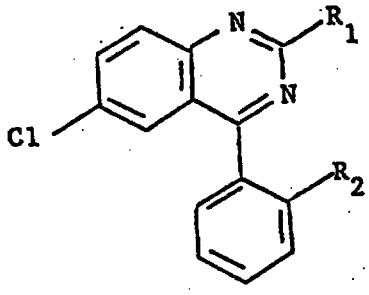
Description

The present invention relates to new derivatives of 2-piperazinyl 4-phenyl quinazoline, to a process for preparing said compounds and to the application thereof as drugs.

Derivatives of 6-chloro 4-phenyl quinazoline substituted in 2 position by a secondary or tertiary amino group and presenting an anti-inflammatory activity are described in patent US 3 509 141.

I an earlier Application (EP-A-79810), Applicants described derivatives of 4-phenyl quinazoline corresponding to general formula :



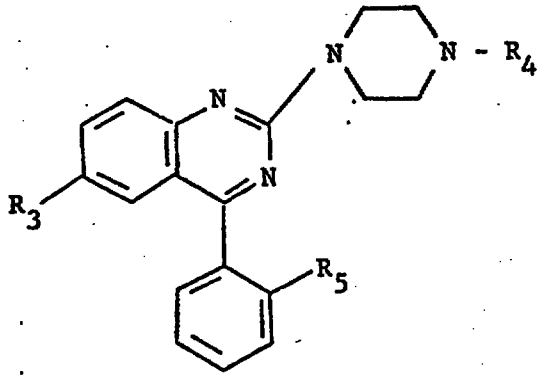
(I)

in which R_1 denotes a tertiary amine group, cyclic or not, itself bearing a hydroxyl group, and R_2 represents an atom of chlorine or of fluorine.

Compounds (I) are endowed with antiepileptic and narcosis potentialization properties allowing them to be used as drug by way of minor tranquillizers, hypnotics and antiepileptics.

It has been unexpectedly found that, by varying the nature of substituent R_1, the products obtained no longer present the pharmacological properties of products (I), but are endowed with highly interesting antidepressant properties.

The compounds according to the invention correspond to general formula :



(II)

in which

R_3 denotes a halogen, preferably chlorine or a nitro group,

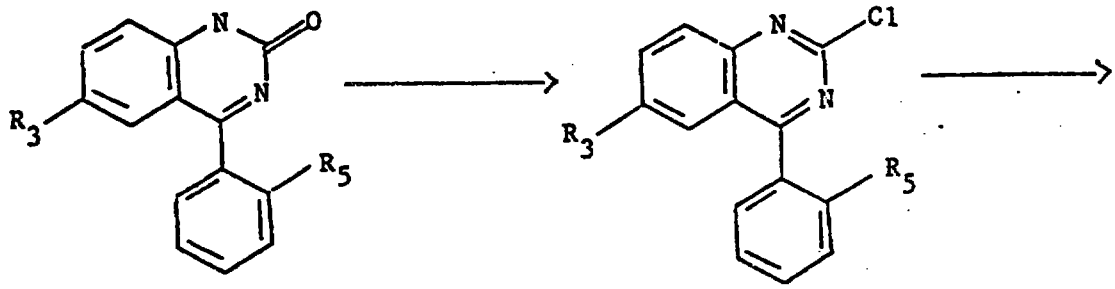
R_4 represents hydrogen or a lower alkyl group having from 1 to 4 atoms of carbon,

R_5 represents an atom of halogen, preferably chlorine or fluorine.

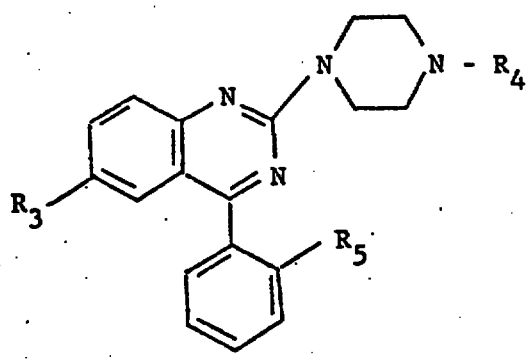
Compounds (II) furnish soluble salts with the mineral or organic acids. These salts, with pharmaceutically acceptable acids, form part of the invention.

It will be ntoed that in Spanish patent 453 982 a process is described for the preparation of derivatives of 2-amino quinazolines, substituted among others in 4 position by a phenyl radical possibly substituted. The products obtained according to the said method and described in said Spanish patent are different from the products described in the present application ; moreover the said Spanish patent does not furnish any usable information concerning the pharmacological properties of the products prepared therein.

Compounds (II) may be prepared from a 4-phenyl 2-quinazoline suitably substituted (I) according to the reaction diagram :



(1) (2)



(II)

By action on the quinazolone (I) of a chlorinated derivative of phosphorus, the derivative (2) chlorinated in 2 position is obtained. Phosphorus oxychloride is most often used. Operation may be carried out within an inert solvent such as an aromatic hydrocarbon (benzene or toluene) but, most often, it is preferred to use an excess of oxychloride as solvent. The reaction takes place at a temperature of between 60 and 120°C and, most often, at the boiling temperature of the solvent used.

Corresponding compound (II) is obtained from the chlorinated derivative (2), by action of an amine H - N⟨ ⟩N - R_4 in excess within an inert solvent such as ethanol. Operation is generally carried out by heating to the boiling temperature of the solvent.

The salts of compounds (II) are conventionally obtained by salifying the base, hot, by a stoichiometric quantity of acid within a suitably chosen solvent so that the salt formed crystallizes by cooling.

The starting quinazolones (1) are known compounds. When R_3 = halogen, they may in particular be prepared by action of potassium cyanate on a suitably substituted 2-amine 5-halogen benzophenone.

When R_3 represents the nitro group, compounds (1) may be obtained by action of the urea on a suitably substituted 2-amino 5-nitro benzophenone.

The following examples are given by way of illustration for the preparation of the compounds (II) according to the method indicated hereinbefore.

EXAMPLE 1

2-(1-methyl 4-piperazinyl) 4-(2-chloro phenyl) 6-nitro quinazoline (CM 40498)

(II) $R_3 = NO_2$; $R_4 = CH_3$; $R_5 = Cl$

a) 2-chloro 4-(2-chloro phenyl) 6-nitro quinazoline

A mixture of 40 g of 4-(2-chloro phenyl) 6-nitro 2-quinazolone and 600 ml of phosphorus oxychloride is heated to reflux for 4 hours. The phosphorus oxychloride is evaporated in vacuo to dryness, then

the residue is poured into an ice-water mixture. It is rendered alkaline with a 10% sodium hydroxide solution. The precipitate is drained and washed with acetonitrile. The product is purified by chromatography over a column of silica. By eluting with a chloroform-methanol (95-5 vol/vol) mixture, the expected product is isolated. Weight: 27 g; m.p.: 228°C (isopropanol).

b) CM 40498

A mixture of 3.2 g of the chlorinated derivative obtained hereinabove and 3 g of N-methyl piperazine in 120 ml of absolute ethanol is heated to reflux for 3 hours. The solvent is evaporated to dryness in vacuo, then the residue is taken up in ethyl acetate. The solution is washed with an aqueous solution of sodium carbonate then with water. The solution is dried over sodium sulfate then evaporated to dryness. The residue is recrystallized in a methanol-dichloromethane mixture. Crystals are obtained. Weight: 3.1 g; m.p.: 204°C.

EXAMPLES 2 to 6

a) By operating as in Example 1a), but by varying the quinazolone, the following are obtained in the same manner:

- 2-chloro 4-(2-fluoro phenyl 6-nitro quinazoline;
  m.p.: higher than 260°C (isopropanol)
- 2,6-dichloro 4-(2-chloro phenyl) quinazoline
  m.p.: 175-176°C (ethanol)
- 2,6-dichloro 4-(2-fluoro phenyl) quinazoline
  m.p. : 208-210°C (acetonitrile)

b) From the various derivatives chlorinated in 2 position mentioned hereinbefore and by varying the H - N⟨ ⟩N - R_4 amine used, the different compounds (II) shown in Table I hereinafter are obtained as indicated in Example 1b).

The products according to the invention have been subjected to pharmacological trials with a view to determining their activity on the central nervous system.

The various tests to which the products have been subjected will be indicated hereinbelow. In all cases, the products under study were adminstered per os.

A - PORSOLT TEST

This test was carried out in the female mouse, CDI (Charles Rivers, France) weighing from 18 to 23 g, according to the method described by Porsolt (Archives Internationales de Pharmacologie, 1977, 229, 327-336).

The principle of this test is as follows: when a mouse is placed in a narrow recipient, filled with water, it struggles then, after 2 to 4 minutes, becomes still and floats on its stomach, its back rounded and its rear paws brought underneath its body; it makes only the few movements to enable it to hold its head out of the water. This is the so-called despair reaction.

Certain psychotherapeutics, particularly antidepressants, lengthen the time during which the mouse struggles.

The following protocol was chosen:

The products to be studied were administered orally to batches of 10 mice. 1 hour later, the animals are placed in a narrow recipient (10 x 10 x 10 cm), filled with water up to a height of 6 cm, the temperature of the water being 24°C. The animals are left in the water for 6 minutes and the time during which the animal remains immobile between the second and the sixth minute is measured - the shorter the time, the more the substance is active.

The results are expressed as the reduction in the immobilization time with respect to controls.

B - ANTAGONISM OF PTOSIS INDUCED BY RESERPINE

The majority of antidepressants antagonize the ptosis induced by reserpine. This test described by Gouret [Journal de Pharmacologie (Paris), 1973, 4 (1), 105-128] was made in the female mouse, CDI (Charles Rivers, France) weighing from 18 to 23 g. The reserpine causes a ptosis 1 hour after its intravenous administration; certain antidepressants, particularly the imipraminics, oppose this ptosis.

The following protocol has been chosen:

The substances to be studied were administered per os to batches of 10 mice. The reserpine was administered simultaneously by the intravenous route at the dose of 2 mg/kg. 1 hour after the administration of reserpine, the number of animals not presenting ptosis

is noted.

C - ANTAGONISM OF THE HYPOTHERMIA INDUCED BY RESERPINE

The majority of antidepressants antagonize the hypothermia induced by reserpine. This test was carried out according to the method described by HINO et Coll [Chem Pharm Bull 28 (9), 2618-2622, 1980] on female mice, CDI (Charles Rivers, France) weighing from 18 to 23 g.

The following protocol was chosen:

The substances to be studied are administered per os to batches of 10 mice, the controls receive the solvent alone, simultaneously, the reserpine is administered i.p. at the dose of 5 mg/kg. The temperature of each animal is taken immediately before administration of the products to be tested and 4 hours afterwards. For each animal, the difference in temperature before and after treatment is calculated. The results are expressed in percentage of antagonism of the hypothermia observed in the controls.

D - POTENTIALIZATION OF THE TOXICITY OF YOHIMBINE

The majority of antidepressants potentialize the toxicity of yohimbine. This test was carried out according to the method described by MALICK (in Antidepressants : Neurochemical Behavioural and Clinical Perspectives, eds S.J. Enna, J.B. Malick, E. Richelson, Raven Press, New York, pages 141-155)on female mice, CDI (Charles Rivers, France).

The substances to be studied are administered per os to batches of 10 mice. The yohimbine is administered i.p. 1 hour later at the dose of 30 mg/kg. Mortality is noted 18 hours later.

E - ANTAGONISM OF THE TREMORS INDUCED BY OXOTREMORINE

The cholinergic effects of the imipramine are considered as being responsible for certain undesirable secondary effects of this substance. These effects are demonstrated by the antagonism of the tremors induced by oxotremorine. This test was carried out on female mice, CDI (Charles Rivers, France) weighing from 18 to 23 g.

The following protocol was chosen:

The products to be studied are administered at time 0 by the oral route to batches of 10 mice. At time 60 mins., the oxotremorine is administered per os at the dose of 1 mg/kg. The number of mice

which do not tremble 30 mins. after the administration of oxotremorine is noted.

All the pharmacological results obtained with various compounds according to the invention are set forth in Table II hereinafter. This Table also shows the results obtained, on the one hand, with imipramine, which is a compound whose antidepressant properties are widely used in therapeutics and, on the other hand, with compound CM 40331 or hydrochloride of 6-chloro 4-(2-chloro phenyl) 2-(4-hydroxy 1-piperidinyl) quinazoline, the compound described by Applicants in its French Patent Application No. 81 19767.

The results of Table II clearly show that the products according to the invention possess a powerful antidepressant activity. This activity is, in the majority of cases, more powerful than that of imipramine and is accompanied by a toxicity and secondary effects of cholinergic type clearly less than those of imipramine.

Furthermore, it may be noted that the product CM 40331 studied in comparison is virtually inactive on the tests carried out.

Consequently, the products according to the invention may be used in human therapeutics for the treatment of neuropsychic disorders such as endogenous, reactional or neurotic depressive states as well as for the treatment of depression in senile involution.

The products may be presented in the galenic forms corresponding to the oral route (tablets, capsules, etc...) and to the parenteral route (injectable ampoules).

Dosage, which varies as a function of the disorders to be treated and of the mode of administration, will be progressive and will be between 50 and 300 mg per day in the adult.

By way of example, the following galenic preparation containing a product of the invention may be indicated:

CAPSULE

CM 40468	0.025 g
Starch STA RX 1500	0.140 g
Aerosil 200	0,0005 g
Magnesium stearate	0.0015 g
for a No. 3 capsule	

TABLE I

Example n°	Code No. of product	R_3	R_4	R_5	Base or salt Melting point (solvent)
2	40460	Cl	CH_3	Cl	Hydrochloride m.p. > 260°C (methanol)
3	40468	Cl	CH_3	F	Base m.p. : 146-148°C (methanol)
4	40508	NO_2	CH_3	F	Base m.p. : 220-222°C (ethanol)
5	41125	Cl	H	F	Hydrochloride m.p. > 260°C (isopropanol)
6	41128	Cl	$-CH_2CH_2CH_3$	F	Base 130-132°C (ethanol)

TABLE II

Products n°	Toxicity	Porsolt test (dose in mg/kg)	Antagonism of ptosis induced by reserpine ED 50 (mg/kg)	Antagonism of hypothermia induced by reserpine (at 10mg/kg)	Potentialization of yohimbine ED 50 (mg/kg)	Antagonism of oxotremorine ED 50 (mg/kg)
40 498	Atoxic at 1g/kg	- 31%** (10)	2,8	+ 68%**	7,8	43,5
40 460	LD 80 = 1g/kg	- 11%* (10)	2,1	+ 71%** (at 20mg/kg)	5,4	142
40 468	Atoxic at 1g/kg	- 61%** (10)	0,98	+ 73%**	1,65	50
41 125	LD 40 = 1g/kg	- 46** (5)	0,48	+ 81%**	0,74	9,5
41 128	Atoxic at 1g/kg	- 31** (5)	6,2	+ 62%**	1,7	-
Imipramine	LD 50 = 453mg/kg	- 30%** (10)	2,4	+ 59%**	9,1	12
40 331	Atoxic at 500mg/kg	-	0% at 100mg/kg	- 20% at 100mg/kg	10% at 100mg/kg	-

* $p < 0,05$ ** $p < 0,01$