Title: TRICYCLIC COMPOUNDS AND THEIR USES AS ANTIARRHYTHMIC ANTIFIBRILLATORY AND DEFIBRILLATORY AGENTS

Abstract: A compound having a general formula (II) wherein R₁ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C=(O)(CH₂)nNR'R", (CH₂)nCHOHCH₂NR'R", wherein n is an integer, R₀, R₁, R", and R" are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, alicyclic, or branched alkyl, substituted or unsubstituted (CH₂)n(hetero)aryl, and sulfonamide; q and r are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof, and the new therapeutic uses thereof and similar compounds as defibrillating, and/or anti-fibrillatory, and/or anti-arrhythmic and/or anti-ischemic drugs.
TRICYCLIC COMPOUNDS AND THEIR USES AS ANTIARRHYTHMIC ANTIFIBRILLATORY AND DEFIBRILLATORY AGENTS

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to tricyclic compounds of the 11-oxo-dibenzodiazepin and dibenzoazepin families, and their new therapeutic uses as defibrillating, and/or anti-fibrillatory, and/or anti-arrhythmic and/or anti-ischemic drugs. More particularly, the present invention relates to 5(N-acyl)-derivatives and 5(N-β-aminoalcohol)-derivatives of 11-Oxo-10,11-dihydro-dibenzo[b,e][1,4]diazepin and 10,11-dihydro-dibenzo[b,f]azepin, compositions including same, methods of their synthesis, purification and formulation and their use in prevention and treatment of cardiac disorders, such as, but not limited to, arrhythmia and ventricular fibrillation.

Sudden cardiac death is a leading cause of mortality, and ventricular fibrillation (VF) is thought to play a major role in sudden cardiac death [1]. Ventricular fibrillation can be divided into two categories: sustained VF (SVF), which is fatal, unless external defibrillating intervention is practiced, or transient VF (TVF), which terminates spontaneously. Currently, only one effective approach has been found to terminate SVF once SVF is initiated, which is the application of electrical defibrillation. Electrical defibrillation can be applied either externally or internally, by implantation. However, this approach has a number of disadvantages. For example, electrical defibrillation must be applied immediately to be effective, yet may not be sufficient, and may even cause damage. In addition, an implanted defibrillator requires invasive treatment. Thus, artificial defibrillation is not a cure, and does not prevent reoccurrence of VF.

Antiarrhythmic drugs constitute an alternative, preferable approach, as they are aimed at preventing initiation of VF by decreasing the incidence of ventricular arrhythmias that can lead to VF [2]. In addition, certain drugs, such as bretylium, have been shown to transform SVF into TVF [3]. The
effectiveness of this treatment, however, is limited, since various mechanisms can be involved in the initiation of VF, such that antiarrhythmic drugs are unlikely to absolutely eliminate arrhythmias and totally prevent VF initiation. Furthermore, recent surveys (such as the Cardiac Arrhythmia Suppression Trial, CAST, II and I [4,5]) have clearly shown limitations to this approach. Thus, a new cardiac protective therapy is needed. For this reason, a new approach has been proposed, to use a new class of antiarrhythmic drugs [6], which can enhance spontaneous termination of VF, once it occurs. In several animal species, and even, though rarely, in humans, VF can revert spontaneously into sinus rhythm, resulting in the non-fatal TVF. It has been previously found that several factors contribute to the ability to self-defibrillate. For example, self-defibrillation is a normal feature of young mammals, but this ability decreases with age [7]. Such spontaneous defibrillation requires a relatively high degree of intercellular synchronization [8], and is enhanced by increased sympathetic activity. Thus, treatments with compounds that elevate extraneuronal catecholamine levels in the heart enhance self-defibrillation and administration of β-adrenergic blockers abolishes this activity [9].

In order to design and synthesize new, more potent and selective defibrillatory drugs, it has been found that certain dibenzoazepins (imipramine, desipramine, maprotiline and bonnecore) and phenothiazins (chlorpromazin, moricizine and trifluoperazin), induce self-defibrillation and increase the threshold for electrical fibrillation [10, 11]. Moreover, tricyclic antidepressants, in addition to their antiarrhythmic and defibrillating effects, have the ability to decrease the ischemic area in the heart following coronary occlusion [12]. However, these cardio-protective effects of the compounds were expressed when relatively high doses were used, resulting in a low therapeutic index.

There is thus a need for, and it would be useful to have, pharmaceutically effective compounds which are safe and useful for the
treatment of ventricular fibrillation, particularly for the induction of TVF once SVF has been initiated, and for both treating and preventing pathological conditions associated with VF.

SUMMARY OF THE INVENTION

The present invention relates to 5(N-acyl)-derivatives and 5(N-β-aminoalcohol)-derivatives of 11-Oxo-10,11-dihydro-dibenzo[b,e][1,4]diazepin and 10,11-dihydro-dibenzo[b,f]azepin, compositions including same, methods of their synthesis, purification and formulation and their use in prevention and treatment of cardiac disorders. It is shown herein for the first time that these new tricyclic compounds and some previously known tricyclic compounds have been synthesized and have been shown to have substantial activity as chemical defibrillating agents.

According to the present invention, there is provided a compound having a general formula (I):

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R_q(q)      R_1
A-B           R_t(t)
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wherein A is CH, CR_2R_3 or C=O; B is CH, CR_4R_5 or NR_6, wherein R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH_2)_n-(hetero)aryl; or A and B together are C=C; R_1 is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C(=O)(CH_2)_nNR'R'', (CH_2)_nC'HOHCH_2NR'R'' (the chiral C, which is marked by * can be the R an antipode, the S an antipode, be in a racemic mixture or in any other ratio between the R and S antipodes), wherein n is an integer; R_q, R_t, R', and R'' are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH_2)_m-(hetero)aryl, and sulfonylamide; q and t are each an integer independently selected from 1-4; and pharmaceutically acceptable salts.
thereof.

Preferably, \( R_1 \) is selected from the group consisting of \( \beta \)-amino-alcohol, \( C(=O)(\text{CH}_2)_n\text{NR'}R'' \) and \( (\text{CH}_2)_n\text{CHOHCH}_2\text{NR'}R'' \) wherein \( n \) is an integer and further wherein the chiral carbon atom can be the R or S enantiomer, a racemic mixture thereof or a mixture of any ratio thereof; and \( R', R'' \) are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl; and pharmaceutically acceptable salts thereof. Examples of suitable alkyl moieties include but are not limited to \( \text{iso}-\text{propyl}, \text{iso}-\text{butyl}, \text{tert}-\text{butyl} \) and \( \text{sec}-\text{butyl} \). Most preferably, \( R'' \) is \( \text{iso}-\text{propyl} \).

According to a preferred embodiment of the present invention, A and B are each an alkyl chain, more preferably a CH moiety, \( R_2, R_3, R_4 \) and \( R_5 \) are each hydrogen, and \( R_1 \) is \( C(=O)(\text{CH}_2)_n\text{NR'}R'' \) and \( (\text{CH}_2)_n\text{CHOHCH}_2\text{NR'}R'' \), \( n \) being 0-5. Preferably, \( R \) and \( R' \) are each hydrogen and \( R'' \) is selected from the group consisting of methyl, ethyl, propyl, \( \text{iso}-\text{propyl}, \text{n}-\text{butyl}, \text{sec}-\text{butyl}, \text{iso}-\text{butyl} \) and \( \text{tert}-\text{butyl} \).

According to a preferred embodiment of the present invention A is \( \text{CR}_2\text{R}_3 \) or \( \text{C}=\text{O} \) and B is \( \text{CR}_4\text{R}_5 \); \( R, R_2, R_3, R_4, R_5 \) and \( R_6 \) are each a hydrogen, and \( R_1 \) is \( C(=O)(\text{CH}_2)_n\text{NR'}R'' \) and \( (\text{CH}_2)_n\text{CHOHCH}_2\text{NR'}R'' \), \( n \) being 0-5.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention relates to a group of compounds, based upon the general backbone structure of tricyclic antidepressants, namely, 11-oxo-dibenzodiazepins and dibenzoazepins N-substituted at the 5 position, as well as to pharmaceutical compositions of these compounds and to their use in the treatment and prevention of ventricular fibrillation and ischemic damage by local or systemic application. More specifically, these compounds are demonstrated to have a defibrillating effect on ventricular fibrillation, once it actually occurs.
Previous studies, aimed at characterizing the structure-activity relationships of dibenzoazepins and phenothiazines accountable to improved defibrillating activity, have indicated the relevance of several structural features of the backbone of these molecules for their efficacy against ventricular fibrillation. First, activity of the tricyclic compounds correlated with higher (more bent) dihedral angle between the two benzo rings in the tricyclic skeleton. This angle is also considered to play a detrimental role in the type of central nervous system activity of these compounds, as well as their different selectivity towards catecholamine reuptake systems (such as noradrenaline, serotone and dopamine). Second, compounds with 5-N-substituted secondary aminoalkyl side chains (such as desipramine) exhibit higher defibrillatory activity, as opposed to tertiary alkylamine (such as in imipramine) and lastly, transition from aminoalkyl to aminoacyl in the side chain at position 10 of the phenothiazine tricyclic nucleus results in an increase in antiarrhythmic activity and decrease in psychotropic activity [10].

The development of the disclosed class of tricyclic compounds was based on the rationalized design of new compounds, aimed at more focused and selective activity as chemical defibrillators, as well as identifying additional molecules which are able to overcome shortcomings of the presently utilized approaches (electrical defibrillation, antiarrhythmic drugs, described above), and which are able to convert the fatal sustained ventricular fibrillation to the non-fatal transient one.

The experiments described below in the Examples section demonstrate that the disclosed compounds are indeed effective in transforming the potentially fatal VF type, SVF, to the spontaneously-defibrillating type, TVF. In addition, the preferred structure is indicated in terms of a structure-activity-relationship, indicating the importance of certain structural elements in obtaining potent, selective therapeutic activity, and minimizing untoward side effects. Thus, a compound according to the present invention includes derivatives of 5-(N-alkyl), 5-(N-acyl) and 5-(N-β-aminoalcohol) dibenzoazepins of the
general formula (II):

![Chemical Structure](image)

[II]

wherein $R_1$ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, $C(=O)(CH_2)_nNR'R''$ or $(CH_2)_nCHOHCH_2NR'R''$, wherein $n$ is an integer; $R_Q$, $R_T$, $R'$, and $R''$ are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted $(CH_2)_m$(hetero)aryl, and sulfonylamide; $q$ and $t$ are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof.

Preferably, $R_1$ is selected from the group consisting of $\beta$-amino-alcohol, $C(=O)(CH_2)_nNR'R''$, and $(CH_2)_nCHOHCH_2NR'R''$ wherein $n$ is an integer and $R'$, $R''$ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl; and pharmaceutically acceptable salts thereof. Examples of suitable alkyl moieties include but are not limited to iso-propyl, iso-butyl, tert-butyl and sec-butyl. Most preferably, $R''$ is iso-propyl. Also most preferably, $R_Q$ and $R_T$ are each a hydrogen, and $q$ and $t$ are each 4.

The compounds of the present invention are also useful as an active ingredient in a composition for treating or preventing a cardiac disorder, such as ventricular fibrillation, featuring a pharmaceutically effective amount of a tricyclic compound in combination with a pharmaceutically acceptable carrier, in which the tricyclic compound is of a general formula (I):

![Chemical Structure](image)
wherein A is CH, CR₂R₃ or C=O; B is CH, CR₄R₅ or NR₆, wherein R₂, R₃, R₄, R₅ and R₆ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH₂)ₙ-(hetero)aryl; or A and B together are C=C; R₁ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C(=O)(CH₂)ₙNR’R’’’, (CH₂)ₙCHOHCH₂NR’R’’’, wherein n is an integer; R₆, R₅, R’, and R’’’ are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH₂)ₙ-(hetero)aryl, and sulfonylamide; q and t are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof.

Preferably, R₁ is selected from the group consisting of β-amino-alcohol, C(=O)(CH₂)ₙNR’R’’, and (CH₂)ₙCHOHCH₂NR’R’’’ wherein n is an integer and R’, R’’’ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl; and pharmaceutically acceptable salts thereof. Examples of suitable alkyl moieties include but are not limited to iso-propyl, iso-butyl, tert-butyl and sec-butyl. Most preferably, R’’’ is iso-propyl.

According to a preferred embodiment of the present invention, A and B are each an alkyl chain, more preferably a CH moiety, R₂, R₃, R₄ and R₅ are each hydrogen, and R₁ is C(=O)(CH₂)ₙNR’R’’ and (CH₂)ₙCHOHCH₂NR’R’’’, n being 0-5. Preferably, R and R’ are each hydrogen and R’’’ is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl and tert-butyl.

According to a preferred embodiment of the present invention A is CR₂R₃ or C=O and B is CR₄R₅; R₁, R₂, R₃, R₄, R₅ and R₆ are each a hydrogen, and R₁ is C(=O)(CH₂)ₙNR’R’’ and (CH₂)ₙCHOHCH₂NR’R’’’, n being 0-5. More preferably, n is 1 or 2.

Hereinafter, the term “tricyclic compound” refers to 5-(N-acyl) or 5-(N-alkylβaminoalcohol)-derivatives or 5-(N-alkyl)-derivatives of
10,11-dihydro-dibenzo[b,f]azepin or 5-(N-acyl) or 5-(N-alkylβ-aminoalcohol)-derivatives or 5-(N-alkyl)-derivatives of 11-Oxo-10,11-dihydro-dibenzo[b,e][1,4]diazepin compounds of the present invention.

Hereinafter, the term “derivative” refers to the result of a chemically altering, modifying or changing a molecule or a portion thereof, such that the molecule either maintains or increases its functionality.

Hereinafter, the term "pharmaceutically acceptable carrier" refers to a carrier or a diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

Hereinafter, the term "pharmaceutically effective amount" refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated.

The composition of the present invention may be optionally and preferably designed for topical application such as a slow release or transdermal patch of the tricyclic compound. The composition for slow release includes particles including a slow release carrier (typically, a polymeric carrier), and the tricyclic compound. Slow release biodegradable carriers are well known in the art. These are materials that may form particles that may capture therein an active compound(s) and slowly degrade/dissolve under a suitable environment (e.g., aqueous, acidic, basic, etc.) and thereby degrade/dissolve in body fluids and release the active compound(s) therein.

Specifically, a slow release formulation or a transdermal patch of the tricyclic compound can be used in patients prone to cardiac disorders, such as arrhythmias, or with a known history of arrhythmic or fibrillatory episodes.

One particularly preferred embodiment of the present invention is parenteral administration of the tricyclic compound, for example intravenously. Further according to the present invention there is provided a method for treating or preventing a cardiac disorder, such as ventricular
fibrillation, in a subject, by administering a pharmaceutically effective amount
of a tricyclic compound of a general formula (I):

\[
R_1(t) \quad R_1(t) \quad R_1(t) \quad R_1(t)
\]

wherein A is CH, CR₂R₃ or C=O; B is CH, CR₄R₅ or NR₆, wherein R₂, R₃, R₄,
R₅ and R₆ are each independently selected from the group consisting of
hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched
alkyl, substituted or unsubstituted \((\text{CH}_₂\text{)_n-(hetero)aryl})\); or A and B together are
C=C; R₁ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl,
and C(=O)(CH₂)_nNR’R’’, (CH₂)_nCHOHCH₂NR’R’’, wherein \(n\) is an integer;
R₀, R₇, R’, and R’’ are each independently a hydrogen, halogen, hydroxyl,
saturated, unsaturated, aliphatic, or branched alkyl, substituted or
unsubstituted \((\text{CH}_₂\text{)_n-(hetero)aryl})\), and sulfonylamide; \(q\) and \(t\) are each an
integer independently selected from 1-4; and pharmaceutically acceptable salts
thereof.

Preferably, R₁ is selected from the group consisting of
\(\beta\)-amino-alcohol, C(=O)(CH₂)_nNR’R’’, and \((\text{CH}_₂)_nCHOHCH₂NR’R’’\) wherein
\(n\) is an integer and R’, R’’ are each independently selected from the group
consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or
branched alkyl; and pharmaceutically acceptable salts thereof. Examples of
suitable alkyl moieties include but are not limited to iso-propyl, iso-butyl,
tert-butyl and sec-butyl. Most preferably, R’’ is iso-propyl.

According to a preferred embodiment of the present invention, A and B
are each an alkyl chain, more preferably a CH moiety, R₂, R₃, R₄ and R₅ are
each hydrogen, and R₁ is C(=O)(CH₂)_nNR’R’’ and \((\text{CH}_₂)_nCHOHCH₂NR’R’’\),
n being 0-5. Preferably, n is 1 or 2. Preferably, R and R’ are each hydrogen
and R’’ is selected from the group consisting of methyl, ethyl, propyl,
iso-propyl, n-butyl, sec-butyl, iso-butyl and tert-butyl.
According to a preferred embodiment of the present invention A is CR₂R₃ or C=O and B is CR₄R₅; R, R₂, R₃, R₄, R₅ and R₆ are each a hydrogen, and R₁ is C=O(CH₂)nNR’R’’ and (CH₂)nCHOHCH₂NR’R’’, n being 0-5.

Preferably, this method of treatment with the compositions of the present invention is used as an adjunct or additive therapy for patients with implanted defibrillators, in order to combine the electrical defibrillation with the chemical defibrillation. The utility of such a combination has been previously shown [M.T. Neuman, PhD Thesis, 1995, Tel Aviv University, Tel Aviv, Israel].

Herein, the term "treating" includes substantially inhibiting or completely stopping episodes of cardiac dysfunction, such as ventricular fibrillation, in a subject.

Herein, the term "preventing" refers to a method for barring a subject from exhibiting symptoms of a cardiac disorder, such as ventricular fibrillation, or alternatively for at least reducing the likelihood and/or severity of such symptoms arising in the subject. Further according to the present invention there is provided a method of locally treating a disorder of a tissue of a subject comprising the step of locally applying the herein above described composition to the tissue. The method includes the steps of applying the composition to an implant and inserting the implant into a tissue, such as cardiac tissue. Alternatively, the composition can be applied to a transdermal patch, which is applied to the skin for system absorption.

Also according to the present invention, there is provided a method for preventing ischemia in the cardiac tissue of a subject, by administering the above-referenced compound of the present invention to the subject.

A precise understanding of the mechanism by which the tricyclic compounds of the present invention cause such chemical defibrillation is not required in order to practice the present invention. However, while not wishing to be bound to any particular mechanism or theory, it is believed that increased catecholamine levels, induced by the compounds of the present invention, are
involved in the process. Several lines of evidence support this hypothesis. For example, the evaluation of intra- and inter-species differences for the ability to defibrillate spontaneously have indicated the central role of cardiac autoregulation. In particular, TVF appears in animals with predominantly sympathetic autoregulation, while SVF appears in animals with predominantly vagal autoregulation. Within members of the same species, the ability to defibrillate spontaneously is a normal feature of young mammals, and this ability decreases with age. Respectively, cardiac autoregulation in young mammals is dominantly sympathetic and turns to a vagal predominance with age.

Furthermore, administration of either β-adrenergic blockers (e.g., propranolol or pindolol) or a parasympathomimetic agonist (e.g., acetylcholine or metacholine) in mammals exhibiting TVF, prolongs the duration of TVF and even transforms it into SVF. Lastly, self-defibrillation requires a relatively high degree of intercellular synchronization, which may be enhanced by elevated catecholamine levels. Thus, compounds which are known to elevate extraneuronal catecholamine levels in the heart, such as dibenzoazepins and phenothiazines, were identified to enhance ventricular self-defibrillation, an effect abolished by co-administration of β-adrenergic blockers [9, 14].

Furthermore, in a recent publication, the efficacy in defibrillating activity of dibenzoazepins and phenothiazines was directly related to their ability to inhibit noradrenaline uptake [10]. Alternatively, the compound, 11-Oxo-10,11-dihydro-5-(N-methyl)-propylaminodibenzo[b,e] diazepin, was previously suggested for application as a muscarinic receptor antagonist in PCT Application No. WO 91/10654], supporting the role of sympathetic predominance in potential defibrillating activity.

Thus, further according to the present invention there is provided a method of treating or preventing a cardiac disorder in a subject, by inducing cardiac sympathetic activity by administering the tricyclic compounds of the present invention as hereinafore described.
Additional objects, advantages, and novel features of the present invention will become apparent to one ordinarily skilled in the art upon examination of the following examples, which are not intended to be limiting. Additionally, each of the various embodiments and aspects of the present invention as delineated hereinabove and as claimed in the claims section below finds experimental support in the following examples.

**EXAMPLES**

Reference is now made to the following examples, which together with the above descriptions illustrate the invention in a non-limiting fashion. The following protocols and experimental details are referenced in the Examples that follow.

**Example 1**

*Synthesis of 10.11-dihydro-5-[(3-N-alkyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrrochloride compounds*

*Synthesis of 10.11-dihydro-5-[(3-chloro)1-oxopropyl]-5H-dibenzo[b,f]azepin:* The synthesis was performed as known in the literature (Schindler W.; Hafliger F.; Helvetica Chimica Acta 1954, 59, 472-483). To a solution of 5H-10,11-dihydro-dibenzo[b,f] azepin (0.85 gr., 4.359 mmol) in benzene (50 ml), 0.5 ml 3-chloropropionyl chloride (5.225 mmol) was added dropwise. The mixture was refluxed for 3 h, the solvent was removed under reduced pressure and the residue was washed with 5 % aq. HCl, followed by extraction with CH$_2$Cl$_2$ (20 ml). The resulting organic layer was dried over Na$_2$SO$_4$, and the crude product was purified by flash chromatography (silica gel, hexane-ethyl acetate 8:2), resulting in 1.133 gr. (91 % yield) of 10,11-dihydro-5-[(3-chloro)1-oxopropyl]-5-H-dibenzo[b,f]azepin, in the form of white crystals. NMR (CDCl$_3$): 7.16 (bs, 8H), 3.82 (m, 2H), 3.46 (m, 1H), 2.85 (m, 2H), 2.51 (m, 1H). MS (Cl): 286 (M$^+$).

Scheme 1 below illustrates the synthesis and structure of 10,11 dihydro-5-[(3-chloro)1-oxopropyl] 5-H-dibenzo[b,f]azepin:
Synthesis of 10,11-dihydro-5-[(3-N-alkyl)1-oxopropyl]5-H-dibenzo[b,f]azepin monohydrochloride: Synthesis of 10,11-dihydro-5-[(3-N-alkyl)1-oxopropyl]5-H-dibenzo[b,f]azepin derivatives was achieved by reaction of the 10,11-dihydro-5-[(3-chloro)1-oxopropyl]5-H-dibenzo[b,f]azepin as a starting material with the corresponding alkyl amine. The succeeding derivatives, wherein the 3-N-substituted alkyl is a methyl, an ethyl or an iso-propyl, (compounds 15a-c) were prepared following the below-described general procedure: A well-stirred suspension of 10,11-dihydro-5-[(3-chloro)1-oxopropyl]5-H-dibenzo[b,f]azepin (1.71 gr., 6.0 mmol) in ethanol (50 ml) was warmed to 65 °C. Alkylamine (10 mmol) was added dropwise. The mixture was stirred for 1 h at 65 °C, and then allowed to cool to room temperature. The mixture was washed with 5% aq. potassium bicarbonate and extracted with CH₂Cl₂ (20 ml). The organic layer was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was recrystallized from EtOAc at 0 °C. The precipitate was filtered to result in the appropriate free base. The solid was then dissolved in toluene and HCl was bubbled till a precipitate formed. The precipitate was filtered and dried under reduced pressure resulting in the appropriate monohydrochloride salt. Alternatively, wherein bulkier alkyl groups were used for substituting the 3-N alkyl, such as tert-butyl, sec-butyl, iso-butyl and benzyl (compounds 15d-g), the following procedure was used: A solution of 10,11-dihydro-5-[(3-chloro)1-oxopropyl]5-H-dibenzo[b,f] azepin (0.285 gr., 1.0 mmol) in iso-propanol (15 ml) and monoamine (15 ml) was refluxed overnight. The solvent was removed under reduced pressure, and the
crude product was recrystallized from EtOAc at 0 °C. The solid was dissolved in toluene and HCl was bubbled till a precipitate was formed. The precipitate was filtered and dried under reduced pressure resulting in the appropriate monohydrochloride salt.

Scheme 2 below illustrates the synthesis and general structure of 10,11-dihydro-5-[(3-N-alkyl)1-oxopropyl]-5-H-dibenzo[b,f]azepin monohydrochloride of both synthetic routes:

![Scheme 2](image)

**SCHEME 2 (15)**

(i) **10,11-dihydro-5-[(3-N-methyl)-1-oxopropyl]-5-H-dibenzo[b,f]azepin monohydrochloride:** The synthesis was performed according to the above synthetic scheme. 1.126 gr. (67 % yield) of light yellow solid was obtained. $^1$H NMR (D$_2$O): δ 6.87 (brm, 8H), 3.15 (s, 1H), 2.82 (brm, 4H), 2.47 (s, 3H), 2.24 (brm, 3H). FAB/MS 281 (M$^+$).

Scheme 3 below illustrates the structure of 10,11-dihydro-5-[(3-N-methyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrochloride:

![Scheme 3](image)

**SCHEME 3 (15 a)**

(ii) **10,11-dihydro-5-[(3-N-ethyl)1-oxopropyl]5-H-dibenzo[b,f]azepin monohydrochloride:** The synthesis was performed according to the above synthetic scheme. 1.129 gr. (64 % yield) of light yellow solid was obtained. $^1$H NMR (D$_2$O): δ 6.89 (brm, 8H), 3.12 (s, 1H), 2.84 (brm, 7H), 2.27
(brm, 2H), 1.02 (t, J=7.4, 3H). FAB/MS 295 (M+).

Scheme 4 below illustrates the structure of 10,11-dihydro-5-[(3-N-ethyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrochloride:

![Chemical Structure]

**SCHEME 4 (15 b)**

(iii) **10,11-dihydro-5-[(3-N-iso-propyl)1-oxopropyl]5-H-dibenzo[b,f]azepin monohydrochloride:** The synthesis was performed according to the above synthetic scheme. 1.219 gr. (66 % yield) of light yellow solid was obtained, with mp 199.1 °C. 1H NMR (D2O): δ 6.97 (brm, 8H), 3.14 (m, 1H), 2.97 (m, 4H), 2.67 (m, 1H), 2.42 (m, 1H), 2.38 (m, 2H), 1.08 (d, J=6.6, 6H). FAB/MS 309 (M+).

Scheme 5 below illustrates the structure of 10,11-dihydro-5-[(3-N-iso-propyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrochloride:

![Chemical Structure]

**SCHEME 5 (15 c)**

(iv) **10,11-dihydro-5-[(3-N-tert-butyl)1-oxopropyl]5-H-dibenzo[b,f]azepin monohydrochloride:** The synthesis was performed according to the above synthetic scheme. 280 mgr. (87 % yield) was obtained. 1H NMR (CDCl3): δ 7.24 (m, 8H), 3.39 (m, 2H), 2.85 (m, 5H), 2.51 (m, 1H), 1.26 (m, 9H). FAB/MS 323 (M+).

Scheme 6 below illustrates the structure of 10,11-dihydro-5-[(3-N-tert-butyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrochloride:
SCHEME 6 (15 d)

**(v)** 10,11-dihydro-5-[(3-N-sec-butyl)1-oxopropyl]5-H-dibenzo monohydrochloride: The synthesis was performed according to the above synthetic scheme. 241 mg. (75 % yield) was obtained. $^1$H NMR (CDCl$_3$): $\delta$ 7.25 (m, 8H), 3.37 (m, 2H), 2.97 (m, 5H), 2.79 (m, 2H), 1.52 (m, 2H). 0.99 (m, 6H). FAB/MS 323 (M$^+$).

Scheme 7 below illustrates the structure of 10,11-dihydro-5-[(3-N-sec-butyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrochloride:

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SCHEME 7 (15 e)

**(vi)** 10,11-dihydro-5-[(3-N-iso-butyl)1-oxopropyl]5-H-dibenzo monohydrochloride: The synthesis was performed according to the above synthetic scheme. 264 mg. (82 % yield) was obtained. $^1$H NMR (CDCl$_3$): $\delta$ 7.23 (m, 8H), 3.35 (m, 2H), 2.82 (m, 4H), 2.47 (m, 2H), 1.84 (m, 1H), 0.95 (d, J=6.6 Hz, 3H), 0.89 (d, J=6.6 Hz, 3H). FAB/MS 323 (M$^+$).

Scheme 8 below illustrates the structure of 10,11-dihydro-5- [(3-N-iso-butyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrochloride:
(vii) **10,11-dihydro-5-[(3-
benzyl)1-oxopropyl]5-H-dibenzo[b,f]azepin monohydrochloride:** The synthesis was performed according to the above synthetic scheme. 367 mg. (67% yield) was obtained. \[^1\text{H}\text{ NMR (CDCl}_3\text{)}: \delta 7.23 \text{ (m, 8H), 3.35 \text{ (m, 2H), 2.82 \text{ (m, 4H), 2.47 \text{ (m, 2H), 1.84 \text{ (m, 1H), 0.95 \text{ (d, J=6.6 Hz, 3H), 0.89 \text{ (d, J=6.6 Hz, 3H). FAB/MS 357 (M^+).}}}}

Scheme 9 below illustrates the structure of 10,11-dihydro-5- [(3-N-benzyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrochloride:

![Image of molecular structure for 10,11-dihydro-5-[(3-N-benzyl)1-oxopropyl]5-H-dibenzo[b,f]azepin monohydrochloride]

**SCHEME 9 (15 g)**

Scheme 9a describes the synthesis of the \(\beta\)-amino alcohol derivative according to the present invention, which was performed in two stages.

![Image of molecular structure for Scheme 9a]
10,11-dihydro-5-[N-2 methylloxirane]-5-H-dibenzo[b,f]azepin (20).

20r, 20s (Stage I):

To a solution of 5H-10,11-dihydro-dibenzo[b,f]azepin (1.320 g, 6.711 mmol, see Scheme 1, above) in benzene (50 ml) was added NaNH₂ (0.5 gr). The mixture was refluxed for 2 hr and epichlorohydrin (1 ml, 12.810 mmol) was added dropwise. The mixture was refluxed for 6 hr. The solvent was removed under reduced pressure, and the residue was washed with 5% aq HCl, and extracted with CH₂Cl₂ (20 ml). The organic layer was dried over Na₂SO₄ and the crude product was purified by flash chromatography (silica gel, hexane-ethyl acetate 9.5:0.5) to give 20, (0.75 g, 45%) in the form of white powder.¹H NMR (chloroform): 7.07 (bs, 4H), 6.93 (m, 2H), 6.73 (bt, 2H) 3.91 (m, 2H), 3.16 (m, 4H), 3.05 (m, 1H), 2.67 (d, 1H), 2.55 (d, 1H). MS (Cl): 251 (M⁺). (Scheme 9b)

10,11-dihydro-5-[N-β isopropylamino-2propanol]-5-H-dibenzo[b,f]azepin monohydrochloride, 25 bi, 25 bis, 25 bir (Stage II)

General procedure: A suspension of 20 (1.5 g, 5.0 mmol) in isopropanol (50 ml) was warmed to 30 °C, isopropyl amine (10 mmol) was added dropwise, the mixture was stirred overnight at this temperature and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the crude product was recrystallized from ethyl acetate at 0 °C. The precipitation was filtered to give the appropriate free base. The solid was dissolved in toluene and HCl was bubbled until a precipitate reappeared. The precipitation was filtered and dried under reduced pressure to give 25 bi salt.
$^1$H NMR (chloroform): 7.07 (bs, 4H), 6.93 (m, 2H), 6.73 (bt, 2H) 3.79 (m, 1H), 3.15 (s, 4H), 2.78 (m, 1H), 2.72 (d, 2H), 2.55 (d, 2H), 1.01 (d, 6H). MS (Cl): 311 (M$^+$).

**Example 2**

**Synthesis of 11-Oxo-10,11-dihydro-5-[(N-alkyl)1-oxopropyl]-5H-dibenzo[b,e][1,4]diazepin monohydrochloride compounds**

**Synthesis of 11 – Oxo - 10, 11 – dihydro - 5H – dibenzo [b,e] [1,4] diazepin:** The synthesis was performed according to the below synthetic scheme. A suspension of 2-chlorobenzoic acid (5.08 gr., 31.81 mmol), o-phenylenediamine (3.46 gr., 31.48 mmol), copper powder (2.14 gr., 31.7 mmol) and molecular sieves (3Å) in chlorobenzene (100 ml) was vigorously stirred at 130 °C for 8 h. The hot mixture was rapidly filtered and the filtrate was concentrated under reduced pressure. The solid precipitate was collected by filtration and then recrystallized from EtOH resulting in 11-Oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin 5.48 gr. (82 % yield) in the form of bright yellow powder. $^1$H NMR (acetone): 8.89 (s, 1H), 7.80 (d, J=7.7 Hz., 1H), 7.33 (t, J=7.3 Hz., 1H), 7.07 (m, 6H). FAB/MS: 211 (M$^+$).

Scheme 10 below illustrates the synthesis and structure of 11-Oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin monohydrochloride:

![Scheme 10 (1)](image)

**SCHEME 10 (1)**

**Synthesis of 11-Oxo-10,11-dihydro-5-[3-chloro]1-oxopropyl]-5H-dibenzo[b,e][1,4]diazepin:** The synthesis was performed according to the below synthetic scheme. To a solution of 11-Oxo-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin (0.376 gr., 1.79 mmol) in dry
THF, (10 ml) NaNH₂ (0.132 gr., 3.39 mmol) was added. The mixture was cooled to 0 °C, and 0.2 ml 3-chloropropionyl chloride (2.09 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C, allowed warming to room temperature, washed with 5 % aq. potassium bicarbonate and extracted with CH₂Cl₂ (20 ml). The resulting organic layer was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure. The crude product was crystallized from ether, resulting in 0.467 gr. (87 % yield) of 11-Oxo-10,11-dihydro-5-[(3-chloro)1-oxopropyl] 5-H-dibenzo[b,e] [1,4]diazepin in the form of a yellow solid, mp 241-242 °C. ¹H NMR (CDCl₃): 8.78 (s, 1H), 7.98 (s, 1H), 7.59 (s, 1H), 7.4-7.26 (m, 6H), 3.77 (m, 4H). FAB/MS: 301 (M⁺).

Scheme 11 below illustrates the synthesis and structure of 11-Oxo 10,11-dihydro-5-[(3-chloro)1-oxopropyl] 5-H-dibenzo[b,e] [1,4] diazepin:

![Scheme 11](image)

**Scheme 11 (6)**

*Synthesis of 11-Oxo-10,11-dihydro-5-[(N-alkyl)1-oxopropyl]5-H-dibenzo[b,e] [1,4]diazepin monohydrochloride*: The synthesis of the below described 11-Oxo-10,11-dihydro-5-[(N-alkyl)1-oxopropyl]5-H-dibenzo[b,e][1,4]diazepin hydrochloride compounds, 11a-c, was performed by reacting 11-Oxo-10,11-dihydro-5-[(3-chloro)1-oxopropyl]-5-H-dibenzo[b,e][1,4]diazepin, as a starting material, with the appropriate alkyl amine. A well-stirred suspension of 11-Oxo-10,11-dihydro-5-[(3-chloro)1-oxopropyl]-5-H-dibenzo[b,e][1,4]diazepin (1.5 gr., 5.0 mmol) in ethanol (50 ml) was warmed to 65 °C. Alkylamine (10 mmol) was added dropwise. The mixture was stirred for 1 h at 65 °C, and then allowed to cool to room temperature. The mixture was then washed with 5 % aq. potassium
bicarbonate and extracted thrice with CH$_2$Cl$_2$ (20 ml). The organic layer was
dried over Na$_2$SO$_4$, filtered and the solvent was removed under reduced
pressure. The crude product was recrystallized from EtOAc at 0 °C. The
precipitate was filtered to result in the appropriate free base. The solid was
then dissolved in toluene and HCl was bubbled till a precipitate formed. The
precipitate was filtered and dried under reduced pressure resulting in the
appropriate hydrochloride salt.

Scheme 12 below illustrates the synthesis and general structure of 11–
Oxo-10,11-dihydro-5-[(N-alkyl)1- oxopropyl] 5-H-dibenzo[b,e] [1,4]diazepin
monohydrochloride:

![Scheme 12](image)

**SCHEME 12 (11)**

(i) **Synthesis of 11–Oxo-10,11-dihydro-5-[(N-methyl)1- oxopropyl]
5-H-dibenzo[b,e] [1,4]diazepin monohydrochloride:** The synthesis was
performed according to the above synthetic scheme. The compound, in the
form of a light-pink solid was obtained, 627 mg. (44 % yield), with
mp=223-225 °C. $^1$H NMR (D$_2$O): δ 7.33 (br m, 8H), 3.06 (t, J=6 Hz, 2H), 2.9
(m, 1H), 2.48 (s, 3H), 2.36 (br m, 1H). FAB/MS 297 (M$^+$).

Scheme 13 below illustrates the structure of 11-Oxo-10,11-
dihydro-5-[(3-N- methyl)1-oxopropyl] 5-H-dibenzo[b,e][1,4]diazepin
monohydrochloride:
(ii) Synthesis of 11-Oxo-10,11-dihydro-5-[(N-ethyl)1-oxopropyl][5-H-dibenzo[b,e][1,4]diazepin monohydrochloride: The synthesis was performed according to the above synthetic scheme. The compound, in the form of light-yellow solid, was obtained, 1.023 gr. (66 % yield), with mp 243-245 °C. $^1$H NMR (D$_2$O): 7.40 (br m, 8H), 3.08 (t, J=6.1 Hz., 2H), 2.86 (m, 3H), 2.38 (m, 1H), 1.06 (t, J=7.3, 3H). FAB/MS: 311 (m$^+$). Scheme 14 below illustrates the structure of 11-Oxo-10,11- dihydro – 5 - [(N-ethyl)1-oxopropyl] – 5 - H-dibenzo [b,e] [1,4] diazepin hydrochloride:

(iii) Synthesis of 11-Oxo-10,11-dihydro-5-[(N-iso-propyl)1-oxopropyl][5-H-dibenzo[b,e][1,4]diazepin monohydrochloride: The synthesis was performed according to the above synthetic scheme. The compound, in the form of light-orange solid, was obtained, 791 mgr. (49 % yield). $^1$H NMR (D$_2$O): 7.35 (br m, 8H), 3.05 (br m., 3H), 2.85 (m, 1H), 2.33
(m, 1H), 1.08 (t, J=7.3, 3H). FAB/MS: 323 (m+).

Scheme 14 below illustrates the structure of 11-Oxo-10,11-dihydro-5-[(N-iso-propyl) 1-oxopropyl] 5-H-dibenzo [b,e] [1,4] diazepin monohydrochloride:

![Chemical structure](attachment:image.png)

**SCHEME 15(11 c)**

**Example 3**


**10,11-dihydro-5-[(N-2 methylloxirane]5-H-dibenzo[b,f]azepin (20).**

**20r, 20s:** To a solution of 5 (1.320 g, 6.711 mmol) in benzene (50 mL) was added NaNH₂ (0.5 gr). The mixture was refluxed for 2 hr and the appropriate epichlorohydrin (1 mL, 12.810 mmol) was added dropwise (racemic to obtain 20, R enantiomer to obtain 20r and S enantiomer to obtain 20s. The mixture was refluxed for 6 hrs. The solvent was removed under reduced pressure, and the residue was washed with 5% aq HCl, and extracted with CH₂Cl₂ (2 x 20 mL). The organic layer was dried over Na₂SO₄ and the crude product was purified by flash chromatography (silica gel, hexane-ethyl acetate 9.5:0.5) to give 20, (0.75 g, 45%) in the form of white powder. 1H NMR (chloroform): 7.07 (bs, 4H), 6.93 (m, 2H), 6.73 (bt, 2H) 3.91 (m, 2H), 3.16 (m, 4H), 3.05 (m, 1H), 2.67 (d, 1H), 2.55 (d, 1H). MS (Cl): 251 (M+).

Scheme 16 below illustrates the synthesis and structure of 10,11-dihydro-5-[(N-2 methylloxirane]5-H-dibenzo[b,f]azepin (20). 20r, 20s
SCHEME 16(20, 20r, 20s)


General procedure: A suspension of 20 (1.5 g, 5.0 mmol) in iso-propanol (50 ml) was warmed to 30 °C, iso-propylamine (10 mmol) was added dropwise, the mixture was stirred overnight at this temperature and then allowed to cool to room temperature. The solvent was removed under reduced pressure, and the crude product was recrystallized from ethyl acetate at 0 °C.

The precipitation was filtered to give the appropriate free base. The solid was dissolved in toluene and HCl was bubbled until a precipitation reappeared. The precipitation was filtered and dried under reduced pressure to give 25 bi salt. 1H NMR (chloroform): 7.07 (bs, 4H), 6.93 (m, 2H), 6.73 (bt, 2H) 3.79 (m, 1H), 3.15 (s, 4H), 2.78 (m, 1H), 2.72 (d, 2H), 2.55 (d, 2H), 1.01 (d, 6H). MS (CI): 311 (M+).

Example 4

Antiarrhythmic defibrillating activity of tricyclic dibenzoazepin and 11-Oxo-dibenzodiazepin compounds

10,11-dihydro-5-[(3-N-alkyl)1-oxopropyl] 5-H-dibenzo[b,f]azepin monohydrochloride, 10,11-dihydro-5-[N-?propylamino-2propanol)] 5-Hdibenzo [b,f]azepin monohydrochloride and 11-Oxo-10,11- dihydro – 5 - [(N-alkyl)1 - oxopropyl] – 5 - H-dibenzo [b,e] [1,4] diazepin hydrochloride were synthesized as is described herein above and tested for their effectiveness in transforming SVF to TVF, as described herein. The desired outcome was determined to be the ability of the drug molecule to reduce or abolish the occurrence of artificially induced SVF, and its transformation to the spontaneously defibrillating TVF. The experimental method was as follows.

Hydrochloride salts of the compounds were dissolved in saline. Activity of each compound was tested in cats of both sexes. Cats were anesthetized with 15-25 mg/kg intravenous sodium pentobarbital. The tested compounds were injected intravenously (1-3 mg/kg). The heart of each experimental subject was exposed through midline thoracotomy, and a room air respirator was applied through a tracheal cannula. Lead II electrocardiogram and intra-arterial blood pressure was recorded on a Grass
Polygraph (Grass Instrument Co., Quincy, MA, USA).

Fibrillating stimuli (a train of rectangular pulses of 2 to 15 V, 100 pulses/sec and duration of 0.1 to 1.0 msec, for a period of 1 sec) were delivered through two silver needle electrodes attached to the pericardium on the left ventricle. Fibrillating stimuli were one and a half to twice the strength of the fibrillating threshold.

Animals were designated as having SVF of VF failed to terminate spontaneously within 90 sec, and required electrical defibrillation. Animals that exhibited two to five consecutive episodes of VF of short (20 to 60 sec) duration were designated as having TVF. VF was induced before and after drug administration, according to a previously described procedure [13]. The type of VF was examined before and 2 to 3 min after drug treatment. Each cat served as its own control. In some experiments, a β-adrenergic blocker (propranolol, 0.1-0.6 mg/kg) was administered after drug administration, in order to evaluate the neutralizing effect of the blocker on the compound-induced catecholamine levels. Table 1 below presents the results.

**TABLE 1**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative activity in dosage of 1 mg/kg</th>
<th>Relative activity in dosage of 2 mg/kg</th>
<th>Relative activity in dosage of 3 mg/kg</th>
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<tr>
<td>15a</td>
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<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>15b</td>
<td>50%</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>15c</td>
<td>64%</td>
<td>67%</td>
<td>83%</td>
</tr>
<tr>
<td>15d</td>
<td>44%</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>15e</td>
<td>0</td>
<td>0</td>
<td>33%</td>
</tr>
<tr>
<td>15f</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
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</tr>
<tr>
<td>11b</td>
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<td>50%</td>
</tr>
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<td>0</td>
</tr>
<tr>
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<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>25bir</td>
<td>50%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>25bis</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
</tr>
</tbody>
</table>
Example 5

Suitable formulations for administration of

cyclic dibenzoazepin and 11-Oxo-dibenzodiazepin compounds

The tricyclic dibenzoazepin and 11-Oxo-dibenzodiazepin derivatives of
the present invention, including free base or salt form, can be administered to a
subject in a number of ways, which are well known in the art. Hereinafter the
term “tricyclic dibenzoazepin derivatives” refers to the group of dibenzoazepin
derivatives in free base form and the group of dibenzoazepin derivatives in a
salt form. Hereinafter the term “tricyclic dibenzodiazepin derivatives” refers to
the group of dibenzodiazepin derivatives in free base form and the group of
dibenzodiazepin derivatives in a salt form. Hereinafter, the term “subject”
refers to the human or any lower animal to which the tricyclic dibenzoazepin
or 11-Oxo-dibenzodiazepin derivative is administered. For example,
administration may be done topically (including ophthalmically, vaginally,
rectally, intranasally), orally, or parenterally, for example by intravenous bolus
or drip, intraperitoneal, subcutaneous, or intramuscular (cardiac) injection.

Formulations for topical administration may include but are not limited
to lotions, ointments, gels, creams, suppositories, drops, liquids, sprays,
transdermal patches and powders. Conventional pharmaceutical carriers,
aqueous, powder or oily bases, thickeners and the like may be necessary or
desirable. In addition to the formulations described previously, a compound of
the present invention may also be formulated as a depot preparation. Such
long acting formulations may be administered by implantation (for example
subcutaneously or intramuscularly) or by intramuscular injection. Thus, for
example, the preparation may be formulated with suitable polymeric or
hydrophobic materials (for example, as an emulsion in an acceptable oil) or
ion exchange resins, or as sparingly soluble derivatives such as sparingly
soluble salts.
Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, sachets, capsules or tablets. Thickeners, diluents, flavorings, dispersing aids, emulsifiers or binders may be desirable.

Formulations for parenteral administration may include but are not limited to sterile aqueous solutions, which may also contain buffers, diluents and other suitable additives.

Dosing is dependent on the severity of the symptoms of arrhythmic or fibrillating occurrence and on the responsiveness of the subject to the tricyclic dibenzoazepin derivatives. Persons of ordinary skill in the art can easily determine optimum dosages, dosing methodologies and repetition rates.

**Example 6**

**Method of treatment or prevention of ventricular fibrillation**

As noted above, the compounds of the present invention, which are tricyclic dibenzoazepin and 11-Oxo-dibenzodiazipin derivatives, have been shown to be effective defibrillating agents. The following example is an illustration only of a method of treating VF with the dibenzoazepin and 11-Oxo-dibenzodiazipin derivatives, and is not intended to be limiting.

The method includes the step of administering the tricyclic dibenzoazepin or 11-Oxo-dibenzodiazipin derivatives, in a pharmaceutically acceptable carrier as described in Example 3 above, to a subject to be treated. The tricyclic dibenzoazepin or 11-Oxo-dibenzodiazipin derivative is administered according to an effective dosing methodology, preferably until a predefined endpoint is reached, such as the prevention of VF occurrence or abnormal cardiac activity. Optionally and preferably, the compound is administered parenterally.

According to another preferred embodiment of the present invention, the compound is used as an adjunct or additive treatment for a patient who has received an implanted defibrillator, such that the compound is administered to the patient as previously described.
Example 7

Method of manufacture of a medicament containing a tricyclic dibenzazepin and 11-Oxo-dibenzodiazepin derivative

The following is an example of a method of manufacturing a tricyclic dibenzazepin and 11-Oxo-dibenzodiazepin derivative. First, the tricyclic dibenzazepin or 11-Oxo-dibenzodiazepin derivative is synthesized in accordance with good pharmaceutical manufacturing practice. Examples of methods of synthesizing the tricyclic dibenzazepin and 11-Oxo-dibenzodiazepin derivatives were given previously herein. Next, the tricyclic dibenzazepin or 11-Oxo-dibenzodiazepin derivative is placed in a suitable pharmaceutical carrier, as described in Example 3 above, again in accordance with good pharmaceutical manufacturing practice.

It will be appreciated that the above descriptions are intended only to serve as examples, and that many other embodiments are possible within the spirit and the scope of the present invention.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims.
LIST OF REFERENCES CITED


11. Kaverina N.V., Skoldinov A.P. New cardiovascular drugs among
WHAT IS CLAIMED IS:

1. A compound having a general formula (II):

   ![Chemical Structure]

   wherein R₁ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C(=O)(CH₂)nNR’R’’, (CH₂)nCHOHCH₂NR’R’’, wherein n is an integer; R₉, R₇, R’, and R’’ are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH₂)m-(hetero)aryl, and sulfonylamide; q and t are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein R₁ is C(=O)(CH₂)nNR’R’’, n being 0-5, R’, R₉, R₇, are each a hydrogen and R’’ is as defined above.

3. The compound of claim 2, wherein n is 2 and R’’ is an alkyl selected from the group consisting of propyl, n-butyl, tert-butyl and with the proviso that R’’ is not a methyl or an ethyl moiety.

4. The compound of claim 2, wherein n is 1 or 2 and R’’ is saturated or unsaturated (CH₂)m-cycloalkyl or (CH₂)m-(hetero)aryl, m being 0-5.

5. The compound of claim 4, wherein m is 1 and R’’ is an aromatic 6-member ring.
6. A composition for treating or preventing a cardiac disorder, comprising a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carrier selected from the group consisting of a slow release carrier, an implant and a transdermal patch, said compound being a member of a group having the formula:

\[
\begin{array}{c}
\text{R}_2(q) \quad \text{A-B} \quad \text{R}_7(t) \\
\text{R}_1
\end{array}
\]

wherein,

A is CH, CR₂R₃ or C=O; B is CH, CR₄R₅ or NR₆, wherein R₂, R₃, R₄, R₅ and R₆ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH₂)m-(hetero)aryl; or A and B together are C=C; R₁ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C(=O)(CH₂)nNR’R’’, (CH₂)nCHOHCH₂NR’R’’, wherein n is an integer; R₀, R₇, R’, and R’’ are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH₂)m-(hetero)aryl, and sulfonylamide; q and t are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof.

7. The composition of claim 6, wherein A and B are each a carbon, R₂, R₃, R₄ and R₅ are each a hydrogen, and R₁ is C(=O)(CH₂)nNR’R’’, n being 0-5, R’ and R are each hydrogen and R’’ is as defined above.

8. The composition of claim 7, wherein n is 1 or 2 and R’’ is an alkyl selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, and tert-butyl.
9. The composition of claim 7, wherein \( n \) is 1 or 2 and \( R'' \) is saturated or unsaturated \((\text{CH}_2)_m\)-cycloalkyl or \((\text{CH}_2)_m\)-(hetero)aryl, \( m \) being 0-5.

10. The composition of claim 9, wherein \( m \) is 1 and \( R'' \) is an aromatic 6-member ring.

11. The composition of claim 6, wherein \( A \) is \( \text{CR}_2\text{R}_3 \) or \( 
\text{C}=\text{O} \) and \( B \) is \( \text{CR}_4\text{R}_5; \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5 \) and \( \text{R}_6 \) are each a hydrogen, and \( R_1 \) is \( \text{C}(=\text{O})(\text{CH}_2)_n\text{NR'}\text{R''} \), \( n \) being 0-5, \( R \) and \( R' \) are each hydrogen and \( R'' \) is as defined above.

12. The composition of claim 11, wherein \( n \) is 2 and \( R'' \) is an alkyl selected from the group consisting of ethyl, propyl, \( \text{n-butyl} \), \( \text{iso-butyl} \), \( \text{tert-butyl} \) and \( \text{sec-butyl} \).

13. The composition of claim 11, wherein \( n \) is 2 and \( R'' \) is saturated or unsaturated \((\text{CH}_2)_m\)-(hetero)aryl, \( m \) being 0-5.

14. A method for treating or preventing a cardiac disorder in a subject, the method comprising the step of administering a pharmaceutically effective amount of a compound, said compound being a member of a group having the formula:

![Chemical Structure](image)

wherein,

\( A \) is \( \text{CH} \), \( \text{CR}_2\text{R}_3 \) or \( 
\text{C}=\text{O} \); \( B \) is \( \text{CH} \), \( \text{CR}_4\text{R}_5 \) or \( \text{NR}_6 \), wherein \( \text{R}_2, \text{R}_3, \text{R}_4, \)
R₅ and R₆ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH₂)m-(hetero)aryl; or A and B together are C=C; R₁ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C(=O)(CH₂)nNR'R'', (CH₂)nCHOHCH₂NR'R'', wherein n is an integer; R₉, R₇, R', and R'' are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH₂)m-(hetero)aryl, and sulfonylamide; q and t are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof.

15. The method of claim 14, wherein A and B are each a CH moiety, R₂, R₃, R₄ and R₅ are each a hydrogen, and R₁ is C(=O)(CH₂)nNR'R'', n being 0-5, R and R' are each hydrogen and R'' is as defined above.

16. The method of claim 14, wherein n is 2 and R'' is an alkyl selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl and sec-butyl.

17. The method of claim 15, wherein n is 2 and R'' is saturated or unsaturated (CH₂)m-(hetero)aryl, m being 0-5.

18. The method of claim 14, wherein A is CR₂R₃ or C=O and B is CR₄R₅; R₂, R₃, R₄, R₅ and R₆ are each a hydrogen, and R₁ is C(=O)(CH₂)nNR'R'', n being 0-5, R and R' are each hydrogen and R'' is as defined above.

19. The method of claim 18, wherein n is 2 and R'' is an alkyl selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, and tert-butyl.
20. The method of claim 18, wherein n is 2 and \( R'' \) is saturated or unsaturated \((CH_2)_m\)-heteroaryl, m being 0-5.

21. The method of claim 14, wherein the cardiac disorder is ventricular fibrillation or ischemia.

22. The method of claim 15, wherein said compound is administered to the subject parenterally.

23. The method of claim 15, wherein an implanted defibrillator is implanted in the subject, such that said compound is an adjunct treatment to defibrillation by said implanted defibrillator.

24. A method for stopping the occurrence of ventricular fibrillation in a subject, the method comprising the step of administering a pharmaceutically effective amount of a compound, said compound being a member of a group having the formula:

\[
\begin{array}{c}
\text{R}_1 \\
N \\
\text{A-B} \\
\text{R}_2(q) \\
\end{array}
\]

wherein,
A is CH, CR_2R_3 or C=O; B is CH, CR_4R_5 or NR_6, wherein R_2, R_3, R_4, R_5 and R_6 are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted \((CH_2)_m\)-heteroaryl; or A and B together are C=C; \( R_1 \) is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C(=O)(CH_2)_nNR''R''', (CH_2)_nCHOHCH_2NR''R''', wherein \( n \) is an integer; \( R_Q \),
R', R', and R'' are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted \((\text{CH}_2)_{m-}\) (hetero)aryl, and sulfonylamide; \(q\) and \(t\) are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof.

25. The method of claim 24, wherein A and B are each a CH moiety, R, R_1, R_3, R_4 and R_5 are each a hydrogen, and R_1 is C(=O)(\text{CH}_2)_n NR'R''', n being 0-5, R and R' are each hydrogen and R'' is as defined above.

26. The method of claim 25, wherein n is 2 and R''' is an alkyl selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, and tert-butyl.

27. The method of claim 25, wherein n is 2 and R''' is saturated or unsaturated \((\text{CH}_2)_m\) (hetero)aryl, m being 0-5.

28. The method of claim 24, wherein A is CR_2R_3 or C=O and B is CR_4R_5; R_2, R_3, R_4, R_5 and R_6 are each a hydrogen, and R_1 is C(=O)(\text{CH}_2)_n NR'R''', n being 0-5 and R' is a hydrogen and R''' is as defined above.

29. The method of claim 28, wherein n is 2 and R''' is an alkyl selected from the group consisting of ethyl, propyl, n-butyl, iso-butyl, tert-butyl and sec-butyl.

30. The method of claim 28, wherein n is 2 and R''' is saturated or unsaturated \((\text{CH}_2)_m\) (hetero)aryl, m being 0-5.

31. The method of claim 24, wherein said compound is administered
32. The method of claim 24, wherein an implanted defibrillator is implanted in the subject, such that said compound is an adjunct treatment to defibrillation by said implanted defibrillator.

33. A method of locally treating or preventing a disorder of a tissue of a subject comprising the step of locally applying onto said tissue a composition for treating or preventing a cardiac disorder, said composition comprising a pharmaceutically effective amount of a compound in combination with a pharmaceutically acceptable carrier, said compound being a member of a group having the formula:

![Chemical structure diagram](image)

wherein A is CH, CR$_2$R$_3$ or C=O; B is CH, CR$_4$R$_5$ or NR$_6$, wherein R$_2$, R$_3$, R$_4$, R$_5$ and R$_6$ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH$_2$)$_m$-(hetero)aryl; or A and B together are C=C; R$_1$ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C(=O)(CH$_2$)$_n$NR’R’’, (CH$_2$)$_n$CHOHCH$_2$NR’R’’, wherein n is an integer; R$_Q$, R$_T$, R’, and R’’ are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH$_2$)$_m$-(hetero)aryl, and sulfonamide; q and t are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof.

34. The method of claim 33, wherein the step of locally applying the
composition onto said tissue further comprises the steps of:

(i) applying the composition to an implant; and
(ii) inserting said implant into said tissue.

35. The method of claim 34, wherein said tissue is cardiac tissue.

36. The method of claim 32, wherein the step of locally applying the composition onto said tissue further comprises the steps of:

(i) applying the composition to a transdermal patch; and
(ii) applying said patch into said tissue.

37. The method of claim 36, wherein said tissue is skin.

38. A method for treating or preventing a cardiac disorder in a subject, the method comprising the step of inducing cardiac sympathetic activity by administering a compound to the subject, said compound being a member of a group having the formula:

\[
\begin{align*}
A & \rightarrow B \\
R_2(q) & \rightarrow R_1(t) \\
\end{align*}
\]

wherein,

- A is CH, CR₂R₃ or C=O; B is CH, CR₄R₅ or NR₆, wherein R₂, R₃, R₄, R₅ and R₆ are each independently selected from the group consisting of hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or unsubstituted (CH₂)ₙ-(hetero)aryl; or A and B together are C=C; R₁ is saturated or unsaturated alkyl, amino-alcohol, diamino, cycloalkyl, and C(=O)(CH₂)ₙNR’R’’; (CH₂)ₙCHOHCH₂NR’R’’, wherein n is an integer; R₉, R₅, R’, and R’’ are each independently a hydrogen, halogen, hydroxyl, saturated, unsaturated, aliphatic, or branched alkyl, substituted or
unsubstituted (CH$_2$)$_m$-(hetero)aryl, and sulfonylamide; $q$ and $t$ are each an integer independently selected from 1-4; and pharmaceutically acceptable salts thereof.

39. The method of claim 38, wherein A and B are each a CH moiety, R$_2$, R$_3$, R$_4$ and R$_5$ are each a hydrogen, and R$_1$ is C(=O)(CH$_2$)$_n$NR’R”, n being 0-5 and R and R’ are each hydrogen and R’” is as defined above.

40. The method of claim 39, wherein n is 2 and R’” is an alkyl selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl and sec-buty.

41. The method of claim 39, wherein n is 2 and R’” is saturated or unsaturated (CH$_2$)$_m$-(hetero)aryl, m being 0-5.

42. The method of claim 38, wherein A is CR$_2$R$_3$ or C=O and B is CR$_4$R$_5$; R$_2$, R$_3$, R$_4$, R$_5$ and R$_6$ are each a hydrogen, and R$_1$ is C(=O)(CH$_2$)$_n$NR’R”, n being 0-5 and R’ is a hydrogen and R’” is as defined above.

43. The method of claim 42, wherein n is 2 and R’” is an alkyl selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, and tert-butyl.

44. The method of claim 42, wherein n is 2 and R’” is saturated or unsaturated (CH$_2$)$_m$-(hetero)aryl, m being 0-5.

45. The method of claim 38, wherein the cardiac disorder is ventricular fibrillation or ischemia.