

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 May 2002 (23.05.2002)

PCT

(10) International Publication Number
WO 02/40005 A2

(51) International Patent Classification⁷: **A61K 31/05**,
31/055, A61P 43/00, 23/02, 9/06, 9/00, 1/06, 21/02

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(21) International Application Number: PCT/EP01/13081

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(22) International Filing Date:
13 November 2001 (13.11.2001)

(81) Designated State (*national*): US.

(25) Filing Language: English

(84) Designated States (*regional*): European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE, TR).

(26) Publication Language: English

(30) Priority Data:
00124870.7 15 November 2000 (15.11.2000) EP

Published:

— without international search report and to be republished
upon receipt of that report

— entirely in electronic form (except for this front page) and
available upon request from the International Bureau

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BLOCKADE OF SODIUM CHANNELS BY PHENOL DERIVATIVES

(57) **Abstract:** The invention relates to a pharmaceutical composition comprising at least one phenol derivative represented by formula (I), wherein R¹ represents a hydrogen atom, a halogen atom or a hydrocarbon group containing up to 12 carbon atoms; R² represents a hydrogen atom or a C₁-C₇ alkyl group; wherein R¹ and R² may optionally form a carbocyclic 5- or 6-membered ring; R³ represents a hydrogen atom, a halogen atom or a C₁-C₇ alkyl group; R⁴ represents a hydrogen atom, a C₁-C₇ alkyl group or a halogen atom; R⁵ represents hydrogen atom, a halogen atom or a C₁-C₇ alkyl group; and R⁶ represents a hydrogen atom, a C₁-C₇ alkyl group or a C₂ or C₃ alkenyl group, under the proviso that R² and R⁴ can only both represent a hydrogen atom if both R¹ and R⁵ represent a C₁-C₇ alkyl group and R³ represents a halogen atom. The composition is particularly useful for the blockade of sodium channels and/or influencing the kinetics of sodium channels and thus can be used as local anesthetic, antidysrhythmic, anticonvulsant/antiepileptic and spasmolytic.



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Blockade of Sodium Channels by Phenol Derivatives

Field of the Invention

The invention relates to a pharmaceutical composition comprising at
5 least one phenol derivative which is particularly useful for the
blockade of sodium channels and/or influencing the kinetics of sodium
channels. In the pharmaceutical field the composition can be used as
local anesthetic, antidysrhythmic, anticonvulsive and spasmolytic.

10 Background of the Invention

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-
15 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, Anaesthesiology, 91 (1999) 512-20; Saint,
Br. J. Pharmacol., 124 (1998) 655-662) and ligand-gated (Sanna *et al.*,
20 *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
25 (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.

20 **Summary of the Invention**

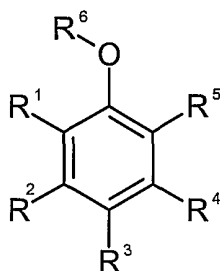
It has been an object of the present invention to provide compounds having a higher potency in blocking voltage operated sodium channels such as muscle sodium channels, neuronal sodium channels and cardiac sodium channels.

25 It has been a further object of the present invention to provide a pharmaceutical composition, in particular a local anesthetic composition, an anticonvulsive/antiepileptic composition, an antidysrhythmic composition and a spasmolytic composition which is more effective, i.e., has an improved potency.

30 The above objectives were solved by

3

a pharmaceutical or cosmetic composition comprising a phenol derivative represented by formula (I)



(I)

5 wherein

- R¹ represents a hydrogen atom, a halogen atom or hydrocarbon group containing up to 12 carbon atoms;
- R² represents a hydrogen atom or a C₁-C₇ alkyl group; wherein

10 R¹ and R² may optionally form a carbocyclic 5- or 6-membered ring;

- R³ represents a hydrogen atom, a halogen atom or a C₁ - C₇ alkyl group;
- R⁴ represents a hydrogen atom, a C₁-C₇ alkyl group or a halogen atom;
- R⁵ represents a hydrogen atom, a halogen atom or a C₁ - C₇ alkyl group; and
- R⁶ represents a hydrogen atom, a C₁-C₇ alkyl group or a C₂ or C₃ alkenyl group,

15 20 under the proviso that R² and R⁴ can only both represent a hydrogen atom if both R¹ and R⁵ represent a C₁-C₇ alkyl group and R³ represents a halogen atom.

The above composition has been found to have an improved potency in blocking sodium channels and/or influencing the kinetics of sodium channels in a mammal.

5 Description of the Figures

Figure 1

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

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

Figure 2

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 $\pm$ SD). Currents were
20 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

Recovery from fast inactivation assessed by a two-pulse protocol in
25 control conditions (circles) and in the presence of 100 μ M 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 $\pm$ 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.

10 Detailed Description of the Invention

The hydrocarbon group containing up to 12 carbon atoms as defined in conjunction with substituent R^1 may be a straight or branched aliphatic or alicyclic group which may be substituted with at least one substituent selected from halogen, hydroxyl, and oxo groups (thus forming keto or aldehyde groups). Independently said hydrocarbon group may optionally contain at least one double-bond or said hydrocarbon group may be an aromatic group (such as a phenyl group) which may optionally be substituted with at least one straight or branched C_1 - C_6 alkyl or C_2 - C_6 alkenyl group. In a preferred embodiment said hydrocarbon group contains up to 7 carbon atoms, more preferably 2 to 6 carbon atoms. Preferably, said hydrocarbon group may represent a C_1 - C_7 alkyl group.

Generally, in conjunction with the present invention the C_1 - C_7 alkyl group as defined for substituents R^1 to R^6 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, iso-

propyl, n-butyl, iso-butyl, sec.-butyl, tert.-butyl, and the isomers of the pentyl and hexyl-group.

It is evident that R^1 and R^2 can only form a ring if R^1 is neither a hydrogen nor a halogen atom. The ring which may be formed by R^1 and R^2 may further contain at least one double bond.

In a preferred embodiment the 5- or 6-membered ring formed by R^1 and R^2 is a 5- or 6-membered saturated or unsaturated carbocyclic ring, to which there can be annealed a phenyl ring, which may optionally be substituted with a C_1 - C_7 alkyl group.

10

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

By a C_2 -alkenyl group there is meant an ethenyl ($CH_2=CH-$) and by C_3 alkylene group there is meant a propenyl ($CH_2=CH-CH_2-$) group.

The substituents R^2 and R^4 can only both represent a hydrogen atom at the same time if both R^1 and R^5 represent a C_1 - C_7 alkyl group and R^3 represents a halogen atom.

It is understood that alternative to the free phenols, i.e., if R^6 represents a hydrogen atom the respective alkalimetal phenolates, for instance, the sodium phenolates, may also be employed. In a preferred embodiment in the above formula (I)

- R^1 represents a hydrogen atom, a halogen atom or a C_1 - C_7 alkyl group;
- R^3 represents a hydrogen atom, a halogen atom or a C_1 - C_7 alkyl group;
- R^4 represents a C_1 - C_7 alkyl group or a halogen atom; and

- R⁵ represents a hydrogen atom, a halogen atom or a C₁-C₇ alkyl group.

In an alternative embodiment in the above formula (I)

- R¹ represents a hydrogen atom or a C₁-C₇ alkyl group;
- 5 - R² represents a C₁-C₇ alkyl group; wherein
R¹ and R² may optionally form a carbocyclic 5- or 6-membered ring;
- R³ represents a halogen atom or a C₁-C₇ alkyl group;
- R⁴ represents a C₁-C₇ alkyl group;
- 10 - R⁵ represents a hydrogen atom or a C₁-C₇ alkyl group;
and
- R⁶ represents a hydrogen atom or a C₁-C₇ alkyl group.

In a still further embodiment in the above formula (I)

- R¹ represents a hydrogen atom;
- 15 - R² represents a C₁-C₇ alkyl group;
- R³ represents a halogen atom;
- R⁴ represents a C₁-C₇ alkyl group;
- R⁵ represents a hydrogen atom; and
- R⁶ represents a hydrogen atom.

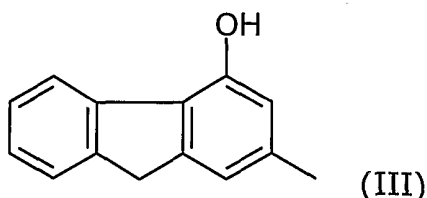
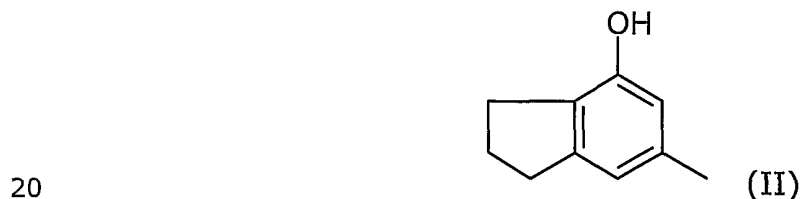
20 Additionally, in the above formula (I)

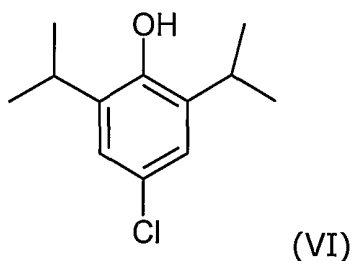
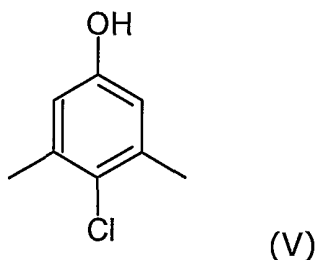
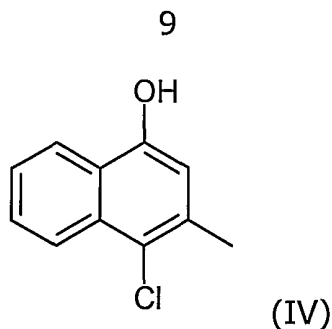
- R¹ and R⁵ may represent a C₁-C₇ alkyl group, preferably a C₁-C₅ alkyl group, more preferably an iso-propyl-group;
- R² and R⁴ may represent a hydrogen atom;
- R³ may represent a halogen atom, preferably a chlorine or
25 a bromine atom; and
- R⁶ may represent a hydrogen atom or a C₁-C₇ alkyl group.

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, spasmolytic, anticonvulsant/antiepileptic and local anesthetic.

- 5 The compounds according to the present invention 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 $500 \mu M$ (Fan *et al.*, J. Physiol., (1996) 275-286), compared with 150
10 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
15 characteristic set of features that describes local anesthetic block.

Exemplary compounds which can be used according to the present invention are the substituted phenols (II) to (VI).





- 5 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 μ M and 666 μ M, respectively. Methylation of the halogenated compound
- 10 further increased potency, reducing the IC_{50} to 268 μ M in 4-chloro-2-methylphenol. The IC_{50} was surprisingly reduced further to 150 μ M in 3,5-dimethyl-4-chlorophenol, a compound falling under the scope of formula (I).
- 15 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.

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.

All the phenol derivatives 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.

Typically, the pharmaceutical compositions 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.

Injection solutions for parenteral administration comprise between about 0.1 and about 5 % by weight, preferably about 0.2 to about 3 % by weight and more preferably up to about 2 % by weight of the phenol derivative of formula (I). For infiltrative anesthesia the solutions contain between about 0.4 and about 0.7 % by weight of the active ingredient. For conduction anesthesia the solutions contain between about 1 and about 2 % by weight, for epidural anesthesia between about 0.5 and about 1 % by weight of the active ingredient. For local topical anesthesia the phenol derivative of formula (I) is contained in the ointment, cream or paste in an amount of about 0.5 to about 5 % by weight, preferably in an amount of about 1 to about 3 % by weight, typically in an amount of up to about 2 % by weight.

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

- 5 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.

The present invention is further described by the experiments which
10 follow hereinafter. The scope of the invention is not limited to these experiments.

Experiments

The sodium channel blocking potency effects of different phenol
15 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.

20

Molecular biology

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
25 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

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, MgCl₂ 1.0, KCl 4.0, CaCl₂ 2.0, Hepes 5.0, dextrose 5.0. Patch electrodes contained (mM) CsCl₂ 130, MgCl₂ 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

Standard whole-cell voltage-clamp experiments (Hamill *et al.*, Pflugers 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
5 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

10 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
15 20 μ s per point. Input resistance of the patch pipettes was at 1.8–2.5 M Ω . Only small cells with capacitances of 9–15 pF were used; residual series resistance (after 50% compensation) was 1.2–2.5 M Ω ; experiments with a rise in series resistance were rejected. The time constant of the voltage settling within the membrane (residual series
20 resistance x cell capacitance) was less than 35 μ s. 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
25 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.*, *Anesthesiology*, 92 (2000) 1385-92).
30 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 $[I/I_{\max}=(1+\exp(-zF(V_{\text{test}}-V_{0.5})/RT))^{-1}]$ 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 ($9.6487 \times 10^4 \text{ C mol}^{-1}$), R is the gas constant ($8.315 \text{ J K}^{-1} \text{ mol}^{-1}$), 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 $\pm$ SD. The residual sodium current ($I_{\text{Na}+}$) 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 $[I_{\text{Na}+} = (1+([C]/IC_{50})^{n_H})^{-1}]$ to the data yielded the concentration for half-maximum channel blockade (IC_{50}) and the Hill coefficient n_H .

Results

Successful Na^+ channel expression was verified electrophysiologically 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 $4.9 \pm 2.1 \text{ nA}$.

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

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
5 concentration-response plots (see Figure 1).

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,
10 blocked inward sodium current at a holding potential of -150 mV, with an IC_{50} value of $2395 \mu M$.

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

Acceleration of the Na⁺ current decay phase by phenol derivatives

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_h 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 IC₅₀ 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 μ M 3,5-dimethyl-4-chlorophenol, 0.27 ± 0.05 ms in 100 μ M 4-chloro-2-methylphenol, 0.23 ± 0.03 ms in 500 μ M 4-chlorophenol, and 0.30 ± 0.08 ms in 1000 μ M 3-methylphenol.

Effects of phenol derivatives on recovery from fast inactivation

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: $I(t) = a_0 + a_1 \exp(-t/\tau_{rec1}) + a_2 \exp(-t/\tau_{rec2})$.

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

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).

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

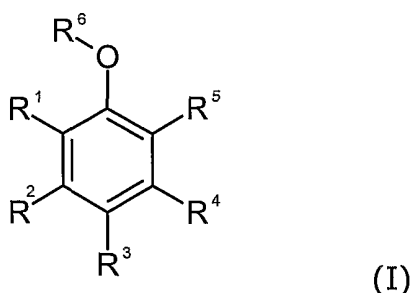
In control conditions, the amplitude of the last pulse relative to the first pulse in a test train was 99 ± 1 % at 10 Hz and 96 ± 3 % at 50 and 100 Hz. Neither compound induced frequency-dependent block over 10 % at 10 Hz. At 50 and 100 Hz, only concentrations exceeding the IC_{50} for rest block produced 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 $\pm$ 5 % in 500 μ M 4-chloro-2-methylphenol, 13 $\pm$ 2 % in 1000 μ M 4-chlorophenol, and 8 $\pm$ 2% in 3000 μ M 3-methylphenol.

Claims:

1. A pharmaceutical composition comprising at least one phenol derivative represented by formula (I)

5



wherein

- R¹ represents a hydrogen atom, a halogen atom or a hydrocarbon group containing up to 12 carbon atoms;
- 10 - R² represents a hydrogen atom or a C₁-C₇ alkyl group; wherein
R¹ and R² may optionally form a carbocyclic 5- or 6-membered ring;
- 15 - R³ represents a hydrogen atom, a halogen atom or a C₁-C₇ alkyl group;
- R⁴ represents a hydrogen atom, a C₁-C₇ alkyl group or a halogen atom;
- R⁵ represents hydrogen atom, a halogen atom or a C₁-C₇ alkyl group; and
- 20 - R⁶ represents a hydrogen atom, a C₁-C₇ alkyl group or a C₂ or C₃ alkenyl group,

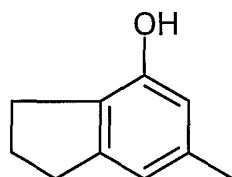
20

under the proviso that R^2 and R^4 can only both represent a hydrogen atom if both R^1 and R^5 represent a C_1 - C_7 alkyl group and R^3 represents a halogen atom.

- 5 2. The composition according to claim 1 wherein the 5- or 6-membered ring formed by R^1 and R^2 is a 5- or 6-membered saturated or unsaturated carbocyclic ring, to which there can be annealed a phenyl ring, which may optionally be substituted with a C_1 - C_7 alkyl group.

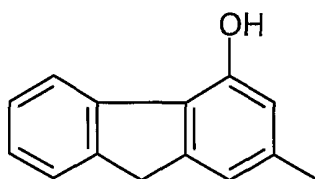
10

3. The composition according to claim 1 wherein the phenol derivative is selected from the group consisting of



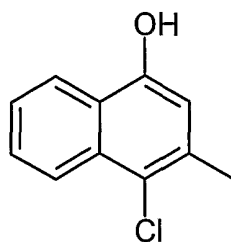
(II)

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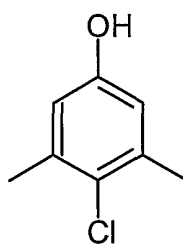


(III)

21

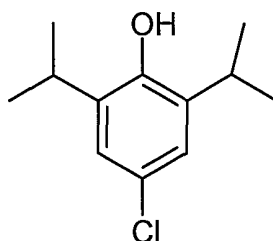


(IV)



(V)

5

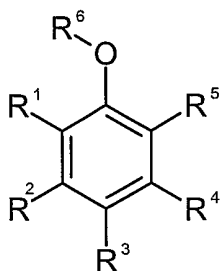


(VI)

10 4. The pharmaceutical composition according to claim 1 for the blockade of sodium channels and/or influencing the kinetics of sodium channels.

15 5. The pharmaceutical composition according to claim 4 being selected from a local anesthetic composition, an antidysrhythmic composition, an anticonvulsive/antiepileptic composition and a spasmolytic composition.

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



(I)

wherein

- R¹ represents a hydrogen atom, a halogen atom or a hydrocarbon group containing up to 12 carbon atoms;
- R² represents a hydrogen atom, a C₁-C₇ alkyl group ;
wherein
- R¹ and R² may optionally form a carbocyclic 5- or 6-membered ring;
- R³ represents a hydrogen atom, a halogen atom or a C₁ - C₇ alkyl group;
- R⁴ represents a hydrogen atom, a C₁-C₇ alkyl group or a halogen atom;
- R⁵ represents a hydrogen atom or a halogen atom or a C₁ - C₇ alkyl group; and
- R⁶ represents a hydrogen atom, a C₁-C₇ alkyl group or a C₂ or C₃ alkenyl group,

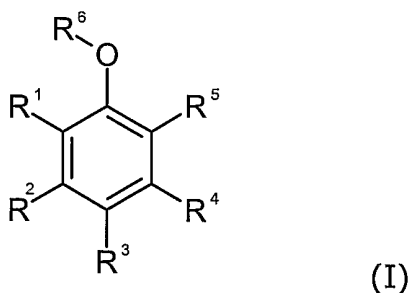
under the proviso that R² and R⁴ can only both represent a hydrogen atom if both R¹ and R⁵ represent a C₁-C₇ alkyl group and R³ represents a halogen atom

for the manufacture of a medicament for the blockade of sodium channels and/or influencing the kinetics of sodium channels.

7. Use according to claim 6 for the manufacture of a local
5 anesthetic, an antidysrhythmic, anticonvulsive or spasmolytic.

8. Method for the treatment of the human or animal body by administering an effective amount of a phenol derivative represented by formula (I)

10



wherein

- R¹ represents a hydrogen atom, a halogen atom or hydrocarbon group containing up to 12 carbon atoms;
- 15 - R² represents a hydrogen atom or a C₁-C₇ alkyl group; wherein
R¹ and R² may optionally form a carbocyclic 5- or 6-membered ring;
- R³ represents a hydrogen atom, a halogen atom or a C₁ -
20 C₇ alkyl group;
- R⁴ represents a hydrogen atom, a C₁-C₇ alkyl group or a halogen atom;

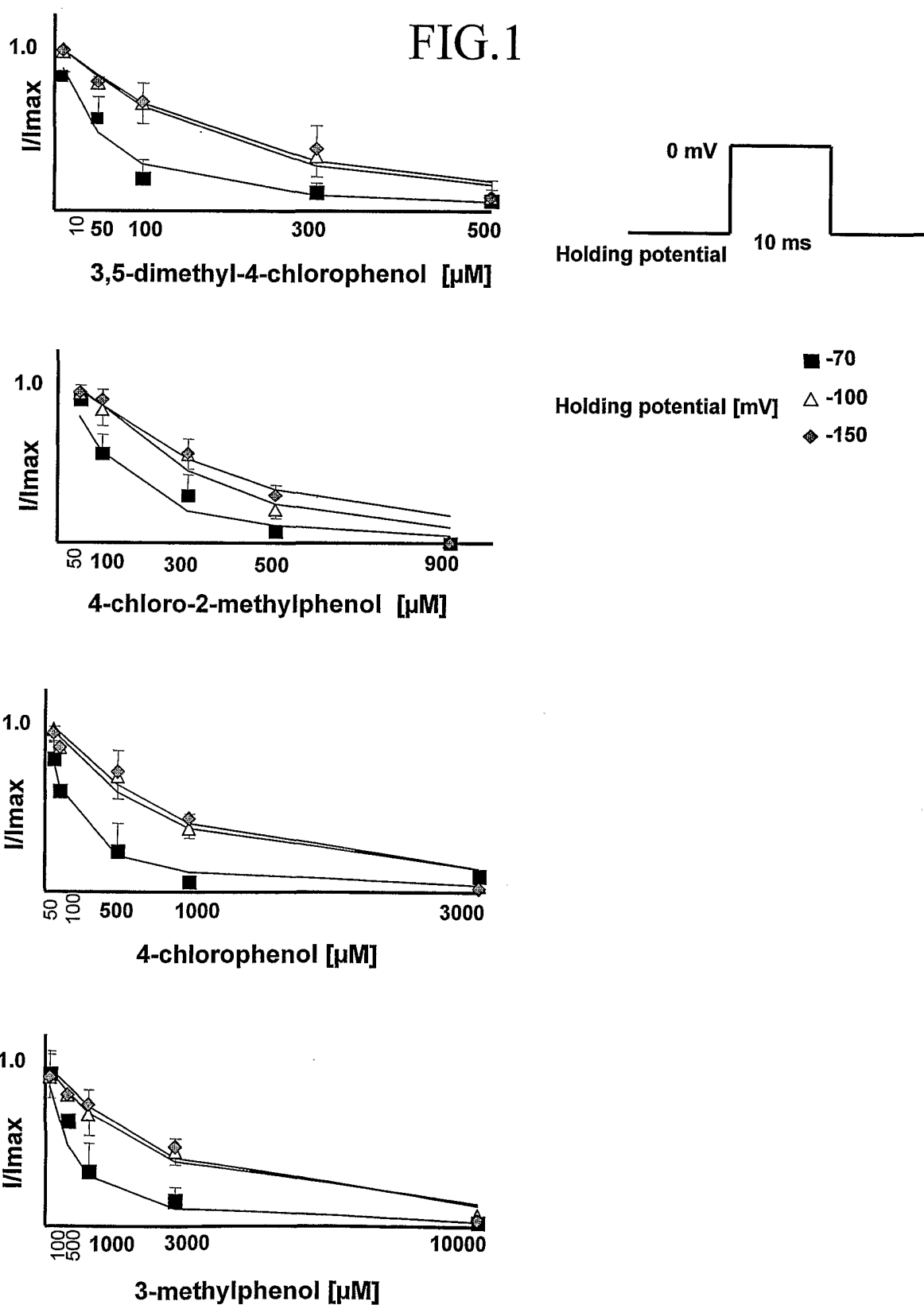
- R^5 represents a hydrogen atom, a halogen atom or a $C_1 - C_7$ alkyl group; and
- R^6 represents a hydrogen atom, a $C_1 - C_7$ alkyl group or a C_2 or C_3 alkenyl group,

5 under the proviso that R^2 and R^4 can only both represent a hydrogen atom if both R^1 and R^5 represent a $C_1 - C_7$ alkyl group and R^3 represents a halogen atom

for the blockade of sodium channels and/or for influencing the kinetics of sodium channels.

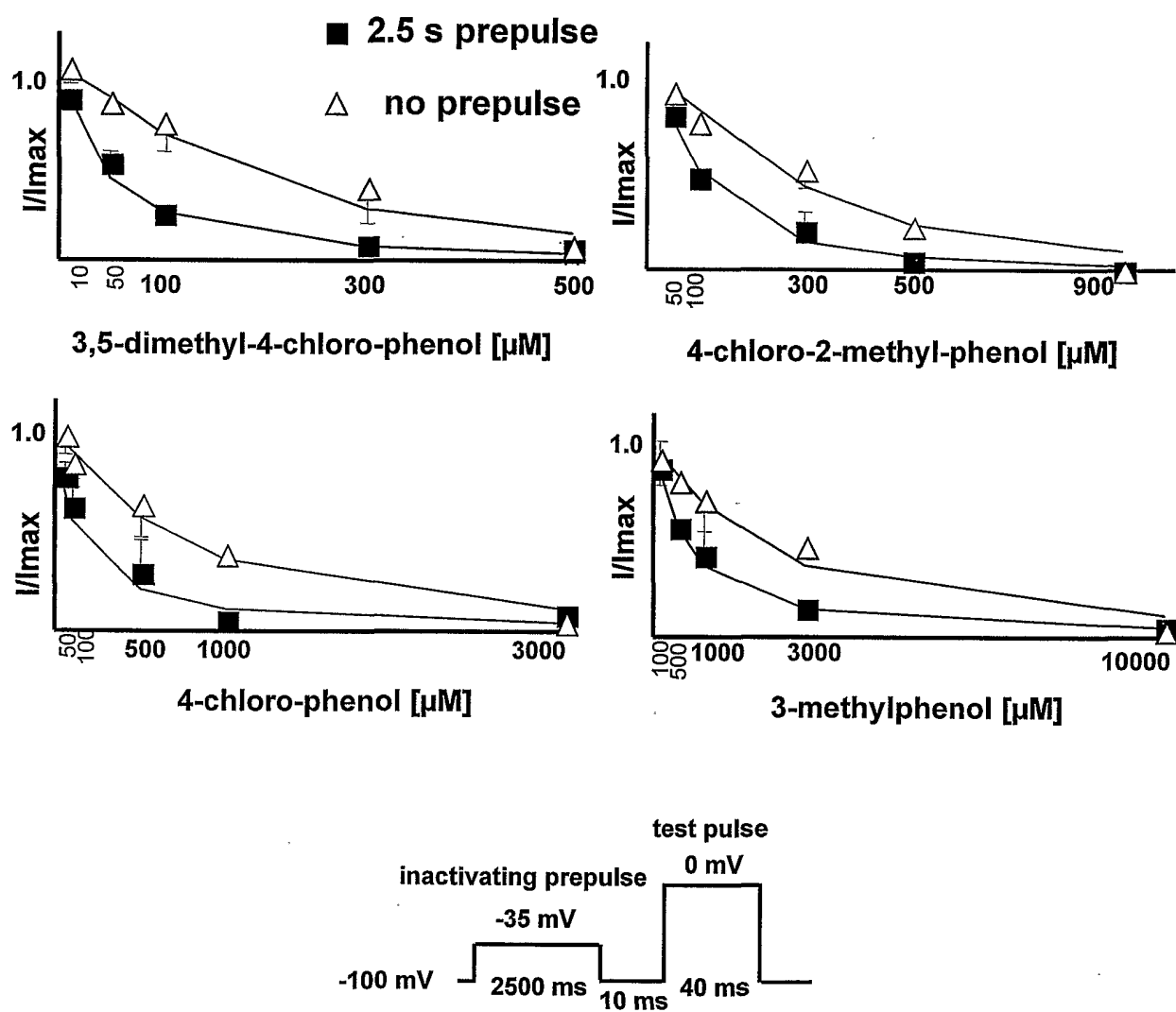
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FIG. 2



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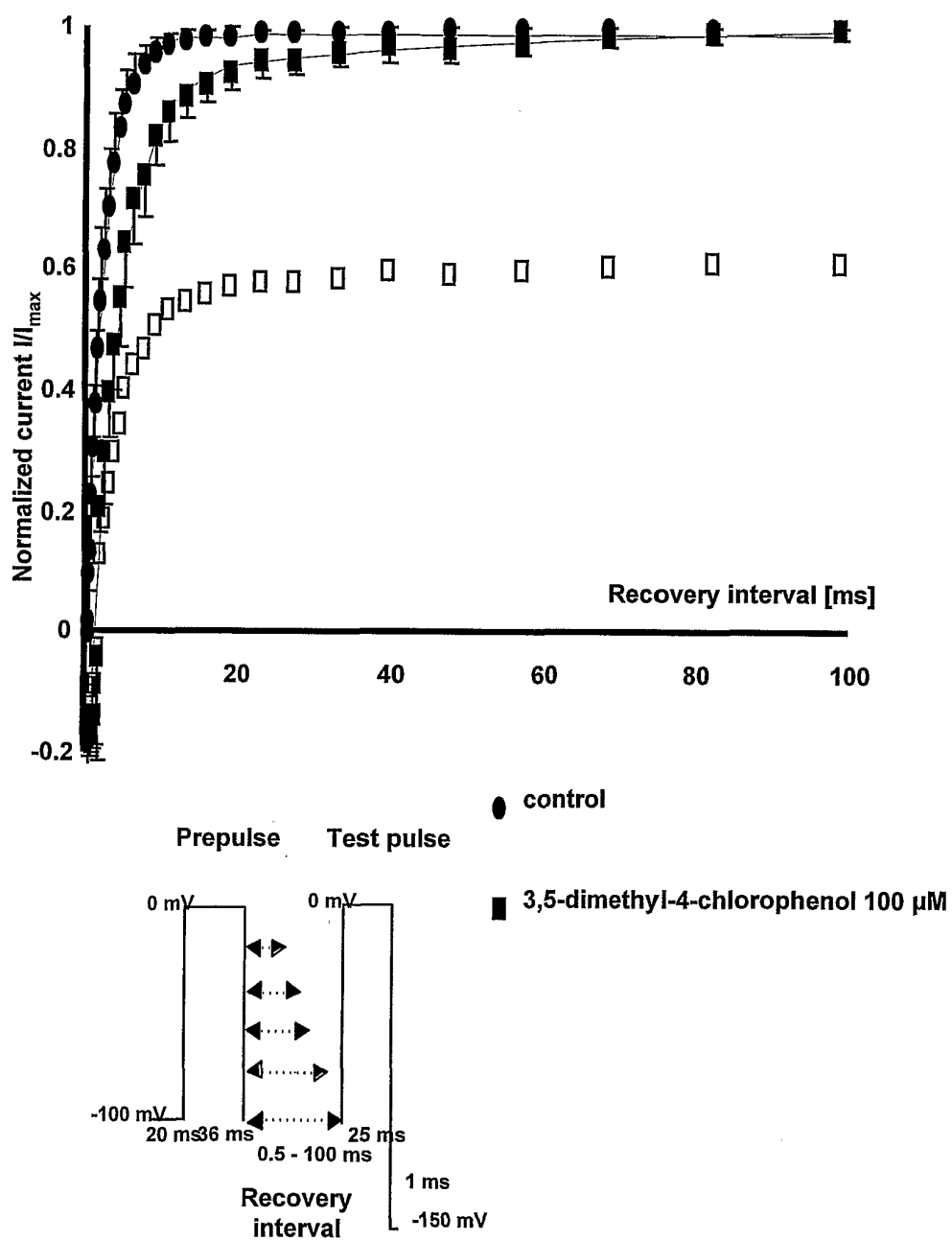


FIG. 3