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(54) **BLOCKADE OF SODIUM CHANNELS BY PHENOL DERIVATIVES**

BLOCKADE DER NATRIUMKANÄLE DURCH PHENOLDERIVATE

BLOCAGE DE CANAUX SODIQUES PAR DERIVES PHENOLES

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

Field of the Invention

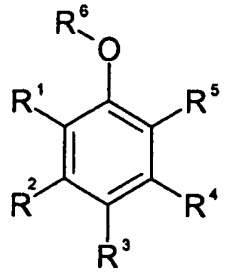
[0001] The invention relates to the use of a phenol derivative for the manufacture of a medicament for the treatment of dysrhythmia.

Background of the Invention

[0002] Phenol derivatives have a wide variety of clinical uses. Some are used as bacteriostatic stabilizers in parenteral drug formulations. We have recently shown that 4-chloro-3-methylphenol (4-chloro-m-cresol) and benzylalcohol both block muscle sodium channels in a voltage-dependent manner (Haeseler *et al.,* Br. J. Pharmacol., 128 (1999) 1259-67; Haeseler *et al.,* Br. J. Pharmacol., 130 (2000) 1321-1330). For the anesthetic propofol (2,6-di-isopropylphenol), various voltage-operated (Rehberg & Duch, Anaesthiology, 91 (1999) 512-20; Saint, Br. J. Pharmacol., 124 (1998) 655-662) and ligand-gated (Sanna *et al.,* Br. J. Pharmacol., 126 (1999) 1444-54) channels, mainly in the central nervous system, have been identified as possible targets. Integrated into larger molecules, phenol derivatives with single substituents form the aromatic tail of most local anesthetics and class Ib antidysrhythmic drugs. The effect of the local anesthetic lidocaine (2-diethylamino-2',6'-dimethylacetanilide) on voltage-operated sodium channels in different excitable tissues has been extensively studied. Lidocaine-induced sodium channel blockade is characterized by a higher affinity of the drug for fast and slow inactivated channels compared with the resting state, and by prolonged recovery from inactivation, introducing a second, slow component representing drug dissociation from inactivated channels (Balser *et al.,* J. Gen. Physiol., 107 (1996) 643-658; Bean *et al.,* J. Gen. Physiol., 81 (1983) 613-642; Fan *et al.*,J. Physiol., 81 (1996) 275-286; Scheuer, J. Gen. Physiol., 113 (1999) 3-6; Vedantham & Cannon, J. Gen. Physiol., 113 (1999) 7-16). Several studies have addressed the structural requirements for pharmacological effects (Ehring *et al.,* J. Pharmacol. Exp. Therapeut., 244 (1988) 479-92; Sheldon *et al.,* Mol. Pharmacol., 39 (1991) 609-614), but have not provided clues about which parts of the lidocaine molecule are responsible for its state-dependent interaction with the sodium channel. The approach of dissecting the lidocaine molecule into phenol and diethylamide (Zamponi & French, Biophys. J. 65 (1993) 2335-2347) did not take into account the fact that the aromatic group of the parent compound is a methylated phenol derivative. Although phenol block mimicked slow block of cardiac sodium channels seen with lidocaine, blocking potency was an order of magnitude lower and skeletal muscle sodium channels were only minimally affected.

Summary of the Invention

[0003] The present invention relates to the use of a phenol derivative represented by formula (I)



(I)

wherein

- R^1 represents a C_1-C_7 alkyl group;
- R^2 represents a hydrogen atom;
- R^3 represents a halogen atom;
- R^4 represents a hydrogen atom;
- R^5 represents a C_1 - C_7 alkyl group; and
- R^6 represents a hydrogen atom;

or

- R^1 represents a hydrogen atom;
- R^2 represents a C_1 - C_7 alkyl group;
- R^3 represents a halogen atom;
- R^4 represents a C_1 - C_7 alkyl group;
- R^5 represents a hydrogen atom; and
- R^6 represents a hydrogen atom;

for the manufacture of a medicament for the treatment of dysrhythmia.

[0004] Preferred embodiments of the invention become apparent from the dependent claims.

[0005] The compounds were found to have a higher potency in blocking voltage operated sodium channels such as muscle sodium channels, neuronal sodium channels and cardiac sodium channels.

Description of the Figures

Figure 1

[0006] Concentration-dependent reduction in test pulse current with respect to control (I/I_{max}, mean ± SD) induced by the different compounds. The data were derived from at least four different experiments for each concentration tested. Depolarizing pulses to 0 mV (10 ms duration) were started from -150, -100, or -70 mV. Solid lines are Hill fits ($I_{Na+} = [1+([C]/IC_{50})^{nH}]^{-1}$) to the data.

[0007] Concentration-response plots at -100 and -150 mV were nearly superimposable for all compounds, while the potency of the drugs was markedly increased at -70 mV.

Figure 2

[0008] Concentration-dependent reduction in test pulse current with (filled squares) or without (empty triangles) a 2.5 s inactivating prepulse introduced before the test pulse (n > 4, mean ± SD). Currents were normalized to the current elicited with the same protocol in control conditions. The solid lines are Hill fits to the data. The 2.5 s prepulse uniformly enhanced sensitivity to all compounds examined.

Figure 3

[0009] Recovery from fast inactivation assessed by a two-pulse protocol in control conditions (circles) and in the presence of 100 μM 3,5-dimethyl-4-chlorophenol (squares). The abscissa represents the recovery time interval between prepulse and test pulse (up to 100 ms), the ordinate represents the fractional current (mean ± SD, n = 5) after recovery from fast inactivation, induced by the prepulse in the same series. In the presence of drug, currents were normalized either to the prepulse in the presence of drug (filled symbols) or in the corresponding control conditions (empty symbols). Solid lines are exponential fits $I(t)=a_0+a_1\exp(-t/\tau_{h1})+a_2\exp(-t/\tau_{h2})$ to the fractional currents after recovery from inactivation or inactivated channel block. Without drug, the data fitted to a monoexponential. In the presence of drug, recovery was delayed and contained a second slow component of 94 ms, which made up 8 % of the current amplitude.

Detailed Description of the Invention

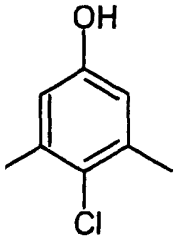
[0010] Generally, in conjunction with the present invention the C_1-C_7 alkyl group denotes a branched or straight (linear) chain hydrocarbon group which may optionally be substituted with a halogen atom, a hydroxyl group or an oxo-group (=O). In another embodiment said hydrocarbon group contains 2 to 6, in a still further embodiment up to 5 carbon atoms. Preferred alkyl-groups, which may be substituted or not as mentioned above, may be selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec.-butyl, tert.-butyl, and the isomers of the pentyl and hexyl-group.

[0011] In terms of the present invention the halogen atoms are selected from fluorine, chlorine, bromine and iodine with chlorine and fluorine being preferred.

[0012] Caused by the high blocking potency in combination with interference with channel gating in voltage-gated sodium channels the compounds can be applied in low dosages as antidisrhythmic.

[0013] The compounds of formula (I) have a higher potency in sodium channel blockade compared to conventional, state of the art compounds. For example, the IC_{50} value for lidocaine block of heterologously expressed muscle sodium channels at -100 mV was 500 μM (Fan *et al.,* J. Physiol., (1996) 275-286), compared with 150 μM for 3,5-dimethyl-4-chlorophenol, i.e., a compound according to the present invention. It has surprisingly been found that the blocking potency of phenol derivatives is increased by halogenation and by increasing the number of alkyl groups. In addition, it has been found that voltage-dependent block by all compounds retains a characteristic set of features that describes local anesthetic block.

[0014] Exemplary compounds which can be used according to the present invention are



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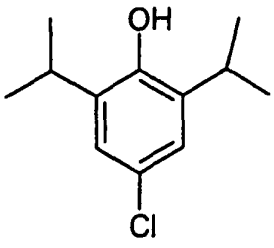


(VI)

[0015] In experiments it was found that all substituted phenols blocked skeletal muscle sodium channels in a concentration-dependent manner. Compounds which are not according to the invention such as 3-methylphenol and 4-chlorophenol blocked sodium currents on depolarization from -100 mV to 0 mV with IC_{50} values of 2161 μM and 666 μM, respectively. Methylation of the halogenated compound further increased potency, reducing the IC_{50} to 268 μM in 4-chloro-2-methylphenol. The IC_{50} was surprisingly reduced further to 150 μM in 3,5-dimethyl-4-chlorophenol, a compound falling under the scope of formula (I).

[0016] Membrane depolarization before the test depolarization significantly promoted sodium channel blockade. When depolarizations were started from -70 mV or when a 2.5 s prepulse was introduced before the test pulse inducing slow inactivation, the IC_{50} was reduced more than three-fold by all compounds. The values of K_D for the fast-inactivated state derived from drug-induced shifts in steady-state availability curves were 14 μM for 3,5-dimethyl-4-chlorophenol. For comparative compounds there was found 19 μM for 4-chloro-2-methylphenol, 26 μM for 4-chlorophenol and 115 μM for 3-methylphenol.

[0017] All compounds used according to the invention

accelerated the current decay during depolarization and slowed recovery from fast inactivation. No relevant frequency-dependent block after depolarizing pulses applied at 10, 50, and 100 Hz was detected for any of the compounds.

[0018] All the phenol derivatives used according to the present invention are effective blockers of sodium channels, such as skeletal muscle sodium channels, especially in conditions that are associated with membrane depolarization.

[0019] Typically, the pharmaceutical compositions used according to the present invention can be applied in various forms such as in the form of emulsions (oil-in-water), sprays, ointments, creams, pastes and capsules. The pharmaceutical compositions thus may be in injectable form or in topically applicable form.

[0020] Injection solutions for parenteral administration comprise between 0.1 and 5 % by weight, preferably 0.2 to 3 % by weight and more preferably up to 2 % by weight of the phenol derivative of formula (I).

[0021] The manufacture of parenteral solutions is conventional in the art. Due to the increased potency of the phenol derivatives the dosage is decreased significantly.

[0022] While the invention has been described in connection with a number of preferred embodiments thereof, those skilled in the art will recognize that many modifications and changes can be made therein without departing from the scope of the invention.

[0023] The present invention is further described by the experiments which follow hereinafter.

Experiments

[0024] The sodium channel blocking potency effects of different phenol derivatives with methyl and halogen substituents have been studied on heterologously expressed human skeletal muscle sodium channels. The phenol derivatives encompassed by formula (I) are either commercially available or can be synthesized by conventional standard laboratory methods.

Molecular biology

[0025] Wild type α-subunits of human muscle sodium channels were heterologously expressed in human embryonic kidney (HEK 293) cells, a stable cell line since 1962 (American Tissue Culture Collection CRL 1573). Transfection was performed using calcium phosphate precipitation (Graham & Van der Eb, Virology, 52 (1973) 456-467). Permanent expression was achieved by selection for resistance to the aminoglycoside antibiotic geneticin G418 (Life Technology, Eggenstein, Germany) (Mitrovic *et al.,* J. Physiol., 478 (1994) 395-402). Successful channel expression was verified electrophysiologically. The clone has been used in several investigations (Haeseler *et al.*,Br. J. Pharmacol., 128 (1999) 1259-67; Haeseler *et al.,* Br. J. Pharmacol. 130 (2000) 1321-1330; Mitrovic *et al.,* ibid.).

Solutions

[0026] 3,5-dimethyl-4-chlorophenol (according to the invention) and 3-methylphenol (not according to the invention) were purchased from Sigma Chemicals, Deisenhofen, Germany; 4-chloro-2-methylphenol (not according to the invention) and 4-chlorophenol (not according to the invention) were from FLUKA, Deisenhofen, Germany. 3,5-Dimethyl-4-chlorophenol was prepared as a 1 M stock solution in methanol; 4-chloro-2-methylphenol, 4-chlorophenol, and 3-methylphenol were dissolved directly in the bath solution immediately before the experiments. Concentrations were calculated from the amount injected into the glass vials. Drug-containing solutions were protected from light and were vigorously vortexed for 60 min. The solution was applied via a glass polytetrafluoroethylene perfusion system and a stainless steel superfusion pipette. The bath solution contained (mM) NaCl 140, $MgCl_2$ 1.0, KCl 4.0, $CaCl_2$ 2.0, Hepes 5.0, dextrose 5.0. Patch electrodes contained (mM) $CsCl_2$ 130, $MgCl_2$ 2.0, EGTA 5.0, Hepes 10. All solutions were adjusted to 290 mosm/l by the addition of mannitol and to pH 7.4 by the addition of CsOH.

Experimental set-up

[0027] Standard whole-cell voltage-clamp experiments (Hamill *et al.,* Pfuegers Arch., 391 (1981) 85-100) were performed at 20°C. Each experiment consisted of test recordings with the drug present at only one concentration, and of drug-free control recordings before and after the test. Each whole-cell patch was exposed to one test concentration only. At least four experiments were performed at each concentration. The amount of the diluent methanol corresponding to the test concentration of 3,5-dimethyl-4-chlorophenol was added to the control solution. Patched cells were lifted into the visible stream of either bath solution or test solution, applied via a two-channel superfusion pipette close to the cell. To ensure adequate adjustment of the application device, one test experiment in distilled water reducing inward sodium current to zero was performed every 6-10 experiments.

Current recordings and analysis

[0028] For data acquisition and further analysis we used the EPC9 digitally-controlled amplifier in combination with Pulse and Pulse Fit software (HEKA Electronics, Lambrecht, Germany). The EPC9 provides automatic subtraction of capacitive and leakage currents by means of a prepulse protocol. The data were filtered at 10 kHz and digitized at 20 μs per point. Input resistance of the patch pipettes was at 1.8-2.5 MΩ. Only small cells with capacitances of 9-15 pF were used; residual series resistance (after 50% compensation) was 1.2-2.5 MΩ; experiments with a rise in series resistance were rejected. The time constant of the voltage settling within the membrane (residual series resistance x cell capacitance) was

less than 35 μs. To minimize a possible contribution of endogenous Na^+ channels in HEK cells that conduct with amplitudes ranging from 50 to 350 pA (Mitrovic *et al.,* 1994, ibid.), but also to avoid large series resistance errors, only currents ranging between 1 and 6 nA were analysed. To minimize time-dependent shifts in the voltage-dependence of steady-state inactivation (Wang *et al.,* 1996), all test experiments were performed within 5 min of patch rupture. Under these experimental conditions, time-dependent hyperpolarizing shifts in control conditions were less than -2 mV (Haeseler *et al.*, Anesthiology, 92 (2000) 1385-92). Voltage-activated currents were studied by applying different voltage-clamp protocols. Either exponential functions [$I(t)=a_0+a_1\exp(-t/\tau_{h1})+a_2\exp(-t/\tau_{h2})$] or Boltzmann functions [$I/I_{max}=(1+\exp(-zF(V_{test}-V_{0.5})/RT))^{-1}$] were fitted to the data, using a non-linear least-squares Marquardt-Levenberg algorithm, yielding the time constant τ of inactivation and recovery from inactivation, the membrane potential at half-maximum channel availability ($V_{0.5}$), and the slope factor z of the steady-state availability curve. F is Faraday's constant (9.6487×10^4 C mol^{-1}), R is the gas constant (8.315 J K^{-1} mol^{-1}), and T is the temperature in degrees Kelvin. Drug effects on the peak current amplitude were assessed at different holding potentials (-70, -100 and -150 mV), or when a 2.5 s prepulse to -35 mV was introduced before the test pulse in order to induce slow inactivation. All data are presented as mean ± SD. The residual sodium current (I_{Na+}) in the presence of drug (with respect to the current amplitude in control solution) was plotted against the applied concentration of each drug [C]. Fits of the Hill equation [$I_{Na+} = (1+([C]/IC_{50})^{nH})^{-1}$] to the data yielded the concentration for half-maximum channel blockade (IC_{50}) and the Hill coefficient n_H.

Results

[0029] Successful Na^+ channel expression was verified electrophysiogically in almost all of the established whole-cell patches. In all 83 cells were included in the study. Average currents in the control experiments after depolarization from -100 mV to 0 mV were 4.9 ± 2.1 nA.

Suppression of peak sodium currents-differences in potency related to methylation and/or halogenation of the phenol ring

[0030] Maximum inward currents elicited by 10 ms pulses going from either -150 mV, -100 mV, or -70 mV to 0 mV were reversibly suppressed by all substances in a concentration-dependent manner. Suppression occurred within 60 s after the start of perfusion with the drug-containing solution. The currents in the presence of drug were normalized to the respective current elicited in control conditions. Normalized currents derived from at least four different experiments for each drug concentration were averaged to establish concentration-response plots (see Figure 1).

[0031] The degree of suppression at all holding potentials increased with halogenation and with the number of methyl groups at the phenol ring. The phenol derivative 3-methylphenol, containing only one methyl group in the meta position with respect to the hydroxyl group, blocked inward sodium current at a holding potential of -150 mV, with an IC_{50} value of 2395 μM.

[0032] The halogenated compound 4-chlorophenol was more potent than the methylated compound, and reduced the IC_{50} to 751 μM. Methylation in addition to halogenation further increased potency, reducing the IC_{50} about two-fold for each methyl group inserted into the halogenated compound (316 μM for 4-chloro-2-methylphenol and 162 μM for 3,5-dimethyl-4-chlorophenol).

Acceleration of the Na^+ current decay phase by phenol derivatives

[0033] To examine the time course of Na^+ channel inactivation during a depolarization, 40 ms voltage steps from a holding potential of -100 mV to 0 mV were performed. The time constant of channel inactivation τ_h was obtained by fitting a single exponential to the decay of current during depolarizations: $I(t)=a_0+a_1\exp(-t/\tau_h)$. In control conditions, τ_n was 0.43 ± 0.08 ms (n = 72). All phenol derivatives accelerated the decay of whole-cell currents. For all compounds, however, this effect was apparent only at concentrations that exceeded the IC_{50} values at a holding potential of -70 mV. Values obtained for τ_h in the presence of drug were: 0.27 ± 0.02 ms in 50 μM 3,5-dimethyl-4-chlorophenol, 0.27 ± 0.05 ms in 100 μM 4-chloro-2-methylphenol, 0.23 ± 0.03 ms in 500 μM 4-chlorophenol, and 0.30 ± 0.08 ms in 1000 μM 3-methylphenol.

Effects of phenol derivatives on recovery from fast inactivation

[0034] After inactivation, channel re-openings are impossible until the channels recover from inactivation, a process that requires several ms after membrane repolarization. Further information about drug effects on the stability of the fast-inactivated state or the kinetics of drug dissociation from the fast-inactivated state can be derived from the rate at which the channels recover from inactivation in the presence of the drug. The time of membrane repolarization required to remove fast inactivation was assessed at -100 mV by a two-pulse protocol with varying time intervals (up to 100 ms) between the inactivating prepulse and the test pulse (see Figure 3). The time constants of recovery, τ_{rec}, were derived from monoexponential or biexponential fits to the fractional current after recovery from inactivation, plotted against the time interval between the inactivating prepulse and the test pulse: $I(t) = a_0 + a_1\exp(-t/\tau_{rec1}) + a_2\exp(t/\tau_{rec2})$. Without drug, the data fitted well to a monoexponential, yielding a time constant, τ_{rec1}, of 2.3 ± 0.7 ms (n = 34). In the

presence of drug, the fit contained a second, slow component of recovery, τ_{rec2} of 94 ± 8 ms (3,5-dimethyl-4-chlorophenol), 36 ± 5 ms (4-chloro-2-methylphenol), and 30 ± 0.1 ms 4-chlorophenol and 3-methylphenol). For all drugs, however, the slow component made up less than 10 % of the current amplitude at concentrations close to the IC_{50} for rest block. The fast component, τ_{rec1}, was prolonged to 3.8 ± 0.8 ms in 100 μM 3,5-dimethyl-4-chlorophenol, to 4.3 ± 1.6 ms in 300 μM 4-chloro-2-methylphenol, to 3.0 ± 0.7 ms in 500 μM 4-chlorophenol, and to 2.8 ± 0.6 ms in 1000 μM 3-methylphenol. Figure 3 shows the time-course of recovery from fast inactivation with and without 100 μM 3,5-dimethyl-4-chlorophenol.

Frequency-dependent block

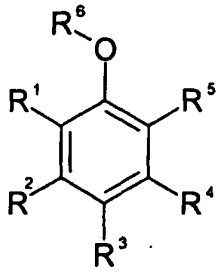
[0035] The accumulation of block during trains of depolarizing pulses indicates that the interval between pulses is too short to allow recovery of Na^+ channel availability. To derive an estimate of the kinetics of drug binding and unbinding during the interpulse interval, we applied series of 1-10 ms depolarizing pulses from -100 mV to 0 mV at high frequencies (10, 50, and 100 Hz).

[0036] Frequency-dependent block was defined as the additional reduction in I_{Na+} for the last pulse relative to the first pulse in a test train in the presence of drug.

[0037] In control conditions, the amplitude of the last pulse relative to the first pulse in a test train was 99 ± 1 % at 10 Hz and 96 ± 3 % at 50 and 100 Hz. Neither compound induced frequency-dependent block over 10 % at 10 Hz. At 50 and 100 Hz, only concentrations exceeding the IC_{50} for rest block produced a small amount of frequency-dependent block. During a 100 Hz train, the additional fall relative to the first pulse was 17 ± 5 % in 300 μM 3,5-dimethyl-4-chlorophenol, 16 ± 5 % in 500 μM 4-chloro-2-methylphenol, 13 ± 2 % in 1000 μM 4-chlorophenol, and 8 ± 2% in 3000 μM 3-methylphenol.

Claims

1. Use of a phenol derivative represented by formula (I)



(I)

wherein

- R^1 represents a C_1-C_7 alkyl group;
- R^2 represents a hydrogen atom;
- R^3 represents a halogen atom;
- R^4 represents a hydrogen atom;
- R^5 represents a C_1 - C_7 alkyl group; and
- R^6 represents a hydrogen atom;

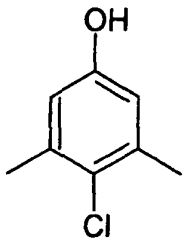
or

- R^1 represents a hydrogen atom;
- R^2 represents a C_1 - C_7 alkyl group;
- R^3 represents a halogen atom;
- R^4 represents a C_1 - C_7 alkyl group;
- R^5 represents a hydrogen atom; and
- R^6 represents a hydrogen atom;

for the manufacture of a medicament for the treatment of dysrhythmia.

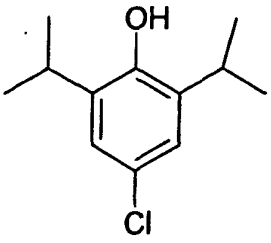
2. Use according to claim 1 wherein R^3 is a chlorine or bromine atom.

3. Use according to any of claims 1 or 2 wherein the phenol derivative is represented by the following formula:



(V).

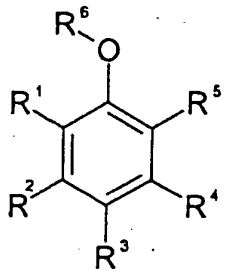
4. Use according to any of claims 1 or 2 wherein the phenol derivative is represented by the following formula



(VI).

Patentansprüche

1. Verwendung eines Phenolderivats, das durch Formel (I)



(I)

dargestellt wird, wobei:

- R^1 eine C_1-C_7-Alkylgruppe darstellt;
- R^2 ein Wasserstoffatom darstellt;
- R^3 ein Halogenatom darstellt;
- R^4 ein Wasserstoffatom darstellt;
- R^5 eine C_1-C_7-Alkylgruppe darstellt; und
- R^6 ein Wasserstoffatom darstellt;

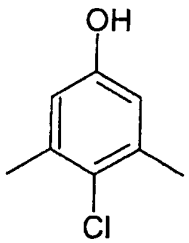
oder

- R^1 ein Wasserstoffatom darstellt;
- R^2 eine C_1-C_7-Alkylgruppe darstellt;
- R^3 ein Halogenatom darstellt;
- R^4 eine C_1-C_7-Alkylgruppe darstellt;
- R^5 ein Wasserstoffatom darstellt; und
- R^6 ein Wasserstoffatom darstellt;

zur Herstellung eines Medikaments zur Behandlung von Dysrhythmie.

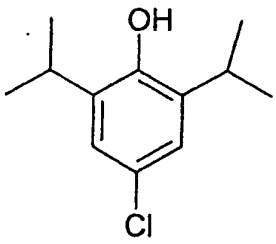
2. Verwendung gemäß Anspruch 1, wobei R^3 ein Chlor- oder Bromatom ist.

3. Verwendung gemäß einem der Ansprüche 1 oder 2, wobei das Phenolderivat durch die folgende Formel dargestellt wird:



(V).

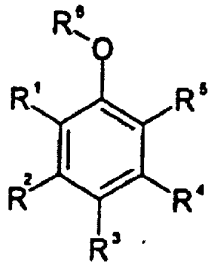
4. Verwendung gemäß einem der Ansprüche 1 oder 2, wobei das Phenolderivat durch die folgende Formel dargestellt wird:



(VI).

Revendications

1. Utilisation d'un dérivé de phénol représenté par la formule (I)



(I)

dans laquelle

- R^1 représente un groupe alkyle en C_1-C_7 ;
- R^2 représente un atome d'hydrogène ;
- R^3 représente un atome d'halogène ;
- R^4 représente un atome d'hydrogène ;
- R^5 représente un groupe alkyle en C_1-C_7 ; et
- R^6 représente un atome d'hydrogène ;

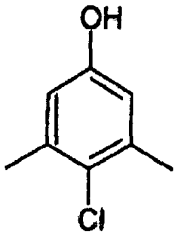
ou

- R^1 représente un atome d'hydrogène ;
- R^2 représente un groupe alkyle en C_1-C_7 ;
- R^3 représente un atome d'halogène ;
- R^4 représente un groupe alkyle en C_1-C_7 ;
- R^5 représente un atome d'hydrogène ; et
- R^6 représente un atome d'hydrogène ;

pour la fabrication d'un médicament destiné au traitement de la dysrythmie.

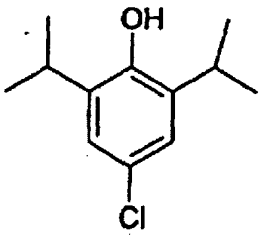
2. Utilisation selon la revendication 1, dans laquelle R^3 est un atome de chlore ou de brome.

3. Utilisation selon l'une quelconque des revendications 1 ou 2, dans laquelle le dérivé de phénol est représenté par la formule suivante :



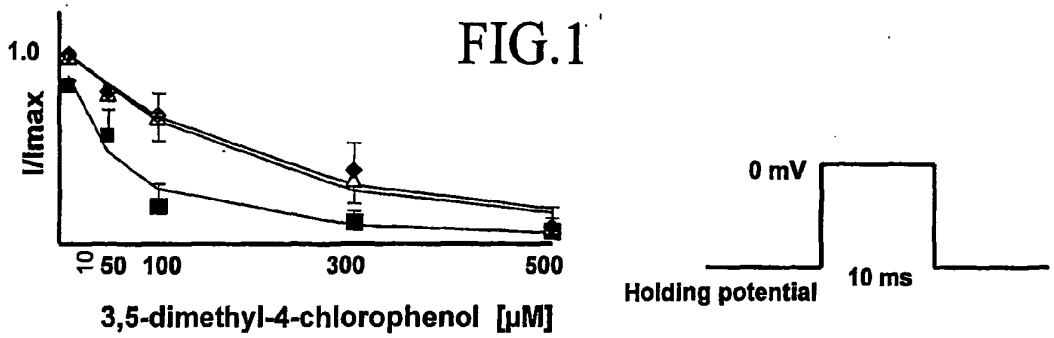
(V).

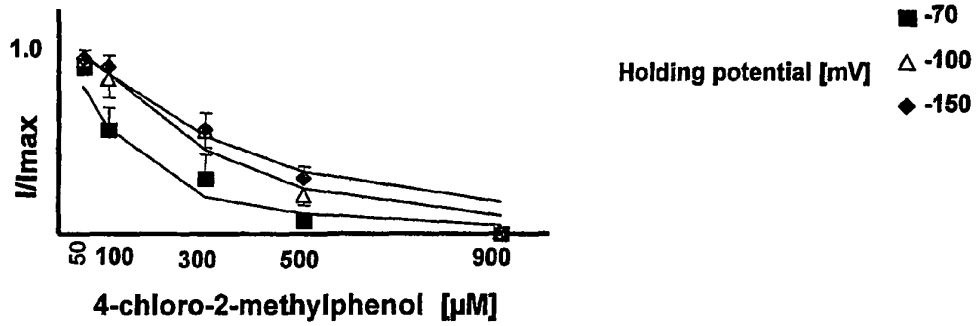
4. Utilisation selon l'une quelconque des revendications 1 ou 2, dans laquelle le dérivé de phénol est représenté par la formule suivante :

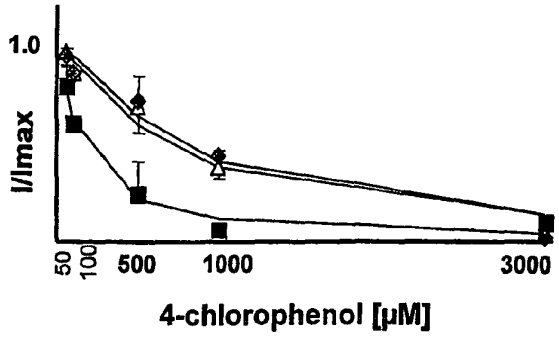


(VI).

FIG.1


1.0
I/Imax
10
50
100
300
500
3,5-dimethyl-4-chlorophenol [µM]
0 mV
10 ms
Holding potential


1.0
I/Imax
50
100
300
500
900
4-chloro-2-methylphenol [µM]
Holding potential [mV]
-70
-100
-150


1.0
I/Imax
50
100
500
1000
3000
4-chlorophenol [µM]

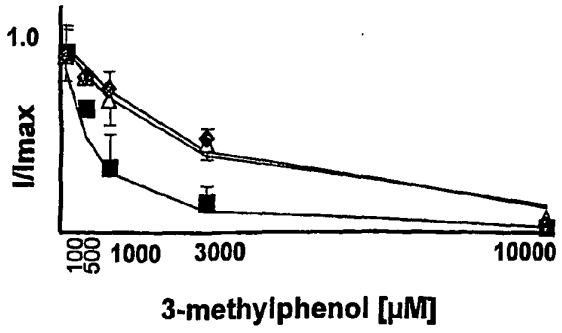
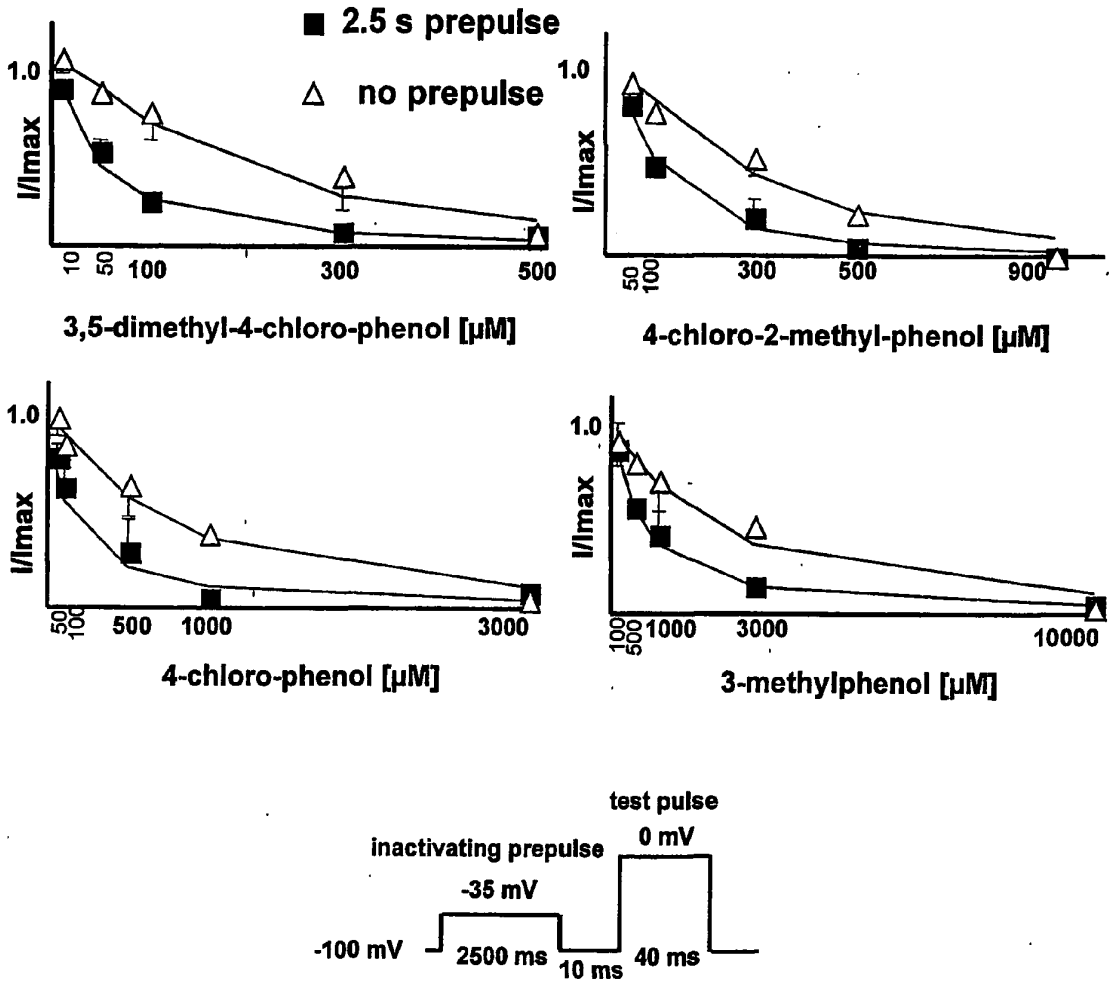

1.0
I/Imax
100
500
1000
3000
10000
3-methylphenol [µM]

FIG. 2


2.5 s prepulse
no prepulse
I/Imax
1.0
10
50
100
300
500
3,5-dimethyl-4-chloro-phenol [µM]
50
100
300
500
900
4-chloro-2-methyl-phenol [µM]
50
100
500
1000
3000
4-chloro-phenol [µM]
100
500
1000
3000
10000
3-methylphenol [µM]
test pulse
0 mV
inactivating prepulse
-35 mV
-100 mV
2500 ms
10 ms
40 ms

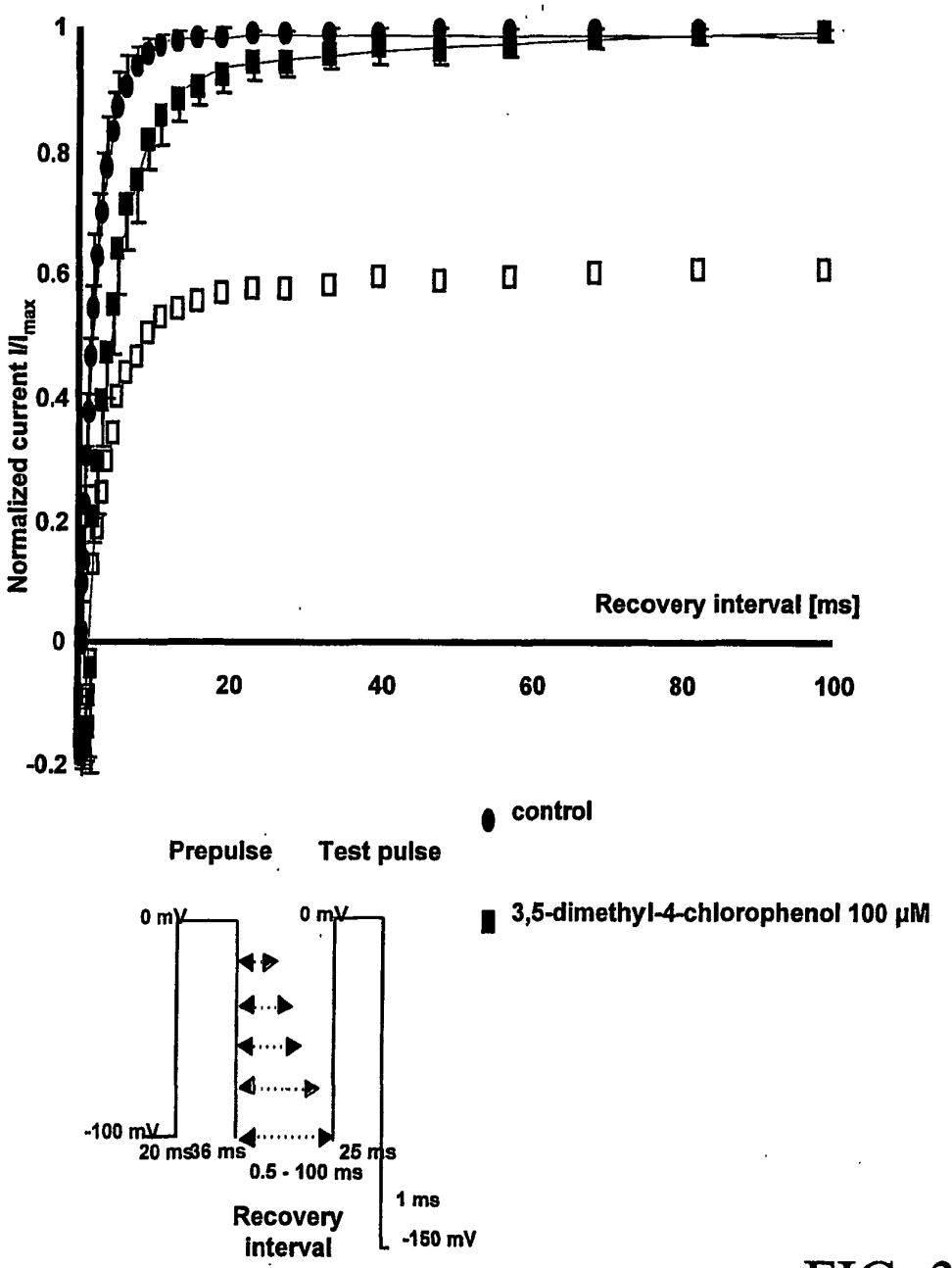

1
0.8
0.6
0.4
0.2
0
-0.2
Normalized current I/I$_{max}$
Recovery interval [ms]
20
40
60
80
100
control
3,5-dimethyl-4-chlorophenol 100 µM
Prepulse
Test pulse
0 mV
0 mV
-100 mV
20 ms
36 ms
25 ms
0.5 - 100 ms
1 ms
-150 mV
Recovery interval

FIG. 3