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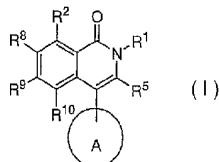
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(54) Title: ISOQUINOLINONE POTASSIUM CHANNEL INHIBITORS



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

TITLE OF THE INVENTION
ISOQUINOLINONE POTASSIUM CHANNEL INHIBITORS

BACKGROUND OF THE INVENTION

5 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, and as Kv1.3 inhibitors for treatment of immunosuppression, autoimmune diseases, and the like.

Voltage gated potassium channels (Kv) are multimeric membrane proteins

10 composed of four α subunits and are often associated with accessory β subunits. Kv channels are typically closed at resting membrane potentials, but open upon membrane depolarization. They are involved in the repolarization of the action potential and thus in the electrical excitability of nerve and muscle fibers. The Kv1 class of potassium channels is comprised of at least seven family members, named Kv1.1, Kv1.3, Kv1.5, etc. Functional voltage-gated K^+

15 channels may exist either as homo-oligomers composed of identical subunits, or hetero-oligomers of different subunit composition. This phenomenon is thought to account for the wide diversity of K^+ channels. However, subunit compositions of native K^+ channels and the physiologic role that particular channels play are, in most cases, still unclear.

The Kv1.3 voltage-gated potassium channel is found in neurons, blood cells,

20 osteoclasts and T-lymphocytes. Membrane depolarization by Kv1.3 inhibition has been shown to be an effective method to prevent T-cell proliferation and therefore has applications in many autoimmune conditions. Inhibition of K^+ channels in the plasma membrane of human T-lymphocytes has been postulated to play a role in eliciting immunosuppressive responses by regulating intracellular Ca^{++} homeostasis, which has been found to be important in T-cell

25 activation. Blockade of the Kv1.3 channel has been proposed as a novel mechanism for eliciting an immunosuppressant response (Chandy *et al.*, *J. Exp. Med.* 160: 369, 1984; Decoursey *et al.*, *Nature*, 307: 465, 1984). However, the K^+ channel blockers employed in these early studies were non-selective. In later studies, Margatoxin, which blocks only Kv1.3 in T-cells, was shown to exhibit immunosuppressant activity in both *in vitro* and *in vivo* models. (Lin *et al.*, *J. Exp. Med.*, 177: 637, 1993). The therapeutic utility of this compound, however, is limited by its potent toxicity. Recently, a class of compounds has been reported that may be an attractive alternative to the above-mentioned drugs (U.S. Patent Nos. 5,670,504; 5,631,282; 5,696,156; 5,679,705; and 5,696,156). While addressing some of the activity/toxicity problems of previous drugs, these compounds tend to be of large molecular weight and are generally produced by synthetic

30 manipulation of a natural product, isolation of which is cumbersome and labor intensive.

35

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. Conservative estimates indicate that AF affects >2 million Americans, represents over 5% of all admissions for cardiovascular diseases and leads to a 3- to 5-fold increase in the risk of stroke

5 (Kannel et al, *Am. J. Cardiol.*, 82:2N-9 N, 1998). 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.

Reentrant excitation (reentry) has been shown to be a prominent mechanism underlying supraventricular arrhythmias in man (Nattel, S., *Nature*, 415:219-226, 2002).

10 Reentrant excitation requires a critical balance between slow conduction velocity and sufficiently brief refractory periods to allow for the initiation and maintenance of multiple reentry circuits to coexist simultaneously and sustain AF. Increasing myocardial refractoriness by prolonging action potential duration (APD) prevents and/or terminates reentrant arrhythmias. Action potential duration is determined by the contributions of the repolarizing potassium currents I_{Kr} ,

15 I_{Ks} , and I_{Kur} , and the transient outward current, I_{to} . Blockers of any one of these currents would therefore be expected to increase the APD and produce antiarrhythmic effects.

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

20 (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.

25

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. For example, torsades de points has been observed when these compounds are utilized (Roden, D.M. "Current Status of Class III Antiarrhythmic Drug Therapy", *Am J. Cardiol.*, 72:44B-49B, 1993).

5 This exaggerated effect at slow heart rates has been termed "reverse frequency-dependence", and is in contrast to frequency-independent or forward frequency-dependent actions (Hondegem, L.M. "Development of Class III Antiarrhythmic Agents". *J. Cardiovasc. Cardiol.*, 20 (Suppl. 2):S17-S22). Amiodarone has been shown to possess interesting Class III properties (Singh B.N., Vaughan Williams E.M. "A Third Class Of Anti-Arrhythmic Action: Effects On Atrial

10 And Ventricular Intracellular Potentials And Other Pharmacological Actions On Cardiac Muscle, of MJ 1999 and AH 3747" *Br. J. Pharmacol.*, 39:675-689, 1970; Singh B.N., Vaughan Williams E. M. "The Effect Of Amiodarone, A New Anti-Anginal Drug, On Cardiac Muscle", *Br. J. Pharmacol.*, 39:657-667, 1970), although it is not a selective Class III agent because it effects multiple ion channels; additionally, its use is severely limited due to its side effect profile

15 (Nademanee, K. "The Amiodarone Odyssey". *J. Am. Coll. Cardiol.*, 20:1063-1065, 1992; Fuster et al, *Circulation*, 104:2118-2150, 2001; Bril, A. *Curr. Opin. Pharmacol.* 2:154-159, 2002). Thus, currently available agents such as amiodarone and Class III drugs confer a significant risk of adverse effects including the development of potentially lethal ventricular proarrhythmia.

20 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. Kv1.5 mRNA (Bertaso, Sharpe, Hendry, and James, *Basic Res. Cardiol.*, 97:424-433, 2002) and protein (Mays, Foose, Philipson, and Tamkun, *J. Clin. Invest.*, 96:282-292, 1995) have been detected in human atrial tissue. In intact human atrial

25 myocytes, an ultra-rapidly activating delayed rectifier K⁺ current (I_{Kur}), also known as the sustained outward current, I_{sus} or I_{so}, has been identified and this current has properties and kinetics identical to those expressed by the human K⁺ channel clone (hKv1.5, HK2) [Wang, Fermini and Nattel, *Circ. Res.*, 73:1061-1076, 1993; Fedida et al., *Circ. Res.* 73:210-216, 1993; Snyders, Tamkun and Bennett, *J. Gen. Physiol.*, 101:513-543, 1993] and a similar clone from rat

30 brain (Swanson et al., *Neuron*, 4:929-939, 1990). Furthermore, because of its rapidity of activation and limited slow inactivation, I_{Kur} is believed to contribute significantly to repolarization in human atrium. Consequently, a specific blocker of I_{Kur}, that is a compound which blocks Kv1.5, would overcome the shortcoming of other compounds by prolonging refractoriness through retardation of the repolarization in the human atrium without causing the

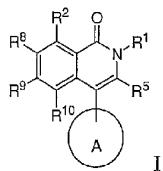
35 delays in ventricular repolarization that underlie arrhythmogenic afterdepolarizations and

acquired long QT syndrome observed during treatment with current Class III drugs. Kv1.5 blockers exhibiting these properties have been described (Peukert et al, *J. Med. Chem.*, 46:486-498, 2003; Knobloch et al, *Naunyn-Schmiedeberg's Arch. Pharmacol.* 366:482-287, 2002; Merck & Co., Inc. WO224655, 2002).

5 The compounds described in this invention represent a novel structural class of Kv1.5 antagonist.

SUMMARY OF THE INVENTION

10 This invention relates to potassium channel inhibitors of general structural Formula I

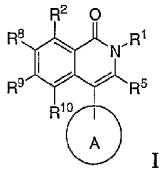


The compounds of this invention are useful in the treatment and prevention of cardiac arrhythmias, and the like. Also within the scope of this invention are pharmaceutical formulations comprising a compound of Formula I and a pharmaceutical carrier.

15

DETAILED DESCRIPTION OF THE DISCLOSURE

The present invention is a compound of formula I



or a pharmaceutically acceptable salt, crystal form, or hydrate, wherein:

20 A is

a) an aryl ring, wherein any stable aryl ring atom is independently unsubstituted or substituted with

- 1) halogen,
- 2) NO₂,

3) CN,
 4) CR⁴⁶=C(R⁴⁷R⁴⁸)₂,
 5) C≡C R⁴⁶,
 6) (CRⁱR^j)_lOR⁴⁶,
 7) (CRⁱR^j)_lN(R⁴⁶R⁴⁷),
 8) (CRⁱR^j)_lC(O)R⁴⁶,
 9) (CRⁱR^j)_lC(O)OR⁴⁶,
 10) (CRⁱR^j)_lR⁴⁶,
 11) (CRⁱR^j)_lS(O)O-2R⁶¹,
 12) (CRⁱR^j)_lS(O)O-2N(R⁴⁶R⁴⁷),
 13) OS(O)O-2R⁶¹,
 14) N(R⁴⁶)C(O)R⁴⁷,
 15) N(R⁴⁶)S(O)O-2R⁶¹,
 16) (CRⁱR^j)_lN(R⁴⁶)R⁶¹,
 17) (CRⁱR^j)_lN(R⁴⁶)R⁶¹OR⁴⁷,
 18) (CRⁱR^j)_lN(R⁴⁶)(CR^kR^l)_sC(O)N(R⁴⁷R⁴⁸),
 19) N(R⁴⁶)(CRⁱR^j)_lR⁶¹,
 20) N(R⁴⁶)(CRⁱR^j)_lN(R⁴⁷R⁴⁸),
 21) (CRⁱR^j)_lC(O)N(R⁴⁷R⁴⁸), or
 22) oxo, or

b) a heteroaryl ring selected from the group consisting of
 a 5-membered unsaturated monocyclic ring with 1, 2, 3 or 4 heteroatom ring atoms
 selected from the group consisting of N, O or S,
 25 a 6-membered unsaturated monocyclic ring with 1, 2, 3 or 4 heteroatom ring atoms
 selected from the group consisting of N, O and S, and
 a 9- or 10-membered unsaturated bicyclic ring with 1, 2, 3 or 4 heteroatom ring atoms
 selected from the group consisting of N, O or S;

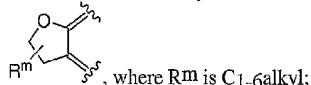
30 wherein any stable S heteroaryl ring atom is unsubstituted or mono- or di-substituted with
 oxo, and any stable C or N heteroaryl ring atom is independently unsubstituted or
 substituted with
 35 1) halogen,
 2) NO₂,
 3) CN,

4) CR⁴⁶=C(R⁴⁷R⁴⁸)₂,
 5) C≡CR⁴⁶,
 6) (CRⁱR^j)_tOR⁴⁶,
 7) (CRⁱR^j)_tN(R⁴⁶R⁴⁷),
 5 8) (CRⁱR^j)_tC(O)R⁴⁶,
 9) (CRⁱR^j)_tC(O)OR⁴⁶,
 10) (CRⁱR^j)_tR⁴⁶,
 11) (CRⁱR^j)_tS(O)₀₋₂R⁶¹,
 12) (CRⁱR^j)_tS(O)₀₋₂N(R⁴⁶R⁴⁷),
 10 13) OS(O)₀₋₂R⁶¹,
 14) N(R⁴⁶)C(O)R⁴⁷,
 15) N(R⁴⁶)S(O)₀₋₂R⁶¹,
 16) (CRⁱR^j)_tN(R⁴⁶)R⁶¹,
 17) (CRⁱR^j)_tN(R⁴⁶)R⁶¹OR⁴⁷,
 15 18) (CRⁱR^j)_tN(R⁴⁶)(CR^kR^l)_sC(O)N(R⁴⁷R⁴⁸),
 19) N(R⁴⁶)(CRⁱR^j)_tR⁶¹,
 20) N(R⁴⁶)(CRⁱR^j)_tN(R⁴⁷R⁴⁸),
 21) (CRⁱR^j)_tC(O)N(R⁴⁷R⁴⁸), or
 22) oxo;
 20 R¹ is selected from the group consisting of
 1) hydrogen,
 2) (C^RaR^b)_nR⁴⁰
 3) (C^RaR^b)_nOR⁴⁰,
 4) (C^RaR^b)_nN(R⁴⁰R⁴¹),
 25 5) (C^RaR^b)_nN(R⁴⁰)C(O)OR⁴¹,
 6) (C^RaR^b)_nN(R⁴⁰)(CR^cR^d)₂N(R⁴¹)C(O)R⁴⁹,
 7) C₃₋₈ cycloalkyl,
 8) (C^RaR^b)_nC(O)OR⁴⁰,
 9) (C^RaR^b)_nN(R⁴⁰)(CR^cR^d)₁₋₃R⁴¹,
 30 10) (C^RaR^b)_nS(O)₀₋₂R⁶,
 11) (C^RaR^b)_nS(O)₀₋₂N(R⁴⁰R⁴¹),
 12) (C^RaR^b)_nN(R⁴⁰)R⁶OR⁴¹,
 13) (C^RaR^b)_nN(R⁴⁰)(CR^cR^d)₀₋₆C(O)N(R⁴¹R⁴²);
 R⁵ is -(CH₂)₂R²² or R⁸⁵;

R², R⁸, R⁹ and R¹⁰ are independently selected from:

- 1) hydrogen,
- 2) halogen,
- 3) NO₂,
- 5 4) CN,
- 5) CR⁴³=C(R⁴⁴R⁴⁵),
- 6) C≡CR⁴³,
- 7) (CReRf)_pOR⁴³,
- 8) (CReRf)_pN(R⁴³R⁴⁴),
- 10 9) (CReRf)_pC(O)R⁴³,
- 10) (CReRf)_pC(O)OR⁴³,
- 11) (CReRf)_pR⁴³,
- 12) (CReRf)_pS(O)O-2R⁶⁰,
- 13) (CReRf)_pS(O)O-2N(R⁴³R⁴⁴),
- 15 14) OS(O)O-2R⁶⁰,
- 15) N(R⁴³)C(O)R⁴⁴,
- 16) N(R⁴³)S(O)O-2R⁶⁰,
- 17) (CReRf)_pN(R⁴³)R⁶⁰,
- 18) (CReRf)_pN(R⁴³)R⁶⁰OR⁴⁴,
- 20 19) (CReRf)_pN(R⁴³)(CRgRh)_qC(O)N(R⁴⁴R⁴⁵),
- 20) N(R⁴³)(CReRf)_pR⁶⁰,
- 21) N(R⁴³)(CReRf)_pN(R⁴⁴R⁴⁵), and
- 22) (CReRf)_pC(O)N(R⁴³R⁴⁴),

or R² and R⁸ are independently as defined above, and R⁹ and R¹⁰, together with the atoms to which they are attached, form the ring



R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^l are independently selected from the group consisting of:

- 1) hydrogen,
- 2) C₁-C₆ alkyl,
- 3) halogen,
- 4) aryl,
- 5) R⁸⁰,

6) C₃-C₁₀ cycloalkyl, and

7) OR⁴,

5 said alkyl, aryl, and cycloalkyl being unsubstituted, monosubstituted with R⁷,
disubstituted with R⁷ and R¹⁵, trisubstituted with R⁷, R¹⁵ and R¹⁶, or
tetrasubstituted with R⁷, R¹⁵, R¹⁶ and R¹⁷;
R⁴, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵¹, R⁵², R⁵³ and R⁵⁴ are
independently selected from the group consisting of

10 1) hydrogen,
 2) C₁-C₆ alkyl,
 3) C₃-C₁₀ cycloalkyl,
 4) aryl,
 5) R⁸¹,
 6) CF₃,

15 7) C₂-C₆ alkenyl, and
 8) C₂-C₆ alkynyl,

20 said alkyl, aryl, and cycloalkyl is unsubstituted, mono-substituted with R¹⁸, di-
 substituted with R¹⁸ and R¹⁹, tri-substituted with R¹⁸, R¹⁹ and R²⁰, or tetra-
 substituted with R¹⁸, R¹⁹, R²⁰ and R²¹;

25 R⁶, R⁶⁰, R⁶¹, and R⁶³ are independently selected from the group consisting of

1) C₁-C₆ alkyl,
2) aryl,
3) R⁸³, and
4) C₃-C₁₀ cycloalkyl;

30 said alkyl, aryl, and cycloalkyl is unsubstituted, mono-substituted with R²⁶, di-
 substituted with R²⁶ and R²⁷, tri-substituted with R²⁶, R²⁷ and R²⁸, or tetra-
 substituted with R²⁶, R²⁷, R²⁸ and R²⁹;

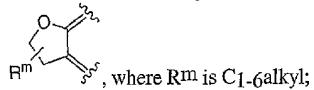
35 R⁷, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²⁶, R²⁷, R²⁸, and R²⁹ are independently selected
from the group consisting of

1) C₁-C₆ alkyl,
2) halogen,
3) OR⁵¹,
4) CF₃,

5) aryl,

- 6) C₃-C₁₀ cycloalkyl,
- 7) R⁸⁴,
- 8) S(O)₀₋₂N(R⁵¹R⁵²),
- 9) C(O)OR⁵¹,
- 5 10) C(O)R⁵¹,
- 11) CN,
- 12) C(O)N(R⁵¹R⁵²),
- 13) N(R⁵¹)C(O)R⁵²,
- 14) S(O)₀₋₂R⁶³,
- 10 15) NO₂,
- 16) N(R⁵¹R⁵²), and
- 17) R⁸²;
- R²² selected from the group consisting of
- 1) NHC(O)R⁸⁸, and
- 2) N(R⁵³R⁵⁴);
- 15 R⁸⁸ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl;
- R⁸⁰, R⁸¹, R⁸², R⁸³, R⁸⁴ and R⁸⁵ are independently selected from a group of unsubstituted or substituted heterocyclic rings consisting of a 3-6 membered unsaturated or saturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms selected from the group consisting N, O and S, and a
- 20 9- or 10-membered unsaturated or saturated bicyclic ring with 1, 2, 3 or 4 heteroatom ring atoms selected from the group consisting of N, O or S; and
- n, p, q, r, and s are independently 0, 1, 2, 3, 4, 5 or 6.
- In a class of compounds of the invention, or pharmaceutically acceptable salts thereof,
- 25 A is an aryl ring selected from phenyl, unsubstituted or substituted as defined above, or a heteroaryl ring, unsubstituted or substituted as defined above, selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, indole, pyrrolopyridine, benzimidazole, benzoxazole, benzothiazole, and benzoxadiazole;
- R², R⁸, R⁹ and R¹⁰ are independently selected from the group consisting of:
- 30 1) hydrogen,
- 2) halogen,
- 3) OR⁴³, and
- 4) (CR⁶R⁷)_pR⁴³,

or R² and R⁸ are independently as defined above, and R⁹ and R¹⁰, together with the atoms to which they are attached, form the ring



R¹ is selected from the group consisting of

- 5 1) hydrogen,
- 2) (C^RaR^b)₁₋₂R⁴⁰
- 3) (C^RaR^b)₁₋₂OR⁴⁰,
- 4) (C^RaR^b)₁₋₂N(R⁴⁰R⁴¹),
- 5) (C^RaR^b)₁₋₂N(R⁴⁰)C(O)OR⁴¹,
- 10 6) (C^RaR^b)₁₋₂N(R⁴⁰)(CR^cR^d)₂N(R⁴¹)C(O)R⁴⁹,
- 7) (C^RaR^b)₁₋₂C(O)OR⁴⁰,
- 8) (C^RaR^b)₁₋₂N(R⁴⁰)(CR^cR^d)₁₋₃R⁴¹, and
- 9) cyclopropyl.

In a subclass of the class of compounds, or pharmaceutically acceptable salts thereof, R², R⁸, R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen and (C^ReR^f)_pOR⁴³.

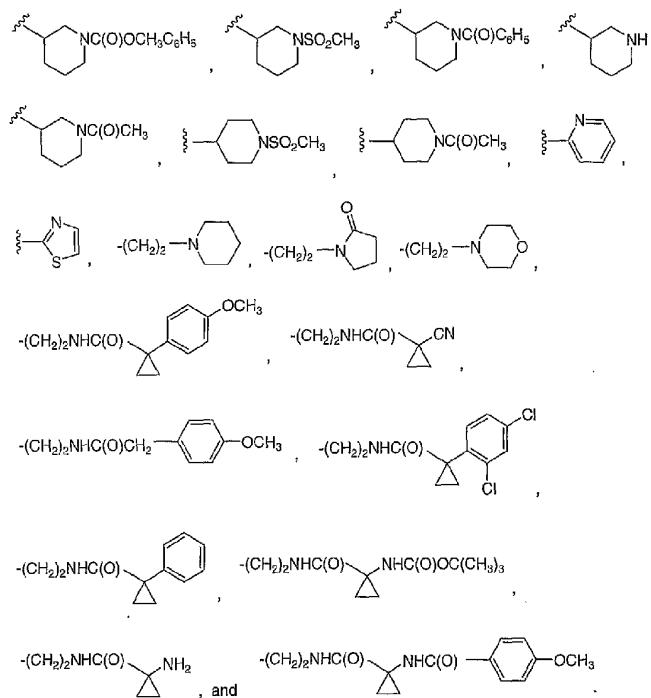
In a group of the subclass of compounds, or pharmaceutically acceptable salts thereof, R¹ is (C^RaR^b)_nR⁴⁰ or C₃-C₁₀ cycloalkyl.

In a subgroup of the group of compounds, or pharmaceutically acceptable salts thereof, A is an unsubstituted aryl ring.

In a family of the subgroup of compounds, or pharmaceutically acceptable salts thereof,

R⁵ is selected from the group consisting of

-(CH₂)₂NH₂, -(CH₂)₂NHC(O)CH₃, -(CH₂)₂N(CH₂CH₃)₂,



A preferred embodiment is a compound selected from the group consisting of

3-(2-Aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one,

5

N-[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]acetamide,

6-Methoxy-2-methyl-4-phenyl-3-(2-piperidin-1-ylethyl)isoquinolin-1(2*H*)-one,

10

6-Methoxy-2-methyl-3-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-phenylisoquinolin-1(2*H*)-one,

6-Methoxy-2-methyl-3-(2-morpholin-4-ylethyl)-4-phenylisoquinolin-1(2*H*)-one

- 11 -

6-Methoxy-2-methyl-3-(2-morpholin-4-ylethyl)-4-phenylisoquinolin-1(2*H*)-one,

6-Methoxy-2-methyl-3-(2-morpholin-4-ylethyl)-4-phenylisoquinolin-1(2*H*)-one,

6-Methoxy-2-methyl-3-(2-morpholin-4-ylethyl)-4-phenylisoquinolin-1(2*H*)-one,

- 11 -

3-[2-(Diethylamino)ethyl]-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one,

N-[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide,

5

1-Cyano-*N*-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide,

N-[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]-1-(4-methoxyphenyl)acetamide,

1-(2,4-Dichlorophenyl)-*N*-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide,

15 15 *N*-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]-1-phenylcyclopropanecarboxamide,

tert-Butyl 1-({[[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]amino}carbonyl)cyclopropyl carbamate,

20

1-Amino-*N*-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide,

25 25 4-Methoxy-*N*-[1-({[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]amino}carbonyl)cyclopropyl]benzamide,

(\pm)-Benzyl 3-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)piperidine-1-carboxylate,

30

(\pm)-6-Methoxy-2-methyl-4-phenyl-3-piperidin-3-ylisoquinolin-1(2*H*)-one,

(\pm)-3-(1-Acetyl piperidin-3-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one,

3-(1-acetyl piperidin-4-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one,

35

6-methoxy-2-methyl-3-[1-(methylsulfonyl)piperidin-4-yl]-4-phenylisoquinolin-1(2H)-one,

(\pm)-6-Methoxy-2-methyl-3-[1-(methylsulfonyl)piperidin-3-yl]-4-phenylisoquinolin-1(2H)-one,

5 (\pm)-3-(1-Benzoylpiperidin-3-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one,

3-(Pyrid-2-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one, and

3-(Thiazol-2-yl)-6-methoxy-2-cyclopropyl-4-phenylisoquinolin-1(2H)-one,

10 or a pharmaceutically acceptable salt thereof.

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 15 condition in a mammal, the treatment or prevention of which is effected or facilitated by Kv1.5 inhibition, which comprises administering an amount of a compound of Formula I that is effective at inhibiting Kv1.5.

A preferred embodiment is a method of treating or preventing cardiac arrhythmias, e.g. atrial fibrillation, atrial flutter, atrial arrhythmia, and supraventricular 20 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.

25 Another preferred embodiment is a method of treating or preventing immunodepression or a disorder involving immunodepression, such as AIDS, cancer, senile dementia, trauma (including wound healing, surgery and shock) chronic bacterial infection, certain central nervous system disorders, and conditions including resistance by transplantation of organs or tissue, graft-versus-host diseases brought about by medulla ossium transplantation.

30 Within this embodiment is a method for treating or preventing immunodepression by administering a compound of the invention with an immunosuppressant compound.

Another preferred embodiment is a method of treating or preventing gliomas including those of lower and higher malignancy, preferably those of higher malignancy.

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.

5 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
10 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.

The compounds of the present invention may have asymmetric centers or
15 asymmetric axes, and this invention includes all of the optical isomers and mixtures thereof. Unless specifically mentioned otherwise, reference to one isomer applies to both isomers.

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.

As used herein except where noted, "alkyl" is intended to include both branched-
20 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 $\text{CH}_2\text{CH}_2\text{CH}_3$, butyl may be represented by "Bu" or $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, etc. "C₁₋₆ alkyl" (or "C_{1-C₆} alkyl") for example, means linear or branched chain alkyl groups, including all isomers, having the specified number of carbon atoms. C₁₋₆ 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. "C₁₋₄ 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.

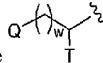
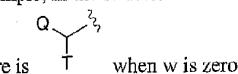
25 30 The term "alkenyl" includes both branched and straight chain unsaturated hydrocarbon groups containing at least two carbon atoms joined by a double bond. The alkene ethylene is represented, for example, by "CH₂CH₂" or alternatively, by "H₂C=CH₂". "C₂₋₅ alkenyl" (or "C_{2-C₅} alkenyl") for example, 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 "C₂₋₃ 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 5 acetylene is represented, for example, by "CHCH" or alternatively, by "HC≡CH". "C₂₋₅ alkynyl" (or "C_{2-C₅} 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 "C₂₋₃ alkynyl" have an analogous meaning.

10 Unless otherwise noted, alkyl, alkenyl and alkynyl groups are unsubstituted or substituted with 1 to 3 substituents on each carbon atom, with halo, C_{1-C₂₀} alkyl, CF₃, NH₂, N(C_{1-C₆} alkyl)₂, NO₂, oxo, CN, N₃, -OH, -O(C_{1-C₆} alkyl), C_{3-C₁₀} cycloalkyl, C_{2-C₆} alkenyl, C_{2-C₆} alkynyl, (C_{0-C₆} alkyl)S(O)O-2-, (C_{0-C₆} alkyl)S(O)O-2(C_{0-C₆} alkyl)-, (C_{0-C₆} alkyl)C(O)NH-, H₂N-C(NH)-, -O(C_{1-C₆} alkyl)CF₃, (C_{0-C₆} alkyl)C(O)-, (C_{0-C₆} alkyl)OC(O)-, (C_{0-C₆} alkyl)O(C_{1-C₆} alkyl)-, (C_{0-C₆} alkyl)C(O)1-2(C_{0-C₆} alkyl)-, (C_{0-C₆} alkyl)OC(O)NH-, 15 aryl, aralkyl, heterocycle, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

The term "C₀" as employed in expressions such as "C₀₋₆ alkyl" means a direct covalent bond. Similarly, when an integer defining the presence of a certain number of atoms in a 20 group is equal to zero, it means that the atoms adjacent thereto are connected directly by a bond.

For example, in the structure , wherein w is an integer equal to zero, 1 or 2, the structure is  when w is zero.

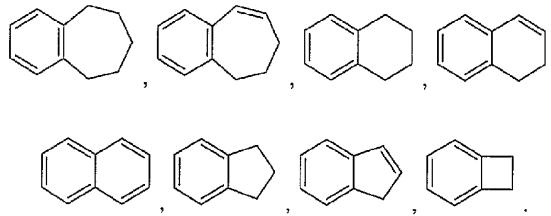
25 The term "C₃₋₈ cycloalkyl" (or "C_{3-C₈} cycloalkyl") means a cyclic ring of an alkane having three to eight total carbon atoms (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl). The terms "C₃₋₇ cycloalkyl", "C₃₋₆ cycloalkyl", "C₅₋₇ cycloalkyl" and the like have analogous meanings.

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)).

30 The term "C₁₋₆ haloalkyl" (which may alternatively be referred to as "C_{1-C₆} haloalkyl" or "halogenated C_{1-C₆} alkyl") means a C₁ to C₆ linear or branched alkyl group as defined above with one or more halogen substituents. The term "C₁₋₄ haloalkyl" has an analogous meaning. The term "C₁₋₆ fluoroalkyl" has an analogous meaning except that the

halogen substituents are restricted to fluoro. Suitable fluoroalkyls include the series (CH₂)₀-4CF₃ (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 C₃ to C₈ monocyclic, 5 saturated or unsaturated ring or (ii) a C₇ to C₁₂ 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 C₇ to C₁₀ bicyclic 10 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 15 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 C₁-6 alkyl, C₁-6 alkenyl, C₁-6 alkynyl, aryl, halogen, NH₂ or OH. A subset of the fused bicyclic unsaturated 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 20 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, 25 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 independent of, or fused to, the other ring or rings and each ring is saturated or unsaturated,

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 5 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.

10 As used herein, the terms cycloalkyl, aryl, and heterocycle, unless otherwise indicated, refer to unsubstituted and substituted moieties. Substituted cycloalkyl, e.g. substituted C3-C6 cycloalkyl, substituted aryl, and substituted heterocycle are intended to include the cyclic group containing from 1 to 3 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 15 limited to, halo, C1-C20 alkyl, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, oxo, CN, N₃, -OH, -O(C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₀-C₆ alkyl)S(O)0-2-, (C₀-C₆ alkyl)S(O)0-2(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, -O(C₁-C₆ alkyl)CF₃, (C₀-C₆ alkyl)C(O)-, (C₀-C₆ alkyl)OC(O)-, (C₀-C₆ alkyl)O(C₁-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)1-2(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)OC(O)NH-, aryl, aryl-C(O)-, , aryl-C(O)NH-, cyano, amino, - 20 NHC(O)O-C₁-C₆ alkyl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo- heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano- heterocyclylalkyl.

25 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 entire 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, 30 isothiazolidinyl, and tetrahydrofuryl (or tetrahydrofuran).

35 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. 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.

5 Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolimyl, isoindolimyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl,

2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e.,

b) (1,3)thiazole, (i.e.,

10 and benzo-1,3-dioxolyl (i.e.,

In certain contexts herein,

10 is alternatively referred to as phenyl having as a substituent methylenedioxy attached to two adjacent carbon atoms.

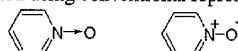
Unless expressly stated to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring. For example, an "unsaturated monocyclic C₆ carbocycle" refers to cyclohexene, cyclohexadiene, and benzene.

15 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.

20 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.

25 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.

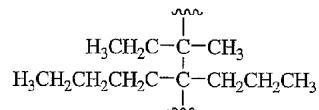
In compounds of the invention having pyridyl N-oxide moieties, the pyridyl-N-oxide portion is structurally depicted using conventional representations such as



which have equivalent meanings.

30 For variable definitions containing terms having repeated terms, e.g., (CRⁱR^j)_r, where r is the integer 2, Rⁱ is a defined variable, and R^j is a defined variable, the value of Rⁱ may

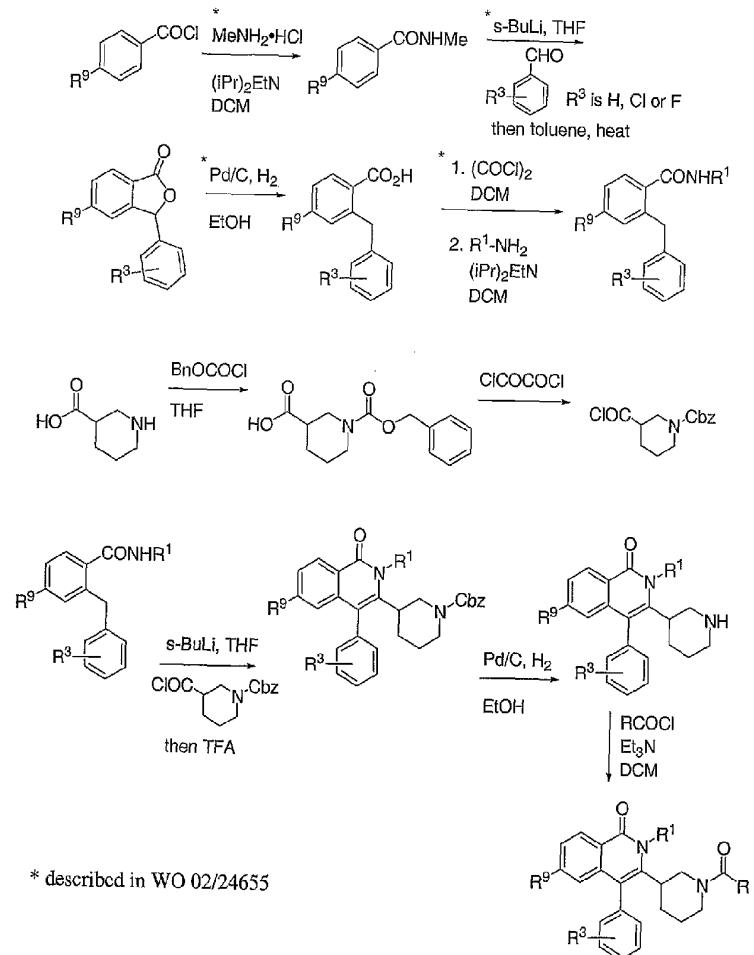
differ in each instance in which it occurs, and the value of R^j may differ in each instance in which it occurs. For example, if R^i and R^j are independently selected from the group consisting of methyl, ethyl, propyl and butyl, then $(CR^iR^j)_2$ can be

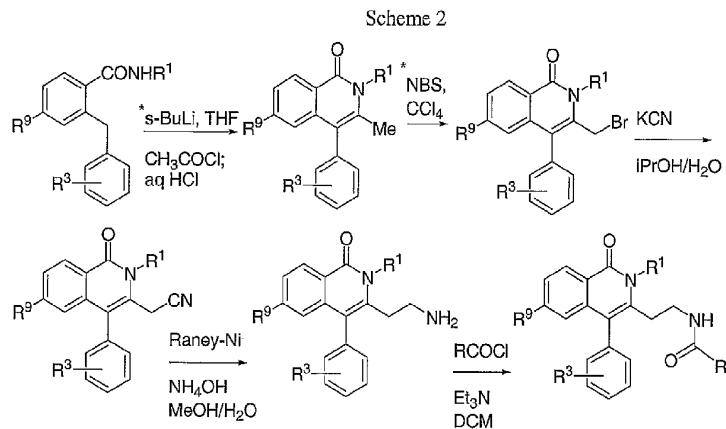


5 Pharmaceutically acceptable salts include both the metallic (inorganic) salts and organic salts; a list of which is given in *Remington's Pharmaceutical Sciences*, 17th Edition, pg. 1418 (1985). It is well known to one skilled in the art that an appropriate salt form is chosen based on physical and chemical stability, flowability, hydro-scopicity and solubility. As will be understood by those skilled in the art, pharmaceutically acceptable salts include, but are not 10 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 15 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, in which variables R^1 and R^9 are as defined above, and R is C₁₋₆ alkyl, aryl, 20 or C₁₋₆ alkylaryl. Other synthetic protocols will be readily apparent to those skilled in the art.

Scheme 1





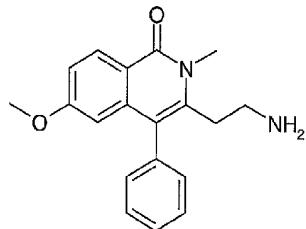
* described in WO 02/24655

The following 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.

5

EXAMPLE 1

3-(2-Aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one hydrochloride



Step A: 3-(Bromomethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one

The titled compound was prepared using a synthetic procedure previously reported in WO 02/24655.

Step B: 3-(Cyanomethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one

To a solution of 3-(bromomethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one (6.82 g, 19.0 mmol) in 100 mL of isopropanol was added a solution of potassium cyanide (2.48 g, 38.1 mmol) in 10 mL of water. The mixture was heated at 80 °C. After one hour, another portion of potassium cyanide solution (300 mg in 5 mL of water) was added, and the reaction

5 stirred for an additional hour. The solution was cooled to room temperature, and partitioned between EtOAc and saturated NaHCO₃ solution. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude solid material was triturated with EtOAc/ether to provide the titled product (5.01 g, 86% yield). HRMS (ES) exact mass calculated for C₁₉H₁₆N₂O₂

10 (M+H⁺): 305.1285. Found 305.1269.

Step C: 3-(2-Aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one hydrochloride

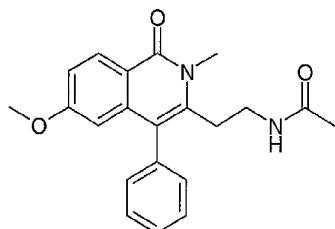
To a solution of 3-(cyanomethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one (2.00 g, 6.57 mmol) in 150 mL of 15% ammonium hydroxide in methanol in a Parr

15 flask was added Raney nickel (~5 g of a 50% slurry in water). The mixture was shaken under 60 psi of hydrogen at room temperature for 2 hours, then filtered through a pad of celite, along with a methanol rinse. The resulting solution was concentrated *in vacuo*, then azeotroped from toluene to remove remaining ammonia and water. The residue was taken up in a solution of dichloromethane and methanol, filtered, and concentrated *in vacuo*. The product was taken up in

20 a minimal amount of dichloromethane, treated with excess ethereal HCl, filtered, and triturated with dichloromethane-ether solution to provide the titled HCl salt. ¹H-NMR (500 MHz, CDCl₃) δ 8.39 (d, *J* = 8.8 Hz, 1H), 7.48 (m, 2H), 7.43 (m, 1H), 7.25 (m, 2H), 7.00 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.25 (d, *J* = 2.5 Hz, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.85 (br t, *J* = 7 Hz, 2H), 2.68 (br t, *J* = 7 Hz, 2H), 1.65 (br s, 2H) ppm. HRMS (ES) exact mass calculated for C₁₉H₂₁N₂O₂ (M+H⁺):

25 309.1589. Found 309.1598.

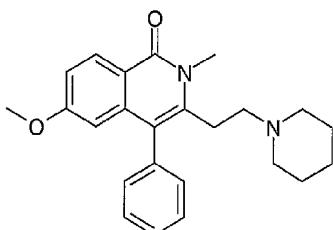
EXAMPLE 2

N-[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]acetamide

To a solution of 3-(2-aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-

5 1(*H*)-one hydrochloride (75 mg, 0.22 mmol) in 2 mL of dichloromethane was added triethylamine (0.076 mL, 0.54 mmol), followed by acetyl chloride (0.017 mL, 0.24 mmol). After 45 minutes, the mixture was partitioned between EtOAc and 10% citric acid solution, and the organic layer was washed with saturated NaHCO₃ solution and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by preparative reversed 10 phase HPLC to provide the titled product as a colorless oil. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₂₁H₂₂N₂O₃ (M+H⁺): 351.1703. Found 351.1681.

EXAMPLE 3

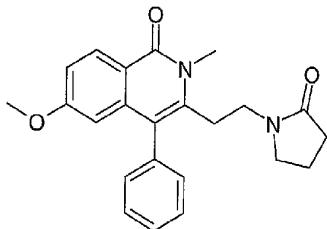
6-Methoxy-2-methyl-4-phenyl-3-(2-piperidin-1-ylethyl)isoquinolin-1(*H*)-one hydrochloride

15

To a solution of 3-(2-aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(*H*)-one hydrochloride (100 mg, 0.290 mmol) in 15 mL of 2-methyl-2-propanol in a pressure

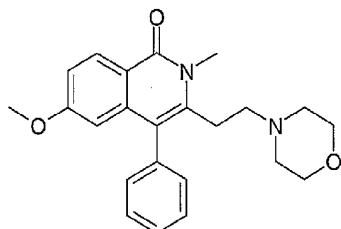
tube was added triethylamine (0.142 mL, 1.02 mmol), followed by 1,5-dibromopentane (0.047 mL, 0.348 mmol). The mixture was heated at 150 °C overnight. Another portion of 1,5-dibromopentane was added (0.023 mL), and the heating continued for another 24 hours. After cooling to room temperature, the mixture was concentrated *in vacuo*. The crude residue was 5 purified by preparative reversed phase HPLC. The pure fractions were concentrated *in vacuo*, taken up in EtOAc and washed with saturated NaHCO₃ solution and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The product was taken up in dichloromethane, treated with excess ethereal HCl, and concentrated *in vacuo* to provide the HCl salt. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 377.19 [M+H]⁺.

10 EXAMPLE 4

6-Methoxy-2-methyl-3-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-phenylisoquinolin-1(2H)-one

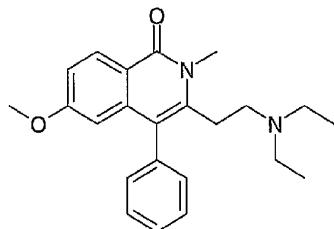
To a solution of 3-(2-aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one hydrochloride (125 mg, 0.362 mmol) in 15 mL of dichloromethane was added 15 triethylamine (0.202 mL, 1.45 mmol), followed by 4-chlorobutanoyl chloride (0.045 mL, 0.40 mmol). After 45 minutes, the mixture was concentrated *in vacuo*. Tetrahydrofuran was added (15 mL), and the solution was cooled to 0 °C. Sodium hydride was added (58 mg, 60% dispersion in mineral oil, 1.45 mmol). The reaction mixture was stirred at 0 °C for 30 minutes, at room temperature for 16 hours, then at 50 °C for 2 hours. The solution was partitioned 20 between EtOAc and saturated NaHCO₃ solution, and the organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by preparative reversed phase HPLC to provide the titled product. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 377.27 [M+H]⁺.

EXAMPLE 5

6-Methoxy-2-methyl-3-(2-morpholin-4-ylethyl)-4-phenylisoquinolin-1(2*H*)-one hydrochloride

Following the procedure described in Example 3, replacing 1,5-dibromopentane with di-(2-bromoethyl)ether, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. $^1\text{H-NMR}$ (500 MHz, d_6 -DMSO) δ 10.69 (br s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 7.57 (m, 2H), 7.52 (m, 1H), 7.35 (br d, J = 7 Hz, 2H), 7.13 (dd, J = 9.0, 2.4 Hz, 1H), 6.16 (d, J = 2.4 Hz, 1H), 3.90 (m, 2H), 3.67 (s, 3H), 3.65 (m, 2H), 3.63 (s, 3H), 3.23 (m, 4H), 2.98 (m, 2H), 2.88 (m, 2H) ppm. HRMS (ES) exact mass calculated for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_3$ ($\text{M}+\text{H}^+$): 379.2016. Found 379.2018.

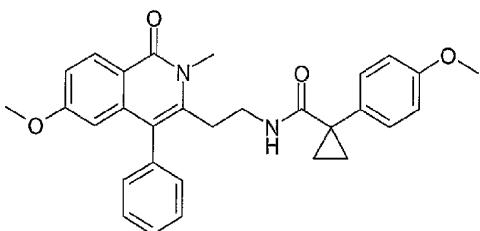
EXAMPLE 6

3-[2-(Diethylamino)ethyl]-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one trifluoroacetate

To a solution of 3-(2-aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one hydrochloride (100 mg, 0.290 mmol) in 3 mL of 1,2-dichloroethane was added acetaldehyde (0.017 mL, 0.29 mmol), sodium triacetoxyborohydride (92 mg, 0.43 mmol), and 100 mg of powdered 4 \AA molecular sieves. After two hours, additional portions of acetaldehyde

(0.017 mL, 0.29 mmol) and sodium triacetoxyborohydride (92 mg, 0.43 mmol) were added, and the reaction was stirred for 3 days. The mixture was partitioned between EtOAc and 10% citric acid solution, and the organic layer was washed with saturated NaHCO₃ solution and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by preparative reversed phase HPLC to provide the titled product. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 365.21 [M+H]⁺.

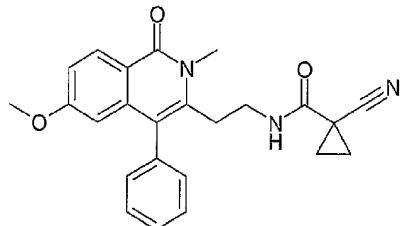
EXAMPLE 7

N-[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide

10

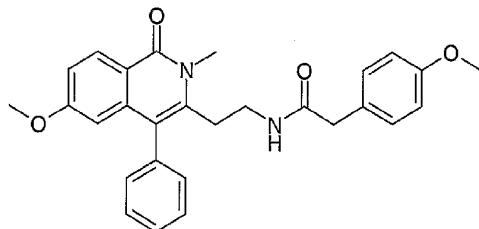
To a solution of 3-(2-aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one hydrochloride (70 mg, 0.20 mmol) in 3 mL of dimethylformamide was added 1-(4-methoxyphenyl)cyclopropanecarboxylic acid (0.39 mg, 0.20 mmol), triethylamine (0.085 mL, 0.61 mmol), 1-hydroxybenzotriazole hydrate (37 mg, 0.24 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (47 mg, 0.24 mmol). After three hours, the mixture was partitioned between EtOAc and water, and the organic layer was washed with saturated NaHCO₃ solution and brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was triturated with ether-hexane solution to provide the titled product. HRMS (ES) exact mass calculated for C₃₀H₃₀N₂O₄ (M+H⁺): 483.2258. Found 483.2279.

EXAMPLE 8

1-Cyano-N-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide

5 Following the procedure described in Example 7, replacing 1-(4-methoxyphenyl)cyclopropanecarboxylic acid with 1-cyano-1-cyclopropanecarboxylic acid, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{24}H_{23}N_3O_3$ ($M+H^+$): 402.1812. Found 402.1803.

10 EXAMPLE 9

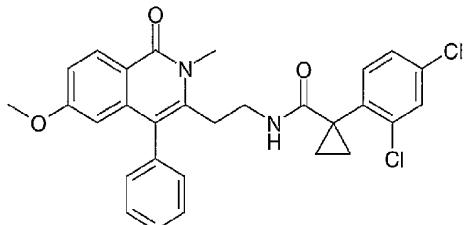
 N -[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]-1-(4-methoxyphenyl)acetamide

15 Following the procedure described in Example 7, replacing 1-(4-methoxyphenyl)cyclopropanecarboxylic acid with 1-(4-methoxyphenyl)acetic acid, the titled compound was obtained after purification by preparative reversed phase HPLC. Proton NMR for

the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{28}H_{28}N_2O_4$ ($M+H^+$): 457.2122. Found 457.2112.

EXAMPLE 10

5 1-(2,4-Dichlorophenyl)-N-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide

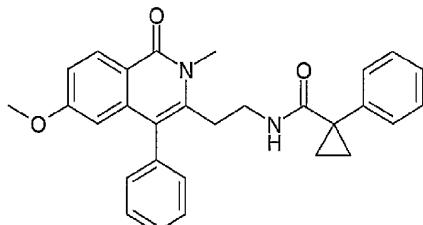


Following the procedure described in Example 7, replacing 1-(4-methoxyphenyl)cyclopropanecarboxylic acid with 1-(2,4-dichlorophenyl)cyclopropanecarboxylic acid, the titled compound was obtained after purification by preparative reversed phase HPLC.

10 Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{29}H_{26}Cl_2N_2O_3$ ($M+H^+$): 521.1393. Found 521.1379.

EXAMPLE 11

N -[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]-1-phenylcyclopropanecarboxamide



15

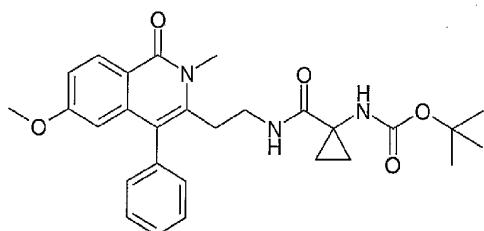
Following the procedure described in Example 7, replacing 1-(4-methoxyphenyl)cyclopropanecarboxylic acid with 1-phenylcyclopropane-1-carboxylic acid, the titled compound was obtained after purification by preparative reversed phase HPLC. 1H -NMR

(500 MHz, CDCl₃) δ 8.39 (d, *J* = 8.8 Hz, 1H), 7.38-7.45 (m, 3H), 7.25-7.30 (m, 5H), 7.11 (m, 2H), 7.00 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 5.34 (m, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 3.21 (m, 2H), 2.68 (m, 2H), 1.57 (m, 2H), 1.02 (dd, *J* = 6.8, 3.7 Hz, 2H) ppm. HRMS (ES) exact mass calculated for C₂₉H₂₈N₂O₃ (M+H⁺): 453.2173. Found 453.2158.

5

EXAMPLE 12

tert-Butyl 1-({[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]amino}carbonyl)cyclopropyl carbamate

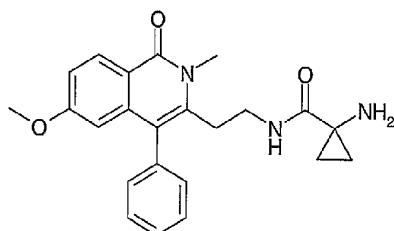


Following the procedure described in Example 7, replacing 1-(4-

10 methoxyphenyl)cyclopropanecarboxylic acid with *N*-(*tert*-butoxycarbonyl)-1-amino-1-cyclopropanecarboxylic acid, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₂₈H₃₃N₃O₅ (M+H⁺): 492.2493. Found 492.2481.

EXAMPLE 13

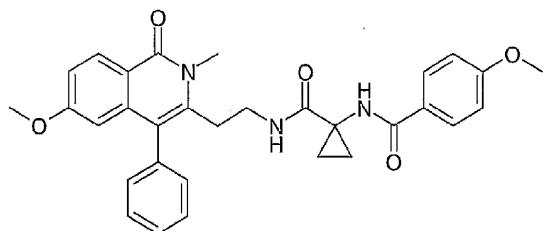
15 1-Amino-*N*-(2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl)cyclopropanecarboxamide hydrochloride



Through a solution of *tert*-butyl 1-({[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]amino}carbonyl)cyclopropyl carbamate (ca. 100 mg) in 10 mL of EtOAc at 0 °C was bubbled anhydrous HCl gas for 3 minutes. The solution was stirred for one hour, then concentrated *in vacuo* to provide the titled salt. Proton NMR for the product was 5 consistent with the titled compound. HRMS (ES) exact mass calculated for C₂₃H₂₅N₃O₃ (M+H⁺): 392.1969. Found 392.1960.

EXAMPLE 14

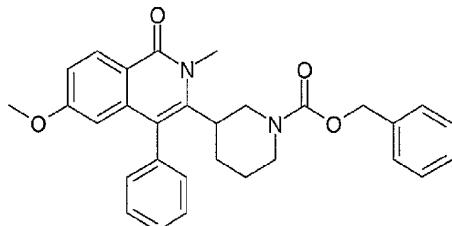
4-Methoxy-N-[1-({[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]amino}carbonyl)cyclopropyl]benzamide



10

To a solution of 1-amino-N-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide hydrochloride (30 mg, 0.117 mmol) in 3 mL of dimethylformamide was added triethylamine (0.049 mL, 0.35 mmol), followed by 4-(methoxy)benzoyl chloride (24 mg, 0.14 mmol). After 3 days, the mixture was concentrated *in vacuo*. Purification by preparative reversed phase HPLC provided the titled compound. ESI+ MS: 526.0 [M+H]⁺.

EXAMPLE 15

(±)-Benzyl 3-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)piperidine-1-carboxylate

5 Step A: (±)-1-[(Benzoyloxy)carbonyl]piperidine-3-carboxylic acid
 To an ice cooled solution of nipecotic acid (10.0 g, 77.5 mmol), sodium hydroxide (3.4 g, 85 mmol), and tetrahydrofuran (50 mL) in water (100 mL) was added by simultaneous dropwise addition benzylchloroformate (13.3 mL, 93 mmol) in tetrahydrofuran (50 mL) and sodium hydroxide (3.4 g, 85 mmol) in water (50 mL). Warmed slowly to room temperature.

10 After 24 hours tetrahydrofuran was removed *in vacuo* and the resulting aqueous mixture acidified with 3 N hydrochloric acid and extracted with dichloromethane (3X). The combined organic portions were dried with anhydrous magnesium sulfate. Filtration followed by evaporation of the filtrate *in vacuo* gave the titled compound. ¹HNMR (CHCl₃, 300MHz) δ 7.45-7.20 (m, 5H); 5.14 (m, 2H); 4.21 (br s, 1H); 3.96 (m, 1H), 3.15 (br s, 1H); 2.93 (m, 1H); 2.51 (m, 1H); 2.09 (m, 1H); 1.80-1.60 (m, 2H); 1.50 (m, 1H) ppm.

15 Step B: (±)-Benzyl-3-(chlorocarbonyl)piperidine-1-carboxylate
 To an ice cooled methylene chloride solution of 1-[(Benzoyloxy)carbonyl]piperidine-3-carboxylic acid (512 mg, 1.95 mmol) under nitrogen was added oxalyl chloride (0.185 mL, 1.95 mmol) and a few drops *N,N*-dimethylformamide. The 20 reaction flask was warmed slowly to room temperature and after 2 hours the solvent was removed *in vacuo*. Toluene was added and removed *in vacuo* (2X) to give the title compound.

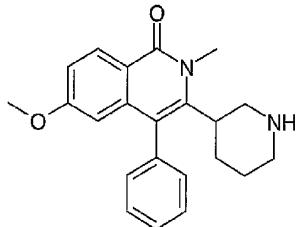
Step C: 4-Methoxy-N-methyl-2-(phenylmethyl)benzamide
 The titled compound was prepared using a synthetic procedure previously reported in WO 02/24655.

Step D: (±)-Benzyl 3-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)piperidine-1-carboxylate

To an isopropanol-dry ice cooled solution of 4-methoxy-*N*-methyl-2-(phenylmethyl)benzamide (500 mg, 1.96 mmol) in tetrahydrofuran (90 mL) was added dropwise 5 a 1.3 M solution of *sec*-butyllithium (3.09 mL, 4.02 mmol). After 15min. a solution of (±)-benzyl-3-(chlorocarbonyl)piperidine-1-carboxylate (550 mg, 1.96 mmol) in tetrahydrofuran (10 mL) was added. After 0.5 hours the contents of the reaction flask were first warmed to room temperature and then the solvent was removed *in vacuo*. The resulting mixture was treated with 10 1 M hydrochloric acid and extracted (3X) with ethyl acetate. The combined organic extracts were dried with anhydrous sodium sulfate, filtered and evaporated *in vacuo*. Trifluoroacetic acid (1 mL) was added and the resulting solution stirred 10 min. The reaction was quenched with water and made basic with saturated sodium bicarbonate. Extracted with ethyl acetate (3X), dried combined organic extracts with anhydrous sodium sulfate and removed solvent *in vacuo* to give a white foam. Flash column chromatography (50% EtOAc/hexane) afforded the title 15 compound as a white foam. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 483.3 [M+H]⁺.

EXAMPLE 16

(±)-6-Methoxy-2-methyl-4-phenyl-3-piperidin-3-ylisoquinolin-1(2*H*)-one

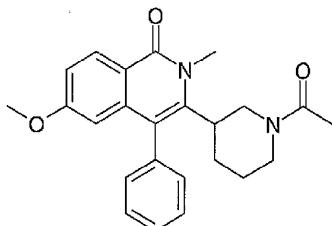


20 To an ethanol (15 mL) solution of (±)-benzyl 3-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)piperidine-1-carboxylate (201 mg, 0.417 mmol) in a Parr hydrogenation jar was added 10% palladium on carbon catalyst (50 mg). The contents of the jar were hydrogenated at 60 psi for four hours. Filtration through celite followed by evaporation of

the filtrate *in vacuo* gave the titled product as a white foam. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 349.2 [M+H]⁺.

EXAMPLE 17

(±)-3-(1-Acetyl piperidin-3-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one

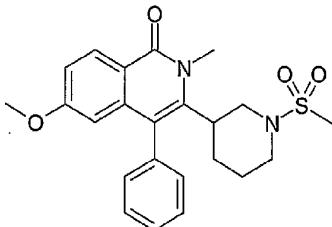


5

To a dichloromethane (0.100 mL) solution of (±)-6-methoxy-2-methyl-4-phenyl-3-piperidin-3-ylisoquinolin-1(2H)-one (30 mg, 0.086 mmol) and *N,N*-diisopropylethylamine (0.017 mL, 0.095 mmol) was added acetyl chloride (0.007 mL, 0.095 mmol). After 24 hours saturated sodium bicarbonate and additional dichloromethane were added. The layers were separated and the organic phase dried with anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by trituration with ether-EtOAc gave a white solid which was isolated by vacuum filtration to give the titled product. ESI+ MS: 391.3 [M+H]⁺.

EXAMPLE 18

(±)-6-Methoxy-2-methyl-3-[1-(methylsulfonyl)piperidin-3-yl]-4-phenylisoquinolin-1(2H)-one

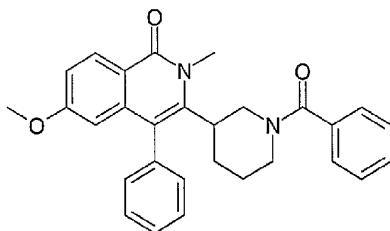


15

To a methylene chloride (0.100 mL) solution of (±)-6-methoxy-2-methyl-4-phenyl-3-piperidin-3-ylisoquinolin-1(2H)-one (30 mg, 0.086 mmol) and *N,N*-

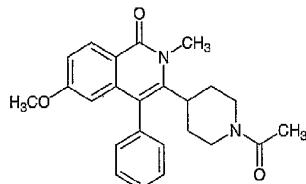
diisopropylethylamine (0.017 mL, 0.095 mmol) was added methanesulfonyl chloride (0.007 mL, 0.095 mmol). After 24 hours saturated sodium bicarbonate and additional methylene chloride were added. The layers were separated and the organic phase dried with anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* followed by trituration with ether-EtOAc gave a 5 white solid which was isolated by vacuum filtration to give the titled product. ESI+ MS: 427.1 [M+H]⁺.

EXAMPLE 19

(±)-3-(1-Benzoylpiperidin-3-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one

10 To a dichloromethane (0.100mL) solution of (±)-6-methoxy-2-methyl-4-phenyl-3-piperidin-3-ylisoquinolin-1(2H)-one (30 mg, 0.086 mmol) and *N,N*-diisopropylethylamine (0.017 mL, 0.095 mmol) was added benzoyl chloride (0.011 mL, 0.095 mmol). After 24 hours saturated sodium bicarbonate and additional dichloromethane were added. The layers were separated and the organic phase dried with anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* 15 followed by trituration with ether-EtOAc gave a white solid which was isolated by vacuum filtration to give the titled product. ESI+ MS: 453.3 [M+H]⁺.

EXAMPLE 20

3-(1-Acetyl piperidin-4-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2H)-one

Step A

To an isopropanol/dry ice cooled solution of 4-Methoxy-*N*-methyl-2-(phenylmethyl)benzamide (250mg, 0.980mmol) in THF (50mL) under argon was added *sec*-butyllithium solution (1.3M, 1.55mL, 2.00mmol) dropwise. After 10min. a THF (10mL) solution of benzyl-4-(chlorocarbonyl)piperidine-1-carboxylate (275mg, 980mmol) was quickly added to the reaction solution. After 10min. the reaction was quenched with water then warmed to room temperature. Saturated sodium bicarbonate was added and the resulting mixture extracted with ethyl acetate (3×) and dried with anhydrous magnesium sulfate. Filtration followed by evaporation of solvent in vacuo gave the crude product which was subjected to flash column chromatography (hexane : ethyl acetate 50:50) to afford benzyl-4-(3-hydroxy-6-methoxy-2-methyl-1-oxo-4-phenyl-1,2,3,4-tetra-hydroisoquinolin-3-yl)piperidine-1-carboxylate as a white foam (242mg, 0.484mmol, 49%). MS [M + H]⁺ 501.2

Step B

To trifluoroacetic acid (1mL) at room temperature was added benzyl-4-(3-hydroxy-6-methoxy-2-methyl-1-oxo-4-phenyl-1,2,3,4-tetra-hydroisoquinolin-3-yl)piperidine-1-carboxylate (215mg, 0.443mmol) with stirring. After 10min. the reaction mixture was made basic with 2N sodium hydroxide, extracted with methylene chloride (3×) and dried with anhydrous sodium sulfate. Filtration followed by evaporation of solvent in vacuo gave a solid which was triturated with hexane – ethyl acetate to afford benzyl-4-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)piperidine-1-carboxylate as a solid (141mg, 0.292mmol, 66%). MS [M + H]⁺ 483.2

Step C

To a Parr bottle containing an ethanol (5mL) solution of benzyl-4-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)piperidine-1-carboxylate (120mg, 0.249mmol) was added 10% palladium on carbon catalyst (30mg). The contents of the Parr bottle were hydrogenated at 60psi for 3h. Filtration of the reaction mixture through celite followed by evaporation of the solvent in vacuo gave, after trituration with ether, 6-Methoxy-2-methyl-4-phenyl-3-piperidin-4-ylisoquinolin-1(2H)-one as a solid (60mg, 0.172mmol, 69%). MS [M + H]⁺ 349.1

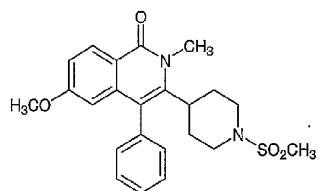
Step D

To a stirred methylene chloride (0.300mL) solution of 6-Methoxy-2-methyl-4-phenyl-3-piperidin-4-ylisoquinolin-1(2H)-one (20mg, 0.057mmol) and *N,N*-diisopropylethylamine (0.011mL, 0.063mmol) under argon was added acetyl chloride (0.005mL, 0.063mmol). After 24h saturated sodium bicarbonate was added and the organic layer separated and dried with anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo gave a solid which after trituration with ether – ethyl acetate afforded the titled compound as a solid.

MS [M + H]⁺ 391.1

10

EXAMPLE 21

6-Methoxy-2-methyl-3-[1-(methylsulfonyl)piperidin-4-yl]-4-phenyl-isoquinolin-1(2H)-one

To a stirred methylene chloride (0.300mL) solution of 6-Methoxy-2-methyl-4-phenyl-3-piperidin-4-ylisoquinolin-1(2H)-one (20mg, 0.057mmol) and *N,N*-diisopropylethylamine (0.011mL, 0.063mmol) under argon was added methanesulfonyl chloride (0.005mL, 0.063mmol). After 24h saturated sodium bicarbonate was added and the organic layer separated and dried with anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo gave a solid which after trituration with ether – ethyl acetate afforded the titled compound as a solid.

20 MS [M + H]⁺ 427.1

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 25 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 5 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 10th pulse than for the 1st pulse of the train.

10 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 15 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 20 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 25 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 resuspended in PBS and the resulting suspension placed in the cell reservoir of the IonWorks™ HT instrument.

30 Electrophysiological recordings are performed with intracellular solution containing (mM): K-gluconate 100, KCl 40, MgCl₂ 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): CaCl₂ 35 0.90, KCl 2.67, KPO₄ 1.47, MgCl₂ 0.50, NaCl 138, NaPO₄ 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 μ L of external buffer.
2. Planar micropipette hole resistances (R_p) 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 μ m 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 % (IC₅₀) are determined by fitting of the Hill equation to the concentration response data:

$$\% \text{ of Control} = 100 \times (1 + ([\text{Drug}]/\text{IC}_{50})^p)^{-1}$$

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

5 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
- 10 3) current run up metric is >-0.2 nA
- 4) pre-read peak metric is <400 pA.

The above-listed compounds provide ≥ 20% inhibition at a concentration of 33 μM or less in the high throughput Kv1.5 planar patch clamp assay described above.

15

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 20 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.
- 25 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% CO₂.
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 30 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.
- 35 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 %

5 FLUX in the presence of 0.25% DMSO.

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

10 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.

15 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.

20 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.

25 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, and supraventricular tachycardia, thromboembolic events such as stroke and congestive heart failure, and

30 immunodepression.

35 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.

5 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 10 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 15 sugar solutions and glycols such as propylene glycol or polyethylene glycols 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 20 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 25 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, 30 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 35 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 5 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 10 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 15 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 20 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.

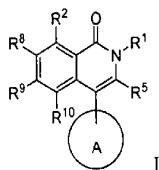
The same dosage forms can generally be used when the compounds of this 25 invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility 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 30 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, clofinium, 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 35 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 immunosuppressant compound, endothelin 5 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 10 ingredient or in combination with a pacemaker or defibrillator device.

The claims defining the invention are as follows:

1. A compound of the structure:



5 or a pharmaceutically acceptable salt, crystal form, or hydrate, wherein:

A is

a) an aryl ring, wherein any stable aryl ring atom is independently
unsubstituted or substituted with

10 1) halogen,
2) NO_2 ,
3) CN ,
4) $\text{CR}^{46}=\text{C}(\text{R}^{47}\text{R}^{48})_2$,
5) $\text{C}\equiv\text{C R}^{46}$,
15 6) $(\text{CR}^i\text{R}^j)_r\text{OR}^{46}$,
7) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46}\text{R}^{47})$,
8) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{R}^{46}$,
9) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{OR}^{46}$,
10) $(\text{CR}^i\text{R}^j)_r\text{R}^{46}$,
11) $(\text{CR}^i\text{R}^j)_r\text{S}(\text{O})_0\text{-2R}^{61}$,
20 12) $(\text{CR}^i\text{R}^j)_r\text{S}(\text{O})_0\text{-2N}(\text{R}^{46}\text{R}^{47})$,
13) $\text{OS}(\text{O})_0\text{-2R}^{61}$,
14) $\text{N}(\text{R}^{46})\text{C}(\text{O})\text{R}^{47}$,
15) $\text{N}(\text{R}^{46})\text{S}(\text{O})_0\text{-2R}^{61}$,
16) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})\text{R}^{61}$,
25 17) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})\text{R}^{61}\text{OR}^{47}$,
18) $(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{46})(\text{CR}^k\text{R}^l)_s\text{C}(\text{O})\text{N}(\text{R}^{47}\text{R}^{48})$,
19) $\text{N}(\text{R}^{46})(\text{CR}^i\text{R}^j)_r\text{R}^{61}$,
20) $\text{N}(\text{R}^{46})(\text{CR}^i\text{R}^j)_r\text{N}(\text{R}^{47}\text{R}^{48})$,
21) $(\text{CR}^i\text{R}^j)_r\text{C}(\text{O})\text{N}(\text{R}^{47}\text{R}^{48})$, or
30 22) oxo, or

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b) a heteroaryl ring selected from the group consisting of
 a 5-membered unsaturated monocyclic ring with 1, 2, 3 or 4 heteroatom
 ring atoms selected from the group consisting of N, O or S,
 a 6-membered unsaturated monocyclic ring with 1, 2, 3 or 4 heteroatom
 ring atoms selected from the group consisting N, O and S, and
 a 9- or 10-membered unsaturated bicyclic ring with 1, 2, 3 or 4
 heteroatom ring atoms selected from the group consisting of N, O or S;

wherein any stable S heteroaryl ring atom is unsubstituted or mono- or di-
 substituted with oxo, and any stable C or N heteroaryl ring atom is independently
 unsubstituted or substituted with

- 1) halogen,
- 2) NO₂,
- 3) CN,
- 4) CR⁴⁶=C(R⁴⁷R⁴⁸)₂,
- 5) C≡CR⁴⁶,
- 6) (CRⁱR^j)_rOR⁴⁶,
- 7) (CRⁱR^j)_rN(R⁴⁶R⁴⁷),
- 8) (CRⁱR^j)_rC(O)R⁴⁶,
- 9) (CRⁱR^j)_rC(O)OR⁴⁶,
- 10) (CRⁱR^j)_rR⁴⁶,
- 11) (CRⁱR^j)_rS(O)O₀₋₂R⁶¹,
- 12) (CRⁱR^j)_rS(O)O₀₋₂N(R⁴⁶R⁴⁷),
- 13) OS(O)O₀₋₂R⁶¹,
- 14) N(R⁴⁶)C(O)R⁴⁷,
- 15) N(R⁴⁶)S(O)O₀₋₂R⁶¹,
- 16) (CRⁱR^j)_rN(R⁴⁶)R⁶¹,
- 17) (CRⁱR^j)_rN(R⁴⁶)R⁶¹OR⁴⁷,
- 18) (CRⁱR^j)_rN(R⁴⁶)(CR^kR^l)_sC(O)N(R⁴⁷R⁴⁸),
- 19) N(R⁴⁶)(CRⁱR^j)_rR⁶¹,
- 20) N(R⁴⁶)(CRⁱR^j)_rN(R⁴⁷R⁴⁸),
- 21) (CRⁱR^j)_rC(O)N(R⁴⁷R⁴⁸), or
- 22) oxo;

R¹ is selected from the group consisting of

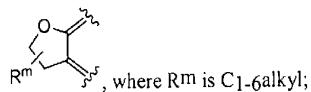
- 1) hydrogen,
- 2) (CR^aR^b)_nR⁴⁰

- 3) $(CR^aRb)_nOR^{40},$
- 4) $(CR^aRb)_nN(R^{40}R^{41}),$
- 5) $(CR^aRb)_nN(R^{40})C(O)OR^{41},$
- 6) $(CR^aRb)_nN(R^{40})(CR^cRd)_2N(R^{41})C(O)R^{49},$
- 7) C₃₋₈ cycloalkyl,
- 8) $(CR^aRb)_nC(O)OR^{40},$
- 9) $(CR^aRb)_nN(R^{40})(CR^cRd)_{1-3}R^{41},$
- 10) $(CR^aRb)_nS(O)O-2R^6,$
- 11) $(CR^aRb)_nS(O)O-2N(R^{40}R^{41}),$
- 12) $(CR^aRb)_nN(R^{40})R^6OR^{41},$
- 13) $(CR^aRb)_nN(R^{40})(CR^cRd)_{0-6}C(O)N(R^{41}R^{42});$

R2, R8, R9 and R10 are independently selected from:

- 1) hydrogen,
- 2) halogen,
- 3) NO_2 ,
- 4) CN ,
- 5) $\text{CR}^4\text{C}(\text{R}^4\text{R}^4\text{R}^4)$,
- 6) $\text{C}\equiv\text{CR}^4$,
- 7) $(\text{CREF})_p\text{OR}^4$,
- 8) $(\text{CREF})_p\text{N}(\text{R}^4\text{R}^4)$,
- 9) $(\text{CREF})_p\text{C}(\text{O})\text{R}^4$,
- 10) $(\text{CREF})_p\text{C}(\text{O})\text{OR}^4$,
- 11) $(\text{CREF})_p\text{R}^4$,
- 12) $(\text{CREF})_p\text{S}(\text{O})_0\text{R}^6$,
- 13) $(\text{CREF})_p\text{S}(\text{O})_0\text{N}(\text{R}^4\text{R}^4)$,
- 14) $\text{OS}(\text{O})_0\text{R}^6$,
- 15) $\text{N}(\text{R}^4)\text{C}(\text{O})\text{R}^4$,
- 16) $\text{N}(\text{R}^4)\text{S}(\text{O})_0\text{R}^6$,
- 17) $(\text{CREF})_p\text{N}(\text{R}^4)\text{R}^6$,
- 18) $(\text{CREF})_p\text{N}(\text{R}^4)\text{R}^6\text{OR}^4$,
- 19) $(\text{CREF})_p\text{N}(\text{R}^4)(\text{CREF})_q\text{C}(\text{O})\text{N}(\text{R}^4\text{R}^4)$,
- 20) $\text{N}(\text{R}^4)(\text{CREF})_p\text{R}^6$,
- 21) $\text{N}(\text{R}^4)(\text{CREF})_p\text{N}(\text{R}^4\text{R}^4)$, and
- 22) $(\text{CREF})_p\text{C}(\text{O})\text{N}(\text{R}^4\text{R}^4)$,

or R² and R⁸ are independently as defined above, and R⁹ and R¹⁰, together with the atoms to which they are attached, form the ring



, where R^m is C₁-alkyl;

R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, Rⁱ, R^j, R^k, and R^l are independently selected from the group consisting of:

- 1) hydrogen,
- 2) C₁-C₆ alkyl,
- 3) halogen,
- 4) aryl,
- 5) R⁸⁰,
- 6) C₃-C₁₀ cycloalkyl, and
- 7) OR⁴,

said alkyl, aryl, and cycloalkyl being unsubstituted, monosubstituted with R⁷,

disubstituted with R⁷ and R¹⁵, trisubstituted with R⁷, R¹⁵ and R¹⁶, or tetrasubstituted with R⁷, R¹⁵, R¹⁶ and R¹⁷;
R⁴, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵¹, R⁵², R⁵³ and R⁵⁴ are independently selected from the group consisting of

- 1) hydrogen,
- 2) C₁-C₆ alkyl,
- 3) C₃-C₁₀ cycloalkyl,
- 4) aryl,
- 5) R⁸¹,
- 6) CF₃,
- 7) C₂-C₆ alkenyl, and
- 8) C₂-C₆ alkynyl,

said alkyl, aryl, and cycloalkyl is unsubstituted, mono-substituted with R¹⁸, di-substituted with R¹⁸ and R¹⁹, tri-substituted with R¹⁸, R¹⁹ and R²⁰, or tetra-substituted with R¹⁸, R¹⁹, R²⁰ and R²¹;

R⁶, R⁶⁰, R⁶¹, and R⁶³ are independently selected from the group consisting of

- 1) C₁-C₆ alkyl,
- 2) aryl,

- 3) R⁸³, and
- 4) C₃-C₁₀ cycloalkyl;

said alkyl, aryl, and cycloalkyl is unsubstituted, mono-substituted with R²⁶, di-substituted with R²⁶ and R²⁷, tri-substituted with R²⁶, R²⁷ and R²⁸, or tetra-substituted with R²⁶, R²⁷, R²⁸ and R²⁹;
R⁷, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²⁶, R²⁷, R²⁸, and R²⁹ are independently selected from the group consisting of

- 1) C₁-C₆ alkyl,
- 2) halogen,
- 10 3) OR⁵¹,
- 4) CF₃,
- 5) aryl,
- 6) C₃-C₁₀ cycloalkyl,
- 7) R⁸⁴,
- 15 8) S(O)₀₋₂N(R⁵¹R⁵²),
- 9) C(O)OR⁵¹,
- 10) C(O)R⁵¹,
- 11) CN,
- 12) C(O)N(R⁵¹R⁵²),
- 20 13) N(R⁵¹)C(O)R⁵²,
- 14) S(O)₀₋₂R⁶³,
- 15) NO₂,
- 16) N(R⁵¹R⁵²), and
- 17) R⁸²;

25 R²² selected from the group consisting of

- 1) NHC(O)R⁸⁸, and
- 2) N(R⁵³R⁵⁴);

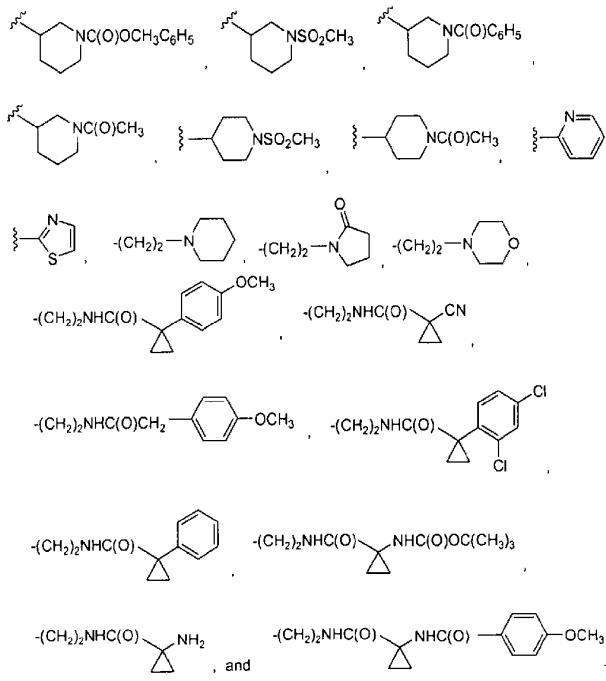
R⁸⁸ is C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

30 R⁸⁰, R⁸¹, R⁸², R⁸³, R⁸⁴ and R⁸⁵ are independently selected from a group of unsubstituted or substituted heterocyclic rings consisting of a 3-6 membered unsaturated or saturated monocyclic ring with 1, 2, or 3 heteroatom ring atoms selected from the group consisting N, O and S, and a 9- or 10-membered unsaturated or saturated bicyclic ring with 1, 2, 3 or 4 heteroatom ring atoms selected from the group consisting of N, O or S; and

35 n, p, q, r, and s are independently 0, 1, 2, 3, 4, 5 or 6,

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wherein R5 is selected from the group consisting of $-(\text{CH}_2)_2\text{NH}_2$, $-(\text{CH}_2)_2\text{NHC(O)CH}_3$, $-(\text{CH}_2)_2\text{N}(\text{CH}_2\text{CH}_3)_2$,



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

3-(2-Aminoethyl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one,

N-[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-

yl)ethyl]acetamide,

6-Methoxy-2-methyl-4-phenyl-3-(2-piperidin-1-ylethyl)isoquinolin-1(2*H*)-one,

6-Methoxy-2-methyl-3-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-phenylisoquinolin-1(2*H*)-

one,

6-Methoxy-2-methyl-3-(2-morpholin-4-ylethyl)-4-phenylisoquinolin-1(2*H*)-one,

3-[2-(Diethylamino)ethyl]-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one,

N-[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]-1-(4-methoxyphenyl)cyclopropanecarboxamide,
1-Cyano-*N*-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide,
5 *N*-[2-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]acetamide,
1-(2,4-Dichlorophenyl)-*N*-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide,
10 *N*-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]-1-phenylcyclopropanecarboxamide,
tert-Butyl 1-({{[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]amino}carbonyl)cyclopropyl carbamate,
15 1-Amino-*N*-[2-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]cyclopropanecarboxamide,
1-(6-Methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)ethyl]amino}carbonyl)cyclopropyl]benzamide,
20 (\pm)-Benzyl 3-(6-methoxy-2-methyl-1-oxo-4-phenyl-1,2-dihydroisoquinolin-3-yl)piperidine-1-carboxylate,
(\pm)-6-Methoxy-2-methyl-4-phenyl-3-piperidin-3-ylisoquinolin-1(2*H*)-one,
25 (\pm)-3-(1-Acetyl piperidin-3-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one,
3-(1-acetyl piperidin-4-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one,
1(2*H*)-one,
30 (\pm)-6-Methoxy-2-methyl-3-[1-(methylsulfonyl)piperidin-3-yl]-4-phenylisoquinolin-1(2*H*)-one,
(\pm)-3-(1-Benzoylpiperidin-3-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one
one
35 3-(Pyrid-2-yl)-6-methoxy-2-methyl-4-phenylisoquinolin-1(2*H*)-one, and
3-(Thiazol-2-yl)-6-methoxy-2-cyclopropyl-4-phenylisoquinolin-1(2*H*)-one.
3. A method of treating a condition in a mammal, the treatment of which is effected or facilitated by K_v1.5 inhibition, which comprises administering a compound of Claim 1 in an amount that is effective at inhibiting K_v1.5 wherein the condition is cardiac arrhythmia.

4. A method of Claim 3, wherein the cardiac arrhythmia is atrial fibrillation.
5. A method of Claim 3, wherein the cardiac arrhythmia is selected from the group consisting of atrial flutter, atrial arrhythmia and supraventricular tachycardia.
6. A pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of Claim 1 or a pharmaceutically acceptable crystal form or hydrate thereof.
7. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.
8. A method of treating cardiac arrhythmia comprising administering a compound of Claim 1 with a compound selected from one of the classes of compounds consisting of antiarrhythmic agents having Kv1.5 blocking activities, ACE inhibitors, angiotensin II antagonists, cardiac glycosides, L-type calcium channel blockers, T-type calcium channel blockers, selective and nonselective beta blockers, endothelin antagonists, thrombin inhibitors, aspirin, nonselective NSAIDs, warfarin, factor Xa inhibitors, low molecular weight heparin, unfractionated heparin, clopidogrel, ticlopidine, IIb/IIIa receptor antagonists, 5HT receptor antagonists, integrin receptor antagonists, thromboxane receptor antagonists, TAFI inhibitors and P2T receptor antagonists.
9. A method for treating tachycardia in a patient which comprises treating the patient with an antitachycardia device in combination with a compound of Claim 1.
10. A compound according to claim 1 and substantially as hereinbefore described with reference to any one of the examples.

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