Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give
notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in
a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art.
Description

[0001] The present invention relates to a crystalline salt of optically active aminocoumaran derivative which is pharmaceutically effective particularly in improving, treating and preventing cerebral dysfunction associated with cerebral stroke or cranial trauma.

[0002] As lipidperoxide formation and related radical reaction in vivo were found to have various adverse effects on the living body via membrane disorder, enzyme disorder etc., there have been various attempts at pharmaceutical application of antioxidants and lipidperoxide formation inhibitors.

[0003] Major lipidperoxide formation inhibitors now in use in the pharmaceutical field are derivatives of natural antioxidants such as vitamin C, vitamin E and the like, and phenol derivatives [Kenji Fukuzawa, Japanese Journal of Clinical Medicine, Vol. 46, pp. 2269-2276 (1988)]. However, none are satisfactory for practical use because of weak action or side effects.

[0004] However, the present inventors have discovered an aminocoumaran derivative, represented by the following general formula (A), which excellently inhibits lipidperoxide formation, and have filed a patent application therefore (EP-A-0483772).

\[
\text{R}_1 \text{R}_2 \text{N} \quad \text{R}_3 \quad \text{R}_4 \quad \text{R}_5
\]

wherein \( \text{R}_1 \) and \( \text{R}_2 \) are the same or different and are a hydrogen atom, an acyl group, an alkoxy carbonyl group, an optionally substituted aliphatic or an optionally substituted aromatic group, \( \text{R}_3, \text{R}_4 \) and \( \text{R}_5 \) are the same or different and are an optionally acylated hydroxyl group, an optionally substituted amino group, an optionally substituted alkoxy group or an optionally substituted aliphatic group or two of \( \text{R}_3, \text{R}_4 \) and \( \text{R}_5 \) may be linked together to form an optionally substituted carbocyclic group; \( \text{R}_6 \) and \( \text{R}_7 \) are the same or different and are an optionally substituted aliphatic group, provided that at least one of \( \text{R}_6 \) and \( \text{R}_7 \) has a methylene at the a-position; \( \text{R}_8 \) and \( \text{R}_9 \) are the same or different and are a hydrogen atom or an optionally substituted aliphatic group or an optionally substituted aromatic group, or a salt thereof.

[0005] Of the aminocoumaran derivatives represented by general formula (A), 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan, represented by formula (B):

\[
\text{H}_2 \text{N} \quad \text{CH}_3 \quad \text{CH}_3 \\
\text{CH}_3 \quad \text{N} \quad \text{CH}_3 \\
\]

is described in the above publication as a sparingly water-soluble free form. Also, having asymmetric carbon atoms in its molecular structure, this derivative (B) occurs in two optical isomers, namely (R) and (S) configurations. Derivative (B) is described as a mixture (racemate) of these enantiomers in the above publication. However, it is not suitable for pharmaceutical preparations because it is hygroscopic and hence unstable. Also, there have been no injectable lipidperoxide formation inhibitors which are satisfactory from the viewpoint of action, water solubility, stability (storage stability) and other aspects. Accordingly, there is demand for the development of such agents.

[0006] The present inventors investigated means of solving the above problems. Specifically, the inventors attempted to separate optical isomers and form salts of 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan compound B, chosen from the above-described compounds represented by general formula (A), which are useful in improving, treating and preventing cerebral dysfunction associated with cerebral stroke or cranial trauma.
Despite the generally accepted fact that any compound is difficult to crystallize for the first time, the inventors succeeded in creating a crystalline salt of an enantiomer of compound B, and unexpectedly found it stable and water-soluble and hence very useful for injectable preparations. The inventors conducted further investigation based on this finding, and developed the present invention.

Accordingly, the present invention provides a crystalline salt of an enantiomer of 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan, particularly the dihydrochloride and fumarate thereof, their production and lipidperoxide formation inhibitory preparation containing them.

The crystalline salt of the present invention is a crystalline salt of a compound (enantiomer) represented by the following formula (I):

\[
\text{(I)}
\]

\[(S)- \text{ configuration}\]

The crystalline salt of the present invention is a crystal of a salt of enantiomer (I) of 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan with a pharmacologically acceptable acid, e.g., an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid or phosphoric acid, an organic acid such as acetic acid, fumaric acid, maleic acid, tartaric acid, mandelic acid, methanesulfonic acid, benzenesulfonic acid or toluenesulfonic acid, or an amino acid such as aspartic acid or glutamic acid.

The crystalline salt of the present invention may be mono- or di-salt of acid.

The crystalline salt of the present invention is preferably a dihydrochloride, fumarate or the like, more preferably dihydrochloride of (S)-(+) configuration or the like.

The crystalline salt of the present invention is produced by

1. reacting 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan (Compound B) with an optically active organic acid or
2. reacting an enantiomer of Compound B with an acid.

In the above-mentioned method (1), the crystalline salt of the present invention can be concretely produced by the following process (a) or (b)

(a) process for producing the crystalline salt which comprises mixing Compound B and an optically active organic acid in a solvent to yield a uniform solution.

(b) process for producing the crystalline salt which comprises condensing Compound B with an optically active organic acid to a diastereomeric mixture of amides, separating and purifying it, and then performing hydrolysis.

In process (a) or (b), typical optically active organic acids include organic carboxylic acids, organic phosphoric acids or organic sulfonic acids having an asymmetric center in the molecule. Preferable examples of optically active organic acids include substituted (-)- or (+)-tartaric acids such as (-)- or (+)-diacetyl tartaric acid, (-)- or (+)-ditoluyl tartaric acid, (-)- or (+)-dibenzoyl tartaric acid, etc., (-)- or (+)-tartaric acid, (-)- or (+)-malic acid, (-)- or (+)-mandelic acid, (-)- or (+)-lactic acid, (-)- or (+)-camphor-10-sulfonic acid, (+)-3-bromocamphor-10-sulfonic acid, MTPA (\(\alpha\)-methoxy-\(\alpha\)-(trifluoromethyl)phenylacetic acid), mentholactylactic acid, etc., especially (-)-or (+)-mandelic acid etc. in process (a) and MTPA, menthoxycycetic acid, etc. in process (b).

In process (a), solvents which can be used include water, alcohols (e.g., methanol, ethanol, propanol, isopropanol, butanol), ethers (e.g., ethyl ether, tetrahydrofuran, dioxane), esters (e.g., ethyl acetate, methyl acetate), ketones (e.g., acetone), nitriles (e.g., acetonitrile), amides (e.g., dimethylformamide, dimethylacetamide) and dimethylsulfoxide. These may be used singly or in combination. It is preferable to use a mixed solvent of methanol, acetonitrile, ethyl acetate, ether etc.
The crystalline salt of the present invention is therapeutically and prophylactically effective against ischemic diseases due to platelet agglutination, thromboxane A2 synthetase inhibitory action, prostaglandin I₂ synthetase retention promoting action, LTD₄ receptor antagonistic action and active oxygen species eliminating action.

Of these actions, the crystalline salt of the present invention exhibits marked lipidperoxide formation inhibitory action (antioxidant action).

The crystalline salt of the present invention is low in toxicity and prevalence of side effects.

The crystalline salt of the present invention is therefore therapeutically and prophylactically effective against thrombosis due to platelet agglutination, ischemic diseases due to arterial smooth muscle contraction or vasospasm in heart, lung, brain or kidney (e.g., myocardial infarction, cerebral stroke), nerve degeneration diseases (e.g., Parkinsonism, Alzheimer's disease, Lou Gehrig's disease, myodystrophy), functional disorders due to central nervous damages such as cranial trauma and spinal trauma, memory or emotional disorders (disorders associated with nerve cell necrosis etc. caused by oxygen deficiency, brain damage, cerebral stroke, cerebral infarction, cerebral thrombosis
etc.), convulsions and epilepsies following cerebral stroke, cerebral infarction, cerebral surgery or cranial trauma, nephritis, pulmonary failure, bronchial asthma, inflammations, arteriosclerosis, atherosclerosis, hepatitis, acute hepatitis, liver cirrhosis, hypersensitive hepatitis, immunodeficiencies, circulatory diseases (myocardial infarction, cerebral stroke, cerebral edema, nephritis etc.) resulting from damage of enzyme, tissue, cell etc. caused by active oxygen species (e.g., superoxide, hydroxyl radical), tissue fibrosis, cancer and other diseases in mammals (e.g., mice, rats, rabbits, dogs, monkeys, humans), and is pharmaceutically useful as an antithrombotic agent, antivasospasmotic agent, antiasthmatic agent, cardiac/cerebral circulation improving agent, nephritis remedy, hepatitis remedy, tissue fibrosis inhibitor, active oxygen species eliminator, arachidonate cascade substance regulation improving agent and as other varieties of agent.

[0032] The crystalline salt of the present invention can be safely administered orally or non-orally, as such or in pharmaceutical compositions (e.g., tablets, capsules, liquids, injections, suppositories) along with pharmacologically acceptable carriers, excipients and other additives. The crystalline salt of the present invention, soluble in water, is advantageously administered as an injectable preparation. Although dose varies depending on subject, route of administration, symptoms and other factors, it is advantageous to administer it normally at about 0.01 mg/kg to 20 mg/kg body weight, preferably about 0.1 mg/kg to 10 mg/kg body weight, and more preferably about 0.5 mg/kg to 10 mg/kg body weight per dose once to three times daily, when non-orally administered to adult patients with circulatory disease.

[0033] The present invention is hereinafter described in more detail by means of the following working examples, analytical example and test example, which are not to be construed as limitative.

Example 1

(S)-(+) -5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan (S)-(+) -mandelate

[0034] To a solution of 35.4 g of (35)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan in 500 ml of chloroform was added a solution of 14.78 g of (S)-(+) -mandelic acid in 300 ml of methanol, followed by concentration. To the residue was added about 500 ml of ether; the resulting precipitate was collected by filtration and washed with ether. The resulting 35.4 g crude crystal was subjected to the following recrystallizing procedure. Specifically, the crude crystal was dissolved in methanol-acetonitrile (2:1) (1 liter). After the solution was concentrated to about 100 ml volume, about 500 ml of ether was added, and the mixture was kept standing at 20°C. The resulting precipitate was finely milled, then filtered and washed with ether. The above procedure was repeated in two cycles (first yield 21.96 g) to yield 19.90 g of (S)-(+) -5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan (S)-(+) -mandelate.

Melting point: 186-190°C

$\left[\alpha\right]_{D}^{27}: + 57.1^\circ$ (c = 1.230, methanol)

Reference Example 2

(R)-(−)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan (R)-(−)-mandelate

[0035] The mother liquor of Example 1 was concentrated to dryness. The resulting 28.2 g residue was dispensed to 500 ml of ethyl acetate and 500 ml of a 0.5 N aqueous solution of sodium hydroxide. The organic layer was washed by sequential additions of a 0.5 N aqueous solution of sodium hydroxide, a saturated aqueous solution of sodium hydrogen carbonate and saturated saline and then dried over anhydrous sodium carbonate, followed by concentration to dryness. The resulting 20 g residue and 8.35 g of (R)-(−)-mandelic acid were treated in the same manner as in Example 1 to yield 20.41 g of (R)-(−)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan (R)-(−)-mandelate.

Melting point: 186-191°C

$\left[\alpha\right]_{D}^{27}: 57.0^\circ$ (c = 1.090, methanol)
Example 3

(S)-( +)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dihydrochloride

19.8 g of (S)-(+) -5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan (S)-(+) -mandelate was dispensed to 500 ml of ethyl acetate and 500 ml of a 0.5 N aqueous solution of sodium hydroxide. The organic layer was washed by sequential additions of a 0.5 N aqueous solution of sodium hydroxide, a saturated aqueous solution of sodium hydrogen carbonate and saturated saline and then dried over anhydrous sodium carbonate, followed by concentration to dryness. The resulting about 15 g residue was dissolved in 140 ml of methanol, and 23.3 ml of an ethyl acetate solution in 4 N hydrochloric acid, followed by concentration to dryness. The resulting residue was recrystallized from ethyl acetate to yield a crude crystal, which was again recrystallized from methanol-ethyl acetate to yield 13.84 g of (S)-(+) -5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dihydrochloride.

Melting point: 226°C (decomposed)

\[ \alpha \]D 20 : +27.8° (c = 1.054, methanol)

Elemental analysis (for C24H32N2O·C8H8O3):

| Found | C, 74.26; H, 7.78; N, 5.54 |

Reference Example 4

(R)-(−)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dihydrochloride

In the same manner as in Example 3, 15.55 g of (R)-(−)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dihydrochloride was obtained from 20.03 g of (R)-(−)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan (R)-(−)-mandelate.

Melting point: 226°C (decomposed)

\[ \alpha \]D 20 : -27.9° (c = 1.284, methanol)

Elemental analysis (for C24H32N2O·H2Cl2):

| Calculated | C, 65.90; H, 7.83; N, 6.40; Cl, 16.21 |
| Found      | C, 65.60; H, 7.89; N, 6.37; Cl, 16.01 |

Example 5

(S)-( +)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dimethanesulfonate

800 mg of (S)-(+) -5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dihydrochloride was dispensed to ethyl acetate (10 ml) and a 0.5 N aqueous solution of sodium hydroxide (10 ml). The organic layer was washed by sequential additions of a saturated aqueous solution of sodium hydrogen carbonate and saturated saline and then dried over anhydrous sodium carbonate, followed by concentration to dryness. The resulting residue and 351 mg of methanesulfonic acid were dissolved in methanol, followed by concentration to dryness. To the resulting crystalline residue was added ethyl acetate; the resulting precipitate was collected by filtration and washed with ethyl acetate, to yield 950 mg of crystal of (S)-(+) -5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dimethanesulfonate.

Melting point: 202 - 211°C

\[ \alpha \]D 25 : +21.4° (c = 1.340, methanol)
Example 6

(S)-(+)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan fumarate

[0039] In the same manner as in Example 5, 543 mg of (S)-(+)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan fumarate was obtained from 800 mg of (S)-(+)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dihydrochloride and 212 mg of fumaric acid.

Melting point: 177 - 180°C

$\alpha_D^{25} = +32.2^\circ$ (c = 1.070, methanol)

Reference Example 7

(R)-(-)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl) 2,3-dihydrobenzo[b]furan dihydrobromide

[0040] (R)-(-)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl) 2,3-dihydrobenzo[b]furan (860 mg) was dissolved in methanol and to the solution was added 25% hydro bromide in acetic acid solution (0.5 ml) and then concentrated. The residue was dissolved in methanol and left. The resulting crystal was collected by filtration and washed with ethanol to yield 810 mg of (R)-(-)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan dihydrobromide.

Melting point: 220.5°C (decomposed)

$\alpha_D^{20} = +23.6^\circ$ (c = 0.86, methanol)

Reference Example 8

(R)-(-)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan L-tartarate

[0041] (R)-(-)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan (870 mg) and L-tartaric acid (354 mg) were dissolved in methanol and then concentrated. The residue was dissolved in ethanol and left. The resulting crystal was collected by filtration and washed with ethanol to yield 970 mg of (R)-(-)-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan L-tartarate monoethanol.

Melting point: 130.5°C

$\alpha_D^{20} = +35.0^\circ$ (c = 0.755, methanol)

Analytical Example 1

[0042] The compound of Example 67 of EP-A-0483772 and the compound of Example 1 were analyzed by high performance liquid chromatography, using an optical resolution column.
Operating conditions:

Column : Chiral Cell OD (4.6 x 250 mm)
Mobile phase: n-hexane-ethanol-diethylamine (100:0.5:0.1, v/v)
Flow rate : 1 ml/min
Detection : UV 254 nm

[0043] The analytical results are given in Figure 1 (the compound of Example 67 of EP-A-0483772) and Figure 2 (the compound of Example 1).

[0044] The abscissa indicates retention time (min). Peaks 1 and 2 correspond to the (S)-( +) and (R)-( -) configurations, respectively.

Analytical Example 2

[0045] The powder X-ray diffraction pattern (CuKα, 40kV, 40mA) of the compound of Example 3 is shown in Figure 3 (showing characteristic peaks at lattice spacings (d) of 13.89, 7.12, 5.36, 4.26, 4.05, 4.00, 3.31, 3.21).

Experiment 1

[0046] Effect on drugs on the change of behavior induced by spinal intrathecal injection of FeCl₂ in mice.

[0047] Male Slc: IcR mice (5 weeks) (10 mice per group) were used. After injection of 5 ml/mouse physiological saline, containing 50 mM dissolved ferrous chloride, to the subarachnoid cavity from lumbar spinal cord VI to sacral spinal cord I, each animal was observed for behavioral changes from 15 minutes to 1 hour following injection. The following criteria were used to score behavioral changes.

<table>
<thead>
<tr>
<th>Score</th>
<th>Behavioral change</th>
</tr>
</thead>
<tbody>
<tr>
<td>0: Normal</td>
<td></td>
</tr>
<tr>
<td>1: Frequent bites to lower limbs and lower abdomen.</td>
<td></td>
</tr>
<tr>
<td>2: One of the following three responses is seen:</td>
<td></td>
</tr>
<tr>
<td>a) Violent bites to lower half of body, with occasionally rolling</td>
<td></td>
</tr>
<tr>
<td>b) Hypersensitive aggressive behavior in response to external stimulation</td>
<td></td>
</tr>
<tr>
<td>c) Tremors</td>
<td></td>
</tr>
<tr>
<td>3: Clonic convulsion</td>
<td></td>
</tr>
<tr>
<td>4: Tonic convulsion, or unilateral or bilateral limb paralysis</td>
<td></td>
</tr>
<tr>
<td>5: Death</td>
<td></td>
</tr>
</tbody>
</table>

[0048] Percent inhibitions were calculated from the scores obtained as above (percent inhibition = [(5-score)/5]x100). The subject compound salt was orally administered during the 30-minute period following administration of ferrous chloride.

[0049] Table 1 shows the mean scores and percent inhibitions obtained after a 25 mg/kg oral administration of the each compound of Example 3 and Reference Example 4.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Score</td>
</tr>
<tr>
<td>25 mg/kg Administered</td>
</tr>
<tr>
<td>Example 3</td>
</tr>
<tr>
<td>Ref. Example 4</td>
</tr>
</tbody>
</table>

[0050] These results demonstrate that the crystalline salts of the present invention are excellent in suppressing action against central nervous disorder associated with lipidperoxide formation by ferrous chloride.

[0051] The present invention provides a lipidperoxide formation inhibitor, particularly a crystalline salt of an enantiomer of 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan which serves well to improve, treat and prevent cerebral dysfunction associated with cerebral stroke or cranial trauma. The crystalline salt of the present invention is more soluble in water and more stable than the free form of the compound.
Claims

1. A crystalline salt of (S)-(+)\textregistered-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan.

2. A crystalline salt as claimed in claim 1, which is a dihydrochloride.

3. A crystalline salt as claimed in claim 2, which shows its characteristic peaks at lattice spacings (d) of 13.89, 7.12, 5.36, 4.26, 4.05, 4.00, 3.31, 3.21 in the powder X-ray diffraction pattern.

4. A crystalline salt as claimed in claim 1, which is a fumarate.

5. A process for producing a crystalline salt of (S)-(+)\textregistered-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan wherein the salt is formed with a pharmacologically acceptable acid, which comprises
   
   (1) reacting a 5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan with an optically active organic acid, or
   
   (2) reacting (S)-(+)\textregistered-5-amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan with an acid.

6. A pharmaceutical composition for inhibition of lipidperoxide formation which comprises an effective amount of the crystalline salt according to claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.

7. A pharmaceutical composition as claimed in claim 6, which is used as a preventive and/or therapeutic agent for cerebral dysfunction.

8. A pharmaceutical composition as claimed in claim 6 for inhibition of lipidperoxide formation in a patient suffering from a disease caused by active oxygen species.

9. Use of the crystalline salt according to claim 1 in the preparation of a pharmaceutical composition for inhibition of lipidperoxide formation.

Patentansprüche

1. Kristallines Salz von (S)-(+)\textregistered-5-Amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo [b]-fur.

2. Kristallines Salz nach Anspruch 1, das ein Dihydrochlorid ist.

3. Kristallines Salz nach Anspruch 2, das charakteristische Peaks bei den Gitterabständen (d) 13.89, 7.12, 5.36, 4.26, 4.05, 4.00, 3.31, 3.21 im Pulverröntgenbeugungsdiagramm zeigt.

4. Kristallines Salz nach Anspruch 1, das ein Fumarat ist.

5. Verfahren zur Herstellung eines kristallinen Salzes von (S)-(+)\textregistered-5-Amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan, wobei das Salz mit einer pharmakologisch annehmbaren Säure gebildet wird, das umfasst, dass

   (1) 5-Amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo [b] furan mit einer optisch aktiven organischen Säure umgesetzt wird oder
   
   (2) (S)-(+)\textregistered-5-Amino-2,4,6,7-tetramethyl-2-(4-phenylpiperidinomethyl)-2,3-dihydrobenzo[b]furan mit einer Säure umgesetzt wird.

6. Pharmazeutische Zusammensetzung zur Hemmung der Lipidperoxidbildung, die eine wirksame Menge des kristallinen Salzes nach Anspruch 1 und einen pharmazeutisch annehmbaren Träger, ein Verdünnungsmittel oder einen Hilfsstoff enthält.

7. Pharmazeutische Zusammensetzung nach Anspruch 6, die als präventives und/oder therapeutisches Mittel für
Verwendung des kristallinen Salzes nach Anspruch 1 zur Herstellung einer pharmazeutischen Zusammensetzung zur Hemmung der Lipidperoxidbildung.
Figure 1
Figure 2