AUSTRALIA

PATENTS ACT 1990

656770

PATENT REQUEST : STANDARD PATENT

I/We being the person(s) identified below as the Applicant(s), request the grant of a patent to the person(s) identified below as the Nominated Person(s), for an invention described in the accompanying standard complete specification.

Full application details follow:

[71/70] Applicant(s)/Nominated Person(s):

Elf Sanofi

of

32-34, rue Marbeuf, F-75008 Paris, France

[54] Invention Title:

Novel 3-aminopyridazine derivatives active on the central nervous system, method of preparation and pharmaceutical compositions in which they are present

[72] Name(s) of actual inventor(s):

Jean-Jacques BOURGUIGNON
Jean-Paul KAN
Camille George WERMUTH

[74] Address for service in Australia:

DAVIES COLLISON CAVE, Patent Attorneys, 1 Little Collins Street,
Melbourne, Victoria, Australia. Attorney Code: DM

Basic Convention Application(s) Details:

[31] Application Number	[33] Country	Code	[32] Date of Application
91 05973	France	FR	16 May 1991

DATED this FIFTEENTH day of MAY 1992

M 036 [illegible]

Keith Leslie
....
a member of the firm of
DAVIES COLLISON CAVE for
and on behalf of the
applicant(s)

AUSTRALIA

PATENTS ACT 1990

NOTICE OF ENTITLEMENT

We, **Elf Sanofi**, the applicant/Nominated Person named in the accompanying Patent Request state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the basic application listed on the patent request because the Nominated Person made the basic application, and because that application was the first application made in a Convention country in respect of the invention.

DATED this FIFTEENTH day of MAY 1992

....

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1496974)

AU9216274

(12) PATENT ABRIDGMENT (11) Document No. **AU-B-16274/92**
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. **656770**

(54) Title
NOVEL 3-AMINOPYRIDAZINE DERIVATIVES ACTIVE ON THE CENTRAL NERVOUS SYSTEM, METHOD OF PREPARATION AND PHARMACEUTICAL COMPOSITIONS IN WHICH THEY ARE PRESENT

$(51)^5$ International Patent Classification(s)
C07D 451/02 A61K 031/50 A61K 031/55 C07D 237/20
C07D 487/04

(21) Application No. : **16274/92** (22) Application Date : **15.05.92**

(30) Priority Data

(31) Number	(32) Date	(33) Country
91 05973	**16.05.91**	**FR FRANCE**

(43) Publication Date : **19.11.92**

(44) Publication Date of Accepted Application : **16.02.95**

(71) Applicant(s)
ELF SANOFI

(72) Inventor(s)
JEAN-JACQUES BOURGUIGNON; JEAN-PAUL KAN; CAMILLE GEORGE WERMUTH

(74) Attorney or Agent
DAVIES COLLISON CAVE , 1 Little Collins Street, MELBOURNE VIC 3000

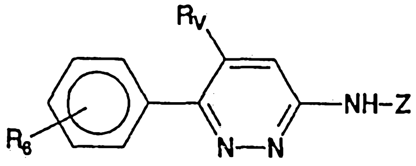
(56) Prior Art Documents
AU 81476/91 C07D 237/20
AU 639043 66672/90 C07D 237/20
AU 21421/88 C07D 237/20

(57)

According to the present invention, novel 3-aminopyridazine derivatives have now been found which are devoid of antidepressant activity but are active as ligands for the cholinergic receptors, more particularly as ligands for the M_1 muscarinic receptors.

CLAIM

1. A compound of the formula:

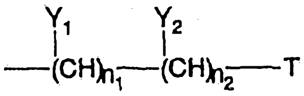


(I)

in which:

- R_V is a linear or branched C_1-C_4 alkyl group;
- R_6 is hydrogen, a C_1-C_3 alkoxy or a hydroxyl group; and
- Z is a group

./2



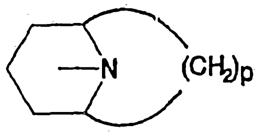
$$-\overset{\overset{Y_1}{|}}{(CH)}_{n_1}-\overset{\overset{Y_2}{|}}{(CH)}_{n_2}-T$$

in which:

* n_1 and n_2 independently are zero or one,

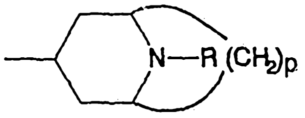
* Y_1 and Y_2 independently are hydrogen or a C_1-C_3 alkyl group, and

* T is a heterocycle selected from:



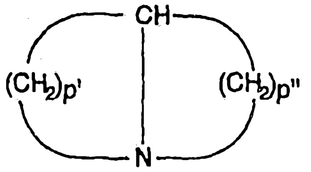
(a)

wherein $n_1 = n_2 = 1$
$Y_1 = Y_2 = H$
and p is 2 or 3;



(b)

wherein $n_1 = n_2 = 0$
and p is 2 or 3 and $R = C_1$-C_3 alkyl;



(c)

wherein $n_1 = 1$, $n_2 = 0$
$Y_1 = H$
and p′ and p″ are 3 or 4;

and its pharmaceutically acceptable salt with organic or mineral acids.

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

656770

NAME OF APPLICANT(S):

Elf Sanofi

ADDRESS FOR SERVICE:

DAVIES COLLISON CAVE
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

INVENTION TITLE:

Novel 3-aminopyridazine derivatives active on the central nervous system, method of preparation and pharmaceutical compositions in which they are present

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

The present invention relates to 3-aminopyridazine derivatives active on the central nervous system.

Numerous pyridazine derivatives have been proposed as drugs active especially on the cardiovascular system or on the central nervous system.

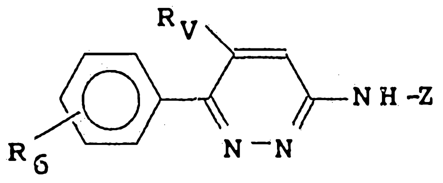
More particularly, French patent application A-2510998 and European patent application A-72726 describe variously substituted pyridazines which all carry in the 3-position an amine substituent of the type

$$-NH-Alkylene-N\begin{matrix}X\\Y\end{matrix}$$

in which X and Y independently are hydrogen or an alkyl group or form, with the nitrogen atom to which they are bonded, a heterocycle such as morpholine. These compounds are active on the central nervous system as antidepressants.

According to the present invention, novel 3-aminopyridazine derivatives have now been found which are devoid of antidepressant activity but are active as ligands for the cholinergic receptors, more particularly as ligands for the M_1 muscarinic receptors.

The present invention therefore relates to pyridazines of the formula



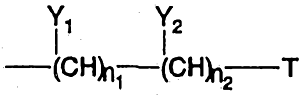
(I)

in which:

- R_V is a linear or branched C_1-C_4 alkyl group;
- R_6 is hydrogen, a C_1-C_3 alkoxy or a hydroxyl group;

and

- Z is a group



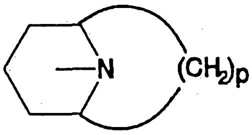
$$-\overset{Y_1}{\overset{|}{(CH)}}_{n_1}-\overset{Y_2}{\overset{|}{(CH)}}_{n_2}-T$$

in which :

* n_1 and n_2 independently are zero or one,

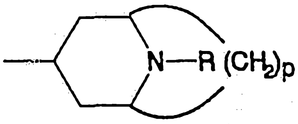
* Y_1 and Y_2 independently are hydrogen or a C_1-C_3 alkyl group, and

* T is a heterocycle selected from:



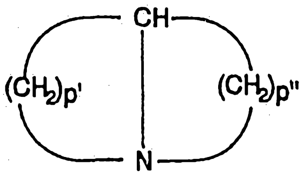
(a)

wherein $n_1 = n_2 = 1$
$Y_1 = Y_2 = H$
and p is 2 or 3;



(b)

wherein $n_1 = n_2 = 0$
and p is 2 or 3 and R = C_1-C_3 alkyl;



(c)

wherein $n_1 = 1$, $n_2 = 0$
$Y_1 = H$
and p' and p" are 3 or 4;

and their pharmaceutically acceptable salts with organic or mineral acids.

The preferred compounds of the invention are those in which:

* either n_1 and n_2 are equal to one, Y_1 and Y_2 are each a methyl or a hydrogen and T is a dialkylamino group in which the alkyls are C_1-C_3;

* or n_1 and n_2 are equal to one, Y_1 is a methyl and Y_2 is hydrogen, or Y_1 is hydrogen and Y_2 is a methyl, and T is a group a);

* or n_1 and n_2 are equal to one, Y_1 and Y_2 are hydrogen and T is the heterocycle b);

* or n_1 and n_2 are equal to zero and T is the heterocycle c);

* or n_1 is equal to one and n_2 is equal to zero, Y_1 is hydrogen and T is the heterocycle d);

and their salts with mineral or organic acids.

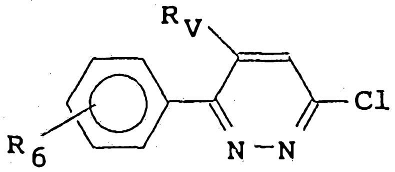
The salts of the compounds of formula (I) according to the present invention include those with mineral or organic acids which permit a suitable separation or crystallization of the compounds of formula (I), such as picric acid or oxalic acid, as well as those with mineral or organic acids which form pharmaceutically acceptable salts such as the hydrochloride, hydrobromide, sulfate, hydrogensulfate, dihydrogenphosphate, methanesulfonate, maleate, fumarate and naphthalene-2-sulfonate.

According to another feature, the present invention relates to a method of preparing the compounds of formula (I).

This method comprises reacting an amine of the formula

$$H_2N\text{-}Z \qquad \text{(II)}$$

in which Z is as defined above for (I), with the 3-chloropyridazine of the formula



(III)

in which R_V and R_6 are as defined above for (I), and, if desired, converting the resulting compound to a salt with a mineral or organic acid.

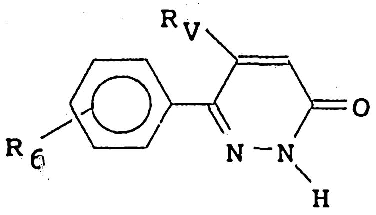
The substitution reaction of the 6-chloropyridazine (III) with the amine (II) is carried out at a temperature of between 100 and 150°C, without a solvent or in the presence of an inert solvent such as an alkanol, and, if appropriate, in the presence of ammonium chloride. The compound (I) is then isolated and purified by the usual methods. The resulting product is isolated in the form of the free base or a salt by the conventional techniques.

When the compound of formula (I) is obtained in the form of the free base, salt formation is effected by treatment with the chosen acid in an organic solvent. Treatment of the free base, dissolved for example in an alcohol such as isopropanol, with a solution of the chosen acid in the same solvent gives the corresponding salt, which is isolated by the conventional techniques. The hydrochloride, hydrobromide, sulfate, hydrogensulfate, dihydrogenphosphate, methanesulfonate, methylsulfate, oxalate, maleate, fumarate and naphthalene-2-sulfonate, for example, are prepared in this way.

When the reaction is complete, the compound of formula (I) can be isolated in the form of one of its salts, for example the hydrochloride; in this case, if necessary, the free base can be prepared by neutralization of said salt with an inorganic or organic base such as sodium hydroxide or triethylamine, or with an alkali metal carbonate or bicarbonate such as sodium or potassium carbonate or bicarbonate.

When the compounds (I) possess a chiral center and are obtained in the form of racemates, which can be separated according to conventional techniques, the corresponding enantiomers form part of the invention.

The 6-chloropyridazines (III) used as starting materials are prepared from the 2H-pyridazin-3-ones of the formula (IV)

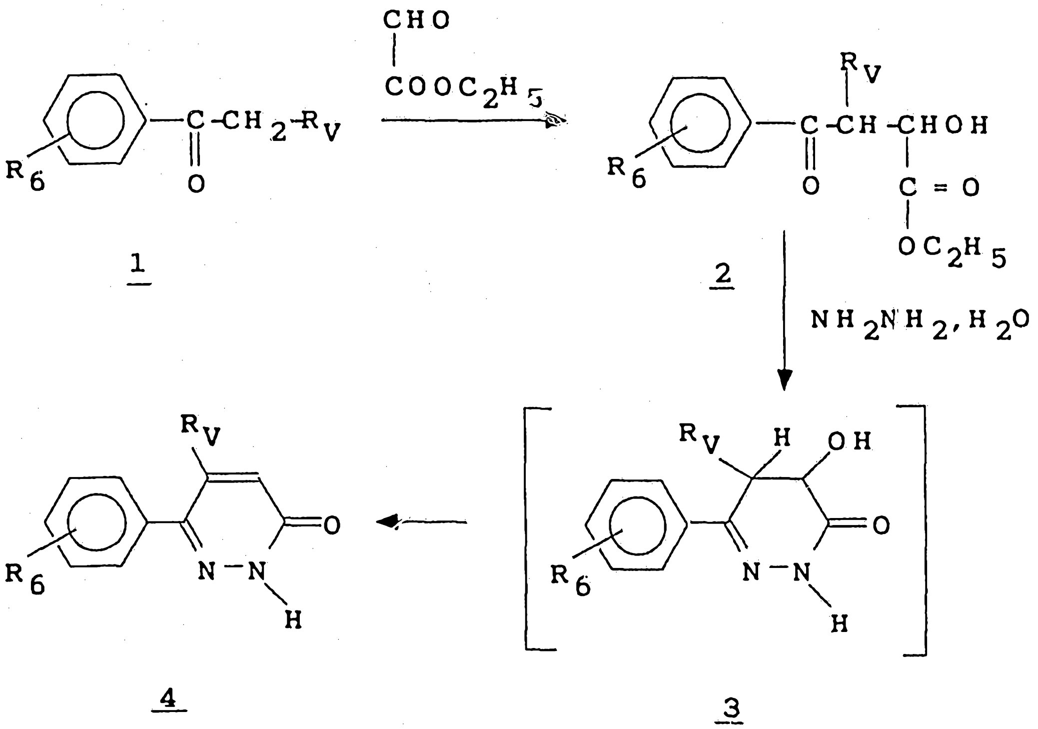


(IV)

by reaction with excess phosphorus oxychloride under the action of heat, without a solvent or in the presence of an inert solvent such as, for example, acetonitrile.

The 2H-pyridazin-3-ones (IV) are known or are prepared by known methods in accordance with the following reaction scheme:

SCHEME 1



The aldolization reaction of an acetophenone derivative 1 with ethyl glyoxylate makes it possible to prepare the hydroxyketoester 2; this is then cyclized with hydrazine hydrate to give the compound 3, which is not isolated.

The hydroxyketoester 2 is converted to the pyridazone 4 in a single step combining cyclization with dehydration.

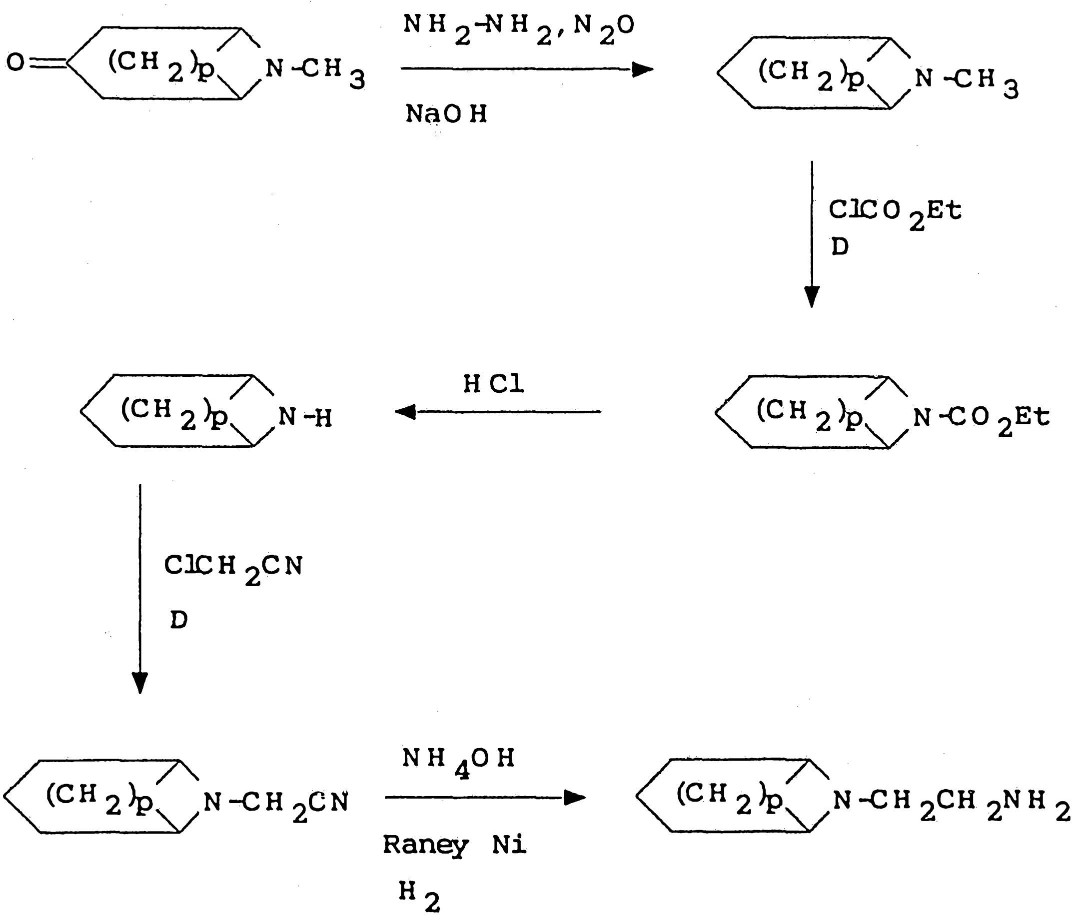
The amines H_2N-Z (II) are known or have been prepared by known methods.

The reaction schemes below illustrate the preparation of the amines H_2N-Z (II) without implying a limitation.

When $n_1 = n_2 = 1$, $Y_1 = Y_2 = H$ and T is the heterocycle

b) in which p = 2 or 3, the corresponding amine (II) is prepared in accordance with the following reaction scheme:

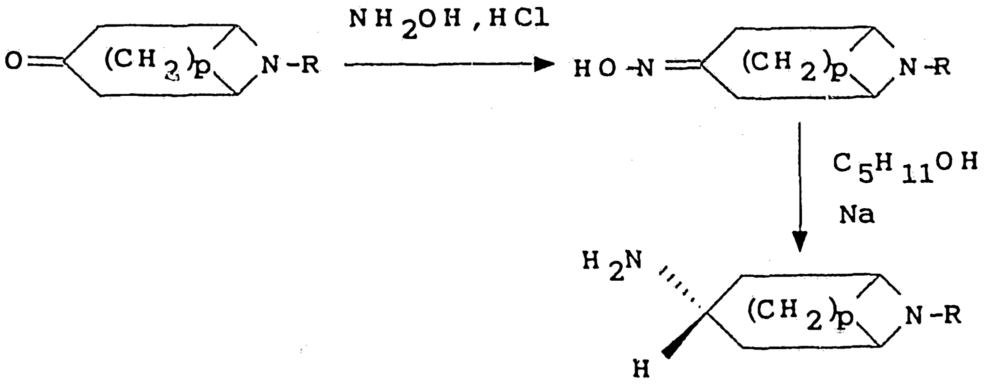
SCHEME 2



When n_1= n_2= 0 and T is the heterocycle c), the corresponding amine (II) is prepared by the method described by Dostert *et al.*, Eur. J. Med. Chem. Chim. Ther., 1984, 19, 2, 105-110, in accordance with the following scheme 3, which makes it possible to prepare the compounds (II) in which the $-NH_2$ group has either the equatorial configuration (IIe) or the axial configuration (IIa).

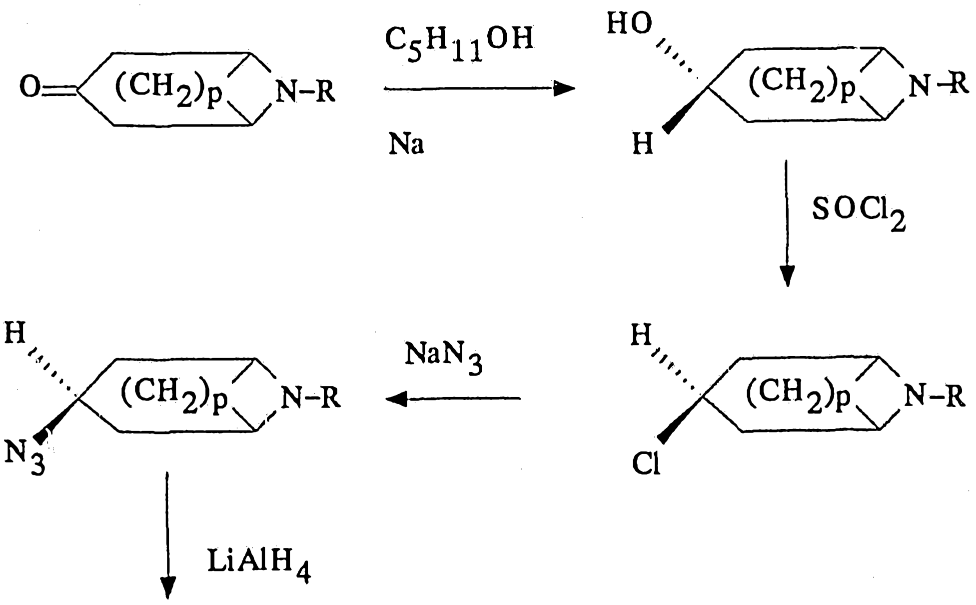
Scheme 3

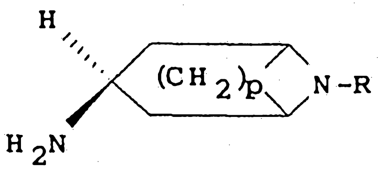
- Configuration of the - NH_2 : equatorial



(IIe)

- Configuration of the - NH_2 : axial

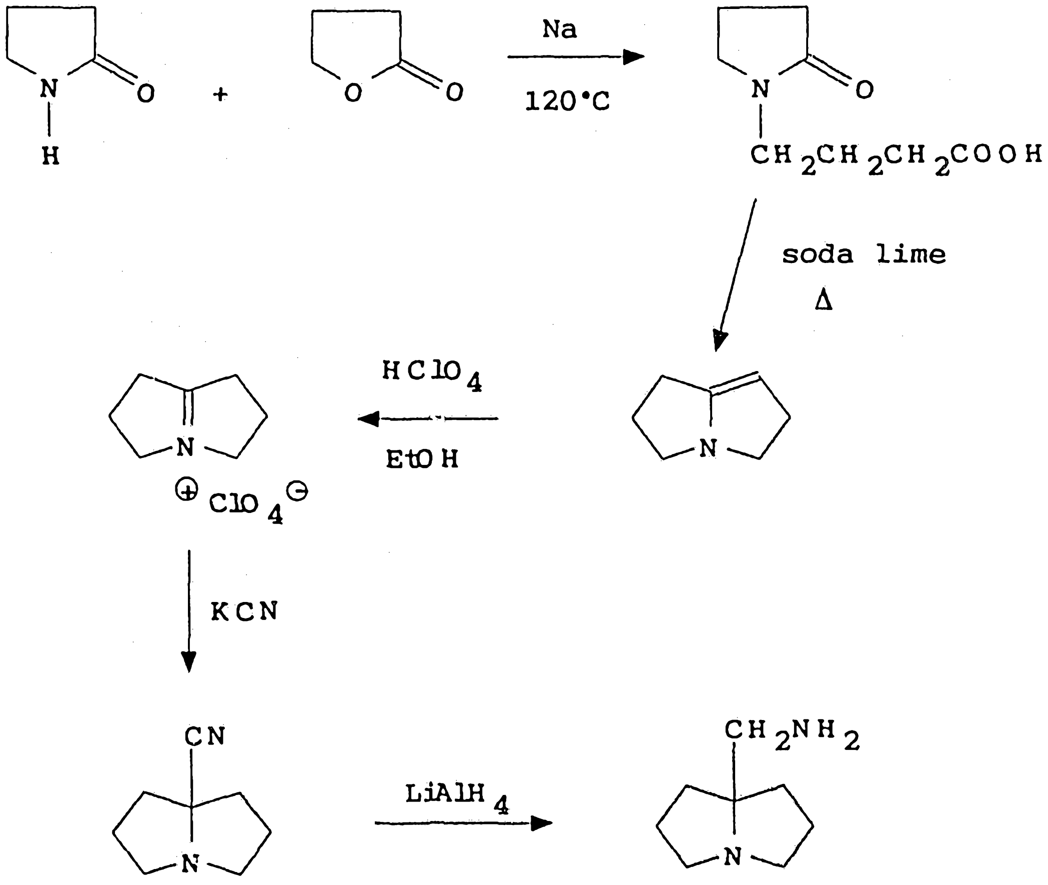




(IIa)

When n_1= 1, n_2= 0, Y_1= H, p'= p''= 3 and Z is 1-azabicyclo[3,3,0]octane, *i.e.* heterocycle d), the corresponding amine, 1-azabicyclo[3,3,0]octyl-2-methylamine, is prepared according to Miyano *et al.*, J. Heterocyclic Chem., 1982, 19, 1465; Miyano *et al.*, Synthesis, 1978, 701; Miyano *et al.*, J. Heterocyclic Chem., 1987, 47, in accordance with the following reaction scheme:

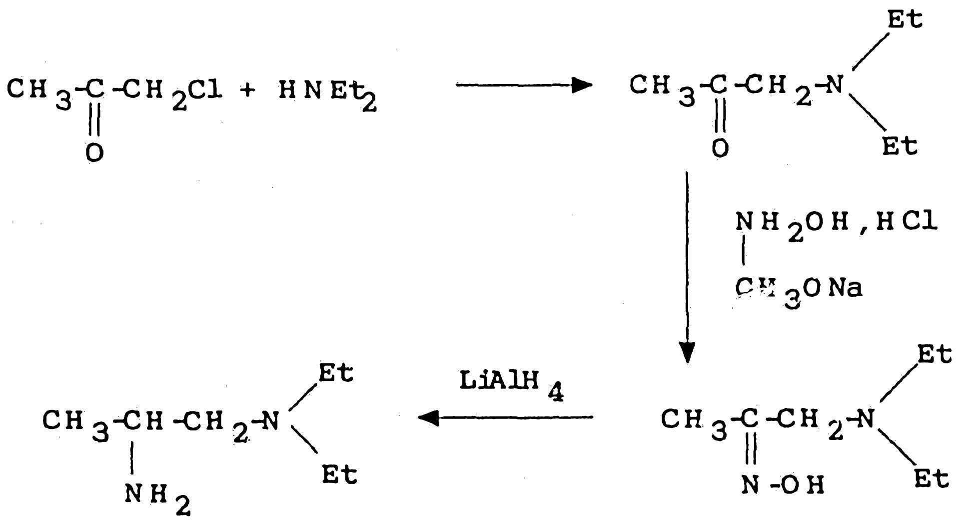
<u>Scheme 4</u>



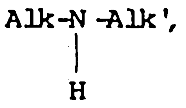
The heterocycle d) can also be prepared according to J. Med. Chem., 1987, 30, 1987, or according to European patent 287 356.

When $n_1 = n_2 = 1$, $Y_1 = CH_3$, $Y_2 = H$ and $T = -N(C_2H_5)_2$, 1-N,N-diethylamino-2-aminopropane is prepared according to an adaptation of the method described by Phillips *et al.*, J. Med. Chem., 1990, 33, 627-633, in accordance with the following reaction scheme:

Scheme 5

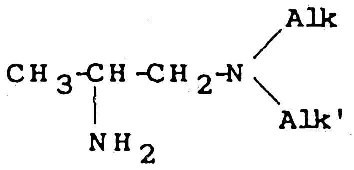


Replacement of the diethylamine with another symmetrical or asymmetrical dialkylamine of formula



$$\text{Alk-}\underset{\displaystyle H}{\underset{|}{N}}\text{-Alk}',$$

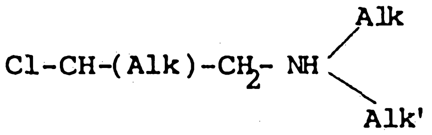
gives the corresponding amines of the formula



in which Alk and Alk' are C_1-C_3 alkyls.

Following the operating procedure described in scheme 5 but using as starting products compounds of formulae $AlkCOCH_2Cl$ and Alk-NH-Alk' in which Alk and Alk' are as defined above, the amines of formula (II) are obtained in which $n_1 = n_2 = 1$; Y_1 = Alk ; Y_2 = H and T is a dialkylaminogroup.

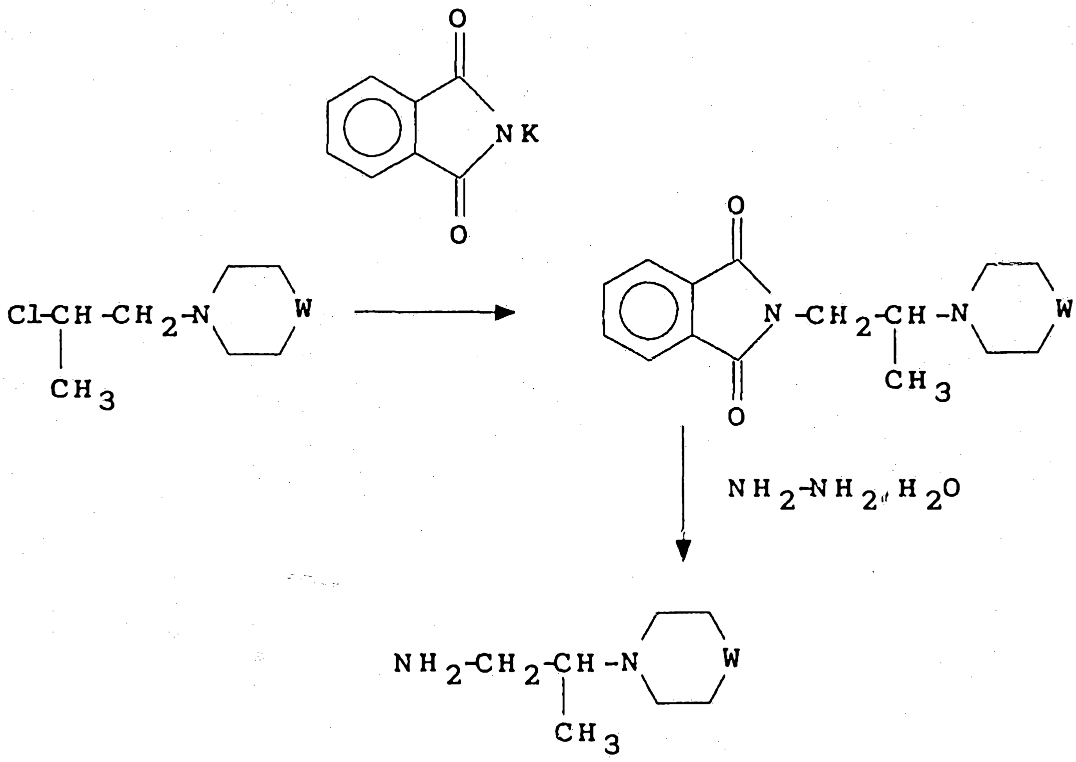
When $n_1 = n_2 = 1$; Y_1 = H ; Y_2 = Alk and T is a dialkylamino group, the amines of formula (II) are obtained by following an operating procedure analogous to that shown in scheme 6 below using an amine of formula



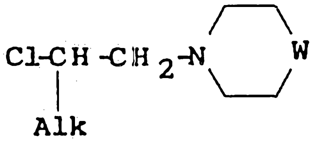
as a starting product.

When $n_1 = n_2 = 1$, Y_1 = H, Y_2 = $-CH_3$ and T is a morpholino or thiomorpholino group, D,L-2-morpholinopropylamine or D,L-2-thiomorpholinopropylamine are prepared in accordance with the following reaction scheme:

Scheme 6



Following the same operating procedure, the amines of formula (II) in which $n_1 = n_2 = 1$; $Y_1 = H$; $Y_2 = Alk$ (Alk $=C_1-C_3$ alkyl) and T represents a morpholino or thiomorpholinogroup can be prepared using an amine of formula



as a starting compound.

The following Examples illustrate the invention without however implying a limitation.

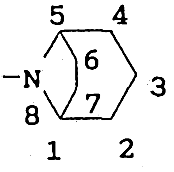
The melting points, m.p., were measured on a Koffler heating bench.

EXAMPLE 1

3-N-(8-Azabicyclo[3,2,1]octyl)ethylamino-6-(2-hydroxyphenyl)-5-methylpyridazine

$R_6 = 2\text{-OH}$; $R_V = \text{-CH}_3$; $Y_1 = Y_2 = H$;

$n_1 = n_2 = 1$; T = –N



A) 3-N-(8-Azabicyclo[3,2,1]octyl)ethylamino-6-(2-methoxyphenyl)-5-methylpyridazine

1.04g of N-(8-azabicyclo[3,2,1]octyl)ethylamine, 1.58 g of 3-chloro-5-methyl-6-(2-methoxyphenyl)-pyridazine and 0.38 g of ammonium chloride are dissolved in 2.5 ml of butanol and refluxed for 48 hours under argon. The reaction mixture is concentrated under vacuum and a 20% aqueous solution of potassium carbonate is then added to the residue until the pH is 13. The mixture is extracted with ethyl acetate, the organic phase is separated off by decantation and 30 ml of a 10 % aqueous solution of citric acid are then added. The aqueous phase is separated off, washed with ethyl acetate and rendered alkaline with 30 ml of a 33 % aqueous solution of sodium hydroxide. The oil formed is extracted with ethyl acetate and the organic phase is separated off, dried over Na_2SO_4, filtered and concentrated under vacuum.

The residue is purified by chromatography on alumina using ethyl acetate and then 9/1 (v/v) ethyl acetate/methanol, with 2 % of triethylamine added, as the eluent.

Concentration of the pure product fractions gives 1.2 g of the expected product.

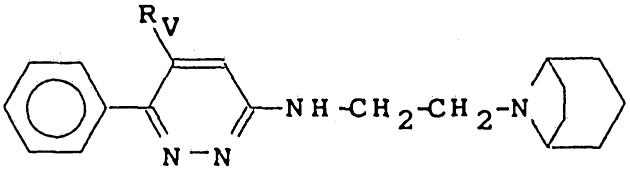
B) 3-N-(8-Azabicyclo[3,2,1]octyl)ethylamino-6-(2-hydroxyphenyl)-5-methylpyridazine

1.2 g of the product obtained above are dissolved in 60 ml of 48 % hydrobromic acid and the solution is refluxed for 48 hours. The reaction mixture is concentrated under vacuum and the residue is taken up in a saturated aqueous solution of potassium carbonate. The oil formed is extracted with methylene chloride and the organic phase is separated off, washed with a saturated solution of sodium chloride, dried over $MgSO_4$ and concentrated under vacuum. The residue is triturated in ether and the mixture is filtered and then purified by chromatography on alumina using 8/2 (v/v) ethyl acetate/methanol plus 2 % of triethylamine as the eluent. Concentration of the pure product fractions gives 0.8 g of the expected product.

M.p. = 208°C.

The compounds listed in Table 1 below are synthesized by following the procedure described in Example 1 and varying the starting 3-chloropyridazine.

Table 1

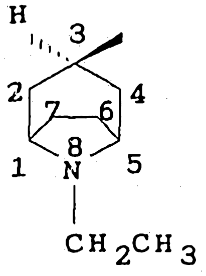


Example n°	R_V	Salt	Melting point; °C
2	$-CH_3$	2HCl	226
3	$-CH_2CH_2CH_3$	dioxalate	150

EXAMPLE 4

3-[8-N-Ethylazabicyclo[3,2,1]octyl-3α-amino]-6-phenyl-5-propylpyridazine difumarate

$R_6 = H$; $R_V = -CH_2CH_2CH_3$; $n_1 = n_2 = 0$; T =



1 g of 3-chloro-6-phenyl-5-propylpyridazine and 1 g of the diamine (IIa) are heated overnight in an autoclave at 160°C. The reaction mixture is taken up in methylene chloride and washed with a saturated aqueous solution of sodium carbonate. The organic phases are decanted, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue is chromatographed on silica gel using 97/3 (v/v) methylene chloride/methanol as the eluent. Concentration of the pure fractions gives a residue which crystallizes with two equivalents of fumaric acid.

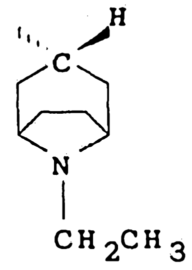
m = 0.44 g.

M.p. = 82°C.

EXAMPLE 5

3-[8-N-Ethylazabicyclo[3,2,1]octyl-3β-amino]-6-phenyl-5-propylpyridazine difumarate

$R_6 = H$; $R_V = -CH_2CH_2CH_3$; $n_1 = n_2 = 0$; T =



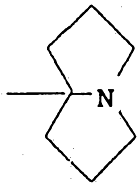
The above compound is prepared by following the procedure of Example 4 and replacing the diamine (IIa) with the diamine (IIe).

m = 0.5 g.

M.p. = 139°C.

EXAMPLE 6

3-(1-Azabicyclo[3,3,0]octyl-5-~~methylamine~~ylmethylamino)-5-methyl-6-phenylpyridazine difumarate

$R_6 = H$; $R_V = -CH_3$; $Y_1 = H$; $n_1 = 1$; $n_2 = 0$; T = 

1.52 g of 1-azabicyclo[3,3,0]octyl-2-methylamine, 2.21 g of 3-chloro-5-methyl-6-phenylpyridazine and 0.58 g of ammonium chloride are dissolved in 10 ml of pentanol and refluxed under argon for 24 hours. The reaction mixture is concentrated under vacuum by forming an azeotrope with water. The residue is rendered alkaline with a 10% aqueous solution of potassium carbonate and then extracted with ethyl acetate. The organic phase is separated off and 30 ml of a 10 % aqueous solution of citric acid are then added. The aqueous phase is separated off, washed twice with ethyl acetate and rendered alkaline with a 33% solution of sodium hydroxide until the pH is 13. The oil formed is extracted with ethyl acetate and the organic phase is decanted, dried over Na_2SO_4, filtered and chromatographed on alumina using ethyl acetate and then 9/1 (v/v) ethyl acetate/methanol, with 2 % of triethylamine added, as the eluent. Concentration of the pure product fractions gives 1 g of the expected product.

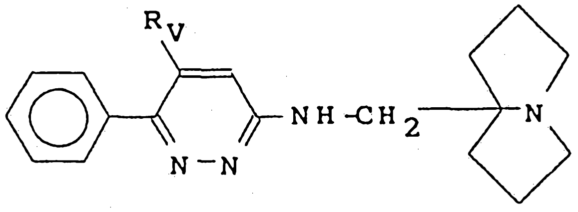
0.6 g of the base obtained is dissolved in the minimum amount of acetone, and a solution of 0.45 g of fumaric acid in acetone is then added.

The crystals are filtered off to give 0.1 g of the fumarate.

M.p. = 153.3°C.

The compound below is prepared by following the procedure described in Example 6 and varying the starting 3-chloropyridazine.

Table 2



Example n°	R_V	Salt	Melting point; °C
7	$-CH_2CH_2CH_3$	difumarate	179

The pharmacological properties of the compounds according to the invention were studied, in particular their affinity for the muscarinic cholinergic receptors of the M_1 and M_2 type.

In vitro, the compounds (I) were tested using the technique described by L. POTTER et al., J. Pharmacol. Exp. Ther., 1989, 284, 974-978, as regards their affinity for the M_1 receptors, and using the technique described by HAMMER R. et al., Life Science, 1986, 38, 1653-1662, as regards their affinity for the M_2 receptors.

The compounds according to the invention have a good affinity for the M_1 receptors and a marked specificity for the M_1 central receptors compared with the M_2 receptors.

By way of example, the compounds (I) according to the invention were found to have a 50 % inhibitory concentration, expressed in nanomol per liter, of the order of 3.2 and 110 on the M_1 and M_2 receptors respectively.

In vivo, the compounds according to the invention were tested using the test for the rotations induced by intrastriatal pirenzepine, described by Worms P. *et al.*, Psychopharmacology, 1987, 93, 489-493.

At a dose of 0.3 mg per kg of body weight, administered orally, the products according to the invention strongly inhibit the number of rotations induced by pirenzepine. Thus, by way of example, the compounds (I) according to the invention cause a 62 % inhibition of the rotations induced by pirenzepine.

Consequently the compounds (I) can be used as drugs.

The compounds according to the invention have a good affinity for the muscarinic receptors and a good activity in the tests for the amnesia induced by scopolamine or pirenzepine. They make it possible to envisage using the products according to the invention in all cases where a cholinergic deficiency is in evidence, and especially for the treatment of cognitive memory disorders and degenerative syndromes associated with senescence and senile dementia.

Finally, the compounds according to the invention showed no sign of toxicity at the doses at which they are active.

According to another feature, the present patent application therefore relates to the pharmaceutically acceptable compositions containing at least one of the compounds of formula (I) or one of their salts as the active principle.

In the pharmaceutical compositions of the present invention for oral, sublingual, transdermal or rectal administration, the active principles of formula (I) above can be administered to humans in unit forms of administration, mixed with the conventional pharmaceutical carriers, especially for the treatment of cognitive memory disorders or degenerative syndromes. The appropriate unit forms of administration include forms for oral administration, such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, forms for sublingual and buccal administration, forms for subcutaneous, intramuscular or intravenous administration and forms for rectal administration.

To achieve the desired effect, the dose of active principle can vary between 0.5 and 500 mg per day.

Each unit dose can contain from 0.1 to 100 mg of active ingredient in combination with a pharmaceutical carrier. This unit dose can be administered 1 to 5 times per day.

When a solid composition is prepared in the form of tablets, the active principle is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose or other appropriate substances or else they can be treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of active principle continuously.

A preparation in the form of gelatin capsules is obtained by mixing the active principle with a diluent and pouring the mixture obtained into soft or hard gelatin capsules.

The water-dispersible granules or powders can contain the active principle mixed with dispersants or wetting agents or with suspending agents such as polyvinylpyrrolidone, as well as with sweeteners or taste correctors.

Rectal administration is effected using suppositories; these are prepared with binders which melt at the rectal temperature, for example cacao butter or polyethylene glycols.

Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersants and/or wetting agents, for example propylene glycol and butylene glycol.

The active principle can also be formulated as microcapsules, together with one or more carriers or additives if appropriate.

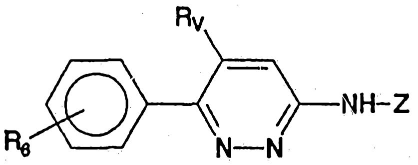
As a pharmaceutical preparation, it is possible to prepare gelatin capsules containing:

Compound of Example 1	0.010 g
Lactose	0.050 g
Magnesium stearate	0.005 g

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

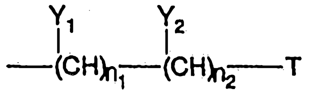
1. A compound of the formula:



(I)

in which:

- R_V is a linear or branched C_1-C_4 alkyl group;
- R_6 is hydrogen, a C_1-C_3 alkoxy or a hydroxyl group; and
- Z is a group



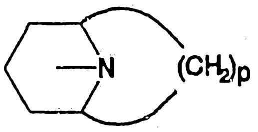
$$-\overset{Y_1}{\overset{|}{(CH)}}_{n_1}-\overset{Y_2}{\overset{|}{(CH)}}_{n_2}-T$$

in which:

* n_1 and n_2 independently are zero or one,

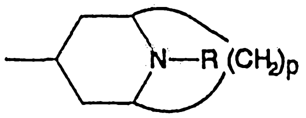
* Y_1 and Y_2 independently are hydrogen or a C_1-C_3 alkyl group, and

* T is a heterocycle selected from:



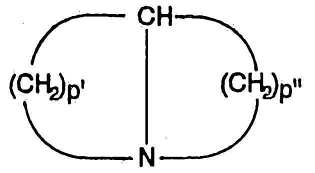
(a)

wherein $n_1 = n_2 = 1$
$Y_1 = Y_2 = H$
and p is 2 or 3;



(b)

wherein $n_1 = n_2 = 0$
and p is 2 or 3 and $R = C_1\text{-}C_3$ alkyl;



(c)

wherein $n_1 = 1$, $n_2 = 0$
$Y_1 = H$
and p' and p'' are 3 or 4;

and its pharmaceutically acceptable salt with organic or mineral acids.

2. A compound according to claim 1 wherein Z-NH- is represented by the group 2-(8-azabicyclo[3.2.1]oct-8-yl)ethylamino, or one of its pharmaceutically acceptable salts.

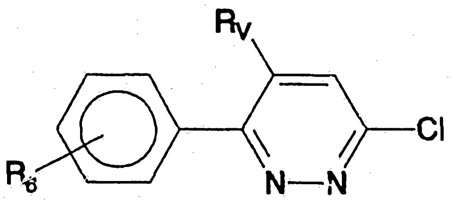
3. A compound according to claim 1 wherein Z-NH- is represented by the group 8-ethyl-8-azabicyclo[3.2.1]oct-3-ylamino, or one of its pharmaceutically acceptable salts.

4. A compound according to claim 1 wherein Z-NH- is represented by the group 1-azabicyclo[3.3.0]oct-5-ylmethylamino, or one of its pharmaceutically acceptable salts.

5. A method of preparing a compound according to claim 1, which comprises reacting an amine of the formula:

$$H_2N\text{-}Z \qquad \text{(II)}$$

in which Z is as defined for (I) in claim 1, with a 3-chloro-pyridazine of the formula:



(III)

in which R_V and R_6 are as defined for (I) in claim 1, and optionally, converting the resulting compound to a salt with a mineral or organic acid.

6. A pharmaceutical composition containing, as the active principle, an effective amount of a compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, mixed with at least one pharmaceutical excipient.

7. A composition according to claim 6 containing from 0.5 to 100 mg of active principle.

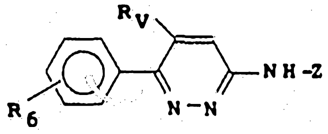
8. A compound according to claim 1, a method for the preparation thereof, or a pharmaceutical composition comprising a said compound, substantially as hereinbefore described with reference to the Examples.

DATED this 7th day of December, 1994
Elf Sanofi
By Its Patent Attorneys
DAVIES COLLISON CAVE

ABSTRACT OF THE DISCLOSURE

The invention relates to 3-aminopyridazine derivatives.

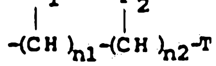
These compounds have the formula



(I)

in which:

- R_V is a linear or branched C_1-C_4 alkyl group;
- R_6 is hydrogen, a C_1-C_3 alkoxy or a hydroxyl group; and
- Z is a group

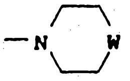


$$-(\overset{Y_1}{\overset{|}{CH}})_{n_1}-(\overset{Y_2}{\overset{|}{CH}})_{n_2}-T$$

in which:

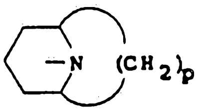
- * n_1 and n_2 independently are zero or one,
- * Y_1 and Y_2 independently are hydrogen or a C_1-C_3 alkyl group, and
- * T is a dialkylamino group in which the alkyls are C_1-C_3, if Y_1 or Y_2 is other than hydrogen, or T is a heterocycle selected from:

a)



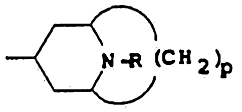
when $n_1 = n_2 = 1$
$Y_1 = CH_3$ and $Y_2 = H$ or
$Y_1 = H$ and $Y_2 = CH_3$
and W is an oxygen or sulfur atom

b)



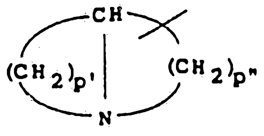
when $n_1 = n_2 = 1$
$Y_1 = Y_2 = H$
and p is 2 or 3 ;

c)



when $n_1 = n_2 = 0$
and p is 2 or 3 and $R = C_1$-C_3 alkyl;

d)



when $n_1 = 1$, $n_2 = 0$
$Y_1 = H$
and p' and p" are 3 or 4 ;

Application: drugs active on the central nervous system.

No figure.