PCT WORLD INTELLECTUAL PROPE
International Bi

INTERNATIONAL APPLICATION PUBLISHED UNDER

WO 9607411A1

(51) International Patent Classification 6 :
A61K 31/445, C07D 211/06

A1

(11) In

(43) International Publication Date: 14 March 1996 (14.03.96)

(21) International Application Number: PCT/US95/11348

(22) International Filing Date: 5 September 1995 (05.09.95)

(30) Priority Data:
301,946 7 September 1994 (07.09.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 301,946 (CON)
Filed on 7 September 1994 (07.09.94)

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

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: SLAUGHTER, Donald, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

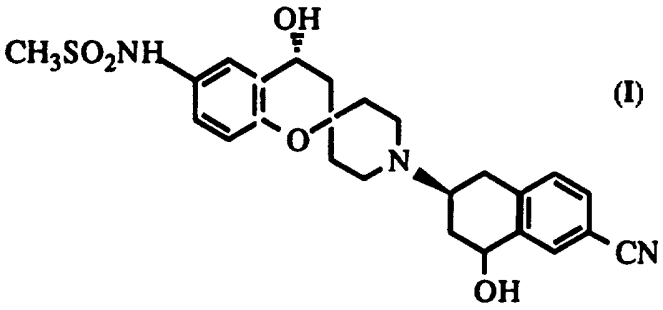
(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL ANTIARRHYTHMIC AGENTS

(57) Abstract

This invention is concerned with novel compounds represented by structural formulae (I) or a pharmaceutically acceptable salt, hydrate or crystal form thereof, which are useful as antiarrhythmic agents.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

TITLE OF THE INVENTION

NOVEL ANTIARRHYTHMIC AGENTS

BACKGROUND OF THE INVENTION

Arrhythmias often occur as complications to cardiac diseases such as myocardial infarction and heart failure. In a serious case, arrhythmias give rise to a ventricular fibrillation and can cause sudden death.

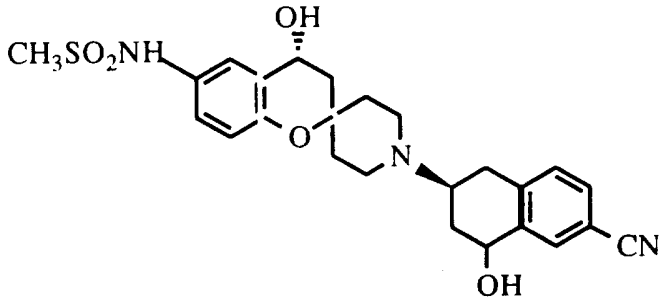
Though various antiarrythmic agents are now available on the market, those, having both satisfactory effects and high safety, have not been obtained. For example, antiarrythmic agents of Class I according to the classification of Vaughan-Williams which cause a selective inhibition of the maximum velocity of the upstroke of the action potential (Vmax) are inadequate for preventing ventricular fibrillation. In addition, they have problems regarding safety, namely, they cause a depression of the myocardial contractility and have a tendency to induce arrythmias due to an inhibition of the impulse conduction. Beta-adrenoceptor blockers and calcium antagonists which belong to Class II and IV respectively, have a defect that their effects are either limited to a certain type of arrhythmia or are contraindicated because of their cardiac depressant properties in certain patients with cardiovascular disease. Their safety, however, is higher than that of the antiarrhythmic agents of Class I.

Antiarrythmic agents of Class III are drugs which cause a selective prolongation of the duration of the action potential without a significant depression of the Vmax. Drugs in this class are limited. Examples such as sotalol and amiodarone have been shown to possess Class III properties. Sotalol also possesses Class II effects which may cause cardiac depression and be contraindicated in certain susceptible patients. Also, amiodarone is severely limited by side effects. Drugs of this class are expected to be effective in preventing ventricular fibrillations. Pure Class III agents, by definition, are not considered to cause myocardial depression or an induction of arrhythmias due

to the inhibition of the action potential conduction as seen with Class I antiarrhythmic agents.

SUMMARY OF THE INVENTION

This invention is concerned with novel compounds represented by structural formula I



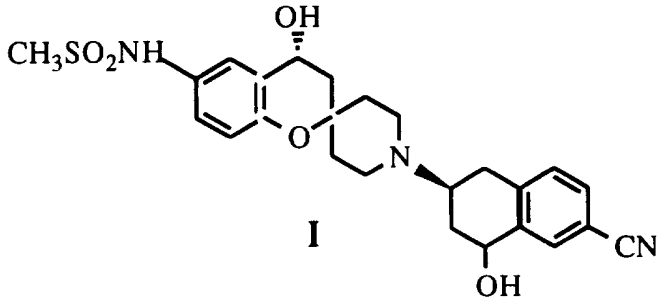
I

or a pharmaceutically acceptable salt , hydrate or crystal form thereof, which are useful as antiarrhythmic agents. The invention is also concerned with pharmaceutical formulations comprising one of the novel compounds as an active ingredient.

The invention is also concerned with a method of treating arrhythmia by the administration of one of the novel compounds or formulation thereof to a patient in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention have structural formula I



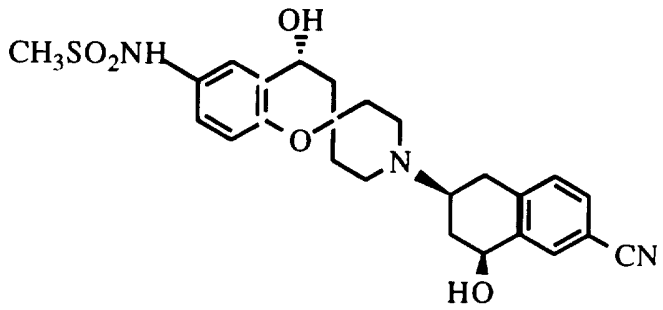
I

or a pharmaceutically acceptable salt, hydrate or crystal form thereof.

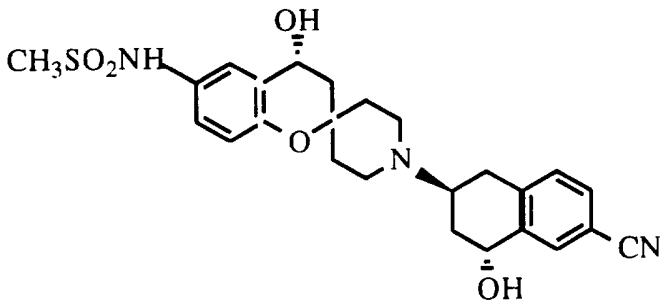
The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quarternary ammonium salts of the compounds of Formulae I formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glucolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

Preferred compound of this invention are the individual diesteriomeric forms of (+)-N-[1'-(6-cyano-4-hydroxy-1,2,3,4-tetrahydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide

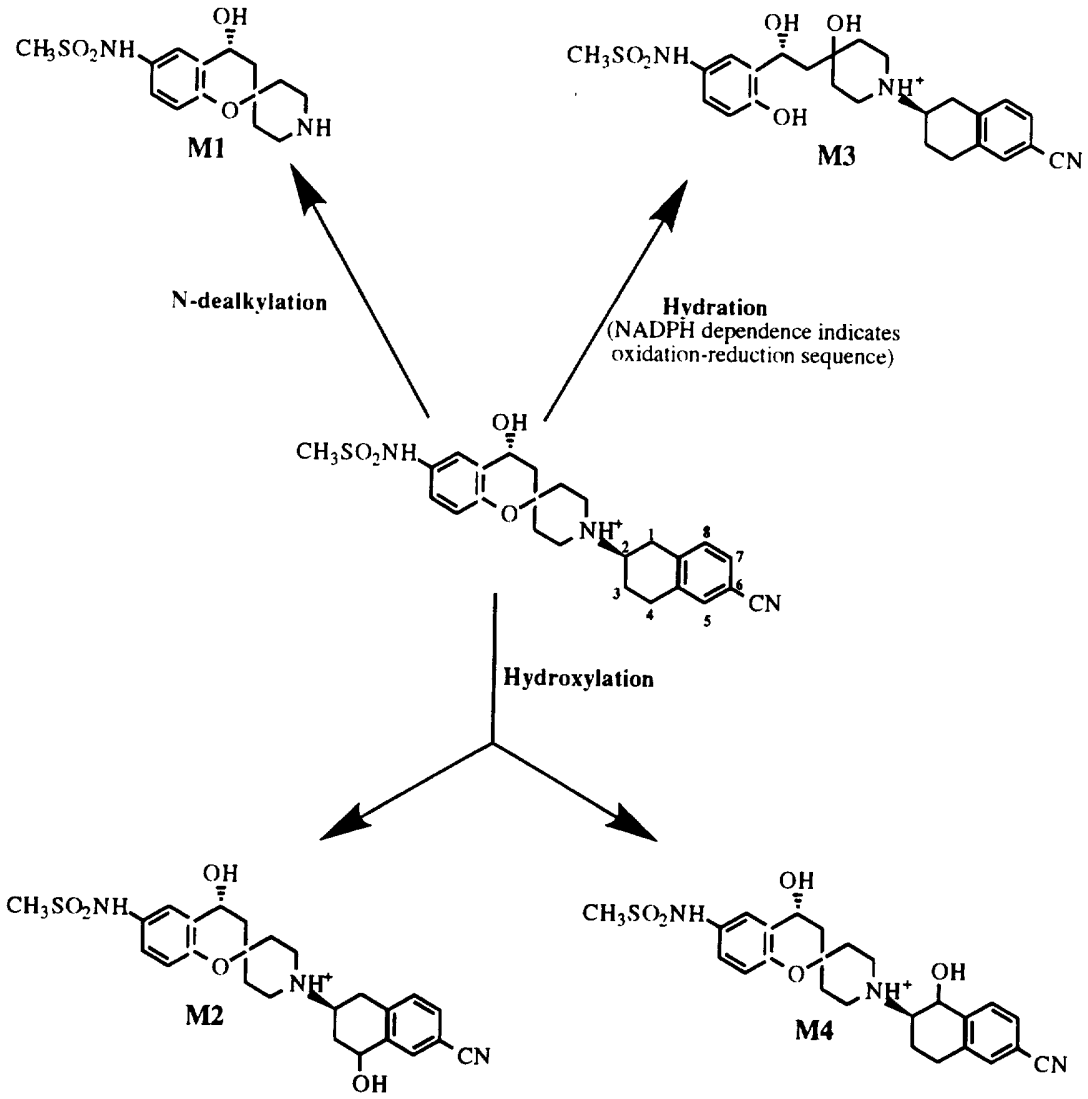


and



The preparation of compounds of this invention is represented schematically in Scheme I.

SCHEME I



The synthesis outlined in Scheme I are further defined as follows: (+)-N-[1'-(6-cyano-1,2,3,4 tetrahydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-'-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide is treated with liver microsomes. Studies have shown that mouse, rat, dog or human liver microsomes all produce the desired metabolite. The metabolite profile, reported above includes among the compounds produced, (+/-)-(4RS, 1",2"-trans)-1'-[1'-(6-cyano-4-hydroxy-1,2,3-trihydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxy-

spiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide (also referred to as M2 in Scheme I and throughout portions of this specification) which may be separated by HPLC.

The most abundant metabolites in rat and mouse are M3 and M1, respectively, while M2, M3 and M4 are created at about the same level when microsomes from dog and human are used. A comparison of rat microsomal and biliary metabolite data suggests that glutathione mediated events represent the major metabolism of (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro [2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide. Purified M4 and to a lesser extent, (+/-)-(4RS, 1",2"-trans)-[1'-(6-cyano-4-hydroxy-1,2,3-trihydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxy-spiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide can undergo microsomal metabolism to hydroxylated analogs of M3. Additionally, when rats are fed (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide, the metabolite (+)-N-[1'-(6-cyano-4-hydroxy-1,2,3-trihydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide is clearly more abundant than the M1, M3 or M4 metabolites found in the bile.

The novel compounds of the present invention will exhibit the pharmacological properties required for antiarrhythmic agents of Class III, namely the prolongation of the myocardial action potential in vitro, without a significant depression of the Vmax, and the prolongation of QTc-interval in anesthetized dogs.

These compounds are effective in treating and preventing all types of arrhythmias including ventricular and atrial (supraventricular) arrhythmias. The compounds of the present invention are especially useful to control reentrant arrhythmias and prevent sudden death due to the ventricular fibrillation. These compounds are also effective in treating and preventing impaired cardiac pump functions.

In the novel method of this invention of treating arrhythmia, one of the compounds or pharmaceutically acceptable salt thereof, is

administered in an amount ranging from about 0.0001 to about 20 mg per kg or body weight per day, preferably from about 0.001 to about 1.0 mg per kg of body weight per day and more preferably from about 0.001 to about .1 mg per kg of body weight per day, in a single dose or in 2 to 4 divided doses.

These compounds can be administered as the sole active ingredient or in combination with other antiarrhythmic agents or other cardiovascular agents. For example, these compounds may be administered along with class I, II or IV antiarrhythmic agents.

These compounds, or pharmaceutically acceptable salts thereof, in the described dosages, are administered orally, intraperitoneally, subcutaneously, intramuscularly, transdermally, sublingually or intravenously. They are preferably administered intravenously or orally, for example in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum, or the like prepared by art recognized procedures. The amount of active compound in such therapeutically useful compositions or preparations is such that a suitable dosage will be obtained.

The activity of the compounds described herein as anti-arrhythmic agents is measured by their ability to block the IKs and IKr as determined by the following test protocol.

Outward potassium currents are measured in single guinea pig ventricular myocytes using a whole-cell voltage clamp technique described in detail elsewhere (Sanguinetti and Jurkiewicz, 1990, two components of cardiac delayed actifier K^+ current: differential sensitivity to block by Class III antiarrhythmic agents. J. Gen Physiol. 96: 195-215). Myocytes are isolated by enzymatic (collagenase and protease) digestion of Langandorf perfused hearts. Single cells are then voltage clamped using 1 mm square-bore pipettes filled with 0.5 M Kgluconate, 25 mM KCl, 5 mM K(2)ATP. Cells are bathed in a solution containing, in mN: 132 NaCl, 4KCl, 1.2 MgCl[2], 10 HEPES, 10, glucose: pH 7.2, temp. 35°C.

Each cell is maintained at a holding potential of -50 mV. Test depolarizations are applied as voltage ramps from -85 to -50 mV,

and as steps to -10 mV (0.5 s) and +50 mV (1.0 s). I[KI] is measured as peak outward current during the voltage ramp. I[Kr] is measured as tail currents upon repolarization from -10 mV to -50 mV. I[KS] is measured as time-dependent current during the pulse to +50 mV. Currents are measured during control, then after exposure to drug at two different concentrations.

Employing this test the compounds described herein have an IC_{50} of less then 1000 nM as an IKr blocker.

EXAMPLE I

(+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide

The title material can be synthesized using the procedure described in United States Patent 5,206,240, which issued to Baldwin et al. on April 27, 1993, which is hereby incorporated by reference. This synthesis is reproduced herein for convenience.

(+)-N-[1'-(6-Cyano-1,2,3,4-tetrahydro-2-napthalenyl)-3,4-dihydro-4-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]yl]methanesulfonamide hydrochloride was prepared as follows, (+)-N-[1'-(6-Cyano-1,2,3,4-tetrahydro-2-napthalenyl)-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]yl]methanesulfonamide (581 mg, 1.25 mmol) was dissolved with warming in methylene chloride (20 ml) and cooled to -20°C. A solution of (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2,c][1,3,2]oxazaborole-borane complex (400 mg, 1.38 mmol) in methylene chloride (4 ml) was added dropwise and the mixture was stirred under argon at -20 to -15°C for 1 h, then at ambient temperature for 30 min. Methanol (20 ml) was added, followed after 10 min. by HCl-H_2O (1M, 10 ml). The mixture was stirred for 1 h., diluted with aqueous sodium hydrogen carbonate (Saturated, 20 ml) and extracted with methylene chloride (3 x 20 ml). The combined organic fractions were dried (Na_2SO_4) and evaporated under

reduced pressure to give a white foam (981 mg). This was dissolved in methylene chloride (25 ml) and cooled in ice. Four portions of acetic anhydride (132 ml, 142 mg, 1.4 mmol) were added at hourly intervals. After 4 h. at 0 °C, the mixture was stirred at ambient temperature for a further 20 h. Methanol (10 ml) and aqueous sodium hydrogen carbonate (Saturated, 10 ml) were added and the mixture was stirred vigorously for 1 h. Aqueous sodium hydrogen carbonate (Saturated, 20 ml) was added and the mixture was extracted with methylene chloride (3 x 20 ml). The combined organic fractions were dried (Na_2SO_4) and evaporated under reduced pressure to give a white foam (1.05 g). The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3-H2O (94:6:0.6 increasing to 90:10:1), re-chromatographing impure fractions. Pure fractions were evaporated under reduced pressure, redissolved in CH_2Cl_2 (20 ml), filtered through anhydrous Na_2SO_4 and evaporated under reduced pressure to give a white foam (369 mg, 63%). The residue was dissolved in ethanol (4 ml) and HCl-EtOH (6M, 0.5 ml) was added dropwise with stirring. The mixture was stirred at ambient temperature for 1 h., then refrigerated over night. The solid was collected by filtration under argon, then dried in vacuo at ambient temperature for 48 h. and at 35 °C for 24 h to give the hydrochloride as a white solid (321 mg), m.p. 211-213°C, $[\alpha]_d$ +30.5° (c = 0.102, MeOH).

HPLC analysis [Ultron ES OVM column; 0.3% n-propanol/ammonium foramate-water (12 g/l)] showed this to be the faster eluting diastereoisomer.

Elementary analysis

Calc'd for $C_{25}H_{30}ClN_3O_4S$:

C 59.57; H 6.00; N 8.34%.

Found: C 59.45; H 5.76; N 8.40%.

The compounds of Table LVIII were prepared according to the method described in Example 556 by reducing

the appropriate ketone with (R)- or (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2,c][1,3,2]oxazaborole-borane complex as indicated.

The preparation of N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl)-3,4-dihydro-4-oxospiro-[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide, its monohydrochloride and separation into its enantiomers was accomplished as follows:

Step 1: Preparation of 6-Bromo-2-tetralone

A single neck 3 liter round bottom flask under an Ar atmosphere was charged with 4-bromo-phenyl acetic acid (250.0 g, 1.15 m), methylene chloride (1.5 L), and dimethylformamide (0.5 mL). This magnetically stirred solution was cooled to 0°C and treated dropwise with oxalyl chloride (156 mL, 1.74 m). The reaction was allowed to reach room temperature and stirred 16 hrs. The reaction was concentrated on a rotary evaporator to approximately 1 L of volume. A separate dry 5 liter 3 neck round bottom flask under Ar, fitted with gas inlet tube, overhead stirrer, and digital thermometer was charged with methylene chloride (1.5 L) and $AlCl_3$ (312.0 g, 2.34 m). This suspension was cooled to 0°C and stirred while the above solution of acid chloride was added to it slowly via cannula. When the addition was complete, ethylene gas was introduced for 1-2 hrs to the vigorously stirred suspension while maintaining the internal temperature at 15°C. Upon completion by HPLC, the reaction was warmed to room temperature and stirred for 0.5 hrs. The mixture was recooled to 0°C and cautiously quenched slowly with water (1.5L). The layers were separated, and the aqueous one washed with 500 mL of methylene chloride. The organic portion was washed with 2N aqueous HCl (2 X 800 mL), brine (400 mL), and saturated aqueous $NaHCO_3$ (2 X 800 mL). Each aqueous extract was washed with the same 500 mL methylene chloride extract from above. The methylene chloride extracts were combined, dried (Na_2SO_4), filtered, and concentrated to

approximately 500 mL of volume. This was then added to 5.0 L of hexane warmed to 50°C. The methylene chloride was distilled off and the hot solution decanted from an insoluble brown tar. The solution was allowed to cool to 25°C and placed in the freezer overnight. The precipitate was collected and washed with hexane (200 mL), and dried in vacuo to give 229.0 g of the compound as a pale yellow solid (88%).

Step 2: Preparation of (+)-1,4-dioxa-8-(6'-bromo-1',2',3',4'-tetrahydronaphth-2'- yl)-8-azaspiro[4.5]decane

A 3 L round bottom flask fitted with an argon inlet, and Deak-Stark apparatus was charged with a solution of 6-bromo-2-tetralone (100.0 g, 445 mmol) in toluene (2.0 L). Para-toluenesulfonic acid (0.50 g) and 1,4-dioxa-8-azaspiro[4,5]-decane (81.5 g, 489 mmol) were added and the stirred mixture heated to reflux and the water removed (4.5 hrs). The mixture was cooled, and concentrated to an oil in vacuo. The oil was dissolved in anhydrous tetrahydrofuran (1.5 L) and cooled to 0°C under argon. Dry HCl gas was introduced (at below 5°C) and a solid precipitate formed. Sodium cyanoborohydride (36.3 g, 578 mmol) was added in four portions. The reaction was allowed to warm gradually to room temperature and stirred 16 hrs. This was quenched with 1N aqueous sodium hydroxide (500 mL) and stirred for 0.5 hr (pH=13.5). The mixture was concentrated on a rotary evaporator to remove THF, and diluted with 1N NaOH (1.1 L) and diethyl ether (1.5 L). This mixture was stirred 15 min and the layers were separated and the aqueous layer was washed with diethyl ether (2 X 200 mL). The organic layers were combined, washed with water (2 X 500 mL) and saturated aqueous NaCl (2 X 250 mL) and then with 1N HCl (1 X 1.0 L, 2 X 500 mL). The acid extracts were combined, stirred with methylene chloride (1.0L), and basified with 40% aq. NaOH (pH=10). The layers were separated, and the aqueous extracted with methylene chloride (500 mL). The

methylene chloride extracts were combined, dried (Na_2SO_4), and concentrated to an oil. The oil was flushed with toluene (2 X 400 mL) and dried in vacuo to give the title compound as a solid on standing (128.8 g, 87%) which was greater than 98% pure by HPLC and used in the next step without purification. Note: The amount of of excess HCl gas present (pH=3-4, THF suspension on wet pH paper) critically determines the yield free amine. Additional HCl may be added during the introduction of the cyano borohydride. In runs in which the pH was not adjusted properly the yield was reduced to 50%; the balance being a borane complex which was isolated from the ether layers. This borane complex could be quantitatively converted to the free amino by heating in 40% aq NaOH/ethylene glycol (1:1) at 100°C.

Step 3(a): Preparation of Phenyl Cyanate

The title compound was prepared by a modification of the procedure described in Organic Syntheses, 61, 35 (1983). A 3-necked, 2 L R.B. flask, equipped with a 500 ml pressure equalized dropping funnel, a mechanical stirrer and a thermometer, was charged with water and coled in an ice-salt bath. Cyanogen bromide (189.1 g, 1.78 mol) was added and the mixture was stirred for 5 min. Phenol (160.0 g., 1.7 mol) in carbon tetrachloride (535 ml) was added in one portion. The mixture was stirred vigorously while triethylamine (236.9 ml, 172.0 g, 1.7 mol) was added dropwise at a rate such that the reaction temperature did not exceed 5°C (total addition time = 45 min.). The mixture was stirred for a further 15 min. then transferred to a 2 L separatory funnel. The organic layer was separated and the aqueous layer was extracted with carbon tetrachloride (2 X 90 ml). The combined organic layers were washed with water (3 X 90 ml) then dried by stirring with phosphorus pentoxide (10 g) for 15 min. The mixture was filtered and the solvent was evaporated under reduced pressure

(water aspirator) at 20°C to give a yellow oil. Polyphosphate ester (Y. Kanaoka, et al., Chem. Pharm. Bull., 13, 1065-1072 (1965)) (0.2 ml) was added and the mixture was distilled under reduced pressure through a 15 cm vigreux column to give phenyl cyanate (165.8 g, 82%) as a colorless oil, b.p. 79-82°C (16 mmHg)[1]. The product was stored under nitrogen at -10°C (freezes).
1H NMR (300 MHz, $CDCl_3$) d: 7.49-7.30 (5H, m).

Step 3 (b): Preparation of(+)-1,4-Dioxa-8-(6'- cyano-1',2',3',4'-tetrahydronapath-2yl)-8-azaspiro[4.5]decane

(+)-1,4-Dioxa-8-(6'-bromo-1',2',3',4-tetrahydronaphth-2-yl)-8-azaspiro[4.5]decane (70.4 g, 0.2 mol) under nitrogen in a 1 L R.B. flask was dissolved in anhydrous THF (600 ml, distilled from Na/benzo-phenone) and cooled to -75°C. Phenyl cyanate (26.06 ml, 28.5 g, 0.24 mol) dissolved in anhydrous THF (400 ml) under nitrogen in a 2 L R.B. flask equipped with a digital_thermometer was cooled to -75°C. n-Butyl lithium (1.6M in hexane, 137.5 mL, 0.22 mmol) was added over 5 min. to the bromide solution. Further n-butyl lithium (12.5 mL, 0.02 mmol) was added to the phenyl cyanate solution. After 5 min., the lithiated bromide solution was added over 5 min., via cannual, to the phenyl cyanate solution (reaction temperature rises to -35°C). The mixture was stirred and cooled to -75°C for 30 min. then the cooling bath was removed and HCl-H_2O (1M, 200 mL) was added with vigorous stirring. The mixture was warmed to room temperature, diluted with HCl-H_2O (1M, 1800 mL) and washed with ether (2 X 1000 mL.). Methylene chloride (1000 mL) was added and the mixture was stirred and cooled in ice during the addition of aqueous sodium hydroxide 10 M, 180 mL). The layers were separated, and the aqueous layer was extracted with_methylene chloride (500 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was

evaporated under reduced pressure to give crude (+) 1,4-dioxa-8-(6'-cyano-1',2',3',4'-tetrahydro-naphth-2'yl)-8-azaspiro[4.5] decane as a tan solid (56.2g). Crude (+)1,4-dioxa-8-(6'-cyano-1',2',3',4'-tetrahydronaphth-2'yl)-8-azaspiro-[4.5]-decane in three batches (56.4 g, 56.2 g, 27.7 g; total 140.3g) were separately dissolved in refluxing methyl-cyclo-hexane (1000 mL each) and combined by decanting into a 5 L, 4-necked flask equipped with a mechanical stirrer, thermometer, reflux condenser and a stopper. The mixture was heated to reflux (clear solution formed), then allowed to cool with stirring to room temperature, then to 5°C. The mixture was stored at -15°C for 15 hr. The solid was collected by filtration, washed with cold methylcyclo-hexane (2 X 150 ml) and dried in vacuo at room temperature to give the spirodecane as a pale yellow solid (121.3 g), .m.p. 136-138°C. Purity = 99.3%

Step 4: Resolution of 1,4-dioxa-8-(6'- cyano-1'2',3'4'-tetrahydronaphth-2'-yl)-8-azaspiro[4.5]decane

A 12 L round bottom flask fitted with a reflux condenser, digital thermometer, and overhead stirrer was charged with absolute ethanol (10.6 L) and 1,4-dioxa-8-(6'-cyano-1',2',3',4'-tetrahy-dronaphth-2'yl)-8-azaspiro[4.5]decane 120.0 g, 402 mmol). The mixture was warmed to 65°C to give a clear solution, and 97% di-p-toluoyl-L-tartaric acid monohydrate (167.7 g, 402 mmol) was added. The resulting clear solution was seeded with this salt and allowed to cool to room temperature with stirring overnight. The precipitate was collected by filtration and washed with absolute ethanol (600 mL). The solid was dried in vacuo to a solid and converted to free base in a stirred mixture of ethyl acetate (2.0 L) and saturated aqueous $NaHCO_3$(3.0L). The layers were separated, and the aqueous one washed with ethyl acetate (2 X 500 mL). The organic layers were combined, washed with brine (2 X 200 mL), dried (Na_2SO_4), and concentrated to 69.4 g of a solid (59% yield).

The solid free base (69.4 g, 233 mmol) was dissolved in absolute ethanol (4.25 L) at 60°C and 97% di-p-toluoyl-D-tartaric acid (92.64 g, 233 mmol) was added. The resulting clear solution was seeded with a sample of this salt and allowed to cool to room temperature overnight. The precipitate which formed was collected, washed with absolute ethanol (800 mL), and dried in vacuo at 40°C to give 122.5 g (44.5%). This + D salt was completely dissolved in absolute ethanol (8.0L) at reflux and concentrated to approximately 7.0 L of volume by distillation at 1 atmosphere. The solution was seeded and cooled to room temperature overnight. The solid was collected, washed with absolute ethanol (800 mL) dried in vacuo to give 100.9 g $[a]_D$=+104.7° (c= 1.0 pyridine)) (36.7%). This salt was dissolved in hot absolute ethanol (8.3L), concentrated at 1 atmosphere to 3.1 L of total volume, seeded and cooled to room temperature overnight. This solid was collected, washed with absolute ethanol (900 mL) and dried in vacuo to give 89.7 g $[a]_D$=105.4° (c=1.0 pyridine)) (32.6%). A further crystallization from 7.0 L hot ethanol concentrated to 2.9 L volume gave 74.3 g ($[a]_D$=+105.4° (c=1.0 pyridine)) (32.6%). A further recrystallization from 7.0 L hot ethanol concentrated to 2.9 L volume gave 74.3 g $[a]_D$=104.9° (c=1.0 pyridine)) (27% yield). The free base was obtained by treating a stirred mixture of saturated aq. $NaHCO_3$ (250 mL) and methylene chloride (250 mL) with 1,4-dioxa-8-(6'-cyano 1',2',3',4'-tetrahydronaphth-2'yl)-8-azaspiro]4.5]decane di-p-toluoyl-D-tartaric acid salt (10.0 g, 33.5 mmol). After 15 min the layers were separated, the aqueous washed with methylene chloride (100 mL), and the combined organics washed with saturated aq. $NaHCO_3$ (100 mL), dried Na_2SO_4) and concentrated to give 4.30 g (99%) of a solid. A sample of free base was analyzed by chiral shift reagent proton NMR to be 99.8% pure (+) enantiomer.

Step 5: Preparation of N-(6'-Cyano-1',2',3',4'-

tetrahydronaphth-2'-yl)piperidin-4-one

A solution of (+)-1,4-dioxa-8-(6'-cyano-1',2',3',4'-tetrahydronaphth-2'yl)-8-azaspiro[4.5]-decane (10.0 g, 33.5 mmol) was dissolved in 1N HC1 (100 mL). This was stirred and heated to 100°C under an argon atmosphere for 1.5 hrs. the solution was cooled in an ice bath to 25°C and methylene chloride added (200 mL). The mixture was stirred and basified to pH=9.0 with saturated aqueous sodium carbonate. The organic layer was separated and the aqueous extracted with methylene chloride(2X 50 mL). The combined organic extract was dried (Na_2SO_4), and concentrated to a foam to give 7.5g(99%) of N-(6'-cyano-1',2',3',4'-tetrahydronaphth-2'-yl)-piperdin-4-one (98% by HPLC).

Step 6: Methanesulfonamide, N-[1'-(6-cyano-1, 2,3,4-tetrahydro-2-naphthalenyl)-3,4- dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, monohydrochloride

A solution of 2-hydroxy-5-methanesulfonamido-acetophenone (26.98 g, 117.7 mmol), and pyrrolidine (9.8 mL, 117.7 mmol) in methanol (480 mL) was stirred at 25 °C for 10 min. (+)-N-(6'-Cyano-1',2'3',4'- tetrahydronaphth-2'-yl)-piperidin-4-one (20.0 g, 78.4 mmol) was added in one portion and the mixture stirred for 24 hrs at 25 °C. The reaction was concentrated to an oil in vacuo and flash chromato-graphed (silica gel, ethyl acetate) to afford the product in appropriate fractions which were combined and concentrated to a foam. This was crystallized from isopropyl alcohol (525 mL) to give a solid which was collected by filtration, washed with IPA (50 mL) and dried in vacuo (30.8 g). This was dissolved in ethyl acetate (1.5L) and treated with 1.3N HCl in IPA (55 mL). The precipitate was stirred 20 hrs, filtered and dried in vacuo (60°C, 0.1 torr) to give 32.3 g (84%) of (+) Methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2-naphthalenyl) -3,4-dihydro-4-

oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, $[\alpha]_D$ = +40.7 (c=0.17, MeOH).

EXAMPLE II

(+)-N-[1'-(6-cyano-4-hydroxy-1,2,3,4-tetrahydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide

The title compound was generated as a metabolite of (+)-N-[1'-(6-cyano-1,2,3,4-trihydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide, both radio labeled (^3H labeled) and unlabled, by incubation in a broth which comprises non-induced rat liver microsomes. The broth was composed of 2 mg microsomal protein/mL; in the presence of a solution containing 10 mM glucose-6-phosphate; 1 mM NADP; 2 I.U. glucose-6-phosphate dehydrogenase/mL used as the NADPH generating system; 0.1 M potassium phosphate buffer, pH 7.4; and 3 mM $MgCl_2$. The incubation conditions were 1 hr incubation at 37°C. Protein was precipitated from incubations by the addition of 0.3 volumes of 15% acetic acid.

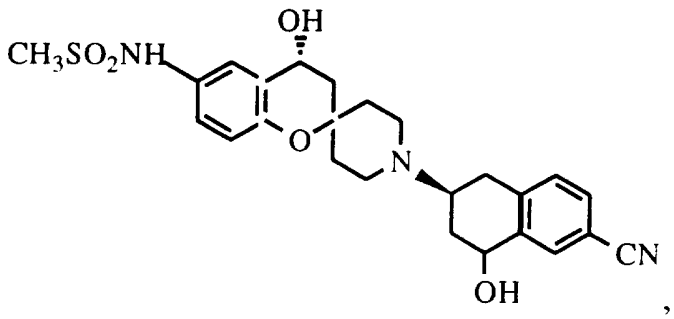
The title compound was purified first by passage through aromatic sulfonic acid solid phase extraction column which had been pre-washed with 75% acetonitrile and water, followed by 0.1% trifluroracetic acid and water. After sample loading, the column was washed sequentially with 0.5M NaCl and water. The starting material and metabolites were eluted with 75% aqueous acetonitrile containing 0.1% trifluroacetic acid. The collected fractions were dried under vacuum, redissolved in 0.1% trifluroracetic acid and purified by HPLC on a Thomson Spherisorb)DS-2 column, using a linear gradient mobile phase of acetonitrile/ 0.1% aqueous trifluroracetic acid as follows: 0-35% acetonitrile in 8 minutes, 35-45% acetonitrile in 18 minutes, stepped to 90% acetonitrile and held 5 minutes. Eluate was monitored by radioflow and or UV detection. Metabolite peaks were hand collected and dried under vacuum. Following repurification using the same

chromatographic conditions, the compound was dried under vacuum and stored at -20°C.

For mass spectral analysis, sample aliquot was dissolved in 50% acetonitrile containing 0.1% aqueous trifluroracetic acid and passed into a Sciex API III mass spectrometer without chromatography through a heated nebulier ionization inlet. The apparent molecular ion (m/z 484) was elucidated by Q1 scanning with mass spectra derived from m/z 484 daughter ion scans.

WHAT IS CLAIMED IS:

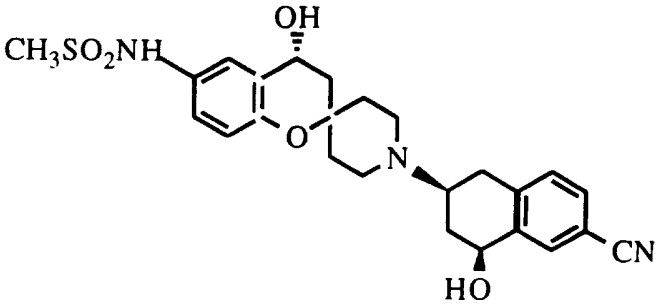
1. A compound of formula I



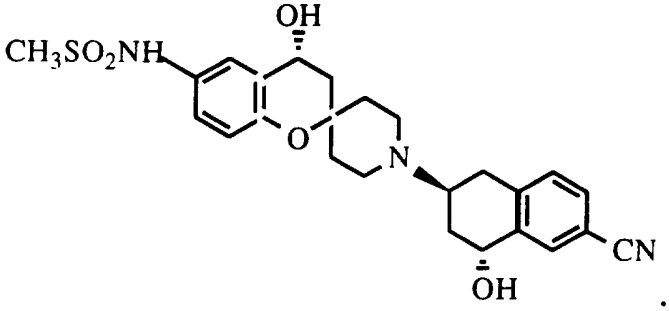
I

(+)-N-[1'-(6-cyano-4-hydroxy-1,2,3,4-tetrahydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide, or a pharmaceutically acceptable salt , hydrate or crystal form thereof.

2. A compound of formula 1 selected from the group consisting of



and



3. A pharmaceutical formulation comprising a carrier and a therapeutically effective amount of a compound of Claim 1.

4. The pharmaceutical formulation of Claim 3, comprising, in addition, a pharmaceutically effective amount of one or more of a Class I, Class II or Class IV antiarrhythmic agent.

5. A method of preparing the compound of Claim 1 comprising the step of incubating (+)-N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthaleneyl-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]methanesulfonamide with liver microsomes.

6. The method of Claim 5 wherein the liver microsomes are selected from the liver microsomes of mouse, rat, dog or human.

7. A method of treating arrhythmia or impaired cardiac pump function in a patient in need of such treatment which comprises administering to such patient a therapeutically effective amount of the compound of Claim 1.

8. The method of Claim 7, comprising, the administration of one or more of a class I, class II or Class IV antiarrhythmic agent in addition to a compound of Claim I.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/11348

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/445; CO7D 211/06
US CL :514/278; 546/17
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/278; 546/17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS online, APS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,206,240 (BALDWIN ET AL) 27 April 1993, column 18, lines 11-13; column 177, Table XXXIII; column 189, Table XLVIII.	1-4, 7-8
X, P	US, A, 5,413,915 (CASE et al) 09 May 1995, column 6, lines 46-62, column 9, lines 6 to 58.	5, 6
A	US, A, 4,173,654 (SCHERER) 06 November 1979, column 2, lines 22-32.	5, 6
X	BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, Volume 35, issued April 1993, T. Ebner et al., "The Metabolism of Aprindine in Relation to the Sparteine/debrisoquine Polymorphism, pages 426-430, see page 426.	5, 6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 DECEMBER 1995	03 JAN 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Evelyn Huang Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★