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(71) Applicant(s)
Merck Sharp & Dohme Corp.

(72) Inventor(s)
Wolkenberg, Scott;Nolt, Brad M.;Bilodeau, Mark T.

(74) Agent / Attorney
Spruson & Ferguson, Level 35 St Martins Tower 31 Market Street, Sydney, NSW, 2000

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(71) Applicant *(for all designated States except US)*: **MERCK & CO., INC.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **WOLKENBERG, Scott** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **BILODEAU, Mark, T.** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). **NOLT, M. Brad** [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(74) Common Representative: **MERCK & CO., INC.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

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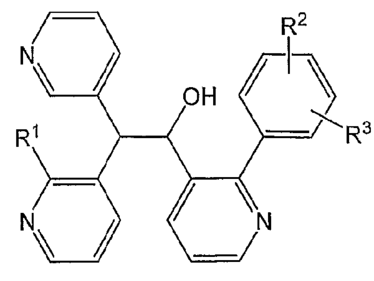
(54) Title: POTASSIUM CHANNEL INHIBITORS



(I)

(57) Abstract: The present invention relates to compounds having the structure useful as potassium channel inhibitors to treat cardiac arrhythmias, and the like.

TITLE OF THE INVENTION
POTASSIUM CHANNEL INHIBITORS

BACKGROUND OF THE INVENTION

The present invention relates broadly to compounds that are useful as potassium channel inhibitors. Compounds in this class may be useful as Kv1.5 antagonists for treating and preventing cardiac arrhythmias, and the like.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and is likely to increase in prevalence with the aging of the population. While AF is rarely fatal, it can impair cardiac function and lead to complications such as the development of congestive heart failure, thromboembolism, or ventricular fibrillation.

Currently available antiarrhythmic agents have been developed for the treatment of ventricular and atrial/supraventricular arrhythmias. Malignant ventricular arrhythmias are immediately life-threatening and require emergency care. Drug therapy for ventricular arrhythmia includes Class Ia (eg. procainamide, quinidine), Class Ic (eg. flecainide, propafenone), and Class III (amiodarone) agents, which pose significant risks of proarrhythmia. These Class I and III drugs have been shown to convert AF to sinus rhythm and to prevent recurrence of AF (Mounsey, JP, DiMarco, JP, *Circulation, 102*:2665-2670), but pose an unacceptable risk of potentially lethal ventricular proarrhythmia and thus may increase mortality (Pratt, CM, Moye, LA, *Am J. Cardiol., 65*:20B-29B, 1990; Waldo et al, *Lancet, 348*:7-12, 1996; Torp-Pedersen et al, *Expert Opin. Invest. Drugs, 9*:2695-2704, 2000). These observations demonstrate a clear unmet medical need to develop safer and more efficacious drugs for the treatment of atrial arrhythmias. Class III antiarrhythmic agents cause a selective prolongation of the APD without significant depression of cardiac conduction or contractile function. The only selective Class III drug approved for clinical use in atrial fibrillation is dofetilide, which mediates its anti-arrhythmic effects by blocking I_{Kr}, the rapidly activating component of I_K found in both atrium and ventricle in humans (Mounsey, JP, DiMarco, JP, *Circulation, 102*:2665-2670). Since I_{Kr} blockers increase APD and refractoriness both in atria and ventricle without affecting conduction per se, theoretically they represent potentially useful agents for the treatment of arrhythmias like AF (Torp-Pedersen, et al, *Expert Opin. Invest. Drugs, 9*:2695-2704, 2000). However, these agents have the major liability of an enhanced risk of proarrhythmia at slow heart rates.

The ultrarapid delayed rectifier K^+ current, I_{Kur}, has been observed specifically in human atrium and not in ventricle. The molecular correlate of I_{Kur} in the human atrium is the potassium channel designated Kv1.5. I_{Kur} is believed to contribute significantly to repolarization in human atrium. Consequently, a specific blocker of I_{Kur}, that is a compound which blocks Kv1.5, would overcome the shortcoming of other compounds by prolonging refractoriness through retardation of the repolarization in the human atrium without causing the delays in ventricular repolarization that underlie arrhythmogenic afterdepolarizations and acquired long QT syndrome observed during treatment with current Class III

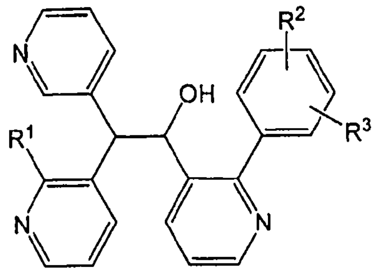
2006306541 10 Jun 2011

drugs. Kv1.5 blockers exhibiting these properties have been described (Peukert et al, *J. Med Chem, 46*:486-498, 2003; Knobloch et al, *Naunyn-Schmedieberg's Arch. Pharmacol. 366*:482-287, 2002; Merck & Co., Inc. WO 0224655, 2002).

The compounds described in this invention are Kv1.5 antagonists.

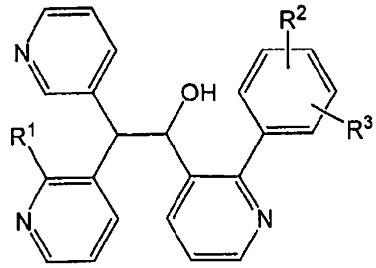
SUMMARY OF THE INVENTION

The invention concerns compounds of Formula I which antagonize the Kv1.5 potassium channel:



I

A first aspect of the invention provides for a compound of formula I,



I

or a pharmaceutically acceptable salt, or an optical isomer thereof, wherein:

R^1, R^2, and R^3 are independently selected from the group consisting of

1) hydrogen,
2) halogen,
3) NO_2,
4) CN,
5) $CR^4{=}C(R^4)_2$,
6) $C{\equiv}CR^4$
7) $(CR^5_2)_nOR^4$,
8) $(CR^5_2)_nN(R^4)_2$,
9) $(CR^5_2)_n\,C(O)R^4$,
10) $(CR^5_2)_n\,C(O)OR^4$,
11) $(CR^5_2)_nR^4$,

2006306541 10 Jun 2011

12) $(CR^5{}_2)_n\,S(O)_mR^4$,

13) $(CR^5{}_2)_n\,S(O)_mN(R^4)_2$,

14) $OS(O)_mR^4$,

15) $N(R^4)C(O)R^4$,

16) $N(R^4)S(O)_mR^4$,

17) $(CR^5{}_2)_nN(R^6)R^4$,

18) $(CR^5{}_2)_nN(R^4)(CR^5{}_2)_nC(O)N(R^4)_2$,

19) $(CR^5{}_2)_nN(R^4)(CR^5{}_2)_nC(O)OR^4$,

20) $N(R^4)(CR^5{}_2)_nR^4$,

21) $N(R^4)(CR^5{}_2)_nN(R^4)_2$,

22) $(CR^5{}_2)_nC(O)N(R^4)_2$,

23) $(CR^5{}_2)_nC(O)NH(CR^5{}_2)_nR^4$,

24) $(CR^5{}_2)_nC(O)NHC(R^4)_2(CR^5{}_2)_nN(R^4)_2$,

25) $C(O)NH(CR^5{}_2)(CR^5{}_3)$,

26) $S(O)_mR^5$, and

27) $N(R^4)(R^5)$;

R^4, in each instance in which it appears, is independently selected from the group consisting of

1) hydrogen,

2) C_1-C_6 alkyl,

3) C_3-C_{10} cycloalkyl,

4) aryl,

5) CF_3,

6) C_2-C_6 alkenyl, and

7) C_2-C_6 alkynyl,

or in the case where R^4 is attached to a nitrogen atom that is disubstituted with R^4, each R^4 is independently selected from C_1-C_6 alkyl, and the nitrogen atom together with each R^4 form a ring;

R^5, in each instance in which it appears, is independently selected from the group consisting of

1) hydrogen,

2) C_1-C_6 alkyl,

3) halogen,

4) aryl,

5) C_3-C_{10} cycloalkyl,

6) OR^4, and

7) CH_2OR^4,

m is independently selected from 0, 1 and 2; and

n is independently selected from 0, 1, 2, 3, 4, 5 and 6.

A second aspect of the invention provides for use of a compound of the first aspect of the invention, in the manufacture of a medicament, for treating a condition in a mammal, the treatment of which is effected or facilitated by $K_v1.5$ inhibition.

A third aspect of the invention provides for use of a compound of the first aspect of the invention, in the manufacture of a medicament, for treating cardiac arrhythmia or a thromboembolic event.

A fourth aspect of the invention provides for use of a compound of the first aspect of the invention, in the manufacture of a medicament, for preventing a condition in a mammal, the treatment of which is effected or facilitated by $K_v1.5$ inhibition.

A fifth aspect of the invention provides for use of a compound of the first aspect of the invention, in the manufacture of a medicament, for preventing cardiac arrhythmia or a thromboembolic event.

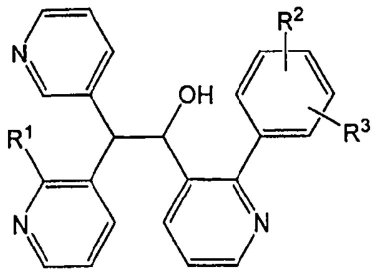
A sixth aspect of the invention provides for a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound the first aspect of the invention, or a pharmaceutically acceptable salt thereof.

A seventh aspect of the invention provides for a method for treating or preventing cardiac arrhythmia or a thromboembolic event in a patient, comprising administering to a patient a compound of the first aspect of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical formulation of the sixth aspect of the invention.

The compounds of this invention are useful in the treatment and prevention of cardiac arrhythmias, and the like. Also within the scope of this invention are pharmaceutical formulations comprising a compound of Formula I and a pharmaceutical carrier.

DETAILED DESCRIPTION OF THE DISCLOSURE

The invention includes compounds of Formula 1:



I

or a pharmaceutically acceptable salt, wherein:

R^1, R^2, and R^3 are independently selected from the group consisting of

1) hydrogen,
2) halogen,
3) NO_2,
4) CN,
5) $CR^4{=}C(R^4)_2$,
6) $C{\equiv}CR^4$,
7) $(CR^5{}_2)_nOR^4$,
8) $(CR^5{}_2)_nN(R^4)_2$,
9) $(CR^5{}_2)_n\,C(O)R^4$,

10) $(CR^5{}_2)_n\, C(O)OR^4$,
11) $(CR^5{}_2)_nR^4$,
12) $(CR^5{}_2)_n\, S(O)_mR^4$,
13) $(CR^5{}_2)_n\, S(O)_mN(R^4)_2$,
14) $OS(O)_mR^4$,
15) $N(R^4)C(O)R^4$,
16) $N(R^4)S(O)_mR^4$,
17) $(CR^5{}_2)_nN(R^6)R^4$,
18) $(CR^5{}_2)_nN(R^4)(CR^5{}_2)_nC(O)N(R^4)_2$,
19) $(CR^5{}_2)_nN(R^4)(CR^5{}_2)_nC(O)OR^4$,
20) $N(R^4)(CR^5{}_2)_nR^4$,
21) $N(R^4)(CR^5{}_2)_nN(R^4)_2$,
22) $(CR^5{}_2)_nC(O)N(R^4)_2$,
23) $(CR^5{}_2)_nC(O)NH(CR^5{}_2)_nR^4$,
24) $(CR^5{}_2)_nC(O)NHC(R^4)_2(CR^5{}_2)_nN(R^4)_2$,
25) $C(O)NH(CR^5{}_2)(CR^5{}_3)$,
26) $S(O)_mR^5$, and
27) $N(R^4)(R^5)$;

R^4, in each instance in which it appears, is independently selected from the group consisting of

1) hydrogen,
2) unsubstituted or substituted C_1-C_6 alkyl,
3) unsubstituted or substituted C_3-C_{10} cycloalkyl,
4) unsubstituted or substituted aryl,
5) unsubstituted or substituted heterocycle,
6) CF_3,
7) unsubstituted or substituted C_2-C_6 alkenyl, and
8) unsubstituted or substituted C_2-C_6 alkynyl,

or in the case where R^4 is attached to a nitrogen atom that is disubstituted with R^4, each R^4 is independently selected from C_1-C_6 alkyl, and the nitrogen atom together with each R^4 form a ring;

R^5, in each instance in which it appears, is independently selected from the group consisting of

1) hydrogen,
2) C_1-C_6 alkyl,
3) halogen,
4) aryl,
5) heterocycle,
6) C_3-C_{10} cycloalkyl,
7) OR^4, and

8) CH_2OR^4,

said alkyl, aryl, heterocycle and cycloalkyl is unsubstituted or substituted with at least one substituent selected from R^6;

R^6, in each instance in which it appears, is independently selected from the group consisting of

1) hydrogen,
2) unsubstituted or substituted C_1-C_6 alkyl,
3) halogen,
4) OR^5,
5) CF_3,
6) unsubstituted or substituted aryl,
7) unsubstituted or substituted C_3-C_{10} cycloalkyl,
8) unsubstituted or substituted heterocycle,
9) $S(O)_mN(R^4)_2$,
10) $C(O)OR^4$,
11) $C(O)R^4$,
12) CN,
13) $C(O)N(R^4)_2$,
14) $N(R^4)C(O)R^4$,
15) $N(R^4)C(O)OR^4$,
16) $N(R^4)C(O)N(R^4)_2$,
17) $OC(O)N(R^4)_2$,
18) $S(O)_mR^4$,
19) $OS(O)_mR^4$,
20) NO_2,
21) $N(R^4)_2$;
22) $SC(O)R^4$,
23) $N(R^4)S(O)_mR^4$, and
24) $S(O)_mR^5$;

wherein R^4 is independently selected from the group as defined above;

m is independently selected from 0, 1 and 2; and

n is independently selected from 0, 1, 2, 3, 4, 5 and 6.

In one embodiment of the compounds of Formula I, or a pharmaceutically acceptable salt thereof, R^1 is selected from the group consisting of hydrogen and halogen. A preferred group of this embodiment consists of hydrogen and F. Within this subset, all other variables are as originally defined.

In another embodiment of the compounds of Formula I, or a pharmaceutically acceptable salt thereof, R^2 is selected from the group consisting of hydrogen, halogen and CF_3. A preferred group of this embodiment consists of hydrogen, Cl and CF_3. Within this subset, all other variables are as originally defined.

In another embodiment of the compounds of Formula I, or a pharmaceutically acceptable salt thereof, R^3 is selected from the group consisting of hydrogen and halogen. A preferred group of this embodiment consists of hydrogen and Cl. Within this subset, all other variables are as originally defined.

Another embodiment of the invention includes a compound selected from the group consisting of:

1 1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol

2 2,2-dipyridin-3-yl-1-{2-[3-(trifluoromethyl)phenyl]pyridin-3-yl}ethanol

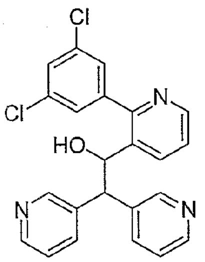
3 1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2-(2-fluoropyridin-3-yl)-2-pyridin-3-ylethanol

4 1-[2-(2-chlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol

5 1-[2-(2,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol

6 1-[2-(2,3-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol

Structures of the compounds listed above are shown below:



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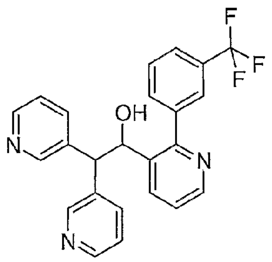

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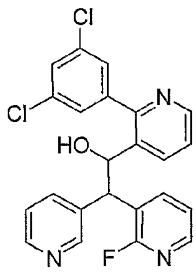

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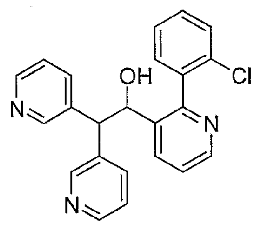

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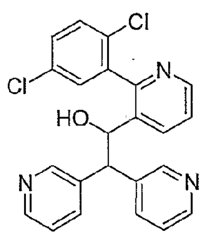

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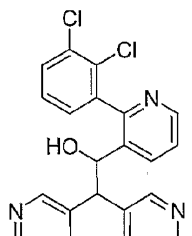

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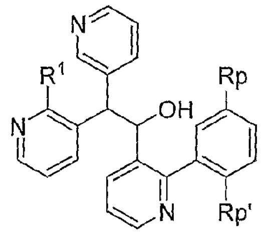
The compounds of the present invention may have chiral centers, e.g. one chiral center (providing for two stereoisomers, (R) and (S)), or two chiral centers (providing for up to four stereoisomers, (R,R), (S,S), (R,S), and (S,R)). This invention includes all of the optical isomers and mixtures thereof. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

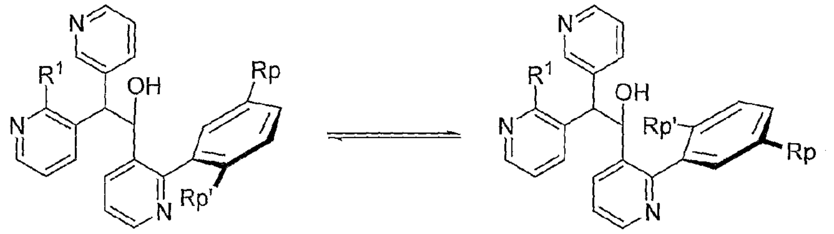
Tautomers of compounds defined in Formula I are also included within the scope of the present invention. For example, compounds including carbonyl $-CH_2C(O)-$ groups (keto forms) may undergo tautomerism to form hydroxyl $-CH=C(OH)-$ groups (enol forms). Both keto and enol forms are included within the scope of the present invention.

In addition compounds with carbon-carbon double bonds may occur in Z- and E- forms with all isomeric forms of the compounds being included in the present invention.

The compounds of the invention may exist as atropisomers, i.e., chiral rotational isomers. The invention encompasses the racemic and the resolved atropisomers. The following illustration generically shows a compound (Z) that can exist as atropisomers as well as its two possible atropisomers (A) and (B). This illustration also shows each of atropisomers (A) and (B) in a Fischer projection. In this illustration, R^1 carries the same definition as set forth for Formula I, R_p' is a substituent within the definition of R^2 or R^3, and R_p is a non-hydrogen substituent within the definition of R^2 or R^3.



Z



A B

The above-listed compounds are active in one or more of the assays for Kv1.5 described below.

Another embodiment of the invention is a method of treating or preventing a condition in a mammal, the treatment or prevention of which is effected or facilitated by $K_V1.5$ inhibition, which comprises administering an amount of a compound of Formula I that is effective at inhibiting $K_V1.5$.

A preferred embodiment is a method of treating or preventing cardiac arrhythmias, e.g. atrial fibrillation, atrial flutter, atrial arrhythmia, and supraventricular tachycardia, in a mammal, which comprises administering a therapeutically effective amount of a compound of Formula I.

Another preferred embodiment is a method of preventing thromboembolic events, such as stroke.

Another preferred embodiment is a method of preventing congestive heart failure.

Another preferred embodiment is a method for inducing in a patient having atrial fibrillation, a condition of normal sinus rhythm, in which the induced rhythm corresponds to the rhythm that would be considered normal for an individual sharing with the patient similar size and age characteristics, which comprises treating the patient with a compound of the invention.

Another preferred embodiment is a method for treating tachycardia, (i.e., rapid heart rate e.g. 100 beats per minute) in a patient which comprises treating the patient with an antitachycardia device (e.g. a defibrillator or a pacemaker) in combination with a compound of Claim 1.

The present invention also encompasses a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of Formula I or a pharmaceutically acceptable crystal form or hydrate thereof. A preferred embodiment is a pharmaceutical composition of the compound of Formula I, comprising, in addition, a second agent.

List of abbreviations:

AAS	atomic absorption spectroscopy
AF	atrial fibrillation
ACE	angiotensin converting enzyme
CHO	Chinese hamster ovary
DAST	(diethylamino)sulfur trifluoride
DMSO	dimethylsulfoxide
dppf	1,1'-(diphenylphosphino)ferrocene
EDTA	ethylenediaminetetraacetic acid
EGTA	ethylenebis(oxyethylenenitrilo)tetraacetic acid
FAAS	flame atomic absorption spetroscopy
FBS	fetal bovine serum
HBSS	Hank's balanced salt solution
HEPES	N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid
HF-Pyr	hydrogen fluoride pyridine
HPLC	high pressure liquid chromatography
LDA	lithium diisopropylamide
LYS	lysate
MS	mass spectrum
NaOtBu	sodium tert-butoxide
NMR	nuclear magnetic resonance
NSAID	non-steroidal antiinflammatory drug
PBS	phosphate-buffered saline
Pd_2dba_3	tris(dibenzylideneacetone)dipalladium(0)
RMS	root mean square deviation
RT	room temperature
SUP	supernatant

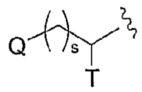
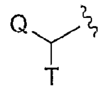
TBAF	tetrabuylammonium fluoride
TBDMSCl	tert-butyldimethylsilyl chloride
TBSCl	tert-butyldimethylsilyl chloride
THF	tetrahydrofuran

As used herein except where noted, "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbon atoms. Commonly used abbreviations for alkyl groups are used throughout the specification, e.g. methyl may be represented by "Me" or CH_3, ethyl may be represented by "Et" or CH_2CH_3, propyl may be represented by "Pr" or $CH_2CH_2CH_3$, butyl may be represented by "Bu" or $CH_2CH_2CH_2CH_3$, etc. "C_{1-6} alkyl" (or "C_1-C_6 alkyl") for example, means linear or branched chain alkyl groups, including all isomers, having the specified number of carbon atoms. C_{1-6} alkyl includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "C_{1-4} alkyl" means n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. The term "alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

The term "alkenyl" includes both branched and straight chain unsaturated hydrocarbon groups containing at least two carbon atoms joined by a double bond. The alkene ethylene is represented, for example, by "CH_2CH_2" or alternatively, by "$H_2C{=}CH_2$". "C_{2-5} alkenyl" (or "C_2-C_5 alkenyl") for example, means linear or branched chain alkenyl groups having from 2 to 5 carbon atoms and includes all of the pentenyl isomers as well as 1-butenyl, 2-butenyl, 3-butenyl, 1-propenyl, 2-propenyl, and ethenyl (or ethylenyl). Similar terms such as "C_{2-3} alkenyl" have an analogous meaning.

The term "alkynyl" includes both branched and straight chain unsaturated hydrocarbon groups containing at least two carbon atoms joined by a triple bond. The alkyne acetlyene is represented, for example, by "CHCH" or alternatively, by "HC≡CH". "C_{2-5} alkynyl" (or "C_2-C_5 alkynyl") for example, means linear or branched chain alkynyl groups having from 2 to 5 carbon atoms and includes all of the pentynyl isomers as well as 1-butynyl, 2-butynyl, 3-butynyl, 1-propynyl, 2-propynyl, and ethynyl (or acetylenyl). Similar terms such as "C_{2-3} alkynyl" have an analogous meaning.

Unless otherwise specifically noted as only "unsubstituted" or only "substituted", alkyl, alkenyl and alkynyl groups are unsubstituted or substituted with 1 to 3 substituents on each carbon atom, with halo, C_1-C_{20} alkyl, CF_3, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, NO_2, oxo, CN, N_3, -OH, -O(C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) S(O)$_{0-2}$-, (C_0-C_6 alkyl)S(O)$_{0-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, -O(C_1-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6 alkyl)O(C_1-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)$_{1-2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heterocycle, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

The term "C_0" as employed in expressions such as "C_{0-6} alkyl" means a direct covalent bond. Similarly, when an integer defining the presence of a certain number of atoms in a group is equal to zero, it means that the atoms adjacent thereto are connected directly by a bond. For example, in the structure , wherein s is an integer equal to zero, 1 or 2, the structure is  when s is zero.

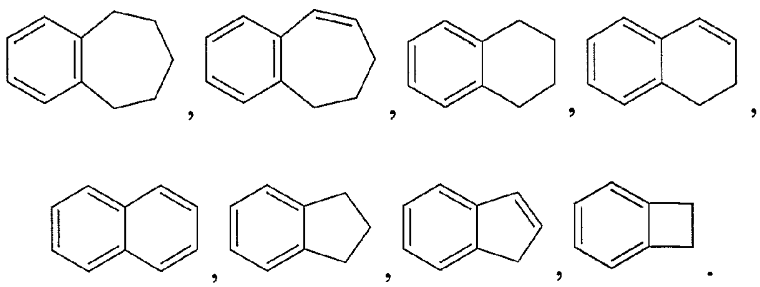
The term "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl). The terms "C_{3-7} cycloalkyl", "C_{3-6} cycloalkyl", "C_{5-7} cycloalkyl" and the like have analogous meanings.

The term "unsaturated", when used with reference to a ring, means a ring having the maximum number of non-cumulative ring double bonds. The term "saturated", when used with reference to a ring, means a ring having either partial (at least one ring double bond but less than the maximal number of ring double bonds) or complete (having no ring double bonds) saturation.

The term "halogen" (or "halo") refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (F), chloro (Cl), bromo (Br), and iodo (I)).

The term "C_{1-6} haloalkyl" (which may alternatively be referred to as "C_1-C_6 haloalkyl" or "halogenated C_1-C_6 alkyl") means a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents. The term "C_1-4 haloalkyl" has an analogous meaning. The term "C_{1-6} fluoroalkyl" has an analogous meaning except that the halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series $(CH_2)_{0-4}CF_3$ (i.e., trifluoromethyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-n-propyl, etc.).

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring or (ii) a C_7 to C_{12} bicyclic saturated or unsaturated ring system. Each ring in (ii) is either independent of, or fused to, the other ring, and each ring is saturated or unsaturated. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. The fused bicyclic carbocycles are a subset of the carbocycles; i.e., the term "fused bicyclic carbocycle" generally refers to a C_7 to C_{10} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. A fused bicyclic carbocycle in which one ring is saturated and the other is saturated is a saturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is saturated is an unsaturated bicyclic ring system. A fused bicyclic carbocycle in which one ring is benzene and the other is unsaturated is an unsaturated ring system. Saturated carbocyclic rings are also referred to as cycloalkyl rings, e.g., cyclopropyl, cyclobutyl, etc. Unless otherwise noted, carbocycle is unsubstituted or substituted with C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, halogen, NH_2 or OH. A subset of the fused bicyclic carbocycles are those bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include the following:



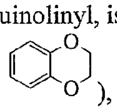
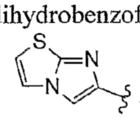
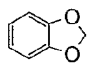
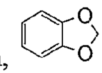
The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems, wherein the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. Suitable aryl groups include phenyl, naphthyl, and biphenylenyl.

The term “heterocycle” (and variations thereof such as “heterocyclic” or “heterocyclyl”) broadly refers to (i) a stable 4- to 8-membered, saturated or unsaturated monocyclic ring, or (ii) a stable 7- to 12-membered bicyclic ring system, wherein each ring in (ii) is bridged, fused, or spirocyclic, and independently saturated or unsatrurated, and the monocyclic ring or bicyclic ring system contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) selected from N, O and S and a balance of carbon atoms (the monocyclic ring typically contains at least one carbon atom and the ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. When the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

Unless otherwise specifically noted as only “unsubstituted” or only “substituted”, cycloalkyl, aryl and heterocycle groups are unsubstituted or substituted. As used herein, the terms “substituted C_3-C_{10} cycloalkyl”, “substituted aryl” and “substituted heterocycle” are intended to include the cyclic group containing from 1 to 4 substituents in addition to the point of attachment to the rest of the compound. Preferably, the substituents are selected from the group which includes, but is not limited to, halo, C_1-C_{20} alkyl, CF_3, NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, NO_2, oxo, CN, N_3, -OH, -O(C_1-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl)-S(O)$_{0\text{-}2}$-, aryl-S(O)$_{0\text{-}2}$-, (C_0-C_6 alkyl)S(O)$_{0\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, -O(C_1-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)$_{1\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

Saturated heterocyclics form a subset of the heterocycles; i.e., the term "saturated heterocyclic" generally refers to a heterocycle as defined above in which the ring system (whether mono- or poly-cyclic) is saturated. The term "saturated heterocyclic ring" refers to a 4- to 8-membered saturated monocyclic ring or a stable 7- to 12-membered bicyclic ring system which consists of carbon atoms and one or more heteroatoms selected from N, O and S. Representative examples include piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, indolyl, tetrahydroquinolinyl, benzoxazinyl, tetrahydroquinoxalinyl, benzodioxinyl, diazaspiro[4.4]nonanyl, piperazinone, and tetrahydrofuryl (or tetrahydrofuranyl).

Heteroaromatics form another subset of the heterocycles; i.e., the term "heteroaromatic" (alternatively “heteroaryl”) generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is an aromatic ring system. The term "heteroaromatic ring" refers a 5- or 6-membered monocyclic aromatic ring or a 7- to 12-membered bicyclic which consists of carbon atoms and one or more heteroatoms selected from N, O and S. In the case of substituted heteroaryl rings containing at least one nitrogen atom (e.g., pyridine), such substitutions can be those resulting in N-oxide formation. Representative examples of heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl.

Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, pyridinone, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e., ), imidazo(2,1-b)(1,3)thiazole, (i.e., ), and benzo-1,3-dioxolyl (i.e., ). In certain contexts herein,  is alternatively referred to as phenyl having as a substituent methylenedioxy attached to two adjacent carbon atoms.

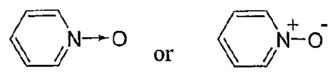
Unless expressly stated to the contrary, a “saturated” ring is a partially or completely saturated ring. For example, a “saturated monocyclic C_6 carbocycle” refers to cyclohexane.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocycle described as containing from "1 to 4 heteroatoms" means the heterocycle can contain 1, 2, 3 or 4 heteroatoms.

When any variable occurs more than one time in any constituent or in any formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

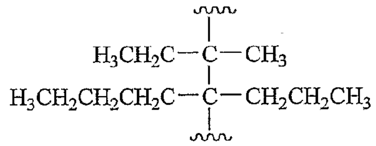
The term "substituted" (e.g., as in "aryl which is optionally substituted with one or more substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed.

In compounds of the invention having N-oxide moieties, e.g., pyridyl N-oxide moieties, the N-oxide moiety is structurally depicted using conventional representations. For example, a pyridyl-N-oxide portion is structurally depicted as



which have equivalent meanings.

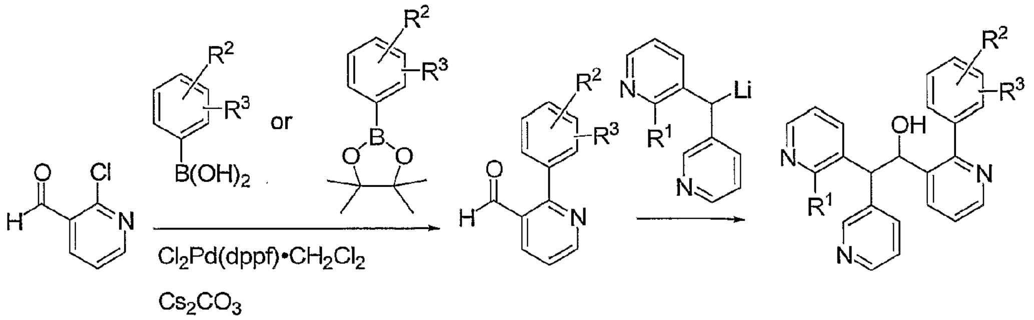
For variable definitions containing terms having repeated terms, e.g., $(CR^iR^j)_r$, where r is the integer 2, R^i is a defined variable, and R^j is a defined variable, the value of R^i may differ in each instance in which it occurs, and the value of R^j may differ in each instance in which it occurs. For example, if R^i and R^j are independently selected from the group consisting of methyl, ethyl, propyl and butyl, then $(CR^iR^j)_2$ can be



Pharmaceutically acceptable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydroscopicity and solubility. As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not limited to salts of inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate or salts of an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate or palmoate, salicylate and stearate. Similarly pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium (especially ammonium salts with secondary amines). Preferred salts of this invention for the reasons cited above include potassium, sodium, calcium and ammonium salts. Also included within the scope of this invention are crystal forms, hydrates and solvates of the compounds of Formula I.

Methods for preparing the compounds of this invention are illustrated in the following schemes and examples. Other synthetic protocols will be readily apparent to those skilled in the art. The schemes and examples illustrate the preparation of the compounds of Formula I and as such are not to be considered as limiting the invention set forth in the claims appended hereto. Examples described hereinafter comprises a further embodiment of the present invention.

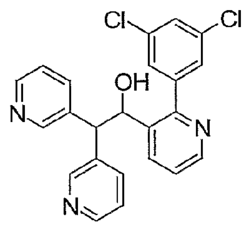
SCHEME 1



The variables R^1, R^2 and R^3 in the scheme are as defined in "Formula I".

EXAMPLE 1

1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol



Step A:

A solution of 2-chloro-3-pyridinecarboxaldehyde (961 mg, 6.79 mmol), 3,5-dichlorophenylboronic acid (1.29 g, 6.79 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (277 mg, 0.34 mmol) in THF (10 mL) was treated with aqueous Cs_2CO_3 (10 mL of a 1 M solution, 10 mmol) and sealed in a 20 mL microwave reaction tube. The mixture was irradiated at 160 °C for 20 min, cooled, diluted with 100 mL H_2O, and extracted with EtOAc (3 x 60 mL). The organic extracts were pooled, dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (120 g SiO_2, 0-20% EtOAc/hexanes gradient elution) to provide 2-(3,5-dichlorophenyl)nicotinaldehyde. ESI+ MS: 252.0 $[M+H]^+$.

Step B:

A solution of 3,3'-methylenedipyridine (340 mg, 1.99 mmol) in THF (20 mL) at -78 °C was treated with lithium diisopropylamide (2.65 mL of a 1.5 M solution of the mono-THF complex in cyclohexane, 3.98 mmol) dropwise. After stirring at -78 °C for 30 min, 2-(3,5-dichlorophenyl)nicotinaldehyde (500 mg as a solution in 6 mL THF, 1.99 mmol) was added dropwise via syringe. The reaction mixture was stirred for 1 h at -78 °C, warmed to 0 °C over 5 min, then quenched with the addition of 100 mL H_2O. The mixture was extracted with EtOAc (3 x 60 mL) and organic extracts were pooled, dried (Na_2SO_4), concentrated under reduced pressure, and purified by flash chromatography (40 g SiO_2, 0-10% MeOH/CH_2Cl_2 gradient elution) to provide racemic 1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol. Resolution was performed by HPLC using a chiral stationary phase (ChiralPak AD, 5 cm x 50 cm, 20 μ, 40-100% *i*-PrOH/hexanes gradient elution modified with 1 mL/L diethylamine, 80 mL/min) and provided the title compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (dd, J = 0.8, 4.7 Hz, 1H), 8.49 (d, J = 1.9 Hz, 1H), 8.46 (dd, J = 1.4, 4.8 Hz, 1H), 8.37 (dd, J = 1.8, 4.3 Hz, 1H), 8.06 (d, J = 1.3 Hz, 1H), 7.99 (dd, J = 1.7, 8.1 Hz, 1H), 7.63 (dt, J = 1.6, 7.9 Hz, 1H), 7.43 (dd, J = 1.8, 1.8 Hz, 1H), 7.34 (dd, J = 4.8, 8.0 Hz, 1H), 7.27 (m, 1H), 7.08 (m, 4H), 5.58 (d, J = 8.2 Hz, 1H), 4.15 (d, J = 8.2 Hz, 1H). HRMS [M+H] $C_{23}H_{17}Cl_2N_3O$ calcd 422.0822, found 422.0835.

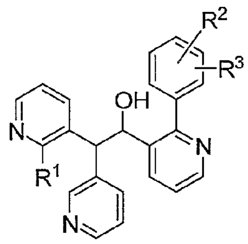
Kv1.5 HT-clamp IC_{50} values for racemic 1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol and specified enantiomers:

Racemic - 116 nM

(R)-1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol - 90 nM

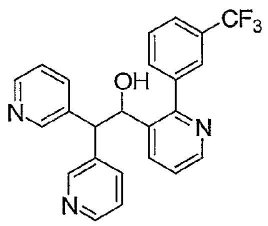
(S)-1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol - 2920 nM

The following compounds were made according to Scheme 1, where intermediates in the scheme were modified according to literature methods. Unless otherwise shown, structures of compounds in Examples 2-6 listed below are represented by defining variables R^1, R^2 and R^3 of the structure



EXAMPLE 2

2,2-dipyridin-3-yl-1-{2-[3-(trifluoromethyl)phenyl]pyridin-3-yl}ethanol



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (dd, J = 1.3, 4.5 Hz, 1H), 8.45 (d, J = 1.5 Hz, 1H), 8.43 (d, J = 4.5 Hz, 1H), 8.31 (d, J = 4.5 Hz, 1H), 8.04 (d, J = 1.5 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.58 (m, 2H), 7.51 (m, 2H), 7.31 (dd, J = 4.7, 7.9 Hz, 1H), 7.23 (dd, J = 4.8, 7.8 Hz, 1H), 7.03 (dt, J

= 1.7, 8.2 Hz, 1H), 6.99 (dd, J = 4.5, 7.8 Hz, 1H), 5.61 (d, J = 7.7 Hz, 1H), 4.12 (d, J = 7.7 Hz, 1H). HRMS [M+H] $C_{24}H_{18}F_3N_3O$ calcd 422.1475, found 422.1484.

Kv1.5 HT-clamp IC_{50} values for racemic 2,2-dipyridin-3-yl-1-{2-[3-(trifluoromethyl)-phenyl]pyridin-3-yl}ethanol and specified enantiomers:

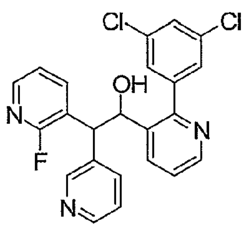
Racemic - 266 nM

Enantiomer A - 290 nM

Enantiomer B - 8218 nM

EXAMPLE 3

1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2-(2-fluoropyridin-3-yl)-2-pyridin-3-ylethanol



Isomer 1

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.81 (m, 1H), 8.59 (m, 2H), 8.15 (d, J = 4.7 Hz, 1H), 8.02 (dd, J = 8.3, 8.3 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.63 (m, 1H), 7.56 (m, 1H), 7.47 (m, 1H), 7.34 (dd, J = 4.9, 7.8 Hz, 1H), 7.24 (m, 3H), 5.77 (d, J = 4.7 Hz, 1H), 4.44 (d, J = 4.8 Hz, 1H). HRMS [M+H] $C_{23}H_{16}Cl_2FN_3O$ calcd 440.0727, found 440.0745.

Isomer 2

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.07 (m, 1H), 8.62 (m, 1H), 8.58 (d, J = 4.4 Hz, 1H), 8.11 (d, J = 5.0 Hz, 1H), 8.09 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.70 (m, 1H), 7.45 (dd, J = 1.8, 1.8 Hz, 1H), 7.41 (dd, J = 4.8, 8.1 Hz, 1H), 7.33 (m, 1H), 7.17 (d, J = 1.8 Hz, 2H), 7.05 (ddd, J = 1.6, 4.9, 7.1 Hz, 1H), 5.71 (d, J = 8.6 Hz, 1H), 4.60 (d, J = 8.3 Hz, 1H). HRMS [M+H] $C_{23}H_{16}Cl_2FN_3O$ calcd 440.0727, found 440.0741.

Kv1.5 HT-clamp IC_{50} values for the mixture of 1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2-(2-fluoropyridin-3-yl)-2-pyridin-3-ylethanol enantiomers and specified enantiomers:

Mix of 4 isomers: 85 nM

Isomer 1, Enantiomer A: 96 nM

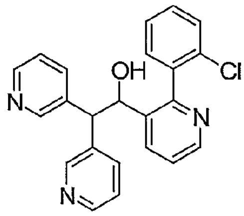
Isomer 1, Enantiomer B: 72% inhibition at 10000 nM

Isomer 2, Enantiomer A: 154 nM

Isomer 2, Enantiomer B: 89% inhibition at 10000 nM

EXAMPLE 4

1-[2-(2-chlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol



Isolated as a 2:1 mixture of atropisomers, as shown by the chemical exchange of various ROESY signals. [1]H NMR (600 MHz, $CDCl_3$): Major isomer δ 8.52 (m, 1H), 8.40 (m, 1H), 8.39 (m, 1H), 8.30 (m, 1H), 8.0 (s, 1H), 7.88 (d, J= 7.9 Hz, 1H), 7.65 (m, 1H), 7.47 (d, J= 8.2 H, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.29 (m, 1H), 7.21 (m, 1H), 7.10 (m, 1H), 7.01 (dd, J= 4.9, 7.6 Hz, 1H), 6.89 (d, J= 7.6 Hz, 1H), 5.32 (d, J= 6.8 Hz, 1H), 4.06 (d, J= 6.8 Hz, 1H). Minor isomer δ 8.52 (m, 1H), 8.45 (s, 1H), 8.40 (m, 1H), 8.29 (m, 1H), 8.23 (s, 1H), 7.66 (m, 1H), 7.59 (d, J= 8.2 Hz, 1H), 7.52 (d, J= 7.9 Hz, 1H), 7.39 (dd, J= 7.6, 7.9 Hz, 1H), 7.37 (m, 1H), 7.28 (m, 1H), 7.23 (m, 1H), 7.14 (m, 2H), 7.09 (m, 1H), 5.36 (m, 1H), 4.10 (m, 1H). HRMS [M+H] $C_{23}H_{18}ClN_3O$ calcd 388.1211, found 388.1219.

Kv1.5 HT-clamp IC_{50} values for racemic 1-[2-(2-chlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol and specified enantiomers:

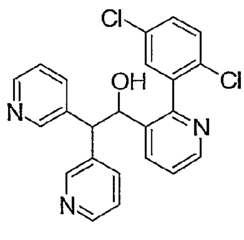
Racemic - 422 nM

Enantiomer A - 171 nM

Enantiomer B - 25000 nM

EXAMPLE 5

1-[2-(2,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol



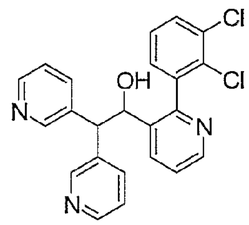
Isolated as a 2.6:1 mixture of atropisomers, as shown by the chemical exchange of various ROESY signals. [1]H NMR (600 MHz, $CDCl_3$): Major isomer δ 8.56 (dd, J= 1.7, 4.9 Hz, 1H), 8.48 (s, 1H), 8.44 (m, 1H), 8.38 (m, 1H), 8.05 (dd, J= 1.6, 8.0 Hz, 1H), 7.96 (m, 1H), 7.63 (dt, J= 1.7, 7.9 Hz, 1H), 7.40 (m, 2H), 7.35 (dd, J= 2.4, 8.5 Hz, 1H), 7.25 (m, 1H), 7.06 (dd, J= 4.8, 8.0 Hz, 1H), 7.01 (dt, J= 1.8, 7.9 Hz, 1H), 6.56 (d, J= 2.4 Hz, 1H), 5.28 (d, J= 8.2 Hz, 1H), 4.12 (d, J= 8.3 Hz, 1H). Minor isomer δ 8.54

(dd, J = 1.7, 4.9 Hz, 1H), 8.44 (m, 1H), 8.43 (m, 1H), 8.37 (m, 1H), 8.32 (s, 1H), 7.67 (dt, J = 1.6, 7.9 Hz, 1H), 7.52 (m, 3H), 7.47 (dt, J = 1.7, 7.9 Hz, 1H), 7.27 (m, 1H), 7.18 (m, 1H), 7.13 (dd, J = 4.6, 7.8 Hz, 1H), 7.07 (m, 1H), 5.33 (m, 1H), 4.12 (m, 1H). HRMS [M+H] $C_{23}H_{17}Cl_2N_3O$ calcd 422.0822, found 422.0835.

Kv1.5 HT-clamp IC_{50} values for racemic 1-[2-(2,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol and specified enantiomers:
Racemic - 77 nM
Enantiomer A - 3197 nM
Enantiomer B - 75 nM

EXAMPLE 6

1-[2-(2,3-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol



Isolated as a 2:1 mixture of atropisomers, as shown by the chemical exchange of various ROESY signals. ^{1}H NMR (600 MHz, $CDCl_3$): Major isomer δ 8.53 (m, 1H), 8.39 (m, 1H), 8.33 (m, 1H), 8.32 (m, 1H), 8.02 (d, J = 1.8 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.66 (dt, J = 1.7, 7.8 Hz, 1H), 7.54 (dd, J = 1.4, 8.0 Hz, 1H), 7.32 (m, 1H), 7.28 (m, 1H), 7.23 (m, 1H), 7.14 (dd, J = 1.6, 8.0 Hz, 1H), 7.04 (dd, J = 4.7, 7.9 Hz, 1H), 6.69 (m, 1H), 5.22 (d, J = 7.1 Hz, 1H), 4.08 (d, J = 7.0 Hz, 1H). Minor isomer δ 8.53 (m, 1H), 8.45 (m, 1H), 8.42 (m, 1H), 8.32 (m, 1H), 8.29 (m, 1H), 7.64 (dt, J = 1.6, 7.9 Hz, 1H), 7.57 (m, 1H), 7.56 (m, 1H), 7.35 (m, 1H), 7.32 (m, 1H), 7.28 (m, 1H), 7.23 (m, 1H), 7.17 (m, 1H), 7.11 (dd, J = 4.9, 7.9 Hz, 1H), 5.35 (d, J = 4.2 Hz, 1H), 4.10 (d, J = 4.0 Hz, 1H). HRMS [M+H] $C_{23}H_{17}Cl_2N_3O$ calcd 422.0822, found 422.0832.

Kv1.5 HT-clamp IC_{50} values for racemic 1-[2-(2,3-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol and specified enantiomers:
Racemic - 110 nM
Enantiomer A - 5212 nM
Enantiomer B - 236 nM

Using the methodologies described below, representative compounds of the invention were evaluated and found to exhibit activity in the Kv1.5 assays, thereby demonstrating and confirming the utility of the compounds of this invention as Kv1.5 inhibitors and antiarrhythmics. Compounds of this type may exhibit forward rate-dependence, blocking the outward K^+ currents to a greater extent or preferentially at faster rates of depolarization or heart rates. Such a compound could be identified in electrophysiological studies as described below. For example, during a train of depolarizations delivered at frequencies of 1 Hz and 3 Hz, the block is "rate-dependent" if the amount of block observed during a 10 second train at 3 Hz is greater than that at 1 Hz. A Kv1.5 blocker may also display use-dependence, during which the block of the outward K^+ currents increases with use, or during repetitive depolarization of a cardiac cell. Use dependence of block occurs to a greater extent with each successive depolarization in a train or sequence of pulses or depolarizations at a given rate or frequency. For example, during a train of 10 depolarizations at a frequency of 1 Hz, the block is "use-dependent" if the amount of block is greater for the 10^{th} pulse than for the 1^{st} pulse of the train. A Kv1.5 blocker may exhibit both use-dependence and rate-dependence.

A Kv1.5 blocker may also be identified through electrophysiological studies of native I_{Kur} using cardiac myocytes or other tissue from various species including, but not limited to, human, rat, mouse, dog, monkey, ferret, rabbit, guinea pig, or goat. In native tissues Kv1.5 may exist as a homo-oligomer, or as a hetero-oligomer with other Kv family members, or may exist in a complex with a β-subunit. Compounds of this invention may block Kv1.5 homo- or hetero-oligomers or Kv1.5 in complexes with β-subunits.

Kv1.5 assays

The high throughput Kv1.5 planar patch clamp assay is a systematic primary screen. It confirms activity and provides a functional measure of the potency of agents that specifically affect Kv1.5 potassium channels. Kiss et al. (Assay and Drug Dev. Tech., 1(1-2):127-135,2003) and Schroeder et al. (J. of Biomol. Screen., 8(1);50-64, 2003) describe the use of this instrument for Kv1.5 as well as other voltage gated ion channels.

Chinese hamster ovary cells (CHO) stably expressing the human Kv1.5 potassium channel alpha subunit, cloned from human heart, are grown to 90-100% confluence in Ham's F12 medium supplemented with 10% FBS, 100 U/ml penicillin, 100 μg/ml streptomycin, 1000 μg/ml G-418 sulfate. Cells are subcultured by treatment with Versene, then suspended in phosphate-buffered saline (PBS) and centrifuged The cell pellet is re-suspended in PBS and the resulting suspension placed in the cell reservoir of the IonWorks™ HT instrument.

Electrophysiological recordings are performed with intracellular solution containing (mM): K-gluconate 100, KCl 40, $MgCl_2$ 3.2, EGTA 3, *N*-2-hydroxylethylpiperazine-N^1-2-ethanesulphonic acid (HEPES) 5, adjusted to pH 7.3. Amphotericin (Sigma) is prepared as 30 mg/ml stock solution and diluted to a final working concentration of 0.1 mg/ml in internal buffer solution. The external solution is Dulbecco's PBS (Invitrogen) and contains (mM): $CaCl_2$ 0.90, KCl 2.67, K_3PO_4 1.47, $MgCl_2$ 0.50, NaCl 138, Na_3PO_4 8.10 and has a pH of 7.4. All compounds are prepared as 10 mM stock solutions in DMSO. Compounds are diluted into external buffer, then transferred from the drug plate to the Patchplate during the experiment (final DMSO concentration <0.66% vol.).

Kv1.5 ionic currents are recorded at room temperature. Membrane currents are amplified (RMS ~10pA) and sampled at 10 kHz. Leak subtraction was performed in all experiments by applying a 160 ms hyperpolarizing (10 mV) pre-pulses 200 ms before the test pulses to measure leak conductance. The patch clamp stimulus protocol is as follows:

1. Patchplate wells are loaded with 3.5 μL of external buffer.
2. Planar micropipette hole resistances (Rp) is determined by applying a 10 mV, 160 ms potential difference across each hole (Hole test).
3. Cells are pipetted into the Patchplate and form high resistance seals with the 1-2 μm holes at the bottom of each Patchplate well. A seal test scan is performed to determine how many of the Patchplate wells have cells that have formed seals.
4. In order to gain electrical access to the cells, intracellular solution containing amphotericin is circulated for 4 minutes on the bottom side of the Patchplate.
5. Pre-compound addition test pulse is applied to each well on the Patchplate. Protocol: Cells are voltage clamped at a membrane holding potential of –80 mV for 15 seconds. This is followed by application of a 5 Hz stimulus train (27 x 150 ms depolarizations to +40 mV). The membrane potential steps to +40 mV evoke outward (positive) ionic currents.
6. Compound is added to each well of the Patchplate. Compounds are allowed to incubate for 5 minutes.
7. Post-compound addition test pulse protocol is applied. Protocol: Cells are voltage clamped at a membrane holding potential of –80 mV for 15 seconds. This is followed by application of a 5 Hz stimulus train (27 x 150 ms depolarizations to +40 mV).

Data analysis is conducted off-line. Paired comparisons between pre-drug and post-drug additions are used to determine the inhibitory effect of each compound. % inhibition of the peak control current during the 27th depolarization to +40 mV (in the 5 Hz train) is plotted as a function of antagonist concentration. The concentrations of drug required to inhibit current by 50 % (IC_{50}) are determined by fitting of the Hill equation to the concentration response data: % of Control = 100 X $(1 + ([Drug]/IC_{50})^{p})^{-1}$

For each cell four arithmetic metrics are obtained:

1) seal resistance
2) baseline metric (the mean current at –70 mV from 5 to 45 ms before the first depolarization to +40 mV)
3) current run up metric (pre-compound mean current amplitude during the 1st depolarization to +40 mV minus the pre-compound mean current amplitude during the 27th depolarization to +40 mV)
4) peak current (maximum current amplitude during the 27th depolarization to +40 mV during the 5 Hz train).

All metrics are obtained during both the pre- and post-compound addition traces. Cells are eliminated from further analysis if:

1) seal resistance is <50 MΩ
2) baseline metric is >±100 pA during the pre-compound
3) current run up metric is >-0.2 nA
4) pre-read peak metric is <400 pA.

The above-listed compounds provide inhibition in the high throughput Kv1.5 planar patch clamp assay described above.

Atomic Absorption Spectroscopy Protocol:

This assay identifies agents that specifically block the human Kv1.5 K+ channel heterologously expressed in CHO cells as measured by Rb^+ efflux using Flame Atomic Absorption Spectroscopy (FAAS). The application of FAAS for measuring ion channel activity was adapted from Terstappen *et al*, *Anal. Biochem.*, 272:149-155, 1999.

CHO cells expressing human Kv1.5 are cultured as described above, then harvested with trypsin-EDTA and washed with medium.

1. 40,000 cells per well are seeded in a 96-well cell culture plate (assay plate) and the cells are allowed to grow for 48 hours at 37°C.
2. The medium is removed and 200 μl of Rb Load Buffer (Aurora Biomed, Vancouver, BC) is added for 3 hours at 37°C under 5% CO_2.
3. The cells are washed 5 times with 200 μl Hank's Balanced Salt Solution (HBSS) followed by the addition of 100 μl HBSS containing test compound or 0.5 % DMSO.
4. After 10 min, 100 μl of HEPES-buffered saline containing 140 mM KCl is added and plate is incubated at RT for 5 min. with gentle shaking.
5. Immediately thereafter, 150 μl of supernatant is transferred to a fresh 96 well plate and the remaining supernatant aspirated.
6. 120 μl of Cell Lysis Buffer (Aurora Biomed, Vancouver, BC) is added to the assay plate and shaken for 10 min. prior to analysis.
7. Rb content is measured in samples of supernatant (SUP) and lysate (LYS) using an ICR-8000 automated AAS instrument (Aurora Biomed, Vancouver, BC).

% FLUX=100%*(SUP/(LYS+SUP)). % INH=100%*(1-(A-B)/(C-B)), where A is % FLUX in the presence of tested compound, B is % FLUX in the presence of 10 mM (6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)-*N*,*N*-dimethylmethanaminium chloride, C is % FLUX in the presence of 0.25% DMSO.

The above-listed compounds provide ≥ 25% inhibition at a concentration of 25 μM or less in the AAS assay described above.

The compounds of this invention can be administered for the treatment or prevention of afflictions, diseases and illnesses according to the invention by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration, can be oral, topical, including transdermal, ocular, buccal, intranasal, inhalation, intravaginal, rectal, intracisternal and parenteral. The term "parenteral" as used herein refers to modes of administration which include subcutaneous, intravenous, intramuscular, intraarticular injection or infusion, intrasternal and intraperitoneal.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 1-500 milligrams per day. Ordinarily, from 10 to 100 milligrams per day in one or more applications is effective to obtain desired results. These dosages are the effective amounts for the treatment and prevention of afflictions, diseases and illnesses described above, e.g., cardiac arrhythmias such as atrial fibrillation, atrial flutter, atrial arrhythmia, supraventricular tachycardia, thromboembolic events such as stroke and congestive heart failure, auto-immune disorders such as immunoregulatory abnormalities, and cardiac insufficiency, in particular as a consequence of diastolic impairment.

Immunoregulatory abnormalities exist in a wide variety of autoimmune and chronic inflammatory diseases, including systemic lupus erythematosis, chronic rheumatoid arthritis, type I and II diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis and other disorders such as Crohn's disease, ulcerative colitis, bullous pemphigoid, sarcoidosis, psoriasis, ichthyosis, Graves ophthalmopathy and asthma. Compounds of the invention are useful for treating and preventing auto-immune disorders such as these immunoregulatory abnormalities.

The invention also includes use of a compound of the invention in the manufacture of a medicament, for treating a condition in a mammal, the treatment of which is effected or facilitated by $K_V1.5$ inhibition, such as cardiac arrhythmia or a thromboembolic event. The invention also includes use of a compound of the invention in the manufacture of a medicament, for preventing a condition in a mammal, the treatment of which is effected or facilitated by $K_V1.5$ inhibition, such as cardiac arrhythmia or a thromboembolic event.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The active ingredient can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the active ingredient as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene gycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For administration by inhalation, the compounds of the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percent solution or suspension of the compounds of Formula I in an appropriate ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions.

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

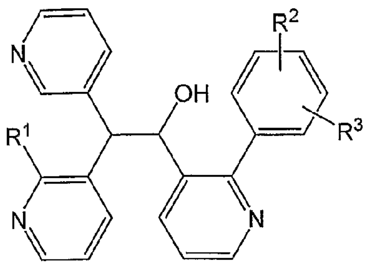
An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of the two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the two active components.

Compounds of the invention can be administered as the sole active ingredient or in combination with a second active ingredient, including other antiarrhythmic agents having Kv1.5 blocking activities such as quinidine, propafenone, ambasilide, amiodarone, flecainide, sotalol, bretylium, dofetilide, almokalant, bepridil, clofilium, other compounds having Kv1.5 blocking activities such as clotrimazole, ketoconazole, bupivacaine, erythromycin, verapamil, nifedipine, zatebradine, bisindolylmaleimide, or other cardiovascular agents such as, but not limited to, ACE inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril erbumine, quinapril, ramipril, and trandolapril, angiotensin II antagonists such as candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan, cardiac glycosides such as digoxin, L-type calcium channel blockers, T-type calcium channel blockers, selective and nonselective beta blockers, an immunosuppresant compound, endothelin antagonists, thrombin inhibitors, aspirin, nonselective NSAIDs other than aspirin such as naproxen, warfarin, factor Xa inhibitors, low molecular weight heparin, unfractionated heparin, clopidogrel, ticlopidine, IIb/IIIa receptor antagonists such as tirofiban, 5HT receptor antagonists, integrin receptor antagonists, thromboxane receptor antagonists, TAFI inhibitors and P2T receptor antagonists. Compounds of the invention can also be administered as the sole active ingredient or in combination with a pacemaker or defibrillator device.

WHAT IS CLAIMED IS:

1. A compound of formula I,



I

or a pharmaceutically acceptable salt, or an optical isomer thereof, wherein: R^1, R^2, and R^3 are independently selected from the group consisting of

1) hydrogen,
2) halogen,
3) NO_2,
4) CN,
5) $CR^4{=}C(R^4)_2$,
6) $C{\equiv}CR^4$,
7) $(CR^5{}_2)_nOR^4$,
8) $(CR^5{}_2)_nN(R^4)_2$,
9) $(CR^5{}_2)_n\ C(O)R^4$,
10) $(CR^5{}_2)_n\ C(O)OR^4$,
11) $(CR^5{}_2)_nR^4$,
12) $(CR^5{}_2)_n\ S(O)_mR^4$,
13) $(CR^5{}_2)_n\ S(O)_mN(R^4)_2$,
14) $OS(O)_mR^4$,
15) $N(R^4)C(O)R^4$,
16) $N(R^4)S(O)_mR^4$,
17) $(CR^5{}_2)_nN(R^6)R^4$,
18) $(CR^5{}_2)_nN(R^4)(CR^5{}_2)_nC(O)N(R^4)_2$,
19) $(CR^5{}_2)_nN(R^4)(CR^5{}_2)_nC(O)OR^4$,
20) $N(R^4)(CR^5{}_2)_nR^4$,
21) $N(R^4)(CR^5{}_2)_nN(R^4)_2$,
22) $(CR^5{}_2)_nC(O)N(R^4)_2$,
23) $(CR^5{}_2)_nC(O)NH(CR^5{}_2)_nR^4$,
24) $(CR^5{}_2)_nC(O)NHC(R^4)_2(CR^5{}_2)_nN(R^4)_2$,
25) $C(O)NH(CR^5{}_2)(CR^5{}_3)$,
26) $S(O)_mR^5$, and

27) $N(R^4)(R^5)$;

R^4, in each instance in which it appears, is independently selected from the group consisting of

1) hydrogen,
2) C_1-C_6 alkyl,
3) C_3-C_{10} cycloalkyl,
4) aryl,
5) CF_3,
6) C_2-C_6 alkenyl, and
7) C_2-C_6 alkynyl,

or in the case where R^4 is attached to a nitrogen atom that is disubstituted with R^4, each R^4 is independently selected from C_1-C_6 alkyl, and the nitrogen atom together with each R^4 form a ring;

R^5, in each instance in which it appears, is independently selected from the group consisting of

1) hydrogen,
2) C_1-C_6 alkyl,
3) halogen,
4) aryl,
5) C_3-C_{10} cycloalkyl,
6) OR^4, and
7) CH_2OR^4,

m is independently selected from 0, 1 and 2; and

n is independently selected from 0, 1, 2, 3, 4, 5 and 6.

2. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein R^1 is selected from the group consisting of hydrogen and halogen.

3. A compound of Claim 2, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein R^1 is selected from the group consisting of hydrogen and F.

4. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein R^2 is selected from the group consisting of hydrogen, halogen and CF_3.

2006306541 10 Jun 2011

5. A compound of Claim 4, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein R^2 is selected from the group consisting of hydrogen, Cl and CF_3.

6. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein R^3 is selected from the group consisting of hydrogen and halogen.

7. A compound of Claim 6, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein R^3 is selected from the group consisting of hydrogen and Cl.

8. A compound of Claim 1, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol,

2,2-dipyridin-3-yl-1-{2[3-(trifluoromethyl)phenyl]pyridin-3-yl}ethanol,

1-{2-(2-chlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol,

1-[2-(3,5-dichlorophenyl)pyridin-3-yl]-2-(2-fluoropyridin-3-yl)-2-pyridin-3-ylethanol,

1[2-(2,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol, and

1[2-(2,3-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol.

9. A compound of Claim 8, or a pharmaceutically acceptable salt thereof, which is

1[2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol.

10. A compound of Claim 9, or a pharmaceutically acceptable salt thereof, which is

(R)-1{2-(3,5-dichlorophenyl)pyridin-3-yl]-2,2-dipyridin-3-ylethanol.

11. Use of a compound of any one of Claims 1 to 10, in the manufacture of a medicament, for treating a condition in a mammal, the treatment of which is effected or facilitated by $K_v1.5$ inhibition.

12. Use of a compound of any one of Claims 1 to 10, in the manufacture of a medicament, for treating cardiac arrhythmia or a thromboembolic event.

13. Use of a compound of any one of Claims 1 to 10, in the manufacture of a medicament, for preventing a condition in a mammal, the treatment of which is effected or facilitated by $K_v1.5$ inhibition.

14. Use of a compound of any one of Claims 1 to 10, in the manufacture of a medicament, for preventing cardiac arrhythmia or a thromboembolic event.

15. A pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of any one of Claims 1 to 10 or a pharmaceutically acceptable salt thereof.

16. A method for treating or preventing cardiac arrhythmia or a thromboembolic event in a patient, comprising administering to a patient a compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, or a pharmaceutical formulation of Claim 15.

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Merck Sharp & Dohme Corp.

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON