MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS 1963 A
COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1959

CONVENTION APPLICATION FOR A PATENT

X

We

SOCIETE CIVILE DE RECHERCHES & D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)
of 264, rue du Faubourg Saint-Honore 75008,
PARIS, FRANCE

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

"NEW PYRIMIDINE DERIVATIVES, THEIR PREPARATION AND THERAPEUTIC COMPOSITIONS CONTAINING THE SAME"

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

29,281

for a patent or similar protection made in

GREAT BRITAIN

on 12th July, 1977

Our address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys,

50 Queen Street, Melbourne, Victoria, Australia.

DATIS: No. 10th day of JULY, 1978

SOCIETE CIVILE DE RECHERCHES & D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)

by: (Stephen K. Plymin)
Reg'd. Patent Attorney

To: THE COMMISSIONER OF PATENTS.
In support of the Convention Application made by

SOCIETE CIVILE DE RECHERCHES & D'APPLICATIONS
SCIENTIFIQUES (S.C.R.A.S.)

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

NEW PYRIMIDINE DERIVATIVES, THEIR PREPARATION AND
THERAPEUTIC COMPOSITIONS CONTAINING THE SAME

I,  Mr. A. Beguin
of  15, rue Georges Vogt, 92190,
MEUDON, 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 GREAT BRITAIN on the 12th day of JULY 1977, by

SOCIETE CIVILE DE RECHERCHES & D'APPLICATIONS
SCIENTIFIQUES (S.C.R.A.S.)

3. Alain BEGUIN of 15, rue Georges Vogt, 92190,
MEUDON, FRANCE

is the actual inventor 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 actual inventor.

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 MEUDON, FRANCE
this 12th day of JUNE 1978

A. Beguin

To: THE COMMISSIONER OF PATENTS.
Claim
1. Derivatives of pyrimidine of the general formula:

```
  HO     CH2OH
  H3C     CH2
```

in which R represents a piperidino radical or a 4-(2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl)-1-piperazinyl radical, and therapeutically acceptable salts thereof.
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952-69

COMPLETE SPECIFICATION
(ORIGINAL)

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name of Applicant:  SOCIETE CIVILE DE RECHERCHES & D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S)

Address of Applicant:  264 rue du Faubourg Sain-Honore
75008 Paris, France.

Actual Inventor:  ALAIN BEGUIN

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

Complete Specification for the invention entitled:

"NEW PYRIMIDINE DERIVATIVES, THEIR PREPARATION AND THERAPEUTIC COMPOSITIONS CONTAINING THE SAME."

The following statement is a full description of this invention, including the best method of performing it known to us.
This invention relates to new complex pyrimidine derivatives which are especially interesting for their activity in the field of atheromas, to their preparation and to therapeutic compositions containing the same.

The compounds according to this invention have the general formula:

\[
\begin{align*}
\text{C}_3 & \quad \text{C}_0: \\
\text{N} & \\
\text{HO} & \\
\text{CH}_2 & \\
\text{R} & \\
\text{H}_3 & \\
\text{C} \\
\end{align*}
\]

in which \( R \) represents a piperidino radical or a 4-(2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl)-1-piperazinyl radical, and therapeutically acceptable salts thereof.

The above compounds can be prepared, by reacting in a polar solvent, at reflux, the piperidine or the 4-(-2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl)-1-piperazine on the corresponding chloride:

\[
\begin{align*}
\text{CH}_2 & \text{OH} \\
\text{HO} & \\
\text{H}_3 & \\
\text{C} \\
\end{align*}
\]

wherein the -OH and -CH\(_2\)OH groups in 3 and 4 positions of the pyridazine moiety have been previously blocked and then by heating at 70-90\(^\circ\)C the compounds thus obtained for breaking the blocking of the said -OH and -CH\(_2\)OH groups.

The compounds according to this invention together with their therapeutically acceptable salts are especially interesting for their anti-atheromatic activity which, considered in its whole, is generally superior to that of standard reference compounds such as acetyl salicylic acid and its
salts, ethyl p-chlorophenoxy-isobutyrate, nicotinic acid and its salts and 2,6-bis(diethanolamino)-4,8-dipiperidinopyrimido-[5,4-d]pyrimidine.

Various experiments have shown a very favourable action of the compounds of the invention on:
(a) the vascular and parietal aspect of the atheromas (test of the oedema by ovalbumin and caragenin on rats; lowering of the capillary permeability on rats);
(b) the platelets aspect (platelets adhesivity in vitro; platelets agglutination in vitro by collagen, adrenalin and adenosine di-phosphate; platelets agglutination in vivo on hamster's cheek pouch); and
(c) the fibrolipidic aspect (triton test on rats for triglycerides and cholesterol and experimental hyperlipemia and hypercholesterolemia tests on rabbits).

It has been noticed, for instance, in the case of the last tests on rabbits that the treated animals present a lowering of the total lipids below the figures found for control animals whereas animals having received only the hyperlipidic diet without treatment show a very important increase of lipemia. This does not occur for instance with ethyl p-chlorophenoxy isobutyrate.

In the triton test the protection given by the products of the invention is, for the same doses, 3 times better than the one given by ethyl p-chlorophenoxy-isobutyrate and 2,6-bis (di-ethanolamino), 4,8-dipiperidinopyrimido-[5,4-d]pyrimidine and is comparable to that given by nicotinic acid.

These remarks apply to compounds of both following examples.
Compound of example 2 and its salts seem to be more active and have been found to act very satisfactorily in the same therapeutic field, as exemplified by the following experimentations:


When administered to normal rats, they do not lower the cholesterol and total lipids rates, in contradistinction with 2-methyl-2[4-(4'-chlorobenzoyl) phenoxy] propionic acid, isopropyl ester; this is accordingly a strong advantage.


Fast induces, in the rabbit, an increase of triglycerids, cholesterol and β-lipoproteins in the blood.

In animals treated with the compound of example 2 or its salts, the rates of these factors remain substantially normal whereas in animals treated with 2-methyl-2[4-(4'-chlorobenzoyl, phenoxy] propionic acid, isopropyl ester, only cholesterol and β-lipoproteins rates remain normal and triglycerids rates are strongly increased (over the rates obtained for rabbits deprived of food and non treated).

TOXICITY

The toxicity of the compounds of examples 1 and 2 has been researched per os on rats and mice: no death for mice at the maximum dose of 4 g/kg and 20% of death for rats at the maximum dose of 3 g/kg. These values confirm the low toxicity of the compounds of the invention.
For the human therapy, the efficient doses per os are from 1.5 g to 10 g of active compound per diem.

Preferred presentations comprise tablets and gelatine capsules containing 0.25 to 1 g of active compound.

The following Examples illustrate this invention.

**Example 1:**

Bis-2,4-[(4-(2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl)-1-piperazinyl]-6-methylpyrimidine.

**Reaction scheme:**

Into a 10-litre reactor fitted with heating, cooling and stirring means, there were placed 277 g (1 mole) of 0,0'-isopropylidenyl-2-methyl-3-hydroxy-4-hydroxymethyl-5-(N-piperazinylmethyl)-pyridine, 3 litres of dry acetonitrile, 404 g (1 mole) of 2-chloro-4-[(4,0,0'-isopropylidenyl-2-
methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl) -1-piperazinyl]-6-methylpyrimidine and 102 g (1 mole) of triethylamine. The mixture was stirred and refluxed for 40 hours and then cooled to 5°C.

A precipitate separated was washed with diethyl ether and then with water until free from chloride ions, and was dried to give 515 g (about 80% yield) of bis-2,4-[4-(0,0'-isopropylidenyl-2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl)-1-piperazinyl]-6-methylpyrimidine.

The 2-chloro-4- 4-(0,0'-isopropylidenyl-2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl)-1-piperazinyl-6-methylpyrimidine used as starting material was obtained by reacting 0,0'-isopropylidenyl-2-methyl-3-hydroxy-4-hydroxymethyl-5-(N-piperazinylmethyl)-pyridine with 2,4-dichloro-6-methylpyridine in stoichiometric quantities in conditions similar to those described above except that the reflux was continued for only 20 hours.

The 2,4-dichloro-6-methylpyridine was obtained by chlorination of methyluracil using phosphorus oxychloride.

The 0,0'-isopropylidenyl-2-methyl-3-hydroxy-4-hydroxymethyl-5-(N-piperazinylmethyl)-pyridine was obtained by blocking the hydroxyl and hydroxymethyl groups at the 3- and 4- positions of pyridoxine by acetone in the presence of hydrochloric acid and reacting the resulting blocked pyridoxine with piperazine.

The bis-2,4-[4-(0,0'-isopropylidenyl-2-methyl-3-hydroxy-4- hydroxymethyl-5-pyridyl-methyl)-1-piperazinyl]-6-methylpyrimidine was treated with hydrochloric acid whilst stirring at about 80°C for 3 hours. This treatment broke the isopropylidene bridges and there was obtained 435 g (about
77% yield) of the desired product which was a white powder melting at about 240°C with decomposition. Analysis showed a good correspondence with the formula $C_{29}H_{40}N_{8}O_{4}$.

The compound was found to be insoluble in water, ethanol, chloroform and transcutanol at room temperature but soluble in dimethylsulphoxide in the same conditions.

Dimaleate and monocitrate are readily obtained by the usual routes. These salts are soluble in water.

**Example 2:**

2-piperidino-4-[$40(2$-methyl-3-hydroxy-4-hydroxy-methyl-5-pyridyl-methyl)-l-piperazinyl]-6-methylpyrimidine.

Example 1 was repeated except that the 0,0'-isopropylidenyl-2-methyl-3-hydroxy-4-hydroxymethyl-5-(N-piperazinylmethyl)-pyridine was replaced by 1 mole of piperidine. There was obtained the desired product which was a white powder melting at 208°C, in a yield of about 76%. Analysis showed a good correspondence with the formula $C_{22}H_{32}N_{6}O_{2}$. The compound was found to be insoluble at room temperature in water but soluble in chloroform, ethanol, transcutanol and dimethylsulphoxide.

The corresponding monocitrate is a white product melting at 118-121°C (Tottoli), fairly soluble in water at room temperature if obtained by crystallization or highly soluble in water, if obtained by lyophilisation.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Derivatives of pyrimidine of the general formula:

![Chemical Structure]

in which R represents a piperidino radical or a 4-(2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl)-1-piperazinyl radical, and therapeutically acceptable salts thereof.

2. Process for the preparation of the derivatives of claim 1, comprising the steps of:

1) Reacting in a polar solvent, at reflux, the piperidine or the 4-(2-methyl-3-hydroxy-4-hydroxymethyl-5-pyridyl-methyl)-1-piperazine on the corresponding chloride:

![Chemical Structure]

wherein the -OH and -CH₂OH groups in 3 and 4 positions of the pyridoxine moiety have been previously blocked and

2) Heating at 70-90°C the compound thus obtained for breaking the blocking of the said -OH and -CH₂OH groups.
3. A composition for therapeutic use comprising as an active ingredient therein one of the compounds according to claim 1, together with an appropriate carrier.

DATED this 28th day of JUNE, 1978

SOCIETE CIVILE DE RECHERCHES & D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)

EDWD. WATERS & SONS
Patent Attorneys
50 Queen Street
MELBOURNE 3000
VICTORIA