AUSTRALIA 610331

The Patents Act 1952

C O N V E N T I O N A P P L I C A T I O N F O R A P A T E N T

WE, DR. KARL THOMAE GmbH, a body corporate organised under the laws of the Federal Republic of Germany, of D-7950 Biberach am der Riss, Federal Republic of Germany, apply for the grant of a Patent for an invention entitled:

"AGENT FOR THE TREATMENT OF BRADYCARDIA AND BRADYARRYTHMIA"

which is described in the accompanying complete specification.

This application is a convention application and is based on the Application Numbered P 38 00 868.8 for a patent of similar protection made in Federal Republic of Germany on 14th January, 1988.

Our address for service is: CALLINANS, Patent and Trade Mark Attorneys, of 48-50 Bridge Road, Richmond 3121, Victoria, Australia.

D A T E D this 13th day of January, 1989.

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 26.2.91

DR. KARL THOMAE GmbH

By its Patent Attorneys:

CALLINANS

TO: The Commissioner of Patents.

COMMONWEALTH OF AUSTRALIA

The Patents Act 1952

DECLARATION IN SUPPORT

of the (Convention) Application made by: DR. KARL THOMAE GmbH
(hereinafter termed "the Applicant" for a patent for an invention entitled:

AGENT FOR THE TREATMENT OF BRADYCARDIA AND BRADYARRYTHMIA

I, Keith William Callinan of 137 Wallace Road, Wantirna South, Victoria 3152, Australia, do solemly and sincerely declare as follows:

I am authorised by the applicant to make this declaration on its behalf.

The basic application as defined by section 141 and 142 of the Act was made

in FEDERAL REPUBLIC OF GERMANY on 14th January, 1988
by DR. KARL THOMAE GmbH

The basic application referred to in this paragraph is the first application made in a Convention country in respect of the invention the subject of the application.

Wolfgang Eberlein, of Obere Au 6, D-7950, Biberach 1, FRG
Wolfhard Engel, of Mozartstrape 13, D-7950 Biberach 1, FRG
Gerhard Mihm, of Nickelschalde 511, D-7950 Biberach 1, FRG
Norbert Mayer of, Friedrich-Ebert-Strasse 66, D-7950 Biberach 1, FRG
Adriaan de Jonge of, de Boomgaard 19, NL-3971 LD Driebergen, Holland

are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:

The applicant would, if a patent were to be granted upon an application made by the said actual inventors, be entitled to have the patent assigned to it.

Declared at RICHMOND, VICTORIA this 17th day of January, 1989.

Signed.....

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(56) Prior Art Documents
EP 177078

(57) Claim

1. A method of treatment of the human or non- human body to combat bradycardia and/or bradyarrhythmia, said method comprising administering to a said body in need of such treatment a compound selected from (±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide (Compound I), (+)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide (Compound II) and the physiologically acceptable acid addition salts thereof.

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PATENTS ACT 1952

Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

This document contains the amendments made under Section 49 and is correct for printing

Application Number:
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Complete Specification—Lodged:
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Lapsed:
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Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: DR. KARL THOMAE GmbH

Address of Applicant: D-7950 Biberach an der Riss, Federal Republic of Germany.

Actual Inventor: WOLFGANG EBERLEIN, WOLFHARD ENGEL, GERHARD MIHM, NORBERT MAYER, ADRIAAN DE JONGE

Address for Service: CALLINANS [redacted], Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Complete Specification for the invention entitled:

"AGENT FOR THE TREATMENT OF BRADYCARDIA AND BRADYARRYTHMIA"

The following statement is a full description of this invention, including the best method of performing it known to me:—*

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* Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

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Agent for the treatment of bradycardia and bradyarrhythmia

The invention relates to an agent for the treatment of bradycardia and bradyarrhythmia.

EP-A-177078 describes compounds useful as muscarinic receptor antagonists, and having specific spasmolytic properties which render them particularly suitable for treating spasm in the gastrointestinal tract.

Surprisingly, it has now been found that compounds described in the above-mentioned patent application specifically

(±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]-amino]-1-oxobutyl]-N,N-dimethyl-4-piperidine-carboxamide (hereinafter "compound I") and

(+)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]-amino]-1-oxobutyl]-N,N-dimethyl-4-piperidine-carboxamide (hereinafter "Compound II")

and the physiologically acceptable acid addition salts thereof, additionally possess entirely different pharmacological properties which enable them to be used as vagal pacemakers for the treatment of bradycardia and bradyarrhythmia.

Thus viewed from one aspect the invention provides a method of treatment of the human or animal body to combat bradycardia and/or bradyarrhythmia, said method comprising administering to a said body in need of such treatment a compound selected from Compound I, Compound II and the physiologically acceptable acid addition salts thereof.

Viewed from another aspect the invention provides the use of a compound selected from Compound I, Compound II and the physiologically acceptable acid addition salts thereof for the manufacturer of a therapeutic agent for use in the treatment of the human or animal body to combat bradycardia and/or bradyarrhythmia.

In a further aspect, the invention provides the use of a compound selected from Compound I, Compound II and the physiologically acceptable acid addition salts thereof, for the treatment of bradycardia and/or bradyarrhythmia.

Compounds I and II have surprisingly been found to show marked selectivity for the muscarinic receptors in the heart. The substantial difference between the dosages resulting in the desired effects on heart rate and those resulting in other, undesirable, anticholinergic effects enables Compounds I and II and their salts to be used as vagal pacemakers for treating various types of bradycardia and bradyarrhythmia whilst avoiding unacceptable side effects.

A favourable relation between tachycardiac effects on the one hand and the undesirable effects of anticholinergic agents on pupil size and the secretion of tears, saliva and gastric acid on the other hand is of particular importance for substances for therapeutic use. The following tests show that the compounds useful according to the invention show surprisingly good relations between the desired tachycardiac effects and the undesirable anticholinergic effects.

A. Studies of binding to muscarinic receptors:

In vitro measurement of the IC_{50} value

Organs were donated by male Sprague-Dawley rats weighing 180-220 g. After removal of the heart and submandibular gland and cerebral cortex all other steps were carried out in ice cold Hepes HCl buffer (pH 7.4; 100 millimolar NaCl, 10 millimolar $MgCl_2$). The whole heart was cut up with scissors. All the organs were then homogenised in a Potter apparatus.

For the binding test the homogenised organs were diluted in the above-mentioned buffer as follows:

Whole heart	1: 400
Cerebral cortex	1: 3000
Submandibular gland	1: 400

The homogenised organs were incubated in an Eppendorf centrifuge tube at 30°C for 45 minutes, at a fixed concentration of radioligand and at a series of concentrations of the non-radioactive test substances. The radioligand used was 0.3 nanomolar ^{3}H-N-methylscopolamine (^{3}H-NMS). Incubation was ended by the addition of ice cold buffer followed by vacuum filtration. The filters were rinsed with cold buffer and their radioactivity was determined. The total radioactivity represents the sum of specific and non-specific binding of ^{3}H-NMS. The proportion of non-specific binding was defined as the radioactivity which was bound in the presence of 1 micromolar quinuclidinylbenzylate. Each measurement was taken four times. The IC_{50} values of the non-labelled test substances were determined graphically, and

represent the concentration of test substance at which the specific binding of ^{3}H-NMS to the muscarinic receptors in the various organs was inhibited by 50%. The results can be seen from Table 1.

B. Investigation of functional selectivity of the antimuscarinic effect

Substances with antimuscarinic properties inhibit the effects of agonists supplied exogenically or of endogenous acetylcholine, released from cholinergic nerve endings. The following is a description of an "in vivo" method which is suitable for the detection of cardioselective antimuscarinic agents.

The objective of this method was to confirm the selectivity of the antimuscarinic effect of the test substance.

Inhibition of the effect of acetylcholine on the bladder, bronchi and heart rate in guinea pigs

5 minutes after the administration of the test substance, 10 microgram/kg of acetylcholine were simultaneously injected intravenously and intra-arterially into anaesthetised guinea pigs. The heart rate was recorded directly by extracorporeal derivation of the ECG, as were the expiration resistance according to Konzett-Rößler and the contraction of the exposed bladder. In order to determine the inhibition of the acetylcholine activity on the organs under investigation, dosage/activity curves were recorded and from them -log ED_{50} values were determined. For the results see Table II.

The following compounds for example were investigated as described above:

A = (±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]-amino]-1-oxobutyl]-N,N-dimethyl-4-piperidine carboxamide and

B = atropine.

Table I:

Receptor Binding Tests in vitro:
Results:

Substance	Receptor Binding Tests IC_{50} [nMl^{-1}] Cortex	Heart	Submandibular gland
A	50	10	300
B	2	4	4

The information in Table I above shows that the test compound (Compound I) distinguishes between muscarinic receptors in different tissues. This is clear from the substantially lower IC_{50} values when the test substance is investigated on preparations from the heart compared with those from the cerebral cortex. However, the binding data in particular show that the heart rate is increased by the above-mentioned compound at dosages at which no restriction of salivation can be expected.

Table II

Inhibition of acetylcholine activity on the bladder, bronchi and heart rate in the guinea pig:

Results:

Substance	$-\log ED_{50}$ [molkg^{-1}] Heart	Bronchi	Bladder
A	7.19	6.83	6.29

The pharmacological data in Table II above indicate a surprisingly high power of distinction between the heart and the smooth muscle of the bladder.

For pharmaceutical use, Compounds I and II or their salts may be incorporated, in a conventional manner, in conventional pharmaceutical preparations, e.g. solutions, suppositories, tablets, coated tablets, capsules or infusions. The daily dosage of the active substance is generally between 0.02 and 5 mg/kg, preferably 0.02 and 2.5 mg/kg, more particularly 0.05 and 1.0 mg/kg of body weight, optionally administered in the form of several, preferably 1 to 3, individual doses, to achieve the desired results.

The therapeutic agents used according to the method of the invention may comprise Compound I or Compound II or a salt thereof or a mixture of one or more of compounds I and II and their physiologically acceptable salts. The preparation of Compounds I and II is described EP-A-177078. Salts of these compounds may be prepared from the free bases according to conventional salt formation techniques.

The following non-limiting Examples illustrate the preparation of some pharmaceutical administration forms useful in the method of the invention :

Example I

Tablets containing 20.0 mg of (±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide

Composition:

1 tablet contains:

Active substance	20.0 mg
Lactose	152.0 mg
Potato starch	65.0 mg
Magnesium stearate	2.0 mg
	239.0 mg

A 10% mucilage is prepared from potato starch by heating. The active substance, lactose and remaining potato starch are mixed together and granulated with the above mucilage through a 1.5 mm mesh screen. The granules are dried at 45°C, rubbed through the same screen again, mixed with magnesium stearate and compressed to form tablets.

Weight of tablet: 239 mg

Punch diameter: 9 mm

Example II

Coated tablets containing 20.0 mg of (±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide

Tablets prepared according to Example I are coated, by a known method, with a coating consisting essentially of sugar and talc. The finished coated

tablets are polished with beeswax.
Weight of coated tablet: 300 mg

Example III

Ampoules containing 4.0 mg of (±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide

Composition:
1 ampoule contains:

Active substance		4.0 mg
Sodium chloride		8.0 mg
Distilled water	ad	1 ml

The active substance and sodium chloride are dissolved in distilled water and then made up to the volume specified. The solution is sterile filtered and transferred into 1 ml ampoules.
Sterilisation: 20 minutes at 120 °C.

Example IV

Suppositories containing 20 mg of (±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide

Composition:
1 suppository contains:

Active substance	20.0 mg
Suppository mass (e.g. Witepsol W 45 (R))	1 690.0 mg
	1 710.0 mg

The finely powdered active substance is suspended in the molten suppository mass which has been cooled to 40°C. The mass is poured at 37°C into slightly chilled suppository moulds.
Weight of suppository 1.71 g

Example V

Drops containing (±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide

Composition:
100 ml of drops solution contain:

Methyl p-hydroxybenzoate		0.035	g
Propyl p-hydroxybenzoate		0.015	g
Aniseed oil		0.05	g
Menthol		0.06	g
Pure ethanol		10.0	g
Active substance		0.8	g
Sodium cyclamate		1.0	g
Glycerol		15.0	g
Distilled water	ad	100.0	ml

The active substance and sodium cyclamate are dissolved in about 70 ml of water and glycerol is added. The p-hydroxybenzoates, aniseed oil and menthol are dissolved in ethanol and this solution is added with stirring to the aqueous solution. Finally, the solution is made up to 100 ml with water and filtered to remove any suspended particles.

Claims

1. A method of treatment of the human or non- human body to combat bradycardia and/or bradyarrhythmia, said method comprising administering to a said body in need of such treatment a compound selected from (±)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide (Compound I), (+)-1-[4-[ethyl[2-(4-methoxyphenyl)-1-methylethyl]amino]-1-oxobutyl]-N,N-dimethyl-4-piperidinecarboxamide (Compound II) and the physiologically acceptable acid addition salts thereof.

2. A method as claimed in claim 1 comprising administering Compound I or a salt thereof to said body at a daily dosage of from 0.02 to 5 mg/kg bodyweight.

3. A method as claimed in claim 1 comprising administering compound II or a salt thereof to said body at a daily dosage of from 0.02 to 5 mg/kg bodyweight.

DATED this 13th day of February 1991

DR KARL THOMAE GMBH

By Their Patent Attorneys:

CALLINAN LAWRIE

Richard J. Hamilton.