The present invention relates to the use of trifluoromethylphenyl–tetrahydropyridines for the preparation of drugs intended for treating anxiety and generally anxio–depressive disorders.

European patents EP–60,176 and EP–101,381 describe some N–substituted trifluoromethylphenyltetrahydropyridines with anorectic activity.

Patent application EP–164,633 describes indole derivatives which act on the central nervous system.

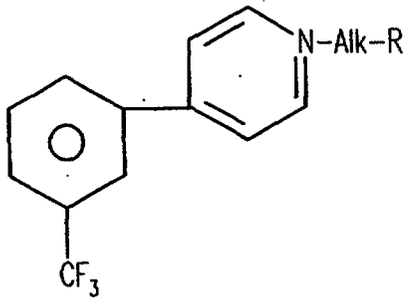
US Patent 4,485,109 describes 4–aryl–4–piperidinecarbinols which are useful as antidepressants and in some cases as anorectic agents.

It has now been found that said trifluoromethylphenyltetra–hydropyridines have a good anxiolytic and antidepressant activity.

It has also been found that the anxiolytic activity of said compounds is not accompanied, at anxiolytically effective doses, by a sedative effect.

It has finally been found that the anxiolytic and antidepressant activities are elicited at doses which are remarkably lower than those which produce anorexia.

Thus, the present invention relates to the use of trifluoromethyl–phenyltetrahydropyridines of the formula



in which Alk represents a straight or branched alkylene group having 1 to 4 carbon atoms and R represents a cyano group, an acetyl group, a cycloalkyl group having 3 to 7 carbon atoms, a pyridyl group, a 1–oxide–pyridyl group or a naphthyl group, and of their pharmaceutically acceptable salts, as active principles for the preparation of drugs for treating anxiety and anxio–depressive disorders.

The compounds of formula I and the preparation thereof are described in EP–60,176 and EP–101,381.

In formula I, when R represents the pyridyl group, said group is attached to Alk by one of the carbon atoms in the 2, 3 or 4–position; when R represents the naphthyl group, it is attached to Alk either in the 1–position or in the 2–position.

Compounds of formula I in which Alk is the ethylene group and R is a 2–pyridyl, 4–pyridyl, 1–oxide–4–pyridyl, cyclohexyl or 2–naphthyl group and those of formula I in which Alk is an ethylene, propylene or butylene group and R is the cyano group as well as their pharmaceutically acceptable salts are the most preferred, 1[2–(2–naphthyl)ethyl]–4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyridine and its pharmaceutically acceptable salts, particularly the hydrochloride (compound of example 7 of EP–101,381, hereinafter indicated as SR 57746 A), being particularly advantageous.

Among the above compounds, 4–(3–trifluoromethylphenyl)–1–(2–cyanoethyl)–1,2,3,6–tetrahydropyridine hydrochloride (formula I, Alk = ethylene and R = cyano, CM 57493, described in examples 2 and 15 of EP–60,176) has been submitted to all the tests required to enter the clinical human phase. It showed to be well tolerated and poorly toxic and substantially devoid of unwanted side–effects. Tested in the human at 80 and 160 mg, this product was well tolerated and favourably affected the mood.

The compounds of formula I which proved to be active, at very low doses, in a range of predictive tests for an anxiolytic and/or antidepressant activity, are therefore useful as anxiolytics and/or antidepressants for the preparation of drugs intended for the treatment of anxiety and anxio–depressive disorders.

The compounds of formula I can be administered orally, sub–lingually, transdermally or parenterally. The amount of active principle which has to be administered for the treatment of anxiety and depression will depend, as usual, on the type and on the severity of the disorders to be treated, as well as on the weight of the patients.

In human beings the dosage may vary from 0.2 to 150 mg of product per day, administered once to three times a day, the lower doses being suitable for children.

For the preparation of pharmaceutical compositions according to the present invention, the active principles (compounds of formula I and their pharmaceutically acceptable salts) are administered in unit dosage forms of from 0.2 to 150 mg, preferably from 0.5 to 50 mg, of said active principle, alone or in admixture with a pharmaceutical excipient.

In particular, when a solid composition is prepared in the form of tablets, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatine, starch, lactose, magnesium stearate, talc, arabic gum and the like. The tablets may be coated with sucrose or other appropriate materials or they may be treated so that their activity is extended or delayed and that they continuously release a predetermined amount of active principle.

A preparation in capsules is obtained by mixing the active ingredient with a diluent and by pouring the mixture obtained in soft or hard capsules.

A preparation in the form of syrup or elixir may contain the active ingredient jointly with a possibly acaloric sweetening agent, methylparaben and propylparaben as antiseptics, as well as a flavoring agent and an appropriate dye.

Water–dispersible powders or granulates may contain the active ingredient mixed with dispersing agents or wetting agents, or suspending agents such as polyvinylpyrrolidone and the like, and with sweetening or flavoring agents as well.

The active principle may also be formulated in the form of microcapsules, possibly with one or more carriers or additives.

For sublingual administration microtablets or microcapsules can be prepared which placed under the tongue will rapidly dissolve. These compositions will generally contain the active ingredient in admixture with wetting and/or dispersing agents and optionally with absorption enhancers.

For transdermic administration the use of polymeric diffusion matrices for the continuous and preferably sustained release of the active principle can be devised as well as the use of the active principle as a microemulsion with excipients adapted for contact with the skin.

For parenteral administration, aqueous suspensions, isotonic saline solutions or sterile injectable solutions are used, which contain

pharmacologically compatible dispersing and/or wetting agents, for example propyleneglycol or butyleneglycol.

The pharmaceutical compositions are prepared according to the known methods, already described in EP-60,176 and EP-101,381.

The following examples further illustrate the invention.

Example 1

An active principle representative of the present invention, SR 57746 A, has been evaluated in the territorial aggressiveness (T.A.) test carried out in mice according to the method described by C.Y. Yen et Al. in Arch. Int. Pharmacodyn., 1959, 123, 179-185. In this test SR 57746 A showed to be active at 1 mg/kg p.o..

In this test, the pharmacological activity of SR 57746 A lasted longer than 7 hours when administered at 3 mg/kg p.o..

Example 2

An active principle representative of the present invention, SR 57746 A, has been evaluated in the Geller-Seifter Conflict (C.G-S) test carried out in rats according to the method described by J. Geller et Al. in Psychopharmacologia, Berlin, 1960, I, 482-492. SR 57746 A elicited an anxiolytic effect at a dose ten times lower than the sedative one. More particularly release of punished responses which is related to the anxiolytic activity was observed at doses as low as 3 mg/kg p.o., whereas reduction of the unpunished responses which correlates with the sedative activity was observed at 30 mg/kg p.o.. Anorectic activity in the rat is obtained at 10.4 mg/kg p.o..

Example 3

SR 57746 A showed to be active also in a test which is specifically claimed to be a model of anxiety i.e. in the conditioned taste adversion test in rats and in particular in the lithium induced taste adversion test (L.A.) which has been performed according to the method described by G.N. Evin et al. in Drug Development Research, 1987, 11, 87-95. The minimal effective dose of SR 57746 A was 3 mg/kg p.o..

Example 4

SR 57746 A was active also in a specific model claimed to be a model of antidepressive activity, i.e. the learned helplessness test which has been carried out in rats according to the method described by A.D. Sherman et al. in Pharmacol. Biochem. Behav., 1982, 16, 449–454. The oral active doses was 0.5 mg/kg/day for 5 days and the elicited effect was identical to that obtained with an oral dose of 32 mg/kg/day of imipramine.

Example 5

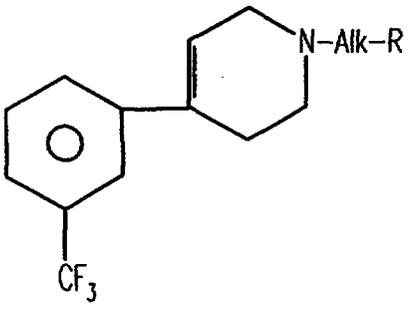
Tablets comprising 2 mg or 4 mg of SR 57746 A, as the free base, are prepared by using the ingredients of Example 11 of EP–101,381 in equivalent proportions.

Analogously tablets comprising 2.5, 5 and 10 mg of active principle are prepared.

* C L M S *

CLAIMS

1. Use of trifluoromethylphenyltetrahydropyridines of the formula



in which Alk represents a straight or branched alkylene group having 1 to 4 carbon atoms and R represents a cyano group, an acetyl group, a cycloalkyl group having 3 to 7 carbon atoms, a pyridyl group, a 1–oxide–pyridyl group or a naphthyl group, and of their pharmaceutically acceptable salts,

as active principles for the preparations of drugs intended for the treatment of anxiety and anxio–depressive disorders.

2. Use according to claim 1, characterized in that in formula I Alk represents an ethylene, propylene or butylene group and R is the cyano group.

3. Use according to claim 1, characterized in that in formula I Alk is the ethylene group and R is a 2–pyridyl, 4–pyridyl, 1–oxide–4–pyridyl, cyclohexyl or 2–naphthyl group.

4. Use according to claim 3, characterized in that in formula I, R is a 2–naphthyl group.

5. Use according to claim 4, characterized in that the active principle is 1–[2–(2–naphthyl)ethyl]–4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyridine hydrochloride.