

**ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ  
ΕΥΡΕΣΙΤΕΧΝΙΑΣ  
THE PATENT OFFICE OF CYPRUS**

**ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ CY1370  
PUBLICATION NUMBER**

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ  
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ  
ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ  
UK PATENT OFFICE  
PUBLICATION NUMBER GB2084570

Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1<sup>η</sup> Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

**The document provided hereafter was filed at "The Patent Office"  
in England under the law CAP.266 before the 1<sup>st</sup> of April 1998.  
It was published afterwards by the UK patent office only in English.**

# (12) UK Patent Application (19) GB (11) 2 084 570 A

(21) Application No 8127079  
(22) Date of filing 8 Sep 1981  
(30) Priority data  
(31) 188184  
(32) 18 Sep 1980  
(33) United States of America (US)

(43) Application published  
15 Apr 1982

(51) INT CL<sup>3</sup>  
C07D 211/26 A61K  
31/445 // B01D 15/08

(52) Domestic classification  
C2C 1532 215 220 22Y  
246 250 251 25Y 280 281  
29X 29Y 30Y 342 34Y  
364 365 36Y 603 623 624  
62X 662 802 80Y AA KP  
B1H 260 281 300 350  
555 665

(56) Documents cited  
GB 1346261  
US 3931195A  
J. Med. Chem. 16  
1015—1020 (1973)  
J. Pharmacology and  
Experimental  
Therapeutics 200  
147—154 (1977)

(58) Field of search  
C2C

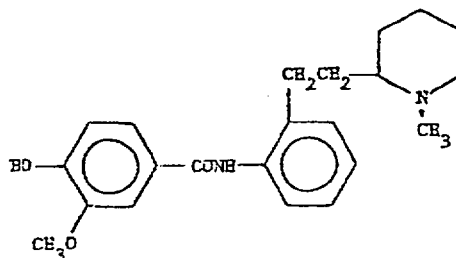
(71) Applicants  
Bristol Myers Company,  
345 Park Avenue, New  
York 10022, United  
States of America

(72) Inventors  
Robert F. Mayol,  
Richard E. Gammans

(74) Agent  
Langner Parry,  
52/54 High Holborn,  
London WC1V 6RR

(54) Benzanilide derivative

(57) 4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny)ethyl]-phenyl]benzamide of the formula:—



is an *antiarrhythmic agent* having relatively low toxicity and increased duration of action.

The quantitative determination of the above compound encainide and O-demethyl encainide in a biological fluid involves extraction from the fluid and separation by high pressure liquid chromatography on a silicic acid column using ethanol:water methanesulphonic acid 500:30:0.1 as mobile phase.

GB 2 084 570 A

## SPECIFICATION

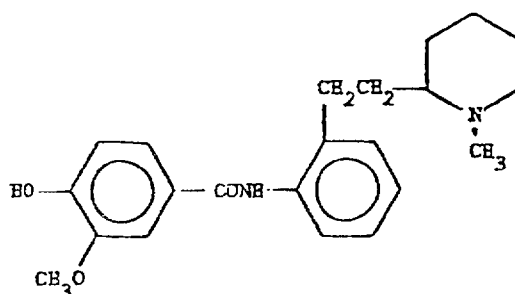
## Benzanilide derivative

## Field of the Invention

4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny)ethyl]phenyl]benzamide is a heterocyclic carbon compound of the piperidine series having an additional ring and having nitrogen attached indirectly to the piperidine ring by non-ionic bonding (Class 546, Subclass 229).

## Summary of the Invention

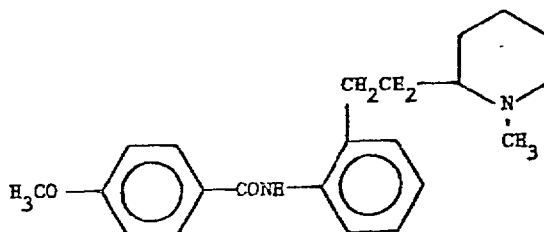
This invention is concerned with the 4-hydroxy-3-methoxy-benzanilide analog of encainide which has the following structural formula.



This substance is a metabolite in man of encainide and an improved antiarrhythmic agent with regard to its extended duration of action relative to encainide.

## Description of the Prior Art

Encainide hydrochloride is an antiarrhythmic compound which is also referred to in the literature as MJ 9067 (USAN And The USP Dictionary of Drug Names 1980, page 122, United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, Library of Congress Catalog Card No. 72—88571). Encainide has the following structural formula.



The following publications describe the chemical synthesis of encainide, a number of analogs thereof, and the antiarrhythmic properties of these compounds in animals.

Dykstra, et al., J. Med. Chem., 16, 1015—1020 (1973).

Dykstra and Minielli, U.S. Patent No. 3,931,195 patented January 6, 1976.

Byrne, et al., J. Pharmacology and Experimental Therapeutics, 200, 147—154 (1977).

Assay methods for encainide and its metabolites are disclosed in the following references.

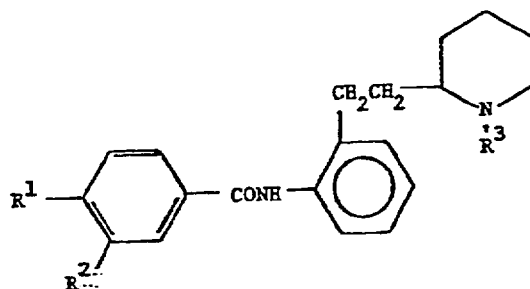
Mayol and Gammans, Therap. Drug Monitoring, 1, 507—524 (1979).

Mayol, U.S. Patent Application Serial No. 155,338 filed June 2, 1980.

## Detailed Description of the Invention

The structure of encainide and a number of analogs thereof which are described in the foregoing Dykstra, et al. publication and patent are shown in the following table in comparison to the structure of the compound of the present invention. The compound numbers used in the table are the same as the example numbers employed in the Dykstra, et al. patent. Compound No. A is the compound of the present invention.

## Structures



Compound No.	R <sup>1</sup>	R <sup>2</sup>	R <sub>3</sub>
89 (O-demethylencaainide, or ODE)	HO—	H—	CH <sub>3</sub> —
107 (encaainide, or E)	CH <sub>3</sub> O—	H—	CH <sub>3</sub> —
108	H—	CH <sub>3</sub> O—	CH <sub>3</sub> —
109	CH <sub>3</sub> O—	CH <sub>3</sub> O—	CH <sub>3</sub> —
139 (N-demethylencaainide, or NDE)	CH <sub>3</sub> O—	H—	H—
A (3-methoxy-O-demethylencaainide, or 3-methoxy ODE)	HO—	CH <sub>3</sub> O—	CH <sub>3</sub> —

- Compound Nos. 89 and 139 have been identified by Mayol and Gammans (*op. cit.*) as metabolites of encaainide (Compound No. 107) in which publication the former is referred to as ODE and the latter as NDE. The former (ODE) has been identified as a principal metabolite which is sometimes present in plasma in amounts several times the concentration of encaainide following treatment with the latter. As a result of an improvement of the high pressure liquid chromatography assay method described in the Mayol and Gammans publication, which improvement constitutes part of the present invention, it has been found that Compound A is also a principal metabolite of encaainide in man following oral administration of the latter, and that it is present in concentrations in the blood plasma substantially greater than that Compound No. 89 two or more hours following the administration of a 50 mg. dose of encaainide hydrochloride orally. The HPLC assay method described in the Mayol and Gammans publication has now been found to have been incapable of distinguishing between Compound Nos. 89 and Compound A. It is thought that Compound A is produced in the body from Compound No. 89 by a biological transformation process.
- The comparative purposes the biological activity of the compounds whose structures are shown in the above table are presented in the following table in which comparative antiarrhythmic activity is given as determined by the laboratory screening test referred to in the Dykstra, et al. paper above. This is referred to in the table as Test I. Test II is an approximation of the oral toxicity of these compounds in mice, and Tests III and IV refer to the human metabolism results observed following oral administration of an antiarrhythmic oral dose of 75 mg/kg of encaainide hydrochloride to patients.

## Biological Activity

- I. Antiarrhythmic activity for ventricular arrhythmia in mice produced by chloroform inhalation; ED<sub>50</sub> expressed as mg/kg body weight, intraperitoneal administration, J. W. Lawson, J. Pharmacol. Expt. Ther. 160 22 (1968).
- II. ALD<sub>50</sub>/ATD<sub>50</sub> mouse treated orally; ALD<sub>50</sub> is the approximate lethal dose for half the animals; ATD<sub>50</sub> is the approximate lowest dose where signs of physiologic or neurologic deficit appear in half the animals, expressed as mg/kg body weight.
- III. Time following oral dosing of humans with 75 mg. of encaainide hydrochloride for clearance (plasma concentration <20 ng./ml.) from blood plasma; hours.
- IV. Approximate half life in human blood plasma following oral dosing with encaainide hydrochloride; hours.

Compound No.	I	II	III	IV
89	1.7—2.8*	25—50/5—10	>16	4—6
107 (encainide)	5.3—15*	50—100/5—10	6	2.5—3
108	10	100/10—25	**	**
109	10	100/25	**	**
139	28	147/15.7	†	†
A	9.5	250/31.3—62.5	>16	4—6

\* Range of various determinations.

\*\* Compounds have not been administered to man nor observed as metabolites of encainide in man or animals.

† Occurrence in plasma following oral administration of encainide to man has been rare, and value has not been determinable.

The foregoing results reflect approximately equivalent antiarrhythmic activity for each of these substances except for Compound No. 89 which is somewhat more potent but also somewhat more toxic in mice. Compound A differs from and enjoys the advantages over each of Compound Nos. 89 and 107 of reduced toxicity and of a more prolonged presence in the blood.

#### Description of Specific Embodiments

##### EXAMPLE 1

##### Assay Procedure

A. *Extraction of Biological Fluid.* — To 1 ml of plasma or urine in a screw-capped tube there is added 0.2 ml of 0.5 M. *Tris*-HCl buffer (2-amino-2-hydroxymethyl-1,3-propanediol), pH 8.5, and 10 ml of *n*-butyl chloride containing 5% by volume of isopropanol. The sample is then shaken on an oscillating mixer followed by centrifugation to separate the phases. A 9 ml aliquot of the organic layer is removed and evaporated to dryness under a stream of nitrogen and the residue is redissolved in 100 ml of ethanol. A 50 ml aliquot of this solution is injected onto the column for high pressure liquid chromatography.

B. *High Pressure Liquid Chromatography (HPLC) Conditions.* — A normal phase silicic acid column having dimensions 3.9 mm by 30 cm in length equipped with a variable wavelength UV detector set at 254 nm is used. The mobile phase employed consists of 500 ml of ethanol, 30 ml of water, and 0.1 ml of methanesulfonic acid at a flow rate of 1 ml per minute. A series of standards containing 0, 25, 100 and 500 ng/ml of each compound to be assayed was prepared using pooled human plasma. These standards were treated as described above. Quantification of the detector response was achieved by digital integration or measurement of peak heights. The standard curve for each component was constructed by linear regression of the detector response versus concentration from the plasma standards. The concentration of compound in the sample was then interpolated from these curves.

C. *Results.* — The relative order of elution of encainide and its O-demethyl and 3-methoxy O-demethyl metabolites from the column and their retention times is as follows: Compound No. 89, 8.3 minutes; Compound A, 9.7 minutes; Compound No. 107, 11.4 minutes. The last endogenous plasma component eluted from the column has a retention time of 3.6 minutes and the baseline is very stable in the region where the metabolites elute. Thus, no interference from endogenous plasma components occurs. Due to differences in extraction efficiencies, specific molar absorptivities, and retention times for the individual components, the sensitivity of the assay for each of these components is as follows: Compound No. 80, 10 ng/ml; Compound A, 20 ng/ml; Compound No. 107, 15 ng/ml.

##### EXAMPLE 2

Synthesis of 4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny) ethyl]phenyl]benzamide (Compound A, 3-Methoxy (ODE))

(I) *Salt With Mucic Acid.* — A solution of 7.3 g (0.033 mole) of 2-(2-aminophenethyl)-1-methylpiperidine in 65 ml of pyridine is treated at ice bath temperature with 9.3 g (0.034 mole) of 4-benzyloxy-3-methoxybenzoylchloride in 30 ml of tetrahydrofuran. The reaction mixture is stirred for 1 hr at room temperature and then volatile materials removed by concentration *in vacuo* to yield an oil. The latter is dissolved in chloroform, washed with dilute aqueous sodium hydroxide water, brine, and then dried over magnesium sulfate. The dried solution is treated with activated carbon and concentrated *in vacuo* to an oil weighing 10.23 g which is shown to contain only one component by thin layer

chromatography. This material is then dissolved in 100 ml of absolute ethanol and catalytically reduced in a low pressure hydrogenation apparatus over 2 g of 10% palladium on carbon catalyst at 60 psig until one molecular proportion of hydrogen has been absorbed. The catalyst is removed by filtration and the solvent distilled *in vacuo* to yield the product in free base form as a foam-like solid. Conversion to the mucate salt is achieved by triturating the residue with hot hexane to yield 5.3 g of a granular solid. The latter is dissolved in warm absolute ethanol and treated with 0.45 molecular equivalents of mucic acid to yield the hemimucate salt which is recrystallized from a mixture of absolute ethanol and ethyl acetate, m.p. 110—165°.

*Anal:* C, 62.58; H, 6.89; N, 5.75; H<sub>2</sub>O, 2.18. The composition corresponds to the monohydrate of the hemimucate salt.

IR: 760, 1290, 1450, 1505, 1605, 1635, 1770, 2940 and 3400 cm<sup>-1</sup>.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 1.55 (10, m), 2.35 (3, s), 2.65 (3, m), 3.84 (3, s), 4.12 (2, m), 6.88 (1, d, 8.0 Hz), 7.25 (5, m), 7.54 (1, m), 9.90 (1, bs).

(2) *Free Base*. — The foam-like solid free base above is dissolved in acetone and decanted from insoluble material. The filtrate is diluted with hexane and concentrated by boiling off the solvent until a light tan colored solid is formed which is collected. Purification of a portion of the tan colored solid by column chromatography on alumina using chloroform containing 5% by volume of methanol for development yielded material m.p. 135—136° which was indistinguishable from the original by analysis.

*Anal:* C, 71.78; H, 7.68; N, 7.48.

IR: 760, 1215, 1290, 1450, 1505, 1585, 1640 and 2940 cm<sup>-1</sup>.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.20 (6, m), 1.90 (4, m), 2.22 (3, s), 2.70 (3, m), 3.90 (3, s), 6.00 (1, bs), 6.89 (1, d, 8.2 Hz), 7.22 (4, m), 7.52 (1, d, 1.8 Hz), 8.08 (1, m), 1.48 (1, bs).

The <sup>1</sup>H NMR spectrum of this material was identical with that of the metabolite isolated from plasma and urine samples by the HPLC assay procedure described above.

The compound of the present invention and its pharmaceutically acceptable salts may be used for therapeutic purposes and particularly for the treatment of cardiac arrhythmias in much the same way and in similar dosage amounts as encainide. Dosage at longer intervals than is necessary with encainide is suitable as is indicated by the relative plasma half-lives of the two compounds. Dosage may be by the oral or parenteral routes including intramuscular, intraperitoneal, subcutaneous and intravenous, the latter being the preferred of the parenteral routes. For normal therapeutic purposes in the prevention or treatment of arrhythmias, oral administration is preferred. Generally, treatment is commenced with a unit dose smaller than anticipated for optimum control of the arrhythmia. Thereafter, the dosage is increased by small increments until the optimal effect is reached. Smaller dosage units are generally required for intravenous treatment than are required for oral treatment. The dosage amount administered is preferably at an effective level which is without harmful or deleterious side effect on the patient.

The compounds are ordinarily administered in combination with a pharmaceutical carrier. The nature and proportion of carrier is determined by the chosen route of administration and by the normal practices of pharmaceutical science. They may be administered orally in the form of tablets, coated tablets, or capsules containing excipients such as starch, lactose, sugar, various pharmaceutical clays, gelatin, stearic acid or salts thereof, vegetable fats or oils, gums, glycols and other known excipients. For parenteral administration sterile solutions are preferred.

The normal dosage range is from 0.01 to 20 mg/kg of body weight of the mammal under treatment. Fixed dosage units containing from 1 to 500 mg and preferably from 5 to 100 mg of the active ingredient are preferred.

### EXAMPLE 3

#### *Pharmaceutical Compositions*

The compounds of the present invention are formulated with pharmacologically acceptable carriers to provide compositions useful in the present invention. Typical of the pharmaceutical compositions are the following:

## A. Tablets

	Material	Amount	
	Compound A (Example 2), as the base	50.0 g	
	Magnesium stearate	1.3 g	
5	Corn starch	12.4 g	5
	Corn starch pregelatinized	1.3 g	
	Lactose	185.0 g	

The foregoing materials are blended in a twin-shell blender and then graulated and pressed into tablets weighing 250 mg. each. Each tablet contains 50 milligrams of active ingredient. The tablet may be scored in quarters so that a dose of 12.5 mg. of active ingredient may be conveniently obtained. 10

## B. Capsules

	Material	Amount	
	Compound A (Example 2), as the base	125.0 mg	
	Lactose	146.0 mg	
15	Magnesium stearate	4.0 mg	15

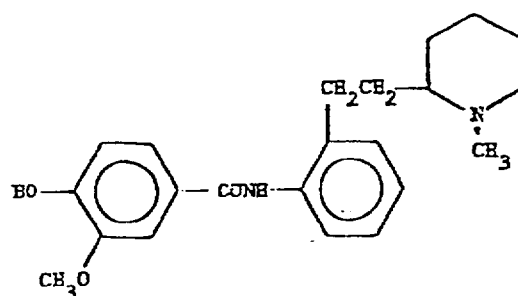
The foregoing materials are blended in a twin-shell blender and then filled into No. 1 hard gelatin capsules. Each capsule contains 125 mg of active ingredient.

## C. Solution for Intravenous Administration

A sterile solution suitable for intravenous injection is prepared by dissolving 10.0 g of Compound A (Example 2) as the base in a minimal amount of 0.5 N hydrochloric acid. This solution is adjusted to pH 4.3 with 0.1 N sodium hydroxide and diluted to 1000 ml total volume with physiologic saline solution. The solution is sterilized by passage through a bacteriological filter and aseptically filled into 10 ml sterile ampoules. Each milliliter of solution contains 10 mg of the active ingredient. 20

## CLAIMS

- 25 1. 4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny)ethyl]phenyl]benzamide and the pharmaceutically acceptable acid addition salts thereof. 25
2. 4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny)ethyl]phenyl]benzamide.
3. 4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny)ethyl]phenyl]benzamide hemimucate.
- 30 4. A process for eliciting an antiarrhythmic effect in a mammal in need thereof which comprises systemic administration to said mammal of a non-toxic effective antiarrhythmic dose of from 0.01 to 20 30 mg/kg of body weight of said mammal of a compound claimed in Claim 1.
5. A pharmaceutical composition in dosage unit form suitable for systemic administration to a mammal comprising a pharmaceutical carrier and from 1 mg to 500 mg of a compound claimed in Claim 1.
- 35 6. In a process for the quantitative determination of encainide and the O-demethyl and 3-methoxy-O-demethyl metabolites thereof in a biological fluid involving extraction thereof from said fluid and separation thereof by high pressure liquid chromatography on a silicic acid column using an organic solvent as mobil phase, the improvement wherein said mobil phase is the mixture ethanol:water:methanesulfonic acid 500:30:0.1. 35
- 40 7. A process for preparing 4-hydroxyl-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny)ethyl]phenyl]- benzamide having the formula 40



or a hemimucate salt thereof, which comprises contacting 2-(2-aminophenethyl-1-methylpiperidine with 4-benzyloxy-3-methoxybenzoylchloride, then catalytically debenzylating the resulting product and, if desired, forming the hemimucate salt thereof.

- 5 8. A pharmaceutical compound as defined in Claim 1 for use in a method of treatment of the human or animal body. 5
9. A compound according to Claim 8 for use in eliciting an antiarrhythmic effect.
10. A compound according to Claim 8 substantially as hereinbefore specifically described in each of the examples for the use hereinbefore specifically described.
- 10 11. A compound as described in Claim 1 substantially as hereinbefore specifically described in each of the examples. 10
12. A pharmaceutical composition containing a compound according to Claim 1 substantially as hereinbefore specifically described in examples.
13. A process for making a compound as defined in Claim 1, substantially as hereinbefore specifically described in the examples. 15
14. A compound when produced by a process as claimed in either of Claims 7 and 13.
15. A process according to Claim 6, substantially as hereinbefore described.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1982. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.