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BRIGARD & CASTRO
PROPIEDAD INTELECTUAL

CARRERA 7 # 71 – 21 TORRE B – PISO 4
BOGOTÁ – COLOMBIA
TEL: (571) 744 22 00
FAX: (571) 742 22 00 – (571) 3214045
www.bc.com.co

AS: 100.823

Señores
SUPERINTENDENCIA DE INDUSTRIA Y
DIVISION DE NUEVAS CREACIONES
E. S. D.

REF.: Expediente No. 06 032016 - Solicitud de Patente FASE NACIONAL
Corresp. a la Solicitud Internacional PCT/JP2004/014892
a nombre de: **ONO PHARMACEUTICAL CO., LTD**.
Titulada: COMPOSICIÓN FARMACÉUTICA PARA INYECCIÓN QUE COMPRENDE ÁCIDO (2R)-2-PROPILOCTANOICO COMO UN INGREDIENTE ACTIVO

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad **ONO PHARMACEUTICAL CO., LTD.**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 08-11,105 por valor de $420.000.

De la Señora Jefe atentamente,

JUAN PABLO CADENA SARMIENTO
C.C. No. 80.410.337 de Usaquén
T.P. No. 57492 del C.S.J.
Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 5 de marzo de 2008
MEV/JCN/aac

As. 100823

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 11,105
FECHA : FEBRERO 11 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	127822	08/02/2008	45,422,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL : $	420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Industria y Comercio
SUPERINTENDENCIA

A62
161

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-32016

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **580** DE

FECHA **28 DE SEPTIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **27 DE DICIEMBRE DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ____X____

(19) Canadian Intellectual Property Office
An Agency of Industry Canada

Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

(11) CA 2 453 478 (13) A1

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(43) 30.01.2003

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(71) ONO PHARMACEUTICAL CO., LTD.,
1-5, Doshomachi 2-chome
Chuo-ku
Osaka-shi
541-8526, OSAKA, XX (JP).

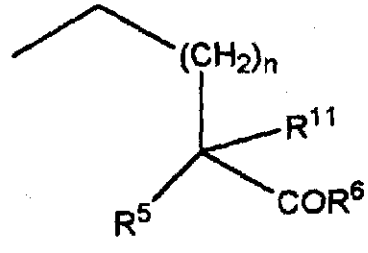
(72) KATSUBE, NOBUO (JP).
TATEISHI, NARITO (JP).
HONJO, KANEYOSHI (JP).

(74) RICHES, MCKENZIE & HERBERT LLP

(54) AGENT POUR LE TRAITEMENT DES MALADIES ISCHEMIQUES CEREBRALES
(54) AGENT FOR TREATMENT OF CEREBRAL ISCHEMIC DISEASES

(57)

Remedies and/or preventives for brain ischemic diseases comprising two active ingredients, namely, an astrocytic function-improving agent, preferably a compound represented by the following general formula (I), and a thrombolytic agent, preferably a tissue plasminogen activator: (I) wherein R6 represents hydroxy, etc.; and (1) n is 1, R11 represents hydrogen, and R5 represents (alkyl having a fluorine atom as a substituent of a carbon atom)-CH2-; or (2) n is 0 or 1, R11 represents hydrogen, etc., and R5 represents alkyl, etc. These drugs show synergistic therapeutic effects compared with the case where an astrocytic function improving agent and a thrombolytic agent are separately administered.



(I)

administration of a thrombolytic agent, followed by administration of an astrocyte function-improving agent. Since the astrocyte function-improving agent is effective even quite a long time after the occurrence of ischemia and does not suppress thrombolytic activity of the thrombolytic agent, as is apparent from the experiments described hereafter, simultaneous administration is not necessarily required.

The compounds represented by the formula (I) according to the present invention are known per se, or can be prepared according to the methods as described in the specification of Japanese Patent Unexamined Publication No. H07-316092 (US patent No. 6201021) or WO 00/48982.

The thrombolytic agents used in the present invention are known per se and, for example, t-PA and urobilinogen are commercially available.

The compounds represented by the formula (I) of the present invention may be converted into the corresponding salts by the common method. Non-toxic and water-soluble salts are preferable. Suitable salts include, for example, salts of alkali metals (sodium, potassium, *etc.*), salts of alkaline earth metals (calcium, magnesium, *etc.*), ammonium salts, salts of pharmaceutically acceptable organic amines (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine, *etc.*), among which sodium salt is particularly preferable.

The compounds represented by the formula (I) of the present invention may be converted into the corresponding acid addition salts by the common method. Non-toxic and water-soluble acid addition salts are preferable. Suitable acid addition salts include, for example, inorganic acid salts (hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, nitrate, *etc.*) and organic acid salts (acetate, lactate, tartrate, oxalate, fumarate, maleate, citrate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, isethionate, glucuronate, gluconate, *etc.*).

Although the dose varies depending on age, body weight, symptom, therapeutic effect, administration route and treatment time, the doses per human adult per dose are generally within a range of 1 mg to 1000 mg, up to several times a day, or within a range of 0.1 mg to 100 mg, up to several times a day, parenteral (preferably intravenous) administration or by continuous intravenous administration over a period of 1 to 24 hours.

As mentioned above, the dose to be prescribed depends upon various conditions, and thus there are cases in which doses lower than or greater than the range as specified above may be required.

When the compounds of the present invention are administered, they are used as solid compositions, liquid compositions or other compositions for oral administration, and as injections, external compositions or suppositories, *etc.* for parenteral administration.

The solid compositions for oral administration include tablets, pills, capsules, dispersible powders, granules, and the like. The oral compositions also include gargles which are to be stuck to oral cavity and sublingual tablets. The capsules include hard capsules and soft capsules.

In such solid compositions for oral use, one or more of the active compound(s) may be admixed solely or with diluents (such as lactose, mannitol, glucose, microcrystalline cellulose, starch, *etc.*), binders (such as hydroxypropyl cellulose, polyvinylpyrrolidone, magnesium aluminometasilicate, *etc.*), disintegrators (such as cellulose calcium glycolate, *etc.*), lubricants (such as magnesium stearate *etc.*), stabilizers, solubilizers (such as glutamic acid, aspartic acid, *etc.*), and then formulated into a preparation in a conventional manner. When necessary, such preparations may be coated with a coating agent such as sucrose, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, *etc.*) or they may be coated with two or more

coating layers. Furthermore, the solid compositions for oral use include capsules of absorbable materials like gelatin.

The liquid compositions for oral administration include pharmaceutically acceptable aqueous solutions, suspensions, emulsions, syrups, elixirs, and the like. In such compositions, one or more of the active compound(s) may be dissolved, suspended or emulsified in a commonly used diluent (such as purified water, ethanol or a mixture thereof, *etc.*). Besides such diluents, said compositions may also contain wetting agents, suspending agents, emulsifiers, sweetening agents, flavoring agents, perfumes, preservatives and buffers and the like.

Injections for parenteral administration include solutions, suspensions, emulsions, and solid injectable compositions which are dissolved or suspended in a solvent immediately before use. The injections are used by dissolving, suspending or emulsifying one or more of the active compounds in a diluent. Examples of said diluents are distilled water for injection, physiological saline, vegetable oil, alcohol (such as propylene glycol, polyethylene glycol, ethanol, *etc.*), and a combination thereof. Further, the injections may contain stabilizers, solubilizers (such as glutamic acid, aspartic acid, polysorbate 80 (registered trade mark), *etc.*), suspending agents, emulsifiers, soothing agents, buffers, preservatives, *etc.* The injections are sterilized in the final formulation step or prepared by sterile procedure. The injections may also be formulated into sterile solid preparations, for example, by freeze-drying, and may be used after sterilized or dissolved in sterile injectable water or other sterile diluent(s) immediately before use.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are provided to illustrate the present invention, but are not to be construed as limiting the invention.

(19) Canadian Intellectual Property Office
An Agency of Industry Canada

Office de la Propri,t, Intellectuelle du Canada
Un organisme d'Industrie Canada

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(71) ONO PHARMACEUTICAL CO., LTD.,
1-5, Doshomachi 2-chome
Chuo-ku
Osaka-shi
541-8526, OSAKA, XX (JP).
TOKYO KASEI KOGYO CO., LTD., , TOKYO, XX (JP).

(72) YAMAGUCHI, KAORU (JP).
TODA, NORIKAZU (JP).
IGUCHI, YOUICHI (JP).

(74) SIM & MCBURNEY

(54) PROCEDE DE PREPARATION D'ACIDE (2R)-2-PROPYLOCTANOIQUE
(54) PROCESS FOR THE PREPARATION OF (2R)-2-PROPYLOCTANOIC ACID

(57)

A process for the preparation of (2R)-2-propyloctanoic acid, characterized by subjecting (2S)-2-(2-propynyl)octanoic acid or (2S)-2-(2-propenyl) octanoic acid to reduction with platinum-carbon. This process gives (2R)-2- propyloctanoic acid having a high optical purity without being accompanied with isomerization.

compounds, for example, described in WO 99/58513.

In the present invention, the hydrogenation of the starting material may be carried out in an organic solvent (e.g. ethyl acetate, tetrahydrofuran, dioxane, dimethoxyethane, diethyl ether, biphenyl ether, methyl alcohol, ethyl alcohol, isopropyl alcohol, benzene, toluene, xylene, HMPA, dimethylformamide, dimethylimidazolidine, mixture thereof), by using a platinum on carbon under an atmosphere of hydrogen at 0-60℃.

Platinum on carbon used in the present invention is commercially available.

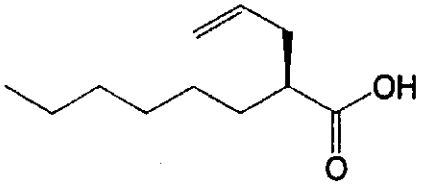
A preferable amount for use is 0.1-20 wt %, more preferably 0.1-10 wt % based on the material.

According to the process of the present invention, there occurs no isomerization and (2R)-2-propyloctanoic acid having high optical purity can be obtained compared to conventional process (wherein, palladium on carbon is used as catalyst).

That is, there happened partial isomerization by the conventional process and the optical purity was decreased, but by the process of the present invention, there occurs substantially no isomerization and present compound having high purity can be obtained.

The following table shows optical purity of the present compound, which prepared by the process of the present invention and a conventional process (comparative example 1

(2S)-2-(2-propenyl)octanoic acid



n-Hexane/ethyl acetate (4/1; 2790 ml) and 2N hydrochloric acid (270 ml) were added to the compound prepared in Reference example 1 (140 g), and the mixture was stirred for 30 minutes. The water layer was removed from the reaction solution, and the organic layer was washed with water (690 ml×3 times), and the product was extracted with 2.6N sodium hydroxide (750 ml). The water layer was washed with n-hexane/ethyl acetate (4/1; 2790 ml×2 times). To the water layer, 2N hydrochloric acid (990 ml) was added, and the product was extracted with n-hexane/ethyl acetate (4/1; 2790 ml). The organic layer was washed with water (690 ml×3 times) and with a saturated aqueous solution of sodium chloride, and concentrated to give the title compound (89 g; yield 98%). Optical purity (measured by gas chromatography): 99.8% e.e.

Example 1

Preparation of (2R)-2-propyloctanoic acid using platinum on carbon

A solution of the compound prepared in Reference example 2 (87 g) in 2-propylalcohol (2.17 L) was added to 5%

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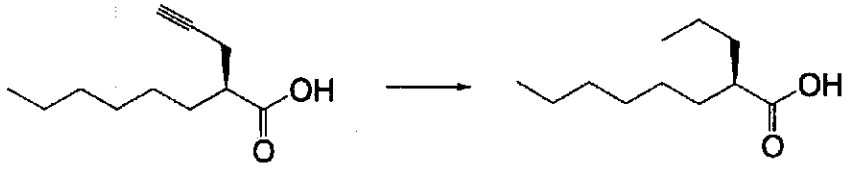
platinum on carbon (44 wet %)(9.91 g), and the mixture was hydrogenated under a pressure of hydrogen (5kg/cm^2), at 30℃ for 4 hours. The reaction mixture was filtered, and the filtrate was concentrated. To the residue, n-hexane/ethyl acetate (5/1; 1.7 L) was added, and the product was extracted with 2N sodium hydroxide (511 mL). A concentrated hydrochloric acid (86 ml) was added to the water layer, and the product was extracted with n-hexane/ethyl acetate (5/1; 1.7L). The organic layer was washed with purified water (430 ml×3 times), a saturated aqueous solution of sodium chloride, dried and concentrated. The residue was distilled to give the title compound (75.0 g; yield: 85%) having the following physical data.

Optical purity (measured by HPLC): 99.4% e.e.

Example 2

Preparation of (2R)-2-propyloctanoic acid using platinum on carbon



5% Platinum on carbon wet (270 g) was added to a solution of (2S)-2-(2-propynyl)octanoic acid (described in JP-A-8-291106) (43.0 kg; 99.90% e.e.) in isopropylalcohol (344 L), and the mixture was hydrogenated under a pressure of hydrogen (3.9 ~ 15.0 kg/cm^2), at 20 ~ 30℃ for 8 hours. Similarly, 5% platinum on carbon wet (149 g) was added to a solution of

(2S)-2-(2-propynyl)octanoic acid (23.7 kg; 99.90% e.e.) in 2-propylalcohol (190 L), and the mixture was hydrogenated under a pressure of hydrogen (2.6 ~ 15.0 kg/cm^2), at 16 ~ 30℃ for 5 hours. A catalyst was removed from the above two reaction solutions. These filtrates were concentrated. The residue was distilled to give the title compound (56.48 kg; yield: 82.8 %) having the following physical data.

Optical purity (measured by HPLC) : 99.34% e.e.

Comparative example 1

Preparation of (2R)-2-propyloctanoic acid using palladium on carbon

10% Palladium on carbon (17 mg) was added to a solution of (2S)-2-(2-propynyl)octanoic acid (168 mg; 99.0% e.e. (measured by gas chromatography)) in a mixed solution of methanol (1.2 ml) and ethyl acetate (1.2 ml). The mixture was stirred for 1 hour at room temperature under an atmosphere of hydrogen gas. The residue was filtered through Celite (product name), and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane : ethyl acetate = 9 : 1 → 4 : 1) to give the title compound (109 mg; yield: 65 %) having the following physical data.

Optical purity (measured by HPLC) : 95.2% e.e.

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(19) **United States**

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Itoyama et al. (43) **Pub. Date: Mar. 14, 2002**

(54) **AGENT FOR TREATING PARKINSON'S DISEASE COMPRISING ASTROCYTE FUNCTION-IMPROVING AGENT AS ACTIVE INGREDIENT**

(75) Inventors: **Yasuto Itoyama**, Miyagi (JP); **Hiroyuki Kato**, Miyagi (JP); **Tsutomu Araki**, Miyagi (JP)

Correspondence Address:
SUGHRUE, MION, ZINN, MACPEAK, SEAS, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, DC 20037 (US)

(73) Assignee: **ONO PHARMACEUTICAL CO., LTD.**

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(30) **Foreign Application Priority Data**

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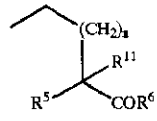
(52) **U.S. Cl.** **514/210.17**; 514/217.11; 514/330; 514/423; 514/529; 514/625

(57) **ABSTRACT**

An agent for preventing and/or treating Parkinson's disease or Parkinson's syndrome, comprising, as an active ingredient, an astrocyte function-improving agent is disclosed. The astrocyte function-improving agent is preferably a compound represented by formula (I), a non-toxic salt thereof, or a hydrate thereof:

(I)



R^5, R^6, R^{11} and n are defined in the specification.

[0025] (1) n is 1;

[0026] R^{11} represents hydrogen; and

[0027] R^5 represents (C1-10 alkyl in which one of the carbon atom(s) is substituted with 1 to 3 fluorine atoms)-CH_2—,

[0028] with the proviso that R^5 does not represent F—$(CH_2)_5$—, F—$(CH_2)_6$—, F—$(CH_2)_7$— and F_3C—$(CH_2)_2$—; or

[0029] (2) n is 0 or 1;

[0030] R^{11} represents hydrogen or chlorine; and

[0031] R^5 represents:

[0032] C3-10 alkyl,

[0033] C3-10 alkenyl,

[0034] C2-10 alkoxy,

[0035] C2-10 alkylthio,

[0036] C3-7 cycloalkyl,

[0037] phenyl,

[0038] phenoxy,

[0039] F—$(CH_2)_m$, in which m is an integer of 5 to 7,

[0040] F_3C—$(CH_2)_2$—,

[0041] (C2-10 alkyl substituted with 1 or 2 chlorine atoms)-CH_2, or

[0042] (C1-5 alkyl substituted with 1 or 2 substituents selected from the group consisting of C1-4 alkoxy, C3-7 cycloalkyl, phenyl and phenoxy)-CH_2—; or

[0043] R^5 and R^{11}, taken together, form C3-10 alkylidene.

[0044] JP-A-7-316092 discloses that the compounds represented by formula (I) have an effect of improving astrocyte function and thus are effective for Alzheimer's disease etc. However, there is no described that these compounds are effective for Parkinson's disease and Parkinson's syndrome. Although the presence of reactive astrocytes was confirmed in Parkinson's disease (*Greenfield's Neuropathology*, 6th edition, Graham D L, Lantos P L (eds), Arnold, London, 1997), it has not been decided so far either these reactive astrocytes causes Parkinson's disease or are formed as the result thereof. It has been confirmed for the first time by the present invention that the compounds represented by formula (I) are effective in an experiment in vivo (Parkinson's disease model).

[0045] In a preferred embodiment, the astrocyte function-improving agents for use in the present invention are a compound of the formula (I) wherein n is 1, R11 is hydrogen, R5 is C3-10 alkyl and R6 is hydroxy and non-toxic salts thereof.

[0046] In a more preferred embodiment, the astrocyte function-improving agents for use in the present invention are (R)-2-propyloctanoic acid and non- toxic salts thereof. However, it is fully expected that not only (R)-2-propyloctanoic acid, which is a typical example of the compounds according to the present invention, but any compounds represented by formula (I) are effective for Parkinson's disease because they have the effect of improving the astrocyte function.

[0047] The compounds represented by formula (I) are publicly known per se or can be produced by the method described in JP-A-7-316092 or PCT00/48982.

[0048] The compounds for use in the present invention can be converted into the corresponding salts by publicly known methods. Non-toxic and water-soluble salts are preferred. Examples of suitable salts include salts of alkali metals (potassium, sodium etc.), salts of alkaline earth metals (calcium, magnesium etc.) and salts of pharmaceutically acceptable amines (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine etc.). The sodium salts are particularly preferred.

[0049] The compounds to be used in the present invention can be converted into the corresponding acid addition salts by publicly known methods. Non-toxic and water-soluble acid addition salts are favorable. Examples of appropriate acid addition salts include inorganic acid salts such as hydrochlorides, hydrobromides, hydroiodides, sulfates, phosphates and nitrates, and organic acid salts such as acetates, lactates, tartarates, oxalates, fumarates, maleates, citrates, benzoates, methanesulfonates, ethanesulfonates, benzenesulfonates, toluenesulfonates, isethionates, glucuronates and gluconates.

[0050] The compounds according to the present invention or salts thereof can be converted into hydrates by publicly known methods.

[0051] Pharmacological activity:

[0052] Because of having an effect of improving the astrocyte function, the compounds of the present invention represented by formula (I) are efficacious in a Parkinson's disease model as will be described hereinafter. Thus, it is expected that these compounds are effective for Parkinson's disease and Parkinson's syndrome.

[0053] Toxicity:

[0054] It has been confirmed that the compounds of the present invention represented by formula (I) have such low toxicity as being sufficiently safe in using as drugs. When (R)-2-propyloctanoic acid was intravenously administered to dogs in a single dose of 100 mg/kg, for example, no case of death was observed.

[0055] Application to Drugs:

[0056] The astrocyte function-improving agents for use in the present invention, salts thereof or hydrates of the same are useful in treating and/or preventing Parkinson's disease or Parkinson's syndrome.

[0057] For the purpose above described, the astrocyte function-improving agents, a salt thereof, or a hydrate thereof may be normally administered to human or animal systemically or locally and orally or parenterally.

[0058] The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the dura-

tion of the treatment etc. In the human adult, the doses per person per dose are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 0.1 mg and 100 mg, by subcutaneous, intravenous or intranasal administration up to several times per day, or by continuous administration between 1 and 24 hours per day into vein.

[0059] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0060] The compounds of the present invention may be administered as inner solid compositions or inner liquid compositions for oral administration, or as injections, liniments or suppositories etc. for parenteral administration.

[0061] Inner solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders and granules etc. Furthermore, they also include gargling agents and sublingual agents for intraoral insertion and adsorption. Capsules contain hard capsules and soft capsules.

[0062] In such inner solid compositions, one or more of the active compound(s) are prepared as pharmaceuticals by known methods as they are, or by mixing with an inert diluent (lactose, mannitol, glucose, microcrystalline cellulose, starch etc.), connecting agents (hydroxypropyl cellulose, polyvinylpyrrolidone, magnesium metasilicate aluminate etc.), disintegrating agents (cellulose calcium glycolate etc.), lubricating agents (magnesium stearate etc.), stabilizing agents, assisting agents for dissolving (glutamic acid, asparaginic acid etc.) etc. If necessary, the pharmaceuticals may be coated with a coating agent (sugar, gelatin, hydroxypropyl cellulose, hydroxypropyl cellulose phthalate etc.), or be coated with two or more films. Furthermore, capsules of absorbable materials such as gelatin are also included.

[0063] Inner liquid compositions for oral administration include pharmaceutically acceptable water agents, suspensions, emulsions, syrups, elixirs etc. In such liquid compositions, one or more of the active compound(s) are dissolved, suspended or emulsified in inert diluent(s) generally used (purified water, ethanol, mixture thereof etc.). Furthermore, the liquid compositions may also contain wetting agents, suspending agents, emulsifying agents, sweetening agents, flavouring agents, perfuming agents, preserving agents, buffer agents etc.

[0064] Injections for parenteral administration include solutions, suspensions, emulsions, and solid injections which are dissolved or suspended in solvent(s) when they are used. One or more active compound(s) are dissolved, suspended or emulsified in solvent(s) when such compositions are used. Examples of the solvents include distilled water for injection and physiological salt solution, plant oil, propylene glycol, polyethylene glycol and alcohol such as ethanol etc., and mixture thereof. Such compositions may contain stabilizing agent, assisting agents for dissolving (glutamic acid, asparaginic acid, POLYSOLBATE80 (registered trade mark) etc.), suspending agents, emulsifying agents, dispersing agents, buffer agents, preserving agents etc. They are manufactured and prepared by sterilization at the final step or aseptic treatment. They may also be manufactured in the form of sterile solid compositions, such as freeze-drying products, and they can be dissolved in sterilized or sterile distilled water for injection or other solvent before use.

[0065] Now, the present invention will be described in greater detail by reference to the following Examples. However, it is to be understood that the present invention is not construed as being limited thereto.

EXAMPLE 1

[0066] Improvement Effect of the Compound of the Present Invention in Experimental Model of Parkinson's Disease Induced by Administration of MPTP

[0067] Male C57BL/6 mice (body weight: 20 to 28 g) were divided into groups each having 6 to 12 animals. Without anesthetizing, MPTP (10 mg/kg; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride) was intraperitoneally administered to the mice 4 times at intervals of 1 hour (*Brain Res.*, 824: 224-231 (1999)). To the models thus prepared, Compound A of the present invention ((R)-2-propyloctanoic acid) was administered after 1, 6, 24 and 48 hours. Three days after the final administration, striata of the mice were collected. After weighing, the striata were immediately frozen and stored. Then, dopamine content and DOPAC (3,4-dihydroxypyenylacetate) content were measured by HPLC in a conventional manner and evaluated. Table 1 shows the results.

[0068] Dunnett's multiple comparison test (both sides) was performed on the basis of the data of the group with the administration of MPTP alone.

[0069] The values in Table 1 are shown by the average ± the standard deviation.

TABLE 1

	Dopamine content(μg/g)	DOPAC content (μg/g)
Control (physiological saline)	13.32 ± 2.34**	2.50 ± 0.38**
Compound A of invention 30 mg/kg	12.17 ± 1.41**	2.97 ± 0.49**
MPTP	2.96 ± 2.07	1.40 ± 0.78
MPTP + compound A of invention 3 mg/kg	4.13 ± 1.48	1.30 ± 0.31
MPTP + compound A of invention 10 mg/kg	5.45 ± 2.00*	2.07 ± 0.77
MPTP + compound A of invention 30 mg/kg	6.75 ± 2.72**	2.26 ± 0.52*

*: $p < 0.05$, **: $p < 0.01$

[0070] Compared with the group of the administration of MPTP alone, the groups of the administration of MPTP+ the compound of the present invention showed significantly increased dopamine and DOPAC content depending on the dose. The data of the group with the compound of the present invention alone were almost the same as the data of the control group, which indicates that it showed no adverse effect when used alone in normal animals.

[0071] Also, the compounds of the present invention are efficacious even in post treatment administration, which makes them epoch-making drugs different from the existing ones.

FORMULATION EXAMPLE 1

Preparation of Capsules

[0072] (R)-2-propyloctanoic acid (1 g) was encapsulated into gelatin capsules to obtain 10 capsules each containing 100 mg of the active ingredient.

[0073] This application is based on Japanese application No. 2000-216763, filed on Jul. 18, 2000, the entire content of which is incorporated herein by reference.

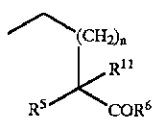
[0074] While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof. All references cited herein are incorporated, by reference, in their entirety.

What is claimed is:

1. An agent for preventing and/or treating Parkinson's disease or Parkinson's syndrome, comprising, as an active ingredient, an astrocyte function-improving agent.

2. The agent according to claim 1, wherein the astrocyte function-improving agent is a compound represented by formula (I), a non-toxic salt thereof, or a hydrate thereof:

(I)



wherein R^6 represents hydroxy, C1-4 alkoxy, C1-4 alkoxy substituted with one phenyl, or $—NR^9R^{10}$,

wherein R^9 and R^{10} each independently represent:

(i) hydrogen,

(ii) C1-4 alkyl,

(iii) phenyl,

(iv) phenyl substituted with C1-4 alkoxy or carboxyl,

(v) a 4- to 7-membered heterocyclic ring containing one nitrogen atom, or

(vi) C1-4 alkyl substituted with phenyl,

C1-4 alkyl substituted with C1-4 alkoxy- or carboxyl-substituted phenyl,

C1-4 alkyl substituted with a 4- to 7-membered heterocyclic ring containing one nitrogen atom,

(vii) a 4- to 7-membered heterocyclic ring having 1 or 2 nitrogen atoms or a 4- to 7-membered heterocyclic ring having one nitrogen atom and one oxygen atom, together with the nitrogen atom to which they are bonded,

(viii) an amino acid residue together with the nitrogen atom to which they are bonded;

(1) n is 1;

R^{11} represents hydrogen; and

R^5 represents (C1-10 alkyl in which one of the carbon atom(s) is substituted with 1 to 3 fluorine atoms)-CH_2—,

with the proviso that R^5 does not represent $F—(CH_2)_5—$, $F—(CH_2)_6—$, $F—(CH_2)_7—$ and $F_3C—(CH_2)_2—$; or

(2) n is 0 or 1;

R^{11} represents hydrogen or chlorine; and

R^5 represents:

C3-10 alkyl,

C3-10 alkenyl,

C2-10 alkoxy,

C2-10 alkylthio,

C3-7 cycloalkyl,

phenyl,

phenoxy,

$F—(CH_2)_m$, in which m is an integer of 5 to 7,

$F_3C—(CH_2)_2—$,

(C2-10 alkyl substituted with 1 or 2 chlorine atoms)-CH_2, or

(C1-5 alkyl substituted with 1 or 2 substituents selected from the group consisting of C1-4 alkoxy, C3-7 cycloalkyl, phenyl and phenoxy)-CH_2—; or

R^5 and R^{11}, taken together, form C3-10 alkylidene.

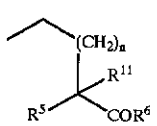
3. The agent according to claim 1 or 2 wherein the astrocyte function-improving agent is a compound of the formula (I) wherein n is 1, R11 is hydrogen, R5 is C3-10 alkyl and R6 is hydroxy, non-toxic salts thereof or hydrate thereof.

4. The agent according to claim 1, 2 or 3, wherein the astrocyte function-improving agent is (R)-2-propyloctanoic acid, a non-toxic salt thereof, or a hydrate thereof.

5. A method for preventing and/or treating Parkinson's disease or Parkinson's syndrome, comprising administering an effective amount of an astrocyte function-improving agent.

6. The method according to claim 5, wherein the astrocyte function-improving agent is a compound represented by formula (I), a non-toxic salt thereof, or a hydrate thereof:

(I)



wherein R^6 represents hydroxy, C1-4 alkoxy, C1-4 alkoxy substituted with one phenyl, or $—NR^9R^{10}$,

wherein R^9 and R^{10} each independently represent:

(i) hydrogen,

(ii) C1-4 alkyl,

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
JUAN PABLO CADENA SARMIENTO
(Apoderado)

ASUNTO	Radicación	06032016
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	- - 08518
	Folios	023

Patente de Invención [X] Patente de Modelo de Utilidad [ ]

Vía Nacional [ ]

Vía PCT (fase nacional) [X] Cap.I [X] Cap. II [ ]

No. Sol. Internacional PCT/JP2004/014892
Fecha de Presentación Internacional 01-10-2004

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

1.1. Descripción: (Folios: 69 a 122) como se radicó inicialmente.

1.2. Reivindicaciones: 1 a 34 (Folios: 123 a 127) como se radicó inicialmente.

1.3. Prioridad: 03/10/2003, JP 2003-345124.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. **Objeto de la invención:**

La presente solicitud se titula: "Fármaco que comprende ácido (2R)-2-propiloctanoico como el ingrediente activo".

El objeto de la presente solicitud se refiere a una composición farmacéutica que comprende ácido (2R)-2-propiloctanoico o una sal del mismo en una concentración alta, el cual es útil como un agente para tratar enfermedades neurodegenerativas incluyendo infarto cerebral, y un procedimiento para producir el mismo.

Según la descripción, para el tratamiento de pacientes con apoplejía cerebral es preferible una preparación adecuada para administración parenteral, tal como una inyección. Es bien conocido que el factor más importante para una composición farmacéutica es la estabilidad, puesto que dicho producto se somete necesariamente a una prueba de estabilidad a largo plazo que tarda varios meses en la etapa de desarrollo. Generalmente, una sustancia química es más estable en el estado sólido que en el estado líquido y como una solución en una concentración alta que en una concentración baja.

Una inyección en particular, se puede almacenar durante largos periodos de tiempo y puede tener una mayor cualidad estable cuando se almacena en forma de un líquido a concentración alta, tal como una inyección enriquecida o una inyección concentrada, o en forma sólida tal como una preparación liofilizada.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 17, 23 a 28, 33 y 34 (folios: 123 a 125 a 127): Una composición farmacéutica que comprende ácido (2R)-2-propiloctanoico o una sal del mismo y un ión metálico básico.

Reivindicación 18 (folio: 125): Un proceso para producir una composición farmacéutica que comprende ácido (2R)-2-propiloctanoico o una sal del mismo y un ión metálico básico.

Reivindicación 19 (folio: 125): Un método para usar un ión metálico básico.

Reivindicaciones 20 a 22 (folios: 125 y 126): Una sal metálica o una sal de aminoácido natural básico de ácido (2R)-2-propiloctanoico.

Reivindicaciones 29 y 30 (folio: 126): Un recipiente hecho de plásticos, el cual se rellena con 4 ml, 8 ml o 20 ml de la composición farmacéutica.
Reivindicación 31 (folio: 126): Un método para prevenir y/o tratar enfermedades neurodegenerativas, trastornos nerviosos o enfermedades en necesidad de regeneración nerviosa.

Reivindicación 32 (folio: 127): Uso de la composición farmacéutica de acuerdo con la reivindicación 1.

El problema planteado en esta solicitud es la necesidad de una inyección que comprenda ácido (2R)-2-propiloctanoico o una sal del mismo en una concentración alta, la cual es útil para el tratamiento de enfermedades neurodegenerativas.

La solución propuesta por la presente solicitud consiste en una composición farmacéutica que comprende ácido (2R)-2-propiloctanoico o una sal del mismo y un ión metálico básico.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/20, 9/00, 9/08, 9/10, 47/02; C07C 53/128, 51/41; A61P 25/00, 25/28.

4. **De la solicitud de Patente**

4.1. Descripción *(artículo 28 D. 486)*

De acuerdo con lo revelado en la descripción, el título de la solicitud no es coherente puesto que se relaciona con un "fármaco que comprende ácido (2R)-2-propiloctanoico" mientras que la descripción se habla de una composición farmacéutica que comprende ácido (2R)-2-propiloctanoico.

4.2. Reivindicaciones *(artículo 30 D 486)*

De acuerdo con lo revelado en el capítulo reivindicatorio, la composición farmacéutica de la reivindicación 1 no está caracterizada en forma clara, de tal manera que se observe el aporte de dicha composición al estado del arte. Cabe recordar que una composición farmacéutica se debe caracterizar por sus componentes, es decir, principios activos o fármacos y excipientes o vehículo en el cual va formulado dicho fármaco, y se observe un salto cualitativo frente a la técnica anterior.

La reivindicación 19 (folio: 125) no es clara puesto que la frase: "Un método para usar un ión metálico básico" no se comprende de qué se trata, si es un método de preparación de un ión metálico básico, o de preparación de una composición farmacéutica; además, hay que recordar que un método o proceso de fabricación debe estar definido por las etapas que suceden allí, incluyendo las variables que intervienen tales como: temperaturas, velocidades, condiciones de humedad, cantidades, etc.

Las sales de las reivindicaciones 20 y 21 (folio: 125) deben definirse en forma más específica, puesto que no son concisas de la manera en que están presentadas.

En el capítulo reivindicatorio se encuentran términos que son demasiado amplios y le restan concisión a la solicitud, por ejemplo: "aproximadamente", "sal de ión metálico básico", "aminoácido natural básico", entre otros.

Las reivindicaciones 33 y 34 (folio: 127) se deben revisar porque tal como están redactadas no son claras, no están definidas como una composición farmacéutica, es decir, por sus componentes, sino por la concentración de un ión sódico básico y por el envase en que se encuentra dicha composición (una ampolla de polietileno).

5. **Unidad de Invención** *(artículo 25 D 486)*

Según lo anterior la (s) reivindicación (es) 29 y 30 (folio: 126), que se refiere(n) a un recipiente hecho de plásticos, no guarda(n) unidad de invención con la reivindicación 1 y sus dependientes, que se relacionan con una composición farmacéutica. El recipiente pertenece a otro campo de la tecnología y debe definirse por sus características propias que lo diferencien de lo conocido en el estado de la técnica y no debe definirse por su contenido, en este caso, una composición farmacéutica de ácido (2R)-2-propiloctanoico.

6. **Excepciones de Patentabilidad** *(artículo 20 D486 literal a)-d))*

De acuerdo con lo anterior, la(s) reivindicación(es): 31 (folio: 126), que se refiere(n) a un método para prevenir y/o tratar enfermedades neurodegenerativas, trastornos nerviosos o enfermedades en necesidad de regeneración nerviosa, no es (son) patentable(s) porque es un método de tratamiento.

7. **Reivindicaciones relativas a un uso o a un uso distinto** *(artículos 14 y 21 D 486)*

La(s) reivindicación (es) 32 (folio: 127), que se refiere(n) a uso de la composición farmacéutica de la reivindicación 1, no se encuentra(n) dentro del campo de la patentabilidad (productos y procedimientos).

8. **Análisis de la(s) Oposición(es):** *(artículo 43 D. 486)*

No se presentaron oposiciones al objeto reivindicado.

9. **Determinación del Estado de la Técnica:**

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 3-10-2003.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	CA 2453478	Agent for treatment of cerebral ischemic diseases	30 de enero de 2003
D2	CA 2364308	Process for the preparation of (2R)-2-propyloctanoic acid	24 de agosto de 2000
D3	US 2002/0032185	Agent for treating Parkinson's disease comprising astrocyte function-improving agent as active ingredient	14 de marzo de 2002

10. Análisis de patentabilidad (artículo 14 D486)

10.1. Novedad *(artículo 16 D486)*

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 06032016, se refiere a:

Una composición farmacéutica que comprende ácido (2R)-2-propiloctanoico o una sal del mismo y un ión metálico básico.

Una sal metálica o una sal de aminoácido natural básico de ácido (2R)-2-propiloctanoico.

La anterioridad: CA2453478 (folios: 163 a 169), se relaciona con: un agente para el tratamiento de isquemia cerebral; este documento describe que el ácido (2R)-2-propiloctanoico puede estar en forma de sal de metal alcalino o sales de aminoácido incluyendo sal de tri(hidroximetil)amina, lisina o arginina. Este documento también describe composiciones farmacéuticas de ácido (2R)-2-propiloctanoico en forma de inyectable (ver folio: 166) y menciona los excipientes que puede llevar dicha composición farmacéutica.

La anterioridad: CA2364308 (folios: 170 a 174), trata sobre: un proceso para la preparación de ácido (2R)-2-propiloctanoico. De acuerdo con el ejemplo 1, este compuesto se produce tras una reacción de reducción, extraído con hidróxido de sodio y se forma la sal sódica del compuesto ácido (2R)-2-propiloctanoico.

El elemento característico de las composiciones farmacéuticas del ácido (2R)-2-propiloctanoico y las sales de dicho ácido reivindicadas, ya era conocido en los documentos CA2453478 y CA2364308; por lo cual las composiciones y sales de ácido (2R)-2-propiloctanoico de las reivindicaciones 1 a 17, 20 a 28, 33 y 34 no pueden considerarse nuevos.

10.2. Nivel inventivo *(artículo18 D486)*

La presente Solicitud de Patente reivindica lo siguiente: Una composición farmacéutica que comprende ácido (2R)-2-propiloctanoico o una sal del mismo y un ión metálico básico.

La anterioridad CA 2453478 (folios: 163 a 169) se relaciona con composiciones farmacéuticas de ácido (2R)-2-propiloctanoico que se pueden administrar vía intravenosa. Este documento menciona que estas composiciones pueden tener componentes buffer para el control de pH.

El documento US 2002/0032185 (folios: 175 a 178) menciona el ácido (2R)-2-propiloctanoico y sus sales tales como las de sodio y de aminoácido. De igual modo, menciona formulaciones farmacéuticas de dicho ácido para administrar en forma parenteral y que deben tener entre sus excipientes agentes buffer.

El problema técnico planteado en esta solicitud: la necesidad de una inyección que comprenda ácido (2R)-2-propiloctanoico o una sal del mismo en una concentración alta, la cual es útil para el tratamiento de enfermedades neurodegenerativas, se había resuelto previamente mediante composiciones farmacéuticas inyectables de ácido (2R)-2-propiloctanoico ya conocidos(as). Por esta razón se considera que las composiciones farmacéuticas reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

La reivindicación 1 a 28, 33 y 34 de esta solicitud no menciona una característica que conceda un efecto inesperado o especial a las composiciones, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1 y D2 divulgaban previamente composiciones inyectables de ácido (2R)-2-propiloctanoico y sales del mismo (folios: 163 a 169 y 175 a 178), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud composiciones farmacéuticas de ácido (2R)-2-propiloctanoico y sales del mismo; de manera que para una persona medianamente versada en la materia sería obvio combinar estos dos documentos. Por lo cual puede no haber Nivel Inventivo.

11. **Conclusión:**

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	CA 2453478	1 a 17, 20 a 28, 33 y 34	Novedad
		1 a 28, 33, 34	Nivel Inventivo
D2	CA 2364308	20 a 22	Novedad
D3	US 2002/0032185	1 a 28, 33, 34	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 24 JUL. 2015

CONCEPTO TÉCNICO No. 2461	**EXAMINADOR TÉCNICO** Código No. 202005