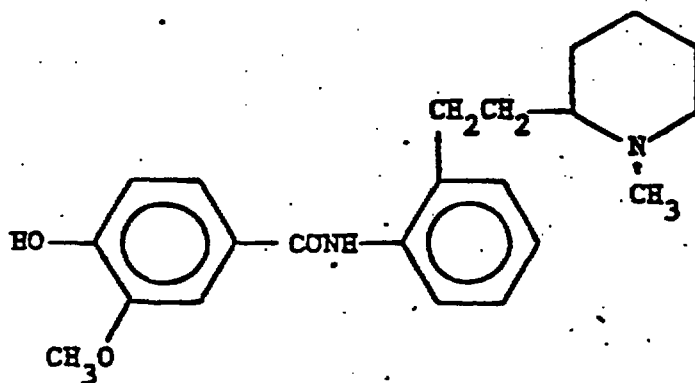


BENZANILIDE DERIVATIVEField of the Invention

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

Summary of the Invention

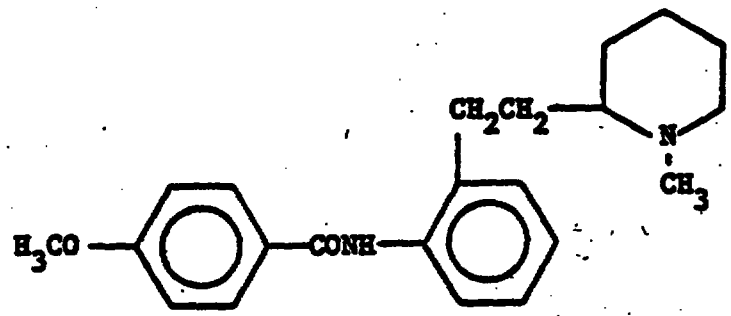
This invention is concerned with the 4-hydroxy-3-methoxy-benzanilide analog of encainide which has the following structural formula.



15 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.

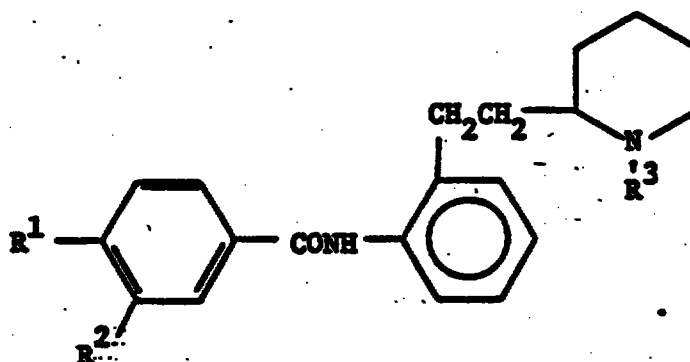
Mayol and Gammons, Therap. Drug Monitoring, 1, 507-524 (1979).

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

Detailed Description of the Invention

The structures 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



10	Compound No.	<u>R¹</u>	<u>R²</u>	<u>R³</u>
	89 (O-demethylencaïnide, or ODE)	HO-	H-	CH ₃ -
	107 (encainide, or E)	CH ₃ O-	H-	CH ₃ -
	108	H-	CH ₃ O-	CH ₃ -
	109	CH ₃ O-	CH ₃ O-	CH ₃ -
15	139 (N-demethylencaïnide, or NDE)	CH ₃ O-	H-	H-
	A (3-methoxy-O-demethyl-encainide, or 3-methoxy ODE)	HO-	CH ₃ O-	CH ₃ -

Compound Nos. 89 and 139 have been identified by Mayol and Gammons (op. cit.) as metabolites of encainide (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

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which is sometimes present in plasma in amounts several times the concentration of encainide 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 is described and claimed in Application No. 8402839 a divisional of the present application, it has been found that Compound A is also a principal metabolite of encainide 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 encainide 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 biological transformation process.

For 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 encainide hydrochloride to patients.

Biological Activity

7. Antiarrhythmic activity for ventricular arrhythmia in mice produced by chloroform inhalation; ED₅₀ expressed as mg/kg body weight, intraperitoneal administration, J. W. Lawson, J. Pharmacol. Expt. Ther. 160, 22 (1968).

II. ALD₅₀/ATD₅₀ mouse treated orally; ALD₅₀ is the approximate lethal dose for half the animals; ATD₅₀ is the approximate lowest dose where signs of physiologic or neurologic deficit appear in half the animals, expressed as mg/kg body weight.

10 III. Time following oral dosing of humans with 75 mg. of encainide hydrochloride for clearance (plasma concentration <20 ng./ml.) from blood plasma; hours.

IV. Approximate half life in human blood plasma following oral dosing with encainide hydrochloride; hours.

15	<u>Compound No.</u>	<u>I</u>	<u>II</u>	<u>III</u>	<u>IV</u>
	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	**	**
20	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.

25 †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
5 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 centrifuga-
tion to separate the phases. A 9 ml aliquot of the organic layer
10 is removed and evaporated to dryness under a stream of nitrogen and
the residue is redissolved in 100 μ l of ethanol. A 50 μ l aliquot
of this solution is injected onto the column for high pressure liquid
chromatography.

B. High Pressure Liquid Chromatography (HPLC) Conditions.-
15 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
20 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
25 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.

5 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
10 the individual components, the sensitivity of the assay for each of these components is as follows: Compound No. 89, 10 ng/ml; Compound A, 20 ng/ml; Compound No. 107, 15 ng/ml.

EXAMPLE 2

15 Synthesis of 4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidinyl)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
20 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
25 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

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carbon catalyst at 60 psig until one molecular proportion of hydrogen has been absorbed. The catalyst is removed by filtration and the vent distilled in vacuo to yield the product in free base form as foam-like solid. Conversion to the mucate salt is achieved by

5 tritulating 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°.

10 Anal: C, 62.58; H, 6.89; N, 5.75; H₂O, 2.18. The composition corresponds to the monohydrate of the hemimucate salt.

IR: 760, 1290, 1450, 1505, 1605, 1635, 1770, 2940, and 3400 cm⁻¹.

HNMR (DMSO-d₆): 1.55 (10, m), 2.35 (3, s), 2.65 (3, m),
15 3.84 (3, s), 4.12 (2, m), 6.88 (1, d, 8.0 Hz), 7.25 (5, m), 7.54 (1, m), 9.80 (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
20 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.

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

IR: 760, 1215, 1290, 1450, 1505, 1585, 1640 and 2940 cm⁻¹.

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NMR (CDCl₃): 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 HNMR spectrum of this material was identical with that
5 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
10 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
15 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
20 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
25 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

(10)

in the form of tablets, coated tablets, or capsules containing excipients such as starch, lactose, sugar, various pharmaceuticals, gelatin, stearic acid or salts thereof, vegetable fats or 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.

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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:

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A. Tablets

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

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The foregoing materials are blended in a twin-shell blender and then granulated and pressed into tablets weighing 250 mg. each.

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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.

B. Capsules

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<u>Material</u>	<u>Amount</u>
Compound A (Example 2), as the base	125.0 mg
Lactose	146.0 mg
Magnesium stearate	4.0 mg

5 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

10 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
15 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.



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CLAIMS :

1. 4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny1)-ethyl] phenyl]benzamide and the pharmaceutically acceptable acid addition salts thereof.

5 2. 4-Hydroxy-3-methoxy-N-[2-[2-(1-methyl-2-piperidiny1)-ethyl]phenyl]benzamide.

3. 4-Hydroxy-3-methoxy-N-[2[2-(1-methyl-2-piperidiny1)-ethyl] phenyl]benzamide hemimucate.

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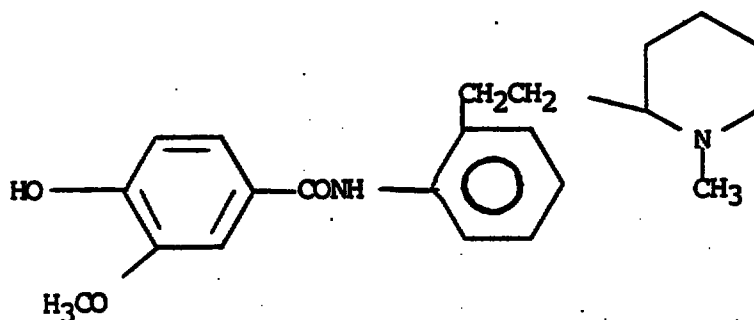
4. A pharmaceutical composition in dosage unit form suitable for systemic administration to a mammal comprising a pharmaceutical carrier and from 1 mg to 500 mg of a compound claimed in Claim 1.

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5. A process for preparing 4-hydroxyl-3-methoxy-N-[2-[2-1-methyl-2-piperidiny1)ethyl]phenyl] benzamide having the formula

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or a hemimucate salt thereof, which comprizes contacting 2-(2-amino-phenethyl-1-methylpiperidine with 4-benzyloxy-3-methoxy-benzoylchloride, then catalytically debenzylating the resulting product and, if desired, forming the hemimucate salt thereof.

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6. A pharmaceutical compound as defined in Claim 1 for use in a method of therapeutic treatment of the human or animal body.



7. A compound according to Claim 6 for use in eliciting an antiarrhythmic effect.

5 8. A compound according to Claim 6 substantially as hereinbefore specifically described in each of the Examples for the use hereinbefore specifically described.

10 9. A compound as described in Claim 1 substantially as hereinbefore specifically described in each of the Examples.

15 10. A pharmaceutical composition containing a compound according to Claim 1 substantially as hereinbefore specifically described in the Examples.

11. A process for making a compound as defined in Claim 1, substantially as hereinbefore specifically described in the Examples.

20 12. A compound when produced by a process as claimed in either of Claims 5 and 11.
