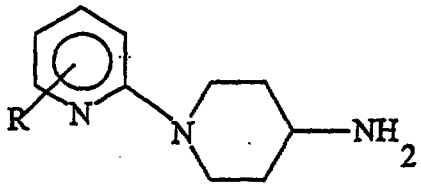
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# USE OF 4-AMINO-1-(2-PYRIDYL) PIPERIDINES AS ANTICONVULSANT AND ANTI-EPILEPTIC AGENTS

The present invention concerns a novel therapeutic use of some 4-amino-1-(2-pyridyl)piperidines.

Patent EP-B-0021973 describes the class of 4-amino-1-(2-pyridyl)piperidines of general formula (I)



(I)

in which R may represent hydrogen, a halogen atom, a methyl, trifluoromethyl, ($C_1$-$C_3$)alkoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, ($C_1$-$C_3$)alkylthio, trifluoromethylthio, or phenoxy or phenylthio group optionally substituted with a halogen atom, a trifluoromethyl group, a ($C_1$-$C_3$)alkyl, ($C_1$-$C_3$)alkoxy, ($C_1$-$C_3$)alkylthio, or cyano group, and of the pharmaceutically acceptable salts thereof as well as a process for their preparation.

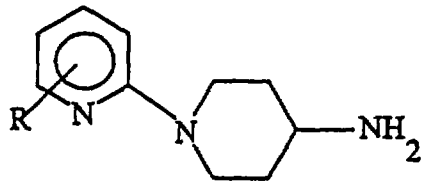
The compounds of formula (I) are described therein as anorexigenic agents, essentially devoid of major secondary effects such as sedative or stimulating activity, locomotor activity inhibition and undesirable cardiovascular effects.

Among the products of formula (I), 4-amino-1-(6-chloro-2-pyridyl)piperidine hydrochloride, described in Example 1 of patent EP-B-0021973 and called CM 57227, has been subjected to all the tests required to enter the clinical phase. Tested in man at 10 mg, the product showed to be well tolerated.

It has now been found that the compounds of formula (I) in which R is as defined above, as well as their pharmaceutically acceptable salts, show a very interesting anticonvulsant activity at doses which do not produce any anorexigenic activity. The compounds of formula (I) and their addition salts are therefore recommended for the treatment of convulsions and epilepsy in man.

A first object of the present invention is therefore the use of at least one compound of formula (I)

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(I)

in which R represents hydrogen, a halogen atom, a methyl, trifluoromethyl, ($C_1$-$C_3$)alkoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, ($C_1$-$C_3$)alkylthio, trifluoromethylthio, or phenoxy or phenylthio group optionally substituted with a halogen atom, a trifluoromethyl group, a ($C_1$-$C_3$)alkyl, ($C_1$-$C_3$)alkoxy, ($C_1$-$C_3$)alkylthio, or cyano group, or of a pharmaceutically acceptable salt thereof, for the preparation of a medicament intended to be used in therapeutics against convulsions and notably those of epileptic origin.

In the text of the present patent application, the term "halogen" identifies one of the four conventional halogens; fluorine, chlorine and bromine being particularly preferred.

The terms "($C_1$-$C_3$)alkyl", "($C_1$-$C_3$)alkoxy", and "($C_1$-$C_3$)alkylthio", designate groups containing the residue of a saturated aliphatic hydrocarbon containing 1, 2 or 3 carbon atoms, i.e. methyl, ethyl, propyl and isopropyl groups.

Pharmaceutically acceptable salts of the compounds of formula (I) comprise the non-toxic salts derived from mineral or organic acids salifying one or both basic functions present in the molecules of the compounds of formula (I) above, such as the hydrochlorides, hydrobromides, sulfates, phosphates, succinates, tartrates, fumarates, maleates, pamoates, napsylates, mesylates, tosylates, etc.

A preferred class of compounds of formula (I) comprises the compounds of formula (I) in which R is at position 6- of the 2-pyridyl radical, as well as their pharmaceutically acceptable salts.

An even more advantageous class comprises the compounds of formula (I) in which R is hydrogen, a halogen atom or a methyl or ($C_1$-$C_3$)alkoxy group at position 6-, as well as their pharmaceutically acceptable salts.

Particularly preferred compounds are 4-amino-1-(6-chloro-2-pyridyl)piperidine and its pharmaceutically acceptable salts, 4-amino-1-(6-

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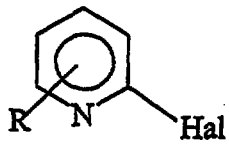


bromo-2-pyridyl)piperidine and its pharmaceutically acceptable salts, 4-amino-1-(6-methyl-2-pyridyl)piperidine and its pharmaceutically acceptable salts, 4-amino-1-(6-methoxy-2-pyridyl)piperidine and its pharmaceutically acceptable salts.

Most preferred, among them, are 4-amino-1-(6-chloro-2-pyridyl)piperidine and its pharmaceutically acceptable salts.

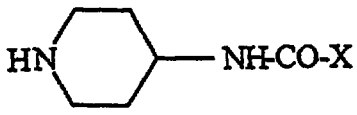
"Preferred or advantageous" shall mean preferred or advantageous in the new therapeutic use of the present invention.

These compounds are easily prepared, according to the general method described in patent EP-B-0021973, by reacting the corresponding 2-halopyridine of formula (II):



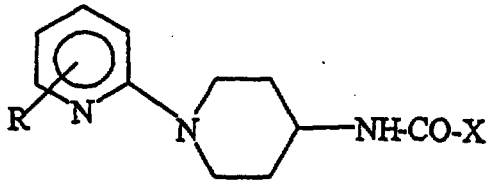

(II)

in which R is as defined above and Hal represents a halogen atom, with a blocked 4-aminopiperidine of formula (III):




(III)

in which X represents a hydrogen atom or a ($C_1$-$C_4$)alkyl group,
and submitting then the thus obtained N-acylated 4-amino-1-(2-pyridyl)piperidine of formula (IV):




(IV)

to hydrolysis under acidic or basic conditions.

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A more detailed description of the general method of preparation of the compounds (I) as well as some specific examples thereof are contained in the above cited European patent EP-B-0021973.

The novel anticonvulsant activity of the compounds of formula (I) has been appraised by assessing the effects of the compounds (I) in the electroshock-induced convulsion test in mice and in the pentylenetetrazol-induced convulsion test in mice in accordance with the procedures outlined by C.S. Goodman, M.Singh Grewal, W.C. Brown and E.A. Swinyard in J. Pharmacol. Exp. Ther. 108, 168-176, (1953).

In these tests, Swiss female mice weighing 22 to 26 g were employed divided in groups of 10 mice each. Each group of 10 mice was housed in a cage one week before the test, kept in a room at constant temperature (21°C ± 1°C), under a dark/light cycle and allowed free access to food and water. The products of formula (I) to be tested as well as pentylenetetrazol have been dissolved in distilled water. The injection volume of the products used was 0.4 ml per 20 g of body weight.

- **Pentylenetetrazol-induced convulsions.**

  The compounds of formula (I) have been administered intraperitoneally 30 minutes before the intraperitoneal administration of 130 mg/kg of pentylenetetrazol (dose necessary for inducing a convulsive crisis in 80% of the control mice). Groups of 10 mice each have been employed for each dose [0 mg/kg (control mice); 3 mg/kg; 10 mg/kg; 30 mg/kg].

- **Electroshock-induced convulsions.**

  These convulsive crises have been induced by electroshock using a RACIA apparatus for small animals with corneal electrodes. A 12 volts shock of 0.4 second's duration is necessary for inducing a convulsive crisis in 80% of the control mice.

  The compounds of formula (I) to be tested have been administered intraperitoneally 30 minutes before the shock.

  The same doses as in the preceding test and groups of 10 mice for each dose have been employed also in this test.

The results obtained in the above tests show that the products of formula (I) exert a remarkable protective effect against convulsions with $ED_{50}$s (doses which protect 50% of the animals) always lower than 30 mg/kg.

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By way of example, in the electroshock-induced convulsion test, 4-amino-1-(6-chloro-2-pyridyl)piperidine (the compound of formula (I) in which R = 6-Cl) showed an $ED_{50}$ well below 3 mg/kg and in the pentylenetetrazol-induced convulsion test an $ED_{50}$ lower than 10 mg/kg.

Furthermore, the compounds of formula (I) are endowed with a low toxicity consistent with a therapeutic use thereof.

On the basis of the thus demonstrated properties, the compounds of formula (I) are therefore recommended for the treatment of convulsions and particularly of epilepsy in man.

For the use as anticonvulsants, the compounds of formula (I) as well as their pharmaceutically acceptable salts, may suitably be administered orally, parenterally, sublingually, rectally or transdermally, formulated in pharmaceutical compositions in which they are generally associated with a compatible and pharmaceutically acceptable adjuvant, diluent and/or coating.

The amount of active principle to be administered daily depends on the particular therapeutic indication, on the severity of the disease to be treated, as well as on the weight of the patient and the administration route.

Anyway the daily total dosage in man may generally vary from 0.05 to 100 mg, e.g. from 0.1 to 50 mg, and more preferably from 0.5 to 20 mg.

The pharmaceutical compositions for the use of the compounds of formula (I) as anticonvulsant agents which contain at least one product selected from the compounds of formula (I) and their pharmaceutically acceptable addition salts in association with an inert pharmaceutical vehicle, may be prepared by the conventional methods well known in the field of industrial pharmacy.

The active principle may be incorporated into excipients usually employed in the pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, aqueous or non-aqueous vehicles, fats of animal or vegetable origin, paraffin derivatives, glycols, the different wetting, dispersing or emulsifying agents, preservatives, etc.

For the oral administration, which is anyway the preferred route of administration, suitable pharmaceutical forms include tablets, delayed

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release tablets, sugar-coated tablets, capsules, suspensions, solutions or even liposomes.

As for the intravenous, subcutaneous or intramuscular administration, sterile or sterilisable solutions are employed, while for the rectal administration, conventional suppositories, or capsules or microenemas can be prepared.

For transdermal administration, conventional patches prepared by techniques well known to the person skilled in the art can be employed.

Unit dosage forms suitable for the new therapeutic use will generally contain from 0.05 to 20 mg, preferably from 0.1 to 10 mg, including for example from 0.5 to 5 mg (i.e. 0.5; 1; 1.5; 2; 2.5; 3; 3.5; 4; 4.5 and 5 mg) of product. Said unitary dosage forms are typically administered once or more times a day, preferably one to three times a day.

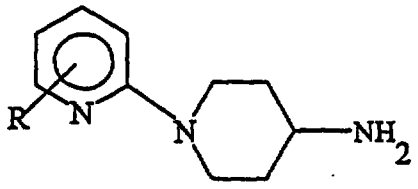
If desired, the pharmaceutical compositions of the present invention may also contain one or more other medicaments known and commonly employed in the same therapeutic indications.

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## CLAIMS

1. Use of at least one compound of formula (I)



(I)

in which R represents hydrogen, a halogen atom, a methyl, trifluoromethyl, ($C_1$-$C_3$)alkoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, ($C_1$-$C_3$)alkylthio, trifluoromethylthio, or phenoxy or phenylthio group optionally substituted with a halogen atom, a trifluoromethyl group, a ($C_1$-$C_3$)alkyl, ($C_1$-$C_3$)alkoxy, ($C_1$-$C_3$)alkylthio, or cyano group, or of a pharmaceutically acceptable salt thereof, for the preparation of a medicament with anticonvulsive activity

2. Use according to claim 1 of at least one compound of formula (I) in which R is at position 6- of the 2-pyridyl radical.

3. Use according to claim 2 of at least one compound of formula (I) in which R represents a hydrogen atom, a halogen atom, a methyl group, or a ($C_1$-$C_3$)alkoxy group at position 6-.

4. Use according to claim 3 of at least one compound of formula (I) selected from 4-amino-1-(6-chloro-2-pyridyl)piperidine, 4-amino-1-(6-bromo-2-pyridyl)piperidine, 4-amino-1-(6-methyl-2-pyridyl)piperidine, 4-amino-1-(6-methoxy-2-pyridyl)piperidine and the pharmaceutically acceptable salts thereof.

5. Use according to claim 4 of at least one compound of formula (I) selected from 4-amino-1-(6-chloro-2-pyridyl)piperidine and the pharmaceutically acceptable salts thereof.

6. Use of a compound mentioned in any one of the preceding claims for the preparation of a medicament with antiepileptic activity.