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(54) Title: POTASSIUM CHANNEL AGONISTS

(57) Abstract

This application discloses a method of treating cardiac ventricular arrhythmias and repolarization abnormalities associated with long QT syndrome and/or congestive heart failure comprising the administration of an agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}).

TITLE OF THE INVENTION

POTASSIUM CHANNEL AGONISTS

BACKGROUND OF THE INVENTION

5   1.   Field of the Invention

This is a method of treatment of cardiac arrhythmias and repolarization abnormalities associated with long QT syndrome (LQTS) and/or congestive heart failure (CHF). This method is also useful in ameliorating or improving contractile dysfunction in CHF by hastening

10   cardiac repolarization and relaxation and/or increasing the diastolic filling time and thereby reducing the workload of the failing heart, reducing oxygen consumption and improving cardiac performance. The method utilizes a compound that acts to enhance or activate cardiac potassium (K^+) channels and shorten the cardiac action potential (AP),

15   thereby hastening repolarization, decreasing systolic contraction time and prolonging the diastolic filling time. Specific examples of compounds that act to enhance the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) are presented. This effect of increasing the repolarizing K^+ current, I_{Ks}, causes a shortening of action potential

20   duration (APD) that occurs as a consequence of a direct action of the compound on slowly activating cardiac delayed rectifier potassium channels in the cardiac plasma membrane underlying I_{Ks}, and not through an effect on other indirect pathways, such as, binding and stimulation of ß-adrenergic receptors. The shortening of APD acts to

25   prevent or reverse the electrophysiologic and contractile abnormalities that occur in LQTS and CHF, including delayed repolarization, ventricular arrhythmias, and delayed relaxation of the myocardium which compromises contractility and the pumping efficiency of the heart.

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          2.   Description of Related Art

Cardiac arrhythmias often occur as a complication of cardiac diseases such as myocardial infarction and heart failure. Certain cardiac arrhythymias result from electrolyte imbalances,

35   dietary deficiencies, exposure to drugs, or congenital abnormalities

(Jackman WN, Friday KJ, Anderson JL, Aliot EM, Clark M and
Lazzara R. (1988). The Long QT syndromes: a critical review, new
clinical observations and a unifying hypothesis. *Prog Cardiovasc Dis* **31:**
115-172.), which produce changes in the density or regulation of various

5   ion channels and cause abnormally long APs. In particular, aberrant
cardiac repolarization, whereby APs become excessively long,
predisposes patients to the risk of dangerous cardiac arrhythmias and
sudden cardiac death (SCD), and is well known to occur in various
acquired and genetic forms of LQTS (Roden DM, Lazzara R, Rosen M,

10   Schwartz PJ, Towbin J and Vincent GM. (1996). Multiple mechanisms
in the Long-QT Syndrome; Current knowledge, gaps and future
directions. *Circulation* **94:** 1996-2012.) , and in CHF (Tomaselli GF,
Beuckelmann DJ, Calkins HG, Berger RD, Kessler PD, Lawrence JH,
Kass D, Feldman AM and Marban E. (1994). Suden cardiac death in

15   heart failure. The role of abnormal repolarization. *Circulation* **90:** 2534-
2539.). In myocardial cells there is an ensemble of inward and outward
currents that results from the flow of various inorganic ions through the
cell membrane. These currents are due to the presence of selective
cation and anion channels in the plasma membrane. The voltage- and

20   time-dependent opening (activation) and closing (inactivation and/or
deactivation) of these ion channels in cardiomyocytes result in the
characteristically long cardiac APs (depolarization with delayed
repolarization). After an initial rapid upstroke or depolarization, there
is a plateau of maintained depolarization followed by repolarization to

25   the resting membrane potential. Thus, APD is primarily responsible for
the time-course of repolarization of the heart; prolongation of APD
produces delays in cardiac repolarization, often manifest as an increase
in the electrocardiographic QT interval. Cardiac APs also underlie a
coordinated conduction of electrical impulses throughout the heart,

30   trigger the synchronized contraction of the heart and, to some extent,
control the force of the contraction. If these APs develop abnormal
configuations and/or automaticity or become unsynchronized, then fatal
cardiac arrhythmias can occur. As a rule, the longer the APD, the
more labile is the cardiac repolarization process. This lability may be

35   exhibited as pronounced variability or excessive prolongation in APD

that can initiate or trigger early after-depolarizations (EAD) in cardiac myocytes, in vitro, which is one mechanism for induction of ventricular arrhythmias (Brugada P and Wellens HJJ. (1985). Early afterdepolarizations: role in conduction block, prolonged repolarization-
5 dependent re-excitation, and tachyarrhythmias in the human heart. *PACE* **8**: 889-896; January CT and Fozzard HA. (1988). Delayed afterdepolarizations in heart muscle: Mechanisms and relevance. *Pharmacol Rev* **40**: 219-227; January CT and Moscucci A. (1992). Cellular mechanisms of early afterdepolarizations. *Annal NY Acad Sci*
10 **644**: 23-32.).

Repolarization from the plateau phase of the AP in ventricular myocytes is controlled by a delicate balance between inward and outward currents in the setting of a high membrane resistance. Prolongation of APD can occur as a consequence of decreases in outward
15 currents or increases in inward currents. Important outward currents that determine repolarization are the rapidly (I_{Kr}) and slowly (I_{Ks}) activating delayed rectifier K^+ currents (Sanguinetti MC and Jurkiewicz NK. (1990). Two components of cardiac delayed rectifier K^+ current: Differential sensitivity to block by class III antiarrhythmic agents. *J Gen*
20 *Physiol* **96**: 195-215.). Several class III antiarrhythmic agents selectively block I_{Kr}, and thereby prolong APD and the QT interval on the electrocardiogram. Excessive APD prolongation by these drugs causes acquired long QT syndrome (LQTS) that is associated with torsades de pointes, a ventricular tachyarrhythmia that can degenerate into
25 ventricular fibrillation and cause SCD.

LQTS can also be inherited. The finding that mutations in *HERG*, the gene that encodes I_{Kr} channels cause inherited LQTS (Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED and Keating MT. (1995). A molecular basis for cardiac arrhythmia: *HERG*
30 mutations cause long QT syndrome. *Cell* **80**: 795-804.; Sanguinetti MC, Curran ME, Spector PS and Keating MT. (1996a). Spectrum of HERG K^+ channel dysfunction in an inherited cardiac arrhythmia. *Proc Natl Acad Sci USA* **93**: 2208-2212.; Sanguinetti MC, Jiang C, Curran ME and Keating MT. (1995). A mechanistic link between an inherited and an
35 acquired cardiac arrhythmia: HERG encodes the I_{Kr} potassium channel.

Cell **81**: 299-307.) provided a mechanistic link between acquired LQTS
and one form of inherited LQTS. The most common form of LQTS is
caused by mutations in *KvLQT1*, a novel K^+ channel gene (Wang Q,
Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen
5   J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Towbin JA,
Moss AJ, Atkinson DL, Landes GM, Connors TD and Keating MT.
(1996). Positional cloning of a novel potassium channel gene: KvLQT1
mutations cause cardiac arrhythmias. *Nature Genetics* **12**: 17-23.).
Expression of *KvLQT1* in either *Xenopus* oocytes or mammalian cell
10   lines induced a K^+ current with biophysical properties unlike any
known cardiac K^+ current. Co-expression of *KvLQT1* with *minK*
induced a current that was essentially identical to cardiac I_{Ks},
indicating that KvLQT1 and minK proteins co-assemble to form I_{Ks}
channels (Barhanin J, Lesage F, Guillemare E, Fink M, Lazdunski M
15   and Romey G. (1996). KvLQT1 and I_{sK} (minK) proteins associate to form
the I_{Ks} cardiac potassium current. *Nature* **384**: 78-80.; Sanguinetti MC,
Curran ME, Zou A, Shen J, Spector PS, Atkinson DL and Keating MT.
(1996b). Coassembly of KvLQT1 and minK (I_{sK}) proteins form cardiac I_{Ks}
potassium channel. *Nature* **384**: 80-83.). Thus, dysfunction of either I_{Kr}
20   or I_{Ks} can increase the risk of cardiac arrhythmia and SCD.

CHF is a common, highly lethal cardiovascular disorder
that affects over 2 million people and claims over 200,000 lives a year in
the U.S. It is estimated that ≥ 50% of deaths in CHF patients are sudden
and that the majority of these are most likely the result of ventricular
25   tachycardia. Myocytes isolated from failing animal and human hearts
consistently exhibit a significant prolongation of APD compared with
those of normal hearts, independent of the mechanism of CHF
(Tomaselli, et al. (1994). Sudden cardiac death in heart failure. The role
of abnormal repolarization. *Circulation* **90**: 2534-2539.). The increase in
30   APD in animal models and human CHF do not appear to occur as a
result of alterations of the inward currents, I_{Na} and I_{Ca}, but decreases in
at least two voltage-dependent outward K^+ currents have been
consistenly observed. Both the transient outward current, I_{to}, and the
inward rectifier K^+ current, I_{K1}, have been shown to be reduced in heart
35   failure. Recent studies have also shown that I_{Ks} is decreased in animal

models of heart failure and human CHF (Li GR, Sun H, Nattel, S (1998).
Action potential and ionic remodelling in a dog model of heart failure.
PACE 21:877; Li GR, Sun H, Feng J, Nattel, S (1998). Ionic mechanisms
of th action potental prolongation in failing human ventricular cells
5   *PACE* 21:877). Reductions in these outward K^+ currents are consistent
with a prolongation of APD because they act to repolarize cardiac cells.
Reductions in the rapid (I_{Kr}) component of the delayed rectifier K^+
currents could also result in an increase in APD, but effects on this
current in CHF remain to be determined.

10   In CHF reductions in outward currents during the plateau phase of
the cardiac AP lead to extraordinary increases in APD predisposing the
heart to ventricular arrhythmias, much like the electrophysiological
changes in LQTS. For example, AP recorded from isolated ventricular
myocytes obtained from human failing myocardium were very
15   prolonged compared to those from normal hearts (Beuckelmann DJ,
Näbauer M and Erdmann E. (1993). Alterations of K^+ currents in
isolated human ventricular myocytes from patients with terminal heart
failure. *Circ Res* **73**: 379-385.). This increase in APD was explained, at
least partly by a decrease in I_{to} as well as decreases in I_{K1} and I_{Ks}
20   (Nabauer M, Beuckelmann DJ and Erdmann E. (1993). Characteristics
of transient outward current in human ventricular myocytes from
patients with terminal heart failure. *Circ. Res.* **73**: 386-394.); Li GR,
Sun H, Feng J, Nattel, S (1998). Ionic mechanisms of th action potental
prolongation in failing human ventricular cells *PACE* **21**:877) .
25   Likewise, in canine (Kääb S, Nuss B, Chiamvimonvat N, O'Rourke B,
Pak PH, Kass DA, Marban E and Tomaselli GF. (1996). Ionic
mechanism of action potential prolongation in ventricular myocytes
from dogs with pacing-induced heart failure. *Circ Res* **78**: 262-273; Li
GR, Sun H, Nattel, S (1998). Action potential and ionic remodelling in a
30   dog model of heart failure. *PACE* **21**:877)and rabbit (Rozanski GJ, Xu Z,
Whitney RT, Murakami H and Zucker IH. (1997). Electrophysiology of
rabbit ventricular myocytes following sustained rapid ventricular
pacing. *J Mol Cell Cardiol* **29**: 721-732.) models of pacing induced-heart
failure, APD of failing myocytes was statisically greater than normal
35   controls. Similar effects on APD were evident in a renovascular

hypertension-induced model of cardiac hypertrophy (Rials SJ, Wu Y, Xu
RA, Filart RA, Marinchak RA and Kowey PR. (1997). Regression of left
ventricular hypertrophy with captopril restores normal ventricular
action potetial duration, dispersion of refractoriness, and vulnerability to

5   inducible ventricular fibrillation. *Circulation* **96:** 1330-1336.).

       Therefore, the disease states LQTS and CHF, exhibit rather
similar electrophysiological abnormalities, that will be similarly
responsive to pharmacological treatment. An agent or intervention that
produces a decrease in APD, by causing opposing changes in the

10   currents that underlie the increases in APD will produce a shortening of
APD and thereby correct or prevent the electrophysiological
abnormalities in LQTS and CHF. Pharmacological agents or other
interventions that lead to an increase in outward current or a decrease
in inward current will oppose prolongation of APD and therefore will be

15   effective against arrhythmias in LQTS and CHF caused by excessive
APD prolongation. For example, an activator of I_{Kr} or I_{Ks} channels will
be useful for the treatment of LQTS that results from excessive
pharmacological block of these channels, or from mutations in the genes
that encode the channel proteins.

20

SUMMARY OF THE INVENTION

       This invention relates to a method of treating cardiac
ventricular arrhythmias and repolarization abnormalities associated
with but not limited to acquired and genetic forms long QT syndrome

25   and/ or congestive heart failure comprising the adminstration of a
therapeutically effective amount of an agonist of the slowly activating
cardiac delayed rectifier potassium current (I_{Ks}) to patients in need of
such treatment. The invention discloses 1,4- benzodiazepin-2-one and
spiro[benzopyran-piperidine agonists useful in this method of treatment.

30

BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1. Effects of R-L3 on action potentials of guinea pig isolated
ventricular myocytes. A-C, Action potentials were recording during

35   stimulation at 1 Hz during control (A), and after 10 min superfusion
with R-L3 at 0.1, 1 and 10 μM in normal HEPES Buffered Saline (HBS);

after 30 nM Isoproterenol (Iso) alone, and following addition of 1 µM
R-L3 (B); after 100 nM timolol alone and following addition of 1 µM R-L3
(C) Bar graphs show the percent changes in APD_{90}, and APA_{50ms}.
Data are mean ± SEM.

5

FIGURE 2. Modulation of I_{Ks} by R-L3 is concentration-dependent in
guinea pig isolated ventricular myocytes. A, Superimposed currents
from a single cell before, and after addition of 0.03 and 0.3 µM R-L3
during a 3 s voltage step from -50 to -10 mV. B, Percent increase in I_{Ks}

10   at a V_t of -10 mV by R-L3 (N ≥ 6). C, Superimposed currents before, and
after addition of 10 µM R-L3 during a 7.5 s voltage step from -50 to +50
mV. D, I-V relationship for the time-dependent I_{Ks} measured at the end
of 7.5 s pulses (N = 6).

15   FIGURE 3. R-L3 shifts the voltage-dependence of I_{Ks} activation in
guinea pig isolated ventricular myocytes. A, Currents recorded at the
indicated V_t before (control) and after addition of 1 µM R-L3. B,
Isochronal activation curves were determined from the normalized
amplitudes of tail currents following 7.5 s pulses. Data were fitted to a

20   Boltzmann function to determine the $V_{1/2}$ and slope factor (k) for the
relationship. The $V_{1/2}$ was 19.2 ± 1.6 mV in control, 3.0 ± 0.8 mV and -
4.9 ± 3.4 mV at 0.1 and 1.0 µM R-L3, respectively (N = 5). The k was 11.0
± 1.2 mV in control and was not significantly changed by R-L3.

25   FIGURE 4. R-L3 slows the rate of I_{Ks} deactivation in guinea pig isolated
ventricular myocytes. Time constants for deactivation were determined
for tail currents upon return to a variable potential after a 3 s activating
pulse from -50 to +30 mV (N ≥ 4). *Significantly different from control (p
< 0.05) by paired t-test.

30

FIGURE 5. Effects of Iso and R-L3, alone and in combination, on the
Current-Voltage (I-V) relationship of I_{Ks} in guinea pig isolated
ventricular myocytes. A, Traces were recorded during control, after
exposure to 10 nM Iso alone and after addition of 1 µM R-L3, then

35   following washout of Iso but in the continued presence of R-L3.

Currents were elicited by 0.5 s pulses from a V_h of -50 mV. B I-V relationship for time-dependent I_{Ks} for each condition (N= 5).

5   FIGURE 6. R-L3 activates cloned KvLQT1 channels expressed in *Xenopus* oocytes. A, Currents were measured in response to 2 s pulses from a V_h of -80 mV to a V_t of -60 mV to +40 mV, applied in 20 mV increments. Tail currents were measured at -70 mV. B, Current-Voltage (I-V) relationships for peak KvLQT1 current during 2 s pulses to the indicated test potential before and after 1 μM . R-L3. C,

10   Voltage-dependence of KvLQT1 activation. Tail current amplitudes were determined from extrapolating a single exponential fit of deactivating currents to the onset of membrane repolarization. Isochronal activation curves were determined by fitting normalized tail current amplitudes to a Boltzmann function. In control, the $V_{1/2}$ was -28 mV and the slope

15   factor (k) was 11 mV for this relation. In the presence of 1 μM . R-L3, $V_{1/2}$ was -40 mV and k was 13 mV (N = 8).

     FIGURE 7. R-L3 slows the rates of activation and deactivation of KvLQT1 expressed in *Xenopus* oocytes. A, To illustrate the change in

20   KvLQT1 kinetics induced by R-L3, the peak current activated by a 2 s pulse to +40 mV was scaled to match the peak current recorded after addition of 1 μM . R-L3. Tail current was measured at -70 mV. B, Time constants for fast component of KvLQT1 activation. C, Time constants for slow component of KvLQT1 activation. D, Relative amplitude of the

25   fast component of KvLQT1 activation. E, Time constants of KvLQT1 deactivation (N = 8 for all graphs).

     DETAILED DESCRIPTION OF THE INVENTION
30   The invention relates to a method of treating cardiac ventricular arrhythmias and repolarization abnormalities associated with but not limited to acquired and genetic forms long QT syndrome and/ or congestive heart failure comprising the adminstration of a therapeutically effective amount of an agonist of the slowly activating

cardiac delayed rectifier potassium current (I_{Ks}) to patients in need of such treatment.

An embodiment of the invention is the method as recited above, wherein the agonist of the slowly activating cardiac delayed

5   rectifier potassium current (I_{Ks}) is a 1,4- benzodiazepin-2-one or a spiro[benzopyran-piperidine].

A sub-embodiment of the invention is the method as recited above, wherein the agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is a (3-R)-3-(1H-indol-3-ylmethyl)-1,4-

10   benzodiazepin-2-one.

A further embodiment of this sub-embodiment is the method as recited above, wherein the 1,4- benzodiazepin-2-one agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is selected from the group consisting of:

15   (3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-1-
         methyl-2H-1,4-benzodiazepin-2-one;

         (3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-2H-1,4-
         benzodiazepin-2-one;

20

         (3-R)-7-chloro-1,3-dihydro-5-phenyl-3-(1H-indol-3-ylmethyl)-2H-1,4-
         benzodiazepin-2-one; and

         1-methyl-5-phenyl-1'-(3-tolyl)-spiro[3H-1,4-benzodiazepine-3,4'-
25   imidazolidine]-2(1H),2',5'-trione,
     or pharmaceutically acceptable salts thereof.

A sub-embodiment of the invention is the method as above wherein the agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is a spiro[benzopyran-piperidine].

30   A further embodiment of this sub-embodiment is the method as recited above, wherein the spiro[benzopyran-piperidine] agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is selected from the group consisting of:
         N-phenyl-1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-
35   4(3H)-one; and

N-(3-tolyl)-1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-
4(3H)-one,

or pharmaceutically acceptable salts thereof.

An embodiment of the invention is a method for improving

5 contractile dysfunction in congestive heart failure patients comprising
the adminstration of a therapeutically effective amount of an agonist of
the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) to
patients in need of such treatment.

An embodiment of the invention is the method as recited

10 above, wherein the agonist of the slowly activating cardiac delayed
rectifier potassium current (I_{Ks}) is a 1,4- benzodiazepin-2-one or a
spiro[benzopyran-piperidine].

A sub-embodiment of the invention is the method as recited
above, wherein the agonist of the slowly activating cardiac delayed

15 rectifier potassium current (I_{Ks}) is a (3-R)-3-(1H-indol-3-ylmethyl)-1,4-
benzodiazepin-2-one.

A further embodiment of this sub-embodiment is the
method as recited above, wherein the 1,4- benzodiazepin-2-one agonist of
the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is

20 selected from the group consisting of:

(3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-1-
methyl-2H-1,4-benzodiazepin-2-one;

(3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-2H-1,4-
25 benzodiazepin-2-one;

(3-R)-7-chloro-1,3-dihydro-5-phenyl-3-(1H-indol-3-ylmethyl)-2H-1,4-
benzodiazepin-2-one; and

30 1-methyl-5-phenyl-1'-(3-tolyl)-spiro[3H-1,4-benzodiazepine-3,4'-
imidazolidine]-2(1H),2',5'-trione,

or pharmaceutically acceptable salts thereof.

A sub-embodiment of the invention is the method as above
wherein the agonist of the slowly activating cardiac delayed rectifier

35 potassium current (I_{Ks}) is a spiro[benzopyran-piperidine].

A further embodiment of this sub-embodiment is the method as recited above, wherein the spiro[benzopyran-piperidine] agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is selected from the group consisting of:

5   N-phenyl-1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one; and

N-(3-tolyl)-1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one,

or pharmaceutically acceptable salts thereof.

10

Isolation of guinea pig ventricular myocytes. Guinea pig ventricular myocytes were isolated as described (Salata JJ, Jurkiewicz NK, Wallace AA, Stupienski RF III, Guinosso PJ Jr and Lynch JJ Jr. (1995). Cardiac electrophysiologic actions of the histamine H_1-receptor

15   antagonists astemizole and terfenadine compared with chlorpheniramine and pyrilamine. *Circ Res* **76**: 110-119.). After isolation, the cells were stored in HEPES-buffered saline (HBS) containing (mM): 132 NaCl, 4 KCl, 1.8 CaCl$_2$, 1.2 MgCl$_2$, 10 HEPES (formal name N-2-Hydoxyethylpiperazine-N-2-ethanesulfonic acid), 10

20   glucose, pH = 7.2, at 24 - 26°C until studied, usually within 8 hours after isolation.

Action potential studies. Transmembrane potentials were recorded using conventional microelectrodes filled with 3 M KCl (tip resistances 30-50 MΩ) using an Axoclamp 2B amplifier (Axon

25   Instruments; Foster City, Ca.) as described (Fermini B, Jurkiewicz NK, Jow B, Guinosso PJ Jr, Baskin EP, Lynch JJ Jr and Salata JJ. (1995). Use-dependent effects of the Class III antiarrhythmic agent NE-10064 (azimilide) on cardiac repolarization: Block of delayed rectifier potassium and L-type calcium currents. *J Cardiovasc Pharmacol* **26**:

30   259-271.). Cells were superfused with HBS maintained at 37°C at a rate of 2 ml/min. APs were evoked with brief current pulses (1 ms, 1.2 times threshold) delivered at a frequency of 1 Hz through the recording electrode using an active bridge circuit. Only cells showing normal AP configurations and resting membrane potentials equal to or more

35   negative than -85 mV were used in this study. APs were studied after a

$\geq$ 5 min control period, and after $\geq$ 5 min of superfusion with each concentration of drug. After reaching a steady state effect under each condition, 20 individual APs were sampled and digitally averaged. The amplitude at 50 ms (APA_{50ms}) and duration at 90% repolarization

5 (APD_{90}) were measured from the digitally averaged records. Concentration-response relationships were determined by measuring APs or currents in each cell under control conditions and during superfusion with successively increasing concentrations of a given drug.

10 **Voltage-clamp of guinea pig ventricular myocytes.** Whole-cell voltage-clamp studies were performed using a List EPC-7 (Medical Systems, Greenvale, NY) or Axopatch 200A (Axon Instruments, Foster City, CA) amplifier as described (Fermini B, Jurkiewicz NK, Jow B, Guinosso PJ Jr, Baskin EP, Lynch JJ Jr and Salata JJ. (1995). Use-

15 dependent effects of the Class III antiarrhythmic agent NE-10064 (azimilide) on cardiac repolarization: Block of delayed rectifier potassium and L-type calcium currents. *J Cardiovasc Pharmacol* **26**: 259-271.). Pipettes were made from square bore (1.0 mm, o.d.) borosilicate capillary tubing (Glass Co. of America, Bargaintown, N.J.).

20 Pipettes were filled with 0.5 M K^+ gluconate, 25 mM KCl and 5 mM K_2ATP to minimize "rundown" (Giles WR and Shibata EF. (1985). Voltage clamp of bull-frog cardiac pace-maker cells: a quantitative analysis of potassium currents. *J. Physiol (Lond)* **368**: 265-292.) and had resistances of 3 to 7 MΩ (average 5.5 $\pm$ 0.3 MΩ). Series resistance was

25 compensated 40-70%. Currents were low-pass filtered (-3 dB at 0.2 kHz) before digitization at 1 kHz. I_{Ks} was measured during superfusion of the cells at a rate of 2-3 ml/min with normal HBS (35°C) containing 0.4-1 μM nisoldipine to block L-type Ca^{2+} current and standard selective I_{Kr} blockers (e.g. 3 μM MK-499) in ~ 100 fold excess of their IC_{50} to completely

30 block I_{Kr} (Sanguinetti M.C. and Salata J.J. (1996): Cardiac Potassium Channel Modulators: Potential for Antiarrhythmic Therapy. In: *Potassium Channels and their Modulators: From Synthesis to Clinical Experience.* Eds. J.M. Evans, T.C. Hamilton, S.D. Longman and G. Stemp. Taylor and Francis, London, UK). Cells were voltage clamped at

35 a holding potential (V_h) of -50 mV to inactivate I_{Na}. Time-dependent I_{Ks}

amplitude was measured as the difference from the initial instantaneous current, following the settling of the capacity transient, to the final current level at the end of a depolarizing pulse. Tail current amplitude, I_{Ktail}, was measured as the difference from the holding

5   current level to the peak tail current amplitude upon return to V_h. I_{Ktail} was normalized to the maximum measured amplitude ($I_{Ktail-max}$) following 7.5 s pulses. Averaged data was fit to a Boltzmann distribution of the form: $I_{Ktail}/I_{Ktail-max} = 1/(1+\exp[(V_{1/2}-V_t)/k])$ with a nonlinear least squares fitting routine (Origin, Microcal Software, Northampton,

10   MA) to estimate the half-point ($V_{1/2}$) and slope factor (k) for this relationship. The time courses of I_{Ks} activation and deactivation were fit with a double exponential relationship of the form: $I_t = A_0 + A_1 e^{-t/t_1} + A_2 e^{-t/t_2}$ using a Chebeshev non-iterative fitting technique (pCLAMP, Axon Instruments, Foster City, CA).

15   **cRNA injection and voltage-clamp of oocytes.** The isolation and maintenance of *Xenopus* oocytes, in vitro transcription of *KvLQT1* complementary RNA (cRNA) and its injection into oocytes were performed as described previously (Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL and Keating MT. (1996b). Coassembly of

20   KvLQT1 and minK (I_{sK}) proteins form cardiac I_{Ks} potassium channel. *Nature* **384**: 80-83.; Sanguinetti MC, Jiang C, Curran ME and Keating MT. (1995). A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the I_{Kr} potassium channel. *Cell* **81**: 299-307.). Stage V and VI oocytes were injected with 11.5 ng of *KvLQT1*

25   cRNA (46 nL of a 250 ng/µL solution) Currents were recorded 2 to 4 days later using standard two-microelectrode voltage clamp techniques and a Dagan TEV-200 amplifier. Oocytes were bathed at room temperature (22-25°C) in a solution containing (mM): 94 NaCl, 2 KCl, 2 $MgCl_2$, 0.1 $CaCl_2$, 5 HEPES; pH 7.6.

30   **Solutions.** . Compounds were dissolved in dimethyl sulfoxide (DMSO) at a stock concentration of 1 or 10 mM and diluted directly into test solutions. Serial dilutions were used to achieve the final test concentrations. DMSO at the concentrations used had no significant effect on any of the parameters measured in these studies. Nisoldipine

35   was prepared as a 4 mM stock solution in DMSO and diluted as needed.

Statistics. Data are expressed as mean ± SEM (N = number of cells). Concentration-dependent changes in AP parameters and individual ionic currents were assessed by repeated-measures analysis of variance (ANOVA). Post-Hoc comparison of the treatment to the

5 control means were made with Dunnett's t-test to determine significant changes between the control and test group means. Statistical comparisons for the time constants of I_{Ks} activation and deactivation were made using a paired t-test. A one-tailed probability (p) < 0.05 was considered significant.

10 **Results.** R-L3 decreases action potential duration of cardiac myocytes. R-L3 (0.1-1.0 μM) caused a concentration-dependent shortening of APD. Fig. 1A shows a representative example of APs recorded at a stimulus frequency of 1 Hz. R-L3 significantly decreased APD_{50} and APD_{90} without significantly affecting other parameters

15 (Table 1). Shortening of APD was maximal at 1 μM; APD_{90} was decreased at concentrations of 1 and 10 μM R-L3 by 14.2 ± 1.6 and 13.8 ± 4.0%, respectively.

Stimulation of ß-adrenergic receptors can also shorten APD of cardiac myocytes (Carmeliet E and Vereecke J. (1969). Adrenaline

20 and the plateau phase of the cardiac action potential. *Pflügers Arch* **313**: 300-315; Sanguinetti MC, Jurkiewicz NK, Scott A and Siegl PKS. (1991). Isoproterenol antagonizes prolongation of refractory period by the Class III antiarrhythmic agent E-4031 in guinea pig myocytes. Mechanism of action. *Circ Res* **68**: 77-84.). Therefore, we determined if the decrease in

25 APD by R-L3 was mediated through the same or parallel pathway. At a concentration of 30 nM, isoproterenol (Iso) decreased APD_{90} by 12.9 ± 2.9%. Iso also increased APA_{50ms} by 6.6 ± 2.9% (Fig. 1B), presumably by enhancement of L-type Ca^{2+} current (Kass RS and Wiegers SE. (1982). The ionic basis of concentration-related effects of noradrenaline on the

30 action potential of calf cardiac Purkinje fibres. *J Physiol (Lond)* **322**: 541-558.). Addition of 1 μM R-L3 in the presence of 30 nM Iso decreased APD_{90} further (26.9 ± 1.4%) and diminished the increase in APA_{50ms}. Block of ß-adrenergic receptors with 100 nM timolol did not alter AP configuration (Fig. 1C), but prevented the effects of 30 nM Iso. In the

35 continued presence of timolol, addition of 1 μM R-L3 decreased APD_{90} by

14.6 ± 2.2%, very similar to the effect observed as in the absence of timolol. Thus, the decrease in APD by R-L3 is additive to the effect mediated by ß-adrenergic stimulation.

R-L3 increases I_{Ks} of guinea pig myocytes in a
5   concentration and stereo-specific manner. The effect of R-L3 on I_{Ks} was measured under voltage-clamp conditions using 3 s depolarizations to a test potential (V_t) of -10 mV from a V_h of -50 mV (Fig 3A). R-L3 enhanced I_{Ks} measured at -10 mV at concentrations as low as 30 nM, and had a maximal effect at 1 μM. At 30 nM, I_{Ks} was increased by a factor of 17 ± 5
10   (n=6). At a concentration of 3 μM or 10 μM, the % increases in I_{Ks} by R-L3 were less than that observed for 1 μM (Fig. 2B). This diminished response at high concentrations was caused by a time- and voltage-dependent block of I_{Ks} that was most obvious during long pulses. For example, I_{Ks} was increased by 10 μM R-L3 during the first few seconds
15   of a 7.5 s pulse to +50 mV . However, when the depolarization exceeded about 3 s, the current measured in the presence of R-L3 was reduced compared to control (Fig. 2C). R-L3 increased time-dependent I_{Ks} at the end of 7.5 s pulses to potentials < +10 mV, but decreased I_{Ks} at more positive potentials (Fig. 1D). Thus, the biphasic concentration-response
20   relationship for the effects of R-L3 on I_{Ks} for 3 s pulses to -10 mV (Fig. 2B) reflects the dual effects of the drug: activation that predominates at low concentrations and voltage-dependent block at higher concentrations.

The increase of I_{Ks} by R-L3 was stereo-specific. S-L3
25   blocked I_{Ks} at all concentrations (1 to 10 μM) and test potentials (-10 to +50 mV) examined. At concentrations of 1 and 10 μM, S-L3 blocked I_{Ks} measured at the end of a 1-s test pulse to +50 mV, by an average of 14.8 ± 4.3% and 68.8 ± 3.4% (N=5).

R-L3 shifts the voltage dependence of activation and slows
30   deactivation of I_{Ks}. The voltage dependence of I_{Ks} activation was estimated using 7.5 s depolarizing steps from a V_h of -50 mV (Fig. 3A). The amplitude of the tail currents was normalized relative to the maximum amplitude and fit to a Boltzmann function (Fig. 3B). Because I_{Ks} does not achieve a steady state, even during extremely long pulses (
35   Hice RE, Folander K, Salata JJ, Smith JS, Sanguinetti MC and Swanson

R. (1994). Species variants of the I_{sK} protein: differences in kinetics, voltage dependence, and La^{3+} block of the currents expressed in *Xenopus* oocytes. *Pflügers Arch* **426**: 139-145.) the activation curves are isochronal. In control, the $V_{1/2}$ was 19.2 ± 1.6 mV and k for this

5   relationship was 11.0 ± 1.2 mV (N=5). In these same cells, R-L3 shifted $V_{1/2}$ to 3.0 ± 0.8 mV at 0.1 μM -4.9 ± 3.4 mV at 1 μM, but had no effect on k. The maximally activated I_{Ks} measured at a V_t of +60 mV (896±196 vs. 953±183 pA, 1 μM) was slightly but not significantly increased by R-L3. Likewise, following pretreatment with 100 nM timolol, 1 μM R-L3 shifted

10   the $V_{1/2}$ by -19 mV without affecting k, indicating that its effect was independent of ß-adrenergic stimulation. These results suggest that the primary mechanism of the increase in I_{Ks} by R-L3 is an effect on channel gating.

       The onset of I_{Ks} activation, following a short delay, was best

15   described by a two exponential function. The fast time constants of activation were slightly, but not significantly, faster in the presence of 1 μM R-L3. This effect was likely due to the negative shift in the voltage dependence of channel activation. In contrast to the modest effect on the kinetics of activation, R-L3 greatly slowed the rate of I_{Ks} deactivation

20   (Fig. 3A). The kinetics of deactivation were determined at potentials of -60 to -10 mV following a 3 s pre-pulse to +30 mV from a V_h of -50 mV. The deactivation of I_{Ks} was best described by a two exponential function before and after addition of R-L3. R-L3 significantly increased the fast (t_{fast}) and the slow (t_{slow}) time constants of deactivation (Fig. 4). The

25   slowing of the rate of deactivation by R-L3 represents an additional mechanism that would increase outward current during repolarization of a cardiac .

       R-L3 activates I_{Ks} independent of ß-adrenergic receptor activation. I_{Ks} was activated by 0.5 s pulses to a V_t ranging from -40 to

30   +50 mV. Iso (10 nM) alone increased I_{Ks} 1.75-fold. Addition of 1 μM R-L3 produced a further increase in I_{Ks}, slowed the rate of deactivation, and shifted the threshold for current activation to more negative potentials (Fig. 5). The effects of R-L3 persisted after washout of the Iso. Similar effects were observed when exposure of cells to R-L3 preceded

35   the addition of Iso. Thus, similar to the decrease in APD caused by

R-L3, the increase in I_{Ks} by R-L3 was additive to that caused by ß-adrenergic receptor stimulation.

R-L3 activates cloned human KvLQT1 channels expressed in *Xenopus* oocytes. At a concentration of 1 µM, R-L3 increased KvLQT1
5   elicited with 2 s pulses to potentials ranging from -70 to +60 mV (Fig. 6A, B). This increase can partially be accounted for by a -10 mV shift in the voltage dependence of activation caused by the drug (Fig. 6C). R-L3 also slowed the kinetics of KvLQT1, an effect that is easily observed when the time-dependent currents recorded before and after exposure to 1 µM
10   R-L3 are superimposed and scaled to match peak current (Fig. 7A). Activation of KvLQT1 current is best described by a two exponential function. The effect of R-L3 on these two components varied with V_t. R-L3 slowed the rate of the fast component at $V_t \geq 0$ mV, (Fig. 7B), but increased the rate of the slow component of activation at $V_t \geq -30$ mV(Fig.
15   7C). The net effect of R-L3 was to slow the rate of KvLQT1 activation, because of a reduction in the relative amplitude of the fast component of activation over the entire voltage range that was examined (Fig. 7D). R-L3 also slowed the rate of KvLQT1 deactivation when assessed at voltages negative to -40 mV (Fig. 7E). Thus, R-L3 increased the
20   magnitude of KvLQT1, shifted the voltage dependence of its activation, and slowed the rates of activation and deactivation. These effects of R-L3 on KvLQT1 current are similar to those observed for I_{Ks} recorded in guinea pig ventricular myocytes.

Summary The properties of R-L3, a 1,4- benzodiazepin-2-
25   one that selectively activates I_{Ks} in myocytes at low concentrations are described in detail. At concentrations of 1 µM and less, R-L3 shortened action potential duration of cardiac myocytes by selective activation of I_{Ks}. At membrane potentials and pulse durations typical for a cardiac action potential, the most important mechanisms of action of R-L3 were
30   a negative shift in the voltage dependence of activation, and a slowing of I_{Ks} deactivation. R-L3 also caused a modest increase in I_{Ks} beyond what could be explained by these two mechanisms. The molecular mechanism of these effects on I_{Ks} channel gating is not clearly known, but it is not mediated through the ß-adrenergic receptor activation
35   pathway.

<u>Dose Ranges</u>

The magnitude of therapeutic dose of useful in this method
of treatment will, of course, vary with the nature of, and the severity of
5   the condition to be treated and with the particular compound utilized
and its route of administration and pharmacokinetic profile and will
vary upon the clinician's judgment. It will also vary according to the
age, weight and response of the individual patient. An effective dosage
amount of the active component can thus be determined by the clinician
10   after a consideration of all the criteria and using is best judgment on the
patient's behalf. Depending on these considerations, anticipated doses
would be in the range of 0.1 µg/kg - 10 mg/kg administered using an
appropriate dosing regimen to maintain an effective plasma
concentration.
15

<u>Pharmaceutical Compositions</u>

Any suitable route of administration may be employed for
providing a mammal, especially a human with an effective dosage of a
compound of the present invention. For example, oral, intraperitoneal,
20   parenteral, subcutaneuous,intramuscular, transdermal, subkingual
intravenous and topical may be employed. Dosage forms include tablets,
troches, dispersions, suspensions, wafers, solutions, capsules, creams,
ointments, aerosols, and the like.

The pharmaceutical compositions of a compound useful in
25   the present method as an active ingredient or a pharmaceutically
acceptable salt thereof, and may also contain a pharmaceutically
acceptable carrier and optionally other therapeutic ingredients. The
term "pharmaceutically acceptable salts" refers to salts prepared from
pharmaceutically acceptable non-toxic bases or acids including
30   inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral,
parenteral. They may be conveniently presented in unit dosage form
and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds exhibiting this activity can
35   be combined as the active ingredient in intimate admixture with a

pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for oral dosage form, any of the usual

5   pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants,

10   binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid

15   pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount

20   of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier

25   which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or

30   molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by

35   molding in a suitable machine, a mixture of the powdered compound

moistened with an inert liquid diluent. Desirably, each tablet contains
from about 1 mg to about 500 mg of the active ingredient and each cachet
or capsule contains from about 1 to about 500 mg of the active ingredient.

5   The examples disclosed herein are representative of the
instant invention, but should not be construed as limiting the scope of
the invention.

EXAMPLES

The 1,4- benzodiazepin-2-ones of this invention can be
10   prepared according to procedures described in US Patent 4,820,834, as
well as the following literature references:

B.E. Evans et al. J. Med. Chem 1987, 30 pp. 1229-1239.

B.E. Evans et al. J. Med. Chem 1988, 31 pp. 2235-2246.

B.E. Evans et al. Proc. Natl. Acad. Sci. USA, Medical Sciences,
15   July 1986, 83 pp.4918-4922.

The spiro[benzopyran-piperidine] compounds of this
invention can be prepared according to procedures described in US
Patent Nos. 5,206240 and 5,633,247.

20   EXAMPLE 1
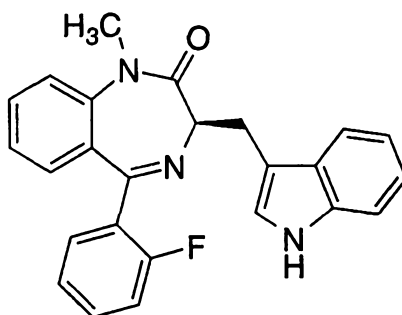
R-L3

(3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-1-methyl-
2H-1,4-benzodiazepin-2-one;

25   R-L3 was prepared as described previously by Evans et. al.
(Evans BE, et al.J Med Chem 30: 1229-1239 (1987)). Its enantiomer, S-L3,
was prepared by the same procedure described for R-L3, with
L-tryptophan acid chloride hydrochloride used in place of the D-isomer:

1H-NMR (CDCl3) identical to that of R-L3. The chemical and chiral
purity of R-L3 and S-L3 were determined to be > 99%. S-L3: HPLC (Vydac
C-18, 15x0.46 cm, 16 min. gradient 95:5 to 5:95 0.1% H3PO4/H2O:CH3CN,
1.5 ml/min, 215 and 254 nM) retention time (rt)=11.0 min, >96%,
5   co-elutes with R-L3. HPLC (Chiralcel OD, 25x0.46 cm, 90/10
hexane/EtOH, 1.5 ml/min, 280 nM) rt=9.95 min, 98.2%, contains <1% of
R-L3 (R-L3: rt=10.94 min, 99.6%, contains <0.5% of S-L3). TLC (silica,
10% Et2O in CH2Cl2): single component, Rf = 0.43, co-elutes with R-L3.
Calc. for C25H20FN3O: C 75.55, H 5.07, N 10.57; Found: C 75.57, H 5.17, N
10   10.46.

EXAMPLES 2-4

Other specific examples of 1,4- benzodiazepin-2-one agonists
15   are as follows:
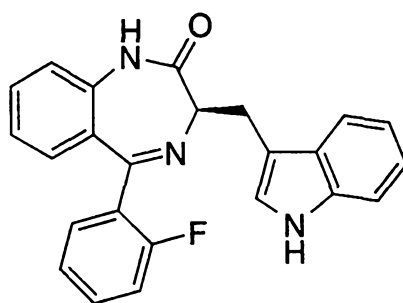
R-L4

(3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-2H-1,4-
benzodiazepin-2-one;
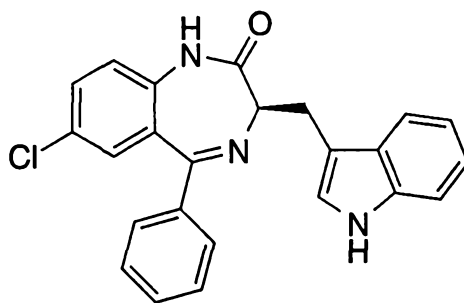
20

R-L5

- 21 -

(3-R)-7-chloro-1,3-dihydro-5-phenyl-3-(1H-indol-3-ylmethyl)-2H-1,4-benzodiazepin-2-one; and
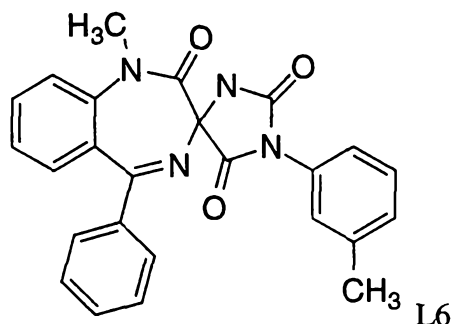
1-methyl-5-phenyl-1'-(3-tolyl)-spiro[3H-1,4-benzodiazepine-3,4'-imidazolidine]-2(1H),2',5'-trione

Compd. Ref.	Conc. [μM]	Agonist Effect — % Increase in IKs		
		No. of runs	Vt -10 mV	Vt +50 mV
R-L3	0.1	6	431±123	25±6
	1		1703±507	40±12
R-L4	1	3	27±7	44±9
	10		153±37	114±13
R-L5	10	3	22±10	22±6
L6	10	3	—	31±9

EXAMPLES 5-6

Specific examples of spiro[benzopyran-piperidine] agonists are as follows:
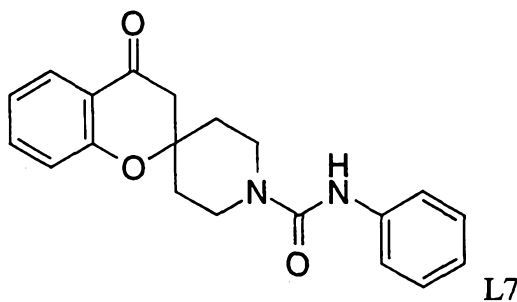
N-phenyl 1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one; and

L8

N-(3-tolyl) 1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-4(3H)-one.

			Agonist Effect — % Increase in IKs	
Compd. Ref.	Conc. [µM]	No. of runs	Vt -10 mV	Vt +50 mV
L7	1	4	no change	111±28
L8	10	4	no change	65±17

WHAT IS CLAIMED IS:

1.   A method of treating cardiac ventricular arrhythmias and repolarization abnormalities associated with long QT
5   syndrome and/ or congestive heart failure comprising the adminstration of a therapeutically effective amount of an agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) to a patient in need of such treatment.

10   2.   The method as recited in Claim 1, wherein the agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is a 1,4- benzodiazepin-2-one or a spiro[benzopyran-piperidine].

15   3.   The method as recited in Claim 2, wherein the agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is a (3-R)-3-(1H-indol-3-ylmethyl)-1,4-benzodiazepin-2-one.

                  4.   The method as recited in claim 2 wherein the 1,4-
20   benzodiazepin-2-one agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is selected from the group consisting of:

           (3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-1-
           methyl-2H-1,4-benzodiazepin-2-one;
25
           (3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-2H-1,4-
           benzodiazepin-2-one;

           (3-R)-7-chloro-1,3-dihydro-5-phenyl-3-(1H-indol-3-ylmethyl)-2H-1,4-
30   benzodiazepin-2-one; and

           1-methyl-5-phenyl-1'-(3-tolyl)-spiro[3H-1,4-benzodiazepine-3,4'-
           imidazolidine]-2(1H),2',5'-trione,
    or pharmaceutically acceptable salts thereof.

35

5.   The method as recited in Claim 2, wherein the agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is a spiro[benzopyran-piperidine].

5   6.   The method as recited in claim 2 wherein the spiro[benzopyran-piperidine] agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is selected from the group consisting of:

N-phenyl-1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-
10   4(3H)-one; and
N-(3-tolyl)-1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-
4(3H)-one,
or pharmaceutically acceptable salts thereof.

15   7.   A method for improving contractile dysfunction in a congestive heart failure patient comprising the adminstration of a therapeutically effective amount of an agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) to a patient in need of such treatment.
20

8.   The method as recited in Claim 7, wherein the agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is a 1,4- benzodiazepin-2-one or a spiro[benzopyran-piperidine].
25

9.   The method as recited in Claim 8, wherein the agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is a (3-R)-3-(1H-indol-3-ylmethyl)-1,4-benzodiazepin-2-one.

30   10.   The method as recited in claim 8 wherein the 1,4-benzodiazepin-2-one agonist of the slowly activating cardiac delayed rectifier potassium current (I_{Ks}) is selected from the group consisting of:

(3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-1-
methyl-2H-1,4-benzodiazepin-2-one;
35

(3-R)-1,3-dihydro-5-(2-fluorophenyl)-3-(1H-indol-3-ylmethyl)-2H-1,4-
benzodiazepin-2-one;

(3-R)-7-chloro-1,3-dihydro-5-phenyl-3-(1H-indol-3-ylmethyl)-2H-1,4-
5   benzodiazepin-2-one; and

1-methyl-5-phenyl-1'-(3-tolyl)-spiro[3H-1,4-benzodiazepine-3,4'-
imidazolidine]-2(1H),2',5'-trione,
or pharmaceutically acceptable salts thereof.

10

11.   The method as recited in Claim 7, wherein the
agonist of the slowly activating cardiac delayed rectifier potassium
current (I_{Ks}) is a spiro[benzopyran-piperidine].

15   12.   The method as recited in claim 8 wherein the
spiro[benzopyran-piperidine] agonist of the slowly activating cardiac
delayed rectifier potassium current (I_{Ks}) is selected from the group
consisting of:
        N-phenyl-1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-
20   4(3H)-one; and
        N-(3-tolyl)-1'-(carboxamido)-spiro[2H-1-benzopyran-2,4'-piperidin]-
        4(3H)-one,
or pharmaceutically acceptable salts thereof.
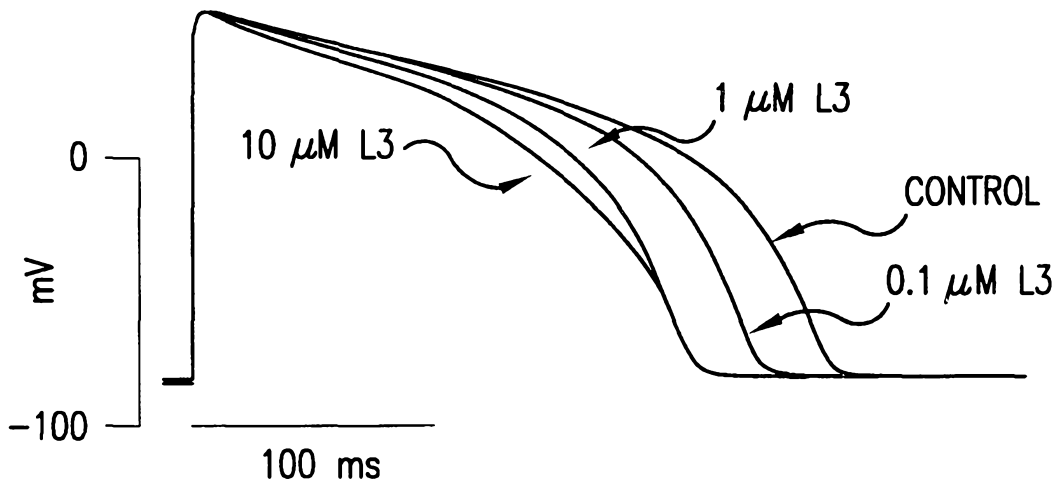
FIG.1A
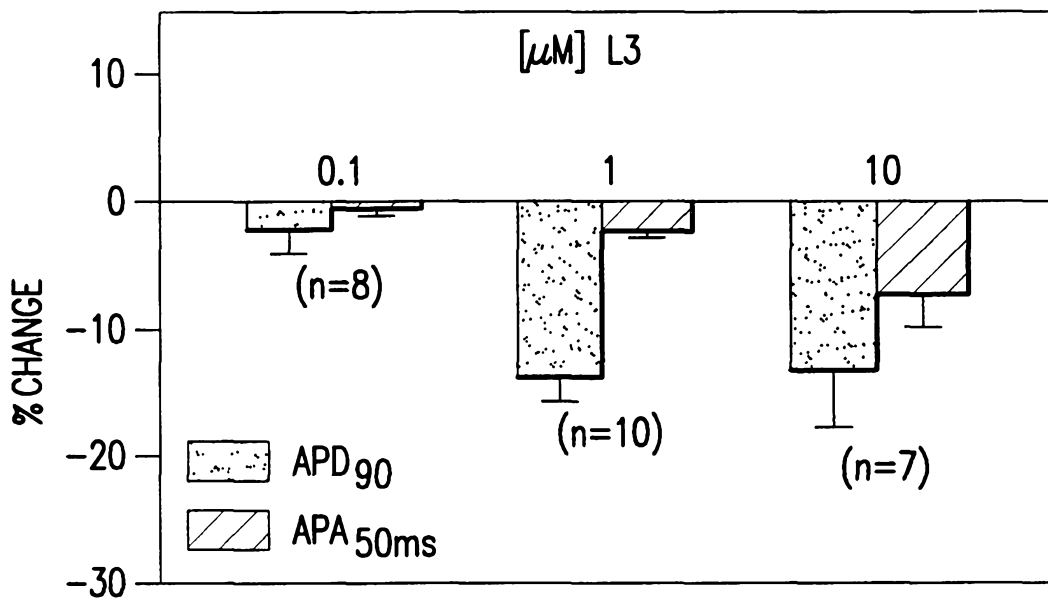
FIG.1A1
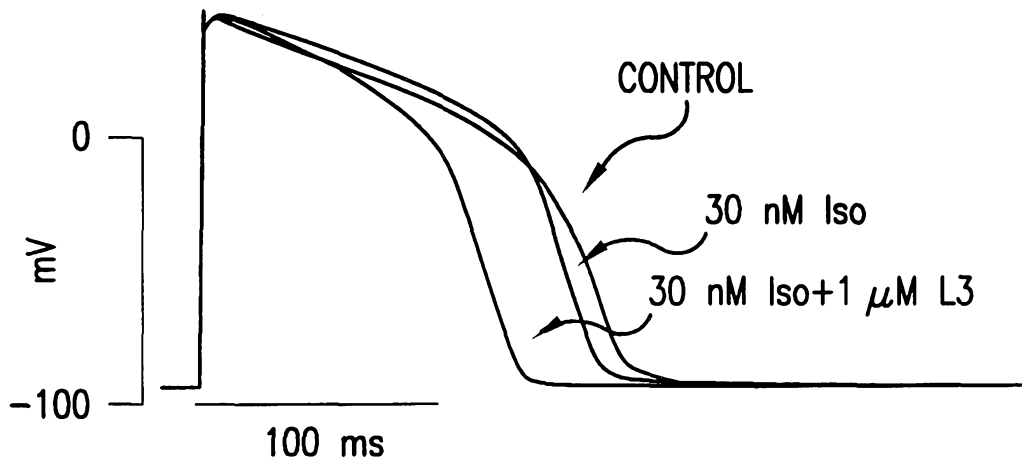
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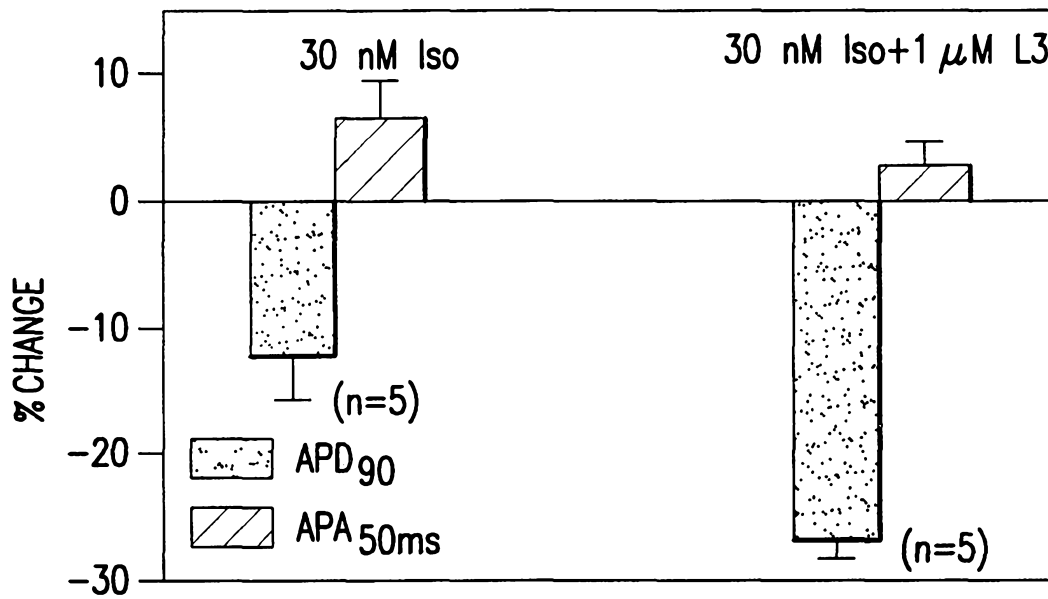
FIG.1B1
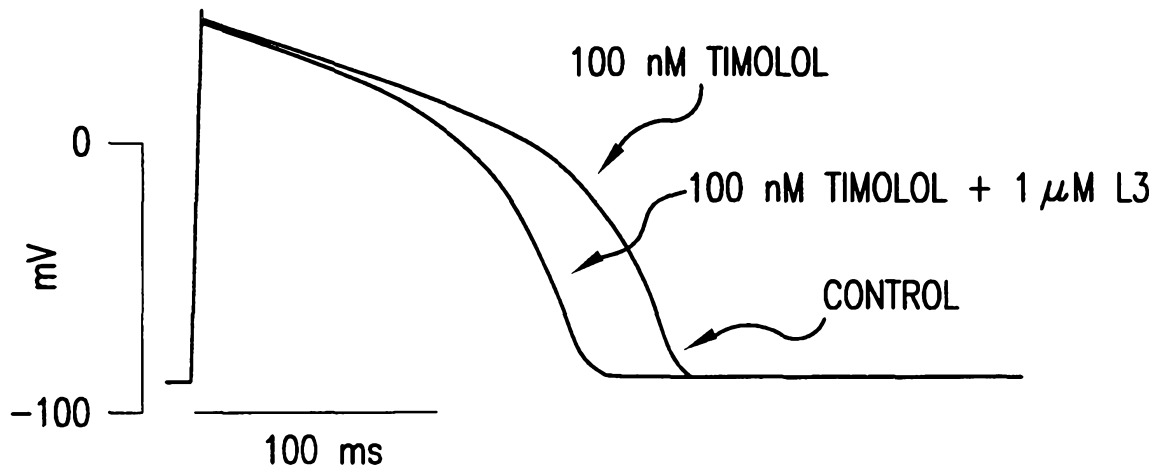
FIG.1C
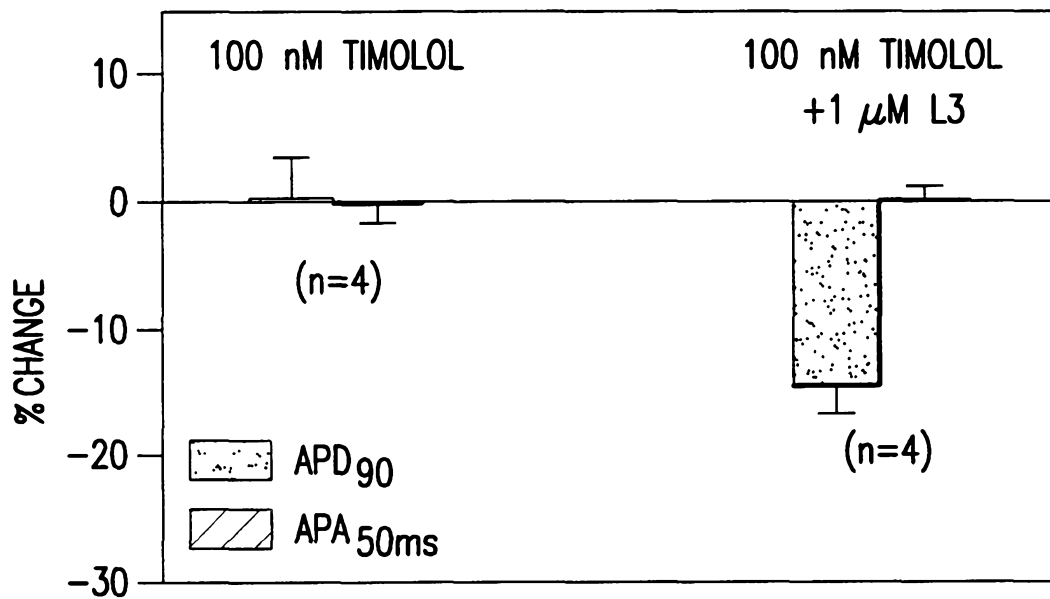
FIG.1C1
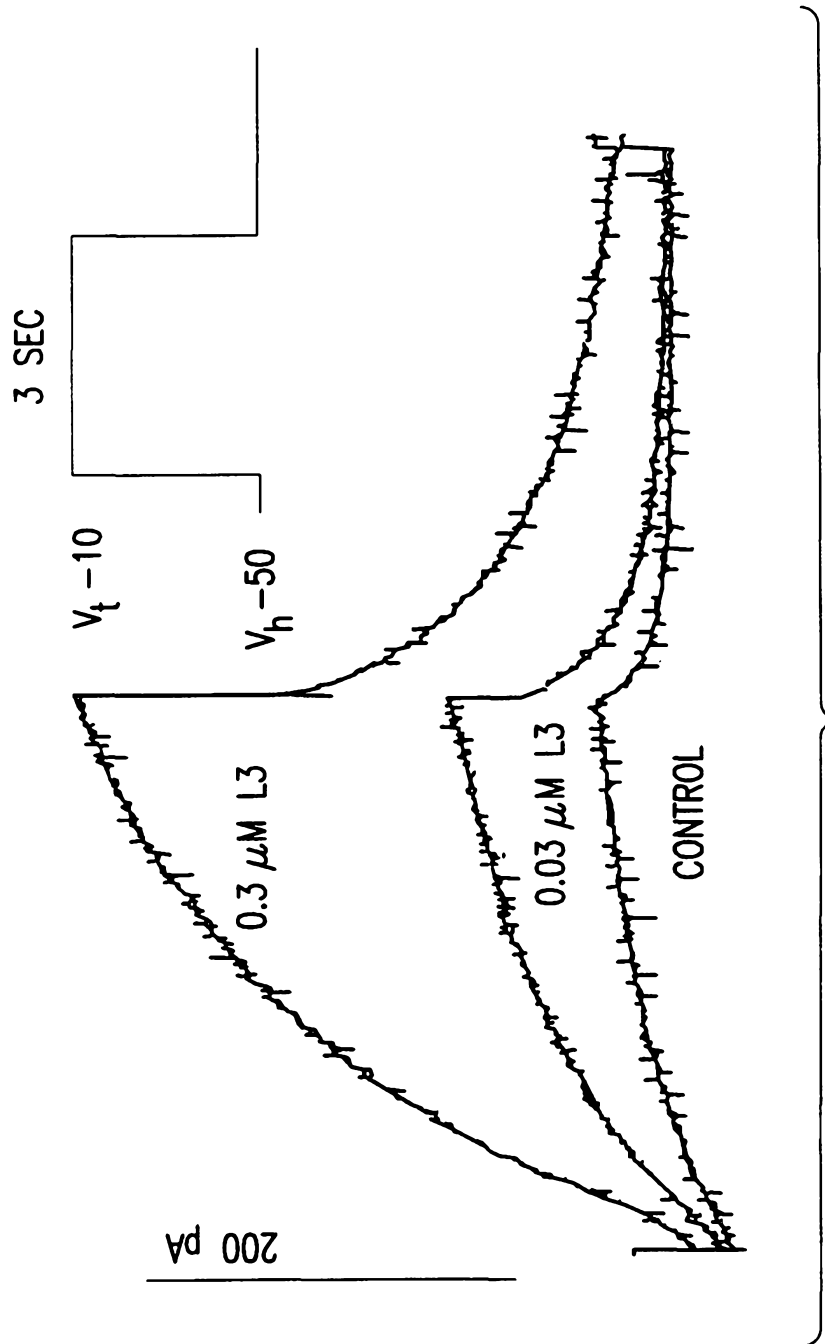
FIG.2A
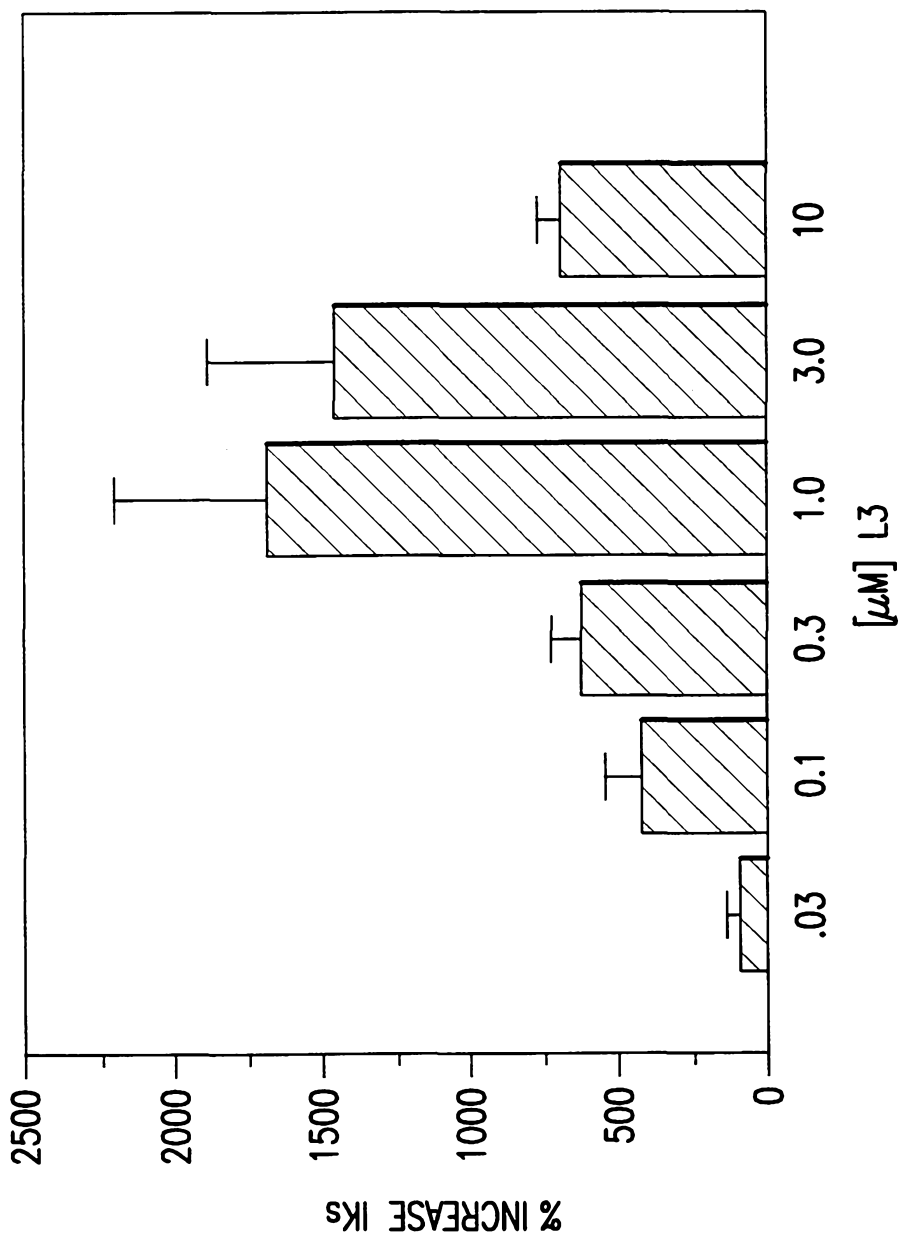
FIG.2B
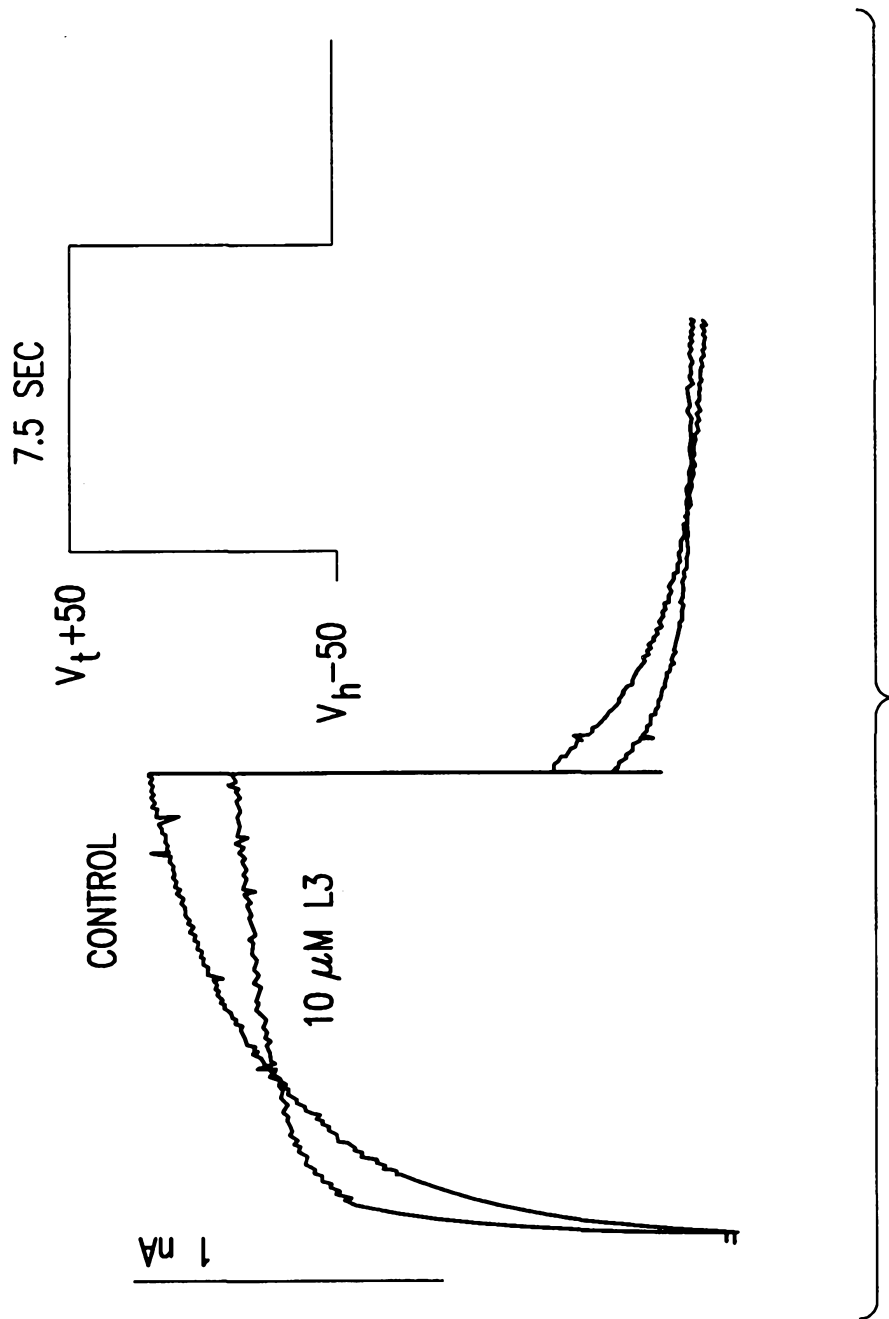
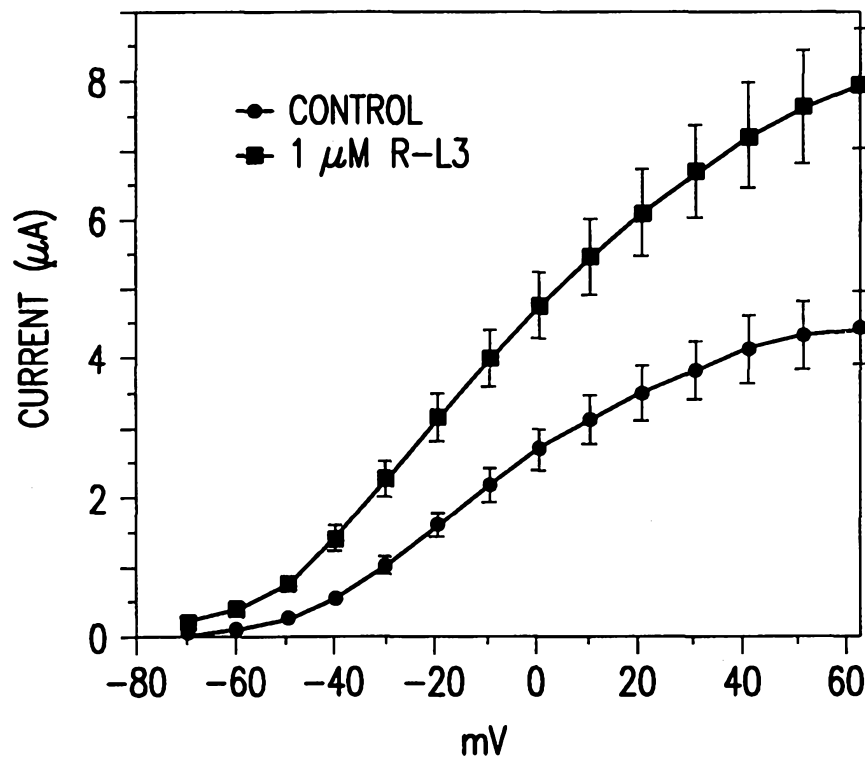FIG.2C
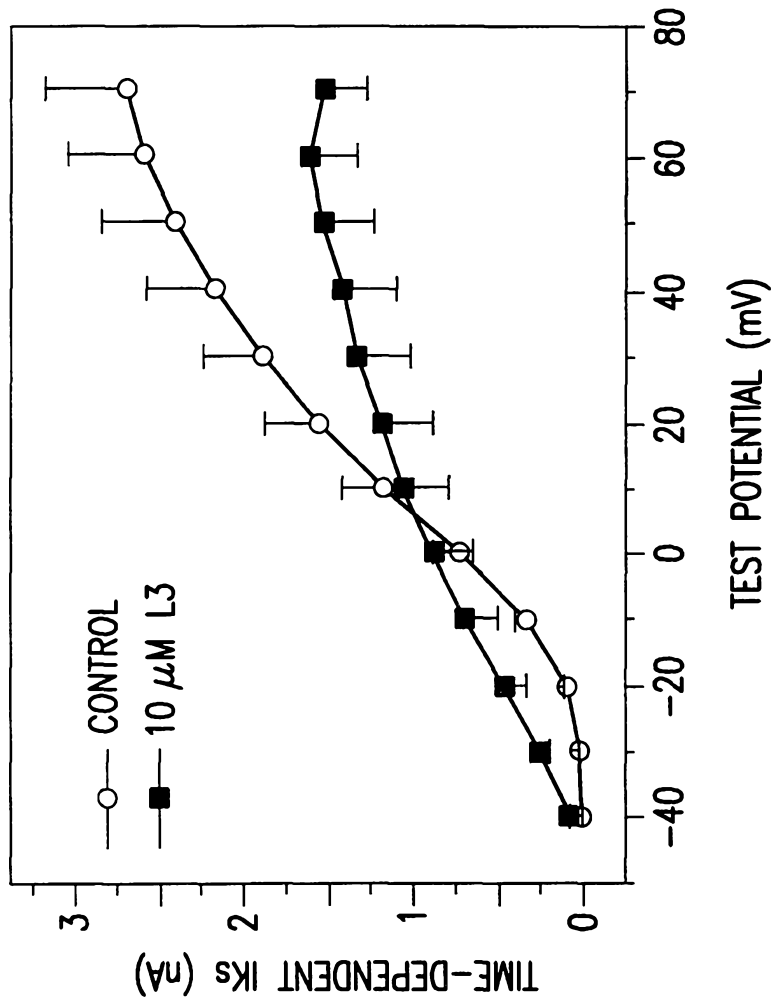
FIG.2D
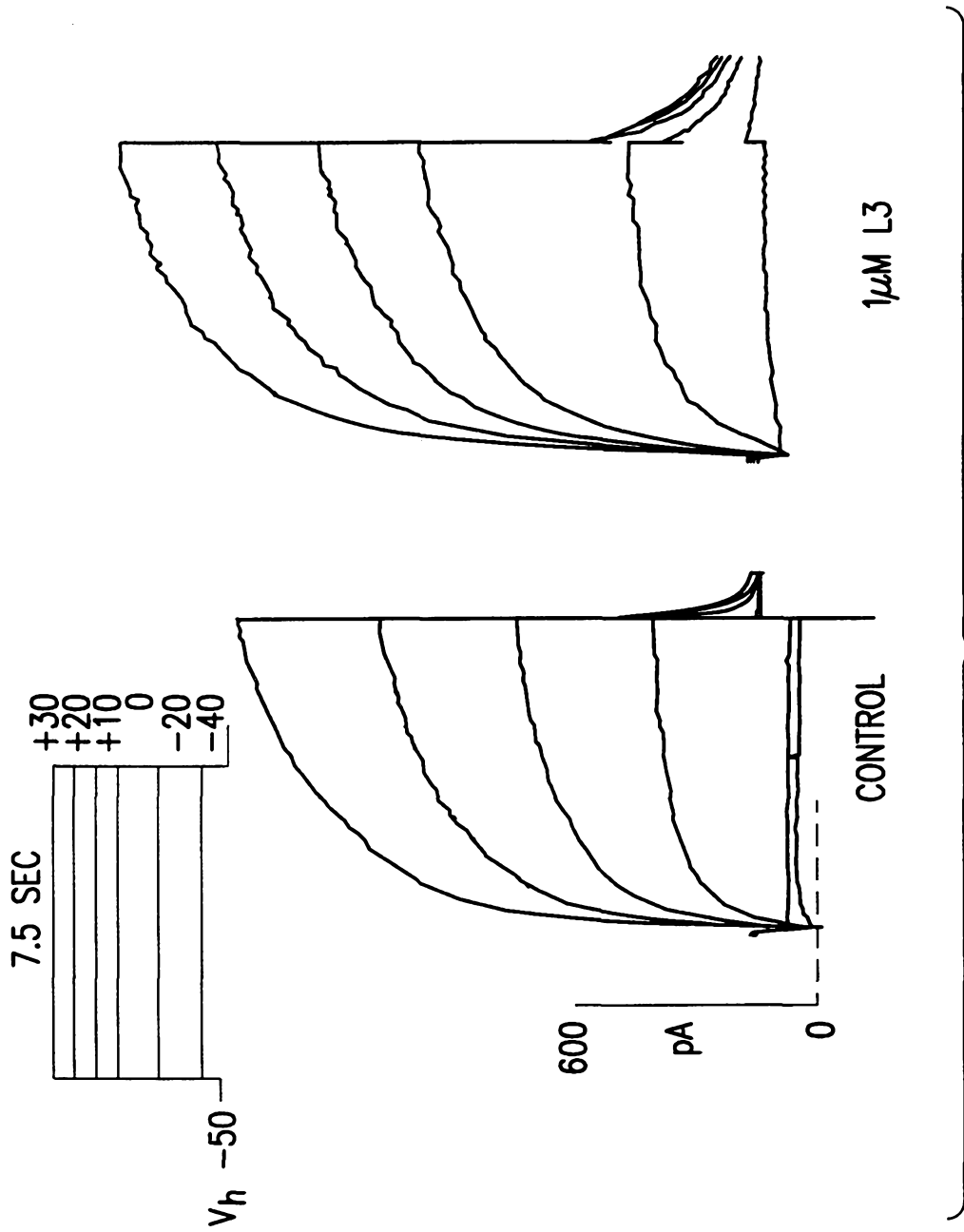
FIG.3A
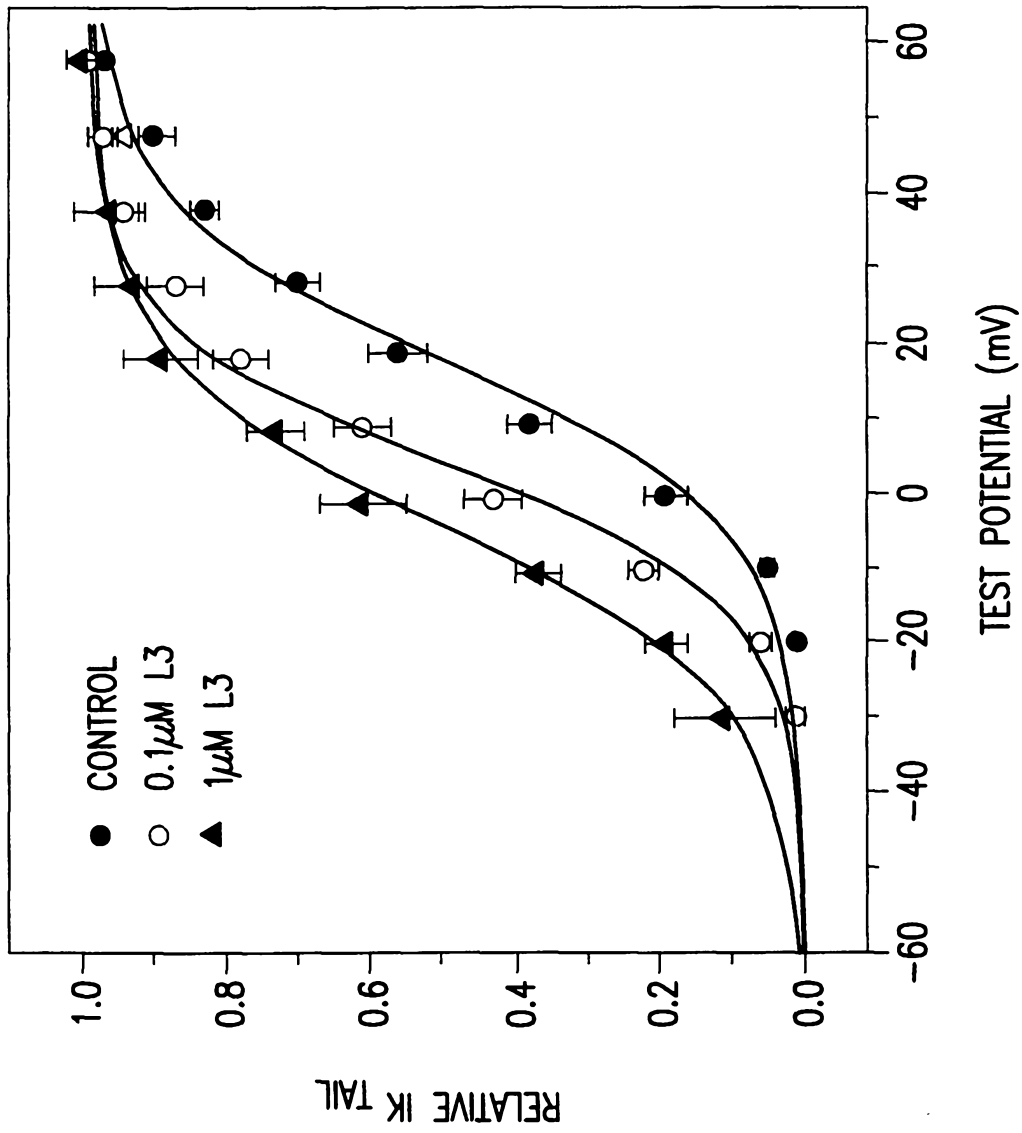
FIG.3B
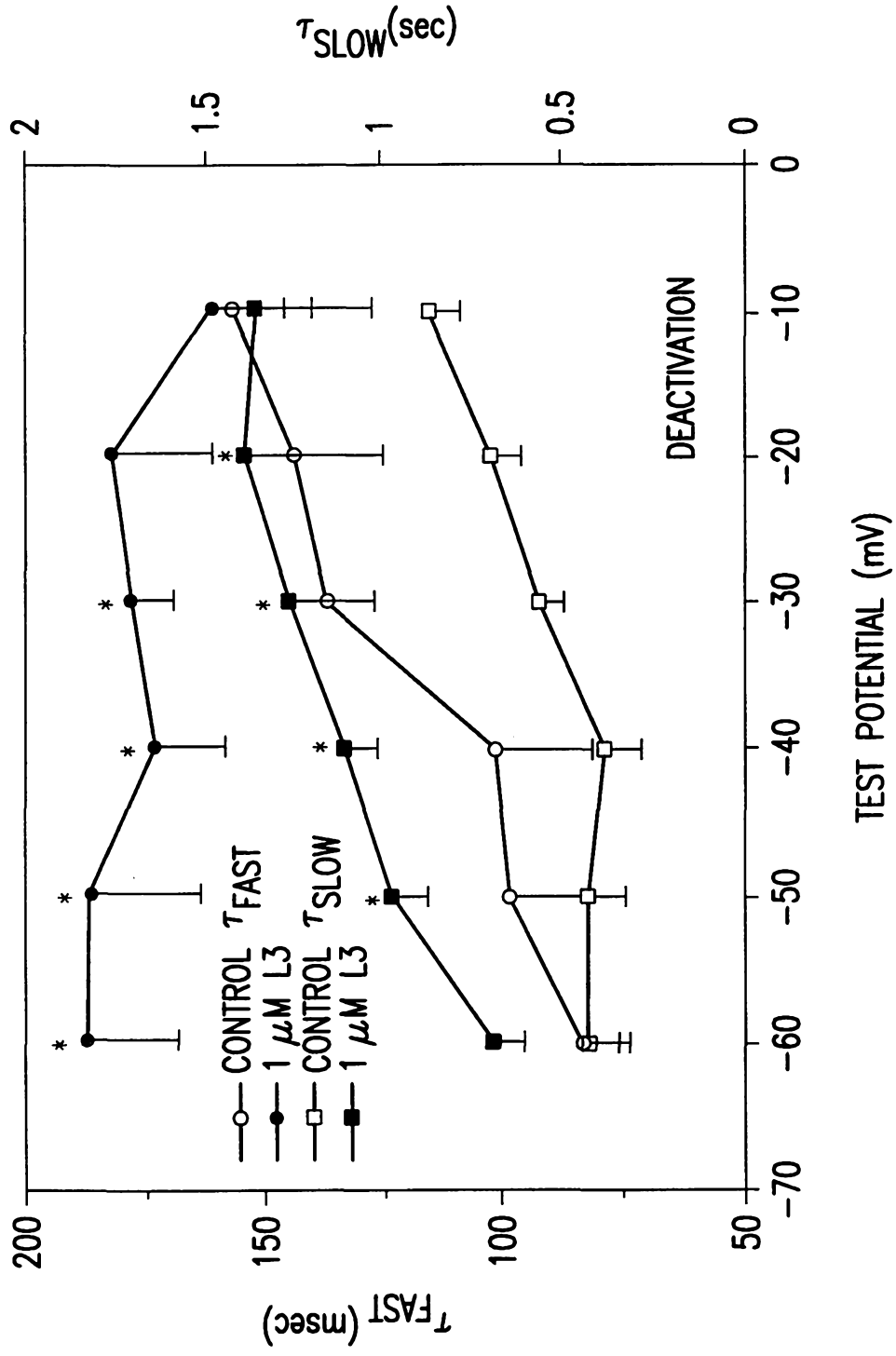
FIG.4
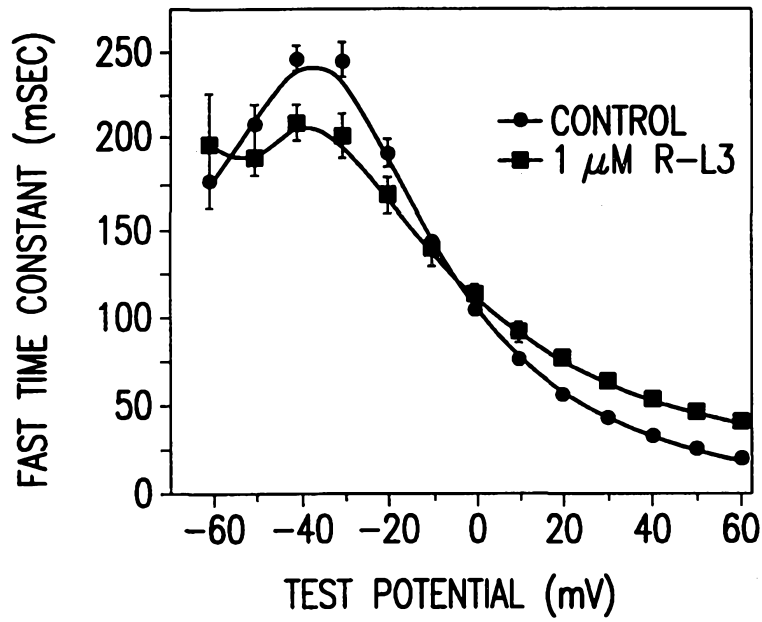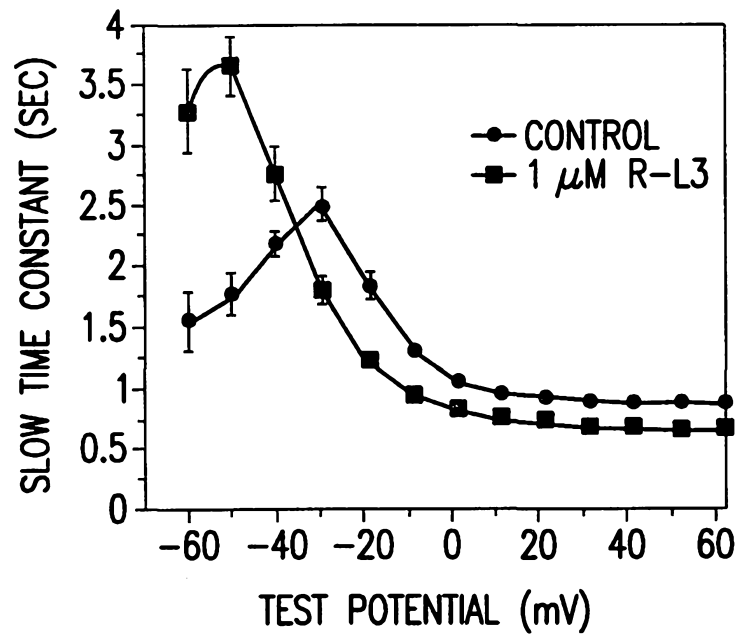
FIG.5A1

FIG.5A2

FIG.5B

CONTROL

1 μA

0.5 SEC

1 μM R-L3

FIG.6A

FIG.6B

FIG.6C

FIG.7A

FIG.7B

FIG.7C

FIG.7D

FIG.7E