The present invention relates to O-carbamoyl-(D)-phenylalaninol compound represented by structural formula (V) and pharmaceutically acceptable salts thereof to treat diseases of the central nervous system, wherein \( R^1 \) and \( R^2 \) may be the same with or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl containing 1 to 8 carbon atoms, and 5 to 7-membered aliphatic cyclic compounds which may comprise not more than two nitrogen or oxygen atoms directly unconnected, the total number of carbon atom of \( R^1 \) and \( R^2 \) ranging from 0 to 16.

\[
\text{Ph} \quad \text{OCNR}^1\text{R}^2 \quad (V) \\
\_\_\_\text{NH}_2
\]
**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<table>
<thead>
<tr>
<th>Code</th>
<th>Country</th>
<th>Code</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>Armenia</td>
<td>GB</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>AT</td>
<td>Austria</td>
<td>GE</td>
<td>Georgia</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
<td>GN</td>
<td>Guinea</td>
</tr>
<tr>
<td>BB</td>
<td>Barbados</td>
<td>GR</td>
<td>Greece</td>
</tr>
<tr>
<td>BE</td>
<td>Belgium</td>
<td>HU</td>
<td>Hungary</td>
</tr>
<tr>
<td>BF</td>
<td>Burkina Faso</td>
<td>IE</td>
<td>Ireland</td>
</tr>
<tr>
<td>BG</td>
<td>Bulgaria</td>
<td>IT</td>
<td>Italy</td>
</tr>
<tr>
<td>BJ</td>
<td>Benin</td>
<td>JP</td>
<td>Japan</td>
</tr>
<tr>
<td>BR</td>
<td>Brazil</td>
<td>KE</td>
<td>Kenya</td>
</tr>
<tr>
<td>BY</td>
<td>Belarus</td>
<td>KG</td>
<td>Kyrgyzstan</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
<td>KP</td>
<td>Democratic People’s Republic of Korea</td>
</tr>
<tr>
<td>CF</td>
<td>Central African Republic</td>
<td>KR</td>
<td>Republic of Korea</td>
</tr>
<tr>
<td>CG</td>
<td>Congo</td>
<td>KZ</td>
<td>Kazakhstan</td>
</tr>
<tr>
<td>CH</td>
<td>Switzerland</td>
<td>LI</td>
<td>Liechtenstein</td>
</tr>
<tr>
<td>CI</td>
<td>Côte d’Ivoire</td>
<td>LK</td>
<td>Sri Lanka</td>
</tr>
<tr>
<td>CM</td>
<td>Cameroon</td>
<td>LR</td>
<td>Liberia</td>
</tr>
<tr>
<td>CN</td>
<td>China</td>
<td>LT</td>
<td>Lithuania</td>
</tr>
<tr>
<td>CS</td>
<td>Czechoslovakia</td>
<td>LU</td>
<td>Luxembourg</td>
</tr>
<tr>
<td>CZ</td>
<td>Czech Republic</td>
<td>LV</td>
<td>Latvia</td>
</tr>
<tr>
<td>DE</td>
<td>Germany</td>
<td>MC</td>
<td>Monaco</td>
</tr>
<tr>
<td>DK</td>
<td>Denmark</td>
<td>MD</td>
<td>Republic of Moldova</td>
</tr>
<tr>
<td>EE</td>
<td>Estonia</td>
<td>MG</td>
<td>Madagascar</td>
</tr>
<tr>
<td>ES</td>
<td>Spain</td>
<td>ML</td>
<td>Mali</td>
</tr>
<tr>
<td>FI</td>
<td>Finland</td>
<td>MN</td>
<td>Mongolia</td>
</tr>
<tr>
<td>FR</td>
<td>France</td>
<td>MR</td>
<td>Mauritania</td>
</tr>
<tr>
<td>GA</td>
<td>Gabon</td>
<td>MW</td>
<td>Malawi</td>
</tr>
<tr>
<td>MX</td>
<td>Mexico</td>
<td>NE</td>
<td>Niger</td>
</tr>
<tr>
<td>NL</td>
<td>Netherlands</td>
<td>NO</td>
<td>Norway</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
<td>PL</td>
<td>Poland</td>
</tr>
<tr>
<td>PT</td>
<td>Portugal</td>
<td>RO</td>
<td>Romania</td>
</tr>
<tr>
<td>RU</td>
<td>Russian Federation</td>
<td>SD</td>
<td>Sudan</td>
</tr>
<tr>
<td>SE</td>
<td>Sweden</td>
<td>SG</td>
<td>Singapore</td>
</tr>
<tr>
<td>SI</td>
<td>Slovenia</td>
<td>SK</td>
<td>Slovakia</td>
</tr>
<tr>
<td>SN</td>
<td>Senegal</td>
<td>SZ</td>
<td>Swaziland</td>
</tr>
<tr>
<td>TD</td>
<td>Chad</td>
<td>TG</td>
<td>Togo</td>
</tr>
<tr>
<td>TJ</td>
<td>Tajikistan</td>
<td>TT</td>
<td>Trinidad and Tobago</td>
</tr>
<tr>
<td>UA</td>
<td>Ukraine</td>
<td>UG</td>
<td>Uganda</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
<td>UZ</td>
<td>Uzbekistan</td>
</tr>
<tr>
<td>VN</td>
<td>Viet Nam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
O-carbamoyl-(D)-phenylalaninol compounds and process for preparing the same

BACKGROUND OF THE INVENTION

Field of the invention

The present invention relates, in general, to novel stereospecific phenylalkylamino carbamate compounds and pharmaceutically useful salts thereof, useful to treat the diseases of the central nervous system. More particularly, the present invention relates to O-carbamoyl-(D)-phenylalaninol compounds and pharmaceutically useful salts thereof. Also, the present invention is concerned with a process for preparing the same.

Description of the Prior Art

Phenylethylamine derivatives, one important class of therapeutical medicines useful for managing central nervous system (CNS) diseases, have been used mainly to treat obesity, narcolepsy, minimal brain dysfunction and mild depression.

Organic carbamates have been effectively used for controlling various CNS disorders. For example, J. Am.
Chem. Soc., 73, 5779 (1951) discloses 2-methyl-2-propyl-1,3-propanediol dicarbamate and its pharmaceutical activity was verified in J. Pharmacol. Exp. Ther., 104, 229 (1952). Besides, there are many carbamate compounds that are suggested as therapeutics for CNS disease in the prior arts. For example, U.S. Pat. Nos. 2,884,444 and 2,937,119 disclose carbamates, such as 2-phenyl-1,3-propanediol dicarbamate and isopropylmeprobamate, respectively. These compounds are found to be very effectively used as therapeutics for treating CNS disorders, especially as antiepileptic and centrally acting muscle relaxant. Research for the development of carbamate therapeutics for CNS diseases has been and continues to be actively advanced.

Recent design of pharmacologically useful compounds has been based on amino acids or the derivatives thereof, which is mainly attributable to the fact that many of the compounds found in biological systems come from amino acids or the derivatives thereof. In addition, in most cases, the function of a pharmaceutically useful compound is effected after it binds to an enzyme or receptor, which may trigger the regulatory mechanisms of the enzyme or receptor.

SUMMARY OF THE INVENTION
As a result of intensive and thorough research, the present inventors found that O-carbamoyl-(D)-phenylalaninol compounds are pharmaceutically useful for CNS disorders, especially for depression and anxiety.

Accordingly, it is a principal object of the present invention to provide novel O-carbamoyl-(D)-phenylalaninol carbamate compounds, represented by the following structural formula V:

\[
\begin{align*}
\text{O} \\
\text{Ph} & \quad \text{OCNR}^1\text{R}^2 \\
\text{NH}_2
\end{align*}
\]

(V)

wherein R\(^1\) and R\(^2\) may be the same with or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl containing 1 to 8 carbon atoms, and 5 to 7-membered aliphatic cyclic compounds which may comprise not more than two nitrogen or oxygen atoms directly unconnected, the total number of carbon atom of R\(^1\) and R\(^2\) ranging from 0 to 16; and pharmaceutically acceptable salts thereof.

It is another object of the present invention to provide a process for preparing O-carbamoyl-(D)-phenylalaninols, represented by the above structural formula V.
DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, the O-carbamoyl-(D)-phenylalaninols represented by the structural formula V and pharmaceutically acceptable salts thereof can be prepared by the characteristic method comprising the steps of: reacting (D)-phenylalaninol represented by the following structural formula II:

\[
\text{Ph} \quad \text{NH}_2 \quad \text{OH}
\]  

(II)

with benzyl chloroformate in a basic aqueous solution to synthesize \( \text{N-benzyloxy carbonyl-(D)-phenylalaninol} \), represented by the following structural formula III:

\[
\text{Ph} \quad \text{NH} \quad \text{OH}
\]

(III)

subjecting \( \text{N-benzyloxy carbonyl-(D)-phenylalaninol} \) of the structural formula III to carbamoylation with phosgene in the presence of an amine base, represented by the following general formula VI:

\[
R^1 R^2 \text{NH}
\]

(VI)

wherein \( R^1 \) and \( R^2 \) are the same as defined above, to produce \( \text{O-carbamoyl-N-benzyloxy carbonyl-(D)-phenylalaninol} \), represented by the following structural formula IV:
wherein $R^1$ and $R^2$ are the same as defined above, deprotecting the benzoxycarbonyl group from O-carbamoyl-N-benzoxycarbonyl-(D)-phenylalaninol of the structural formula IV through hydrogenolysis in the presence of a catalyst, to afford O-carbamoyl-(D)-phenylalaninol compound, represented by the following structural formula V:

wherein $R^1$ and $R^2$ are the same as defined above; and treating O-carbamoyl-(D)-phenylalaninol compound of the structural formula V with an anhydrous acid, in an ethereal solution without further purification, to give a pharmaceutically acceptable salts thereof, represented by the following structural formula I:

wherein $R^1$ and $R^2$ are the same as defined above and HX is
an acid capable of forming a pharmaceutically useful salt with the intramolecular basic nitrogen atom.

The compound of Structural Formula I is prepared as set forth in Reaction Scheme below.

\[
\text{REACTION SCHEME}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH} & \quad \text{CbzCl} & \quad \text{Ph} & \quad \text{OH} & \quad \text{C(O)Cl}_2 & \quad \text{Ph} & \quad \text{OCNR}^1\text{R}^2 \\
\text{NH}_2 & \quad \text{II} & \quad & \quad & \quad & \quad & \quad & \quad \\
\text{NHCbz} & \quad \text{III} & \quad \text{R}^1\text{R}^2\text{NH} & \quad \text{IV} & \quad \text{NHCbz} & \quad \text{V} & \quad \text{H}_2/\text{Pd-C} & \quad \text{O} \\
\text{NH}_2 \cdot \text{HX} & \quad \text{I} & \quad & \quad & \quad & \quad & \quad & \quad \\
\text{OCNR}^1\text{R}^2 & \quad \text{HX} & \quad \text{Ph} & \quad \text{OCNR}^1\text{R}^2 & \quad \text{NH}_2 & \quad \text{V}
\end{align*}
\]

As shown in Reaction Scheme I, (D)-phenylalaninol (II) is first reacted with benzyl chloroformate in a basic aqueous solution, to give N-benzoxycarbonyl-(D)-phenylalaninol (III) which is subjected to carbamoylation with phosgene in the presence of an amine base. Ammonolysis of the carbamoylated intermediate is carried out and an amine represented by the general formula VI is used to produce O-carbamoyl-N-benzoxycarbonyl-(D)-phenylalaninol (IV) in a high yield within a short time.
Removal of the benzyloxy carbonyl group, a nitrogen protecting group, from the O-carbamoyl-N-benzyloxy carbonyl-(D)-phenylalaninol (IV) through hydrogenolysis in the presence of a catalyst, affords O-carbamoyl-(D)-phenylalaninol (V) which is, then, treated with an anhydrous acid (HX) in an ether solution without further purification, to provide the salts (I) of O-carbamoyl-(D)-phenylalaninol. In Reaction Scheme, HX represents an acid suitable for the formation of pharmaceutically acceptable salts with the intramolecular basic nitrogen atom.

Details of the reaction conditions described in Reaction Scheme I are as follows. In the first step, the concentration of the starting material (II) is between 0.1 and 3 mole and benzyl chloroformate is used at 1 to 2 equivalents. The basic aqueous solution has a pH value between 7 and 14 and the conversion reaction is carried out at temperatures ranging from -10 to 70 °C.

For the conversion of the compound (III) to the compound (IV), 1 to 2 molar equivalent of phosgene, either neat or as solution in toluene, is used at 0.01 to 2 molar concentration of the compound (III). Halogenated alkane such as methylene chloride, aromatic solvents such as toluene, or the mixtures thereof can be used as a solvent. Use of a base such as acid scavenger is recommended.
Typically, a tertiary amine, such as triethylamine, diisopropylethylamine, triisopropylamine, DBU (1,6-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), antipyrine and dimethylphenylamine, can be used for this purpose. The reacting amine can be used as neat or as solution in water or lower alkyl alcohol such as methanol, ethanol, n-propanol and isopropanol and 1 to 2 molar equivalent is used. The conversion reaction is carried out at temperatures ranging from -30 to 60 °C.

As for the hydrogenation from the compound (IV) to the compound (V), an ethereal solvent such as THF, an alcoholic solvent such as methanol, water, an aromatic solvent such as toluene, benzene or xylene, an ester solvent such as ethyl acetate or any compositional mixture thereof is used as a reaction medium. The hydrogenation from the compound (IV) to the compound (V) is carried out at a temperature of -10 to 150 °C under a 1 to 100 atm hydrogen pressure. This reaction is performed in the presence of a catalyst, such as palladium, platinum, platinum oxide, rhodium, and iridium.

Concrete examples of the anhydrous acid used for the preparation of the compound (I) from the compound (V) include hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, benzoic acid, citric acid, malonic acid,
salicylic acid, malic acid, fumaric acid, oxalic acid, succinic acid, tartaric acid, lactic acid, gluconic acid, ascorbic acid, maleic acid, aspartic acid, benzene sulfonic acid, methane sulfonic acid, ethane sulfonic acid, hydroxymethane sulfonic acid and hydroxyethane sulfonic acid and the like. Additional acids can refer to "Pharmaceutical Salts", J. Pharm. Sci., 1977; 66(1): 1-19. This preparation is executed in a reaction media which can be exemplified by an ethereal solvent such as THF, an alcoholic solvent such as methanol, an ester solvent such as ethyl acetate, an aromatic solvent, and any compositional mixture thereof. An ethereal solvent is recommended as an addition solution, including ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether. The concentration of the compound (V) is on the order of 0.01 to 5 mole.

Representative examples of the compound (V) are suggested with structural formulas below:

\[
\begin{align*}
\text{Ph} & \quad \text{OC} & \quad \text{NHMe} & \quad \text{O} \\
\text{NH}_2 & & & \\
\text{Ph} & \quad \text{OC} & \quad \text{N}(\text{Me})_2 & \quad \text{O} \\
\text{NH}_2 & & & \\
\text{Ph} & \quad \text{OC} & \quad \text{NHEt} & \quad \text{O} \\
\text{NH}_2 & & & \\
\text{Ph} & \quad \text{OC} & \quad \text{N}(\text{Et})_2 & \quad \text{O} \\
\text{NH}_2 & & & 
\end{align*}
\]
For therapeutic use in medicines for treating pain, depression, anxiety, epilepsy, stroke, demential and
Parkinson's disease, the compounds of the present invention, alone or in combination with pharmaceutically acceptable carrier, are administered to patients at a dosage of from 0.7 to 7,000 mg per day. For a normal human adult with a body weight of approximately 70 kg, the administration amount is translated into a daily dose of 0.01 to 100 mg per kg of body weight. The specific dosage employed, however, may vary depending upon the requirements of the patient, the severity of patient's condition and the activity of the compound. The determination of optimum dosages for a particular situation must clinically be done and is within the skill of the art.

In utilizing the compounds of the present invention for the central nervous system, particularly to treat depression, it is preferred to administer the compounds orally. Since the compounds absorb well orally, it usually will not be necessary to resort to parenteral administration. For oral administration, the compound (I) is preferably combined with a pharmaceutical carrier. The ratio of the carrier to the compound of Structural Formula (I) is not critical to express the effects of the medicine on the central nervous system, and they can vary considerably depending on whether the composition is to be filled into capsules or formed into tablets. In
tableting, various edible pharmaceutical carriers or the mixture thereof can be used. A suitable carriers, for example, are a mixture of lactose, diabasic calcium phosphate and/or corn starch. Other pharmaceutically acceptable ingredients can be further added, including lubricants such as magnesium stearate.

Besides the compound of Structural Formula I, compositions comprising it are within the scope of the present invention. Furthermore, the present invention includes uses of the compound (I) and/or the composition.

A better understanding of the present invention may be obtained in light of following examples which are set forth to illustrate, but are not to be construed to limit, the present invention.

EXAMPLE I

O-(N-Methyl)-Carbamoyl-N-Benzylloxycarbonyl-
D-Phenylalaninol

In a 250 mL flask, N-benzylloxycarbonyl-D-phenylalaninol (314 g, 0.011 mol) was dissolved in 150 mL of anhydrous THF under a nitrogen atmosphere and was added with antipyrine (2.27 g, 0.012 mol). The reaction mixture was cooled to 0 °C in an ice/water bath and phosgene (6.05 mL of 2 M solution in toluene, 0.012 mol) was added at one
try. After stirring for 1 hour, methylamine (0.38 g, 0.012 mol) was added. Following stirring at ambient temperatures for an extra 4 hours, water was added to terminate the reaction. The organic layer was extracted 3 times with dichloromethane, dried over magnesium sulfate and distilled in vacuo, to give a solid. This was recrystallized in a solution mixture of ethyl acetate and diethyl ether, to produce 2.93 g of O-(N-methyl)-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol: Yield 78%.

\[
_{1}H-NMR(CDCl_3, \text{200 MHz}), \text{ ppm(δ): 2.58-2.98(m,5H), 3.98-4.22(br,3H), 4.58-4.75(br,1H), 5.08(s,3H), 7.12-7.48(m,10H)}
\]

**EXAMPLE II**

O-(N-Isopropyl)-Carbamoyl-N-BenzylOxyCarbonyl-

D-Phenylalaninol

The procedure given in Example I was followed using isopropyl amine as a reactant, instead of methyl amine, to give O-(N-isopropyl)-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol. A yield of 88% was obtained.

\[
_{1}H-NMR(CDCl_3, \text{200 MHz}), \text{ ppm(δ): 1.25(d,6H), 2.72-3.02(m,2H), 3.68-3.90(m,1H), 3.98-4.25(m,3H), 4.51-4.65(br,1H), 5.18(s,3H), 7.08-7.51(m,10H)}
\]
EXAMPLE III

O-(N-n-Octyl)-Carbamoyl-N-Benzylloxycarbonyl-
D-Phenylalaninol

The procedure given in Example I was followed using octyl amine as a reactant, instead of methyl amine, to give O-(N-n-octyl)-carbamoyl-N-benzylloxycarbonyl-D-phenylalaninol. A yield of 96% was obtained.

$^1$H-NMR(CDC$_3$, 200 MHz), ppm(s): 0.85(t, 3H), 1.08-
1.58(m, 12H), 2.72-2.98(m, 2H), 3.15(q, 2H), 3.39-4.26(m, 3H),
3.39-4.26(m, 3H), 4.65-4.78(br, 1H), 5.10(s, 3H), 7.08-
7.48(m, 10H)

EXAMPLE IV

O-(N-Cyclohexyl)-Carbamoyl-N-Benzylloxycarbonyl-
D-Phenylalaninol

The procedure given in Example I was followed using cyclohexyl amine as a reactant, instead of methyl amine, to give O-(N-cyclohexyl)-carbamoyl-N-benzylloxycarbonyl-D-phenylalaninol. A yield of 79% was obtained.

$^1$H-NMR(CDC$_3$, 200 MHz), ppm(s): 0.95-2.05(m, 10H),
2.68-3.02(m, 2H), 3.32-3.58(m, 1H), 3.90-4.25(br, 3H), 4.58-
4.75(m, 1H), 5.10(s, 3H), 7.01-7.56(m, 10H)
EXEMPLARY V

O-(N,N'-Dimethyl)-Carbamoyl-N-Benzoxycarbonyl-
D-Phenylalaninol

The procedure given in Example I was followed using
dimethyl amine as a reactant, instead of methyl amine, to
give O-(N,N'-dimethyl)-carbamoyl-N-benzoxycarbonyl-D-
phenylalaninol. A yield of 94% was obtained.

${^1}$H-NMR(CDCl$_3$, 200 MHz), ppm(5): 2.55-3.05(br,6H),
3.85-4.28(m,3H), 4.90-5.48(m,4H), 6.80-7.70(m,10H)

EXEMPLARY VI

O-(N-Pyrrolidyl)-Carbamoyl-N-Benzoxycarbonyl-
D-Phenylalaninol

The procedure given in Example I was followed using
pyrrolidine as a reactant, instead of methyl amine, to
give O-(N-pyrrolidyl)-carbamoyl-N-benzoxycarbonyl-D-
phenylalaninol. A yield of 80% was obtained.

${^1}$H-NMR(CDCl$_3$, 200 MHz), ppm(5): 1.85-2.05(br,4H),
2.82-3.18(m,2H), 3.18-3.48(m,4H), 3.92-4.28(m,3H),
5.08(s,2H), 5.12-5.31(m,1H), 6.98-7.55(m,10H)

EXEMPLARY VII

O-(N-Piperidyl)-Carbamoyl-N-Benzoxycarbonyl-
D-Phenylalaninol

The procedure given in Example I was followed using piperidine as a reactant, instead of methyl amine, to give O-(N-piperidyl)-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol. A yield of 80% was obtained.

$^1$H-NMR(CDC$_3$, 200 MHz), ppm(δ): 1.35-1.85(br, 6H), 2.72-3.05(m, 2H), 3.32-3.58(m, 4H), 3.95-4.38(m, 3H), 5.05-5.28(m, 3H), 7.05-7.52(m, 10H)

EXAMPLE VIII

O-(N-Morpholino)-Carbamoyl-N-Benzyl oxycarbonyl-
D-Phenylalaninol

The procedure given in Example I was followed using morpholine as a reactant, instead of methyl amine, to give O-(N-morpholino)-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol. A yield of 85% was obtained.

$^1$H-NMR(CDC$_3$, 200 MHz), ppm(δ): 2.72-3.02(m, 2H), 3.25-3.55(br, 4H), 3.55-3.80(br, 4H), 3.95-4.30(m, 3H), 5.15(s, 3H), 7.05-7.51(m, 10H)

EXAMPLE IX

O-[N-(N-Phenyl)piperazino]-Carbamoyl-N-Benzyl oxycarbonyl-
D-Phenylalaninol
The procedure given in Example I was followed using N-phenylpiperazine as a reactant, instead of methyl amine, to give O-[N-(N-phenyl)piperazino]-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol. A yield of 93% was obtained.

\[ ^1H\text{-NMR(CDCl}_3,\text{ 200 MHz), ppm(6): 2.72-3.02(m,2H), 3.05-3.23(br,4H), 3.45-3.75(br,4H), 4.02-4.31(m,3H), 5.10(s,3H), 6.80-7.50(m,15H)} \]

**EXAMPLE X**

O-(N-Methyl)-Carbamoyl-D-Phenylalaninol Hydrochloric Acid Salt

In a 500 mL Parr reactor, O-(N-methyl)-carbonyl-N-benzyloxy carbonyl-D-phenylalaninol (2.80 g) obtained in Example I was dissolved in 80 mL of anhydrous methanol and added with palladium(carbon powder 10%, 0.10 g). Then, the reactor was closed and purged with hydrogen for 1 min. The reaction was completed in 7 hours under 50 psi hydrogen pressure at ambient temperatures, which was confirmed on thin layer chromatography. The catalyst was filtered off. Thereafter, the organic layer thus obtained was concentrated through distillation into 1.43 g (84 %) of pale yellow liquid. The liquid was poured in 30 mL of
anhydrous THF and cooled to 0 °C. Anhydrous hydrochloric acid was then added, to give a desirable white precipitate. Addition of 30 mL of anhydrous ether maximized the precipitation. Filtration provided 1.36 g of the title compound as a white solid: Yield 68%.

Melting point = 162-163 °C

\(^1\)H-NMR(DMSO-D6, 200 MHz), ppm(δ): 2.28-3.18(m,5H), 3.48-3.75(br,1H), 3.80-4.22(m,2H), 6.98-7.65(m,6H), 8.45(br,3H)

EXAMPLE XI

O-(N-Isopropyl)-Carbamoyl-D-Phenylalaninol Hydrochloric Acid Salt

The title compound was prepared in a similar manner to that of Example X, except that O-(N-isopropyl)-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol was used as the starting material.

Melting Point: 170-171 °C

\(^1\)H-NMR(DMSO-D6, 200 MHz), ppm(δ): 1.08(d,6H), 2.82-3.18(m,2H), 3.48-3.75(m,2H), 3.85-4.15(m,2H), 7.15(s,1H), 7.22-7.45(m,5H), 8.45(br,3H)

EXAMPLE XII

O-(N-Octyl)-Carbamoyl-D-Phenylalaninol
Hydrochloric Acid Salt

The title compound was prepared in a similar manner to that of Example X, except that O-(N-octyl)-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol was used as the starting material.

Melting Point: 105-106 °C

$^1$H-NMR(DMSO-d$_6$, 200 MHz), ppm($\delta$): 1.08(t,3H), 1.18-1.55(m,12H), 2.78-3.16(m,4H), 3.62(br,1H), 3.82-4.15(m,2H), 7.05(t,1H), 7.25-7.45(m,5H), 8.35(br,3H)

EXAMPLE XIII

O-(N-Cyclohexyl)-Carbamoyl-D-Phenylalaninol Hydrochloric Acid Salt

The title compound was prepared in a similar manner to that of Example X, except that O-(N-cyclohexyl)-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol was used as the starting material.

Melting Point: 232-233 °C

$^1$H-NMR(DMSO-d$_6$, 200 MHz), ppm($\delta$): 0.98-1.88(m,10H), 2.78-3.16(m,2H), 3.25(br,1H), 3.65(br,1H), 3.82-4.12(m,2H), 7.15(d,1H), 7.22-7.45(m,5H), 8.35(br,1H)

EXAMPLE XIV

O-(N,N'-Dimethyl)-Carbamoyl-D-Phenylalaninol
20

Hydrochloric Acid Salt

The title compound was prepared in a similar manner to that of Example X, except that \(\text{O-}(\text{N,N'}\text{-dimethyl})\text{-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol}\) was used as the starting material.

Melting Point: 129-130 °C

\(^1\text{H-NMR(DMSO-d6, 200 MHz), ppm(δ): 2.65-2.99(m,6H), 2.99-4.16(m,5H), 7.05-7.45(m,5H), 8.48(br,3H)}\)

EXAMPLE XV

10 O-(N-Pyrrolidyl)-Carbamoyl-D-Phenylalaninol

Hydrochloric Acid Salt

The title compound was prepared in a similar manner to that of Example X, except that \(\text{O-}(\text{N-pyrrolidyl})\text{-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol}\) was used as the starting material.

Melting Point: 224-225 °C

\(^1\text{H-NMR(DMSO-d6, 200 MHz), ppm(δ): 1.52-1.98(m,4H), 2.72-3.76(m,7H), 3.78-4.22(m,2H), 7.02-7.52(m,5H), 8.58(br,3H)}\)

EXAMPLE XVI

O-(N-Piperidyl)-Carbamoyl-D-Phenylalaninol
Hydrochloric Acid Salt

The title compound was prepared in a similar manner to that of Example X, except that O-(N-piperidyl)-
carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol was used as the starting material.

Melting Point: 190-191 °C

$^1$H-NMR(DMSO-d$_6$, 200 MHz), ppm(δ): 1.18-1.72(m,6H),
2.68-3.76(m,7H), 3.78-4.22(m,2H), 7.02-7.52(m,5H),
8.58(br,3H)

EXAMPLE XVII

O-(N-Morpholino)-Carbamoyl-D-Phenylalaninol

Hydrochloric Acid Salt

The title compound was prepared in a similar manner to that of Example X, except that O-(N-morpholino)-
carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol was used as the starting material.

Melting Point: 207-208 °C

$^1$H-NMR(DMSO-d$_6$, 200 MHz), ppm(δ): 2.76-3.25(m,2H),
3.25-3.82(m,9H), 3.86-4.22(m,2H), 7.12-7.52(m,5H),
8.48(br,3H)

EXAMPLE XVIII

O-[N-(N-Phenyl)piperazino]-Carbamoyl-D-Phenylalaninol
Hydrochloric Acid Salt

The title compound was prepared in a similar manner to that of Example X, except that O-[(N-(N-phenyl)piperazino)-carbamoyl-N-benzyloxy carbonyl-D-phenylalaninol was used as the starting material.

Melting Point: 241-242 °C

$^1$H-NMR(CDCl$_3$, 200 MHz), ppm(δ): 2.76-4.32(m, 13H), 6.98-7.82(m, 10H), 8.72(br, 3H)

As described hereinbefore, the compounds represented by Structural Formula I were observed to be useful for the prophylaxis and treatment of CNS disorder including pain, depression, anxiety, epilepsy, stroke, demential and Parkinson's disease.

The present invention has been described in an illustrative manner, and it is to be understood that the terminology used is intended to be in the nature of description rather than of limitation.

Many modifications and variations of the present invention are possible in light of the above teachings. Therefore, it is to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described.
WHAT IS CLAIMED IS:

1. An O-carbamoyl-(D)-phenylalaninol compound, represented by the following structural formula V:

\[
\begin{align*}
\text{O} \\
\text{Ph} & \text{OCNR}^1 R^2 \\
\text{NH}_2
\end{align*}
\]

(V)

wherein \( R^1 \) and \( R^2 \) may be the same with or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl containing 1 to 8 carbon atoms, and 5 to 7-membered aliphatic cyclic compounds which may comprise not more than two nitrogen or oxygen atoms directly unconnected, the total number of carbon atom of \( R^1 \) and \( R^2 \) ranging from 0 to 16; and the pharmaceutically acceptable salts thereof.

2. The compound in accordance with claim 1, wherein O-carbamoyl-(D)-phenylalaninol of the structural formula V comprises the compounds having the following general formulas:

\[
\begin{align*}
\text{O} \\
\text{Ph} & \text{OC-NHMe} \\
\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{O} \\
\text{Ph} & \text{OC-N(Me)}_2 \\
\text{NH}_2
\end{align*}
\]
3. A process for preparing an O-carbamoyl-(D)-phenylalaninol represented by the following structural formula V:

\[
\text{O} \quad \text{O}
\]

\[
\text{Ph} \quad \text{OC} \quad \text{NH(n-Oct)} \quad \text{Ph} \quad \text{OC} \quad \text{NH}
\]

\[
\text{NH}_2 \quad \text{NH}_2
\]

wherein \( R^1 \) and \( R^2 \) may be the same with or different from each other and are independently selected from the group consisting of hydrogen, lower alkyl containing 1 to 8 carbon atoms, and 5 to 7-membered aliphatic cyclic compounds which may comprise not more than two nitrogen or oxygen atoms directly unconnected, the total number of carbon atom of \( R^1 \) and \( R^2 \) ranging from 0 to 16; comprising the steps of:

20 reacting (D)-phenylalaninol represented by the following structural formula II:

\[
\text{Ph} \quad \text{OH}
\]

\[
\text{NH}_2
\]

with benzyl chloroformate in a basic aqueous solution, to give N-benzyloxy carbonyl-(D)-phenylalaninol represented
by the following structural formula III:

\[
\begin{array}{c}
\text{Ph} \\
\text{NH} \\
\text{Cbz}
\end{array}
\]

subjecting the compound of the structural formula III to carbamoylation with phosgene in the presence of an amine base, represented by the following general formula VI:

\[
\text{R}^1\text{R}^2\text{NH} 
\]

wherein \( \text{R}^1 \) and \( \text{R}^2 \) are the same as defined above, to provide 0-carbamoyl-N-benzyloxy carbonyl-(D)-phenylalaninol, represented by the following structural formula IV:

\[
\begin{array}{c}
\text{Ph} \\
\text{OCN} \\
\text{H}
\end{array}
\]

wherein \( \text{R}^1 \) and \( \text{R}^2 \) are the same as defined above; and deprotecting the benzyloxy carbonyl group from the compound of the structural formula IV through hydrogenolysis in the presence of a catalyst, to afford 0-carbamoyl-(D)-phenylalaninol compound represented by the structural formula V.

4. The process in accordance with claim 3, wherein the concentration of (D)-phenylalaninol of the structural formula II is between 0.1 and 3 mole and benzyl chloroformate is used at 1 to 2 equivalent.

5. The process in accordance with claim 3, wherein said basic aqueous solution has a pH value between 7 and
14 and the reaction is carried out at temperatures ranging from -10 to 70 °C.

6. The process in accordance with claim 3, wherein N-benzyloxycarbonyl-(D)-phenylalaninol of the structural formula III is used at 0.01 to 2 molar concentration.

7. The process in accordance with claim 3, wherein said phosgene, either neat or as solution in toluene, is used at an amount of about 1 to 2 molar equivalent.

8. The process in accordance with claim 3, wherein the carbamoylation step is carried out in a solvent selected from the group consisting of halogenated alkane such as methylene chloride, aromatic solvents such as 1-toluene, and the mixtures thereof.

9. The process in accordance with claim 3, wherein said amine base used for the carbamoylation is selected from a tertiary amine group consisting of triethylamine, diisopropylethylamine, triisopropylamine, DBU (1,6-diazabicyclo[5.4.0]undec-7-ene), DBN (1,5-diazabicyclo[4.3.0]non-5-ene), antipyrine and dimethylphenylamine.

10. The process in accordance with claim 3, wherein said amine base is used at an amount of about 1 to 2 molar equivalent.

11. The process in accordance with claim 3, wherein the carbamoylation step is carried out at a temperature of -30 to 60 °C.
12. The process in accordance with claim 3, wherein said deprotecting step is carried out in a solvent selected from the group consisting of ethereal solvents, alcoholic solvents, water, aromatic solvents, ester solvents, and the mixtures thereof.

13. The process in accordance with claim 3, wherein said deprotecting step is carried out at a temperature of -10 to 150 °C under a 1 to 100 atm hydrogen pressure.

14. The process in accordance with claim 3, wherein said catalyst used for deprotecting step is selected from the group consisting of palladium, platinum, platinum oxide, rhodium, and iridium.

15. The process in accordance with claim 3, further comprising the step of treating O-carbamoyl-(D)-phenylalaninol compound of the structural formula V with an anhydrous acid in an ethereal solution without further purification, to provide a pharmaceutically acceptable salt of O-carbamoyl-(D)-phenylalaninol, represented by the following structural formula I:

\[
\begin{align*}
\text{O} & \\
\text{Ph} & \text{OCNR}^1\text{R}^2 \\
\text{NH}_2 & \text{HX}
\end{align*}
\]  

(I)

wherein \( R^1 \) and \( R^2 \) are the same as defined above and HX is an acid suitable for the formation of a pharmaceutically
useful salts with the intramolecular basic nitrogen atom.

16. The process in accordance with claim 15, wherein the concentration of O-carbamoyl-(D)-phenylalaninol of the structural formula V is on the order of 0.01 to 5 mole.

17. The process in accordance with claim 15, wherein said treating step is carried out in a solvent selected from the group consisting of ethereal solvents, alcoholic solvents, aromatic solvents, ester solvents, and the mixtures thereof, with an addition solution of ethereal solvent.

18. The process in accordance with claim 15, wherein said anhydrous acid is selected from the group consisting of hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, benzoic acid, citric acid, malonic acid, salicylic acid, malic acid, fumaric acid, oxalic acid, succinic acid, tartaric acid, lactic acid, gluconic acid, ascorbic acid, maleic acid, aspartic acid, benzene sulfonic acid, methane sulfonic acid, ethane sulfonic acid, hydroxymethane sulfonic acid and hydroxyethane sulfonic acid.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC: C 07 C 271/12, 269/04, 295/205

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 C 271/12, 269/04; C 07 D 295/205; C 07 C 271/10, 271/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT-Patents

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

QUE DARC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>CH 522 599 A (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE) 30 June 1972 (30.06.72), example 1; columns 5,6, lines 1-3 from the bottom; claim.</td>
<td>1-3,7,8,15,17,18</td>
</tr>
<tr>
<td>A</td>
<td>DE 14 70 277 A (SIEGFRIED AG) 29 May 1969 (29.05.69), example 1; claim; page 17, lines 1-15.</td>
<td>1-3,7,8,11,15-18</td>
</tr>
<tr>
<td>A</td>
<td>AT 387 572 B (AB FEROSAN) 10 February 1989 (10.02.89), page 3, lines 3-22; example 1; claim 1.</td>
<td>1-3,8</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search: 20 March 1996 (20.03.96)

Date of mailing of the international search report: 07 May 1996 (07.05.96)

Name and mailing address of the ISA/AT
AUSTRIAN PATENT OFFICE
Rohrmarkt 8-10
A-1014 Vienna
Facsimile No. 1/53424/535

Authorized officer: Körber
Telephone No.: 1/53424/457

Form PCT/ISA/210 (second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Patent document cited</th>
<th>Date of publication</th>
<th>Patent family member(s)</th>
<th>Date of publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH A 522599</td>
<td>15-05-72</td>
<td>BE A 7467868</td>
<td>25-05-72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH A 5188845</td>
<td>10-02-72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE A 1046666</td>
<td>01-02-72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D A 1228666</td>
<td>19-02-72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E B 1334666</td>
<td>19-02-72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES A 1241440</td>
<td>02-05-70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR E4 5001022</td>
<td>02-05-70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB A 1354674</td>
<td>02-05-70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IT A 3514250</td>
<td>20-01-70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP A 6314572</td>
<td>20-01-70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US A 3714250</td>
<td>20-01-70</td>
</tr>
<tr>
<td>DE A 1470277</td>
<td>25-05-68</td>
<td>keine - none - rien</td>
<td></td>
</tr>
<tr>
<td>AT E 587572</td>
<td>10-02-69</td>
<td>AT A 1451584</td>
<td>15-02-86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK A 482784</td>
<td>24-05-84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D E 1466172</td>
<td>21-11-84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DK A 1354712</td>
<td>21-11-84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E B 1240711</td>
<td>19-05-81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES A 1354712</td>
<td>19-05-81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES A 1327670</td>
<td>19-05-81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SE A 8308866</td>
<td>20-05-83</td>
</tr>
</tbody>
</table>