Use of 1-[4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyrid-1-yl]-2-(6,7-dimethoxynaphth-2-yl)ethane for preparing medicines for the treatment of cerebral and neuronal disorders

The present invention relates to the use of 1-[4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyrid-1-yl]-2-(6,7-dimethoxynaphth-2-yl)ethane (I) for the preparation of drugs intended for the treatment and/or prophylaxis of cerebral and neuronal diseases.

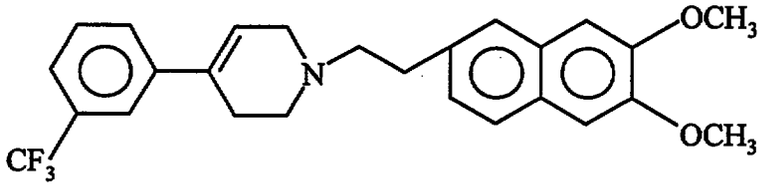
EP 0 458 696 describes the use of 1-[2-(naphth-2-yl)ethyl]-4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine for the preparation of drugs intended for the treatment of neurodegeneration.

The compound (I), its salts and their preparation are described in EP 0 458 697. The laxative activity of the compound of formula (I) and its pharmaceutically acceptable salts is also described in said patent application.

Surprisingly, it has now been found that, among the products described in EP 0 458 697, the compound of formula (I) and its pharmaceutically acceptable salts and solvates exert neurotrophic effects on the nervous system which have proved to be similar to the effects of nerve growth factor (NGF).

Furthermore the compound of formula (I) and its pharmaceutically acceptable salts have the ability to increase neuronal survival.

The present invention therefore relates to the use of 1-[4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyrid-1-yl]-2-(6,7-dimethoxynaphth-2-yl)ethane of formula (I):



(I)

and its pharmaceutically acceptable salts and solvates for the preparation of drugs intended for the treatment and/or prophylaxis of diseases associated with neuronal degeneration.

Among the pharmaceutically acceptable salts of the compound of formula (I), there may be mentioned those formed with pharmaceutically acceptable acids, for example those with mineral acids, such as the hydrochloride, hydrobromide, borate, phosphate, sulfate, hydrogensulfate and hydrogenphosphate, and those with

organic acids, such as the citrate, benzoate, ascorbate, methylsulfate, naphthalene-2-sulfonate, picrate, fumarate, maleate, malonate, oxalate, succinate, acetate, tartrate, mesylate, tosylate, isethionate, α-ketoglutarate, α-glycerophosphate and glucose-1-phosphate.

This discovery is particularly surprising because the compound of formula (I) seems to be the only compound, among those of the class described in EP 0 458 697, to possess this neurotrophic activity.

The activity of the compound of formula (I) and its pharmaceutically acceptable salts on the nervous system was demonstrated by tests carried out using neurons isolated from dissections of the septal region of rat embryos.

More particularly, the septal region of 17- to 18-day-old rat embryos was removed under a dissecting microscope under sterile conditions and then dissociated in a trypsin/ethylenediaminetetraacetic acid (EDTA) medium. The cellular suspension was placed in a culture flask in a DME/Ham's F12 (v:v) medium (Dulbecco Modified Eagle's medium/Ham's F12 nutrient mixture - R.G. Ham, Proc. Nat. Sci., 1965, 53, 288) containing 5% of calf serum and 5% of horse serum, and was kept at 37°C for 90 minutes. This treatment makes it possible to remove the non-neuronal cells.

The neuroblasts are then inoculated at a rate of 17×10^4 cells/cm^2 into a non-serum culture medium consisting of DME/Ham's F12 medium containing selenium (30 nM) and transferrin (1.25 µM) in the wells of a titer plate. Each well has been treated with poly-L-lysine beforehand. The inoculated plates are placed in an incubator in the oven (37°C; 5% CO_2).

The test compounds are dissolved in dimethyl sulfoxide (DMSO) and diluted with the culture medium as required.

The neuroblasts are kept in plates containing the test compound or the corresponding solvent for 4 days without the medium being changed.

After 4 days the medium is replaced with a tetrazolium salt dissolved in the culture medium (0.15 mg/ml). The cells are then placed in the oven at 37°C for 4 hours. The mitochondrial succinate dehydrogenases of the living cells reduce the tetrazolium salt to formazan blue, whose optical density is measured at 540 nm after dissolution in DMSO. This density has a linear correlation with the number of living cells (Manthorpe et al., Dev. Brain Res., 1988, 25, 191 - 198).

The difference between the groups containing the test compounds and the controls was evaluated by statistical analysis using the two-tailed Dunnett t-test.

In this test the compound of formula (I) was found to be more active than the compounds described in EP 0 458 696, a significant activity being apparent at very low concentrations, starting from 2.5 nM.

Moreover the compound of formula (I) and its pharmaceutically acceptable salts and solvates have advantages over the compounds described in EP 0 458 696 through the presence of the methoxy groups. This substitution in fact prevents the formation of metabolites due to oxidation on the naphthalene group.

By virtue of this potent neuroprotective activity and their low toxicity compatible with use as drugs, the compound of formula (I), its pharmaceutically acceptable addition salts and its solvates can be used for the preparation of pharmaceutical compositions indicated in the treatment and/or prophylaxis of all diseases involving neuronal degeneration. More particularly, the compounds of the invention can be used, either by themselves or in co-administration or association with other CNS active principles, for example selective M1 cholinomimetics, NMDA antagonists and nootropics such as piracetam, especially in the following indications: memory disorders, vascular dementia, postencephalitic disorders, postapoplectic disorders, post-traumatic syndromes due to a cranial traumatism, disorders deriving from cerebral anoxia, Alzheimer's disease, senile dementia, subcortical dementia such as Huntington's chorea and Parkinson's disease, dementia caused by AIDS, neuropathies deriving from morbidity or damage to the sympathetic or sensory nerves, and brain diseases such as cerebral edema, spinocerebellar degenerations and motor neuron degenerations, for example amyotrophic lateral sclerosis.

The compounds of the invention can conveniently be administered orally, parenterally, sublingually or transdermally. The amount of active principle to be administered in the treatment of cerebral and neuronal disorders by the method of the present invention depends on the nature and severity of the complaints to be treated and on the weight of the patients. Nevertheless the preferred unit doses will generally comprise from 0.5 to 700 mg, advantageously from 2 to 300 mg and preferably from 5 to 150 mg, for example between 5 and 50 mg, i.e. 1, 2, 5, 10, 15, 20, 25, 30, 40 or 50 mg of product. These unit doses will normally be administered one or more times a day, for example 2, 3, 4 or 5 times a day and preferably one to three times a day, the overall dose in man varying between 0.5 and 1400 mg per day, advantageously between 1 and 1000 mg per day, for example from 2 to 500 mg and more conveniently from 5 to 200 mg per day.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, transdermal or rectal administration, the active principle can be administered to animals and humans in unit forms of administration, either as such, for example in lyophilized form, or mixed with conventional pharmaceutical carriers, for the treatment of the above-mentioned complaints. The appropriate unit forms of administration include oral forms such as tablets, which may be divisible, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, sublingual and buccal forms of administration, subcutaneous, intramuscular or intravenous forms of administration, local forms of administration and rectal forms of administration.

A solid composition in the form of tablets is prepared by mixing the main active ingredient with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talcum, gum arabic or the like. The tablets can be coated with sucrose or other appropriate substances or they can be treated so as to have a sustained 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 ingredient with a diluent and pouring the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir can contain the active ingredient together with a sweetener, which is preferably calorie-free, methylparaben and propylparaben as antiseptics, as well as a flavoring and an appropriate color.

Water-dispersible powders or granules can contain the active ingredient mixed with dispersants or wetting agents, or with suspending agents such as polyvinylpyrrolidone, and with sweeteners or taste correctors.

Rectal administration is effected using suppositories, which are prepared with binders melting at the rectal temperature, for example cocoa butter or polyethylene glycols.

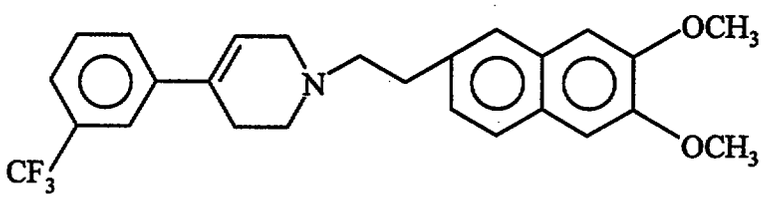
Parenteral administration is effected using aqueous suspensions, saline solutions or injectable sterile solutions containing pharmacologically compatible dispersants and/or wetting agents, for example propylene glycol or butylene glycol.

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

In the pharmaceutical compositions according to the present invention, the active principle can also be in the form of an inclusion complex in cyclodextrins, their ethers or their esters.

CLAIMS

1. Use of 1-[4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyrid-1-yl]-2-(6,7-dimethoxynaphth-2-yl)ethane of formula (I):



(I)

and its pharmaceutically acceptable salts and solvates for the preparation of drugs intended for the treatment and/or prophylaxis of diseases associated with neuronal degeneration.

2. Use according to claim 1 for the treatment of memory disorders, vascular dementia, postencephalitic disorders, postapoplectic disorders, post-traumatic syndromes due to a cranial traumatism, disorders deriving from cerebral anoxia, Alzheimer's disease, senile dementia, subcortical dementia such as Huntington's chorea and Parkinson's disease, dementia caused by AIDS, neuropathies deriving from morbidity or damage to the sympathetic or sensory nerves, brain diseases such as cerebral edema, and spinocerebellar degenerations, motor neuron degenerations such as amyotrophic lateral sclerosis.

3. Use according to claim 2 for the treatment of vascular dementia, senile dementia and Alzheimer's disease.