Title: 4-ARYLPYPERIDINE DERIVATIVES AND USE THEREOF FOR PREPARING A MEDICAMENT FOR THE TREATMENT OF CNS DISORDERS

Abstract: The invention relates to novel 4-arylpiperidine derivatives and organic or inorganic acid addition salts thereof. The compounds of the invention and the salts thereof display pharmacological activity towards the central nervous system, particularly antidepressant activity. The invention further relates to pharmaceutical compositions comprising a 4-arylpiperidine derivative of the invention or a pharmaceutically acceptable salt thereof, as well as a process for the preparation of said derivatives.
4-arylpiperidine derivatives and use thereof for preparing a medicament for the treatment of CNS disorders

The present invention relates to novel 4-arylpiperidine compounds, pharmaceutical compositions comprising the same, the use of novel 4-arylpiperidine compounds for the preparation of a medicament, as well as a process for the preparation of said compounds.

Various arylpiperidine derivatives are described in the prior art. For example the US patents US 4,146,629, US 4,268,095 and US 4,048,314 describe arylpiperidine derivatives substituted in positions 3 and 4 of the piperidine ring, as well as the activities of said compounds as antidepressants.

The present invention now provides novel arylpiperidine derivatives useful for the treatment of disorders affecting the central nervous system (CNS), particularly as antidepressants, characterised by having significant affinity and selectivity towards the serotonin transporter (SERT).

The compounds forming the subject of the invention are piperidine derivatives, di-substituted in position 4 of the piperidine ring, and having the following general formula (I):

![Chemical Structure](image)

wherein:
R₁ is selected from hydrogen and lower alkyls; X is a
heteroatom selected from the group consisting of oxygen, sulphur and nitrogen; \( R_2 \) is \(-(\text{CH}_2)_n-Y\), wherein \( n \) is an integer comprised between 1 and 4 and \( Y \) is aryl substituted with one or more substituents independently selected from the group consisting of halogen, trifluoromethyl \(-\text{CF}_3\), methyl \(-\text{CH}_3\), 3,4-methylenedioxy \(3,4-\text{O-CH}_2-\text{O-}\) and phenyl; when \( X \) is an oxygen or nitrogen atom, \( Ar \) is phenyl substituted with one or more substituents independently selected from the group consisting of halogen, trifluoromethyl \(-\text{CF}_3\), methyl \(-\text{CH}_3\) and phenyl; when \( X \) is a sulphur atom, \( Ar \) is phenyl substituted with one or more substituents in position 3 and/or 4 and/or 5 independently selected from the group consisting of halogen, trifluoromethyl \(\text{CF}_3\), methyl \(\text{CH}_3\), 3,4-methylenedioxy \(3,4-\text{O-CH}_2-\text{O-}\) and phenyl.

The expression "lower alkyl" indicates a saturated or unsaturated, linear or branched alkyl group having from 1 to 6 carbon atoms, preferably from 1 to 4 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl and each of the hexyl isomers.

Within the scope of the present invention, the compounds most preferred for their pharmacological properties are the compounds of formula (I) wherein \( X \) is an oxygen atom, \( R_1 \) is a hydrogen atom and \( R_2 \) is \(-(\text{CH}_2)_n-Y\), wherein \( Y \) is mono-substituted phenyl and \( n \) is 1.

The derivatives of formula (I) wherein \( X \) is oxygen or sulphur are obtained by means of synthetic processes involving the obtainment of the alcohol intermediate of formula (II) starting from the corresponding piperidone.
In formula (II), Ar and R₁ have the same meanings indicated previously with reference to formula (I).

When the R₁ substituent of the final derivative of formula (I) is a hydrogen atom, the nitrogen atom of the piperidine ring is protected, starting from the piperidone stage onwards, with a protecting group for example benzyl or BOC (tert-butyloxycarbonyl), which are removed by catalytic hydrogenolysis, or by treatment with trifluoroacetic acid, respectively, in the final step of the synthetic process.

A process for the preparation of compounds of formula (I) wherein R₁ is hydrogen and X is oxygen or sulphur includes the following steps:

i) Grignard reaction of the protected piperidone of formula (III), wherein Z is a protecting group such as for example benzyl, with the arylmagnesium halide of formula (IV), wherein Alog is a halogen (preferably chlorine or bromine) and Ar has the same meaning indicated previously with reference to formula (I), in order to obtain the alcohol of formula (V):

\[
\text{O} \quad \text{ArMgAlog} \quad \rightarrow \quad \text{Ar} \quad \text{OH}
\]

\[
\begin{align*}
\text{N} & \quad \text{Z} \\
\text{O} & \quad (\text{III}) \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{Z} \\
\text{O} & \quad (\text{IV}) \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \quad \text{Z} \\
\text{O} & \quad (\text{V}) \\
\end{align*}
\]
ii) To obtain derivatives wherein X is oxygen:

the reaction of the alcohol of formula (V) with a halide of formula Alog-R₂, wherein Alog is a halogen and R₂ has the same meaning indicated previously with reference to formula (I), in order to give the ether (VI)ₐ:

\[
\begin{align*}
\text{Ar} & \quad \text{OH} \\
\text{Z} & \quad (V) \\
\text{Ar} & \quad \text{XR}_2 \\
\text{Z} & \quad (VI)_a
\end{align*}
\]

ii) To obtain derivatives wherein X is sulphur:

reaction of the alcohol of formula (V) with an arylmercaptan HSR₂, in order to obtain the compound of formula (VI)ₐ wherein X is sulphur and R₂ has the same meaning indicated previously with reference to formula (I):

\[
\begin{align*}
\text{Ar} & \quad \text{OH} \\
\text{Z} & \quad (V) \\
\text{Ar} & \quad \text{XR}_2 \\
\text{Z} & \quad (VI)_b
\end{align*}
\]

iii) Catalytic hydrogenolysis of compound (VI)ₐ, wherein X is oxygen, or compound (VI)ₐ, wherein X is sulphur, in order to remove the protective group Z and obtain the compound of formula (I) wherein R₁ is hydrogen:

\[
\begin{align*}
\text{Ar} & \quad \text{XR}_2 \\
\text{Z} & \quad (VI)_a \text{ or } (VI)_b \\
\text{Ar} & \quad \text{XR}_2 \\
\text{R}_1 & \quad (I)
\end{align*}
\]
iv) Finally, the nitrogen atom of compound (I) wherein \( R_1 \) is hydrogen may optionally be alkylated in order to give a compound of formula (I) wherein \( R_1 \) is lower alkyl, as defined previously.

Benzylpiperidone, which may be easily obtained commercially, for example from Aldrich (catalogue No. B29806), is preferably used as the starting material in the above-described synthetic process. Other suitable protecting groups include for example 4-methoxybenzyl and diphenylmethyld.

Step i) of the process is carried out in an organic solvent, preferably tetrahydrofuran (THF), at reflux temperature. This reaction is preferably carried out under an atmosphere of inert gas. The alcohol of formula (V) may be recovered from the reaction mixture by the addition of ice, with subsequent extraction using ethyl acetate, and then purified by crystallisation from hexane/methylene chloride. Step ii)\(_a\) is preferably carried out in the presence of NaH in order to obtain the alcoholate in situ which reacts with the halide. The reaction is preferably carried out in anhydrous THF, at a temperature of 0°C, in the presence of a catalytic quantity of tetrabutylammonium iodide, and under an inert atmosphere. Step ii)\(_b\) is preferably carried out in glacial acetic acid and boron trifluoride at a temperature of 60°C. The products of formula (VI) may be purified by means of silica gel chromatography, preferably using a mixture of ethyl acetate/hexane, in a ratio of 2:3, as the eluent. Step iii) may be carried out, in an acid environment, in anhydrous ethanol in the presence of a catalytic quantity of palladium (10%) on carbon. The hydrochloride of the end product of formula (I) wherein \( R_1 \) is H may be purified by
crystallisation from ethanol/ether. Alkylation, step iv), is carried out with the appropriate halide, preferably in acetonitrile in the presence of a base. The reaction product of formula (I) wherein R₁ is other than hydrogen is purified, for example, using chromatography or crystallisation.

A process for the preparation of compounds of formula (I) wherein R₁ is hydrogen and X is nitrogen includes the following steps:

i) Reaction of the protected piperidone of formula (III) wherein Z is a protecting group, for example BOC, with alkaline cyanide and the amine of formula (VIII), wherein R₂ has the same meaning indicated previously with reference to formula (I), in order to obtain the compound of formula (IX):

\[
\text{O} \quad \text{H}_2\text{NR}_2 \quad \text{NC} \quad \text{NHR}_2 \\
\text{N} \quad \text{Z} \quad \text{Z} \\
(\text{III}) \quad (\text{VIII}) \quad (\text{IX})
\]

ii) Grignard reaction of the compound of formula (IX) with an arylmagnesium halide of formula (IV), wherein Alog is a halogen and Ar has the same meaning indicated previously with reference to formula (I), in order to obtain the compound of formula (X):

\[
\text{NC} \quad \text{NHR}_2 \quad \text{Ar} \quad \text{NHR}_2 \\
\text{N} \quad \text{Z} \quad \text{Z} \\
(\text{IX}) \quad (\text{IV}) \quad (\text{X})
\]
iii) Deprotection of the nitrogen of the compound of formula (X), preferably using TFA in CH₂Cl₂ in order to obtain the compound of formula (I) wherein R₁ is hydrogen and X is nitrogen:

\[
\begin{align*}
\text{Ar} & \quad \text{NHR₂} & \text{Ar} & \quad \text{XR₂} \\
\text{N} & \quad \text{Z} & \quad \text{N} & \quad \text{R₁}
\end{align*}
\]

(X) (I)

The compound thus obtained, wherein R₁ is hydrogen, may then be alkylated as described previously (see step iv).

1-Boc-4-piperidone, which may be easily obtained commercially, for example from Aldrich (catalogue No. 461350), is preferably used as the starting material in the above-described synthetic process.

The compounds of formula (I), forming the subject of the present invention, form salts through the addition of inorganic and organic acids. Said salts are included within the scope of the invention as well.

The compounds of the invention and the salts thereof display pharmacological activity at the level of the central nervous system, particularly as antidepressants. Hence, among the salts of the compounds of formula (I) falling within the scope of the invention the pharmaceutically acceptable salts are preferred, such as for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid, acetic acid, oxalic acid, tartaric acid, succinic acid, citric acid, ascorbic acid, lactic acid, malonic acid and fumaric acid. Among the above salts, the
pharmacologically acceptable salts of the derivatives of formula (I) wherein R₁ is hydrogen and X is oxygen are most preferred.

Given their pharmacological activity, the compounds of the invention and the salts thereof are suitable for use in therapeutic applications for the treatment of disorders of the central nervous system, particularly as antidepressants.

Hence, a further subject of the invention is the use of a compound of formula (I) as defined previously, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of disorders of the central nervous system, particularly a medicament having antidepressant activity.

Yet another subject of the invention is a pharmaceutical composition comprising at least one 4-arylpiperidine compound of the invention, or a pharmaceutically acceptable salt thereof, as the active ingredient, and a pharmaceutically acceptable carrier or diluent.

The composition of the invention may be administered orally, in a dosage form suitable for this route of administration, for example tablets, capsules, oral solutions or drops.

The pharmaceutical composition of the invention, in unit dosage form, contains a pharmaceutically effective amount of the active ingredient, preferably comprised within the range of 100 mg - 1 g of active ingredient. Pharmaceutical compositions in unit dosage form usually contain from 10 mg to 100 mg of the active ingredient.
Suitable carriers or diluents for use with the pharmaceutical composition of the invention include, for example, purified water and glycerine for oral solutions; propylene glycol and glycerine for drops.

The composition of the invention may additionally comprise suitable excipients. Of course, the selection of both the pharmaceutical carrier or diluent and any optional excipient depends on several factors, including the selected dosage form and the solubility of the active ingredient. Said choice falls within the ability of the skilled in the art.

The pharmacological activities of the compounds of the invention were tested with binding assays, which evaluated the affinities of some of the compounds falling within the scope of the invention, towards the biogenic amine transporters [serotonin (SERT) and dopamine (DAT)]. The tests were performed on rabbit frontal cortex membranes for SERT, or rabbit striate nucleus membranes for DAT. The control drugs used in the tests are fluoxetine and paroxetine, which represent the antidepressant drugs most used clinically, and which act precisely as inhibitors of the serotonin transporter (SERT). The test results indicated that the compounds of the invention possess a very high affinity towards the serotonin transporter (SERT), which entirely overlaps to that of paroxetine and which is significantly higher than that of fluoxetine. Furthermore, the high affinity towards SERT is advantageously accompanied by high selectivity. Indeed, the following table shows that the affinities of the compounds of the invention towards the dopamine transporter (DAT) are negligible.
<table>
<thead>
<tr>
<th></th>
<th>SERT $K_i$ pM</th>
<th>DAT $K_i$ pM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound A</td>
<td>26.8</td>
<td>&gt; 1,000,000</td>
</tr>
<tr>
<td>Compound B</td>
<td>34.5</td>
<td>&gt; 1,000,000</td>
</tr>
<tr>
<td>Compound C</td>
<td>316.4</td>
<td>&gt; 1,000,000</td>
</tr>
<tr>
<td>Compound D</td>
<td>250.0</td>
<td>11,200</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5,800</td>
<td>&gt; 1,000,000</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>47.0</td>
<td></td>
</tr>
</tbody>
</table>

COMPOUND $A = 4$-(4-fluorophenyl)-4-[(4-trifluoromethyl)benzyloxy]piperidine hydrochloride;
COMPOUND $B = 4$-(4-fluorophenyl)-4-[(3,4-methylenedioxy)benzyloxy]piperidine hydrochloride;
COMPOUND $C = 4$-[(4-trifluoromethyl)phenyl]-4-[(4-trifluoromethyl)benzyloxy]piperidine hydrochloride;
COMPOUND $D = 4$-[(4-trifluoromethyl)phenyl]-4-[(3,4-methylenedioxy)benzyloxy]piperidine hydrochloride.

From the above table, it may be observed that the affinities of the compounds of the invention towards the serotonin transporter entirely overlap with that of paroxetine and are markedly higher than that of fluoxetine, but are significantly lower towards the dopamine transporter, thus indicating a higher selectivity of such compounds.

The following examples are provided by way of illustration only without limiting the scope of the invention as defined in the appended claims.

**EXAMPLE 1**

4-(4-fluorophenyl)-4-[(4-trifluoromethyl)benzyloxy]piperidine
hydrochloride (compound A)

A solution of 4-bromo-fluorobenzene (107.3 mmol, 18.8 g, 11.8 ml) in anhydrous THF (107 ml) is added dropwise to a suspension of metallic Mg (107.3 mmol, 2.6 g) in anhydrous THF (214 ml) stirred under nitrogen atmosphere. The mixture is refluxed for 30 minutes, then it is allowed to return to room temperature, and then a solution of N-benzyl-4-piperidone (52.8 mmol, 10 g, 9.9 ml) in anhydrous THF (107 ml) is added dropwise and with constant stirring to the solution of 4-fluorophenylmagnesium bromide, and the mixture is refluxed for 15 hours.

The reaction mixture is left cooling to room temperature, then the solution is taken up with ice and water and extracted with AcOEt. The combined organic phases are dried over Na₂SO₄, filtered and evaporated under reduced pressure, to provide a crude yellow oil which is purified by crystallisation from hexane and CH₂Cl₂ to obtain 4-(4-fluorophenyl)-4-hydroxy-N-benzylpiperidine.

50% NaH (4 mmol, 0.192 g), tetrabutylammonium iodide (0.04 mmol, 0.0129 g) and 98% 4-trifluoromethylbenzyl bromide (4 mmol 0.976 g) are added to a solution of 4-(4-fluorophenyl)-4-hydroxy-N-benzylpiperidine (3.5 mmol, 1 g) in anhydrous THF
(18 ml) cooled to 0°C. The mixture thus obtained is stirred at room temperature for 3 days, then diluted with water and extracted with Et₂O. The organic extracts, once dried, filtered and evaporated under reduced pressure, provide a crude oil (1.778 g), which was chromatographed on a silica gel column, using AcOEt/hexane 4:6 as the eluent, to provide 4-(4-fluorophenyl)-4-[(4-trifluoromethyl)benzyloxy]-N-benzylpiperidine as a yellow oil (0.751 g).

To a solution of 4-(4-fluorophenyl)-4-[(4-trifluoromethyl)benzyloxy]-N-benzylpiperidine (1.62 mmol, 0.717 g) in anhydrous EtOH (50 ml) hydrochloric ethanol was added until an acidic pH is reached, as well as 10% Pd/C (0.145 g). After hydrogenation for 25 hours at room temperature, a glassy solid is obtained which, after crystallisation from EtOH/Et₂O, provides 4-(4-fluorophenyl)-4-[(4-trifluoromethyl)benzyloxy]piperidine hydrochloride.

Elémental analysis: C 58.73; H 5.38; N 3.78; [¹H NMR (CDCl₃, 200 MHz) δ 7.63-7.42 (m, 6H), 7.29-7.05 (m, 2H), 4.14 (s, 2H), 3.46 (br. m, 4H) 2.38 (br. m, 4H).

**EXAMPLE 2**

4-(4-fluorophenyl)-4-[(3,4-methylenedioxy)benzyloxy]piperidine hydrochloride (compound B)
A solution of 4-bromo-fluorobenzene (107.3 mmol, 18.8 g, 11.8 ml) in anhydrous THF (107 ml) is added dropwise to a suspension of metallic Mg (107.3 mmol, 2.6 g) in anhydrous THF (214 ml) stirred under nitrogen atmosphere. The mixture is refluxed for 30 minutes, then it is allowed to return to room temperature, and then a solution of N-benzyl-4-piperidone (52.8 mmol, 10 g, 9.9 ml) in anhydrous THF (107 ml) is added dropwise and with constant stirring to the solution of 4-fluorophenylmagnesium bromide, and the mixture is refluxed for 15 hours.

The reaction mixture is left cooling to room temperature, then the solution is taken up with ice and water and extracted with AcOEt. The combined organic phases are dried over Na₂SO₄, filtered and evaporated under reduced pressure, to provide a crude yellow oil which is purified by crystallisation from hexane and CH₂Cl₂ to obtain 4-(4-fluorophenyl)-4-hydroxy-N-benzylpiperidine.

50% NaH (4 mmol, 0.192 g), tetrabutylammonium iodide (0.04 mmol, 0.0129 g) and 3,4-(methylenedioxy)benzyl bromide (4 mmol 0.87 g) are added to a solution of 4-(4-fluorophenyl)-4-hydroxy-N-benzylpiperidine (3.5 mmol, 1 g) in anhydrous THF (18 ml) cooled to 0°C. The mixture thus obtained is stirred at room temperature for 6 days, then diluted with water and
extracted with AcOEt. The organic extracts are dried, filtered and evaporated under reduced pressure to provide a crude oil (1.778 g), which was chromatographed on a silica gel column, using AcOEt/hexane 4:6 as the eluent, to provide 4-(4-fluorophenyl)-4-[(3,4-methylenedioxy)benzyl]oxyl-N-benzylpiperidine (0.670 g).

To a solution of 4-(4-fluorophenyl)-4-[(3,4-methylenedioxy)benzyl]oxyl-N-benzylpiperidine (1.60 mmol, 0.670 g) in anhydrous EtOH (50 ml) hydrochloric EtOH was added until an acidic pH is reached, as well as 10% Pd/C (0.140 g). After hydrogenation for 24 hours at room temperature, a glassy solid is obtained which, after crystallisation from Et₂O, provides 4-(4-fluorophenyl)-4-[(3,4-methylenedioxy)benzyl]piperidine hydrochloride. Elemental Analysis: C 62.21; H 5.61; N 3.64.

EXAMPLE 3

4-[(4-trifluoromethyl)phenyl]-4-[(4-trifluoromethyl)benzyl]oxylpiperidine hydrochloride (compound C)

A solution of 1-bromo-4-(trifluoromethyl)benzene (107.3 mmol, 24.14 g, 14.99 ml) in anhydrous THF (107 ml) is added
dropwise to a suspension of metallic Mg (107.3 mmol, 2.6 g) in anhydrous THF (214 ml) stirred under nitrogen atmosphere. The mixture is refluxed for 30 minutes, then it is allowed to return to room temperature, and then a solution of N-benzyl-4-piperidine (52.8 mmol, 10 g, 9.9 ml) in anhydrous THF (107 ml) is added dropwise and with constant stirring to the solution of 4-(trifluoromethyl)phenylmagnesium bromide, and the mixture is refluxed for 15 hours.

The reaction mixture is left cooling to room temperature, then the solution is taken up with ice and water and extracted with AcOEt. The combined organic phases are dried over Na₂SO₄, filtered and evaporated under reduced pressure, to provide a crude oil which is purified by chromatography on a silica gel column, using AcOEt/hexane 4:6 as the eluent, to obtain 4-[(4-trifluoromethyl)phenyl]-4-hydroxy-N-benzylpiperidine as a white solid.

50% NaH (4 mmol, 0.192 g), tetrabutylammonium iodide (0.04 mmol, 0.0129 g) and 98% 4-trifluoromethylbenzyl bromide (4 mmol 0.976 g) are added to a solution of 4-[(4-trifluoromethyl)phenyl]-4-hydroxy-N-benzylpiperidine (3.5 mmol, 1.17 g) in anhydrous THF (18 ml) cooled to 0°C. The mixture thus obtained is stirred at room temperature for 4 days, then diluted with water and extracted with AcOEt. The organic extracts are dried, filtered and evaporated under reduced pressure to provide a crude oil (1.28 g), which was chromatographed on a silica gel column, using AcOEt/hexane 1:1 as the eluent, to provide 4-[(4-trifluoromethyl)phenyl]-4-[(4-trifluoromethyl)benzylkoxy]piperidine as an oil (0.680 g).
To a solution of 4-[(4-trifluoromethyl)phenyl]-4-[(4-trifluoromethyl)benzyloxy]piperidine (1.62 mmol, 0.653 g) in anhydrous EtOH (50 ml) hydrochloric EtOH was added until an acidic pH is reached, as well as 10% Pd/C (0.145 g). After hydrogenation for 25 hours at room temperature, a glassy solid is obtained which, after crystallisation from EtOH/Et₂O, provides 4-[(4-trifluoromethyl)phenyl]-4-[(4-trifluoromethyl)benzyloxy]piperidine hydrochloride (m.p. 189-190 ºC); Elemental analysis: C 54.83; H 4.76; N 3.38.

EXAMPLE 4

4-[(4-trifluoromethyl)phenyl]-4-[(3,4-methylenedioxy)benzyloxy]piperidine hydrochloride (compound D)

![Chemical structure](image)

A solution of 1-bromo-4-(trifluoromethyl)benzene (107.3 mmol, 24.14 g, 14.99 ml) in anhydrous THF (107 ml) is added dropwise to a suspension of metallic Mg (107.3 mmol, 2.6 g) in anhydrous THF (214 ml) stirred under nitrogen atmosphere. The mixture is refluxed for 30 minutes, then it is allowed to return to room temperature, and then a solution of N-benzyl-4-piperidone (52.8 mmol, 10 g, 9.9 ml) in anhydrous THF (107 ml) is added dropwise and with constant stirring to the solution of 4-(trifluoromethyl)phenylmagnesium bromide, and
the mixture is refluxed for 15 hours.

The reaction mixture is left cooling to room temperature, then the solution is taken up with ice and water and extracted with AcOEt. The combined organic phases are dried over Na₂SO₄, filtered and evaporated under reduced pressure, to provide a crude yellow oil which is purified by chromatography on a silica gel column, using AcOEt/hexane 4:6 as the eluent, to obtain 4-[(4-trifluoromethyl)phenyl]-4-hydroxy-N-benzylpiperidine as a white solid.

50% NaH (4 mmol, 0.192 g), tetrabutylammonium iodide (0.04 mmol, 0.0129 g) and 3,4-(methyleneedioxy)benzyl bromide (4 mmol 0.87 g) are added to a solution of 4-[(4-trifluoromethyl)phenyl]-4-hydroxy-N-benzylpiperidine (3.5 mmol, 1.17 g) in anhydrous THF (18 ml) cooled to 0°C. The mixture thus obtained is stirred at room temperature for 6 days, then diluted with water and extracted with AcOEt. The organic extracts are dried, filtered and evaporated under reduced pressure to provide a crude oil (1.778 g), which was chromatographed on a silica gel column, using AcOEt/hexane 4:6 as the eluent, to provide 4-[(4-trifluoromethyl)phenyl]-4-[(3,4-methyleneedioxy)benzyloxy]-N-benzylpiperidine as a pure oil (0.70 g).

To a solution of 4-(4-fluorophenyl)-4-[(3,4-methyleneedioxy)benzyloxy]-N-benzylpiperidine (1.60 mmol, 0.670 g) in anhydrous EtOH (50 ml) hydrochloric EtOH was added until an acidic pH is reached, as well as 10% Pd/C (0.140 g). After hydrogenation for 24 hours at room temperature, a glassy solid is obtained which, after crystallisation from Et₂O, provides 4-[(4-trifluoromethyl)phenyl]-4-[(3,4-
methylenedioxy)benzyloxy]piperidine hydrochloride (m.p. 232-233 °C); Elemental Analysis: C 57.98; H 5.28; N 3.55.

EXAMPLE 5

**Binding assays**

The affinities of the compounds of examples 1-4 for the serotonin and dopamine transporters were evaluated using binding displacement assays. The serotonin transporters were labelled in rabbit frontal cortex membranes using \[^3\text{H}\]paroxetine (15.1-17 Ci/mmol), whilst the dopamine transporters were labelled in rabbit striate nucleus membranes using \[^3\text{H}\]WIN 35,428 (84.5 Ci/mmol). Non-specific binding to the SERT or the DAT was defined in the presence of serotonin (200 μM) or dopamine (2 nM). The results obtained are illustrated in the above table.
CLAIMS

1. A 4-arylpiperidine compound of formula (I):

\[
\begin{array}{c}
\text{Ar} \\
\text{X} \\
\text{R}_2 \\
\text{R}_1 \\
\end{array}
\]

wherein:
- \( \text{R}_1 \) is selected from hydrogen and saturated or unsaturated, linear or branched alkyl having 1 to 6 carbon atoms; \( \text{X} \) is a heteroatom selected from the group consisting of oxygen, sulphur and nitrogen; \( \text{R}_2 \) is \(-(\text{CH}_2)_n\)-\( \text{Y} \), wherein \( n \) is an integer comprised between 1 and 4 and \( \text{Y} \) is aryl substituted with one or more substituents independently selected from the group consisting of halogen, trifluoromethyl, methyl, 3,4-methylenedioxy and phenyl; when \( \text{X} \) is an oxygen or nitrogen atom, \( \text{Ar} \) is phenyl substituted with one or more substituents independently selected from the group consisting of halogen, trifluoromethyl, methyl and phenyl; when \( \text{X} \) is a sulphur atom, \( \text{Ar} \) is phenyl substituted with one or more substituents in position 3 and/or 4 and/or 5, independently selected from the group consisting of halogen, trifluoromethyl, methyl, 3,4-methylenedioxy and phenyl; or a salt thereof.

2. The compound according to claim 1, wherein \( \text{X} \) is an oxygen atom, \( \text{R}_1 \) is a hydrogen atom and \( \text{R}_2 \) is \(-(\text{CH}_2)_n\)-\( \text{Y} \), wherein \( \text{Y} \) is mono-substituted phenyl and \( n \) is 1.

3. The compound according to claim 1, selected from the group consisting of:
4-(4-fluorophenyl)-4-[(4-trifluoromethyl)benzyloxy]piperidine,
4-(4-fluorophenyl)-4-[(3,4-ethylenedioxy)benzyloxy]piperidine,
4-[(4-trifluoromethyl)phenyl]-4-[(4-
trifluoromethyl)benzyloxy]piperidine,
4-[(4-trifluoromethyl)phenyl]-4-[(3,4-
methyleedioxy)benzyloxy]piperidine.

4. The compound according to any of claims 1 to 3, wherein said salt is a pharmaceutically acceptable salt.

5. The compound according to claim 4, wherein said salt is an organic or inorganic acid addition salt selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid, acetic acid, oxalic acid, tartaric acid, succinic acid, citric acid, ascorbic acid, lactic acid, malonic acid and fumaric acid.

6. The compound according to any of claims 1 to 3 or a pharmaceutically acceptable salt thereof, as a medicament.

7. A pharmaceutical composition comprising at least one compound according to any of claims 1 to 3 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

8. Use of a compound according to any of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of disorders of the central nervous system.

9. The use according to claim 8, for the preparation of a medicament with antidepressant activity.
10. A process for the preparation of a compound according to claim 1, wherein X is oxygen or sulphur, comprising the steps of:

i) Grignard reaction of the piperidone of formula (III), wherein Z is a protecting group, with the arylmagnesium halide of formula (IV), wherein Alog is halogen and Ar is as defined in claim 1, in order to obtain the alcohol of formula (V):

\[
\begin{align*}
\text{O} & \quad + \quad \text{ArMgAlog} \\
\text{N} & \quad \text{Ar} \\
\text{Z} & \quad \text{OH} \\
\text{N} & \quad \text{Z} \quad \text{(III)} \\
\text{N} & \quad \text{Ar} \\
\end{align*}
\]

(IV)

(V)

ii) a reaction of the alcohol of formula (V) with the halide of formula Alog-R₂, wherein Alog is halogen and R₂ is as defined in claim 1, in order to give the ether of formula (VI) a wherein X is oxygen:

\[
\begin{align*}
\text{Ar} & \quad \text{OH} \\
\text{N} & \quad \text{Alog-R₂} \\
\text{Z} & \quad \text{XR₂} \\
\text{N} & \quad \text{Z} \\
\text{N} & \quad \text{Ar} \\
\end{align*}
\]

(V)

(VI) a

or

ii) b reaction of the alcohol of formula (V) with the arylmercaptan HSR₂, wherein R₂ is as defined in claim 1, in order to give the compound of formula (VI) b wherein X is sulphur:

\[
\begin{align*}
\text{Ar} & \quad \text{OH} \\
\text{N} & \quad \text{HSR₂} \\
\text{Z} & \quad \text{XR₂} \\
\text{N} & \quad \text{Z} \\
\text{N} & \quad \text{Ar} \\
\end{align*}
\]

(V)

(VI) b
iii) catalytic hydrogenolysis of compound (VI)$_a$, wherein X is oxygen, or compound (VI)$_b$, wherein X is sulphur, in order to remove the protecting group Z and obtain the compound of formula (I) wherein $R_1$ is hydrogen and X is oxygen or sulphur:

\[
\begin{array}{c}
\text{Ar} \quad X \quad \text{XR}_2 \\
\text{Z} \\
(\text{VI})_a \text{ or (VI)}_b
\end{array} \quad \rightarrow \quad
\begin{array}{c}
\text{Ar} \quad X \quad \text{XR}_2 \\
\text{Z} \\
(\text{I})
\end{array}
\]

11. A process for the preparation of a compound according to claim 1, wherein X is a nitrogen atom, comprising the steps of:

i) reaction of the piperidone of formula (III), wherein Z is a protecting group, with alkaline cyanide and the amine of formula (VIII), wherein $R_2$ is as defined in claim 1, in order to obtain the compound of formula (IX):

\[
\begin{array}{c}
\text{O} \\
\text{Z} \\
(\text{III})
\end{array} \quad + \quad \text{H}_2\text{NR}_2 \quad \rightarrow \quad
\begin{array}{c}
\text{NC} \quad \text{NHR}_2 \\
\text{Z} \\
(\text{IX})
\end{array}
\]

ii) Grignard reaction of the compound of formula (IX) with the arylmagnesium halide of formula (IV), wherein $\text{Alog}$ is halogen and Ar is as defined in claim 1, in order to obtain the compound of formula (X):
iii) deprotection of the nitrogen of the compound of formula (X), in order to obtain the compound of formula (I) wherein $R_1$ is hydrogen and $X$ is nitrogen:

12. The process according to claim 10 or 11, further comprising the alkylation of the nitrogen atom of the compound of formula (I) wherein $R_1$ is hydrogen, so as to obtain a compound of formula (I) wherein $R_3$ is an alkyl group as defined in claim 1.