(54) Title: NOVEL N-HYDROXYALKYL-SUBSTITUTED 1,2,3,6-TETRAHYDROPYRIDINE AND PIPERIDINE DERIVATIVES

(II)

(57) Abstract

The invention relates to novel N-hydroxy-substituted 1,2,3,6-tetrahydropyridine and piperidine derivatives of formula (I) wherein A stands for hydrogen or halogen; alkoxy; cyano; phenyl; phenyl monosubstituted by halogen; benzyl; benzyl monosubstituted by halogen; 2-phenylethyl monosubstituted by halogen on the phenyl moiety; or 2-picolyl group; B represents hydrogen; alkoxy or nitro group; D represents hydrogen or halogen; or alkoxy group; or B and D together stand for a -CH = CH- group; R represents hydrogen; alkyl or phenyl group; G is hydrogen; I stands for hydrogen or hydroxy group; or G and I together represent a single chemical bond; E stands for hydrogen or halogen; alkoxy or trifluoromethyl group; and m is 0, 1 or 2, with the proviso that: m is 0 or 2, or both G and I mean hydrogen, when A stands for benzyl or halogen-monosubstituted benzyl group; and m is 1, when A stands for 2-picolyl group, as well as their acid addition salts. The invention further relates to pharmaceutical compositions containing these compounds as active ingredients as well as to a process for the preparation of compounds of formula (I) and their intermediates. The compounds of formula (I) are useful for enhancing the tolerance of mammals (including man) against hypoxic and/or ischaemic states as well as for treating the degenerative and functional disturbances arising from hypoxic and/or ischaemic insults.
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NOVEL N-HYDROXYALKYL-SUBSTITUTED 1,2,3,6-TETRAHYDROPYRIDINE AND PIPERIDINE DERIVATIVES

The invention relates to novel N-hydroxyalkyl substituted 1,2,3,6-tetrahydropyridine and piperidine derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medical use.

International Patent Application PCT/HU90/00076 describes tetrahydropyridine derivatives structurally related to the compounds of the invention which are said to have antiamnesic activity. In contrast to the present compounds, however, said compounds can be considered as α- or β-amino ketone compounds the nitrogen atom of which is closed as a ring member into said substituted tetrahydropyridine ring.

The invention relates to novel, therapeutically active N-hydroxyalkyl-substituted 1,2,3,6-tetrahydropyridine and piperidine derivatives of the formula

\[
\text{(I)}
\]

wherein

- \(A\) stands for hydrogen or halogen; alkoxy; cyano; phenyl; phenyl monosubstituted by halogen; benzy1; benzy1 monosubstituted by halogen; 2-phenylethyl monosubstituted by halogen on the phenyl moiety; or 2-picolyl group;
B represents hydrogen; alkoxy or nitro group; 
D represents hydrogen or halogen; or alkoxy group; or 
5 B and D together stand for a \(-\text{CH=CH-CH=CH-}\) group; 
R represents hydrogen; alkyl or phenyl group; 
G is hydrogen; 
I stands for hydrogen or hydroxy group; or 
G and I together represent a single chemical bond; 
10 E stands for hydrogen or halogen; alkoxy or tri-
fluoromethyl group; and 
m is 0, 1 or 2, with the proviso that: 
m is 0 or 2, or both G and I mean hydrogen, when A 
15 stands for benzyl or halogen-monosubstituted 
benzyl group; and 
m is 1, when A stands for 2-picolyl group, 
as well as their acid addition salts. 
Alkyl group as used herein either in itself or as a 
20 moiety of an other group, represents a straight or 
branched chain saturated hydrocarbon group containing 1-10 
carbon atoms such as methyl, ethyl, n- and isopropyl, n-, 
o-, sec- and tert-butyl groups as well as the various 
pentyl, hexyl, heptyl, octyl, nonyl and decyl groups. 
25 C\(_1\)-alkyl groups are preferred, C\(_1\)-4alkyl groups are 
more preferable and methyl group is particularly favourable. 
Halogen may mean fluorine, chlorine, bromine or 
iiodine. 
The following compounds are particularly preferred: 
30 1-[4-(4-chlorobenzyl)phenyl]-2-(4-phenyl-1,2,3,6-tetra-
hydro-1-pyridyl)ethanol, 
1-[4-(4-chlorobenzyl)phenyl]-3-(4-phenyl-1-piperidyl)- 
propanol, 
35 1-[4-(4-chlorobenzyl)phenyl]-4-(4-phenyl-1,2,3,6-tetra-
hydro-1-pyridyl)butanol,
3-[4-(4-fluorophenyl)-1-piperidyl]-1-(1,1'-biphenyl-4-yl)-propanol,
3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(2,4-dichlorophenyl)propanol.

The present invention also relates to a pharmaceutical composition for treating conditions selected from hypoxia and ischaemia comprising an amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof effective in treating such conditions and a pharmaceutically acceptable carrier.

Furthermore, the present invention also relates to a process and intermediates for the preparation of the compounds of formula (I), as well as acid addition salt thereof.

Additionally, the present invention relates to a process for the preparation of pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

The present invention also relates to a method of treatment, which comprises administering a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof to a mammal (including man) for strengthening its tolerance against hypoxic and/or ischaemic conditions as well as for treating degenerative and functional disturbances arising from hypoxic and/or ischaemic insults.

Surprisingly, it has been found that the compounds of formula (I) are capable to protect the brain from the cognitive function-injuring effect of various harmful conditions, e.g. hypoxia and/or ischaemia; or they are useful to enhance the tolerance against hypoxic and/or ischaemic conditions, respectively as well as to treat degenerative and functional disturbances arising from hypoxic and ischaemic insults.
The biological effects of compounds according to the invention are hereinafter illustrated by using the following test methods.

Male CFLP mice (from the Hungarian stock LATI) weighing 24-26 g each and spontaneously hypertensive (SH) male rats weighing 160-180 g each, respectively were used in these investigations. The compounds to be tested were orally administered in a volume of 10 ml/kg one hour prior to start the experiment.

10 Antihypoxic effect in mice

1. The cytotoxic hypoxia test

After a 1-hour pretreatment, the animals were intravenously injected with 5 mg/kg of potassium cyanide. Survival time was measured as an interval lasting from the administrating of potassium cyanide to the last respiratory movement. In the groups consisting of 10 animals each treated with the compounds, the animals having a survival time longer by 30% than the average survival time of the placebo-treated group were considered to be protected.

The ED$_{50}$ values (i.e. the doses being effective in 50% of the animals) were calculated from the percentage of the surviving animals by using probit analysis.

2. The hypobaric hypoxia test

After a 16-hour starving and 1-hour pretreatment period, the animals were placed in a desiccator of 6 litres volume, where the pressure was decreased to 170 mmHg within 20 seconds. The survival time was registered from this time point up to the last respiratory movement of the animals. Animals having a survival time longer by 30% than the average survival time of the control group were considered to be protected. The ED$_{50}$ values were calculated from the percentage of the animals protected by using probit analysis.

The results obtained are summarized in Table 1.
Table 1

<table>
<thead>
<tr>
<th>Compound (Sign)</th>
<th>Oral ED$_{50}$ (mg/kg)</th>
<th>Cytotoxic hypoxia in mice</th>
<th>Hypobaric hypoxia in SH rats</th>
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<tbody>
<tr>
<td>A</td>
<td>11.9</td>
<td></td>
<td>18.5</td>
</tr>
<tr>
<td>B</td>
<td>19.8</td>
<td></td>
<td>11.5</td>
</tr>
<tr>
<td>C</td>
<td>18.8</td>
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<tr>
<td>D</td>
<td>50.0</td>
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<tr>
<td>E</td>
<td>&gt;50.0</td>
<td></td>
<td>8.3</td>
</tr>
<tr>
<td>Vincamine</td>
<td>27.0</td>
<td></td>
<td>27.9</td>
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<tr>
<td>Piracetam</td>
<td>131.5</td>
<td></td>
<td>293.0</td>
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</table>

The chemical names of compounds listed in Table 1 are as follows.

"A": 1-[4-(4-chlorobenzyl)phenyl]-2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)ethanol;

"B": 1-[4-(4-chlorobenzyl)phenyl]-3-(4-phenyl-1-piperidyl)propanol;

"C": 1-[4-(4-chlorobenzyl)phenyl]-4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butanol;

"D": 3-[4-(4-fluorophenyl)-1-piperidyl]-1-(1,1'-bi-phenyl-4-yl)propanol; and

"E": 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(2,4-dichlorophenyl)propanol.

Various forms of hypoxia were used for investigating the compounds. The functional dysorganization and destruction of cells and death, respectively in otherwise healthy mice are caused by a decrease in the oxygen-saturation of haemoglobin in the hypobaric hypoxia and the inhibition of the mitochondrial respiratory enzyme in the
cytotoxic hypoxia. Spontaneously hypertensive (SH) rats are more sensitive against hypoxic conditions than normotensive animals; similarly, patients suffering from hypertension have a less chance of survival after hypoxic injuries.

Vincamine [chemically (+)-14β-hydroxy-14α-methoxy-carbonyl-14,15-dihydroeburnamenine] and piracetam (chemically 2-oxo-1-pyrrolidinylacetic acid amide) were used as reference drugs. Vincamine increases the oxygen supply (vasodilatory effect) and modulates the metabolic processes of brain (cerebroprotective effect) whereas piracetam improves mainly the adaptation ability of brain in pathologic states.

The antihypoxic effect of vincamine is most pronounced in cytotoxic hypoxia and in addition, it has a prominent tolerance-enhancing action in the hypobaric hypoxia. Essentially, piracetam exerts its effect in the same two tests.

The compounds according to the invention are more active in both tests in comparison to the reference drugs. It is particularly favourable that the antihypoxic effect is strongest in spontaneously hypertensive animals, which is a substantial therapeutical advantage under pathologic conditions.

The antihypoxic effect of compound "A" is the most favourable, since its effects are the same in the various tests of hypoxia and it is 2- or 3-times as effective as vincamine.

**Acute toxicity study in mice**

OF-1 mice of either sex weighing 19-21 g were used. The test compound was administered through a catheter inserted into the stomach. A series of solutions was prepared, the concentrations were chosen to give a constant dosage volume of 0.1 ml/10 g. The observation time after the treatment was 72 hours. The LD$_{50}$ value was calculated
according to Litchfield and Wilcoxon from six dose responses (maximal dose 1000 mg/kg p.o., n = 10).

<table>
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<th>Compound</th>
<th>LD_{50} (mg/kg p.o.)</th>
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<tr>
<td>A</td>
<td>&gt; 1000</td>
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<tr>
<td>E</td>
<td>&gt; 1000</td>
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<tr>
<td>B</td>
<td>697</td>
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The active agents of formula (I) can be formulated in pharmaceutical compositions by mixing them with non-toxic, inert, solid or liquid carriers and/or auxiliaries commonly used in the therapy for parenteral or enteral administration. Useful carriers are e.g. water, gelatine, lactose, starch, pectin, magnesium stearate, talc, vegetable oils such as peanut oil, olive oil and the like. The active agent can be formulated in any usual pharmaceutical composition, particularly solid composition, e.g. rounded or edged tablet, dragée or capsule such as gelatine capsule, pill, suppository and the like. The amount of the solid active ingredient may be varied within a broad range in a dosage unit of the composition (tablet, capsule, one unit of the formulated solution and the like), preferably it is between about 25 mg and 1 g. Optionally, these compositions may also contain other commonly used pharmaceutical auxiliaries, e.g. stabilizers, preservatives, wetting agents, emulsifying agents and the like. The compositions can be prepared in a known manner, e.g. by sieving, mixing, granulating and compressing the components in the case of solid compositions. The compositions may be subjected to other usual operations of the pharmaceutical technology, e.g. sterilization.

The dose to be used may be varied between wide limits depending on the body-weight and responsiveness of the
person or animal to be treated, as well as on the severity of the state to be influenced, frequency and route of administration; however, the suitable dose can easily be determined by a physician skilled in the art.

The proposed daily doses of the active compounds of the invention for oral or enteral administration to the subject for the treatment of the conditions referred to above are between 0.1 to 50 mg of the active ingredient per kg body weight; however, this limit may be exceeded depending on the severity of the pathological state to be treated since the toxicity of the compounds of the invention is low. The daily dose of the active compound may be administered once or in subdoses to the patient to be treated.

According to an other aspect of the invention, there is provided a process for the preparation of compounds of the formula (I), which comprises treating an oxo derivative of the formula

\[
\text{II}
\]
wherein A, B, D, R, G, I, E and m are as defined above, or an acid addition salt thereof with a reducing agent in an organic solvent and then, if desired, converting the obtained N-hydroxyalkyl-substituted 1,2,3,6-tetrahydropyridine or piperidine derivative of formula (I), wherein A, B, D, R, G, I, E and m are as defined above, to an acid addition salt thereof by reacting it with a mineral or organic acid.

Useful reducing agents for this purpose are complex metal hydrides, preferably sodium borohydride, though this reduction can also be accomplished e.g. by means of the Meerwein-Ponndorf-Verley reduction [Ann. Chem. 444, 221 (1926); Angew. Chem. 39 138 (1926)], e.g. by using an aluminium alkoxide in isopropanol medium.

The reduction of the oxo derivatives of formula (II) by sodium borohydride is preferably carried out in such a way that an acid addition salt of a compound of formula (II) is used as starting substance and the base is liberated in situ in the reaction medium. The reduction is accomplished in a lower alcohol or in the mixture of such an alcohol and water. In order to make the reaction complete, the reducing agent is employed in an excess or the temperature of the reaction is elevated to the boiling point in the final period.

The product obtained is isolated by filtration or extraction. It is suitable to dilute the reaction medium with water for completing the precipitation of the product. When extraction is used, a part of alcohol is evaporated, then the reaction mixture is diluted with water and the product is extracted into a water-immiscible hydrocarbon, chlorinated hydrocarbon, ethyl acetate or ether. The final product may be purified by recrystallization. If desired, the compounds of formula (I) obtained in the base form can be converted to their acid addition salts by reacting them with an organic or inorganic acid.
for the salt formation in a known way. Hydrochloride salts are preferred.

The oxo compounds of formula (II) and their addition salts are also novel. These compounds can advantageously be prepared from hydrogenated pyridine derivatives of the formula

![Chemical Structure (Formula III)](image)

wherein G, I and E are as defined above as starting material by either of two methods, which comprises

a) alkylating a compound of formula (III) with a halogenated ketone of formula

![Chemical Structure (Formula IV)](image)
wherein A, B, D and R are as defined above and X stands for halogen, preferably chlorine or bromine, to obtain compounds of formula (II), wherein m is 0 or 2; or

b) reacting a compound of formula (III) with an acetophenone or propiophenone of formula

\[
\begin{array}{c}
\text{A} \\
\text{B} \\
\text{D}
\end{array}
\]

wherein A, B, D and R are as defined above and \( R^1 \) means hydrogen or methyl group, in the presence of formaldehyde under conditions of the Mannich's reaction [Arch. Pharm. 250, 647 (1912)] to obtain compounds of formula (II), wherein m is 1.

A number of substances of formula (IV), e.g. phenacyl halides, \( \alpha \)-bromopropiophenone [J. Chem. Soc. 125, 2343 (1924)], desyl bromide or 2-bromoacetophenone [Ann. 155, 68 (1870)] are known from the literature. Both latter compounds can be prepared by brominating the appropriate ketone; whereas the compounds of formula (IV), wherein m is 2 are mainly prepared by reacting an aromatic compound of formula

\[
\begin{array}{c}
\text{A} \\
\text{B} \\
\text{D}
\end{array}
\]

(V)
wherein A is as defined above and B as well as D preferably stand for hydrogen, with 4-chlorobutyryl chloride under Friedel-Crafts condition.

Starting compounds of formula (V) are commercially available products.

Compounds of formula (VI) can be produced by reacting a compound of formula (V) with an appropriate acid chloride under Friedel-Crafts condition. The ketone synthesis is not necessarily the final step of preparing the compounds of formula (VI); the formation of a substituent on the aromatic ring may also be the last step.

The invention is illustrated in detail by the following non-limiting Examples.

**Example 1**

**Preparation of 1-(4-chlorophenyl)-3-[4-hydroxy-(4-chlorophenyl)-1-piperidy1]propanol**

To a solution containing 1.2 g (0.03 mol) of sodium hydroxide in 50 ml of an 50% by volume ethanol/water mixture, 12.41 g (0.03 mol) of 1-(4-chlorophenyl)-3-[4-hydroxy-(4-chlorophenyl)-1-piperidy1]propanone hydrochloride and then, during 1 hour 1.17 g of sodium borohydride are added. The suspension is heated at a temperature of 50 °C for 2 hours. After cooling down, the reaction mixture is filtered and washed with water to give 11.45 g of product, m.p.: 129-132 °C. After recrystallization of the latter product from 215 ml of acetonitrile, 9.1 g of title compound are obtained.

Analysis for C_{20}H_{23}Cl_{2}NO_{2} (molecular weight 380.30) calculated: C 63.16; H 6.10; Cl 18.65; N 3.68%;
found: C 62.94; H 6.17; Cl 18.41; N 3.48%.

**Example 2**

**Preparation of 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(2,4-dichlorophenyl)propanol**

After adding 12.93 g (0.03 mol) of 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(2,4-dichloro-
phenyl)propanone hydrochloride to a solution of 1.2 g (0.03 mol) of sodium hydroxide in 50 ml of methanol, 1.17 g of sodium borohydride are portionwise added to the above mixture during 1 hour. After terminating the addition, the reaction mixture is boiled under reflux for 3 hours, then the reaction mixture is poured into 150 ml of water. The major part of methanol is distilled off from the so-obtained oily precipitate, which is then twice extracted with 50 ml of ethyl acetate each. After evaporating the solvent, 12.3 g of evaporation residue are obtained to give a crystalline product on addition of 50 ml of diisopropyl ether. In this way 8.32 g of title product are obtained, which is recrystallized from 28 ml of isopropanol to obtain 6.3 g of title compound, m.p.: 96-98 °C.

Analysis for C$_2$O$_2$H$_2$OCl$_3$NO (molecular weight 396.74) calculated: C 60.54; H 5.08; Cl 26.81 N 3.53%; found: C 60.80; H 5.03; Cl 26.62; N 3.60%.

The compounds listed hereinafter are prepared as described above by using the appropriate propanone derivatives of formula (II) as starting materials. The hydrochloride salts are obtained by adding ethanolic hydrogen chloride solution to the corresponding base.

1) 1-[4-(4-Chlorobenzyl)phenyl]-2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)ethanol,
yield 93.2%, m.p.: 135-137 °C;

2) 1-[4-(4-chlorobenzyl)phenyl]-3-(4-phenyl-1-piperidyl)-propanol,
yield 93.8%, m.p.: 98-101 °C;

3) 1-[4-(4-chlorobenzyl)phenyl]-4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butanol,
yield 78.5%, m.p.: 108-111 °C;

4) 3-[4-(4-fluorophenyl)-1-piperidyl]-1-(1,1'-bi-phenyl-4-yl)propanol,
yield 90.7%, m.p.: 129-132 °C;
5) 1-phenyl-2-[4-(3-trifluoromethylphenyl)-1,2,3,6-tetrahydro-1-pyridyl]ethanol,
yield 80.5%, m.p.: 188-190 °C;
6) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-2-methyl-1-phenyl-propanol,
yield 80.9%, m.p.: 103-105 °C;
7) 1-(4-chlorophenyl)-3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]propanol,
yield 82.8%, m.p.: 154-155 °C;
8) 1-(4-chlorophenyl)-3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-2-methylpropanol,
yield 84.0%, m.p.: 110-112 °C;
9) 1-(4-chlorophenyl)-2-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]ethanol,
yield 60.4%, m.p.: 152-153 °C;
10) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(3-methoxyphenyl)propanol,
yield 87.4%, m.p.: 100-102 °C;
11) 1-(4-chlorophenyl)-3-[4-(4-chlorophenyl)-1-piperidyl]propanol,
yield 84.7%, m.p.: 152-154 °C;
12) 1-(4-chlorophenyl)-3-[4-(4-fluorophenyl)-1-piperidyl]propanol,
yield 70.5%, m.p.: 108-110 °C;
13) 1-(4-chlorophenyl)-3-[4-phenyl-1,2,3,6-tetrahydro-1-piridyl]propanol,
yield 74.1%, m.p.: 141 °C;
14) 1-(4-fluorophenyl)-3-[4-hydroxy-(4-chlorophenyl)-1-piperidyl]propanol,
yield 93.4%, m.p.: 116-118 °C;
15) 1-(2,4-dichlorophenyl)-3-[4-hydroxy-(4-chlorophenyl)-1-piperidyl]propanol,
yield 78.8%, m.p.: 146-148 °C;
16) 1-(2,4-dimethoxyphenyl)-3-[4-hydroxy-(4-chlorophenyl)-1-piperidyl]propanol,
yield 69.2%, m.p.: 129-130 °C;

17) 4-{4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl}-1-(4-fluorophenyl)butanol,
yield 90.1%, m.p.: 103-105 °C;

18) 1-{4-(4-chlorobenzyl)phenyl}-4-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]butanol,
yield 90.7%, m.p.: 104-105 °C;

19) 1-(4-cyanophenyl)-3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]propanol,
yield 76.5%, m.p.: 117-118 °C;

20) 1-{4-[2-(4-chlorophenyl)ethyl]phenyl}-3-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)propanol,
yield 83.1%, m.p.: 158-160 °C;

21) 1-(4-cyanophenyl)-3-[4-(4-methoxyphenyl)-1,2,3,6-tetrahydro-1-pyridyl]propanol,
yield 74.7%, m.p.: 144-145 °C;

22) 1,2-diphenyl-3-[4-hydroxy-(4-chlorophenyl)-1-piperidyl]propanol,
yield 68.7%, m.p.: 150-151 °C;

23) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-[4-(2-picolyl)phenyl]propanol,
yield 40.0%, m.p.: 129-131 °C;

24) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1,2-diphenylpropanol,
yield 82.7%, m.p.: 135-137 °C;

25) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(4-methoxyphenyl)propanol,
yield 82.9%, m.p.: 116-118 °C;

26) 1-(1-naphthyl)-3-[4-phenyl-1,2,3,6-tetrahydro-1-pyridyl]propanol,
yield 88.8%, m.p.: 93-94 °C;

27) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(1-naphthyl)propanol,
yield 75.4%, m.p.: 122-123 °C;

28) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-
1-(2,4-dimethoxyphenyl)propanol,
yield 54.7%, m.p.: 112-114 °C;
29) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(4-fluoro-3-nitrophenyl)propanol,
yield 30.0%, m.p.: 154-156 °C;
30) 1-[4-(4-chlorobenzyl)phenyl]-3-[4-(4-fluorophenyl)-1-piperidyl]propanol,
yield 83.4%, m.p.: 94-95 °C;
31) 1-(1,1'-biphenyl-4-yl)-3-(4-phenyl-1-piperidyl)propanol,
yield 87.7%, m.p.: 99-101 °C;
32) 3-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(4-fluorophenyl)propanol,
yield 90.5%, m.p.: 130-132 °C;
33) 1-[4-(4-chlorobenzyl)phenyl]-2-[4-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]ethanol,
yield 87.3%, m.p.: 149-152 °C;
34) 1-(2,4-dichlorophenyl)-3-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)propanol, yield 57.3%, m.p.: 103-104 °C;
35) 1-(1,1'-biphenyl-4-yl)-2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)ethanol,
yield: 68.8 %, m.p.: 190-197 °C;
36) 1-(1,1'-biphenyl-4-yl)-2-[4-(4-fluorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]ethanol,
yield: 76.9 %, m.p.: 202-207 °C;
37) 2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)-1-(4'-fluoro-1,1'-biphenyl-4-yl)ethanol,
yield: 96.6 %, m.p.: 207-210 °C; and
38) 2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)-1-[4-(4-fluoro-benzyl)phenyl]butanol,
yield: 76.2 %, m.p.: 164-167 °C.

Example 3
Preparation of tablets
a) Tablets weighing 150 mg, containing 5 mg of active
ingredient each
Active ingredient 5 g
Gelatine 3 g
Magnesium stearate 2 g
Talc 5 g
Potato starch 40 g
Lactose 95 g

b) Tablets weighing 300 mg, containing 50 mg of active ingredient each

Active ingredient 50 g
Polyvidone 6 g
Magnesium stearate 3 g
Talc 9 g
Potato starch 84 g
Lactose 148 g

After wet granulation, the powder mixture containing the ingredients given above under a) or b), respectively is compressed to tablets. Each tablet weighs 150 mg or 300 mg, respectively and contains 5 or 50 mg, respectively of active ingredient.
CLAIMS

1. A novel N-hydroxyalkyl-substituted 1,2,3,6-tetrahydropyridine and piperidine derivative of the formula

\[
\begin{align*}
\text{A} & \quad \text{CH} & \quad \text{CH} & \quad (\text{CH}_2)_m & \quad \text{N} & \quad \text{G} & \quad \text{I} & \quad \text{E} \\
\text{B} & \quad \text{D} & \quad \text{OH} & \quad \text{R} & \quad \text{I} & \quad \text{E} \\
\end{align*}
\]

15 wherein

- A stands for hydrogen or halogen; alkoxy; cyano; phenyl; phenyl monosubstituted by halogen; benzyl; benzyl monosubstituted by halogen; 2-phenylethyl monosubstituted by halogen on the phenyl moiety; or 2-picolyly group;
- B represents hydrogen; alkoxy or nitro group;
- D represents hydrogen or halogen; or alkoxy group; or
- B and D together stand for a \(-\text{CH} = \text{CH} = \text{CH} = \text{CH}\) group;
- R represents hydrogen; alkyl or phenyl group;
- G is hydrogen;
- I stands for hydrogen or hydroxy group; or
- G and I together represent a single chemical bond;
- E stands for hydrogen or halogen; alkoxy or tri-fluoromethyl group; and
- \(m\) is 0, 1 or 2,
with the proviso that:
- \(m\) is 0 or 2, or both G and I mean hydrogen, when A stands for benzyl or halogen-monosubstituted benzyl group; and
m is 1, when A stands for 2-picolyl group, as well as their acid addition salts.

2. 1-[4-(4-chlorobenzyl)phenyl]-2-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)ethanol or an acid additions salt thereof as defined in claim 1.

3. 1-[4-(4-chlorobenzyl)phenyl]-3-(4-phenyl-1-piperidyl)-propanol or an acid additions salt thereof as defined in claim 1.

4. 1-[4-(4-chlorobenzyl)phenyl]-4-(4-phenyl-1,2,3,6-tetrahydro-1-pyridyl)butanol or an acid additions salt thereof as defined in claim 1.

5. 3-[4-(4-fluorophenyl)-1-piperidyl]-1-(1,1'-biphenyl-4-yl)propanol, or an acid additions salt thereof as defined in claim 1.

6. 3-[4-(4-fluorophenyl)-1,2,3,6-tetrahydro-1-pyridyl]-1-(2,4-dichlorophenyl)propanol or an acid additions salt thereof as defined in claim 1.

7. A pharmaceutical composition for treating disorders arising from hypoxia and/or ischaemia, which comprises as active ingredient a therapeutically effective amount of an N-hydroxyalkyl-substituted 1,2,3,6-tetrahydropyridine or piperidine derivative of the formula (I), wherein A, B, D, R, G, I, E and m are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof in admixture with one or more carriers and/or additives commonly used in the pharmaceutical industry.

8. A process for the preparation of a novel N-hydroxyalkyl-substituted 1,2,3,6-tetrahydropyridine or piperidine derivative of formula
wherein

A stands for hydrogen or halogen; alkoxy, cyano, phenyl, phenyl monosubstituted by halogen; benzyl, benzyl monosubstituted by halogen;

2-phenylethyl monosubstituted by halogen on the phenyl moiety; or 2-picoly1 group;

B represents hydrogen; alkoxy or nitro group;

D represents hydrogen or halogen; or alkoxy group; or

B and D together stand for a \(-\text{CH}=\text{CH}=\text{CH}=\text{CH}\) group;

R represents hydrogen; alkyl or phenyl group;

G is hydrogen;

I stands for hydrogen or hydroxy group; or

G and I together represent a single chemical bond;

E stands for hydrogen or halogen; alkoxy or trifluoromethyl group; and

m is 0, 1 or 2,

with the proviso that:

m is 0 or 2, or both G and I mean hydrogen, when A stands for benzyl or halogen-monosubstituted benzyl group; and

m is 1, when A stands for 2-picoly1 group,
as well as their acid addition salts which comprises treating an oxo derivative of the

formula
wherein A, B, D, R, G, I, E and m are as defined above, or an acid addition salt thereof with a reducing agent in an organic solvent and then, if desired, converting the obtained N-hydroxyalkyl-substituted 1,2,3,6-tetrahydropyridine or piperidine derivative of formula (I), wherein A, B, D, R, G, I, E and m are as defined above, to an acid addition salt thereof by reacting it with a mineral or organic acid.

9. The process according to claim 8, which comprises using a complex metal hydride as reducing agent.

10. The process according to claim 9, which comprises using sodium borohydride as complex metal hydride.

11. The process according to claim 9, which comprises using a C_1-4 alkanol or a mixture of a C_1-4 alkanol with water as organic solvent.

12. The process according to claim 8, which comprises using an aluminum alkoxide in isopropanol medium as reducing agent.

13. A process for the preparation of a pharmaceutical composition, which comprises mixing as active ingredient a therapeutically effective amount of a novel N-hydroxyalkyl-substituted 1,2,3,6-tetrahydro-
pyridine or piperidine derivative of formula (I), wherein A, B, D, R, G, I, E and m are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof with one or more carriers and/or additives commonly used in the pharmaceutical industry and formulating the mixture in a pharmaceutical composition.

14. A method for enhancing the tolerance of mammals (including man) against hypoxic and/or ischaemic states as well as for treating the degenerative and functional disturbances arising from hypoxic and/or ischaemic insults, which comprises administering to a subject to be treated a therapeutically effective amount of an N-hydroxyalkyl-substituted 1,2,3,6-tetrahydropyridine or piperidine derivative of formula (I), wherein A, B, D, R, G, I, E and m are as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof alone or in the form of a pharmaceutical composition.

15. A compound of formula

\[
\text{II}
\]

wherein A stands for hydrogen or halogen; alkoxy; cyano; phenyl; phenyl monosubstituted by halogen; benzyl; benzyl monosubstituted by halogen; 2-phenylethyl monosubstituted by halogen on the phenyl moiety; or 2-picolyl group; B represents hydrogen; alkoxy or nitro group; D represents hydrogen or halogen; or alkoxy group; or
B and D together stand for a \(-\text{CH} = \text{CH} = \text{CH} = \text{CH} -\) group;
R represents hydrogen; alkyl or phenyl group;
G is hydrogen;
I stands for hydrogen or hydroxy group; or
5 G and I together represent a single chemical bond;
E stands for hydrogen or halogen; alkoxy or tri-fluoromethyl group; and
m is 0, 1 or 2,
with the proviso that:
10 m is 0 or 2, or both G and I mean hydrogen, when A stands for benzyl or halogen-monosubstituted benzyl group; and
m is 1, when A stands for 2-picoly group,
as well as their acid addition salts.
15 16. A process for the preparation of a novel compound of formula

![Chemical Structure](II)

wherein
A stands for hydrogen or halogen; alkoxy; cyano;
phenyl; phenyl monosubstituted by halogen;
benzyl; benzyl monosubstituted by halogen;
2-phenylethyl monosubstituted by halogen on
the phenyl moiety; or 2-picoly group;
30 B represents hydrogen; alkoxy or nitro group;
D represents hydrogen or halogen; or alkoxy group;
or
B and D together stand for a \(-\text{CH} = \text{CH} = \text{CH} -\) group;
35 R represents hydrogen; alkyl or phenyl group;
G is hydrogen; I stands for hydrogen or hydroxy group; or G and I together represent a single chemical bond; E stands for hydrogen or halogen; alkoxy or trifluoromethyl group; and m is 0, 1 or 2, with the proviso that: m is 0 or 2, or both G and I mean hydrogen, when A stands for benzyl or halogen-monosubstituted benzyl group; and m is 1, when A stands for 2-picolyl group, as well as their acid addition salts, which comprises a) alkylating a compound of formula

![Chemical Structure](III)

with a halogenated ketone of formula

![Chemical Structure](IV)

wherein A, B, D and R are as defined above and X stands for halogen, preferably chlorine or bromine, to obtain compounds of formula (II), wherein m is 0 or 2; or b) reacting a compound of formula (III) with an acetophe-
none or propiophenone of formula

![Chemical Structure](attachment:structures.png)

5

wherein A, B, D and R are as defined above and \( R^1 \) means hydrogen or methyl group, in the presence of formaldehyde under conditions of the Mannich's reaction to obtain compounds of formula (II), wherein m is 1.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC*: C 07 D 211/06, 211/70; A 61 K 31/44, 31/445
   According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
   Minimum documentation searched (classification system followed by classification symbols)
   IPC*: C 07 D; A 61 K
   Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
   AT
   Electronic database consulted during the international search (name of database and, where practicable, search terms used)
   DAR

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X,P</td>
<td>EP, A1, 0490 560 (RICHTER GEDEON VEGYESZETI GYAR RT.) 17 June 1992 (17.06.92), claims 1-5, 7, 32.</td>
<td>1, 7, 8-12</td>
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<td>US, A, 3209 006 (W. R. WRAGG) 28 September 1965 (28.09.65), claim 1.</td>
<td>1, 7</td>
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☐ Further documents are listed in the continuation of Box C.  ☑ See patent family annex.

* Special categories of cited documents:
   "A" document defining the general state of the art which is not considered to be of particular relevance
   "B" earlier document but published on or after the international filing date
   "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
   "O" document referring to an oral disclosure, use, exhibition or other means
   "P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search
04 March 1993 (04.03.93)

Date of mailing of the international search report
09 March 1993 (09.03.93)

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Form PCT/ISA/210 (second sheet) (July 1992)
**INTERNATIONAL SEARCH REPORT**

### Box I  Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **x** Claims Nos.: 14 because they relate to subject matter not required to be searched by this Authority, namely:
   - Claim 14 directed to a method for enhancing the tolerance of mammals against hypoxic and/or ischaemic states is considered to be a method for treatment of the human or animal body by therapy and is subject matter which the International Searching Authority is not required to search under Article 17(2)(a)(i) and Rule 39 (iv).

2. **☐** Claims Nos.:
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. **☐** Claims Nos.:
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II  Observations where unity of Invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. **☐** As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. **☐** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. **☐** As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. **☐** No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- **☐** The additional search fees were accompanied by the applicant’s protest.
- **☐** No protest accompanied the payment of additional search fees.
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