CONVENTION APPLICATION FOR A PATENT

We hereby apply for the grant of a Patent for an invention entitled:

NEW DERIVATIVES OF 4-[(3-(4-QUINOLYL) PROPYL]- Piperidine and Their Use as Medicines

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered

78 22968

for a patent or similar protection made in France on 3rd August 1978.

Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys,
50 Queen Street, Melbourne, Victoria, Australia.

DATED this 1st day of August 1979.

{Signature}

LOUIS C. SEBHAUT
Reg'd. Pat't. Attorney

To: The Commissioner of Patents.
COMMONWEALTH OF AUSTRALIA
Patents Act 1952-1969

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

In support of the Convention Application made by PHARMINDUSTRIE

(hereinafter referred to as the applicant) for a Patent for an invention entitled:

NEW DERIVATIVES OF 4-[[3-(4-QUINOLYL) PROPYL] PIPERIDINE AND THEIR USE AS MEDICINES

I, JEAN HOUSIN of 35, Quai du Moulin de Cage, 92231 Gennevilliers, France

do solemnly and sincerely declare as follows:

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

2. The basic application as defined by Section 141 of the Act was made in France on the 1st day of August 1978, by PHARMINDUSTRIE

3. ALAIN CHAMPEIX, of 12 rue Hector Berlioz, Forges Les Eaux 91470 Limours, France, CLAUDE GUEREMY, of 3 rue Daumesnil, 78800 Houilles, France and GERARD LE FUR, of 17 rue du 11 Novembre, 92390 Villeneuve La Garenne, France are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of the said ALAIN CHAMPEIX, CLAUDE GUEREMY and GERARD LE FUR

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application

DECLARED at Paris, France this 2nd day of July 1979.

To: THE COMMISSIONER OF PATENTS.

Edel, Waters & Sons, Melbourne.
1. Compounds of the formula:

\[
\begin{align*}
X' & \quad \text{CH}_2\text{-CH}_2\text{-CH}_2 \quad \text{N} - H \\
\text{CH}_2\text{-CH}_2\text{-CH}_2 & \quad \text{R'} \\
\end{align*}
\]

in which X' is a hydrogen atom or a methoxy group, R' is a vinyl or ethyl group, the carbon atom carrying the group R' has the sinister (S) configuration and that carrying the 3-(4-quinolyl) propyl group has the rectus (R) configuration, and their acid addition salts.

2. A pharmaceutical composition which contains as active agent a compound and its pharmaceutically acceptable salts as claimed in claim 1, and a pharmaceutically acceptable carrier or diluent.
Name of Applicant: PHARMININDUSTRIE

Address of Applicant: 35, Quai du Moulin de Cage, 92231 GENNEVILLIERS, France.

Actual Inventor: Alain Champêseix, Claude Gueremy and Gerard Le Fur

Address for Service: EDWD. WATERS & SONS, 50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

NEW DERIVATIVES OF 4-[3-(4-QUINOLYL) PROPYL] - PIPERIDINE AND THEIR USE AS MEDICINES.

The following statement is a full description of this invention, including the best method of performing it known to us.
In French Patent No. 2,354,771, are described medicaments containing as the active principle a compound corresponding to the general formula:

\[
\begin{align*}
\text{CH}_2-\text{CH}_2-\text{CH}_2-\overset{\text{N-H}}{\text{R}}
\end{align*}
\]

in which either \( X \) and \( R \) are hydrogen atoms or \( R \) is a vinyl or ethyl group and \( X \) is a hydrogen atom or a methoxy group in the 6 position, the carbon atoms of the piperidine ring which bear the \( R \) group and the 3-(4-quinolyl) propyl group both having the rectus (\( R \)) configuration.

The present invention relates to new derivatives of 4-[3-(4-quinolyl) propyl] piperidine and their use as medicaments.

\[
\begin{align*}
\text{CH}_2-\text{CH}_2-\text{CH}_2-\overset{\text{N-H}}{\text{R'}}
\end{align*}
\]

in which \( X' \) is a hydrogen atom or a methoxy group, \( R' \) is a vinyl or ethyl group, the carbon atom carrying the group \( R' \) has the sinister configuration (\( S \)) and the carbon atom carrying the 3-(4-quinolyl) propyl group, that is the carbon in position 4 on the piperidine ring, has the rectus configuration (\( R \)).

The compounds of formula (II) may be prepared by reduction, particularly by means of hydrazine hydrate in the presence of an alkali metal hydroxide and a solvent such as an alcohol, of the compounds of formula:
in which $X'$ and $R'$ have the same significance as in the formula (II), the carbon carrying the $R'$ group has the sinister configuration (S) and the carbon in position 4 on the piperidine ring has the rectus configuration (R).

The compounds of formula (III) for which $R'$ is a vinyl group may themselves be prepared by heating in an acid medium the compounds of formula:

in which $R'$ is a vinyl group and the carbon atom carrying the group $R'$ and that in position 4 on the piperidine ring both have the rectus configuration (R).

The compounds of formula (II) for which $R'$ is an ethyl group may also be prepared by catalytic hydrogenation of the corresponding compounds of formula (II) for which $R'$ is a vinyl group. This hydrogenation, for example, may be effected at ambient temperature, under a hydrogen pressure equal to the atmospheric pressure, in an inert solvent such as an alcohol (for example methanol or ethanol) or an acid (for example acetic acid), in the presence of a catalyst such as palladium, nickel, rhodium, ruthenium or platinum.

Finally the compounds of formula (II) for which $R'$ is a vinyl group may also be prepared by heating in acid
medium compounds of the formula:

\[
\text{CH} = \text{CH}_2 \quad \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N-H} \quad (\text{IV})
\]

in which the carbon atom carrying the vinyl group and that in position 4 on the piperidine ring have the rectus configuration (R).

When the reaction has finished, the reaction mixture obtained in the above processes is treated according to conventional methods, physical (evaporation, solvent extraction, distillation, crystallisation, chromatography, etc....) or chemical (formation of the salt and regeneration of the base, etc.....) so as to isolate the products of formula (II) in a pure state, either as the free base or as a salt thereof with an acid.

The compounds of formula (II) in the form of the free base may if desired be converted into salts of addition with a mineral or organic acid by the action of such an acid in a suitable solvent.

As has been indicated in the French Patent application No. 76,18555, the compounds of formula (I) are useful for the treatment of the pathological states caused by a disturbance in the functioning of the serotoninergic systems and in particular find applications as psychotropic agents, more especially as antidepressants. These applications are connected with the capacity of the compounds of formula (I) for inhibiting the uptake of the serotonine by the membranes of the cerebral neurons.
The compounds of formula (I) also possess the property of causing the release of the serotonine contained either in the neurones or in the blood platelets.

The compounds of formula (II) have the two properties mentioned above for the compounds of formula (I). For the compounds of formula (II), the property of causing the release of the serotonine is considerably more marked than that of inhibiting the uptake of this amine. This could result therapeutically in a very rapid action during the treatment of depression (in this case the product acts on the serotonine of the cerebral neurones) and during the treatment of migraines (in this case the product acts on the serotonine of blood platelets).

The following examples illustrate the invention without it being limited thereto.

EXAMPLE I

4(R)-[3-(6-methoxy-4-quinolyl) propyl] 3(S)-vinyl piperidine.

0.31 g of potassium hydroxide is added to a suspension of 1.1 g of 1-(6-methoxy 4-quinolyl)-3-[3(S)-vinyl 4(R)-piperidyl] -1-propanone dihydrochloride in 3.5 ml of diethylene-glycol and 0.18 ml of an 85% aqueous solution of hydrazine hydrate. The mixture is slowly heated to 150°C, then cooled to 100°C, and 0.47 g of potassium hydroxide is introduced. The reaction mixture is heated to 150°C and maintained at this temperature for 5 hours.

After cooling the reaction mixture is treated with 15 ml of water. The oil which separates out is extracted with ethyl acetate. The organic phase is decanted, washed, dried over magnesium sulphate and then evaporated. The crude oil obtained is fixed on a column containing 45 g of silica
and then eluted with a mixture containing 90% of chloroform and 10% of diethylamine.

The purified product thus isolated is dissolved in acetone and converted into the hydrochloride by addition of a solution of hydrochloric acid in ether. 0.24 g of 4(R)-[3-(6-methoxy 4-quinolyl propyl) 3(S)-vinyl piperidine hydrochloride is obtained. This product melts at 151°C.

The starting ketone was prepared as follows:

20 ml of distilled water were added to 2.1 g of 1-(6-methoxy 4-quinolyl) -3-[3(R) - vinyl 4(R) - piperidyl] - 1-propanone (quinicine) and the pH was brought to 3.5 by adding a 1N solution of sulfuric acid. The mixture was introduced in a 225 ml autoclave made of stainless steel and heated for 48 hours at 140°C. The solution was then made alkaline by adding a 2N solution of sodium hydroxide and extracted with ether. The ethereal extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness.

The residue obtained (1.7 g) was dissolved in a small amount of a 9 toluene - diethylamine mixture and fixed on a column containing 500 g of silica. It was then eluted with a 9 toluene-diethylamine mixture, under a pressure of 4 bars. 0.51 g of the starting product (quinicine) and 1.08 g of 1-(6-methoxy 4-quinolyl)-3-[3(5)-vinyl 4(R) - piperidyl] -1-propanone were thus isolated. The latter compound was dissolved in methanol and converted into its hydrochloride by adding a 8N solution of hydrochloric acid in methanol.

EXAMPLE 2

4(R) - [3-(6-methoxy 4-quinolyl)propyl] 3(5)-vinyl piperidine
2.1 g of 4(R)-[3-(6-methoxy 4-quinolyl)propyl] 3(R)-vinyl piperidine were dissolved in 20 ml of distilled water and the
pH was adjusted to 2 by adding a 5N solution of sulfuric acid. The mixture was introduced into a 225 ml stainless steel autoclave and heated for 48 hours at 140°C. Then the solution was made alkaline by adding a 2N solution of sodium hydroxide and extracted with ether. The ethereal extract was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue obtained (1.9 g) was dissolved in a little 9/1 toluene - diethylamine mixture and fixed on a column containing 500 g of silica. By eluting with a 9 toluene - diethyl-

\[ \text{amine mixture under a pressure of 4 bars, 0.71 g of the starting product and 0.68 g of 4 (R) -[3-(6-methoxy 4-quinolyl) propyl] 3(5)-vinyl piperidine were isolated in the form of an oil.} \]

The latter compound was dissolved in methanol and converted into its hydrochloride by adding a solution of hydrochloric acid in methanol.

Characteristics of 4(R) -[3- (6-methoxy 4-quinolyl) propyl] 3(5)- vinyl piperidine hydrochloride :

- Melting point 151°C
- Optical rotation (measured in water at 25°C) :

\[ \left[ \alpha \right]_D^{25} = -31^{\circ} \]

N.M.R. spectrum (solvent: deuterochloroform; reference: tetramethylsilane) :

The chemical shifts $\delta$ of the hydrogen atoms numbered 10, 11 and 11' in the formula (V) hereinafter are :

- $\delta_{10} = 5.4 \text{ ppm}$
- $\delta_{11, 11'} = 5 \text{ ppm}$

- 7 -
The preparation of the 4(R)-[3-(6-methoxy-4-quinolyl) propyl] 3(R) - vinyl piperidine used as starting substance is described in the French application No. 76 18555.

EXAMPLE 3

4(R) -[3-(6-methoxy 4-quinolyl) propyl] 3(5)-ethyl piperidine

A well-stirred suspension containing 2 g of 10% palladium palladized carbon and 6.8 g of 4(R)-[3-(6-methoxy 4-quinolyl) propyl] 3(5)-vinyl piperidine monohydrochloride in solution in 100 ml of absolute ethanol was maintained at ambient temperature under a pressure of hydrogen corresponding to an excess pressure of 50 mm of water relative to atmospheric pressure, until the absorption of hydrogen ceased.

The palladized carbon was then separated by filtration and the alcoholic solution was concentrated. The residue was then dissolved in 50 ml of water and the solution was brought to pH 10 by adding a solution of sodium hydroxide.

The oil which salted out was extracted with chloroform and the extract was washed with water, then dried over magnesium sulfate. After evaporation of chloroform, the residual oil (5.6 g) was converted into fumarate by dissolution in ethanol and addition of 2.1 g of fumaric acid.

5.5 g of the acid fumarate of 4(R)-[3-(6-methoxy 4-quinolyl) propyl] 3(5)-ethyl piperidine are obtained. This compound melts at 180°C

Analysis for C_{20}H_{28}N_{2}O, C_{4}H_{4}O_{4}

Calculated : % N = 6.54
EXAMPLE 4

4(R) -[3 - (4-quinolyl) propyl] 3(S) - vinyl piperidine

By operating as in example 2, but replacing the 2.1 g of 4 (R) -[3-(6-methoxy 4-quinolyl) propyl] 3(R)-vinyl piperidine with 1.3 g of 4 (R) -[3-(4-quinolyl) propyl] 3(R)-vinyl piperidine, 0.8 g of 4(R) -[3-(4-quinolyl) propyl] 3(S) - vinyl piperidine are obtained in the form of an oil.

Characteristics of 4(R)-[3-(4-quinolyl)propyl] 3(S)-vinyl piperidine :

N.M.R. spectrum :

The chemical shifts of the hydrogen atoms numbered 10, 11 and 11' in the formula (V) are:

$\delta$ 10 = 5.4 ppm

$\delta$ 11, 11' = 5.05 ppm

The preparation of the 4(R)- [3- (4-quinolyl) propyl] 3(R)-vinyl piperidine used as starting substance is described in the French application No. 76 18555.

PHARMACOLOGICAL PROPERTIES

It is known that the uptake of serotonine by the blood plates is a good model of the uptake of this amine by neurons [see J. TUOMISTO, J. Pharm., Pharmac., 26, 92 (1974)]. When it is applied to the investigation of medicaments, a method which brings into play the blood plates presents a great interest because it makes it possible to use human cells, which enables the method to give a good anticipation of the effect of the products on human beings.

The capacity of the products for inhibiting the uptake of serotonine or for causing its release has been shown on human blood plates, according to J.L. DAVID et al. "Platelets

a) Inhibition of the uptake of serotonin

The results are expressed by a 50 % inhibiting dose $I_{50}$, which represents the product dose in micromoles per liter reducing the uptake of serotonin by 50 %.

b) Release of serotonin

The action of the products on the release of serotonin has been tested at two concentrates : $5 \times 10^{-6}$ mole per liter and $5 \times 10^{-5}$ mole per liter.

The results obtained are expressed by a percentage of increase of the release of serotonin in comparison with the results obtained with the controls.

The results obtained are compiled in the following Table. In this table are also given for comparison the results obtained with two reference products (imipramine, p-chloroamphetamine)
<table>
<thead>
<tr>
<th>Compound of example 1</th>
<th>Inhibition of the uptake of serotonine $I_{50}$ (µM/l)</th>
<th>Percentage of increase of the release of serotonine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inhibition of the uptake of serotonine $I_{50}$ (µM/l)</td>
<td>Percentage of increase of the release of serotonine</td>
</tr>
<tr>
<td></td>
<td>Concentration of the product $5 \times 10^{-6}$ mole per liter</td>
<td>Concentration of the product $5 \times 10^{-5}$ mole per liter</td>
</tr>
<tr>
<td>Compound of example 1</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>Compound of example 3</td>
<td>$&gt; 0.1$</td>
<td>30</td>
</tr>
<tr>
<td>4(R)-[3-(6-methoxy-4-quinolyl)propyl]-3(R)-vinyl piperidine, epimer of the compound of example 1</td>
<td>0.01</td>
<td>7</td>
</tr>
<tr>
<td>4(R)-[3-(6-methoxy-4-quinolyl)propyl]-3(R)-ethyl piperidine, epimer of the compound of example 3</td>
<td>0.01</td>
<td>34</td>
</tr>
<tr>
<td>Imipramine</td>
<td>0.4</td>
<td>3</td>
</tr>
<tr>
<td>p-chloroamphetamine</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

It can be seen from the Table that the compounds of examples 1 and 3 are much less effective than their epimers as inhibitors of uptake of serotonine (the compound of example 1 is one hundred times less effective than its epimer, and the compound of example 3 is at least ten times less effective than
its epimer).

The compounds of examples 1 and 3 are powerful agents for the release of serotonine. They are even more effective than p-chloro amphetamine.

**TOXICOLOGICAL PROPERTIES**

The acute toxicity of the products has been determined on the male mouse CD₁ (Charles River) given orally.

The LD₅₀ calculated, after 3 days of observation, by the cumulative method of J.J. REED and Coll. (Am.J.Hyg., 1938, 27, 493) is 225 mg/kg for the compound of Example 1 and about 200 mg/kg for the compound of Example 3.

The compounds according to the invention are a toxic at 100 mg/kg and then behave like substances or relatively little toxicity to mice.

**THERAPEUTIC USE**

The compounds of the invention and their pharmaceutically acceptable salts may be used in human therapeutics in the form of compressed tablets, capsules, gelatine-coated pills, suppositories, ingestable or injectable solutions, etc... as regulators of the serotonin-dependant vascular tonicity, especially for the treatment of migraines, and as thymoanaleptic medicaments with a particularly rapid action (owing to their action on the release of serotonine).

The posology depends on the effects sought and on the method of administration used. For example, taken orally, it may be between 15 and 250 mg of active substance per day, with single doses from 5 to 50 mg.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Compounds of the formula:

\[
\begin{align*}
&X' \quad CH_2-CH_2-CH_2 \quad N - H \\
&R' \quad \text{[Chemical structure]} \\
\end{align*}
\]

in which \( X' \) is a hydrogen atom or a methoxy group, \( R' \) is a vinyl or ethyl group, the carbon atom carrying the group \( R' \) has the sinister (S) configuration and that carrying the 3-(4-quinolyl) propyl group has the rectus (R) configuration, and their acid addition salts.

2. A pharmaceutical composition which contains as active agent a compound and its pharmaceutically acceptable salts as claimed in claim 1, and a pharmaceutically acceptable carrier or diluent.

DATED THIS 30TH DAY OF JULY, 1979.

PHARMINDUSTRIE

EDWD. WATERS & SONS, PATENT ATTORNEYS, 50 QUEEN STREET, MELBOURNE, VICTORIA, AUSTRALIA.