FORM 1

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

600676

APPLICATION FOR A STANDARD PATENT

I\We,

PANMEDICA S.A.

of ZONE INDUSTRIELLE
ILOT J
06510 CARROS
FRANCE

hereby apply for the grant of a standard patent for an invention entitled:

ALKYLCARBOXAMIDES OF PYRIDYLALKYLAMINES, THEIR PREPARATION AND THEIR USE IN HUMAN AND VETERINARY MEDICINE.

which is described in the accompanying complete specification

Details of basic application(s):

Number of basic application	Name of Convention country in which basic application was filed	Date of basic application
20776	MA	11 OCT 85

My/our address for service is care of CLEMENT HACK & CO., Patent Attorneys, 601 St. Kilda Road, Melbourne 3004, Victoria, Australia.

DATED this 23rd day of September 1986

PANMEDICA S.A.

CLEMENT HACK & CO.

TO: The Commissioner of Patents.

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 13.6.90

PATENT OFFICE
$140 —
-087326
Collector of Public Moneys

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 13.6.90

Australia Patent Declaration Form

Forms 7 and 8

AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

Name(s) of Applicant(s)

In support of the application made by PANMEDICA S.A.

Title

for a patent for an invention entitled ALKYLCARBOXAMIDES OF PYRIDYLALKYLAMINES, THEIR PREPARATION AND THEIR USE IN HUMAN AND VETERINARY MEDICINE

Name(s) and address(es) of person(s) making declaration

I/We, Claude LARUELLE, Managing Director of PANMEDICA
Zone Industrielle, Ilot J
06510 CARROS, FRANCE

do solemnly and sincerely declare as follows:-

1. I am/we are the applicant(s) for the patent, or am/are authorised by the abovementioned applicant to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 of the Act was/were made in the following country or countries on the following date(s) by the following applicant(s) namely:-

Country, filing date and name of Applicant(s) for the or each basic application

in MOROCCO on October 11 1985
by PANMEDICA S.A.
in ____ on ____ 19__
by ____

3. The said basic application(s) was/were the first application(s) made in a Convention country in respect of the invention the subject of the application.

Name(s) and address(es) of the or each actual inventor

4. The actual inventor(s) of the said invention is/are
Claude LARUELLE, Avenue Bellevue, 06270 VILLENEUVE LOUBET, FRANCE
Marcel LEPANT, 7 rue Mellarède, 06100 NICE, FRANCE
Bernard RAYNIER, 9 Chemin du Malvan, 06800 CAGNES, FRANCE

See reverse side of this form for guidance in completing this part

5. The facts upon which the applicant(s) is/are entitled to make this application are as follows:-
The applicant would be entitled to have assigned to it a patent granted to any of the actual inventors in respect of the said invention.

DECLARED at CARROS this 11th day of September 19 87

Claude Laruelle

Claude LARUELLE
Managing Director

(12) PATENT ABRIDGMENT (11) Document No. AU-B-63068/86
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 600676

(54) Title
ALKYLCARBOXAMIDES OF PYRIDYLALKYLAMINES, THEIR PREPARATION AND USE AS PHARMACEUTICAL PREPARATIONS

International Patent Classification(s)
(51)[4] C07D 213/40 A61K 031/44 C07D 213/89

(21) Application No. : 63068/86 (22) Application Date : 23.09.86

(30) Priority Data

(31) Number	(32) Date	(33) Country
20776	11.10.85	MA MOROCCO

(43) Publication Date : 16.04.87

(44) Publication Date of Accepted Application : 23.08.90

(71) Applicant(s)
PANMEDICA S.A.

(72) Inventor(s)
BERNARD RAYNIER; MARCEL LEPANT; CLAUDE LARUELLE

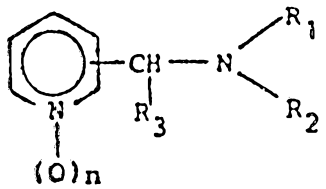
(74) Attorney or Agent
GRIFFITH HACK & CO. MELBOURNE

(56) Prior Art Documents
US 3951995

(57) The compounds according to the present invention have particularly interesting pharmacological properties, namely parasympathomimetic, hypertensive, bradycardiac, antianoxic, analgesic, antispasmodic and broncholytic.

CLAIM

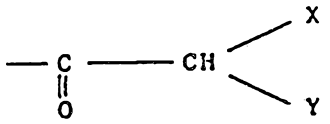
1. Compound of the general formula I or one of its pharmaceutically acceptable salts:



(I)

in which:
n = zero or 1,
R_3 represents an alkyl group of C_1 to C_3 or a hydrogen atom,
R_1 represents a hydrogen atom,
R_2 represents a group

.../2



(II)

in which:
X and Y are different and
each represents a linear or branched, saturated or unsaturated hydrocarbon chain of 1 to 16 carbon atoms, or X and Y form together saturated or unsaturated cyclic radicals, comprising from 3 to 12 carbon atoms and possibly substituted by a methyl group.

AUSTRALIA

PATENTS ACT 1952

600676

Form 10

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

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

Short Title:

Int. Cl:

Application Number: 63068/86.
Lodged:

Complete Specification-Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant:
PANMEDICA S.A.

Address of Applicant: ZONE INDUSTRIELLE
ILOT J
06510 CARROS
FRANCE

Actual Inventor:

Address for Service: CLEMENT HACK & CO.,
601 St. Kilda Road,
Melbourne, Victoria 3004,
Australia.

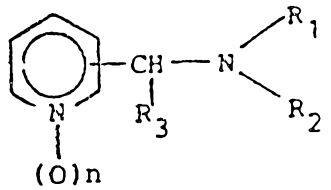
Complete Specification for the invention entitled:
ALKYLCARBOXAMIDES OF PYRIDYLALKYLAMINES, THEIR PREPARATION AND THEIR USE IN HUMAN AND VETERINARY MEDICINE.

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

ALKYLCARBOXAMIDES OF PYRIDYLALKYLAMINES, THEIR PREPARATION AND THEIR USE IN HUMAN AND VETERINARY MEDICINE

Background of the Invention

The present invention relates to novel aliphatic and cycloaliphatic amides of pyridylalkylamines or their N-oxide derivatives of the general formula:



(I)

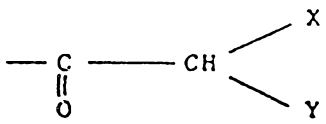
in which:

n = zero or 1,

R_3 represents an alkyl group of C_1 to C_3 or a hydrogen atom,

R_1 represents a hydrogen atom,

R_2 represents a group:



(II)

in which:

X and Y are different, and

each represents a linear or branched, saturated or unsaturated hydrocarbon chain of 1 to 16 carbon atoms, or X and Y form together saturated or unsaturated cyclic radicals, comprising from 3 to 12 carbon atoms and possibly substituted by a methyl group.

The compounds according to the present invention have particularly interesting pharmacological properties, namely parasympathomimetic, hypertensive, bradycardiac, antianoxic, analgesic, antispasmodic and broncholytic.

SANOFI in its patent E.P. 101,380 described the nicotinic amide of picolylamine. Later, Riker in US 4,452,983 claimed picolinic 2-trifluoro 2-ethoxy 5-hydroxy benzamide.

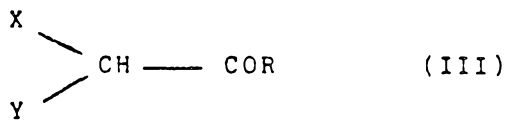
Benoit-Guyod in Chimie Therapeutique (1968) - 336 studied the activities of the amides of dipropyl-acetic acid and noted the absence of anticonvulsant properties of the series.

Applicant has discovered surprisingly that the amides according to the general formula I possessed the previously mentioned pharmacological activities and could consitute particularly interesting medicaments.

GENERAL DESCRIPTION OF THE INVENTION

According to the invention there are provided compounds of the general formula I or one of its pharmaceutically acceptable salts.

The present invention also relates to the process of the preparation of the derivatives of the general formula I. The process consists of reacting a pyridylalkylamine with a reactive derivative of the general formula (III):



(III)

This reactive derivative may be a halogenide (R= halogen) or an acid anhydride, a reactive ester or a mixed anhydride.

Among the acid halogenides it is the chloride which is used preferably; it is mostly available or can be prepared in customary manner. In this case, the reaction is normally performed with pyridyl-methanamine in an inert solvent such as benzene, toluene ether or a halogenalkane.

A hydrogen acceptor is used which can be tertiary amines such as triethylamine, pyridine, picoline or again an excess of the pyridylmethanamine which is then recovered in the form of

the hydrochloride. The reaction temperatures may be comprised between ordinary temperature and the reflux temperature of the reaction medium. The highest reaction temperatures may be employed with the least reactive derivatives of formula III.

Other derivatives of the general formula III may be used, like esters such as the pentachlorophenyl ester, in which case the operation is at ambiant temperature and in an inert polar solvent such as dimethylformamide preferably at ordinary temperature.

It is also possible to use a mixed anhydride such as a reactive derivative of the general formula (III) carried out, for example, with pivaloyl chloride or ethylchloroformate in the presence of a tertiary amine like triethylamine in solution in acetone.

It is also possible to react the carboxylic acid general formula III (R = OH) with pyridinemethanamine in the presence of a dehydrating catalyst like a carbodiimide, for example, dicyclohexylcarbodiimide in solution in dimethylformamide or in an inert chlorinated solvent, at ordinary temperature.

According to a particular modality of the present invention, it is possible to carry out the reaction of the acid chloride of formula III (R = Cl) in solution in chloroform with the equimolecular amount of pyridinemethanamine. The basic amide formed remaining in solution in the solvent then serves as hydrochloric acid acceptor and it is possible to recover from the chloroform solution, after filtration of traces of insoluble pyridinemethanamine chloride, the derivatives of the present invention.

It is also possible to take up again in water the residue from evaporation of the chloroform and to obtain the base in the pure state after alkalinisation by an inorganic base. The amides thus isolated may be salified with pharmaceutically acceptable inorganic or

organic acids.

The N-oxide derivatives of general formula I may be prepared from the amides of pyridinemethanamine by the action of hydrogen peroxide in solution in acetic acid.

The temperature of the reaction medium can be regulated between ordinary temperature and reflux temperature preferably between 60° and 100° C.

The isolation of the desired N-oxide derivatives is done by evaporation of the acetic acid under reduced pressure, extraction by a water immiscible solvent, washing with dilute caustic soda and evaporation.

The taking up of the evaporate with ether results in the N-oxide derivatives of the present application in the pure state. The products according to the invention are pure by thin layer chromatography in the solvent systems indicated and their elementary analysis corresponds to the calculated theoretical results.

The present application relates also to a pharmaceutical composition comprising at least one derivative of the general formula I in the state of base or in one of its pharmaceutically acceptable salts. These compositions may be prepared for the purpose of oral or parenteral administration with the adjuvants generally employed. The administration can also be performed by suppository or percutaneous preparation with suitably selected vectors.

PHARMACOLOGICAL STUDY

1) Potentiation of the hypnotic action of pentobarbital

The derivatives according to the invention are injected intraperitoneally into mice, then after 30 min., 50 mg/kg of pentobarbital i.p. A very significant potentiation of narcosis for doses comprises between 6 and 24 mg/kg is noted.

2) Analgesic activity

By administration to the mouse of the derivatives at the dose of 6, 12, 24 mg/kg, there is noted in the acetic acid test a very significant analgesic action from 12 mg/kg.

In the heated plate test, this activity is noted from 6 mg/kg by the intraperitoneal route and at 24 mg/kg by the oral route.

No analgesic response with respect to electric stimulation is noted at the doses employed.

3) Antispasmodic activity

Tested on the rabbit jejunum and on the guinea pig ileum, the derivatives according to the invention exert an antagonistic effect with respect to histamine varying from 10 to 50% for concentrations in the medium of 1 to 2 x 10^{-2} μg/ml.

The spasmolitic action is confirmed for certain derivatives on the isolated uterus.

4) Bronchodilator activity

A protective effect with respect to histamine bronchospasm is noted in the anesthetized animal from the dose of 20 mg/kg for certain derivatives of the present application.

In acetylcholine spasm, the derivative of Example 7 administered at 50 mg/kg by mouth exerts a bronchial protection of 100%.

5) Antianoxic activity

The derivatives according to the invention also protect against experimental hypoxia in the mouse.

In curare anoxia (Flaxedyl at 16 mg/kg), a delay in the convulsive crisis of 30 to 50 % is noted particularly with the derivatives of examples 5, 7, 11, 16, after intraperitoneal administration at the dose of 100 mg/kg. The anticurarizaring effect is sufficient

for certain animals to survive the convulsive crisis.

In the test of anoxia by confinement; the products claimed increase the survival level up to 60% in some cases.

6) Anticonvulsant activity

The derivatives according to the invention do not protect the mouse in the convulsive crisis caused by pentetrazole.

Some non-limiting examples of the present application are described below.

EXAMPLE 1 - N-(3-PYRIDYL METHYL)-CYCLOHEPTANE-CARBOXAMIDE HYDROCHLORIDE

In one hour at ordinary temperature 0.1 mole of picolylamine in solution in 30 ml of chloroform are run into 0.11 mole of cycloheptane carboxylic acid chloride dissolved in 75 ml chloroform.

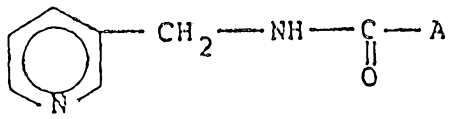
It is kept at ordinary temperature with stirring for 24 hours, a light and soluble product constituted by the amine hydrochloride is filtered off if nessessary, and it is evaporated to dryness. The residue taken up again in water is treated with aqueous caustic soda to pH 10 and extracted with choloroform.

After washings with water of the organic layer and evaporation, the crude product is recrystallized in a benzene/cyclohexane mixture.

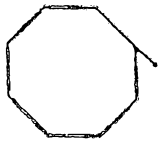
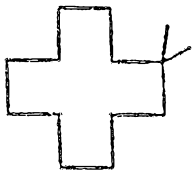
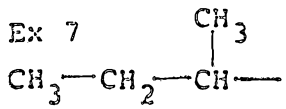
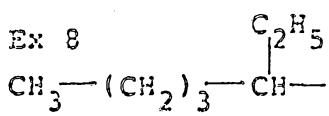
In this way the derivative of the title is obtained in the form of the base with a yield of 80% in the form of a white solid of m.p. 65/66 °C showing in thin layer chromatography on silica a single spot of Rf 0.95 in the system A: ethyl acetate 2, isopropanol 2, concentrated ammonia 1 and Rf = 0.60 in the system B: benzene 80, methanol 20.

By treatment of the acetone solution of this base with hydrochloric acid, the hydrochloride is isolated, i.e. the title derivative, in the form of white crystals of m.p. 83/85 °C.

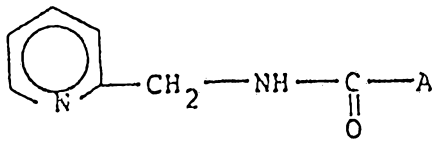
By operating under the conditions of Example 1 with the corresponding acid chlorides, the derivatives of the formula:



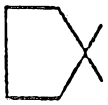
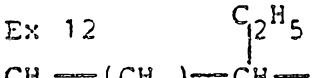
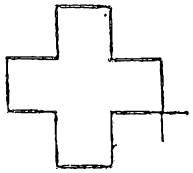
are obtained, having the following physico-chemical characteristics:

A	Yield	m.p. base	m.p. HCl	Rf in A	Rf in B
Ex 2 	82 %	98/99	79/80	0.95	0.50
Ex 3 	67 %	oil	87	0.95	0.50
Ex 4 	75 %	71	117	0.95	0.50
Ex 5 	70 %	70	178/79	0.95	0.55
Ex 6 	83 %	129/130	181/183	0.95	0.59
Ex 7 	80 %	oil	65	0.95	0.65
Ex 8 	90 %	35/36	78/80	0.95	0.67

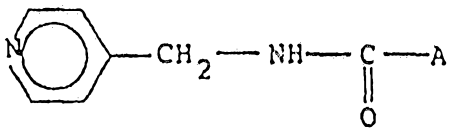
By operating under the conditions of example 1 and by using 2-pyridylmethanamine pyridylmethanamine with suitable acid chlorides, the derivatives of the formula:



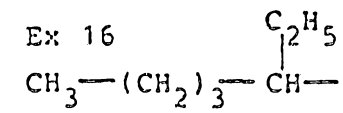
are obtained, having the following physico-chemical characteristics:

A	Yield	m.p. base	m.p. HCl	Rf in A	Rf in B
Ex 9 	85 %	95	135	0.90	0.60
Ex 10 	65 %	65	130	0.90	0.60
Ex 11 	70 %	oil	70	0.90	0.65
Ex 12 	92 %	40	85/87	0.90	0.70
Ex 13 	85 %	136/138	190	0.90	0.65

By operating under the conditions of Example 1 and by using 4-pyridylmethanamine and the corresponding acid chlorides, the derivatives of the general formula:



are obtained having the following physico-chemical characteristics:

A	Yield	m.p.base	m.p. HCl	Rf in A	Rf in B
Ex 14 	72 %	60	135	0.92	0.50
Ex 15 	80 %	80/85	100	0.92	0.50
Ex 16 	85 %	oil	85/90	0.92	0.60

EXAMPLE 17 - N_1 OXIDE OF N-(3-PYRIDYL METHYL) 2-ETHYL HEXANAMIDE

20 millimoles of N-(3-pyridyl methyl) 2-ethyl hexanamide base (Example 7) are dissolved in 50 ml of acetic acid then 10 ml of 40% hydrogen peroxide added. It is taken then for 3 hours to 80° and then on the water

bath under vacuum the major part of the acetic acid is evaporated; it is taken up again with ice water and made alkaline at pH 10.5 with dilute sodium hydroxide. It is extracted with chloroform, washed with water and the solvent evaporated.

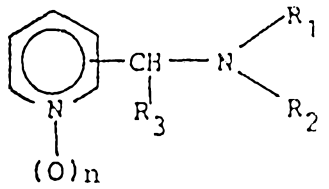
After taking up again with ether, the derivative of the title is obtained in a yield of 61% in the form of white crystals of m.p. 107/108 °C showing on TLC on silica a single spot of Rf = 0.05 in the system A and of 0.45 in the system: n butanol 8, acetic acid 1, water 1. The IR spectrum recorded in KBr shows a band N→O at 1290 cm^{-1}.

EXAMPLE 19 - N_1 OXIDE OF N-(2-PYRIDYL METHYL) CYCLOHEXYL CARBOXAMIDE

By operating under the conditions of the preceding example from the N-(2-pyridyl methyl) cyclohexane carboxamide base described in Example 2, the title derivative is obtained in the form of white crystals of m.p. 160/162 °C, showing a simple spot in TLC in the system A of Rf = 0.30 and a single spot of Rf 0.33 in the system n butanol 8, water 1, acetic acid 1. The I.R. spectrum recorded in KBr shows a band N→O at 1290 cm^{-1}.

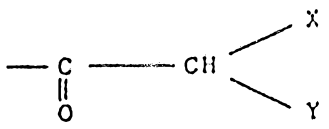
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Compound of the general formula I or one of its pharmaceutically acceptable salts:



(I)

in which:
n = zero or 1,
R_3 represents an alkyl group of C_1 to C_3 or a hydrogen atom,
R_1 represents a hydrogen atom,
R_2 represents a group



(II)

in which:
X and Y are different and
each represents a linear or branched, saturated or unsaturated hydrocarbon chain of 1 to 16 carbon atoms, or X and Y form together saturated or unsaturated cyclic radicals, comprising from 3 to 12 carbon atoms and possibly substituted by a methyl group.

2. A compound according to claim 1 in which the ring nitrogen of the pyridine is in a state of N oxide.

3. N-(3-pyridyl methyl)-cyclooctane carboxamide
N-(3-pyridyl methyl)-cycloheptane carboxamide
N-(3-pyridyl methyl)-cyclohexane carboxamide
N-(3-pyridyl methyl)-cyclopentane carboxamide
N-(3-pyridyl methyl)-cyclopropane carboxamide
N-(3-pyridyl methyl)-2 ethyl hexanamide
N-(3-pyridyl methyl)-cyclododecane carboxamide

4 N-(4-pyridyl methyl)-cyclopropane carboxamide

N-(4-pyridyl methyl)-cyclohexane carboxamide

N-(4-pyridyl methyl) 2-ethyl hexanamide

5. N-(2-pyridyl methyl)-cyclododecane carboxamide

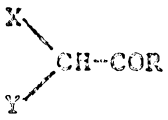
N-(2-pyridyl methyl)-cyclobutane carboxamide

N-(2-pyridyl methyl) 2-ethyl hexanamide

6. N_1 oxide of N-(3-pyridyl methyl)-cyclohexane carboxamide

N_1 oxide of N-(3-pyridyl methyl) 2-ethyl hexanamide

7. Process for the preparation of the derivatives according to claims 1, 3, 4, or 5, wherein a reaction is realized between a compound of formula III

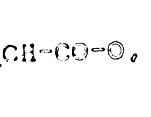


(III)

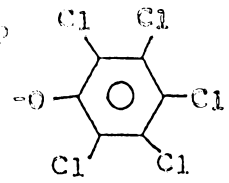
wherein

X and Y have the same definitions as hereinbefore defined;

R represents an halogen atom,

a group  ,

a group OH,

a group 

a group $(CH_3)_3C-CO-O$, or

a group $C_2H_5-C-CO-O$,

and a pyridylalkylamine in an inert solvent, possibly in the presence of a tertiary amine.

8. Process according to claim 7, wherein the reactive derivative of formula II is an acid halogenide which is reacted with a molecular equivalent of pyridinemethanamine, the reaction being conducted in chloroform at ordinary temperature.

9. Process for obtaining derivatives according to claim 2, comprising treating the products of the general formula I with hydrogen peroxide in solution in acetic acid at a temperature comprised between ambiant temperature and boiling.

10. A pharmaceutical composition comprising at least one of the derivatives according to claim 1 or 2.

11. Medicaments for veterinary and/or human use, constituted by at least one of the compounds according to claims 1 or 2.

DATED THIS 31ST DAY OF JANUARY, 1990

PANMEDICA S.A.

By Its Patent Attorneys:

GRIFFITH HACK & CO.,

Fellows Institute of Patent
Attorneys of Australia