has a fairly arduous elimination process. This increased elimination and decreased toxicity makes antiarrhythmic therapy using dexrazoxane or compositions comprising the subject compounds easier to manage.

[0064] In addition, the novel compounds can be included in a composition comprising a second active ingredient. The second active ingredient can be useful for concurrent or synergistic treatment of arrhythmia or for the treatment of an unrelated condition which can be present with or result from arrhythmia or other cardiomyopathy. These compounds, and compositions thereof, may include additional compounds known to be useful for the treatment of cardiac arrhythmias, cardioprotective agents, antibiotics, antiviral agents, or thrombolytic agents (e.g., streptokinase, tissue plasminogen activator, or recombinant tissue plasminogen activator). The compounds and compositions of the invention can have particular usefulness for treating life-threatening ventricular tachyarrhythmias, especially in patients with congestive heart failure (CHF). Post-myocardial infarction patients can also benefit from the administration of the subject compounds and compositions; thus, methods of treating post-myocardial infarction patients are also provided by the subject invention.

[0065] Cardioprotective agents include vasodilators and beta blockers described for use in patients with coronary insufficiency (such as those of U.S. Pat. No. 5,175,187 or others known to the skilled artisan). Other cardioprotective agents include known anti-hypertensive agents, e.g., (S)- 1-[6-amino-2-[[hydroxy(4-phenylbutyl)phosphinyl]oxyl]-L-proline (U.S. Pat. No. 4,962,095) and zofenopril (U.S. Pat. No. 4,931,464). Additional cardioprotective agents include, but are not limited to, aspirin, heparin, warfalin, digitalis, digitoxin, nitroglycerin, isosorbide dinitrate, hydralazine, nitroprusside, captopril, enalapril, and lisinopril.

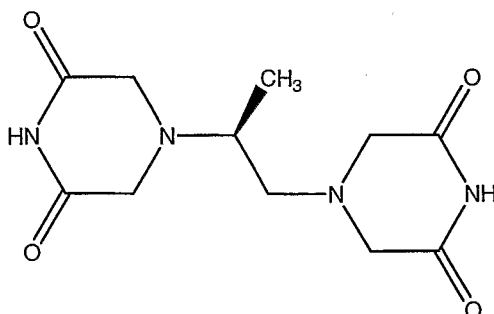
- [0066] The compounds and compositions also provide effective management for ventricular arrhythmias and supraventricular arrhythmias, including atrial fibrillation and re-entrant tachyarrhythmias involving accessory pathways. Compounds and compositions of the invention are also useful for the treatment of ventricular and supra-ventricular arrhythmias, including atrial fibrillation and flutter, paroxysmal supraventricular tachycardia, ventricular premature beats (VPB), sustained and non-sustained ventricular tachycardia (VT), and ventricular fibrillation (VF). Other non-limiting examples of the arrhythmias which may be treated by the compounds of the instant invention include: narrow QRS tachycardia (atrial, intra- /para- A-V node, or accessory pathway), ventricular tachycardia, and ventricular arrhythmias in cardiomyopathy.
- [0067] The term "effective amount" is an amount necessary or sufficient to realize a desired biological effect. For example, an effective amount of a compound to treat cardiac arrhythmias may be an amount necessary to resume a regular heart beat, or to positively affect a mechanism associated with irregularity, such as sodium channel blockage, beta blocking or modulating adrenergic receptors, APD modulating, decreasing QT intervals, or calcium channel antagonism. The effective amount may vary, depending, for example, upon the arrhythmic condition treated, weight of the subject and severity of the disease. One of skill in the art can readily determine the effective amount empirically without undue experimentation.
- [0068] A "subject" or "patient" is meant to describe a human or vertebrate animal including a dog, cat, pocket pet, marmoset, horse, cow, pig, sheep, goat, elephant, giraffe, chicken, monkey, owl, rat, squirrel, slender loris, and mouse.
- [0069] The compounds of the present invention can be used in the form of salts as in "pharmaceutically acceptable salts" derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, phosphate, sulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate,

p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

[0070] The term "metabolite" refers to a compound that is rapidly transformed *in vivo* from the parent compound, for example by hydrolysis in blood.

[0071] Conversely, the term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987. Prodrugs as described in U.S. Patent No. 6,284,772 for example may be used as well as those described in Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology, Bernard Testa et al., 2003 and The Organic Chemistry of Drug Design and Drug Action [Chapter 8], Richard Silverman, 2004. Additional prodrugs are described herein, particularly in the Examples section, such as Table 1.

[0072] Reference to "dexrazoxane" indicates a compound of the following structure:



or chemical name: (S)-4,4'-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione. The racemate and R-enantiomer, namely (R)-4,4'-(1-methyl-1,2-ethanediyl)bis-2,6-piperazinedione are also contemplated to fall within the scope of the present invention. Dexrazoxane is also referred to as ICRF-187 and has associated Trade Names: Cardioxane®, Zinecard®, and Eucardion®.

[0073] Reference to “halo,” “halide,” or “halogen” refers to F, Cl, Br, or I atoms, especially F, Cl, and Br.

[0074] The phrase “alkyl” refers to substituted and unsubstituted alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase “C₁₋₆ alkyl” has the same meaning as alkyl, except that it is limited to alkyl groups of six carbons or less. The phrase C₁₋₆ alkyl also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: -CH(CH₃)₂, -CH(CH₃)(CH₂CH₃), -CH(CH₂CH₃)₂, -C(CH₃)₃, -CH₂CH(CH₃)₂, -CH₂CH(CH₃)(CH₂CH₃), -CH₂CH(CH₂CH₃)₂, -CH₂C(CH₃)₃, -CH(CH₃)CH(CH₃)(CH₂CH₃), -CH₂CH₂CH(CH₃)₂, -CH₂CH₂CH(CH₃)(CH₂CH₃), -CH₂CH₂C(CH₃)₃, -CH(CH₃)CH₂CH(CH₃)₂, -CH(CH₃)CH(CH₃)CH(CH₃), and others. The phrase C₁₋₆ alkyl further includes cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and such rings substituted with straight and branched chain alkyl groups as defined above. The phrase alkyl also includes polycyclic alkyl groups such as, but not limited to, adamantyl norbornyl, and bicyclo[2.2.2]octyl and such rings substituted with straight and branched chain alkyl groups as defined above.

[0075] The phrase “aryl” refers to substituted and unsubstituted aryl groups that do not contain heteroatoms. The phrase “C₆₋₁₀ aryl” has the same meaning as aryl, except that it is limited to aryl groups of six to ten carbons atoms. The phrase aryl includes, but is not limited to, groups such as phenyl, biphenyl, and naphthyl by way of example. Aryl groups also include those in which one of the aromatic carbons is bonded to an alkyl, alkenyl, or alkynyl group as defined herein. This includes bonding arrangements in which two carbon atoms of an aryl group are bonded to two atoms of an alkyl, alkenyl, or alkynyl group to define a fused ring system (e.g. dihydronaphthyl or tetrahydronaphthyl). Thus, the phrase “aryl” includes, but is not limited to tolyl, and hydroxyphenyl among others.

[0076] The phrase “alkenyl” refers to straight chain, branched chain, and cyclic groups such as those described with respect to alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. The phrase “C₂₋₆ alkenyl” has the same meaning as alkenyl, except that it is limited to alkenyl groups of two to six carbons. Examples include, but are not limited to, vinyl, -CH=C(H)(CH₃), -CH=C(CH₃)₂, -C(CH₃)=C(H)₂, -C(CH₃)=C(H)(CH₃),

-C(CH₂CH₃)=CH₂, cyclohexenyl, cyclopentenyl, cyclohexadienyl, butadienyl, pentadienyl, hexadienyl, and the like. The phrase "C₁₋₆ alkenyl" indicates that the double bond may be the point of attachment of the alkenyl group.

[0077] The phrase "alkynyl" refers to straight and branched chain groups such as those described with respect to alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. The phrase "C₂₋₆ alkynyl" has the same meaning as alkynyl, except that it is limited to alkynyl groups of two to six carbons. Examples include, but are not limited to, -C≡C(H), -C≡C(CH₃), -C≡C(CH₂CH₃), -C(H)₂C≡C(H), -C(H)₂C≡C(CH₃), -C(H)₂C≡C(CH₂CH₃), and the like.

[0078] The phrase "alkoxy" refers to groups having the formula -O-alkyl, wherein the point of attachment is the oxy group and the alkyl group is as defined above. The phrase "C₁₋₆ alkoxy" has the same meaning as alkoxy, except that it is limited to alkoxy groups having from one to six carbon atoms.

[0079] The phrase "aryloxy" refers to groups having the formula -O-aryl, wherein the point of attachment is the oxy group and the aryl group is as defined above. The phrase "C₆₋₁₀ aryloxy" has the same meaning as aryloxy, except that it is limited to aryloxy groups of six to ten carbon atoms.

[0080] The phrase "heterocyclyl" refers to both aromatic and nonaromatic ring compounds including monocyclic, bicyclic, and polycyclic ring compounds such as, but not limited to, quinuclidyl, containing 3 or more ring members of which one or more is a heteroatom such as, but not limited to, N, O, and S. Examples of heterocyclyl groups include, but are not limited to: unsaturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl etc.), tetrazolyl, (e.g. 1H-tetrazolyl, 2H tetrazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 4 nitrogen atoms such as, but not limited to, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl; condensed unsaturated heterocyclic groups containing 1 to 4 nitrogen atoms such as, but not limited to, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl; unsaturated 3 to 8 membered rings containing 1 to 2 oxygen atoms such as, but not limited to furanyl; unsaturated 3 to 8 membered

rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms such as, but not limited to, morpholinyl; unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, benzoxazolyl, benzoxadiazolyl, benzoxazinyl (e.g. 2H-1,4-benzoxazinyl etc.); unsaturated 3 to 8 membered rings containing 1 to 3 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.); saturated 3 to 8 membered rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, thiazolodinyll; saturated and unsaturated 3 to 8 membered rings containing 1 to 2 sulfur atoms such as, but not limited to, thienyl, dihydrodithiinyll, dihydrodithionyl, tetrahydrothiophene, tetrahydrothiopyran; unsaturated condensed heterocyclic rings containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms such as, but not limited to, benzothiazolyl, benzothiadiazolyl, benzothiazinyl (e.g. 2H-1,4-benzothiazinyl, etc.), dihydrobenzothiazinyl (e.g. 2H-3,4-dihydrobenzothiazinyl, etc.), unsaturated condensed heterocyclic rings containing 1 to 2 oxygen atoms such as benzodioxolyl (e.g. 1,3-benzodioxoyl, etc.); unsaturated 3 to 8 membered rings containing an oxygen atom and 1 to 2 sulfur atoms such as, but not limited to, dihydrooxathiinyll; saturated 3 to 8 membered rings containing 1 to 2 oxygen atoms and 1 to 2 sulfur atoms such as 1,4-oxathiane; unsaturated condensed rings containing 1 to 2 sulfur atoms such as benzothiényll, benzodithiinyll; and unsaturated condensed heterocyclic rings containing an oxygen atom and 1 to 2 oxygen atoms such as benzoxathiinyll.

Heterocyclyl group also include those described above in which one or more S atoms in the ring is double-bonded to one or two oxygen atoms (sulfoxides and sulfones). For example, heterocyclyl groups include tetrahydrothiophene, tetrahydrothiophene oxide, and tetrahydrothiophene 1,1-dioxide. Preferred heterocyclyl groups contain 5 or 6 ring members. More preferred heterocyclyl groups include morpholine, piperazine, piperidine, pyrrolidine, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, thiomorpholine, thiomorpholine in which the S atom of the thiomorpholine is bonded to one or more O atoms, pyrrole, homopiperazine, oxazolidin-2-one, pyrrolidin-2-one, oxazole,

quinuclidine, thiazole, isoxazole, furan, and tetrahydrofuran. "Heterocyclyl" also refers to those groups as defined above in which one of the ring members is bonded to a non-hydrogen atom such as described above with respect to substituted alkyl groups and substituted aryl groups. Examples, include, but are not limited to, 2-methylbenzimidazolyl, 5-methylbenzimidazolyl, 5-chlorobenzthiazolyl, 1-methyl piperazinyl, and 2-chloropyridyl among others. Heterocyclyl groups are those limited to having 2 to 15 carbon atoms and as many as 6 additional heteroatoms as described above. More preferred heterocyclyl groups have from 3 to 5 carbon atoms and as many as 2 heteroatoms. Most preferred heterocyclyl groups include piperidinyl, pyrrolidinyl, azetidiny, and aziridinyl groups.

[0081] The term "substituted" refers to the replacement of one or more hydrogen atom with a monovalent or divalent radical. Suitable substitution groups include, for example, hydroxyl, nitro, amino, imino, cyano, halo, thio, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, alkyl, heterocyclyl, aryl, haloalkyl, alkoxy, alkoxyalkyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkylthio, aminoalkyl, alkylamino, cyanoalkyl, and the like. For example, one preferred "substituted C₁₋₆ alkyl" is tertbutanol. Another preferred substituted C₁₋₆ alkyl is $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{NH}-\text{SO}_2\text{CH}_3$.

[0082] The substitution group can itself be substituted one time. For example, an alkoxy substituent of an alkyl group may be substituted with a halogen, and oxo group, an aryl group, or the like. The group substituted onto the substitution group can be carboxyl, halo, nitro, oxo, amino, cyano, hydroxyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₆₋₁₀ aryl, aminocarbonyl, -SR, thioamido, -SO₃H, -SO₂R or cycloalkyl, where R is typically hydrogen, hydroxyl or C₁₋₆ alkyl.

[0083] When the substituted substituent includes a straight chain group, the substitution can occur either within the chain (e.g., 2-hydroxypropyl, 2-aminobutyl, and the like) or at the chain terminus (e.g., 2-hydroxyethyl, 3-cyanopropyl, and the like). Substituted substituents can be straight chain, branched or cyclic arrangements of covalently bonded carbon atoms or heteroatoms.

[0084] Dexrazoxane, metabolites, prodrugs, or derivatives thereof of formula I may exhibit the phenomenon of tautomerism, and the formula drawings within this specification can represent only one of the possible tautomeric forms. It is to be

understood that the invention encompasses any tautomeric form which possesses antiarrhythmic activity and is not to be limited merely to any one tautomeric form utilized within the formula drawings.

[0085] Dexrazoxane, metabolites, prodrugs, or derivatives thereof of formula I also may exist in solvated as well as unsolvated forms such as, for example, hydrated forms. The invention encompasses both solvated and unsolvated forms which possess activity.

[0086] The compounds of this invention can be administered as the sole active ingredient or in combination with other antiarrhythmic agents or other cardiovascular agents. The compounds, or pharmaceutically acceptable salts thereof, of the present invention, in the described dosages, are administered orally, intraperitoneally, subcutaneously, intramuscularly, transdermally, sublingually or intravenously. They are preferably administered intravenously, for example reconstituted in an aqueous solution. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained.

[0087] Commercially, dexrazoxane is currently formulated as a lyophilized acid salt of hydrochloride acid. The acid salt is unstable in aqueous solution and so is lyophilized for stability. To manufacture the commercial product, dexrazoxane is dissolved in 0.1 M HCl at a concentration of 20 mg/ml and placed into vials. The vials are partially stoppered and loaded on the shelves of a lyophilization chamber. Compounding and vial-filling processes are carried out at ambient temperature. The solutions are frozen and the chamber evacuated until lyophilization is complete.

[0088] Typically, the solution occupies less than the full vial volume to optimize lyophilization time and to allow for expansion of the solution upon freezing. The vials are then supplied to clinics in 250 mg or 500 mg doses. When needed, dexrazoxane is reconstituted in the clinic. A current recommended dose is 2g for an adult human. Thus, preparing a dose for injection previously required pooling four 500 mg doses.

[0089] Dexrazoxane is subject to decomposition in aqueous solutions. Because of this, the time span from compounding to beginning of freezing in the lyophilizer must not exceed 7 hours without significant decomposition. Lyophilized dexrazoxane is stable for extended periods of time, on the order of 12 months

without significant decomposition. Reconstituted dexrazoxane is stable for about 6 hours at room temperature.

[0090] The solubility of dexrazoxane in water at 25°C is about 10 mg/ml water. Dexrazoxane (ICRF-187) and its racemate, razoxane (ICRF-159) are sparingly soluble in 0.1 N HCl, slightly soluble in polar solvents such as ethanol and methanol and practically insoluble in non-polar, organic solvents [Repta, Baltezor and Bansal, J. Pharm Sci. 65 (1976) 238-242]. Generally speaking, the solubility of dexrazoxane increases as pH decreases. Formulating dexrazoxane as a salt of hydrochloric acid improves its solubility. Solubility of hydrochloric acid as high as 35 mg/ml in 0.1 N HCl at 25 °C has been reported (U.S. Patent No. 4,963,551), though therapeutic concentrations around 20-25 mg/ml are preferred (see U.S. Patent No. 5,760,039, hereby incorporated by reference). A 20 mg/ml solution is known to be used commercially. The concentration of dexrazoxane in the bulk solutions may also be quantified in terms of dexrazoxane molarity. A 35 mg/ml solution of dexrazoxane in 0.01 N HCl is a 0.13 M dexrazoxane (the molecular weight of dexrazoxane being 268.28 g/mol).

[0091] Therapeutic and prophylactic application of the subject compounds, and compositions comprising them, can be accomplished by any suitable method and technique presently or prospectively known to those skilled in the art. Further, the compounds of the invention have use as starting materials or intermediates for the preparation of other useful compounds and compositions. The compounds of the invention are useful for various non-therapeutic and therapeutic purposes. It is apparent from the testing that the compounds of the invention have effective antiarrhythmic activity. Specifically, they are useful in regulating cardiac arrhythmia, including atrial fibrillation, in animals and humans.

[0092] The administration of the subject compounds of the invention is useful as an antiarrhythmic agent. Thus, pharmaceutical compositions containing compounds of the invention as active ingredients are useful in prophylactic or therapeutic treatment of cardiac arrhythmias in humans or other mammals.

[0093] The dosage administered will be dependent upon the response desired; the type of host involved; its age, health, weight, kind of concurrent treatment, if any; frequency of treatment; therapeutic ratio and like considerations. Expressed in terms of concentration, dexrazoxane can be present in the new compositions for use dermally, intranasally, bronchially, intramuscularly, intravaginally,

intravenously, or orally in a concentration of from about 0.01 to about 50% w/w of the composition, and especially from about 0.1 to about 30% w/w of the composition. Preferably, the novel compound is present in a composition from about 1 to about 10% and, most preferably, the novel composition comprises about 5% novel compound.

[0094] The compositions of the invention are advantageously used in a variety of forms, e.g., tablets, ointments, capsules, pills, powders, aerosols, granules, and oral solutions or suspensions and the like containing the indicated suitable quantities of the active ingredient. Such compositions are referred to herein and in the accompanying claims generically as "pharmaceutical compositions." Typically, they can be in unit dosage form, namely, in physically discrete units suitable as unitary dosages for human or animal subjects, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic or prophylactic effect in association with one or more pharmaceutically acceptable other ingredients, e.g., diluent or carrier.

[0095] Where the pharmaceutical compositions are aerosols, the active ingredients can be packaged in pressurized aerosol containers with a propellant, e.g., carbon dioxide, nitrogen, propane, etc. with the usual adjuvants such as cosolvents, wetting agents, etc.

[0096] Where the pharmaceutical compositions are ointments, the active ingredient can be mixed with a diluent vehicle such as cocoa butter, viscous polyethylene glycols, hydrogenated oils, and such mixtures can be emulsified if desired.

[0097] In accordance with the invention, pharmaceutical compositions comprise, as an inactive ingredient, an effective amount of one or more non-toxic, pharmaceutically acceptable ingredient(s). Examples of such ingredients for use in the compositions include ethanol, dimethyl sulfoxide, glycerol, silica, alumina, starch, calcium carbonate, talc, flour, and equivalent non-toxic carriers and diluents. Additionally, adjuvants may be administered in conjunction with the compositions described herein for treatment of cardiac arrhythmias.

[0098] The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLES

[0099] Isolation of single guinea-pig ventricular myocytes

[00100] Myocytes were isolated enzymatically from guinea-pig ventricle as previously described (Powell et al, 1980; Mitchell et al, 1984). Briefly, male guinea-pigs were killed by cervical dislocation following stunning. Myocytes were isolated after perfusion of the heart with a physiological salt solution containing reduced calcium and 0.8 mg/mL of collagenase Type 1 (Worthington Biochemicals). Cells were stored at room temperature in Dulbecco's MEM (Life Technologies, Scotland) and used for electrophysiological investigation on the day of preparation.

[00101] Recording of action potentials from single ventricular myocytes.

[00102] Action potentials were recorded from single guinea-pig ventricular myocytes using the standard control conditions and criteria as adopted by CCTT Ltd. (see <http://www.cctt.ltd.uk/ap1.htm>). Briefly, action potentials were recorded using conventional glass microelectrodes filled with 1 M KMeSO₄ and 10 mM KCl. Electrode resistances were in the range of 40 to 60 M Ω . An Axoclamp 2B (Axon Instruments Inc) amplifier was used for electrical recording. Action potentials were continuously stimulated by application of a brief (1-2 ms) current stimuli applied via the intracellular microelectrode in 'bridge' mode. Following penetration of the cell with the microelectrode, a stabilisation period of at least 5 min was allowed before recordings were started. The frequency of stimulation was 1Hz. Recorded signals were digitised at a sampling frequency of 5 kHz and stored for subsequent off line analysis. Action potential signals were continuously monitored online using an oscilloscope (Tektronix digital storage oscilloscope) to check for development of effects of dexrazoxane. All recordings are made at 36 $\pm$ 1°C.

[00103] Action potential recording criteria amplitude and resting potential

[00104] The stability of several parameters of the action potential profile (resting potential, action potential amplitude and action potential duration) was ensured before recordings were commenced. Resting potential was measured over a 5-10 ms period before the stimulus artefact and values for the resting potential falling

between -75 to -85 mV were taken as normal. Action potential amplitude was measured following the stimulus artefact and values falling between 110 to 130 mV were taken as normal.

[00105] Statistics

[00106] All data are presented as mean $\pm$ SEM. The effect of dexrazoxane on action potential characteristics was assessed using Student's t-test (MicroSoft Excel) and $P < 0.05$ was taken to indicate statistical significance.

[00107] Action potential duration

[00108] Action potential duration was measured from the peak amplitude of the action potential to 90 % repolarisation level (APD₉₀), and values for APD₉₀ falling between 150 to 300 ms were taken as normal. Parameters measured in this study were action potential duration at 40, and 90% repolarisation levels (APD₄₀ and APD₉₀) using Clampfit 9.0.

[00109] For each cell, APD₄₀ and APD₉₀ values were calculated in the absence (control) and presence of a drug. As an index of 'Triangulation' APD₉₀ - APD₄₀, (APD₉₀₋₄₀ ms) in the absence (APD₉₀₋₄₀ control) and presence of dexrazoxane (APD₉₀₋₄₀ drug) were calculated. This was normalised to the starting (control) APD₉₀ to express APD₉₀₋₄₀ duration as a % of control APD₉₀. Calculations were made for each cell individually; the values for each drug concentration were then averaged.

[00110] Mean data showing the effect of dexrazoxane (10 μ M) on action potential duration (APD₉₀) is shown in Figure 3. The data shows that perfusion with dexrazoxane (27 minutes) caused an 18 ± 3 % shortening of APD₉₀ from 212 ± 9 ms to 168 ± 12 ms ($n=4$, $P < 0.005$). The addition of dexrazoxane to the superfusion solution caused an 18 ± 4 % a decrease in APD₄₀ from 175 ± 8 ms to 136 ± 15 ms ($n=3$, $P < 0.005$, see Figure 4). Superfusion of dexrazoxane did not significantly alter the APD₉₀₋₄₀ duration which is taken as an index of triangulation (see Figure 5). Accordingly, time control data show that under control condition there was no change in either APD₉₀ (Figure 3), APD₄₀ (Figure 4), or in APD₉₀₋₄₀ (Figure 5). Furthermore, Figure 8 shows typical action potential records taken from a single ventricular myocytes under control conditions and in the presence of

dexrazoxane (10 μ M) superfused for 10 minutes, 20 minutes and 30 minutes. Dexrazoxane (under these conditions) shortened action potential duration.

[00111] Measurement of Unloaded Cell Shortening

[00112] Measurement of unloaded cell shortening (UCS) of single ventricular myocytes was achieved using a video-edge detection system with a temporal resolution of ~4.2 ms (SoftEdge™, IonWizard Analysis Software, IonOptix Corp). Peak amplitude UCS is expressed as either absolute contraction (μ m) or normalised and therefore expressed as a percentage of resting cell length (%RCL). Mean data for the peak amplitude of action potential driven unloaded cell shortening (UCS) measured in single ventricular myocytes is shown in Figure 6. Application of dexrazoxane (10 μ M, 27 minutes) did not significantly alter the amplitude of UCS expressed as absolute cell shortening (control, $9.4 \pm 3.4 \mu$ m; dexrazoxane $10.7 \pm 3.2 \mu$ m, n=3, P=ns; the left panel of Figure 6 shows contraction in μ m while the right panel shows percentage change from control). Similar findings as depicted in Figure 6 were made when shortening was expressed as percentage of resting cell length as in Figure 7 (control, $8.5 \pm 2.7 \%$ RCL; dexrazoxane $8.0 \pm 2.0 \%$ RCL, n=3, P=ns; the left panel of Figure 7 shows shortening as percentage of cell length while the right panel shows percentage change from control).

[00113] Test substance and solution formulation

[00114] i. Composition of bath solution

[00115] Bath solution was prepared daily. The composition of the bath solution was (mM): NaCl 125; NaHCO₃ 25; KCl 5.4; CaCl₂ 1.8; MgCl₂ 1.0; NaH₂PO₄ 1.2; D-glucose 5.5; pH 7.4 when bubbled with 95% CO₂ and 5% O₂ mixture.

[00116] ii. Test substance and formulation

[00117] The test substance (dexrazoxane) was made up as a stock solution in H₂O (10-1M) and then diluted into the bath solution to prepare the test substance perfusion solution. This was done daily. The initial test concentration for dexrazoxane was 10 μ M.

[00118] In conclusion, although the number of cells tested was small these preliminary data show that under these conditions application of dexrazoxane

(10 μ M) to single ventricular myocytes caused shortening of action potential duration and did not significantly alter the amplitude of contraction.

In Vivo Cardiac Electrophysiologic and Antiarrhythmic Effects of Dexrazoxane

[00119] The ability of dexrazoxane to alter cardiac electrophysiologic parameters and to terminate atrial arrhythmia is assessed in a pentobarbital-anesthetized canine model of atrial flutter. In this model, atrial flutter is induced following a Y-shaped surgical lesion comprised of an intercaval incision and a connecting incision across the right atrium. Bipolar epicardial electrodes are placed on the inferior vena cava and right atrium for atrial pacing, recording local atrial activation, and for measurement of atrial excitation threshold (AET) and atrial relative (ARRP at 2 $\times$ AET) and effective refractory periods (AERP at 10 $\times$ AET). Bipolar electrodes also are sutured to the left ventricle for measurement of ventricular excitation threshold (VET) and ventricular relative (VRRP at 2 $\times$ VET) and effective refractory periods (VERP at 10 $\times$ VET). The following cardiac electrophysiologic parameters also are measured before dexrazoxane administration and at the termination of the study: AH interval, an index of AV nodal conduction; HV interval, an index of His-ventricular conduction time; P-A interval, an index of intra-atrial conduction; and H-EG interval, an index of ventricular conduction; and paced ECG QT interval. AV nodal functional refractory period (AVNFRP) and SA conduction time (SACT) are determined by the introduction of atrial extrastimuli during sinus rhythm, and the monitoring of ventricular response. Electrocardiographic intervals are determined during sinus rhythm; the rate-corrected ECG QTc interval is calculated as: $QTc = QT \text{ (msec)} / R - R \text{ (sec)}$. Dexrazoxane is administered as cumulative i.v. doses of 1, 3 and 10 mg/kg, with each dose administered as an intravenous bolus in a vehicle of PEG-200. Additionally, ADR-925 is administered in equal amounts, in order to determine the active moiety of dexrazoxane.

[00120] Sustained atrial flutter is initiated in three dogs by electrical burst pacing (6-20 Hz) of the atria; atrial rates range from 440-530 cycles/min. Intravenous bolus administration of PEG-200 vehicle alone has no effect on the atrial arrhythmia in all three animals. Intravenous bolus administration of 3 mg/kg of dexrazoxane (and ADR-925 => side-by-side) in two animals, and 10 mg/kg of dexrazoxane (and ADR-925) in the third animal is preformed.

Dexrazoxane protective effects

[00121] In this procedure [Lawson, *J. Pharmacol. Exper. Therap.*, Vol. 160, pages 22-31 (1968)], the test substance dexrazoxane is administered i.p. (100 mg/kg) to a group of three mice thirty minutes before exposure to deep chloroform anesthesia and observed during the ensuing 15-minute period. Absence of EKG recorded cardiac arrhythmias and heart rates above 200 beats per minute present (usual =400-480 beats per minute) in none or only one (<2) of three animals indicates significant protection.

Further Anti-Arrhythmic Dexrazoxane Studies

[00122] Animals are implanted with a 25 mg pellet of DOCA and maintained on the 1% saline as their drinking fluid. The animals are anesthetized with Avertin (tribromoethanol, 2.5%), and prepared for the recording of blood pressure and the EKG. In addition, the animal's left jugular vein is also cannulated with PE-50 tubing. The tubings are filled with saline and exteriorized dorsally between the animal's shoulders. Isoproterenol (a proarrhythmic agent) is administered s.c. at a dose of 150 µg/kg and an arrhythmia was allowed to develop for five minutes. After this time, either propranolol (control) or dexrazoxane is given as an intravenous bolus at one-half of the effective s.c. dose. Continuous blood pressure, heart rate and EKG readings are obtained. Additional Avertin is given as needed to maintain anesthesia. The hearts of the animals are perfused with buffered formalin immediately after the onset of ventricular fibrillation or one hour after the administration of isoproterenol.

Synthesis of Dexrazoxane

[00123] Propane-1,2-diamine tetra-acetic acid (9 g), and formamide (250 mL) are heated at 110°C together under reduced pressure (ca 100 mm.) for 2 hours. The heat is then raised to 160°C and stirred for 3 additional hours. The reaction is cooled until precipitate forms and product is filtered and then washed with formamide and ethanol. Further purification is performed by column chromatography (C₁₁H₁₆N₄O₄, MH⁺ 269.3, m.p. 191-197°C).

Synthesis of Dexrazoxane Derivatives

- [00124] Useful synthetic routes are described in US Patent No. 3,941,790.
- [00125] A diamino alkane (such as diaminoethane, diaminocyclobutane, or propane-1,2-diamine) tetra-acetic acid, and formamide are heated at 110°C together under reduced pressure for 1-2 hours. The heat is then raised to 150°C and stirred for 2-3 additional hours. The reaction is cooled, filtered and then washed with ethanol.
- [00126] Compounds with variable terminal rings are synthesized as follows: the nitrogen-containing heterocyclyl with the desired terminal ring structure (such as 1,3-dimethylpiperazine-2,6-dione or morpholin-2-one) are added to a solution containing an alkyl dihalide (such as 1,2-dichloropropane) in THF and the solution is heated until complete. Final compounds are identified by GC or LCMS and purified by column chromatography.

Synthesis of N,N'-[(1S)-1-methyl-1,2-ethanediyl]bis[N-(2-amino-2-oxoethyl)glycine] (ADR-925) and monocyclic analogs (B and C, see Figure 13):

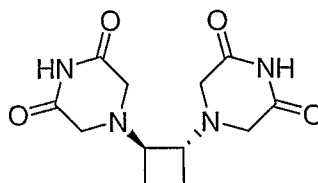
- [00127] The above are prepared by hydrolyzing 5 mg/ml dexrazoxane with NaOH (40 μ l/ml of 1 M NaOH) at 25°C for 40 min and quenching the reaction with HCl (45 μ l/ml of 1 M HCl) to pH 3 as described previously. Under these conditions a mixture of dexrazoxane, B, C, and ADR-925 is produced. Dexrazoxane is efficiently removed from the reaction mixture by loading 500 μ l of the mixture on a Sep-Pak Plus C₁₈ cartridge (Waters, Mississauga, ON, Canada) and eluting with 2% (v/v) methanol at a flow rate of 1 ml/min. Although dexrazoxane is highly retained on the cartridge, B, C, and ADR-925 eluted together and are collected at elution volumes between 1.5 and 2.5 ml. HPLC analysis confirmed that dexrazoxane is not detectable in this fraction. This 1-ml fraction, pH 6, is loaded on three Sep-Pak Accell Plus QMA (Waters) ion exchange cartridges connected in series and eluted with 2% (v/v) methanol at a flow rate of 5 ml/min. Fractions containing B are collected at elution volumes between 3 and 4.5 ml, and those containing C between 5 and 9 ml. The B fraction contains less than 0.1 mol% and 0.01 mol% of C and ADR-925, respectively. The C fraction contains less than 0.1 mol% B and 0.05 mol% of ADR-925, respectively. These fractions are brought to pH 2 with 5 M HCl and evaporated to dryness under a stream of nitrogen, stored at -80°C, and reconstituted in water just before use. Neither of

these fractions contain detectable amounts of dexrazoxane (<0.001 mol%).

Typical yields of **B** and **C** are 10 and 6 μ g, respectively.

[00128] Synthesis of cyclic dexrazoxane derivatives:

[00129] Preparation of (+-.) trans-1,2-bis(3,5- dioxopiperazin- 1-yl)cyclobutane (US Patent No. 5,438,057):



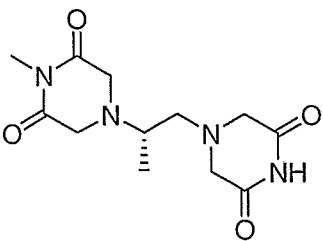
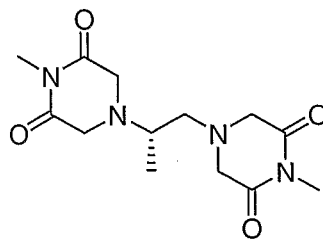
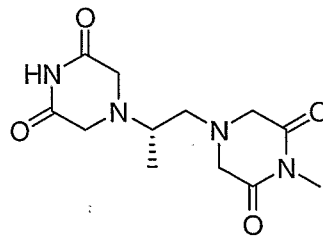
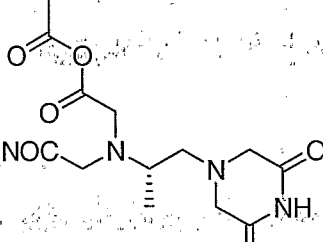
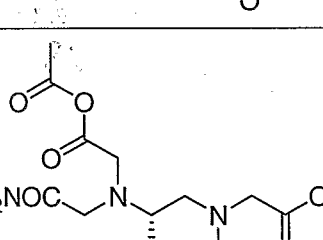
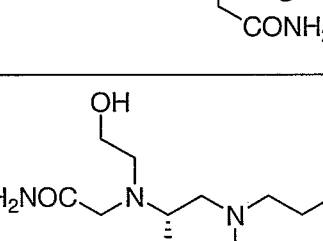
[00130] Trans-1,2-Diaminocyclobutane tetra-acetic acid monohydrate (100 g) (melting point 234.degree.-235.degree. C.; prepared in 56% yield by the method of Dwyer and Garvan, J. Amer. Chem. Soc., 1959, 81, 2956), is heated with 400 ml of formamide under nitrogen at reduced pressure at 100.degree.-110.degree. C. for 1 hour and then at 150.degree.-155. degree. C. for 4 hours. The brown solution is evaporated under reduced pressure at 80.degree.-90.degree. C. and the residue taken up in 120 ml of methanol and cooled in a refrigerator overnight. Filtration, follows by washing with cold methanol and vacuum drying at 65.degree. C. Gives a 69% yield of (+-.) trans-1,2-bis(3,5-dioxopiperazin-1-yl)cyclobutane, melting point is reported at 257.degree.-259.degree. C.

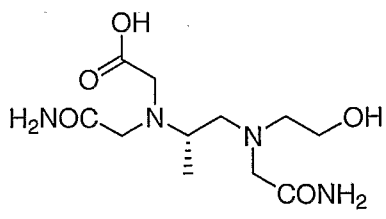
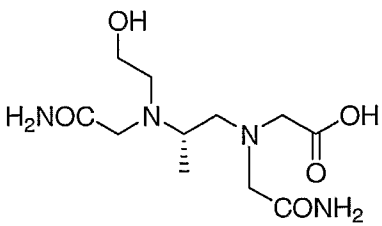
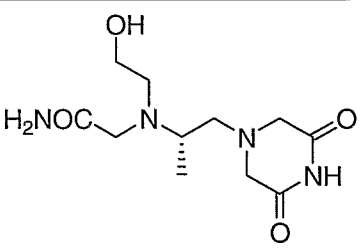
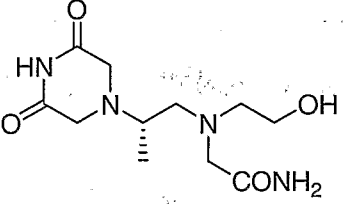
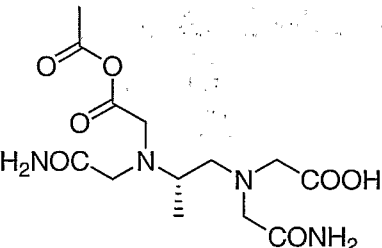
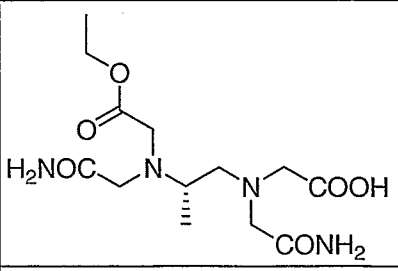
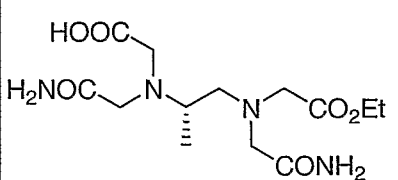
[00131]

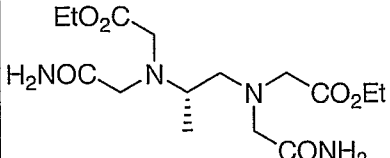
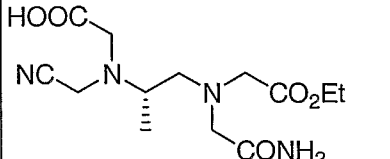
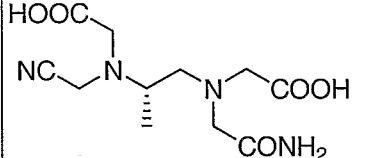
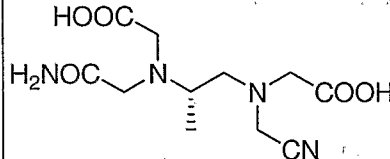
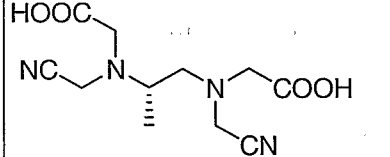
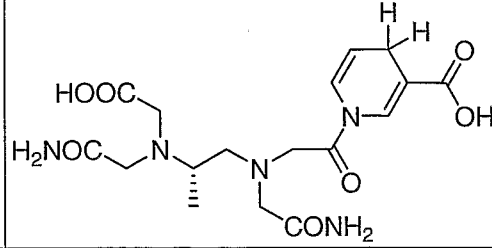
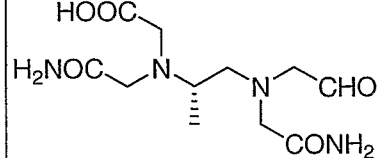
[00132] Prodrugs of the compositions of the present invention, particularly of IB (ADR-925), are provided in Table 1.

[00133] Table 1. ADR-925 Prodrug Examples

Example	Structure	MW	Formula	Metabolic Pathway
1		268.27	C ₁₁ H ₁₆ N ₄ O ₄	DHO

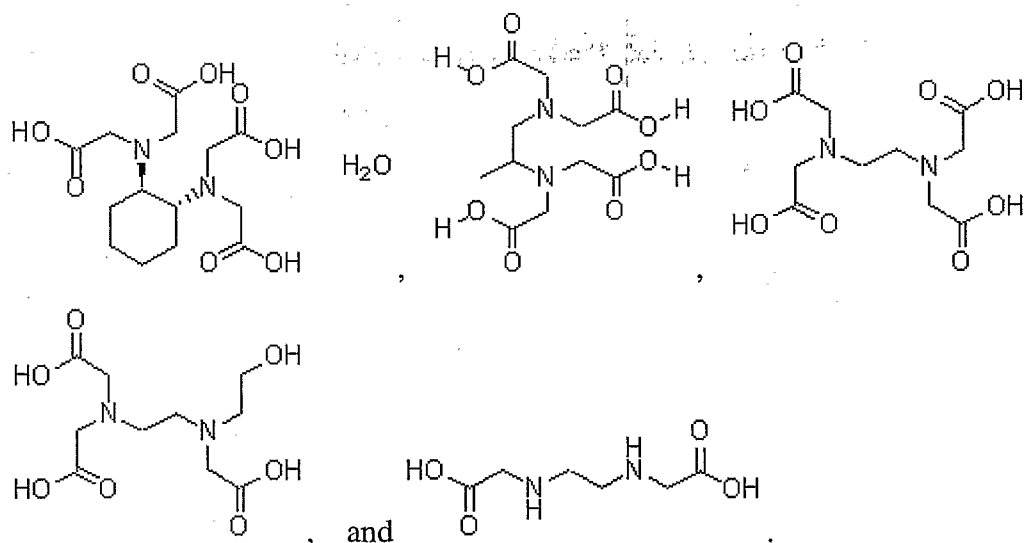
2		282.13	C12H18N4O4	Cytochrome P450; DHO
3		296.32	C13H20N4O4	Cytochrome P450; DHO
4		282.13	C12H18N4O4	Cytochrome P450; DHO
5		328.32	C13H20N4O6	Acid-catalyzed hydrolysis; DHO
6		388.37	C15H24N4O8	Acid-catalyzed hydrolysis; DHO
7		276.33	C11H24N4O4	Cytochrome P450;

8		290.32	C11H22N4O5	Cytochrome P450;
9		290.32	C11H22N4O5	Cytochrome P450;
10		272.3	C11H20N4O4	Cytochrome P450; DHO
11		272.3	C11H20N4O4	Cytochrome P450; DHO
12		346.34	C13H22N4O7	Acid-catalyzed hydrolysis
13		332.35	C13H24N4O6	Esterase
14		332.35	C13H24N4O6	Esterase

15		360.41	C15H28N4O6	Esterase
16		314.34	C13H22N4O5	Esterase, Acid Catalysis
17		286.28	C11H18N4O5	Acid Catalysis
18		286.28	C11H18N4O5	Acid Catalysis
19		268.27	C11H16N4O4	Acid Catalysis
20		411.41	C17H25N5O7	Esterase
21		288.3	C11H20N4O5	Cytochrome P450

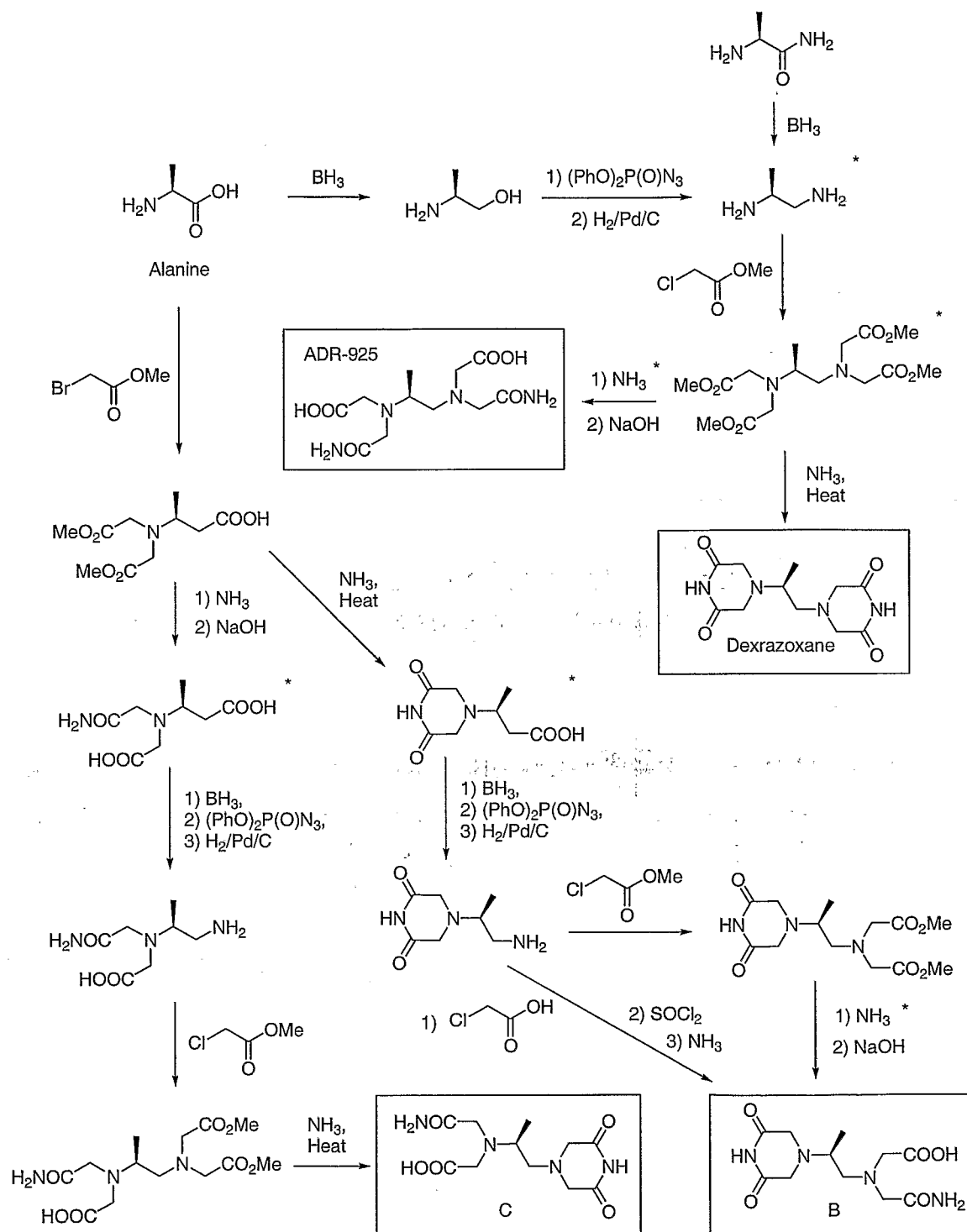
22		288.3	C ₁₁ H ₂₀ N ₄ O ₅	Cytochrome P450
23		272.3	C ₁₁ H ₂₀ N ₄ O ₄	Cytochrome P450
24		346.34	C ₁₃ H ₂₂ N ₄ O ₇	Acid-catalyzed hydrolysis

[00134] The following analogs identified under formula IB are commercially available from Acros Organics:



[00135] Dexrazoxane, ADR-925, and mono-cyclic compounds shown in Figure 13 are synthesized as described above and according to Scheme 1.

[00136] SCHEME 1:



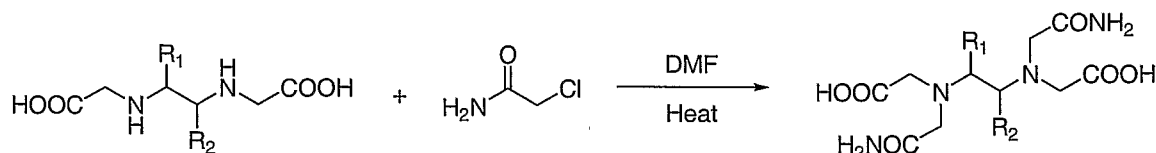
[00137] Additionally, other analogs and prodrugs of the compounds, particularly those falling under Formula IA, IB, IC, and prodrugs of IB, particularly prodrugs of ADR-925 are synthesized by modifying useful intermediates (*) depicted in Scheme 1, which will be readily apparent to those skilled in the art. For instance,

Examples 13-15 in Table 1 are prepared from (S)-propane-1,2-diamine (depicted in top right of Scheme 1*) by substituting with ethyl 2-chloroacetate in place of methyl 2-chloroacetate and subsequently mild treatment with ammonia (no NaOH) in the following step yields the desired/separable products.

[00138] Additionally, compounds of formula IA, IB and IC are synthesized according to the following schemes:

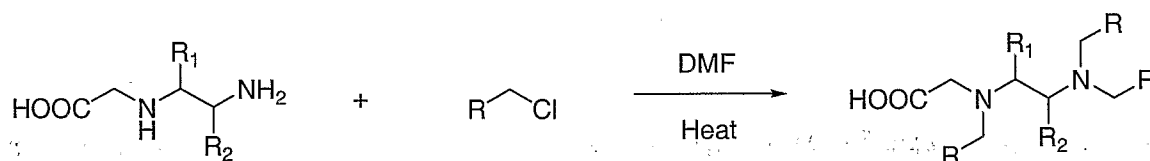
[00139] Compounds and prodrugs of formula IB are synthesized according to Scheme 2.

[00140] SCHEME 2:



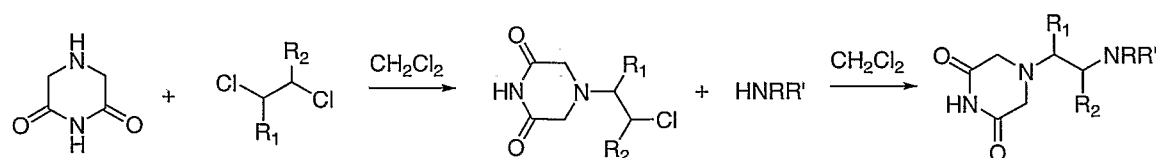
[00141] Additional compounds and prodrugs of formula IB are synthesized according to Scheme 3.

[00142] SCHEME 3:



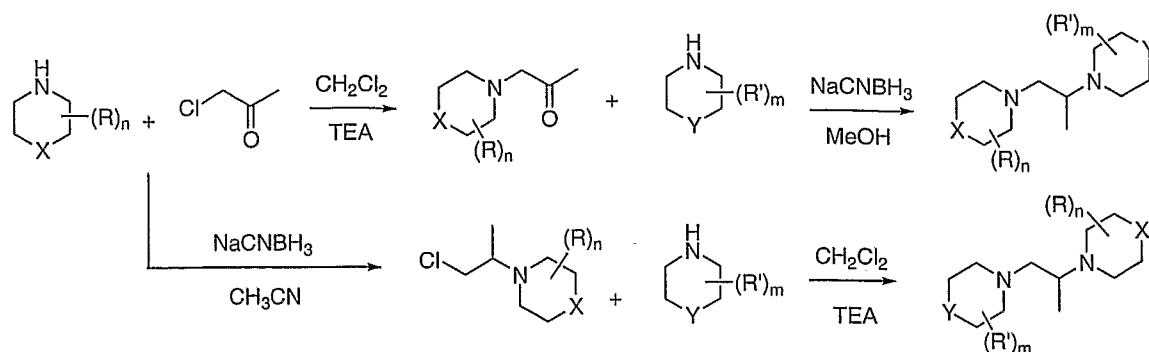
[00143] Compounds of formula IC are synthesized according to Scheme 3.

[00144] SCHEME 4:



[00145] Compounds of formula IA are synthesized according to Scheme 5.

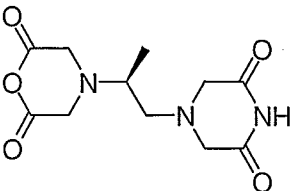
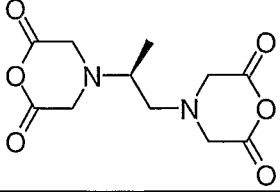
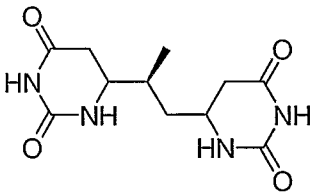
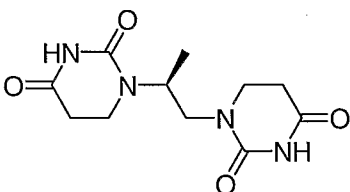
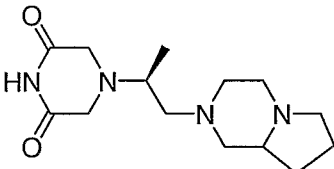
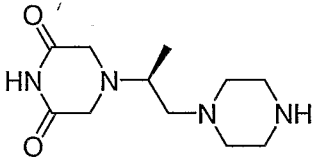
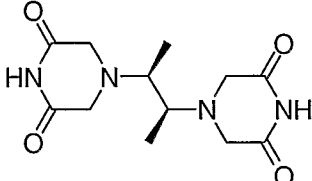
[00146] SCHEME 5:

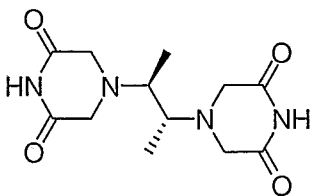
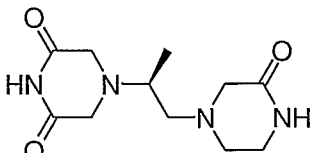


[00147] Further derivatives of dextrazoxane are provided in Table 2:

Table 2: Dextrazoxane Derivatives

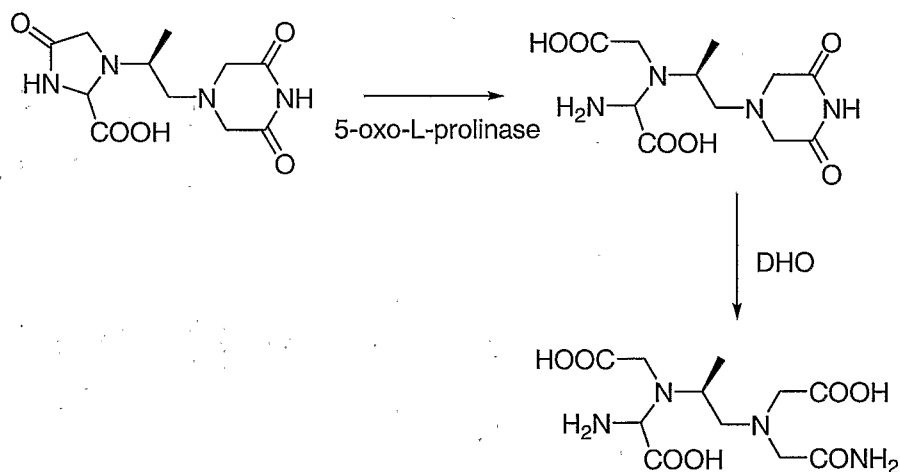
Example	Structure	MW	Formula
25		284.27	C ₁₁ H ₁₆ N ₄ O ₅
26		284.27	C ₁₁ H ₁₆ N ₄ O ₅
27		254.33	C ₁₂ H ₂₂ N ₄ O ₂
28		269.25	C ₁₁ H ₁₅ N ₃ O ₅

29		269.25	C11H15N3O5
30		270.24	C11H14N2O6
31		268.27	C11H16N4O4
32		268.27	C11H16N4O4
33		280.37	C14H24N4O2
34		240.3	C11H20N4O2
35		282.3	C12H18N4O4

36		282.3	C ₁₂ H ₁₈ N ₄ O ₄
37		254.29	C ₁₁ H ₁₈ N ₄ O ₃

[00148] The mechanistic profile for Example 25 is provided in Scheme 6:

[00149] SCHEME 6:

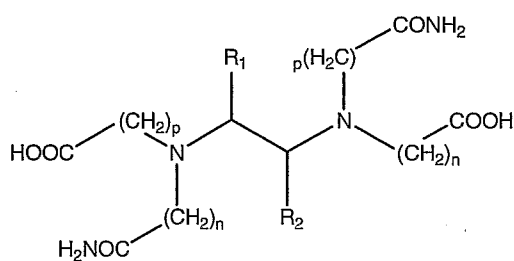
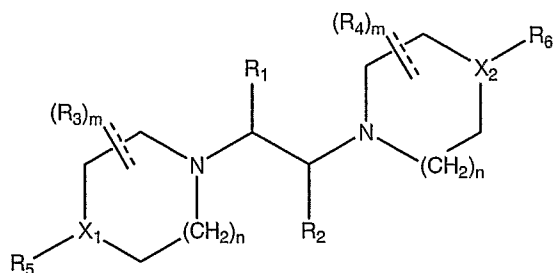


[00150] While the invention has been described with respect to specific examples including presently preferred modes of carrying out the invention, those skilled in the art will appreciate that there are numerous variations and permutations of the above described systems and techniques that fall within the spirit and scope of the invention.

[00151] The contents of all of the above cited patents, patent applications and journal articles are incorporated by reference as if set forth fully herein.

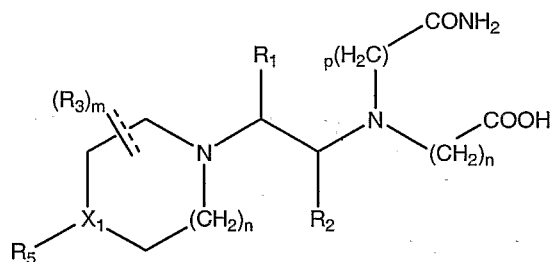
CLAIMS

1. A method of treating a subject suffering from a cardiac arrhythmia comprising administering a compound of Formula (IA), (IB), (IC), or a pharmaceutically acceptable salt, tautomer, stereoisomer, or prodrug thereof:



IA

IB



IC

wherein,

X_1 and X_2 are independently selected from CH, N, S, or O;

each R_1 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl;

each R_2 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl,

substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl,

substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl; or

R₁ and R₂ are taken together to form a 3-7 membered substituted or unsubstituted carbocyclyl or heterocyclyl group;

each R₃ and R₄ group is independently selected from =O, =S, =NH, H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ alkoxy, substituted or unsubstituted C₁₋₆ alkenyl, substituted or unsubstituted C₆₋₁₀ aryl, or substituted or unsubstituted heterocyclyl, wherein the dotted line represents the optional placement of a double bond;

R₅ and R₆ are independently selected from H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ alkoxy, substituted or unsubstituted C₁₋₆ alkenyl, substituted or unsubstituted C₆₋₁₀ aryl, or substituted or unsubstituted heterocyclyl, with the proviso that if X₁ is O or S, R₅ is absent, or if X₂ is O or S, R₆ is absent;

each m is independently 1, 2, or 3;

each n is independently 0, 1, or 2; and

each p is independently 0, 1, or 2;

wherein the cardiac arrhythmia is treated in the subject after administration of the compound of Formula (IA), (IB), (IC), or a pharmaceutically acceptable salt, tautomer, stereoisomer, or prodrug thereof.

2. The method of claim 1, wherein the compound has the Formula (IA).

3. The method of claim 2, wherein X₁ and X₂ are N and each n is 1.

4. The method of claim 1, wherein R₃ and R₄ are both =O, m is 2, and n is 1.

5. The method of claim 1, wherein R₁ is unsubstituted C₁₋₆ alkyl and R₂ is H.

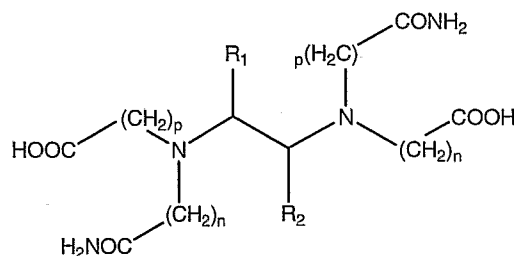
6. The method of claim 1, wherein the compound has the Formula (IC), R₂ is unsubstituted C₁₋₆ alkyl and R₁ is H.

7. The method of claim 2, wherein R₅ and R₆ are both H.

8. The method of claim 1, wherein the compound has the Formula (IB) or (IC) and each n and p is 1.

9. The method of claim 4, wherein each of R₃ and R₄ are appended to the adjacent (alpha) carbon to X₁ and X₂.

10. A method of treating a subject suffering from a cardiac arrhythmia comprising administering a compound of Formula (IB) or a prodrug of a compound of Formula (IB):



IB

wherein,

X₁ and X₂ are independently selected from CH, N, S, or O;

each R₁ is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ alkoxy, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₆₋₁₀ aryl, or substituted or unsubstituted heterocyclyl;

each R₂ is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ alkoxy, substituted or unsubstituted C₂₋₆ alkenyl, substituted or unsubstituted C₆₋₁₀ aryl, or substituted or unsubstituted heterocyclyl; or

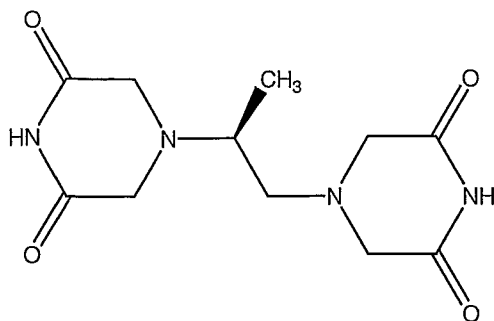
R₁ and R₂ are taken together to form a 3-7 membered substituted or unsubstituted carbocyclyl or heterocyclyl group;

each n is independently 0, 1, or 2; and

each p is independently 0, 1, or 2;

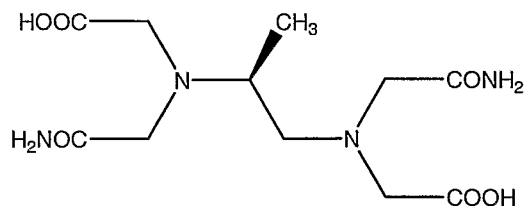
wherein the cardiac arrhythmia is treated in the subject after contacting the compound of Formula (IB) with a cell and/or tissue in the subject.

11. The method of claim 1, wherein the compound is:

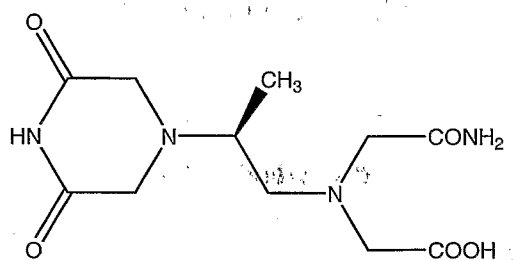


or a pharmaceutically acceptable salt, tautomer, or stereoisomer thereof.

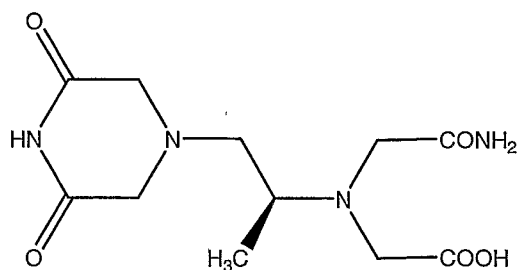
12. The method according to claim 1 or claim 10, wherein the compound is:



13. The method of claim 1, wherein the compound is:



14. The method of claim 1, wherein the compound is:

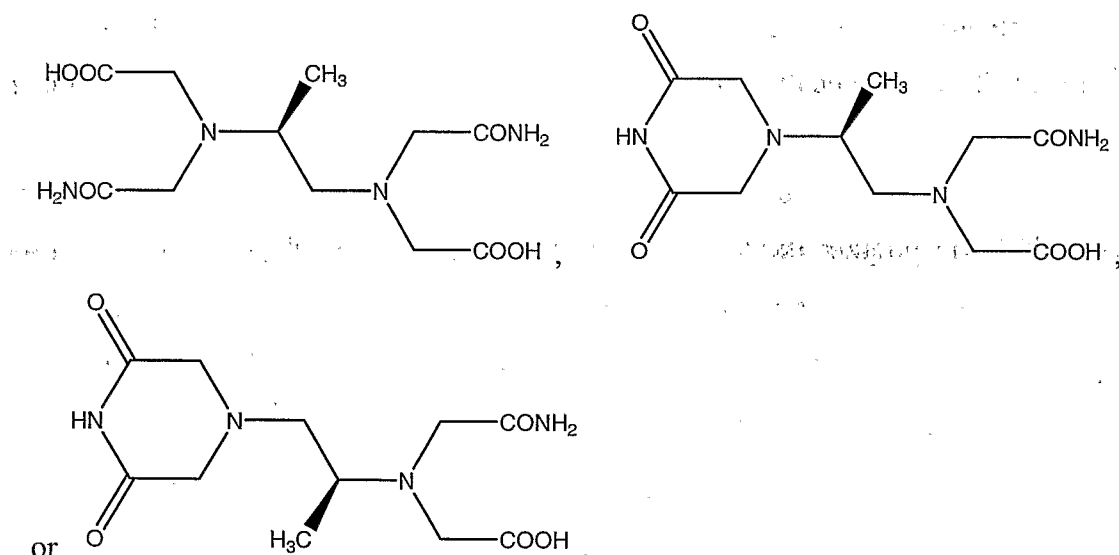


15. The method of claim 1, wherein the prodrug of Formula (IA), (IB) or (IC) is administered to the subject.

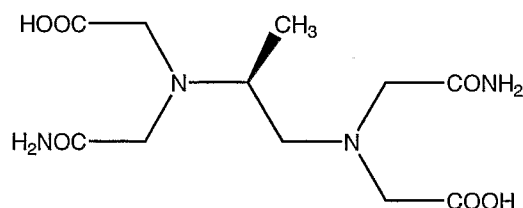
16. The method according to claim 10, wherein the prodrug has the Formula (IA) or (IC).

17. The method according to claim 12, wherein the prodrug that is administered to the subject is a compound listed in Table 1.
18. The method according to any of the previous claims, wherein the myocardial action potential duration (APD) decreases in the subject.
19. The method according to any of the previous claims, wherein the QT interval is maintained or decreased in the subject.
20. The method according to any of the previous claims, wherein the compound or a pharmaceutically acceptable salt, tautomer, stereoisomer, or prodrug thereof, does not decrease contractility in the subject.
21. The method according to any of the previous claims, wherein the compound is not co-administered nor used in conjunction with an anthracycline compound.
22. The method according to any of the previous claims, wherein the compound is not co-administered nor used in conjunction with doxorubicin.
23. The method according to any of the previous claims, wherein the subject has minimal myelosuppression after administration of the compound, tautomer, stereoisomer or prodrug thereof.
24. The method according to any of the previous claims, wherein the cardiac arrhythmia is a ventricular or supraventricular arrhythmia.
25. The method according to any of the previous claims, wherein the cardiac arrhythmia is a ventricular tachyarrhythmia.
26. The method according to any of the previous claims, wherein the cardiac arrhythmia is re-entrant tachyarrhythmia.

27. The method according to any of the previous claims, wherein the subject is suffering from congestive heart failure (CHF).
28. The method according to any of the previous claims, wherein the compound is administered after an ischemic insult.
29. The method according to any of the previous claims, wherein the compound contacts a cell or tissue in the subject's heart.
30. The method of claim 29, wherein a compound of Formula (IA) is administered to the subject and a compound of Formula (IB) or (IC) contacts the cell or tissue in the subject's heart.
31. The method of claim 30, wherein the compound that contacts the cell is:

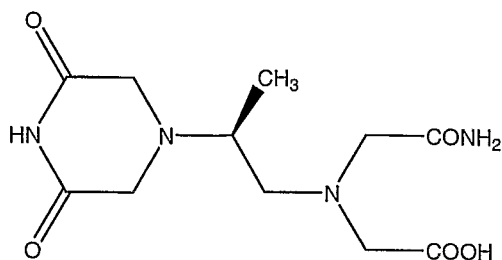


32. A pharmaceutical composition, comprising:



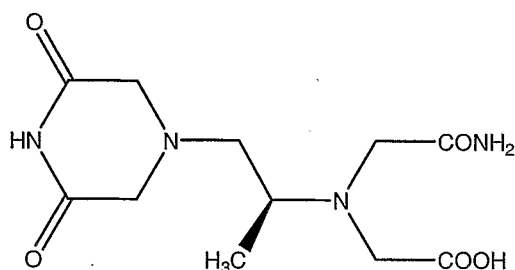
the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

33. A pharmaceutical composition, comprising:



the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

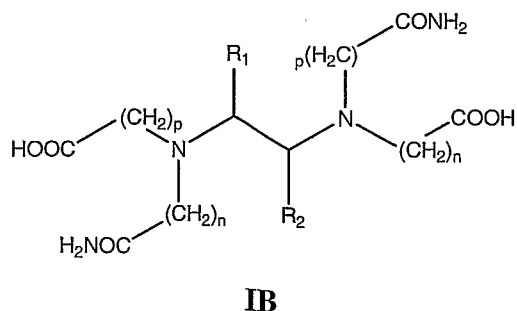
34. A pharmaceutical composition, comprising:



the tautomer thereof, the pharmaceutically acceptable salt thereof, the pharmaceutically acceptable salt of the tautomer, or the mixture thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

35. A method of treating a subject suffering from cardiac arrhythmia comprising: administering to the subject an effective amount of the pharmaceutical composition of any one of claims 32-34.

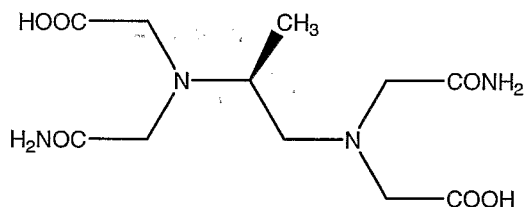
36. A prodrug of a compound of Formula (IB):



wherein,

X_1 and X_2 are independently selected from CH, N, S, or O;
 each R_1 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl;
 each R_2 is H, halogen, cyano, nitro, hydroxyl, substituted or unsubstituted amino, substituted or unsubstituted carbonyl, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{6-10} aryl, or substituted or unsubstituted heterocyclyl; or
 R_1 and R_2 are taken together to form a 3-7 membered substituted or unsubstituted carbocyclyl or heterocyclyl group;
 each n is independently 0, 1, or 2; and
 each p is independently 0, 1, or 2;
 wherein the cardiac arrhythmia is treated in the subject after contacting the compound of Formula (IB) with a cell and/or tissue in the subject;
 wherein the prodrug is not dexrazoxane.

37. The prodrug of claim 36, wherein the compound is:



38. A method of preventing or treating cardiomyopathy comprising: administering to the subject an effective amount of the prodrug of any one of claims 36-37.

39. A composition comprising human serum from a patient suffering from a cardiac arrhythmia and a compound having the following structure:

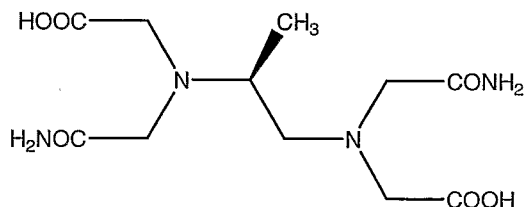


FIGURE 1

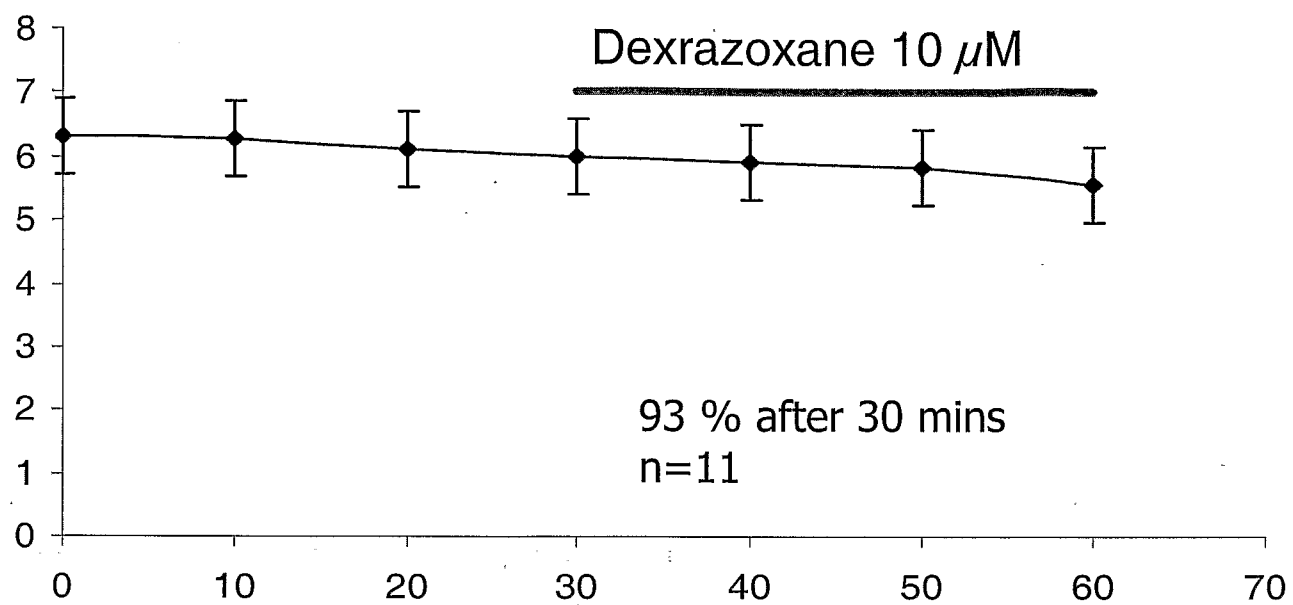


FIGURE 2

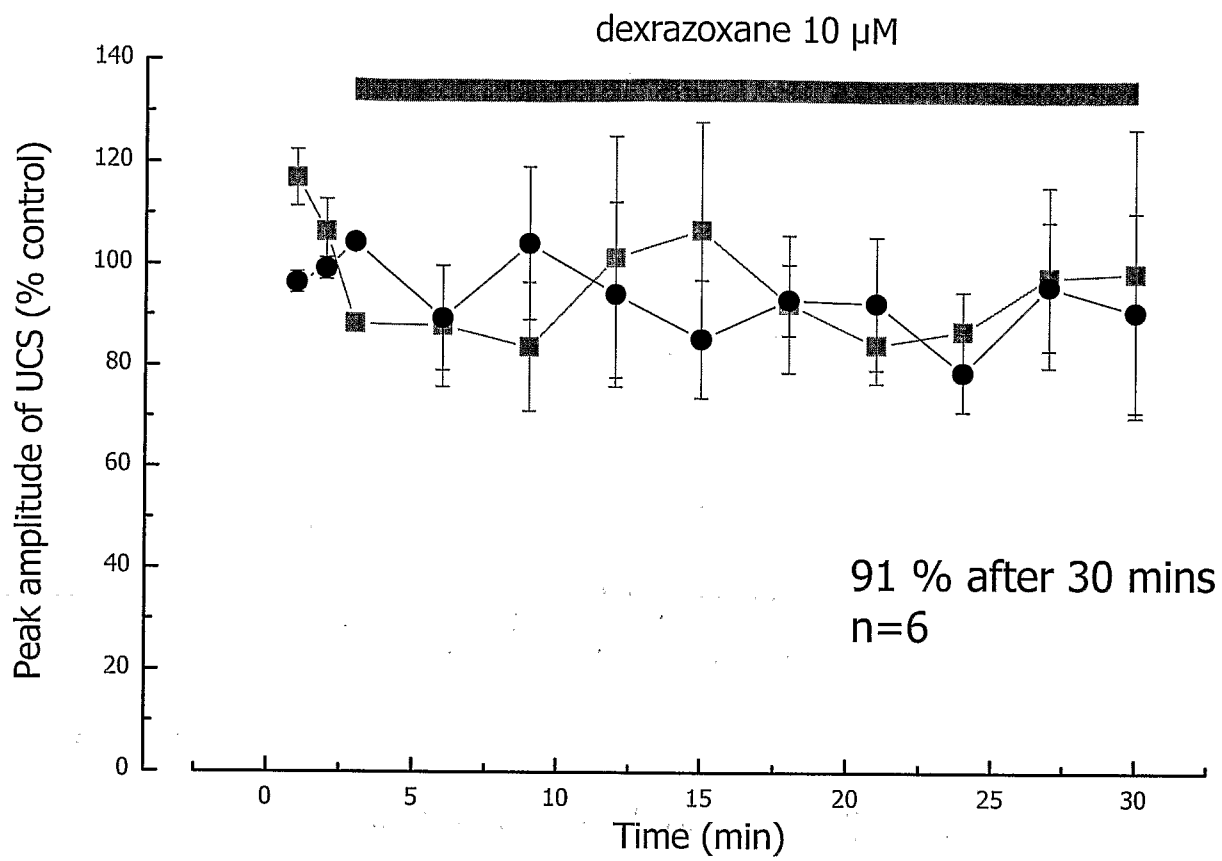


FIGURE 3

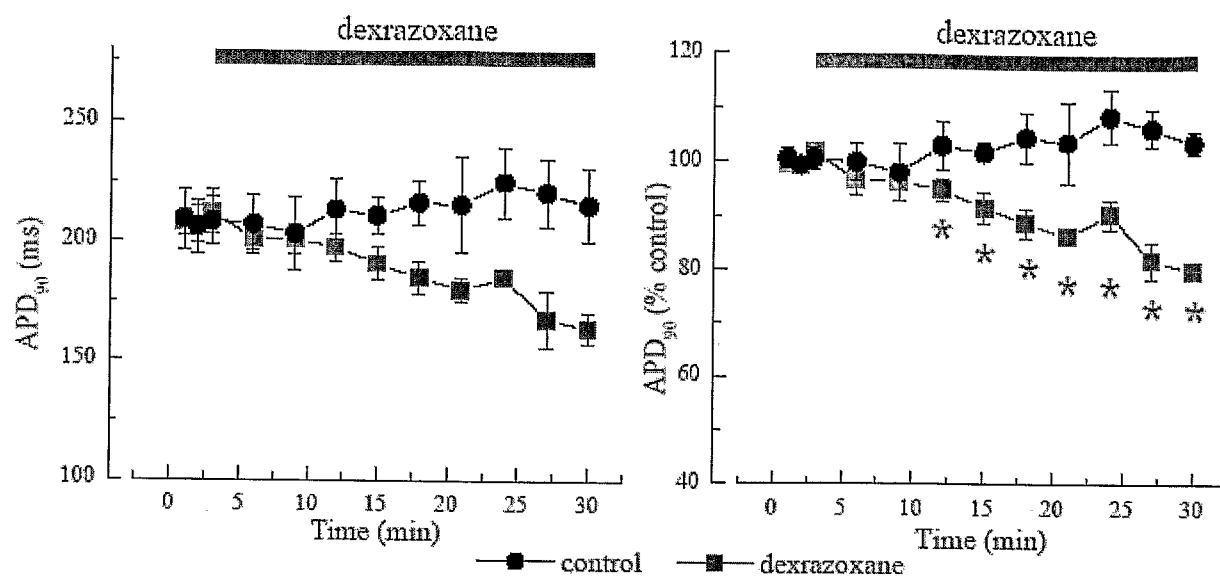
Effects of dexrazoxane (10 μ M) on APD₉₀

FIGURE 4

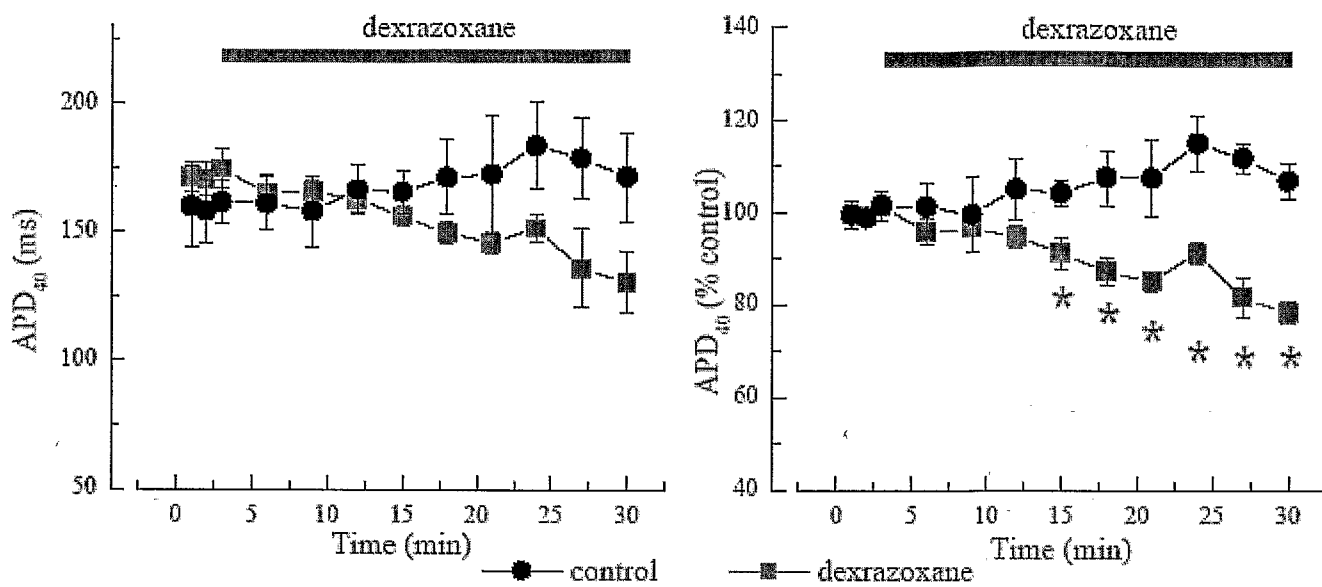
Effects of dexrazoxane (10 μ M) on APD₄₀

FIGURE 5

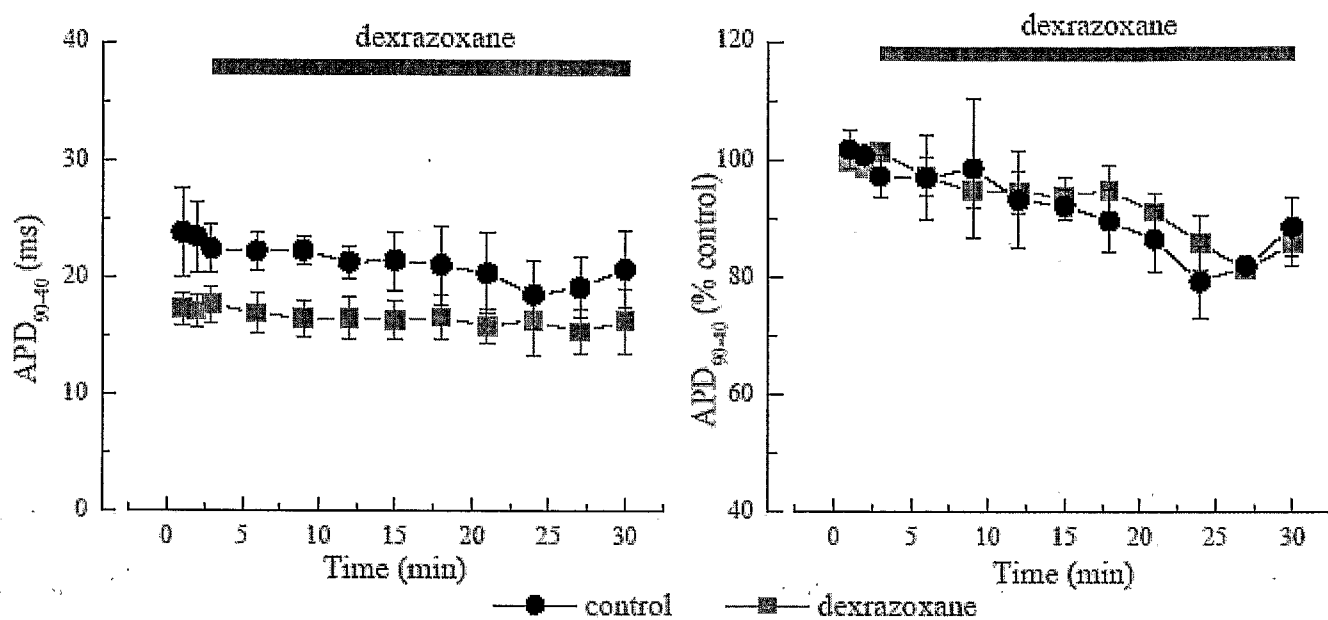
Effects of dexrazoxane (10 μ M) on APD₉₀₋₄₀

FIGURE 6

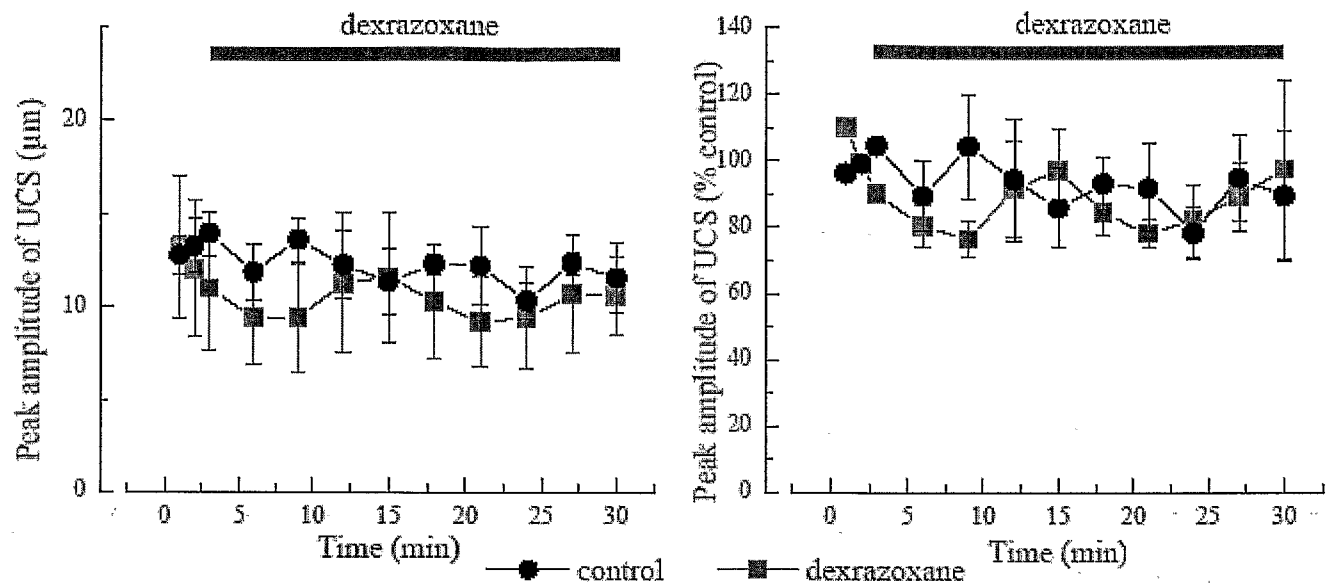
Effects of dexrazoxane (10 μ M) on cell shortening

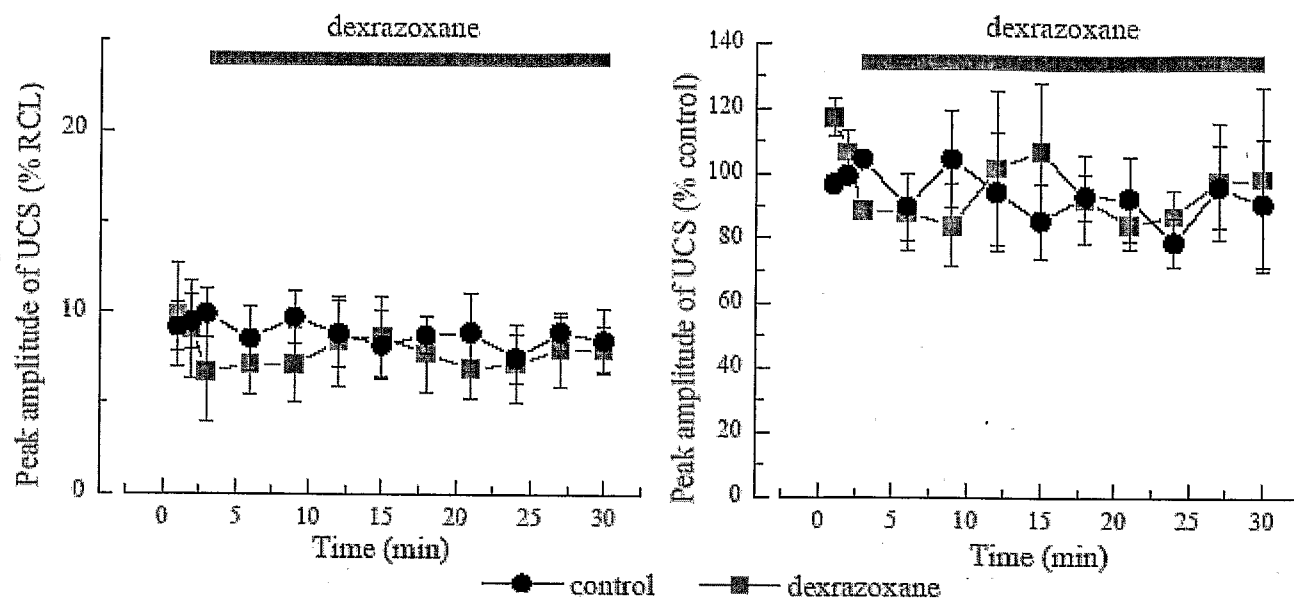
FIGURE 7Effects of dexrazoxane (10 μ M) on cell shortening

FIGURE 8

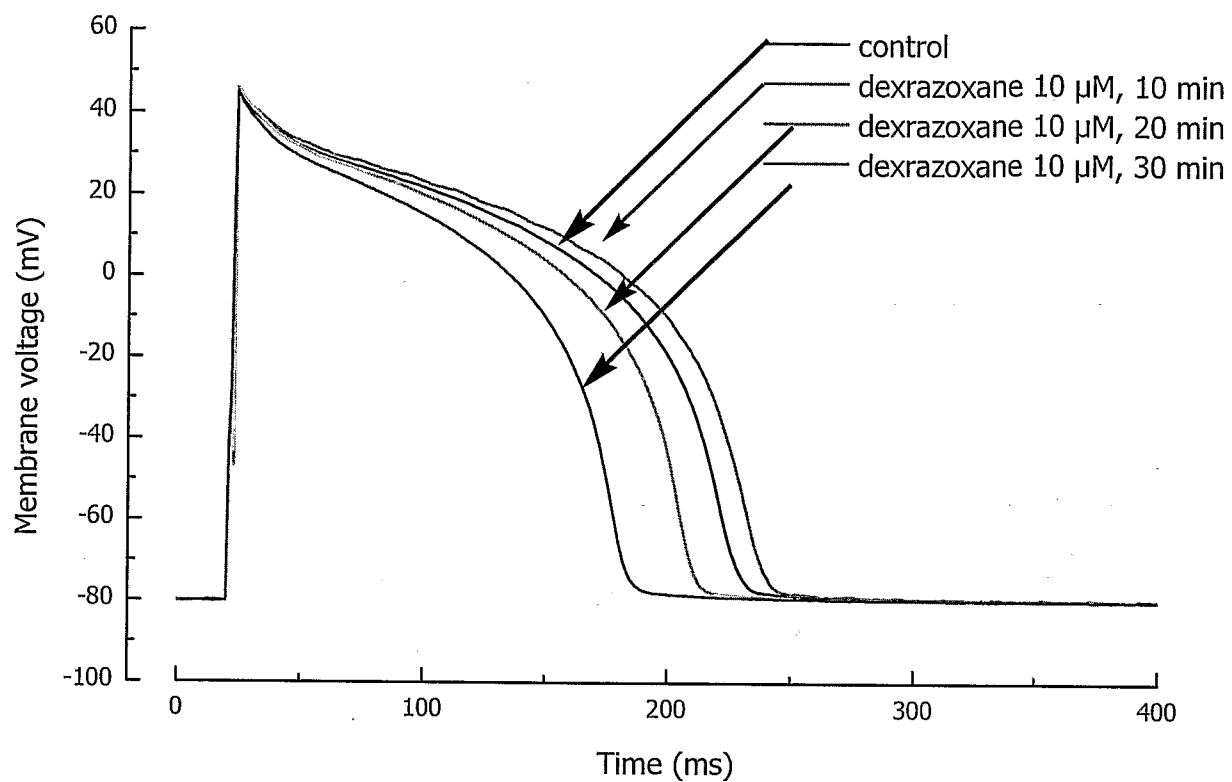


FIGURE 9

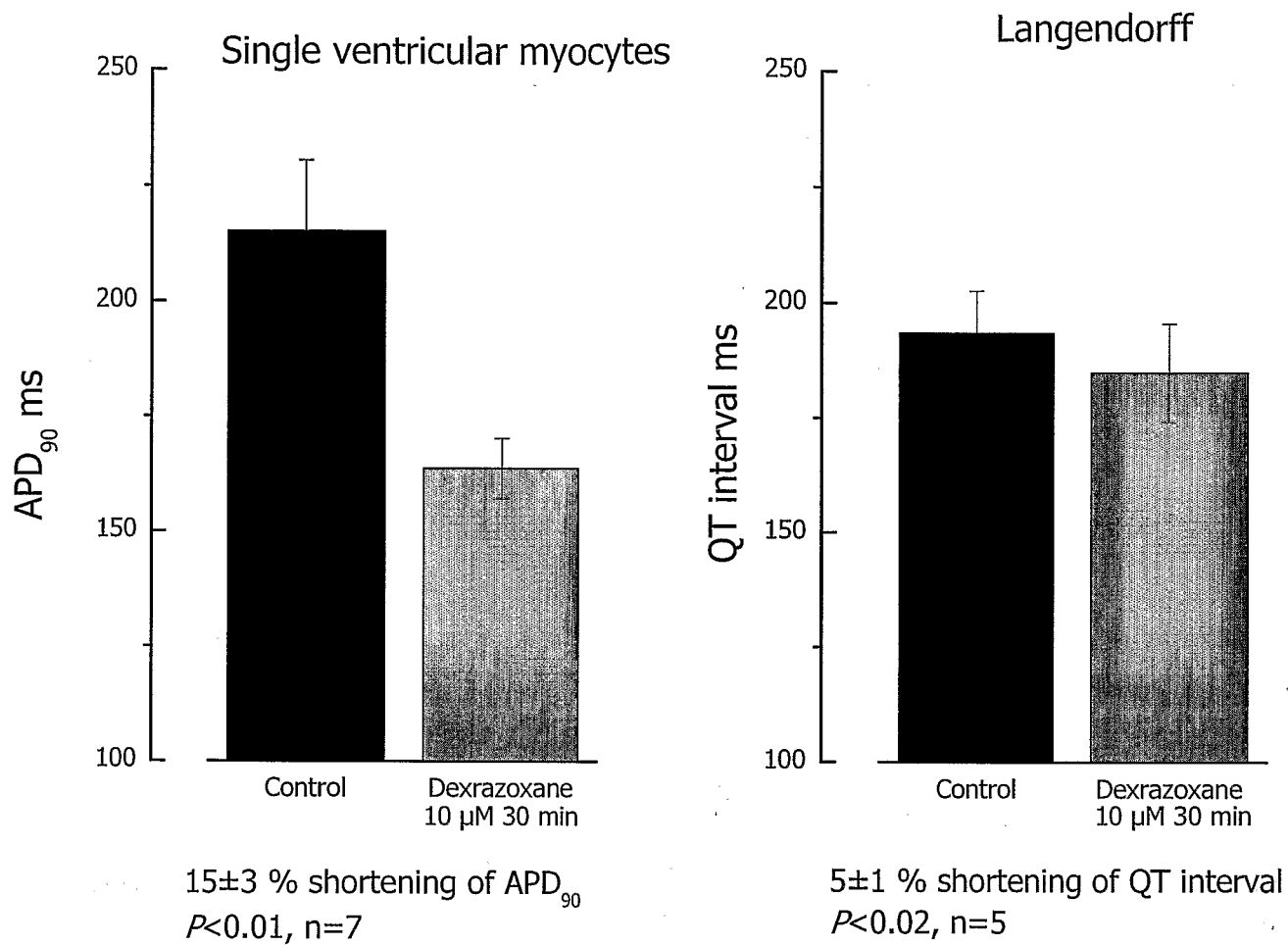
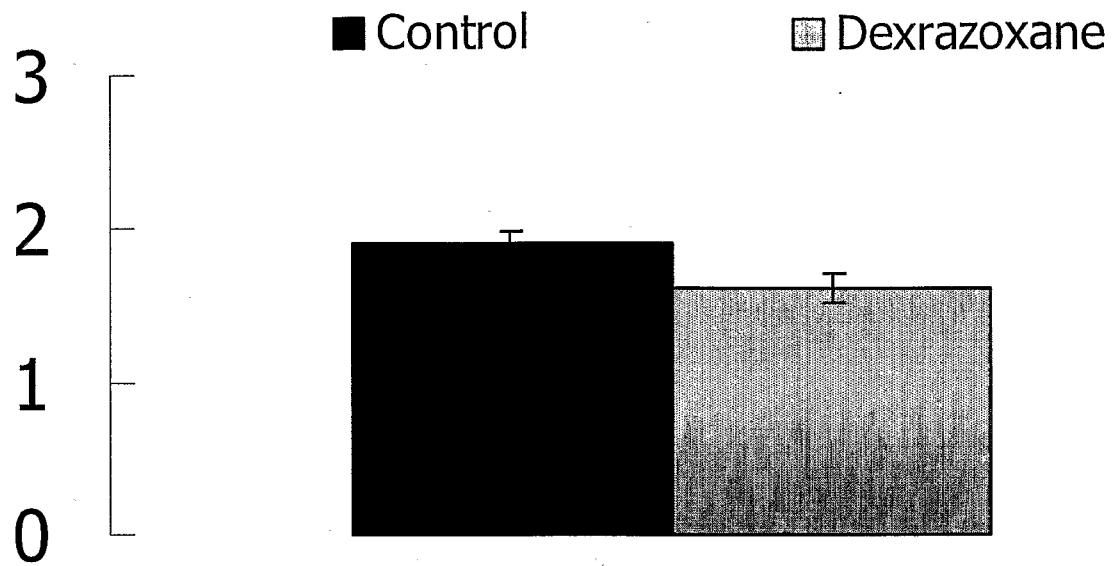
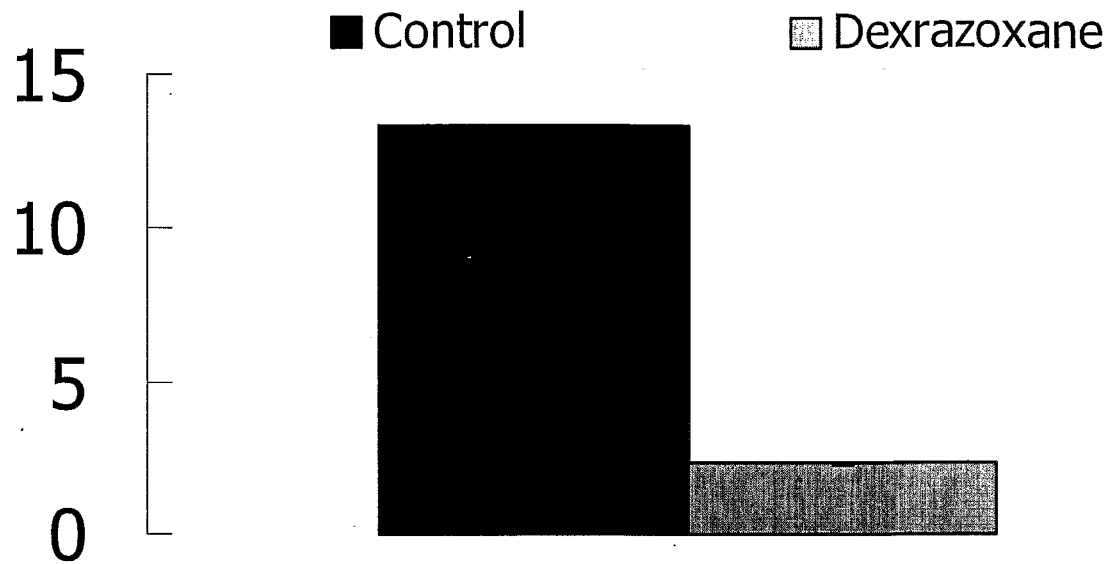


FIGURE 10



Coefficient of Variation was reduced by 15% of control
n=5

FIGURE 11



Coefficient of Variation was reduced by 83% of control
From 13.0 ± 0.02 to 2.3 ± 0.05 , $n=2$, $P<0.001$

FIGURE 12

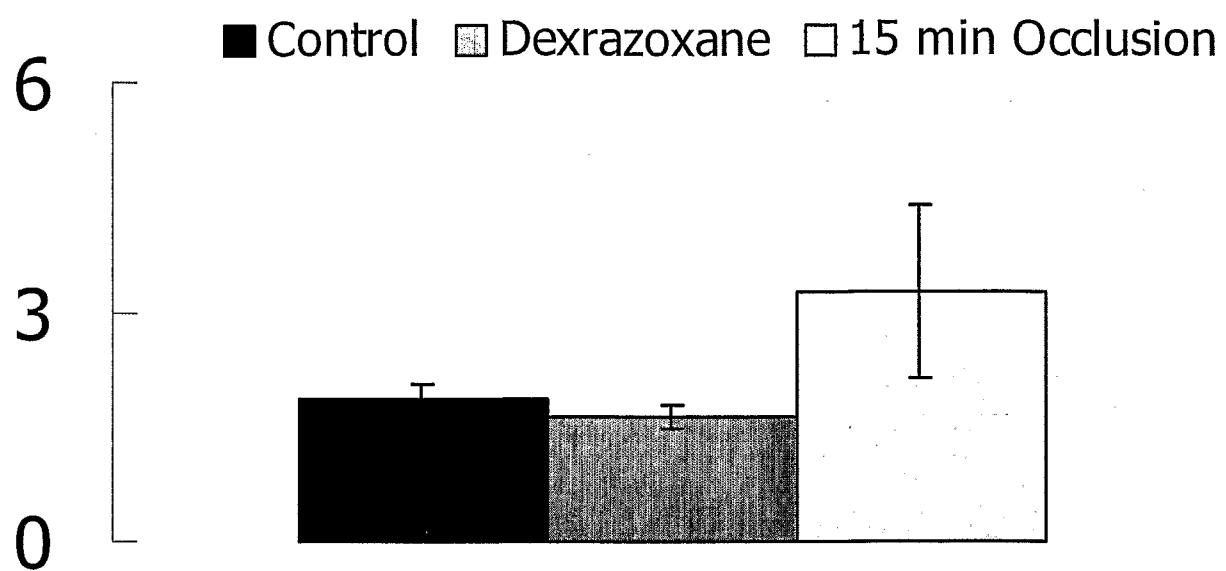


Figure 13

