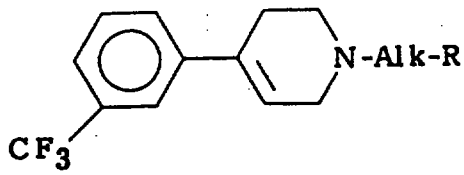
The present invention refers to a new therapeutic use of some tetrahydropyridine derivatives as well as to the new products thus employed.

European Patent Application EP–A–101,381 discloses a class of tetrahydropyridine derivatives of general formula (A)



(A)

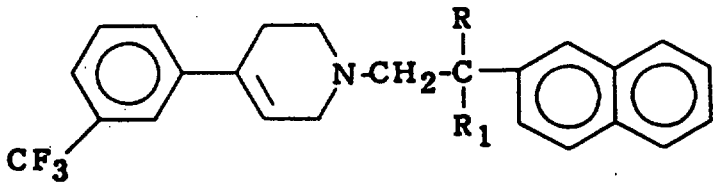
in which Alk represents a straight or branched alkylene chain of from 2 to 4 carbon atoms and R is pyridyle, pyridyle N–oxide, unsubstituted naphthyl or naphthyl substituted with a lower alkyl group.

For the products of this class an anorexigenic activity has been indicated and claimed in the above patent application.

Another Patent Application, EP–A–369,887, describes the use of some derivatives of formula (A) where R is inter alia a naphthyl group, as therapeutic agents for treating anxiety and anxio–depressive disorders.

It has now been found that the compounds of formula (A) above, in which R is a 2–naphthyl group and Alk stands for an ethylene group optionally substituted with one or two methyl groups on the carbon atom linked to the R group, as well as their addition salts are endowed with a very interesting activity as free radical scavengers.

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



(I)

in which R and R_1, each independently, may represent a hydrogen atom or a methyl group, or one of its pharmaceutically acceptable acid addition salts, for the preparation of a pharmaceutical composition for the treatment or prevention of those clinical conditions in which free radicals are implicated.

Free radicals are chemical species containing one or more unpaired electrons which being highly reactive may start uncontrollable chain reactions at cell level.

They are capable therefore of reversibly or unreversibly damaging compounds of all biochemical classes including proteins, amino acids, lipids, lipoproteins, nucleic acids, and carbohydrates thus affecting such cell main activities as membrane function, metabolism, and gene expression.

There are many clinical disorders wherein an important role of free radicals, either as primary or secondary etiological agents or as amplifiers of the original disease, has been envisaged (see Oxygen Radicals and Human Disease – *Annals of Internal Medicine, 1987, 107, 526–545* and more particularly Table 1 on page 527 which is incorporated within the present application by reference).

Substantial evidence has recently been produced to confirm the role of free radicals in post–injury degeneration of the brain and spinal cord and in ischemic–reperfusion tissue damage (B. Halliwell Ed., *Proceedings of the Upjohn Symposium on Oxidants and Disease – Bethesda: Federation of American Societies for Experimental Biology, 1987,* and J.M. McCord, N.Eng.J.Med., 1985, 312, 159–163).

It seems to be certain in fact that in ischemias the secondary lesions due to the hypoxia are less damaging than those caused by the large flux in the ischemic tissues of free radicals whose production is triggered by molecular oxygen, that occurs when blood circulation is restored.

It has also been demonstrated that the lesions which are caused by reperfusion are not limited to heart and brain but also affect kidney, liver, pancreas, and the endothelial vascular and smooth muscle system.

Particularly apparent is the role of oxygen radicals in myocardial injury caused by ischemia–reperfusion (S.R. Jolly et al., *Circ. Res., 1984, 54, 277–85*; L.C. Becker et al., *Prog. Cardiovasc. Dis., 1987, 30, 23–44*; and R. Bolli et al., *Circ. Res., 1989, 65, 607–622*).

It has also been demonstrated that injury by free radicals may also occur in inflamed rheumatoid joints (T. Woodruff et al., *Am. Rheum. Dis., 1986, 45, 608–611).*

In general the compounds of formula (I) may be employed in therapy in any pathological process which involves cellular damage as it has been shown that in all these processes oxygen radicals are implicated.

More precisely, clinical applications where the compounds of formula (I) may suitably be used include therefore protection against post-injury degeneration of the brain and spinal cord, and ischemia-reperfusion injury.

Other clinical applications in which the compounds of formula (I) and their pharmaceutically acceptable acid addition salts, as free radical scavengers, may be employed include protection against damage in the cornea or in the retina caused by oxygen radicals, such as cataract of oxidative origin and retinopathy of prematurity; organ preservation, particularly kidney preservation, for transplantations; protection against damage by radiation; prevention of relapse of duodenal ulcers; and protection against tissue damage caused by toxic agents whose toxicity is due to the production of free radicals.

For the use as free radical scavengers the compounds of formula (I) as well as their pharmaceutically acceptable salts may suitably be administered orally, sublingually, parenterally, transdermally or topically, formulated in pharmaceutical compositions.

Said pharmaceutical compositions contain at least one product selected from the compounds of formula (I) and their pharmaceutically acceptable acid addition salts, in admixture with an inert pharmaceutical carrier.

Both organic and inorganic acids can be employed to form non-toxic and pharmaceutically acceptable acid addition salts of the compounds of formula (I).

Illustrative acids are sulfuric, nitric, phosphoric, hydrochloric, citric, acetic, lactic, tartaric, pamoic, ethanedisulfonic, sulfonic, succinic, cyclohexylsulfonic, fumaric, maleic, and benzoic acid.

As for the oral or sublingual administrations, optionally sugar-coated tablets, capsules, optionally sustained-release granules, drops, and liposomes, are preferably employed. As for the intravenous, subcutaneous, or intramuscular administration, sterile or sterilisable solutions are employed, particularly those suitable as intravenous infusions, while conventional patches may be used for transdermal administration. For

topical administration, ointments or lotions to be applied to the skin, solutions or ophthalmic ointments for the eyes can be employed.

The pharmaceutical compositions according to the present invention may be prepared according to procedures well known in the pharmaceutical field.

In the preparation of said pharmaceutical compositions the active principle may be incorporated in the ordinarily used excipients such as talc, gum arabic, lactose, starch, magnesium stearate, aqueous or non aqueous vehicles, fats of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing, or emulsifying agents, preservatives, etc.

The pharmaceutical compositions of the invention may advantageously contain a compound of formula (I) or one of its pharmaceutically acceptable addition salts in combination with one or more other known drugs generally employed for the same therapeutical indications.

The amount of active principle to be administered daily, according to the method of the present invention, depends on the particular therapeutical indication, the severity of the conditions to be treated as well as the weight of the patient and the administration route.

For systemic administration the overall daily dosage in humans is generally comprised between 2 and 900 mg, for instance between 3 and 500 mg, and more suitably between 10 and 300 mg.

Unit dosage forms for systemic administration will typically contain from 2 to 300 mg, preferably from 5 to 150 mg, comprising for instance from 5 to 50 mg (namely 5, 10, 20, 30, 40, and 50 mg) of product. Generally, said unit dosage forms will be administered once or more times a day, preferably 1 to 3 times a day.

For topical administration, the pharmaceutically compositions typically contain from 0.0001 to 1% of active principle and preferably from 0.01 to 0.5%. The unit dosage form for topical administration for the eyes (a drop) will generally contain from 10 ng to 10 mg, and preferably from 100 ng to 1 mg.

A further specific object of the present invention is therefore a method to prevent and control any pathological conditions implicating free radicals which method comprises administering to a mammal in need

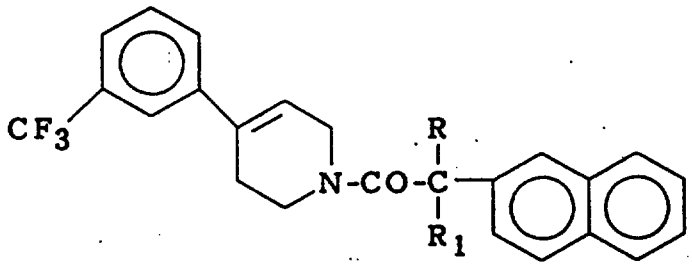
thereof an effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) where one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom or a methyl group as well as their acid addition salts are new products and represent a further specific object of the present invention.

The compound of formula (I) where one of R and R_1 is a methyl group and the other is a hydrogen atom contains a chiral center.

The present invention relates to the pure isomers of this compound as well as any mixture thereof.

These compounds may be prepared, according to a general method, by the reduction of the corresponding amide of formula (II)



(II)

in which one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom or a methyl group.

Said reduction may suitably be carried out by means of an aluminum hydride or a complex lithium aluminum hydride in an inert organic solvent at a temperature comprised between 0°C and the reflux temperature of the reaction mixture. The thus obtained product may then be optionally converted into one of its acid addition salts.

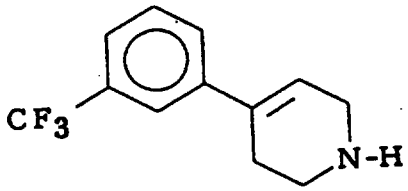
The reduction reaction is carried out according to well known procedures by using, as the reducing agent, aluminum hydride or a complex lithium aluminum hydride, such as $LiAlH_4$, $LiAlH(OCH_3)_3$ and the like. Generally the reaction is carried out in an inert solvent such as an ether, e.g. diethyl ether, tetrahydrofuran, dioxane or 1,2–dimethoxyethane.

According to a preferred embodiment, the reaction is carried out using a double molar proportion of lithium aluminum hydride, $LiAlH_4$, with respect to the starting compound (II), at a temperature of 20–30°C, in diethyl ether and under inert atmosphere. After about one hour, the

reduction reaction is complete and the desired compound is isolated according to conventional techniques as the free base or as a salt thereof.

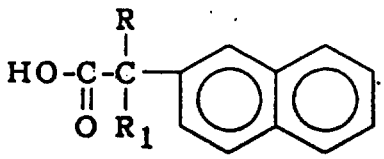
The free base may be converted into one of its salts by simple salification in an organic solvent such as an alcohol, preferably ethanol or isopropanol, an ether, such as 1,2–dimethoxyethane, ethyl acetate or a hydrocarbon such as hexane.

The compounds of formula (II) are prepared by reacting 4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyridine of formula (III)



(III)

with a functional derivative of a carboxylic acid of formula (IV)



(IV)

where one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom or a methyl group, in an organic solvent at a temperature comprised between –10°C and the reflux temperature of the reaction mixture.

As suitable functional derivatives there may be used the activated free acid (e.g. with BOP), the anhydride, mixed anhydrides, active esters and acid halides, preferably acid chlorides. Among the active esters, particularly preferred is the p–nitrophenyl ester, but methoxyphenyl, trityl, benzhydryl and the like esters are also suitable.

The reaction temperature may range between –10°C and the reflux temperature but generally the reaction is carried out at room temperature or at a temperature of 30–50°C. It may be preferable to carry out the reaction in the cold when it is exothermic, e.g. when an acid chloride is employed as functional derivative of the acid of formula (IV).

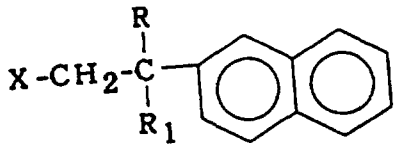
As for the reaction solvent, preferably an alcohol is employed such as methanol or ethanol, or a halogenated solvent such as methylene chloride, dichloroethane, chloroform and the like solvents, but other organic

solvents compatible with the reactants used, such as for example dioxane, tetrahydrofuran, or hydrocarbons, e.g. hexane, may be employed as well.

The reaction may conveniently be carried out in the presence of a proton acceptor such as an alkali metal carbonate or a tertiary amine.

The product obtained at the end of the reaction is generally an oil which may be isolated and characterised according to conventional techniques or employed as such in the reduction of the hydride.

Alternatively, the new compounds of formula (I) may also be prepared by reacting 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydro-pyridine (III) with a compound of formula (V)



(V)

in which one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom or a methyl group and X represents a chlorine, bromine, iodine atom or an electron-attracting group such as methanesulfonyloxy or p-toluenesulfonyloxy.

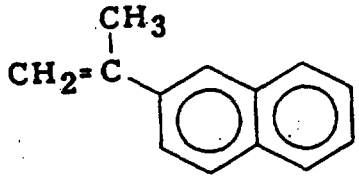
The reaction is carried out in an organic solvent at a temperature ranging between room temperature and 200°C.

Preferred organic solvents are aliphatic alcohols of 1 to 6 carbon atoms, such as methanol, ethanol, n-butanol, n-pentanol, but other solvents such as hexane, dimethylformamide, dimethylsulfoxide, sulfolane, acetonitrile, pyridine, and the like may be employed as well.

The reaction is conveniently carried out in the presence of a basic condensation agent, such as triethylamine, particularly when X represents a halogen atom.

The reaction temperature may range between room temperature (about 20°C) and 200°C and the reaction time will depend on the temperature employed. In general, the reaction is complete after heating at 100-150°C for 4-5 hours and the thus obtained end product can then be isolated according to conventional techniques and optionally converted into a salt thereof by simple salification in an organic solvent such as an alcohol, preferably ethanol or isopropanol, an ether, such as 1,2-dimethoxyethane, ethyl acetate or a hydrocarbon, such as hexane.

Furthermore, when a compound of formula (I) is desired in which one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom, it may also be prepared by reacting 4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyridine (III) with the compound (VI)



(VI)

in the presence of a basic condensation agent.

PREPARATION 1

1–[4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyrid–1–yl]–2–(naphth–2–yl)–propane hydrochloride

a) A solution of 2–(naphth–2–yl)propanoic acid ethyl ester (8 g, 0.035 mol) and potassium hydroxide (8 g) in a mixture of methanol (80 ml) and water (80 ml) is heated to 40°C for 2 hours. The reaction mixture is then concentrated to dryness, the residue is dissolved in water (100 ml) and concentrated hydrochloric acid is added thereto to bring the pH to 3.5. The precipitate which forms is recovered by filtration and dissolved in ethyl ether and the thus obtained solution is filtered on celite and concentrated to dryness thus affording 2–(naphth–2–yl)propanoic acid (4.4 g). M.p. 112–114°C.

b) A solution of the product obtained in step a) above (4.2 g, 0.021 mol) and 1,1–carbonyldiimidazole (3.5 g, 0.021 mol) in tetrahydrofuran (40 ml) is stirred at room temperature for 1 hour. A solution of 4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyridine (4 g, 0.018 mol) in tetrahydrofuran (20 ml) is then added thereto and the reaction mixture is stirred at room temperature for 2 hours and concentrated to dryness. The thus obtained residue is dissolved in ethyl ether and the solution is then washed with water, 2N of hydrochloric acid, water, 10% $NaHCO_3$, and finally with water. The solution is filtered on celite and concentrated to dryness thus affording an oily product (6.3 g) consisting of 1–[4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyrid–1–yl]–1–oxo–2–(naphth–2–yl)propane.

c) A solution of the compound obtained in step b) above (6.3 g, 0.015 mol) in ethyl ether (60 ml) is added dropwise to a suspension of $LiAlH_4$ (1.15 g, 0.031 mol) in ethyl ether (20 ml) and the reaction mixture is then stirred at room temperature for 2 hours.
Excess reducing agent is then destroyed by the very slow addition of water, the mixture is filtered and the filtrate is concentrated to dryness. The residue is dissolved in acetone and the compound of the title, as a raw product, is precipitated from the obtained solution by the addition of gaseous hydrochloric acid. The precipitate is separated by filtration, the free base is obtained therefrom by neutralization with sodium hydroxide, extraction with ethyl acetate and evaporation of the organic solvent. The obtained product, as the free base, is then purified by flash chromatography using a cyclohexane/ethyl acetate 9/1 mixture as the eluant, and converted into the corresponding hydrochloride by treatment with gaseous hydrochloric acid in propanol. The product is allowed to crystallise and is recovered by filtration affording the compound of the title (1.5 g). M.p. 178–180°C.

PREPARATION II

1–[4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyrid–1–yl]–2–methyl–2–(naphth–2–yl)propane hydrochloride

a) A solution of 2–methyl–2–(naphth–2–yl)propanoic acid ethyl ester (7 g, 0.028 mol) and potassium hydroxide (7 g) in a mixture of ethanol (40 ml) and water (40 ml) is heated to the reflux temperature for 2 hours. The reaction mixture is then concentrated to dryness, the residue is dissolved in water and the aqueous solution is washed with ethyl ether. Concentrated hydrochloric acid is added thereto to bring the pH to 1, the precipitate which forms is recovered by filtration and crystallised from ethanol 50° (40 ml) thus affording 2–methyl–2–2(naphth–2–yl)propanoic acid (3 g). M.p. 125–127°C.

b) A solution of the compound obtained in step a) above (3 g, 0.014 mol), 4–(3–trifluoromethylphenyl)–1,2,3,6–tetrahydropyridine (3.6 g, 0.014 mol), benzotriazol–1–yloxytris–(dimethylamino)–phosphonium hexafluorophosphate (BOP) (5.6 g, 0.014 mol), and triethylamine (4 ml, 0.028 mol) in methylene chloride (40 ml) is allowed to stand at room temperature for 4 hours. The reaction mixture is then concentrated to

dryness, the residue is taken up with ethyl acetate and the solution is then washed sequentially with water, a 2N hydrochloric acid solution, water, a 2N sodium hydroxide solution, and water. The solution is filtered on celite and concentrated to dryness thus affording 1-[4-(3-trifluoromethyl-phenyl)-1,2,3,6-tetrahydropyrid-1-yl]-1-oxo-2-methyl-2-(naphth-2-yl)propane (4 g).

c) A solution of the compound obtained in step b) above (4 g, 0.0094 mol) in ethyl ether (40 ml) is added dropwise into a suspension of $LiAlH_4$ (0.7 g, 0.0184 mol) in ethyl ether (40 ml). The reaction mixture is then stirred at room temperature for 4 hours and excess reducing agent is then destroyed by the very slow addition of water (1.5 g). The solution is filtered, washed with water and concentrated to dryness. The obtained residue is then purified by flash chromatography eluting with a cyclohexane/ethyl acetate 15/1 mixture. The free base is thus obtained (1.4 g) which is then dissolved in isopropanol. Hydrochloric acid in ethanol is added thereto and the compound of the title is then allowed to crystallise yielding 1.2 g. M.p. 231-233°C.

PHARMACOLOGICAL EVALUATION

The anti-radical properties of the compounds of formula (I) have been determined by means of a lipid peroxidation test carried out as follows: rat brain homogenates (1.5 mg/ml) have been incubated in Krebs buffer (100 μl) (composed of 15 mM HEPES, pH 7.4, 10 mM glucose, 140 mM NaCl, 3.6 mM KCl, 1.5 mM $CaCl_2$, 1.4 mM KH_2PO_4, and 0.7 mM $MgCl_2$), at 37°C for 20 minutes following the addition of 200 μM Fe^{2+} to initiate the reactions.

Lipid peroxidation has been assessed by the formation of thiobarbituric acid-reactive oxidation products (TBAR) during the 20 minute incubation as described by J. Braughler et al. in *J. Biol. Chem., 1986, 261, 10282-10289.*

By the addition of different concentrations of the compounds of formula (I) in Krebs buffer, the IC_{50} of these compounds, i.e. the concentration of these compounds which affords a 50% inhibition of lipid peroxidation over the controls, has been easily calculated.

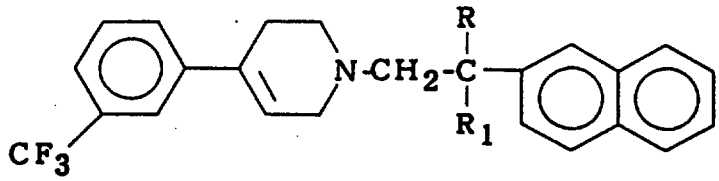
In this test the compounds of formula (I) showed to be very active. In particular the compound of formula (I) in which R and R_1 are both

hydrogen, as the hydrochloride, is characterised by an IC_{50} of approximately 1–2 μM.

The compounds described in Preparation I and Preparation II, which have almost the same activity level, have the advantage over the compound of formula (I) where R and R_1 are hydrogen of a very limited serotoninergic activity (the compound of Preparation I) or of no serotoninergic activity (the compound of Preparation II).

CLAIMS

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



(I)

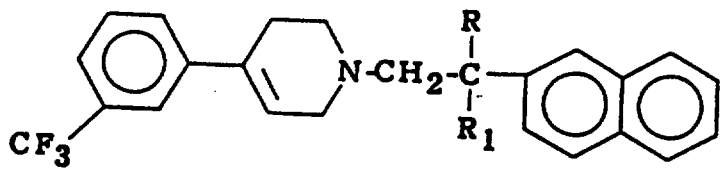
in which R and R_1, each independently, represent a hydrogen atom or a methyl group, or of a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment and/or prevention of any pathological conditions implicating free radicals.

2. Use according to claim 1 for the preparation of a medicament for the treatment and/or prevention of pathological processes involving cell damage.

3. Use according to claim 2 for the preparation of a medicament for the control and/or prevention of post-injury degeneration of the brain and spinal cord, ischemic-reperfusion injury, damage in the cornea or retina due to oxygen radicals, organ damage in transplantations, cell damage by radiation, relapse of duodenal ulcers, tissue damage due to toxic agents which produce free radicals, and injury by free radicals in inflamed rheumatoid joints.

4. Use according to any one of claims 1 to 3, in which the compound of formula (I) is 1-[4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyrid-1-yl]-2-(naphth-2-yl)ethane or a pharmaceutically acceptable acid addition salt thereof.

5. Compound of formula (I)



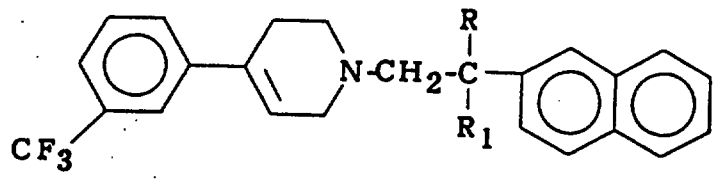
(I)

in which one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom or a methyl group, and its acid addition salts.

6. Compound according to claim 5 selected from 1-[4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyrid-1-yl]-2-(naphth-2-yl)propane and its acid addition salts.

7. Compound according to claim 5 selected from 1-[4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyrid-1-yl]-2-methyl-2-(naphth-2-yl)propane and its acid addition salts.

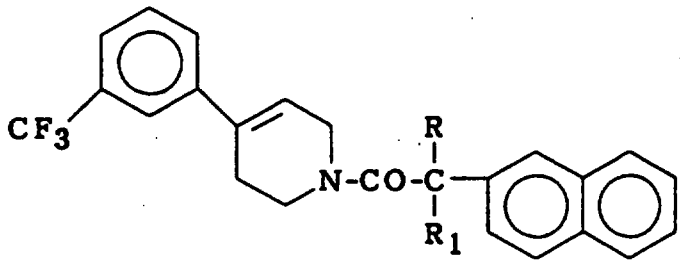
8. Process for the preparation of a compound of formula (I)



(I)

in which one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom or a methyl group and its acid addition salts, which comprises

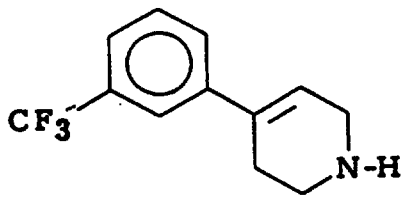
a) reducing the corresponding amide of formula (II)



(II)

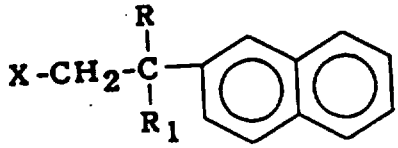
in which R and R_1 are as defined above; or

b) reacting 4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydropyridine of formula (III)



(III)

with a compound of formula (V)

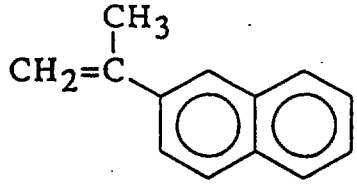


(V)

in which R and R_1 are as defined above and X represents a chlorine, bromine, iodine atom or an electron-attracting group;

or

c) when a compound of formula (I) is desired in which one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom, reacting the compound of formula (III) with the compound (VI)

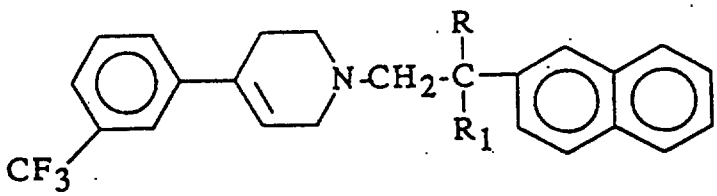


(VI)

in the presence of a basic condensation agent;

optionally followed by conversion of the thus obtained product into an acid addition salt thereof.

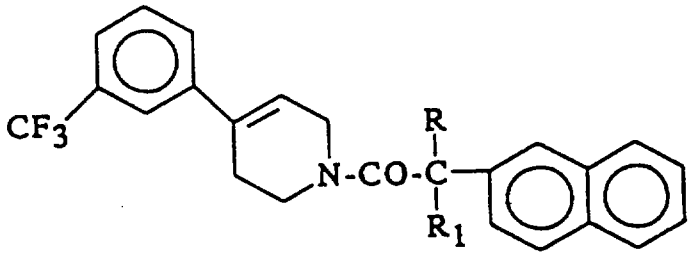
9. Pharmaceutical composition containing as the active principle at least one compound of formula (I)



(I)

in which one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom or a methyl group, or a pharmaceutically acceptable acid addition salt thereof.

10. Compound of formula (II)



(II)

in which one of the radicals R and R_1 is a methyl group and the other is a hydrogen atom or a methyl group.