



DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

- ☒ Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: **13-133036**

Solicitante: **ELI LILLY AND COMPANY**

Apoderado: **CARLOS REINALDO OLARTE GARCIA**

Título de la Nueva Creación: **"COMPUESTOS 3-FENILSULFANILMETIL-BICICLO [3.1.0]HEXANO 4-SUSTITUIDOS COMO ANTAGONISTAS DE MGLUR 2/3"**

Gaceta: **676 DEL 1/OCT/2013 PUBLICACIÓN No. 1385**

2. Datos del Opositor

☐ Persona Natural

☒ Persona Jurídica

LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.

Nombre o denominación /Razón social completa

VÍCTOR JULIO CHUNCO

Nombre del representante legal

Documento de identificación: C.C. ☐ C.E. ☐ NIT ☒ Otr ☐Cuál _____

Número **890.301.463-8**

Dirección: **Cra. 1 # 46-84**

Ciudad: **Cali - Valle**

Teléfono: **052 6877700**

Fax: _____ Correo electrónico **tparra@lafrancol.com**

☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

PARRA MURILLO TITO NOE

79.579.680

71168 C.S.J.

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección del representante

CALLE 108 # 51-45

Dirección electrónica

tparralfarncol.com

No. Fax

7424092

Número telefónico

7422525

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo d-e poder general _____

4. Fundamentos de la oposición

Causal: VER ANEXO

Justificación: VER ANEXO

Prórroga:

SI

☐

NO

☐

5. Anexos

- ☒ Comprobante de pago de la tasa. No. 13-131185 de 18/DIC/2013
- ☒ Poder, si fuera el caso.
- ☐ Fundamentos de la oposición. Se anexan ____ folios (obligatorios indicar cuántos).
- ☐ Anexo de fundamentos de la oposición. Se anexan ____ folios (obligatorios indicar cuántos)
- ☒ Copias para traslado.
- Copia de la solicitud y sus anexos en formato magnético.

6. Firma

TITO NOE PARRA MURILLO

Nombre del Firmante

79.579.680 DE BOGOTA

C.C

Firma

71168 C.S.J.

Tarjeta Profesional

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 131185

Bogotá D.C., Diciembre 18 de 2013 - 16:22:28

RECIBIDO DE : LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.

NI 890.301.463

RE

***** Soporte del Pago *****

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
RECIBO DE CA	999999999	129961	16/12/2013		250.000.00
CONSIGNACION	BANCO DE BOGOTA	062754387	610280296	18/12/2013	3.000.000.00

***** Conceptos Pagados *****

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 OPOSICION POR CADA CLASE-MARCAS Y LEMAS COMERCIALES	325.000.00	325.000.00
				\$325.000.00

SON: **TRESCIENTOS VEINTICINCO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-133036- -00003-0000

Fecha: 2013-12-30 16:04:04 Dep. 2020 DIR.NUEVASCR
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Act. 400 OPOSIOBSERVTER Folios: 60

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, Diciembre 18 de 2013 - 16:22:29

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: EXPEDIENTE 13-133-036

TÍTULO SOLICITADO: "COMPUESTOS 3-FENILSULFANILMETIL-BICICLO
[3.1.0]HEXANO 4-SUSTITUIDOS COMO
ANTAGONISTAS DE MGLUR 2/3"

PUBLICACIÓN: Gaceta 676 de 1 de octubre de 2013, N° de publicación
1385

PRIORIDAD: US 61/415.121 18/11/2010

SOLICITANTE: ELI LILLY AND COMPANY

APODERADO: CARLOS REINALDO OLARTE GARCIA

TRÁMITE: PRESENTACION DE OPOSICIÓN

TITO NOÉ PARRA MURILLO, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 71168 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad LAFRANCOL S.A.S., en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente 13-133-036 por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LAFRANCOL S.A.S.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

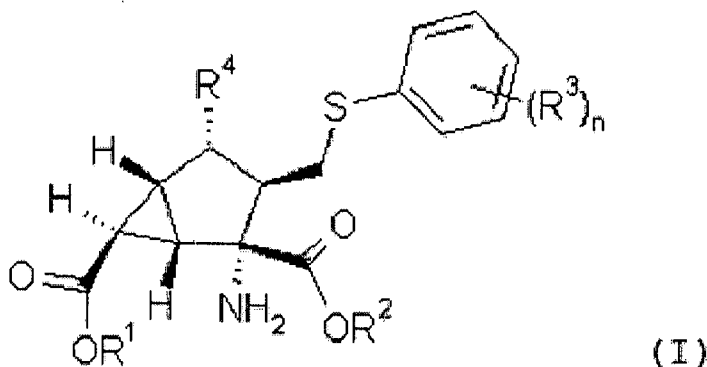
III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite 13-133-036 referida a una familia de compuestos 4-sustituido-3-fenilsulfanilmetil- 25 bicyclo[3.1.0]hexano con alta potencia antagonista para los receptores mGlu2 y mGlu3, presenta defectos en la solicitud y no cumple con los requisitos de patentabilidad como se demuestra a continuación:

3.1. Falta de nivel inventivo

- Compuestos

La presente solicitud se dirige a compuestos de la fórmula



donde R1 y R2 son hidrógeno, alcóxicarboniloximetilo C1-C3, alquilcarboniloximetilo C1-C5, o cicloalquilcarboniloximetilo C3-6; R3 es independientemente en cada caso metilo, fluoro o cloro; R4 es hidroxilo, amino, metilcarbonilamino, o 1,2,4-triazoltio; y n es 1 o 2; o una sal del mismo farmacéuticamente aceptable.

También se refiere a una composición farmacéutica que comprende un compuesto de conformidad con cualquiera de las reivindicaciones 1 a 11, o una sal del mismo farmacéuticamente aceptable, en combinación con al menos un portador, excipiente o diluyente farmacéuticamente aceptable.

De acuerdo a lo anterior, en el estado del arte se encuentran dos anterioridades que afectan el nivel inventivo de la presente solicitud, veamos:

1. La patente americana US 20060142388 2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative, 29 Junio 2006, p. 19
2. La publicación internacional WO1999047490 Bicyclo[2.2.1]heptanes and related compounds, 23 Septiembre 1999, p. 34 y 35

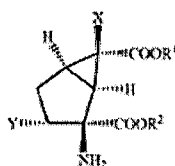
El documento D1 parece ser el más cercano y difiere de la reivindicación 1 en que la secuencia del azufre y grupo metileno unida al anillo fenilo está invertida, como se muestra ahora:

- En la solicitud 13-133-036 el azufre está unido al fenilo seguido por el grupo metileno directamente unido al azufre,
- En D1 el grupo metileno está directamente unido al fenilo y el azufre está directamente unido al azufre;

Sin embargo, la inversión del grupo azufre y metileno NO cambia las propiedades fisicoquímicas totales de los compuestos, pues los compuestos de D1 pertenecen al mismo campo técnico de tratamiento y prevención de trastornos depresivos. Dado que no hay un efecto inesperado o sorprendente en la actividad biológica de este tipo de compuestos se considera que la reivindicación 1 no es inventiva.

[0167] The structure and physical data of the compounds described in Examples 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11, as well as those of compounds obtained by means of the same methods are shown in table 1 below.

The structure and property data of the compounds obtained in the Examples



Compound	X	R ¹	R ²	Y	NMR	MS	Specific rotatory power	m.p. (° C.)	Example
1	F	H	H		(300 MHz, D ₂ O, TMSF) 2.16-2.32(m, 2 H) 2.41-2.50(m, 2H) 3.06-3.18(m, 1H) 4.97(s, 2H) 6.97-7.10(m, 2H) 7.35-7.43(m, 1H)	ESI (Negs) 339 (M - H) ⁻	[α] _D ²⁵ +38.7(C = 0.35 1N NaOH)	>230	2
2	F	H	H		(300 MHz, D ₂ O, TMSF) 2.08-2.35(m, 4H) 2.87-3.06(m, 1H) 3.78-4.01(m, 2H) 7.26-7.62(m, 9H)	ESI (Negs) 409 (M - H) ⁻	[α] _D ²⁴ +49.3(C = 0.21 1N NaOH)	>230	2
3	F	H	H		(300 MHz, D ₂ O, TMSF) 2.16-2.42(m, 4H) 3.03-3.13(m, 1H) 3.77-3.87(m, 5H) 7.0 qd, J=8.7 Hz, 2H) 7.35(d, J=8.7 Hz, 2H)	ESI (Negs) 354 (M - H) ⁻	[α] _D ²⁶ +31.0(C = 0.48 1N NaOH)	>240	2
4	F	H	H		(300 MHz, D ₂ O, TMSF) 2.13-2.54(m, 4H) 2.97-3.19(m, 1H) 3.84(s, 2H) 7.03-7.29(m, 2H) 7.33-7.55(m, 2H)	ESI (Negs) 342 (M - H) ⁻	[α] _D ²⁵ +25.4(C = 0.20 1N NaOH)	>243	2
5	F	H	H		(300 MHz, D ₂ O, TMSF) 1.31(s, 9H) 2.20-2.47(m, 4H) 3.06-3.20(m, 1H) 3.83(s, 2H) 7.32-7.40(m, 2H) 7.46-7.56(m, 2H)	ESI (Negs) 380 (M - H) ⁻	[α] _D ²⁶ -1.14(C = 0.63 1N NaOH)	>271	2
6	F	H	H		(300 MHz, D ₂ O, TMSF) 2.16-2.47(m, 4H) 3.04-3.15(m, 1H) 3.89(d, J=13.2 Hz, 1H) 3.94(d, J=13.2 Hz, 1H) 7.50-7.78(m, 4H)	ESI (Negs) 392 (M - H) ⁻	[α] _D ²⁴ +38.9(C = 0.36 1N NaOH)	>271	2

3.2. Composiciones farmacéuticas

Las composiciones farmacéuticas de las reivindicaciones 12, 20-30 se refieren a composiciones que contienen los compuestos de la reivindicación 1.

De acuerdo a lo anterior, el documento D1 se refiere a compuestos similares a los acá reclamados, con la misma actividad biológica y sin efectos inesperados o sorprendentes.

Por su lado, el documento D2 se refiere a composiciones para modular la neurotransmisión del glutamato:

15 A pharmaceutical composition for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising

(a) a compound of the formula I, or a pharmaceutically acceptable salt thereof,

(b) a serotonin reuptake inhibitor or a serotonin-1A (5HT_{1A}) receptor ligand, or a pharmaceutically acceptable salt of such inhibitor or ligand, and

(c) a pharmaceutically acceptable carrier, wherein the amounts of the compound of formula I and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are contained in such composition are such that the combination of the two active ingredients is effective in treating such disorder or condition

16 A pharmaceutical composition according to claim 15, wherein (b) is a serotonin reuptake inhibitor selected from sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, and femoxetine

Por lo tanto, las reivindicaciones 12, 20-30 no son inventivas en vista de la combinación de los documentos D1 y D2, pues la combinación de un antidepresivo conocido con compuestos que también muestran propiedades anti-depresivas es una medida obvia. □ De este modo, la materia reclamada no involucra una altura inventiva.

3.3. Método de tratamiento

Por otro lado, las reivindicaciones 20 a 27 se refieren a un método para tratar trastornos depresivos en un mamífero que comprende administrar a un mamífero en necesidad de tal tratamiento una cantidad efectiva de un compuesto de conformidad con la reivindicación 1, o una sal del mismo farmacéuticamente aceptable, lo cual de acuerdo a la D.486 no es patentable pues es considerada una excepción de Patentabilidad.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

1. La patente americana US 20060142388 2-Aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative, 29 Junio 2006, p. 19
2. La publicación internacional WO1999047490 Bicyclo[2.2.1]heptanes and related compounds, 23 Septiembre 1999, p. 34 y 35

VI. ANEXOS

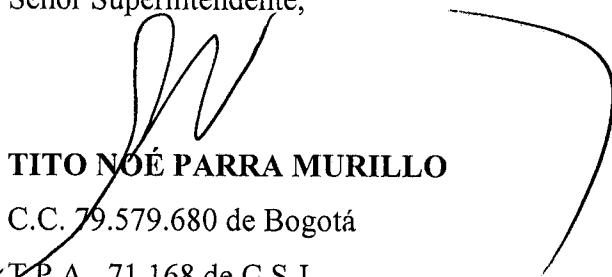
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de Lafrancol S.A.S.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. Las mencionadas en el acápite de pruebas

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Calle 108 No. 51-45 de Bogotá, D.C.

Señor Superintendente,


TITO NOÉ PARRA MURILLO

C.C. 79.579.680 de Bogotá

✓ T.P.A. 71.168 de C.S.J.

PCT

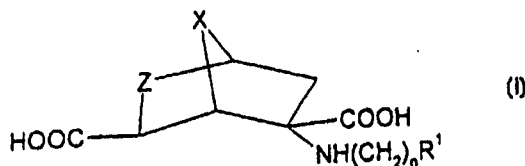
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International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 229/50, A61K 31/195		A1	(11) International Publication Number: WO 99/47490 (43) International Publication Date: 23 September 1999 (23.09.99)
(21) International Application Number: PCT/IB99/00376 (22) International Filing Date: 4 March 1999 (04.03.99) (30) Priority Data: 60/078,346 17 March 1998 (17.03.98) US (71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): CHENARD, Bertrand, Leo [US/US]; 7 Whaling Drive, Waterford, CT 06385 (US). (74) Agents: SPIEGEL, Allen, J. et al.; c/o SIMPSON, Alison, Urquhart-Dykes & Lord, 91 Wimpole Street, London W1M 8AH (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: BICYCLO[2.2.1]HEPTANES AND RELATED COMPOUNDS



(57) Abstract

The present invention relates to compounds of formula (I), wherein n is 0-6; X is CH₂, CH₂CH₂ or oxygen; Z is CHR² or NR²; R¹ and R² are selected independently from hydrogen, (C₁-C₆)alkyl, aryl and heteroaryl, wherein said aryl is selected from phenyl and naphthyl and said heteroaryl is selected from 5 and 6 membered aromatic heterocyclic rings that contain from one to four heteroatoms selected, independently, from nitrogen, oxygen and sulfur, and wherein said aryl and heteroaryl moieties can optionally be substituted with one or more substituents that are selected, independently, from halo, -S(C₁-C₆)alkyl, -S(O)(C₁-C₆)alkyl, -S(O)₂(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with from one to seven fluorine atoms, (C₁-C₆)alkoxy optionally substituted with from one to seven fluorine atoms, amino, nitro, cyano, carboxy, -CO₂(C₁-C₆)alkyl, (C₁-C₆)alkylamino, di-[(C₁-C₆)alkyl]amino phenoxy, anilino and phenylthio; pharmaceutical compositions containing such compounds (I) and the use of such compounds (I) to treat neurological and psychiatric disorders.

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BICYCLO[2.2.1]HEPTANES AND RELATED COMPOUNDS

This Application claims the benefit of U.S. Provisional Application No. 60/078,346, filed March 17, 1998.

Background of the Invention

5 The present invention relates to compounds of the formula I, as described below, their pharmaceutically acceptable salts, pharmaceutical compositions containing them and their use in treating neurological and psychiatric disorders.

10 The role of excitatory amino acids, such as glutamic acid and aspartic acid, as the predominant mediators of excitatory synaptic transmission in the central nervous system has been well established. Watkins & Evans, *Ann. Rev. Pharmacol. Toxicol.*, 21, 165 (1981); Monaghan, Bridges, and Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); Watkins, Krogsgaard-Larsen, and Honore, *Trans. Pharm. Sci.*, 11, 25 (1990). These amino acids function in synaptic transmission primarily through excitatory amino acid receptors. These amino acids also participate in a variety of other physiological processes such as motor control, respiration, 15 cardiovascular regulation, sensory perception, and cognition.

Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic." This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists N-methyl-D-aspartate 20 (NMDA), α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid (KA). The second general type is the G-protein or second messenger-linked "metabotropic" receptor. This second type, when activated by the agonists quisqualate, ibotenate, or trans-1-aminocyclopentane-1,3-dicarboxylic acid or 2-amino-4-phosphonobutyric acid activates second messenger systems. A subset of these second messenger-linked receptors is negatively coupled 25 to adenylate cyclase. Both types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways, but also participate in the modification of synaptic connection during development and changes in the efficiency of synaptic transmission throughout life. Schoepp, Bockaert, and Sladeczek. *Trends in Pharmacol. Sci.*, 11, 508 (1990); McDonald and Johnson, *Brain Research Reviews*, 15, 41 (1990).

30 The excessive or inappropriate stimulation of excitatory amino acid receptors leads to neuronal cell damage or loss by way of a mechanism known as excitotoxicity. This process has been suggested to mediate neuronal degeneration in a variety of conditions. The medical consequences of such neuronal degeneration makes the abatement of these degenerative neurological processes an important therapeutic goal.

Excitatory amino acid excitotoxicity has been implicated in the pathophysiology of a number of neurological disorders. This excitotoxicity has been implicated in the pathophysiology of acute and chronic neurodegenerative conditions including stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, epilepsy, AIDS-induced dementia, perinatal hypoxia, hypoxia (such as conditions caused by strangulation, surgery, smoke inhalation, asphyxiation, drowning, choking, electrocution or drug or alcohol overdose), cardiac arrest, hypoglycemic neuronal damage, ocular damage and retinopathy, idiopathic and drug-induced Parkinson's Disease and cerebral deficits subsequent to cardiac bypass surgery and grafting. Other neurological conditions that are caused by glutamate dysfunction require neuromodulation. These other neurological conditions include muscular spasms, migraine headaches, urinary incontinence, psychosis, addiction withdrawal (such as alcoholism and drug addiction including opiate, cocaine and nicotine addiction), opiate tolerance, anxiety, emesis, brain edema, chronic and acute pain, convulsions, retinal neuropathy, tinnitus and tardive dyskinesia. The use of a neuroprotective agent, such as an AMPA receptor antagonist, is believed to be useful in treating these disorders and/or reducing the amount of neurological damage associated with these disorders. The excitatory amino acid receptor (EAA) antagonists are also believed to be useful as analgesic agents.

The metabotropic glutamate receptors are a highly heterogeneous family of glutamate receptors that are linked to multiple second-messenger pathways. Generally, these receptors function to modulate the presynaptic release of glutamate, and the postsynaptic sensitivity of the neuronal cell to glutamate excitation. The metabotropic glutamate receptors (mGluR) have been pharmacologically divided into three subtypes. One group of receptors ("Class I receptors") is positively coupled to phospholipase C, which causes hydrolysis of cellular phosphoinositides (PI). This first group are termed PI-linked metabotropic glutamate receptors. The second group of receptors ("Class II and Class III receptors") is negatively coupled to adenylate cyclase, which prevents the forskolin-stimulated accumulation of cyclic adenosine monophosphate (cAMP). Schoepp and Conn, Trends Pharmacol. Sci., 14, 13 (1993). Class II and Class III receptors are distinguished by selective activation with trans-1-aminocyclopentane-1,3-dicarboxylic acid and 2-amino-4-phosphonobutyric acid, respectively. Receptors within this second group are termed cAMP-linked metabotropic glutamate receptors. Agonists of the cAMP-linked metabotropic glutamate receptors should be useful for the treatment of acute and chronic neurological conditions and psychiatric conditions.

Compounds have recently been discovered that effect metabotropic glutamate receptors, but have no effect on ionotropic glutamate receptors. (1S,3R)-1-Aminocyclopentane-

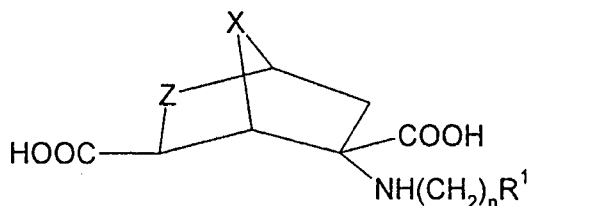
1,3-dicarboxylic acid (1S,3R-ACPD) is an agonist of PI-linked and cAMP-linked metabotropic glutamate receptors. Schoepp, Johnson, True, and Monn., *Eur. J. Pharmacol.*, **207**, 351 (1991); Schoepp, Johnson, and Monn., *J. Neurochem.*, **58**, 1184 (1992). (2S,3S,4S)-2-(carboxycyclopropyl) glycine (L-CCG-1) was recently described as a selective cAMP-linked metabotropic glutamate receptor agonist: however, at higher concentrations, this compound has activity at PI-linked metabotropic receptors. Nakagawa, *et al.*, *Eur J. Pharmacol.*, **184**, 205 (1990); Hayashi, *et al.*, *Br. J. Pharmacol.*, **197**, 539 (1992); Schoepp *et al.*, *J. Neurochem.*, **63**, 769-772 (1994).

European Patent Application EP 696577A1, which was published on February 14, 1996, refers to certain synthetic amino acids that are described as being selective for the negatively coupled cAMP linked metabotropic glutamate receptors (*i.e.*, Class II metabotropic glutamate receptors).

The compounds of formula I and their pharmaceutically acceptable salts are metabotropic glutamate receptor ligands that are selective for Class II metabotropic glutamate receptors.

Summary of the Invention

This invention relates to compounds of the formula



wherein n is 0-6;

X is CH₂, CH₂CH₂ or oxygen;

Z is CHR² or NR²; and

R¹ and R² are selected independently, from hydrogen, (C₁-C₆)alkyl, aryl and heteroaryl, wherein said aryl is selected from phenyl and naphthyl and said heteroaryl is selected from 5 and 6 membered aromatic heterocyclic rings that contain from one to four heteroatoms selected, independently, from nitrogen, oxygen and sulfur, and wherein said aryl and heteroaryl moieties can optionally be substituted with one or more substituents, preferably with one or two substituents, that are selected, independently, from halo (*e.g.*, fluoro, chloro, bromo or iodo), -S(C₁-C₆)alkyl, -S(O)(C₁-C₆)alkyl, -S(O)₂(C₁-C₆)alkyl, (C₁-C₆)alkyl optionally substituted with from one to seven fluorine atoms, (C₁-C₆)alkoxy optionally substituted with

from one to seven fluorine atoms, amino, nitro, cyano, carboxy, $-\text{CO}_2(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, di- $[(\text{C}_1\text{-C}_6)\text{alkyl}]\text{amino}$ phenoxy, anilino and phenylthio;

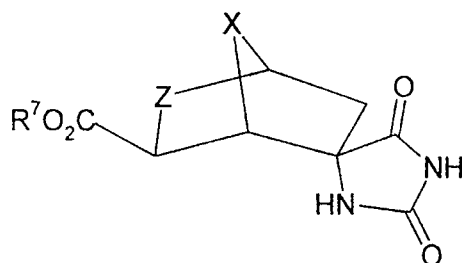
with the proviso that none of the foregoing heteroaryl moieties may contain more than one ring oxygen atom or more than one ring sulfur atom;

5 and the pharmaceutically acceptable salts of such compounds.

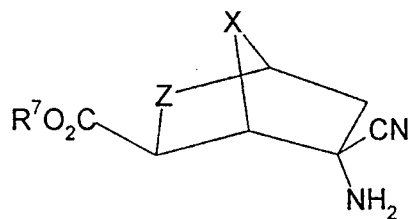
Examples of the heteroaryl moieties of said heteroaryl- $(\text{C}_0\text{-C}_6)\text{alkyl}$ are the following: oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, pyrazolyl, pyrrolyl, tetrazolyl, triazolyl, thienyl, imidazolyl, pyridinyl, and pyrimidinyl.

This invention also relates to compounds of the formulas

10

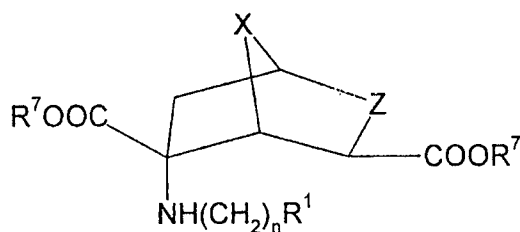


II



III

and



IV

wherein X and Z are defined as for formula I above and R^7 is hydrogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$ or benzyl.

Compounds of the formula II, III and IV are intermediates in the synthesis of compounds of the formula I.

Preferred compounds of the formula I include those wherein R^1 is a pyrid-3-yl or pyrid-4-yl group.

5 Other preferred compounds of formula I include those wherein R^1 is hydrogen, unsubstituted phenyl, or phenyl substituted with one or two substituents. When R^1 is a substituted phenyl, preferred substituents on said phenyl are independently selected from (C_1-C_6) alkyl, nitro, cyano, halo, CF_3 , (C_1-C_5) alkyl substituted with CF_3 , (C_1-C_5) alkoxy substituted with CF_3 , and $-O-CF_3$.

10 Other preferred compounds of the formula I include those wherein n is 1-6. Compounds of formula I wherein n is 1 or 2 are more preferred.

Other preferred compounds of formula I include those wherein Z is CH_2 .

Other preferred compounds of formula I include those wherein X is CH_2 .

Other preferred compounds of formula I include those wherein both X and Z are CH_2 .

15 R^1 is hydrogen and n is zero.

Other embodiments of this invention include compounds of the formula I wherein:

- (a) Z is NH ;
- (b) Z is NR^2 and R^2 is (C_1-C_6) alkyl;
- (c) Z is NR^2 and R^2 is phenyl;
- 20 (d) Z is NR^2 , n is zero and R^1 is phenyl or substituted phenyl;
- (e) one of R^1 and R^2 is aryl or heteroaryl; or
- (f) both R^1 and R^2 are selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl.

Preferred compounds of formula I include, but are not limited to:

- 25 2-(endo)-amino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid;
- (+)-2-(endo)-aminobicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid;
- (-)-2-(endo)-aminobicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid;
- 2-(endo)-benzylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid; and
- 2-(endo)-phenylethylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylate.

30 Preferred compounds of formulas II, III, and IV include those wherein R^7 is hydrogen, (C_1-C_6) alkyl, or benzyl. In one embodiment, a compound of formula II, III, or IV includes R^7 , wherein R^7 is (C_1-C_6) t -alkyl, for example t -butyl.

The compounds of formula I and their pharmaceutically acceptable salts are metabotropic glutamate receptor ligands and are useful in the treatment of a variety of
 35 neurological and psychiatric disorders. Examples of neurological disorders that can be

treated with the compounds of formula I and their pharmaceutically acceptable salts are cerebral deficits subsequent to cardiac bypass surgery and grafting, cerebral ischemia (e.g., stroke and cardiac arrest), spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's disease, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine headache, urinary incontinence, convulsions, perinatal hypoxia, hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., a dependency on, or addiction to opiates, benzodiazepines, cocaine, nicotine or ethanol), drug or alcohol withdrawal symptoms, ocular damage and retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's Disease, emesis, brain edema, acute or chronic pain, sleep disorders, Tourette's syndrome, attention deficit disorder and tardive dyskinesia. Examples of psychiatric disorders that can be treated with the compounds of formula I and their pharmaceutically acceptable salts are schizophrenia, anxiety and related disorders (e.g., General Anxiety Disorder, panic attack and stress-related disorders such as Post Traumatic Stress Syndrome), depression, bipolar disorders, psychosis, and obsessive compulsive disorders.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

The present invention also relates to the pharmaceutically acceptable base addition salts of compounds of the formula I. These salts are all prepared by conventional techniques. The chemical bases that are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula I. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc.

This invention also relates to a pharmaceutical composition for treating a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating (i.e., increasing or decreasing) glutamate neurotransmission in a mammal, comprising an amount of a compound of the formula I, or a pharmaceutically effective salt thereof, that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

This invention also relates to a method of treating a disorder or condition, the treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I, or a pharmaceutically effective salt thereof, that is effective in treating such disorder or condition.

This invention also relates to a pharmaceutical composition for treating a condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, epilepsy, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia (such as conditions caused by strangulation, surgery, smoke inhalation, asphyxiation, drowning, choking, electrocution or drug or alcohol overdose), cardiac arrest, hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), ocular damage, retinopathy, retinal neuropathy, tinnitus, idiopathic and drug induced Parkinson's Disease, anxiety (e.g., Post Traumatic Stress Syndrome, panic disorder, General Anxiety Disorder, simple phobias and social phobias), schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting in a mammal, comprising a glutamate neurotransmission modulating effective amount of a compound of the formula I, or a pharmaceutically salt thereof, and a pharmaceutically acceptable carrier.

This invention also relates to a method for treating a condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, epilepsy, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia (such as conditions caused by strangulation, surgery, smoke inhalation, asphyxiation, drowning, choking, electrocution or drug or alcohol overdose), cardiac arrest, hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), ocular damage, retinopathy, retinal neuropathy, tinnitus, idiopathic and drug induced Parkinson's Disease, anxiety (e.g., panic disorder, Post Traumatic Stress Syndrome, General Anxiety Disorder, simple phobias and social phobias), schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting in a mammal, comprising administering to a mammal requiring such treatment a glutamate neurotransmission modulating effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof.

This invention also relates to a pharmaceutical composition for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising a glutamate neurotransmission modulating effective amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

This invention also relates to a method for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising administering to a mammal requiring such treatment a glutamate neurotransmission modulating effective amount of a compound of the formula I or a pharmaceutically acceptable salt thereof. This invention also relates to a method of treating a condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, epilepsy, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia (such as conditions caused by strangulation, surgery, smoke inhalation, asphyxiation, drowning, choking, electrocution or drug or alcohol overdose), cardiac arrest, hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), ocular damage, retinopathy, retinal neuropathy, tinnitus, idiopathic and drug induced Parkinson's Disease, anxiety (e.g., panic disorder, Post traumatic Stress Syndrome, General Anxiety disorder, simple phobias and social phobias), schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting in a mammal, comprising administering to a mammal in need of such treatment an amount of a compound of the formula I that is effective in treating such condition.

This invention also relates to a pharmaceutical composition for treating a condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, epilepsy, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia (such as conditions caused by strangulation, surgery, smoke inhalation, asphyxiation, drowning, choking, electrocution or drug or alcohol overdose), cardiac arrest, hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), ocular damage, retinopathy, retinal neuropathy, tinnitus, idiopathic and drug induced Parkinson's Disease, anxiety (e.g., panic disorder, Post Traumatic Stress Syndrome, General Anxiety Disorder, simple phobias and social phobias), schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's

syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting in a mammal, comprising an amount of a compound of the formula I that is effective in treating such condition and a pharmaceutically acceptable carrier.

5 This invention also relates to a method for treating a disorder or condition, the treatment of which can effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising administering to a mammal requiring such treatment:

(a) a compound of the formula I, or a pharmaceutically acceptable salt thereof; and

10 (b) a serotonin reuptake inhibitor (e.g., sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, femoxetine, etc.) or a serotonin-1A (5HT_{1A}) receptor ligand (e.g., buspirone, flesinoxan, etc.) or a pharmaceutically acceptable salt of such inhibitor or ligand;

wherein the amounts of the compound of formula I and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are employed in such method are such that the combination of the two active ingredients is effective in treating such disorder or condition.

This invention also relates to a pharmaceutical composition for treating a disorder or condition, the treatment of which can effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising:

20 (a) a compound of the formula I, or a pharmaceutically acceptable salt thereof;

(b) a serotonin reuptake inhibitor (e.g., sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, femoxetine, etc.) or a serotonin-1A (5HT_{1A}) receptor ligand (e.g., buspirone, flesinoxan, etc.) or a pharmaceutically acceptable salt of such inhibitor or ligand; and

25 (c) a pharmaceutically acceptable carrier;

wherein the amounts of the compound of formula I and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are contained in such composition are such that the combination of the two active ingredients is effective in treating such disorder or condition.

30 This invention also relates to a method for treating a disorder or condition, the treatment of which can effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising administering to a mammal requiring such treatment:

(a) a glutamate neurotransmission modulating compound, or a pharmaceutically acceptable salt thereof; and

35 (b) a serotonin reuptake inhibitor (e.g., sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, femoxetine, fenfluramine, etc.) or a serotonin-1A (5HT_{1A}) receptor

ligand (e.g., buspirone, flesinoxan, etc.) or a pharmaceutically acceptable salt of such inhibitor or ligand;

wherein the amounts of the glutamate neurotransmission modulating compound and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are employed in such method
5 are such that the combination of the two active ingredients is effective in treating such disorder or condition.

This invention also relates to a pharmaceutical composition for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising:

10 (a) a glutamate neurotransmission modulating compound or a pharmaceutically acceptable salt thereof;

(b) a serotonin reuptake inhibitor (e.g., sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, femoxetine, etc.) or a serotonin-1A (5HT_{1A}) receptor ligand (e.g., buspirone, flesinoxan, etc.) or a pharmaceutically acceptable salt of such inhibitor
15 or ligand; and

(c) a pharmaceutically acceptable carrier;

wherein the amounts of the glutamate neurotransmission modulating compound and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are contained in such composition are such that the combination of the two active ingredients is effective in treating
20 such disorder or condition.

This invention also relates to a method for treating a disorder or condition, selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, epilepsy, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia (such as conditions caused by strangulation, surgery, smoke inhalation, asphyxiation, drowning, choking, electrocution or drug or alcohol overdose), cardiac arrest, hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), ocular damage, retinopathy, retinal neuropathy, tinnitus, idiopathic and drug induced Parkinson's Disease, anxiety (e.g., panic disorder, Post Traumatic Stress Syndrome, General Anxiety Disorder, simple phobias and social phobias), schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting in a mammal, comprising administering to a
30 mammal requiring such treatment:

(a) a compound of the formula I, or a pharmaceutically acceptable salt thereof;
and

(b) a serotonin reuptake inhibitor (e.g., sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, femoxetine, etc.) or a serotonin-1A (5HT_{1A}) receptor
5 ligand (e.g., buspirone, flesinoxan, etc.) or a pharmaceutically acceptable salt of such inhibitor or ligand;

wherein the amounts of the compound of formula I and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are employed in such method are such that the combination of the two active ingredients is effective in treating such disorder or condition.

10 This invention also relates to a pharmaceutical composition for treating a disorder or condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, epilepsy, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia (such as conditions caused by strangulation, surgery, smoke inhalation,
15 asphyxiation, drowning, choking, electrocution or drug or alcohol overdose), cardiac arrest, hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), ocular damage, retinopathy, retinal neuropathy, tinnitus, idiopathic and drug induced Parkinson's Disease, anxiety (e.g., panic disorder, Post Traumatic Stress Syndrome, General Anxiety
20 Disorder, simple phobias and social phobias), schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting in a mammal, comprising:

(a) a compound of the formula I, or a pharmaceutically acceptable salt thereof;
25 and

(b) a serotonin reuptake inhibitor (e.g., sertraline, fluoxetine, fluvoxamine, citalopram, paroxetine, fenfluramine, femoxetine, etc.) or a serotonin-1A (5HT_{1A}) receptor ligand (e.g., buspirone, flesinoxan, etc.) or a pharmaceutically acceptable salt of such inhibitor or ligand; and

30 (c) a pharmaceutically acceptable carrier;

wherein the amounts of the compound of formula I and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are contained in such composition are such that the combination of the two active ingredients is effective in treating such disorder or condition.

Unless otherwise indicated, the alkyl groups referred to herein, as well as the alkyl
35 moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched (e.g., t-

butyl), and they may also be cyclic (e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl) or be linear or branched and contain cyclic moieties.

The term "treating" as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

Unless otherwise indicated, "halo" and "halogen", as used herein, refer to fluorine, bromine, chlorine or iodine.

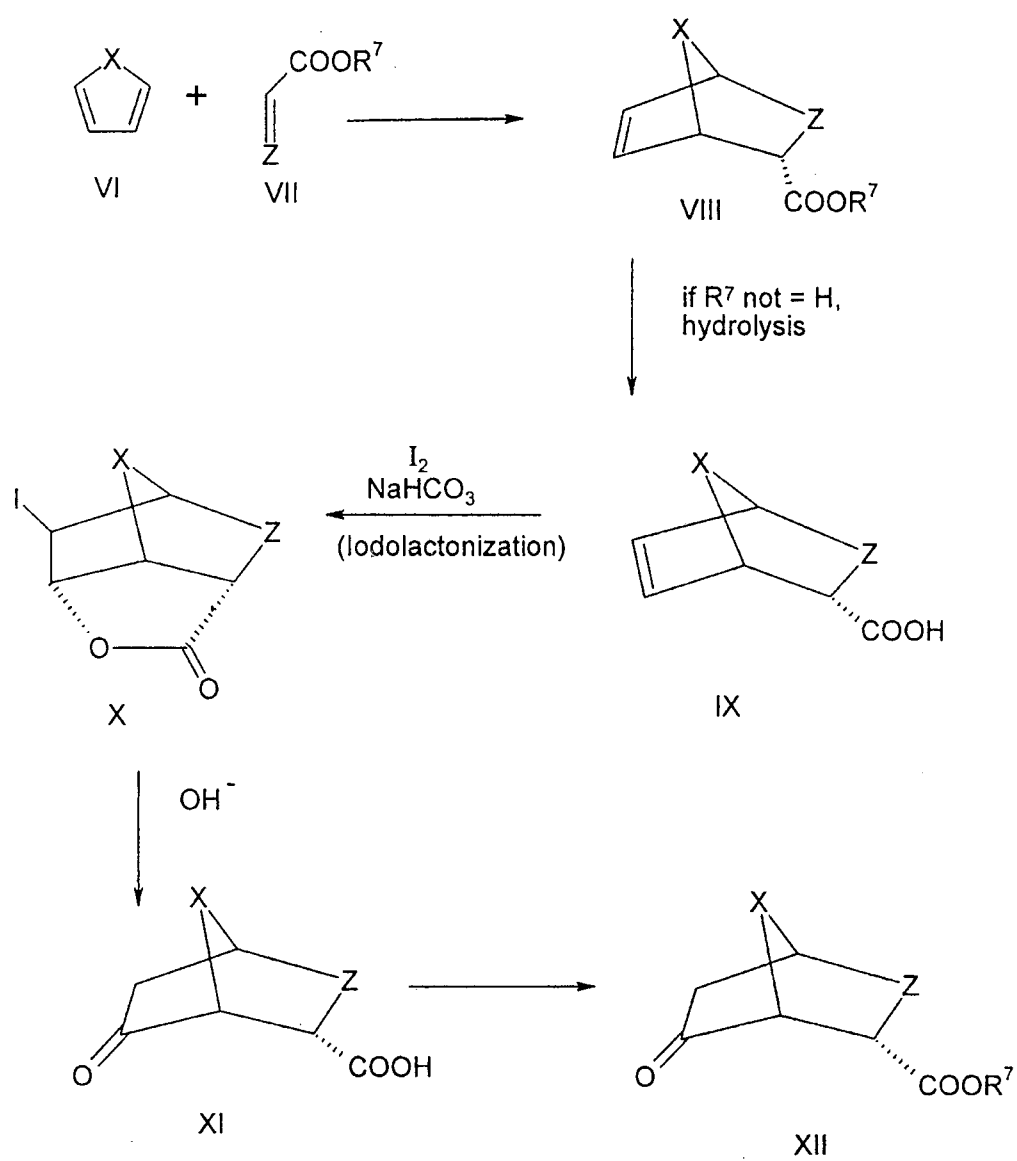
Compounds of the formula I may have chiral centers and therefore may exist in different enantiomeric and diastereomeric forms. This invention relates to all optical isomers and all other stereoisomers of compounds of the formula I, and to all racemic and other mixtures thereof, and to all pharmaceutical compositions and methods of treatment defined above that contain or employ such isomers or mixtures.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds of the present invention and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula I of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

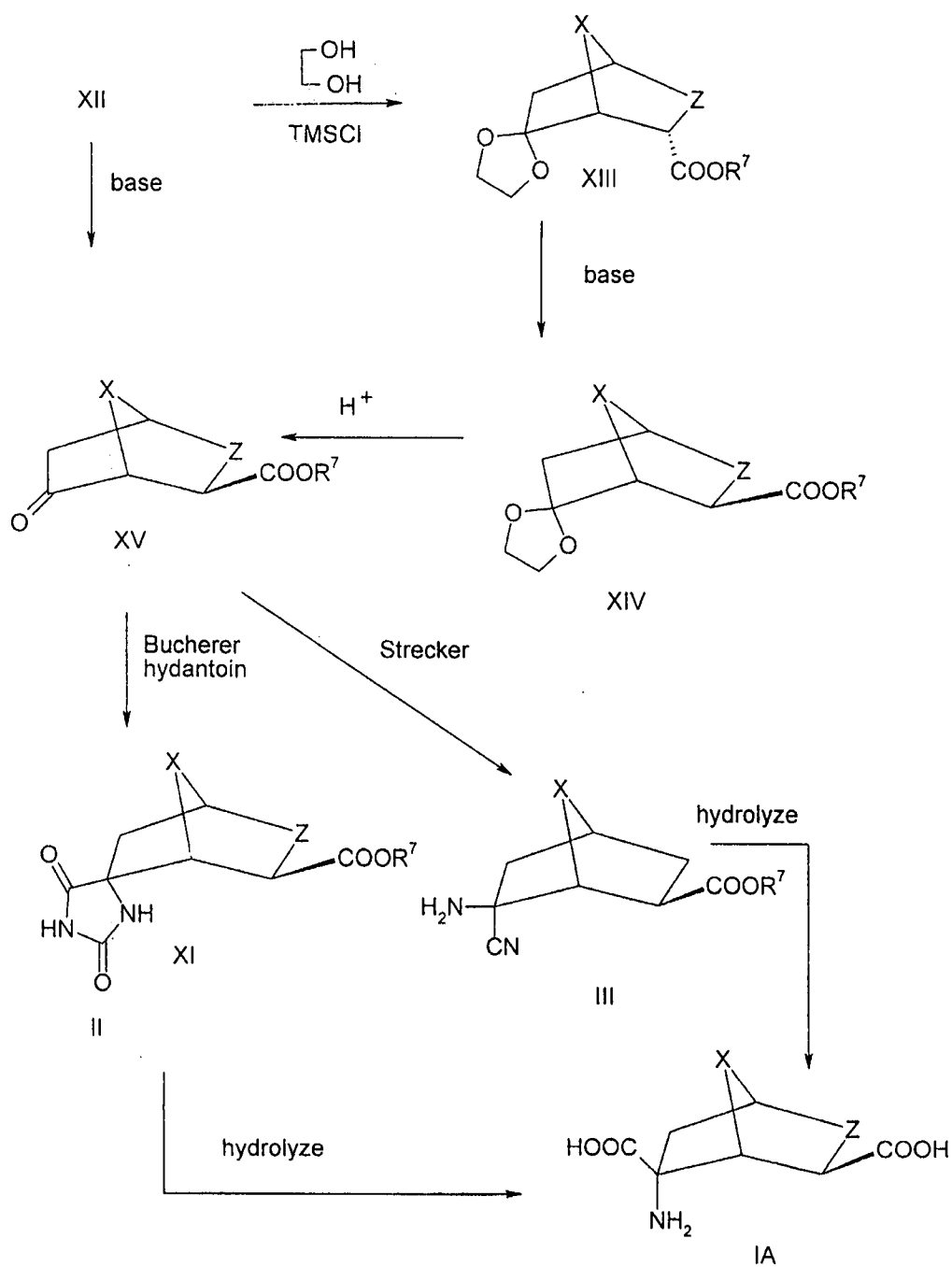
Detailed Description of the Invention

The compounds of formula I can be prepared according to the methods of Scheme 1. In the reaction Scheme and discussion that follow, unless otherwise indicated, n, X, Z, R¹, R², and R⁷ and structural formulas I, II, III and IV are defined as above.

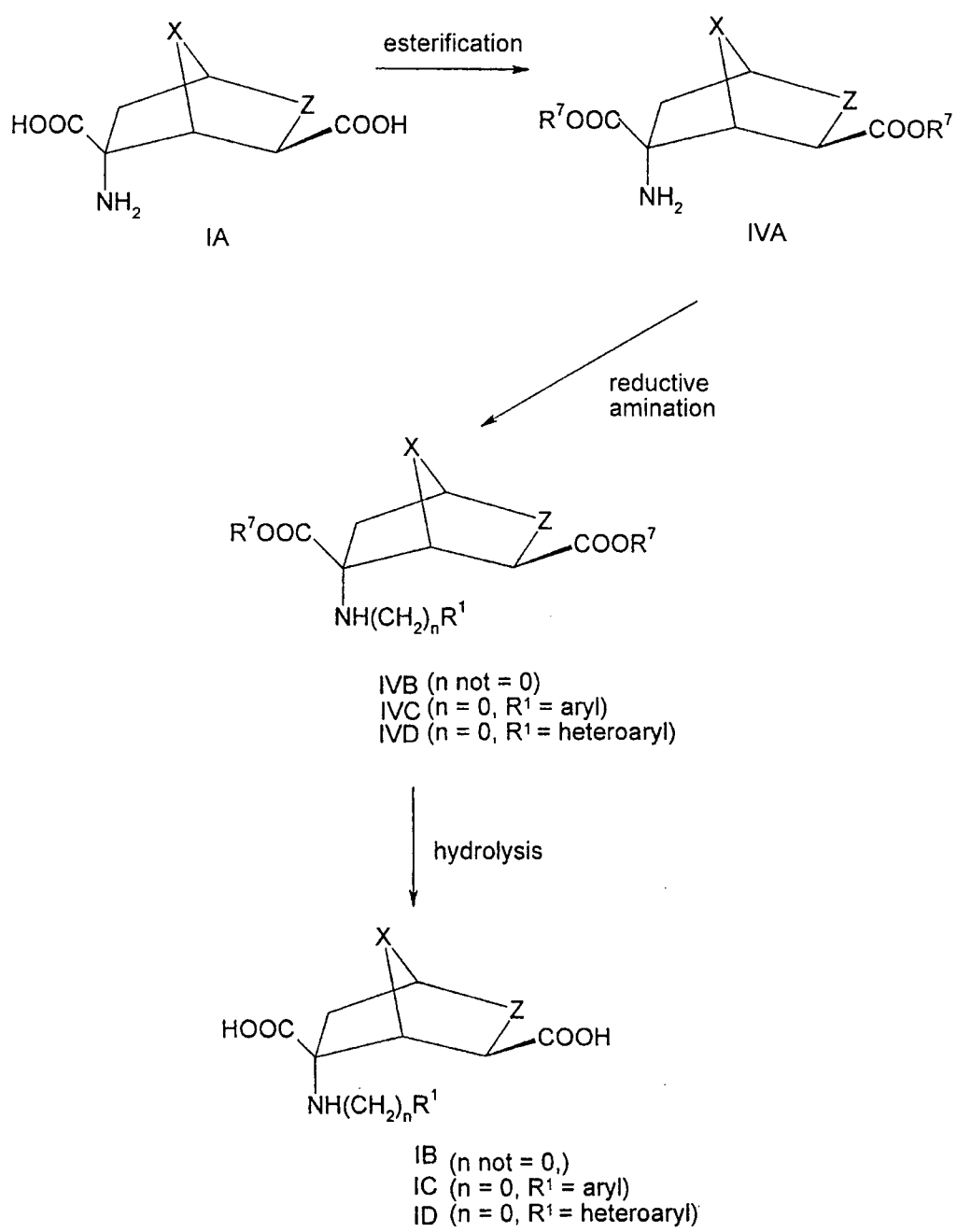
SCHEME 1



SCHEME 1 continued



SCHEME 2



Scheme 1 illustrates the preparation of all compounds of the formula I wherein n is zero and R¹ is hydrogen. Such compounds are referred to in Scheme 1 and hereinafter as compounds of the formula IA. Referring to Scheme 1, a diene of the formula VI is reacted with a dienophile of the formula VII using the well known Diels Alder reaction. (See Organic Reactions, 1948, Vol IV, pp. 1-173). This reaction may be conducted in the absence of a solvent, or in any of a variety of solvents, including water, ether, tetrahydrofuran, benzene, toluene, and dichloroethane. It may be run at atmospheric pressure or in a closed vessel under 1-10 atmospheres of pressure. The reaction time will vary depending on the particular Diels Alder reaction. The reaction may occur upon admixing of the reagents or may require up to several days to complete. In the case where Z is NR², the starting material of formula VII may be formed in situ from the corresponding aldehyde wherein Z is oxygen and an amine of the formula NH₂R², and the reaction may be performed in water (Tetrahedron Lett., 1990, 31, 2603; J. Amer. Chem. Soc., 1985, 107, 1768-1769; Bull. Chem. Soc. Japan, 1992, 65, 61).

The Diels Alder reaction product of formula VIII wherein R⁷ is other than H may be hydrolyzed to the free acid using an aqueous acid such as hydrochloric acid (HCl), hydromoromic acid (HBr) or sulfuric acid (H₂SO₄), or using an aqueous hydroxide. A diluent such as tetrahydrofuran, methanol, ethanol or isopropanol may be added. The hydrolysis may be conducted at a temperature from about 0°C to about 150°C, and is preferably conducted at a temperature from about room temperature to about 65°C.

The resulting compound of formula IX is further reacted with iodine and a base in an iodolactonization reaction (J. Org. Chem., 1976, 41, 1229), to form the corresponding compound of formula X. This reaction is generally carried out in a solvent such as water, methanol, ether, or tetrahydrofuran, or mixtures of two or more of the foregoing solvents, and the base is generally an alkali metal bicarbonate. The reaction is typically conducted at a temperature from about 0°C to about 50°C, and is preferably conducted at about ambient temperature for a period of about 30 minutes to about 48 hours, usually for about 8 to 24 hours.

The iodolactone intermediate of formula X is then treated with a base, generally an alkali metal hydroxide in water, methanol or ethanol, or a mixture of two or more of these solvents, according to the procedure of Bastiaansen (J. Org. Chem., 1995, 60, 4240) to prepare the corresponding intermediate having formula XI.

The compound of formula XI is then esterified according to standard conditions well known in the art (e.g., reaction with diazomethane or trimethylsilyldiazomethane, or with

trimethylsilyl chloride and an alcohol, or with an acid such as hydrochloric or sulfuric acid and an alcohol, or with a chloroformate such as methyl, ethyl or benzyl chloroformate.

The ketone of the resulting ketoester of formula XII may be protected as a ketal by treatment with ethylene glycol or an orthoformate such as trimethylorthoformate, under
5 dehydrating conditions such as molecular sieves or azeotropic removal of water, to produce the protected intermediate of formula XIII. A catalyst such as trimethylsilyl chloride, or an acid such as para-toluenesulfonic acid, sulfuric acid or benzenesulfonic acid, or pyridinium tosylate may be employed to facilitate this reaction. The reaction temperature can range from about ambient temperature to about the reflux temperature of the solvent. Suitable solvents include
10 aprotic solvents such as toluene, benzene, tetrahydrofuran, dimethoxyethane, methylene chloride and dichloroethane. Treatment of the keto ester (XII) or the ketal ester (XIII) with a base such as sodium methoxide or sodium ethoxide, in an alcoholic solvent, at a temperature from about ambient temperature to about the reflux temperature of the solvent, from about 6 hours to about 5 days, equilibrates the ester predominantly into the exo position.
15 Deketalization with an acid such as hydrochloric, sulfuric, oxalic, or acetic acid in water, alone or admixed with methanol, tetrahydrofuran or ether, affords the intermediate of formula XV.

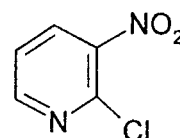
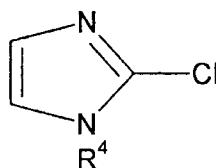
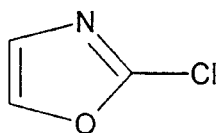
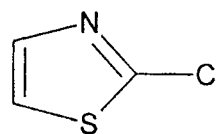
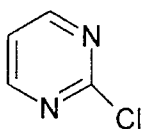
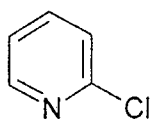
The compound of formula XV is further reacted under Bucherer hydantoin forming conditions (See J. Org. Chem., 1982, 47, 4081 and the references cited therein; Vogel's Textbook of Practical Organic Chemistry, 4th Ed., 1978, p. 876) to afford the hydantoin
20 intermediate of formula XI. Such conditions include for example, reaction with an alkali metal cyanide and ammonium carbonate in water, methanol or ethanol, at a temperature from about ambient temperature to about 150°C, and a pressure from about ambient pressure to about 150 psi, for about 30 minutes to about 48 hours. Hydrolysis of the resulting hydantoin using a mineral acid or aqueous alkali metal hydroxide or aqueous barium hydroxide, generally at
25 temperatures from about 50°C to about 150°C, affords the desired final product of formula IA.

Alternatively, the compound of formula XV can be reacted under Strecker synthesis conditions (Jerry March, Advanced Organic Chemistry, 4th Ed, 1992, p. 965; Vogel, Textbook of Practical Organic Chemistry 4th Ed., 1978, p. 546) to prepare the alpha amino nitrile intermediate of formula III. Such conditions include, for example, using either (a) ammonia
30 and hydrogen cyanide, (b) ammonium cyanide, (c) an alkali metal cyanide and ammonium chloride, or (d) trimethylsilyl cyanide, in an alcoholic solvent such as methanol or ethanol, optionally adding an acid such as acetic acid, at a temperature from about 20°C to about 100°C, for about 0.5 to about 24 hours, generally at a temperature between about 40°C and 80°C for about 1-8 hours. Hydrolysis of this intermediate, as described above for hydrolysis
35 of the hydantoin, affords the desired final product of formula IA.

As illustrated in Scheme 2, compounds of formula IA may be esterified to form the corresponding diesters of formula IVA using the standard conditions described above. The resulting diesters containing a free amino group may be further functionalized on the amino group by standard reductive amination procedures to form the corresponding compounds of formulas IVB (n is not zero), IVC (n is zero and R¹ is aryl) and IVD (n is zero and R¹ is heteroaryl). When there is an alkyl linkage of R¹ to the amino nitrogen of formula I, i.e., n is not zero, a compound of the formula IVA is reacted with the appropriate aldehyde of the formula R¹(CH₂)_mCHO, wherein m is equal to n-1 (i.e., m is one less than n) to form a compound of the formula IVB. The above reductive amination reaction can be carried out using standard methods well known to those of skill in the art. This reaction is typically carried out in the presence of a reducing agent such as sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, hydrogen (or a chemical hydrogen source such as formic acid or ammonium formate) and a metal catalyst such as platinum, palladium or rhodium, zinc and hydrochloric acid, borane dimethylsulfide or formic acid, at a temperature from about -60°C to about 50°C. Suitable reaction inert solvents for this reaction include lower alcohols (e.g., methanol, ethanol and isopropanol), dioxane, methylene chloride, dichloroethane, acetic acid and tetrahydrofuran (THF). Preferably, the solvent is methylene chloride or dichloroethane, the temperature is about 25°C, and the reducing agent is sodium triacetoxyborohydride.

Compounds of the formula IVC and IVD are compounds identical to those of formula IVB except that n is zero and R¹ is aryl or heteroaryl, respectively. Such compounds can also be formed from the corresponding compounds of the formula IVA. This is accomplished by reacting the corresponding compounds of the formula IVA with a compound of the formula R¹X, wherein X is a leaving group such as halo, triflate, mesylate or tosylate. This reaction is generally carried out in a solvent such as ethanol, N,N-dimethylformamide (DMF), N,N-dimethylacetamide, acetonitrile, nitromethane, dioxane or dichloroethane, preferably DMF, at a temperature from about 0°C to about 160°C, preferably from about 80°C to about 150°C.

In an analogous fashion, compounds of the formula IVD can be prepared by reacting the corresponding compound of formula IVA with a heteroaromatic compound of the formula AX, wherein A is a nitrogen containing heterocycle and X is a leaving group, as defined above, which is ortho to a ring nitrogen. Examples of compounds of the formula AX are the following:



The presence on the above heteroaryl groups of electron withdrawing groups, for example esters, nitriles, sulfones, and nitro groups, further activates them.

The compounds of formulas IVB, IVC and IVD formed in the above reaction can be converted onto the corresponding desired compounds of formulas IB, IC and ID by subjecting them to acid or base hydrolysis, using methods well known to those of skill in the art. Suitable acids for the use in acid hydrolysis of compounds of the formula IVB include mineral acids such as hydrofluoric acid, sulfuric acid, hydrochloric acid and hydrobromic acid. Suitable bases for use in base hydrolysis of compounds of the formula IVB include alkali metal hydroxides and barium hydroxide. The reaction temperature for the acid and base hydrolysis reactions can range from about 0°C to about 100°C. Preferably, these reactions are carried out at about the reflux temperature of the reaction mixture.

Additional compounds of the formula IC or ID, wherein R¹ is substituted aryl or heteroaryl, respectively, may be obtained from compounds of the formula IC or ID wherein R¹ is a nitroaryl or nitroheteroaryl group, respectively, by employing well known synthetic chemical methods. For example, following procedures such as those described by Jerry March, Advanced Organic Chemistry, 4th edition, pp. 721-725 and 1216-1217, the nitro group can be reduced to an amine. The newly formed amine can be replaced with other substituents by diazotization and further reaction as summarized in the above reference. For example, compounds of the formula I wherein R¹ is an aryl or heteroaryl group substituted with amino, mercapto, halo, cyano, or phenyl can be prepared in this manner.

The starting materials of formulas VI and VII, and those of formulas R¹X and AX, are either commercially available, known in the literature, or readily obtainable from commercially available or known compounds using methods that are known in the art.

Unless indicated otherwise, the pressure of each of the above reactions is not critical. Generally, the reactions will be conducted at a pressure of about one to about three atmospheres, preferably at ambient pressure (about one atmosphere).

The preparation of other compounds of the formula I not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

The compounds of the formula I that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. The acid that can be used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

Compounds of the formula that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. These salts are all prepared by conventional techniques. The chemical bases that are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of formula I. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably

employed in order to ensure completeness of reaction and maximum yields of the desired final product.

The compounds of the formula I and the pharmaceutically acceptable salts thereof (hereinafter, also referred to, collectively, as "the active compounds of the invention") are useful
5 for the treatment of neurodegenerative, psychotropic and drug or alcohol induced deficits and are potent metabotropic glutamate receptor ligands antagonists. The active compounds of the invention may therefore be used in the treatment or prevention of stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, epilepsy, AIDS-induced dementia, muscular spasms, migraine headaches, urinary
10 incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia (such as conditions caused by strangulation, surgery, smoke inhalation, asphyxiation, drowning, choking, electrocution or drug or alcohol overdose), cardiac arrest, hypoglycemic neuronal damage, chemical dependencies and addictions (e.g., addictions to or dependencies on alcohol, opiates, benzodiazepines, nicotine, heroin or cocaine), ocular damage, retinopathy, retinal neuropathy, tinnitus, idiopathic
15 and drug induced Parkinson's Disease, anxiety, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting.

The following procedure can be used to determine the activity of the therapeutic agents of this invention as agonists and as antagonists of metabotropic glutamate receptors.

Chinese hamster ovary (CHO) cells were transfected with cDNA (mGluR2 and pcDNA3)
20 using a calcium-phosphate method. Positive clones were selected for using geneticin (G418, Gibco, 500-700 µg/ml), and analyzed with RT-PCR for the presence of mGluR2 mRNA (primers for mGluR2: 5'-AAG TGC CCG GAG AAC TTC AAC GAA-3' AND 5'-AAA GCG ACG ACG TTG TTG AGT CCA-3'). Positive clones were grown to confluency and cAMP responses were measured in the presence of 10µM forskolin. Confluent clones were frozen and stored in liquid
25 nitrogen.

Chinese hamster ovary (CHO) cells stably transfected with the rat metabotropic glutamate receptor, mGluR2, were grown to confluence in Dulbecco's Modified Eagle Medium (DMEM) (Gibco catalog # 11960-044), containing 10% dialysed fetal bovine serum, 1% proline, 0.11 mg/ml sodium pyruvate, 0.5 mg/ml Geneticin, 2 mM l-glutamine, and penicillin/streptomycin.
30 Cells were harvested using a 5 mM ethylenediaminetetraacetic acid (EDTA) solution, and then spun down at 800 rpm in a 4°C refrigerated centrifuge. The remaining pellet was resuspended in a phosphate-buffered saline solution containing 30mM HEPES (Gibco, catno.15630-080) 5 mM magnesium chloride (MgCl₂), 300 µM 3-Isobutyl-1-methylxanthine (IBMX), and 0.1% dextrose. The cell suspension was added in 200 µl aliquots to flat bottomed polypropylene tubes
35 that were then placed in a 37°C heated water bath for 22 minutes. If a compound was being

tested for antagonist activity, it was allowed to preincubate with the cells in the bath during the first 11 minutes. At the end of the 11 minutes, 5 μ M forskolin plus a known concentration of an the test compound were added, and the incubation was continued for another 11 minutes. If a compound was being tested for agonist activity, the cells were allowed to shake in the bath for the initial 11 minutes, and then 5 μ M forskolin plus a known concentration of agonist were added for the remaining 11 minute incubation. In either case, the reaction was stopped with 25 μ l of 6N perchloric acid (PCA), and each tube was transferred immediately to an ice water bath. The pH of each sample was adjusted to approximately 8.0 with the addition of potassium hydroxide (KOH), and stabilized with the addition of Tris, pH 7.4. Aliquots (25 μ l) were assayed in a commercial competitive binding kit (Amersham TRK.432). The samples were then harvested onto GF/B filters coated in 0.5% PEI using a 96-well Skatron harvester. Samples were quantified using a 1205 Betaplate liquid scintillation counter.

CPMs from the Betaplate reader were converted to pmoles cAMP/mg protein/minute of incubation with forskolin using an Excel spreadsheet. EC_{50} 's and IC_{50} 's can be calculated from linear regression of the concentration response data.

The following proceeding can be used to determine the agonist activity of the therapeutic agents of this invention as agonists of metabotropic glutamate receptors.

Chinese hamster ovary (CHO) cells stably transfected with the rat metabotropic glutamate receptor, mGluR2, were grown to confluence in DMEM (Gibco catalog # 11960-044), containing 10% dialyzed fetal bovine serum, 1% proline, 0.11 mg/ml sodium pyruvate, 0.5 mg/ml Geneticin, 2 mM l-glutamine, and penicillin/streptomycin. Cells are harvested using a 5 mM EDTA solution, and homogenized for 10 strokes with a glass-teflon hand held homogenizer, then 50 volumes of a phosphate buffered saline solution (PBS) are added and the solution is spun at 18,000 RPM for 10 minutes at 4°C. The pellet is rehomogenized and resuspended in assay buffer (100 mM HEPES, 1 mM EGTA, pH 7.5) at a concentration that will result in approx. 0.009 mg protein/well. A reaction mix containing 6mM $MgCl_2$, 0.5 mM adenosine triphosphate (ATP), 0.5 mM 3-isobutyl-1-methylxanthine (IBMX), 0.1 mM guanosine triphosphate (GTP), 10 mM phosphocreatine, 0.31 mg/ml creatine phosphokinase (final concentrations in assay) is prepared just prior to the initiation of the experiment. 20 μ l of test compound, 20 μ l of forskolin (5 μ M final), 20 μ l of reaction mix, and 40 μ l of tissue are added in consecutive order to a 96-well polypropylene plate. The plate is incubated at 37°C in a heated water bath for 15 minutes. The reaction is stopped with the addition of 50 μ l of 40 mM EDTA. The plate is then transferred to ice and shaken for 10-15 minutes before a 25 μ l aliquot is removed for analysis in a commercial competitive binding kit (Amersham TRK.432). After a 2-18 hour incubation in the refrigerator, the samples are harvested onto GF/B filters coated in 0.5% polyethylenimine (PEI) using a 96-

well Skatron harvester. Samples were quantified using a 1205 Betaplate liquid scintillation counter.

CPMs from the Betaplate reader are converted to pmoles cAMP/well using an Excel spreadsheet. Agonist compounds are identified by percent reduction of the forskolin signal, also
5 in Excel. EC₅₀'s are calculated from linear regression of the concentration response data.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, transdermal (e.g., patch), intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable
10 for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium
15 phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycollate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations
20 may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges
25 formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions
30 or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (e.g., stroke) is 0.01 to 50 mg/kg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

Aerosol formulations for treatment of the conditions referred to above (e.g., stroke) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20mg to 1000mg of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 mg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The following Examples illustrate the preparation of the compounds of the present invention. Commercial reagents were utilized without further purification. Melting points are uncorrected. All NMR data were recorded at 250, 300 or 400 MHz in deuteriochloroform unless otherwise specified and are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. All non-aqueous reactions were carried out in dry glassware with dry solvents under an inert atmosphere for convenience and to maximize yields. All reactions were stirred with a magnetic stirring bar unless otherwise stated. Unless otherwise stated, all mass spectra were obtained using chemical impact conditions. Ambient or room temperature refers to 20-25°C. Melting points are uncorrected.

The following Examples 1-4 are examples of compounds of formula I. These Examples are provided to merely illustrate aspects of the subject invention. They are not intended and should not be construed to limit the invention set forth in the claims and more fully described herein.

EXAMPLE 1**2-(ENDO)-AMINO-BICYCLO [2.2.1] HEPTANE-2-(EXO),6-(EXO)-DICARBOXYLIC ACID****A. Methyl bicyclo [2.2.1] heptan-2-one-6-carboxylate Hydantoin (85-15 mixture of endo:exo hydantoin nitrogen)**

To a mixture of methyl bicyclo[2.2.1]heptan-2-one-6-exo-carboxylate (0.557 g, 3.31 mmol, J. Org. Chem., 1995, 60, 4240-4245) and ammonium carbonate (1.6 g, 16.65 mmol) in water (9 mL) and methanol (9 mL) was added potassium cyanide (0.456 g, 7 mmol). The mixture was warmed to 41.5° C and stirred overnight. The mixture was diluted with water and repeatedly extracted with ethyl acetate. The combined organic phase was washed with water, dried over magnesium sulfate, and concentrated to afford a white solid. This solid was flash chromatographed on silica gel (40 x 80 mm) with elution proceeding as follows: 50% ethyl acetate/hexane, 112 mL, nil; 42 mL, unidentified impurity; 322 mL, nil; 322 mL, 0.299 g of title product as a white solid which had: ¹H NMR (CDCl₃) (major diastereomer with endo hydantoin nitrogen) δ 10.60 (s, 1 H), 8.23 (s, 1 H), 3.55 (s, 3 H), 2.81 (q, J = 4.5 Hz, 1 H), 2.42 (s, 1 H), 2.26 (s, 1 H), 2.04 (d, J = 10.1 Hz, 1 H), 1.92 (dt, J = 3.5, 12.25 Hz, 1 H), 1.84-1.76 (m, 1 H), 1.60-1.52 (m, 1 H), 1.30 (d, J = 10.1 Hz, 1 H), 1.20 (d, J = 12.7 Hz, 1 H).

B. 2-(endo) Amino-bicyclo[2.2.1]heptane-2,6 di (exo)carboxylic acid

A mixture of methyl bicyclo [2.2.1] heptan-2-one-6-exo-carboxylate hydantoin (0.10 g, 0.41 mmol) in 6N hydrochloric acid (10 mL) was refluxed 24 hours, cooled and allowed to stand at ambient temperature 72 hours. The reaction was concentrated to a white solid in vacuo. The solid was dissolved in water with the aid of 2 drops of 6 N hydrochloric acid and applied to a Dowex 50 x8 100 ion exchange column (7 mL of resin prepared by eluting with water until the eluent pH = 4). The column was eluted with water until the pH reached 4.5. Elution was continued with 1 N ammonium hydroxide. Ninhydrin positive fractions were combined and lyophilized to afford 0.032 g of white solid product which had: ¹H NMR (D₂O) δ 2.53 (s, 1 H), 2.30-2.22 (m, 1 H), 2.20-2.16 (br s, 1 H), 2.12-2.04 (m, 1 H), 1.75 (d, J = 11.8 Hz, 1 H), 1.72-1.64 (m, 1 H), 1.52-1.44 (m, 1 H), 1.28-1.20 (m, 1 H), 1.08 (dd, J = 2.7, 13.5 Hz, 1 H), APCI MS m/e = 200.2 (P+1).

EXAMPLE 2

(+)-2-(endo)-Amino-bicyclo [2.2.1] heptane-2-(exo), 6-(exo)-dicarboxylic acid hydrochloride and (-)-2-(endo)-Amino-bicyclo [2.2.1] heptane-2-(exo), 6-(exo)-dicarboxylic acid hydrochloride

5 **A. Bicyclo [2.2.1] heptan-2-one-6-carboxylic acid hydantoin**

A solution of methyl bicyclo [2.2.1] heptan-2-one-6-exo-carboxylate hydantoin (1.02 g, 4.28 mmol) in 6 N hydrochloric acid (20 mL) was refluxed 1 hour. Upon cooling to ambient temperature the white solid product precipitated. The solid was collected and air dried to afford 0.776 g of title product which had: ¹H NMR (D₂O) δ 2.65 (br s, 1 H), 2.56 (s, 1 H), 2.25
10 (s, 1 H), 2.02-1.83 (m, 2 H), 1.82-1.72 (m, 1 H), 1.58-1.46 (distorted t, 1 H), 1.34-1.19 (distorted t, 2 H).

B. Resolution of bicyclo [2.2.1] heptan-2-one-6-exo-carboxylic acid hydantoin

Bicyclo [2.2.1] heptan-2-one-6-carboxylic acid hydantoin (0.776 g) was combined
15 with methanol (20 mL) and (s)-(-)-α-methylbenzylamine (0.470 mL) was added. The mixture was stirred at ambient temperature for 2 hours. During this time the solution became homogeneous and then a white precipitate formed. The precipitate was collected (0.50 g) and recrystallized twice from methanol. The recrystallized salt was treated with 1 N hydrochloric acid and extracted repeatedly with ethyl acetate. The combined organic layer was dried over
20 magnesium sulfate and concentrated to afford 0.120 g of the (-) enantiomer of bicyclo [2.2.1] heptan-2-one-6-carboxylic acid hydantoin which had an NMR spectrum identical to that of the racemic material and [α]_D = -36.11° (c = 0.925 methanol). Chiral HPLC analysis (chiralcel OG column, 95/5 hexane/ethanol with 0.1% trifluoroacetic acid solvent, flow rate = 1 mL/min, 214 nM UV detection) showed the compound to be 100% enantiomerically pure with a retention
25 time of 14.50 min.

The mother liquors from the salt resolution above were combined and treated with 1 N hydrochloric acid. Repeated extraction with ethyl acetate allowed the recovery of bicyclo [2.2.1] heptan-2-one-6-carboxylic acid hydantoin enriched in the (+) enantiomer. This material was treated with (R)-(+)-α-methylbenzylamine as above to afford 0.066 g of (+)-
30 bicyclo [2.2.1] heptan-2-one-6-carboxylic acid hydantoin as a white solid which had: [α]_D = +32.77° (c = 0.900 methanol). Chiral HPLC according to the method above showed the sample to have an enantiomeric excess of 98.1% with a retention time of 17.56 min.

C. (+)-2-(endo)-Amino-bicyclo [2.2.1] heptane-2-(exo), 6-(exo)-dicarboxylic acid hydrochloride

(+)-Bicyclo [2.2.1] heptan-2-one-6-carboxylic acid hydantoin (0.098 g, 0.4 mmol) was combined with 6 N hydrochloric acid (20 mL) and refluxed for 48 hours. The mixture was concentrated in vacuo to afford 0.095 g of title product which had: $[\alpha]_D = +20.31^\circ$ (c = 1.07 methanol).

5 D. (-)-2-(endo)-Amino-bicyclo [2.2.1] heptane-2-(exo), 6-(exo)-dicarboxylic acid hydrochloride

Using the same hydrolysis procedure described above, (-)-bicyclo [2.2.1] heptan-2-one-6-carboxylic acid hydantoin was converted to the (-) title product which had: $[\alpha]_D = -24.06^\circ$ (c = 0.575 methanol).

EXAMPLE 3**2-(Endo)-benzylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid****A. Dimethyl 2-(endo)-benzylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylate**

5 A mixture of dimethyl 2-(endo)-amino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylate (0.25g, 1.1 mmol) (see Preparation 1, below), methylene chloride (10 mL), benzaldehyde (0.134 mL), and sodium triacetoxyborohydride (1.2g, 5.5 mmol) was stirred 16 hours. The reaction was quenched with 0.5 N HCl (20 mL) and stirred 30 minutes. The phases were separated and the organic layer was washed with saturated aqueous
10 bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate and concentrated to leave 0.225g of colorless oil. This oil was chromatographed on silica gel (using a Flash 40s cartridge from Biotage (Charlottesville, Virginia, USA); the Flash 40s cartridge contains KP sil) with elution proceeding as follows: 10% ethyl acetate/hexane, 100 mL, nil; 100 mL, 0.043 g of dimethyl-2-(endo)-benzylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylate as a colorless oil which had: NMR (CDCl₃) δ 7.31-7.29 (m, 5 h), 3.73 (s, 3 H), 3.66 (s, 3H), 3.51 (ABq, $\delta v_{1,3}$ =40 Hz, J=13 Hz, 2 H), 3.32, (dd, J=5, 9 Hz, 1 H), 2.95 (s, 1 H), 2.28 (br s, 1 H), 2.21-2.15 (m, 1 H), 1.97-1.90 (m, 1 H), 1.88 (s, 1 H), 1.59-1.54 (m, 1 H), 1.45 (ABq, $\delta v_{1,3}$ =24 Hz, J=11 Hz, 2 H), 1.10 (dd, J=3, 13 Hz, 1 H).

B. Hydrolysis of ester groups

20 A mixture of dimethyl 2-(endo)-benzylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylate (0.04 g, 0.126 mmol), obtained as described in the preceding paragraph (A), and 6 N HCl (5 mL) was warmed to 80° C overnight. Additional 6 N HCl (5 mL) was added and the reaction was heated at 103° C for 24 hours. The mixture was cooled and
25 concentrated. NMR of the residue indicated that monohydrolysis had occurred. The residue was combined with water (5 mL) and ethanol (5 mL) and LiOH (0.15 g, 6.2 mmol) was added. The mixture was heated at 65° for 16 hours. The reaction was concentrated and most of the residual solid was taken up in ethanol. Residual solids were removed from the ethanol solution by filtration through celite. The ethanol filtrate was concentrated to afford 0.242 g of
30 off white solid. The solid was taken up in 1N HCl (1 mL) and applied to AG50w-x8 ion exchange resin (0.15 g which had been previously washed with water until the pH increased to 4.5). This mixture was stirred over the weekend. An SCX column (0.5 g, strong cation exchange, from Burdick and Jackson (Muskegon, Michigan, USA) (catalog #9094) was prepared by flushing with water until the eluent pH was 4.5. The ion exchange resin and its
35 associated solution were applied to the SCX column and eluted as follows: water, 3 mL,

unknown material; water, 30 mL, nil; 1 N ammonium hydroxide, 28 mL, 0.02 g of title product of this Example as a white solid which had : NMR (D₂O) δ 7.23-7.15 (m, 5 H), 3.32 (ABq, δv_1 , δv_2 =20 Hz, J=12 Hz, 2 H), 2.63 (s, 1 H), 2.55 (dd, J=5, 9.5 Hz, 1 H), 2.03 (s, 1 H), 1.87-1.81 (br d, 1 H), 1.58-1.51 (m, 1 H), 1.41 (t, J=10.5 Hz, 1 H), 1.26 (m, 2 H), 0.88 (d, J=11.5 Hz, 1 H);
5 APCI MS, p+1=290.2.

EXAMPLE 4

2-(Endo)-phenylethylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid

10 Following substantially the same procedure described for Example 3, above, but with a direct LiOH hydrolysis (without the acidic partial hydrolysis step), the title compound of the current Example was prepared from dimethyl 2-(endo)-aminobicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylate (0.015 g, 0.066 mmol), methylene chloride (2 mL), phenylacetaldehyde (0.01 mL, 0.08 mmol), and sodium triacetoxymethylborohydride (0.07 g, 0.33 mmol). The title
15 compound of the current Example had: NMR (D₂O) δ 7.19-7.11 (m, 5 H), 2.70-2.44 (m, 5 H), 2.38 (dd, J=5, 9 Hz, 1 H), 2.05- 2.01 (m, 1 H), 1.82 (ddd, J=3, 5, 13 Hz, 1 H), 1.58-1.51 (m, 1 H), 1.41 (t, J=10.5 Hz, 1 H), 1.24-1.16 (m, 2 H), 0.85 (dd, J=2, 11.5 Hz, 1 H); APCI MS, p+1=304.1.

20

PREPARATION 1

Dimethyl 2-(endo)-amino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylate hydrochloride

2 (Endo)-amino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid (0.010 g, 0.05 mmol) was dissolved in methanol (5 mL) and the solution was saturated with HCl gas. The
25 mixture was heated under reflux overnight. The reaction was cooled and concentrated to afford the title compound of this Preparation as a white solid which had: NMR (CD₃OD) δ 3.84 (s, 3 H), 3.68 (s, 3 H), 2.90 (s, 1 H), 2.74-2.62 (m, 1 H), 2.54-2.40 (m, 2 H), 2.06-1.96 (m, 1 H), 1.88 (d, J=11 Hz, 1 H), 1.84-1.74 (m, 1 H), 1.52 (dd, J=4.5, 11 Hz, 1 H), 1.34 (dd, J=1.9, 13.5 Hz, 1 H).

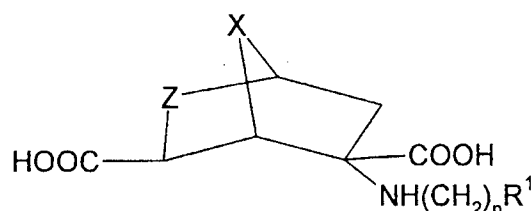
PREPARATION 2

Diethyl 2-(endo)-amino-bicyclo[2.2.1]heptane-2-(exo)-dicarboxylate

- The compound of this Preparation is also useful for preparing compounds of formula
- 5 I. 2-(Endo)-amino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid (0.392 g, 1.96 mmol) was dissolved in ethanol (15 mL) and the solution was saturated with HCl gas. The mixture was heated under reflux overnight. the solution was concentrated and the residue was treated with saturated aqueous sodium bicarbonate. This aqueous mixture was further treated with sodium carbonate to bring the pH to 10. The aqueous layer was repeatedly
- 10 extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate and concentrated to afford the pale yellow oil title compound of this Preparation which had: NMR (CDCl₃) δ 4.20-4.05 (m, 4 H), 3.30 (dd, J=5, 8.5 Hz, 1 H), 2.69 (s, 1 H), 2.37 (ddd, J=3, 4.8, 13 Hz, 1 H), 2.27 (s, 1 H), 1.94-1.86 (m, 1 H), 1.95-1.75 (br s, 2 H), 1.55 (t, J=11 Hz, 1 H), 1.42 (ABq, $\delta v_{1,3}=23$ Hz, J=11 Hz, 2 H), 1.27-1.21 (m, 6 H), 0.91 (dd, J=2, 13 Hz, 1 H).

CLAIMS

1. A compound of the formula



wherein n is 0-6;

- 5 X is CH_2 , CH_2CH_2 or oxygen;

Z is CHR^2 or NR^2 ;

- R^1 and R^2 are selected independently from hydrogen, $(\text{C}_1\text{-C}_6)$ alkyl, aryl and heteroaryl, wherein said aryl is selected from phenyl and naphthyl and said heteroaryl is selected from 5 and 6 membered aromatic heterocyclic rings that contain from one to four heteroatoms selected, independently, from nitrogen, oxygen and sulfur, and wherein said aryl and heteroaryl moieties can optionally be substituted with one or more substituents that are selected, independently, from halo, $-\text{S}(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{S}(\text{O})(\text{C}_1\text{-C}_6)\text{alkyl}$, $-\text{S}(\text{O})_2(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with from one to seven fluorine atoms, $(\text{C}_1\text{-C}_6)\text{alkoxy}$ optionally substituted with from one to seven fluorine atoms, amino, nitro, cyano, carboxy, $-\text{CO}_2(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, di- $[(\text{C}_1\text{-C}_6)\text{alkyl}]\text{amino}$ phenoxy, anilino and phenylthio;

with the proviso that none of said heteroaryl moieties contains more than one ring oxygen atom or more than one ring sulfur atom;

or a pharmaceutically acceptable salt of such compound.

2. A compound according to claim 1 wherein Z is CH_2 .
- 20 3. A compound according to claim 1 wherein R^1 is selected from the group consisting of hydrogen, unsubstituted phenyl, and phenyl substituted with one or two substituents.

4. A compound according to claim 1 wherein n is zero, 1 or 2.

5. A compound according to claim 1 wherein X is CH_2 .

- 25 6. A compound according to claim 1 selected from the group consisting of:

2-(endo)-amino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid;

(+)-2-(endo)-aminobicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid;

(-)-2-(endo)-aminobicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid;

2-(endo)-benzylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid; and

- 30 2-(endo)-phenylethylamino-bicyclo[2.2.1]heptane-2-(exo)-6-(exo)-dicarboxylic acid.

7. A pharmaceutical composition for treating a disorder or condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia, cardiac arrest, hypoglycemic neuronal damage, chemical dependencies and addictions, ocular damage and retinopathy, idiopathic and drug induced Parkinson's Disease, anxiety, including panic disorder, General Anxiety Disorder, Post Traumatic Stress Syndrome, simple phobias, and social phobia; schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition for treating a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising an amount of a compound according to claim 1 that is effective in treating such disorder or condition and a pharmaceutically acceptable carrier.

9. A method for treating a disorder or condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia, cardiac arrest, hypoglycemic neuronal damage, opiate tolerance and withdrawal, ocular damage and retinopathy, idiopathic and drug induced Parkinson's Disease, anxiety, including panic disorder, General Anxiety disorder, Post Traumatic Stress Syndrome, simple phobias, and social phobia; schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting, in a mammal, comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 that is effective in treating such condition.

10. A method for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising administering to a mammal requiring such treatment an amount of a compound according to claim 1 that is effective in treating such disorder or condition.

11. A pharmaceutical composition for treating a disorder or condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine

headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, opiate tolerance and withdrawal, ocular damage and retinopathy, idiopathic and drug induced Parkinson's Disease, anxiety, including panic disorder, General Anxiety Disorder, Post Traumatic Stress Syndrome, simple phobias, and social phobia, schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting, in a mammal, comprising a metabotropic glutamate neurotransmission modulating effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

10 12. A pharmaceutical composition for treating a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising a metabotropic glutamate neurotransmission modulating effective amount of a compound according to claim 1 and a pharmaceutically acceptable carrier.

15 13. A method for treating a disorder or condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, opiate tolerance and withdrawal, ocular damage and retinopathy, idiopathic and drug induced Parkinson's Disease, anxiety, including panic disorder, General Anxiety Disorder, Post Traumatic Stress Syndrome, simple phobias, and social phobia; schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass surgery and grafting in a mammal, comprising administering to a mammal requiring such treatment a metabotropic glutamate neurotransmission modulating effective amount of a compound according to claim 1.

20 14. A method for treating a disorder or condition, the treatment or prevention of which can be effected or facilitated by reducing or inhibiting glutamate neurotransmission in a mammal, comprising administering to a mammal requiring such treatment a metabotropic glutamate neurotransmission modulating effective amount of a compound according to claim 1.

30 15. A pharmaceutical composition for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising:

- (a) a compound of the formula I, or a pharmaceutically acceptable salt thereof;
- (b) a serotonin reuptake inhibitor or a serotonin-1A (5HT_{1A}) receptor ligand, or a pharmaceutically acceptable salt of such inhibitor or ligand; and

(c) a pharmaceutically acceptable carrier;

wherein the amounts of the compound of formula I and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are contained in such composition are such that the combination of the two active ingredients is effective in treating such disorder or condition.

5 16. A pharmaceutical composition according to claim 15, wherein (b) is a serotonin reuptake inhibitor selected from sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, and femoxetine.

17. A method for treating a disorder or condition, the treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising
10 administering to a mammal requiring such treatment:

(a) a compound of the formula I, or a pharmaceutically acceptable salt thereof;
and

(b) a serotonin reuptake inhibitor or a serotonin-1A (5HT_{1A}) receptor ligand, or a pharmaceutically acceptable salt of such inhibitor or ligand;

15 wherein the amounts of the compound of formula I and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are employed in such method are such that the combination of the two active ingredients is effective in treating such disorder or condition.

18. A method according to claim 17, wherein (b) is a serotonin reuptake inhibitor selected from sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, and
20 femoxetine.

19. A pharmaceutical composition for treating a condition selected from stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, hypoxia, cardiac arrest,
25 hypoglycemic neuronal damage, chemical dependencies and addictions, ocular damage and retinopathy, idiopathic and drug induced Parkinson's Disease, anxiety, including panic disorder, General Anxiety Disorder, Post Traumatic Stress Syndrome, simple phobias, and social phobia; schizophrenia, depression, bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema, chronic and acute pain, tardive dyskinesia and cerebral deficits
30 subsequent to cardiac bypass surgery and grafting in a mammal, comprising:

(a) a compound according to claim 1 or a pharmaceutically acceptable salt thereof;

(b) a serotonin reuptake inhibitor or a 5HT_{1A} receptor ligand, or a pharmaceutically acceptable salt of such inhibitor or ligand; and

35 (c) a pharmaceutically acceptable carrier;

wherein the compound according to claim 1 and the 5HT_{1A} receptor ligand or serotonin reuptake inhibitor that are contained in such composition are present in amounts such that the combination of the two active ingredients is effective in treating such condition.

20. A pharmaceutical composition according to claim 19, wherein (b) is a serotonin
5 reuptake inhibitor selected from sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, and femoxetine.

21. A method for treating a condition selected from stroke, cerebral ischemia, spinal
cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral
sclerosis, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence,
10 psychosis, convulsions, perinatal hypoxia, hypoxia, cardiac arrest, hypoglycemic neuronal
damage, opiate tolerance and withdrawal, ocular damage and retinopathy, idiopathic and drug
induced Parkinson's Disease, anxiety, including panic disorder, General Anxiety Disorder, Post
Traumatic Stress Syndrome, simple phobias, and social phobia; schizophrenia, depression,
bipolar disorder, obsessive-compulsive disorder, Tourette's syndrome, emesis, brain edema,
15 chronic and acute pain, tardive dyskinesia and cerebral deficits subsequent to cardiac bypass
surgery and grafting, in a mammal, comprising administering to a mammal requiring such
treatment;

(a) a compound according to claim 1 or a pharmaceutically acceptable salt
thereof; and

20 (b) a serotonin reuptake inhibitor or a 5HT_{1A} receptor ligand, or a
pharmaceutically acceptable salt of such inhibitor or ligand;

wherein the amounts of the compound according to claim 1 and the 5HT_{1A} receptor
ligand or serotonin reuptake inhibitor that are employed in such method are such that the
combination of the two active ingredients is effective in treating such condition.

22. A method according to claim 21, wherein (b) is a serotonin reuptake inhibitor
25 selected from sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, and
femoxetine.

23. A pharmaceutical composition for treating a disorder or condition, the
treatment of which can be effected or facilitated by modulating glutamate neurotransmission in a
30 mammal, comprising:

(a) a glutamate neurotransmission modulating compound or a pharmaceutically
acceptable salt thereof;

(b) a serotonin reuptake inhibitor or a serotonin-1A (5HT_{1A}) receptor ligand, or a
pharmaceutically acceptable salt of such inhibitor or ligand; and

35 (c) a pharmaceutically acceptable carrier;

wherein the amounts of the glutamate neurotransmission modulation compound and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are contained in such composition are such that the combination of the two active ingredients is effective in treating such disorder or condition.

- 5 24. A pharmaceutical composition according to claim 23, wherein (b) is a serotonin reuptake inhibitor selected from sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, and femoxetine.

25. A method for treating a disorder or condition, the treatment of which can effected or facilitated by modulating glutamate neurotransmission in a mammal, comprising
10 administering to a mammal requiring such treatment:

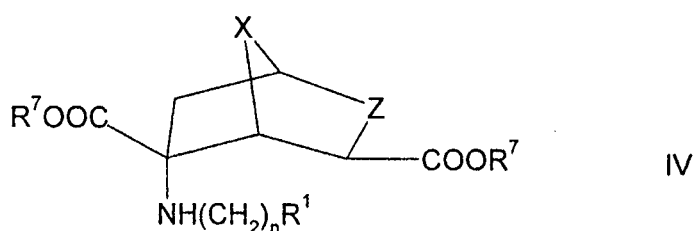
(a) a glutamate neurotransmission modulating compound or a pharmaceutically acceptable salt thereof; and

(b) a serotonin reuptake inhibitor or a serotonin-1A (5HT_{1A}) receptor ligand, or a pharmaceutically acceptable salt of such inhibitor or ligand;

- 15 wherein the amounts of the glutamate neurotransmission modulating compound and the serotonin reuptake inhibitor or 5HT_{1A} receptor ligand that are employed in such method are such that the combination of the two active ingredients is effective in treating such disorder or condition.

26. A method according to claim 25, wherein (b) is a serotonin reuptake inhibitor
20 selected from sertraline, fluoxetine, fluvoxamine, paroxetine, citalopram, fenfluramine, and femoxetine.

27. A compound of the formula



- 25 wherein n is 0-6;

X is CH₂, CH₂CH₂ or oxygen;

Z is CHR² or NR²;

- R¹ and R² are selected independently from hydrogen, (C₁-C₆)alkyl, aryl and heteroaryl, wherein said aryl is selected from phenyl and naphthyl and said heteroaryl is
30 selected from 5 and 6 membered aromatic heterocyclic rings that contain from one to four heteroatoms selected, independently, from nitrogen, oxygen and sulfur, and wherein said aryl

and heteroaryl moieties can optionally be substituted with one or more substituents that are selected, independently, from halo, $-S(C_1-C_6)alkyl$, $-S(O)(C_1-C_6)alkyl$, $-S(O)_2(C_1-C_6)alkyl$, $(C_1-C_6)alkyl$ optionally substituted with from one to seven fluorine atoms, $(C_1-C_6)alkoxy$ optionally substituted with from one to seven fluorine atoms, amino, nitro, cyano, carboxy, $-CO_2(C_1-C_6)alkyl$, $(C_1-C_6)alkylamino$, di- $[(C_1-C_6)alkyl]amino$ phenoxy, anilino and phenylthio; and

5 R^7 is hydrogen, $(C_1-C_6)alkyl$ or benzyl

with the proviso that none of said heteroaryl moieties contains more than one ring oxygen atom or more than one ring sulfur atom.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/00376

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C229/50 A61K31/195

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 6 C07C A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 696 577 A (ELI LILLY) 14 February 1996 cited in the application see claims; examples ---	1-27
A	EP 0 774 455 A (ELI LILLY) 21 May 1997 see claims; examples ---	1-27
A	EP 0 774 454 A (ELI LILLY) 21 May 1997 see claims; examples -----	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 June 1999

Date of mailing of the international search report

18/06/1999

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Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB 99/00376

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 9,10,13,14,17,18,21,22,25,26
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
- ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
- ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

- ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
- ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
- ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 99/00376

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 696577 A	14-02-1996	US 5750566 A	12-05-1998
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		WO 9717952 A	22-05-1997



US 20060142388A1

(19) **United States**

(12) **Patent Application Publication**
Yasuhara et al.

(10) **Pub. No.: US 2006/0142388 A1**

(43) **Pub. Date: Jun. 29, 2006**

(54) **2-AMINOBIKCYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID DERIVATIVE**

(57) **ABSTRACT**

(76) Inventors: **Akito Yasuhara**, Tokyo (JP); **Kazunari Sakagami**, Tokyo (JP); **Hiroshi Ohta**, Tokyo (JP); **Atsuro Nakazato**, Tokyo (JP)

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One object of the present invention is to provide a drug that is effective in treatments for and prevention of psychiatric disorders and in treatments for and prevention of neurological diseases, inhibiting a Group II metabotropic glutamate receptor.

The object is solved by a 2-amino-bicyclo[3.1.0]hexane-2, 6-dicarboxylic acid derivative represented by formula [I]:

(21) Appl. No.: **10/562,010**

(22) PCT Filed: **Jun. 25, 2004**

(86) PCT No.: **PCT/JP04/09384**

(30) **Foreign Application Priority Data**

Jun. 26, 2003 (JP) 2003-181931

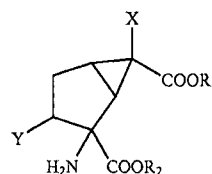
Publication Classification

(51) **Int. Cl.**

A61K 31/195 (2006.01)

C07C 229/28 (2006.01)

(52) **U.S. Cl.** **514/531; 514/562; 514/564; 560/119; 562/501**



(wherein R^1 and R^2 are the same or different, and each represents a hydrogen atom, C_{1-10} alkyl group, etc; X represents a hydrogen atom or a fluorine atom; and Y represents an amino group, $-SR^3$, $-S(O)_nR^7$, $-SCHR^3R^4$, $-S(O)_nCHR^3R^4$, $-NICH^3R^4$, $-N(CH^3R^4)(CH^5R^6)$, $-NHCOR^3$ or $-OCOR^7$), a pharmaceutically acceptable salt thereof, or a hydrate thereof and so on.

2-AMINOBICYCLO[3.1.0]HEXANE-2,6-DICARBOXYLIC ACID DERIVATIVE

FIELD OF THE INVENTION

[0001] The present invention relates to pharmaceutically effective 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative, a pharmaceutically acceptable salt thereof and a hydrates thereof, and drug containing them as an active ingredient. More specifically, the present invention relates to a novel 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative effective for the treatments and preventions of psychiatric disorders such as schizophrenia, anxiety and related ailments, bipolar disorder and epilepsy, and those of neurological diseases such as drug dependence, cognitive disorder, Alzheimer's disease, Huntington's chorea, Parkinson's disease, dyskinesia associated with muscular rigidity, cerebral ischaemia, cerebral failure, myelopathy and head trauma.

BACKGROUND OF THE INVENTION

[0002] In recent years, successive clonings of glutamate receptor genes have revealed that glutamate receptors have a surprisingly large number of subtypes. At present, glutamate receptors are classified into two major groups: an "ionotropic type in which the receptor has a ion channel type structure" and a "metabotropic type in which the receptor is coupled with G-protein" (see Science, 258, p. 597-603, 1992 (Non-Patent Document 1 mentioned below)). The ionotropic glutamate receptors are classified pharmacologically into three sub-groups: N-methyl-D-asparaginic acid (NMDA); α -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA); and kainate (see Non-Patent Document 1). The metabotropic glutamate receptors are classified into eight sub-groups from type 1 to type 8 (see J. Neurosci., 13, p. 1372-1378, 1993 (Non-Patent Document 2 mentioned below), and Neuropharmacol., 34, p. 1-26, 1995 (Non-Patent Document 3 mentioned below)).

[0003] The metabotropic glutamate receptors are classified pharmacologically into three groups. Of these, the Group II receptors (mGluR2/mGluR3) bind with adenylylase, and inhibit the Forskolin stimulated accumulation of cyclic adenosine monophosphate (cAMP) (see Trends Pharmacol. Sci., 14, 13, 1993 (Non-Patent Document 4 mentioned below)). Thus, it is suggested that compounds, which antagonize the action of Group II metabotropic glutamate receptors, will be effective for the treatment and prevention of acute and chronic psychiatric disorders and neurological diseases.

LIST OF RELATED DOCUMENTS

Non-Patent Document 1:	Science, 258, p. 597-603, 1992
Non-Patent Document 2:	J. Neurosci., 13, p. 1372-1378, 1993
Non-Patent Document 3:	Neuropharmacol., 34, p. 1-26, 1995
Non-Patent Document 4:	Trends Pharmacol. Sci., 14, p. 13, 1993

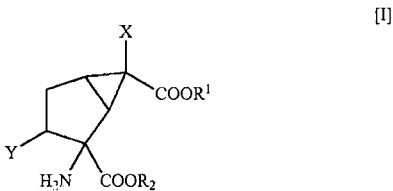
[0004] The object of the present invention is to provide a drug that antagonizes the action of Group II metabotropic glutamate receptors, and would be effective for the treatment and prevention of psychiatric disorders such as schizophrenia, anxiety and related ailments thereof, depression, bipolar

disorder and epilepsy, and also effective for the treatment and prevention of neurological diseases such as drug dependence, cognitive disorder, Alzheimer's disease, Huntington's chorea, Parkinson's disease, dyskinesia associated with muscular rigidity, cerebral ischaemia, cerebral failure, myelopathy and head trauma.

DISCLOSURE OF THE INVENTION

[0005] The present inventors have conducted extensive examinations into pharmacological effects of 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives, and discovered novel 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives and esters of the derivatives affect of activity of Group II metabotropic glutamate receptors, thereby completing the present invention.

[0006] The compound of the present invention is a 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative, (hereafter referred as 'the compound of the present invention') represented by formula [I] and a pharmaceutically acceptable salt and or a hydrate of the derivative.



[wherein R¹ and R² are the same or different, and each represents, a hydrogen atom, a C₁₋₁₀ alkyl group, a phenyl group, a naphthyl group, a C₁₋₁₀ alkyl group substituted by one or two phenyl groups, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a hydroxyl C₂₋₁₀ alkyl group, a C₁₋₁₀ alkoxy-carbonyl C₁₋₁₀ alkyl group, an amino C₂₋₁₀ alkyl group or a C₁₋₁₀ alkoxy C₁₋₁₀ alkyl group;

X represents a hydrogen atom or a fluorine atom;

Y represents an amino group, —SR³, —S(O)_nR⁷, —SCHR³R⁴, —S(O)_nCHR³R⁴, —NHCHR³R⁴, —N(CHR³R⁴)(CHR⁵R⁶), —NHCOR³ or —OCOR⁷ (wherein R³, R⁴, R⁵ and R⁶ are the same or different, and each represents a hydrogen atom, a C₁₋₁₀ alkyl group, a phenyl group, a naphthyl group, a naphthyl group substituted by one to seven halogen atoms, a hetroaromatic group or else represents "a phenyl group substituted by one to five substituents selected from a group consisting of a halogen atom, a phenyl group, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkoxy group and a trifluoromethyl group";

R⁷ represents a C₁₋₁₀ alkyl group, a phenyl group, a naphthyl group, a naphthyl group substituted by one to seven halogen atoms, a hetroaromatic group or else represents "a phenyl group substituted by one to five substituents selected from a group consisting of a halogen atom, a phenyl group, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkoxy group and a trifluoromethyl group", and n represents an integer 1 or 2]

[0007] The terms used in the present specification are defined as follows.

[0008] The C₁₋₁₀ alkyl group means a straight-chain alkyl group having one to ten carbon atoms, a branched chain

alkyl group having three to ten carbon atoms or a cyclic alkyl group having three to ten carbon atoms. Examples of the straight-chain alkyl group include a methyl group, an ethyl group, a propyl group, a butyl group, a pentyl group, a hexyl group, a heptyl group, an octyl group, a nonyl group and a decyl group. Examples of the branched chain alkyl group include an isopropyl group, an isobutyl group, a 1-methylpropyl group, a t-butyl group, a 1-methylbutyl group, a 2-methylbutyl group, a 3-methylbutyl group, a 1-ethylpropyl group, a 1,1-dimethylpropyl group, a 2,2-dimethylpropyl group, a 1,2-dimethylpropyl group, a 1-methylpentyl group, a 2-methylpentyl group, a 3-methylpentyl group, a 4-methylpentyl group, a 1-ethylbutyl group, a 2-ethylbutyl group, a 1,1-dimethylbutyl group, a 1,2-dimethylbutyl group, a 1,3-dimethylbutyl group, a 2,2-dimethylbutyl group, a 2,3-dimethylbutyl group, a 3,3-dimethylbutyl group, a 5-methylhexyl group, a 3-ethylpentyl group, a 1-propylbutyl group, a 1,4-dimethylpentyl group, a 3,4-dimethylpentyl group, a 1,2,3-trimethylbutyl group, a 1-isopropylbutyl group, a 4,4-dimethylpentyl group, a 5-methylheptyl group, a 4-ethylhexyl group, a 2-propylpentyl group, a 2,5-dimethylhexyl group, a 4,5-dimethylhexyl group, a 2-ethyl-3-methylpentyl group, a 1,2,4-trimethylpentyl group, a 2-methyl-1-isopropylbutyl group, a 3-methyloctyl group, a 2,5-dimethylheptyl group, a 1-(1-methylpropyl)-2-methylbutyl group, a 1,4,5-trimethylhexyl group, a 1,2,3,4-tetramethylpentyl group, a 6-methylnonyl group, a 5-ethyl-2-methylheptyl group, a 2,3-dimethyl-1-(1-methylpropyl)butyl group, a cyclopropylmethyl group, a 2-(cyclopropyl)ethyl group, a 3-(cyclobutyl)pentyl group, a cyclopentylmethyl group and a cyclohexylmethyl group. Examples of the cyclic alkyl group include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group.

[0009] The C_{2-10} alkenyl group means a straight-chain alkenyl group with at least one double bond having two to ten carbon atoms or a branched chain alkenyl group with at least one double bond having three to ten carbon atoms or a cyclic alkenyl group with at least one double bond having five to ten carbon atoms, examples of which include a vinyl group, an allyl group, a 3-butenyl group, a 4-pentenyl group, a 5-hexenyl group, a 6-heptenyl group, a 7-octenyl group, a 8-nonenyl group, a 9-decenyl group, a 1-methyl-2-butenyl group, a 2-methyl-2-butenyl group, a 2-methyl-3-butenyl group, a 2-pentenyl group, a 2-methyl-2-hexenyl group and a 2-cyclopentenyl group.

[0010] The C_{2-10} alkynyl group means a straight-chain alkynyl group with at least one triple bond having two to ten carbon atoms or a branched chain alkynyl group with at least one triple bond having four to ten carbon atoms, examples of which include a 2-propynyl group, a 3-butylnyl group, a 4-pentylnyl group, a 5-hexynyl group, a 6-heptylnyl group, a 7-octynyl group, a 8-nonyl group, a 9-decynyl group, a 3-pentylnyl group and a 4-methyl-2-pentylnyl group.

[0011] The C_{1-10} alkyl group substituted by one or two phenyl groups means, for example, a benzyl group, a diphenylmethyl group, a 2-phenylethyl group, a 2-phenylpropyl group, a 1-methyl-1-phenylethyl group or a 1-methyl-2-phenylpentyl group.

[0012] The hydroxy C_{2-10} alkyl group means a C_{2-10} alkyl group substituted by at least one hydroxyl group, examples of which include a 2-hydroxyethyl group, a 3-hydroxypro-

pyl group, a 4-hydroxybutyl group, a 5-hydroxypentyl group, a 6-hydroxyhexyl group, a 7-hydroxyheptyl group, a 8-hydroxyoctyl group, a 9-hydroxynonyl group, a 10-hydroxydecyl group, a 2-hydroxypropyl group, a 2,3-dihydroxypropyl group and a 2-hydroxy-3-methylbutyl group.

[0013] The C_{1-10} alkoxy carbonyl C_{1-10} alkyl group means a alkyl group having one to ten carbons which is substituted by a straight-chain or branched chain alkoxy carbonyl group having one to six carbons, examples of which include a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group, a propyloxycarbonylmethyl group, an isopropoxycarbonylmethyl group, a butyloxycarbonylmethyl group, an isobutoxycarbonylmethyl group, a t-butoxycarbonylmethyl group, a pentyloxycarbonylmethyl group, a hexyloxycarbonylmethyl group, a 2-(ethoxycarbonyl)ethyl group, a 3-(ethoxycarbonyl)propyl group, a 4-(ethoxycarbonyl)butyl group, a 4-(ethoxycarbonyl)pentyl group and a 4-(ethoxycarbonyl)-3-methylpentyl group.

[0014] The amino C_{2-10} alkyl group means a C_{2-6} alkoxy group substituted by at least one amino group, examples of which include a 2-aminoethyl group, a 3-aminopropyl group, a 4-aminobutyl group, a 5-aminobutyl group, a 7-aminoheptyl group, a 2-aminopropyl group and a 2,4-diaminobutyl group.

[0015] The C_{1-10} alkoxy C_{1-10} alkyl group means a alkyl group having one to ten carbons which is substituted by a straight-chain or branched chain alkoxy group having one to ten carbons, examples of which include a 2-methoxyethyl group, a 2-ethoxyethyl group, a 2-propoxyethyl group, a 2-isopropoxyethyl group, a 2-butoxyethyl group, a 2-isobutoxyethyl group, a 2-t-butoxyethyl group, a 2-pentyloxyethyl group, a 2-hexenyloxyethyl group, a 3-ethoxypropyl group, a 4-ethoxybutyl group, a 4-ethoxy-3-methoxybutyl group and a 4-ethoxy-3-methylpentyl group.

[0016] The naphthyl group substituted by one to seven halogen atoms means a naphthyl group substituted by at least one fluorine atom, chloride atom, bromine atom or iodine atom, examples of which include a 1-fluoro-2-naphthyl group, a 2-fluoro-1-naphthyl group, a 1-chloro-2-naphthyl group, a 2-chloro-1-naphthyl group, a 1-bromo-2-naphthyl group, a 2-bromo-1-naphthyl group, a 1-iodo-2-naphthyl group, a 2-iodo-1-naphthyl group, and a 1,3-difluoro-2-naphthyl group.

[0017] The hetroaromatic group means a monocyclic aromatic 5 membered or 6 membered ring containing at least an oxygen atom, a nitrogen atom or a sulfur atom; a monocyclic ring such as above which is fused with a benzene ring; or a hetrocyclic aromatic ring which is fused with one another. Examples of the hetroaromatic group include furyl, pyrrolyl, thiophenyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, benzofuranyl, indolyl, benzothiophenyl, indazolyl, benzoisoxazolyl, benzoisothiazolyl, benzoimidazolyl, benzoisoxazolyl, benzothiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyradinyl, cinnolinyl, phthalazinyl, quinazolinyl and quinoxalinyl.

[0018] The "phenyl group substituted by one to five substituents selected from a group containing a halogen atom, a phenyl group, a C_{1-10} alkyl group, a C_{1-10} alkoxy group and a trifluoromethyl group" means a phenyl group substituted by one to five substituents selected from a fluorine

atom, a chloride atom, a bromine atom, an iodine atom, a phenyl group, a C₁₋₁₀ alkyl group, a C₁₋₁₀ alkoxy group and a trifluoromethyl group, examples of which include a 2-fluorophenyl group, a 3-fluorophenyl group, a 4-fluorophenyl group, a 2-chlorophenyl group, a 3-chlorophenyl group, a 4-chlorophenyl group, a 2-bromophenyl group, a 3-bromophenyl group, a 4-bromophenyl group, a 2-iodophenyl group, a 3-iodophenyl group, a 4-iodophenyl group, a 2-phenylphenyl group, a 3-phenylphenyl group, a 4-phenylphenyl group, a 2-methylphenyl group, a 3-methylphenyl group, a 4-methylphenyl group, a 2-ethylphenyl group, a 3-ethylphenyl group, a 4-ethylphenyl group, a 2-(1-propyl)phenyl group, a 3-(1-propyl)phenyl group, a 4-(1-propyl)phenyl group, a 2-isopropylphenyl group, a 3-isopropylphenyl group, a 4-isopropylphenyl group, a 2-*t*-butylphenyl group, a 3-*t*-butylphenyl group, a 4-*t*-butylphenyl group, a 2-cyclopropylphenyl group, a 3-cyclopropylphenyl group, a 4-cyclopropylphenyl group, a 2-cyclohexylphenyl group, a 3-cyclohexylphenyl group, a 4-cyclohexylphenyl group, a 2-methoxyphenyl group, a 3-methoxyphenyl group, a 4-methoxyphenyl group, a 2-ethoxyphenyl group, a 3-ethoxyphenyl group, a 4-ethoxyphenyl group, a 2-(1-peroxyloxy)phenyl group, a 3-(1-peroxyloxy)phenyl group, a 4-(1-peroxyloxy)phenyl group, a 2-isopropoxyphenyl group, a 3-isopropoxyphenyl group, a 4-isopropoxyphenyl group, a 2-cyclobutylphenyl group, a 3-cyclobutylphenyl group, a 4-cyclobutylphenyl group, a 2-cyclohexylphenyl group, a 3-cyclohexylphenyl group, a 4-cyclohexylphenyl group, a 2-trifluoromethylphenyl group, a 3-trifluoromethylphenyl group, a 4-trifluoromethylphenyl group, a 2,3-difluorophenyl group, a 2,4-difluorophenyl group, a 2,5-difluorophenyl group, a 2,6-difluorophenyl group, a 3,4-difluorophenyl group, a 3,5-difluorophenyl group, a 2,3-dichlorophenyl group, a 2,4-dichlorophenyl group, a 2,5-dichlorophenyl group, a 2,6-dichlorophenyl group, a 3,4-dichlorophenyl group, a 3,5-dichlorophenyl group, a 2,3-dibromophenyl group, a 2,4-dibromophenyl group, a 2,5-dibromophenyl group, a 2,6-dibromophenyl group, a 3,4-dibromophenyl group, a 3,5-dibromophenyl group, a 2,3-diiodophenyl group, a 2,4-diiodophenyl group, a 2,5-diiodophenyl group, a 2,6-diiodophenyl group, a 3,4-diiodophenyl group, a 3,5-diiodophenyl group, a 2,3-dicyanophenyl group, a 2,4-dicyanophenyl group, a 2,5-dicyanophenyl group, a 2,6-dicyanophenyl group, a 3,4-dicyanophenyl group, a 3,5-dicyanophenyl group, a 2,3-diphenylphenyl group, a 2,4-diphenylphenyl group, a 2,5-diphenylphenyl group, a 2,6-diphenylphenyl group, a 3,4-diphenylphenyl group, a 3,5-diphenylphenyl group, a 2,3-dimethylphenyl group, a 2,4-dimethylphenyl group, a 2,5-dimethylphenyl group, a 2,6-dimethylphenyl group, a 3,4-dimethylphenyl group, a 3,5-dimethylphenyl group, a 2,3-diisopropylphenyl group, a 2,4-diisopropylphenyl group, a 2,5-diisopropylphenyl group, a 2,6-diisopropylphenyl group, a 3,4-diisopropylphenyl group, a 3,5-diisopropylphenyl group, a 2,3-di(*t*-butyl)phenyl group, a 2,4-di(*t*-butyl)phenyl group, a 2,5-di(*t*-butyl)phenyl group, a 2,6-di(*t*-butyl)phenyl group, a 3,4-di(*t*-butyl)phenyl group, a 3,5-di(*t*-butyl)phenyl group, a 2,3-dicyclohexylphenyl group, a 2,4-dicyclohexylphenyl group, a 2,5-dicyclohexylphenyl group, a 2,6-dicyclohexylphenyl group, a 3,4-dicyclohexylphenyl group, a 3,5-dicyclohexylphenyl group, a 2,3-dimethoxyphenyl group, a 2,4-dimethoxyphenyl group, a 2,5-dimethoxyphenyl group, a 2,6-dimethoxyphenyl group, a 3,4-dimethoxyphenyl group, a 3,5-dimethoxyphenyl

group, a 2,3-difluoromethylphenyl group, a 2,4-difluoromethylphenyl group, a 2,5-difluoromethylphenyl group, a 2,6-difluoromethylphenyl group, a 3,4-difluoromethylphenyl group, a 3,5-difluoromethylphenyl group, a 2-chloro-3-fluorophenyl group, a 2-chloro-4-fluorophenyl group, a 2-chloro-5-fluorophenyl group, a 2-chloro-6-fluorophenyl group, a 3-chloro-4-fluorophenyl group, a 3-chloro-6-fluorophenyl group, a 5-chloro-2-fluorophenyl group, a 4-chloro-3-fluorophenyl group, a 4-chloro-2-fluorophenyl group, a 3-chloro-2-fluorophenyl group, a 3-bromo-2-chlorophenyl group, a 4-bromo-2-chlorophenyl group, a 5-bromo-2-chlorophenyl group, a 2-bromo-6-chlorophenyl group, a 4-bromo-3-chlorophenyl group, a 3-bromo-5-iodophenyl group, a 4-bromo-2-iodophenyl group, a 4-bromo-3-iodophenyl group, a 3-bromo-2-iodophenyl group, a 2-chloro-3-methylphenyl group, a 2-chloro-4-methylphenyl group, a 2-chloro-5-methylphenyl group, a 2-chloro-6-methylphenyl group, a 3-chloro-4-methylphenyl group, a 3-fluoro-5-methoxyphenyl group, a 5-fluoro-2-methoxyphenyl group, a 4-fluoro-2-methoxyphenyl group, a 3-fluoro-2-methoxyphenyl group, a 2-fluoro-3-trifluoromethylphenyl group, a 2-fluoro-4-trifluoromethylphenyl group, a 2-fluoro-5-trifluoromethylphenyl group, a 2-fluoro-6-trifluoromethylphenyl group, a 3-fluoro-4-trifluoromethylphenyl group, a 2,3,4-trichlorophenyl group, a 2,3,5-trichlorophenyl group, a 2,4,5-trichlorophenyl group, a 2,4,6-trichlorophenyl group, a 3,4,5-trichlorophenyl group, a 2,3,4-tribromophenyl group, a 2,3,5-tribromophenyl group, a 2,4,5-tribromophenyl group, a 2,4,6-tribromophenyl group, a 3,4,5-tribromophenyl group, a 2,3,4-trifluorophenyl group, a 2,3,5-trifluorophenyl group, a 2,4,5-fluorophenyl group, a 2,4,6-trifluorophenyl group, a 3,4,5-trifluorophenyl group, a 2,3,4-triiodophenyl group, a 2,3,5-triiodophenyl group, a 2,4,5-triiodophenyl group, a 2,4,6-triiodophenyl group, a 3,4,5-triiodophenyl group, a 2,3,4-triphenylphenyl group, a 2,3,5-triphenylphenyl group, a 2,4,5-triphenylphenyl group, a 2,4,6-triphenylphenyl group, a 3,4,5-triphenylphenyl group, a 2,3,4-trimethylphenyl group, a 2,3,5-trimethylphenyl group, a 2,4,5-trimethylphenyl group, a 2,4,6-trimethylphenyl group, a 3,4,5-trimethylphenyl group, a 2,3,4-triethylphenyl group, a 2,3,5-triethylphenyl group, a 2,4,5-triethylphenyl group, a 2,4,6-triethylphenyl group, a 3,4,5-triethylphenyl group, a 2,3,4-triisopropylphenyl group, a 2,3,5-triisopropylphenyl group, a 2,4,5-triisopropylphenyl group, a 2,4,6-triisopropylphenyl group, a 3,4,5-triisopropylphenyl group, a 2,3,4-tri(*t*-butyl)phenyl group, a 2,3,5-tri(*t*-butyl)phenyl group, a 2,4,5-tri(*t*-butyl)phenyl group, a 2,4,6-tri(*t*-butyl)phenyl group, a 3,4,5-tri(*t*-butyl)phenyl group, a 2,3,4-trimethoxyphenyl group, a 2,3,5-trimethoxyphenyl group, a 2,4,5-trimethoxyphenyl group, a 2,4,6-trimethoxyphenyl group, a 3,4,5-trimethoxyphenyl group, a 2,3,4-tri(trifluoromethyl)phenyl group, a 2,3,5-tri(trifluoromethyl)phenyl group, a 2,4,5-tri(trifluoromethyl)phenyl group, a 2,4,6-tri(trifluoromethyl)phenyl group, a 3,4,5-tri(trifluoromethyl)phenyl group, a 4-chloro-2,3-difluorophenyl group, a 5-chloro-2,3-difluorophenyl group, a 2-chloro-5,6-difluorophenyl group, a 4-chloro-2,5-difluorophenyl group, a 4-chloro-5,6-difluorophenyl group, a 2-chloro-4,6-difluorophenyl group, a 4-chloro-2,6-difluorophenyl group, a 3-chloro-2,6-difluorophenyl group, a 2-chloro-3,6-difluorophenyl group, a 2-chloro-3,4-difluorophenyl group, a 2-chloro-4,5-difluorophenyl group, a 2-chloro-3,5-difluorophenyl group, a 2,3-dichloro-5,6-difluorophenyl group, a 4,5-dichloro-2,3-dif-

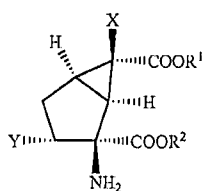
luorophenyl group, a 4,6-dichloro-2,3-difluorophenyl group, a 3,5-dichloro-2,4-difluorophenyl group, a 2,3-dichloro-4,6-difluorophenyl group, a 3,6-dichloro-2,4-difluorophenyl group, a 2,3-dichloro-5,6-dimethylphenyl group, a 4,5-dichloro-2,3-dimethylphenyl group, a 4,6-dichloro-2,3-dimethylphenyl group, a 3,5-dichloro-2,4-dimethylphenyl group, a 2,3-dichloro-4,6-dimethylphenyl group, a 3,6-dichloro-2,4-dimethylphenyl group and a 2,3,4,5,6-pentafluorophenyl group.

[0019] The pharmaceutically acceptable salt of the present invention means, for example, a salt with a mineral acid such as sulfuric acid, hydrochloric acid or phosphoric acid, a salt with an organic acid such as acetic acid, oxalic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, methanesulfonic acid or benzenesulfonic acid, a salt with an amine such as trimethylamine or methylamine, or a salt with a metal ion such as sodium ion, potassium ion or calcium ion.

[0020] The hydrate of the present invention means pharmaceutically acceptable hydrates of the compound of the present invention or their salts. The compound of the present invention and their salts may absorb moisture, accumulate drops of water, or become a hydrate by being exposed to the atmosphere or by recrystallization. The hydrate used in the present invention includes such a hydrate.

[0021] In the compounds represented by formula [I], there are five asymmetric carbon atoms are present in the bicyclo [3.1.0]hexane ring.

[0022] The compounds of the present invention are optically active bodies, and have stereo structure represented by formula [II] below, its enantiomers or enantiomer mixtures such as racemic bodies. The compounds of the present invention include all of these optically active compounds represented by formula [II], the enantiomer mixtures such as racemic bodies, and the diastereomer mixtures.

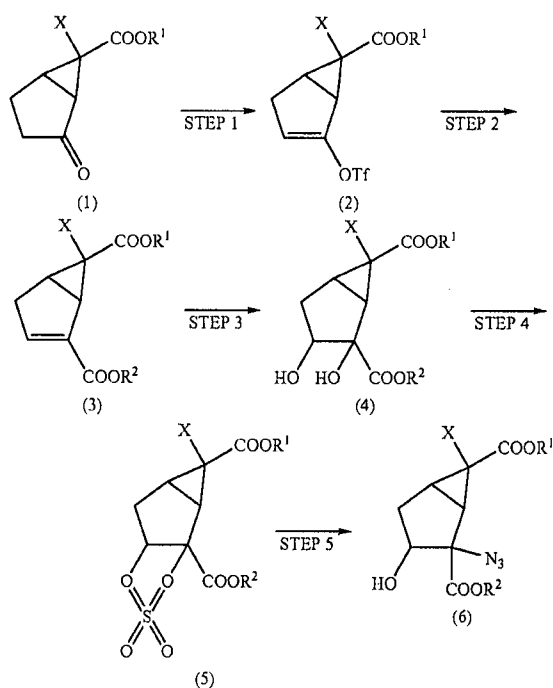


[0023] Notably the derivatives of the present compound in which either one or both of R¹ and R² in formula [I] or [II] are other than a hydrogen atom, in other words ester derivatives has no effect on Group II metabotropic glutamate receptors. However, this ester derivatives are hydrolyzed in vivo and converted into 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives which have a strong antagonistic effect on Group II metabotropic receptors. Therefore, these ester derivatives may be extremely effective compounds useful as prodrugs.

BEST METHOD FOR CARRYING OUT THE INVENTION

[0024] The present invention relates to a compound of the present invention represented by formula [I], a pharmaceutically acceptable salt thereof and a hydrate thereof. Com-

pounds of the present invention represented by formula [I] may be synthesized by means of publicly known methods of organic synthesis, and may be prepared, for example, according to the preparation methods below. Also, synthetic intermediate (6), which is required to synthesize the compounds of the present invention represented by formula [I], may be prepared according to the following method. (In the formulas below, X, Y, n, and R¹ to R⁷ are the same as described above. R⁸ represents an aryl group or alkylsulfonyl group such as a mesyl group, a phenylsulfonyl group, a tosyl group or a trifluoromethylsulfonyl group; a benzoyl group; or a 4-nitrobenzoyl group. R⁹ represents a protecting group for an amino group, examples of which include an alkoxycarbonyl group such as a methoxycarbonyl group, an ethoxycarbonyl group, a t-butoxycarbonyl group or a benzyloxycarbonyl group; an acyl group such as a benzoyl group, a p-phenylbenzoyl group or a (pyridine-2-yl) carbonyl group; an alkyl group such as an allyl group, a benzyl group, a p-methoxybenzyl group or a di(p-methoxyphenyl)methyl group; an alkenyl group such as a 5,5-dimethyl-3-oxo-1-cyclohexenyl group; a sulfenyl group such as a benzenesulfenyl group or a 2,4-dinitrosulfenyl group; a benzylsulfonyl group; a diphenylphosphinyl group; or an alkylphosphoryl group. A¹ represents —R³ or —CHR³R⁴. A² represents —R⁵ or —CHR⁵R⁶. Q represents —SR³, —S(O)ₙR⁷, —SCHR³R⁴ or —S(O)ₙCHR³R⁴).



[0025] Step 1: Compound (2) may be prepared, for example, by reacting compound (1) with a trifluoromethanesulfonylating agent such as trifluoromethanesulfonic acid anhydride or N-phenyl-bis(trifluoromethanesulfonimide), in an inert solvent, in the presence of a base. Compound (1) may be prepared, for example, by means of the method described in "J. Med. Chem. 40, pp. 528-537, (1997)". Examples of the inert solvent include hydrocarbon type

solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; or a mixture of these solvents. Examples of the base include amines such as triethylamine, N-methylmorpholine, diisopropylethylamine and pyridine; inorganic bases such as potassium hydride and sodium hydride; metal amides such as lithium diisopropylamide, potassium bis(trimethylsilyl)amide and lithium bis(trimethylsilyl)azide; and metal alcoholates such as sodium, methoxide and potassium t-butoxide. The reaction temperature of Step 1 is, for example, -78°C . to room temperature. A preferred example of Step (1) is to synthesize compound (2) by reacting compound (1) with N-phenyl-bis(trifluoromethanesulfonimide), in a solvent of tetrahydrofuran, in the presence of lithium hexamethyldisilazane.

[0026] Step 2: Compound (3) may be prepared, for example, by reacting compound (2) with carbon monoxide and R^2OH , in the presence of organic bases such as triethylamine, N-methylmorpholine, diisopropylethylamine and pyridine or in the presence of inorganic bases such as potassium carbonate and sodium hydrogen carbonate, in an inert solvent, in the presence of a transition metal catalyst (see Tetrahedron Letters 26, 1109(1985)). Examples of a transition metal catalyst include a zero-valent palladium reagent, which may be prepared in the reaction system, for example, by using a divalent palladium such as palladium (II) acetate, and a ligand such as triphenylphosphine or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP). It is also possible to directly use a zero-valent palladium reagent such as tetrakis(triphenylphosphine)palladium(0). Examples of the inert solvent include hydrocarbon type solvents such as benzene, toluene and hexane; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; N,N-dimethylformamide; or a mixture of these solvents. Step 2 may be carried out, for example, at room temperature. A preferred example of Step 2 is to synthesize compound (3) by reacting compound (2) with carbon monoxide and R^2OH at room temperature, in N,N-dimethylformamide, in the presence of palladium(II) acetate, diisopropylethylamine and triphenylphosphine.

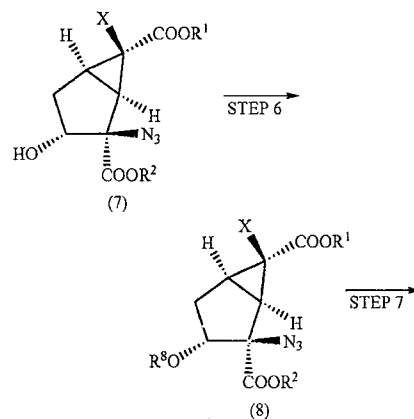
[0027] Step 3: Compound (4) may be prepared by oxidizing compound (3) into diol by means of a common diol-forming reaction with osmium tetroxide, etc (see M. Hudlicky, "Oxidations in Organic Chemistry") or by means of a Sharpless asymmetric cishydroxylation reaction (Sharpless AD) with AD-mix as the reagent (see Tetrahedron Asymmetry 4, 133(1993), J. Org. Chem. 57, 2768(1992), J. Org. Chem. 61, 2582(1996)), in an inert solvent. Examples of the inert solvent include alcohol type solvents such as t-butylalcohol; hydrocarbon type solvents such as benzene, toluene and hexane; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; acetone; N,N-dimethylformamide; water; or a mixture of these solvents. Step 3 may be carried out, for example, at room temperature. A preferred example of Step 3 is to synthesize compound (4) by oxidizing compound (3) into diol with osmium tetroxide at room temperature in a mixture of acetonitrile and water.

[0028] Step 4: Compound (5) may be prepared, for example, by reacting compound (4) with thionyl chloride in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and

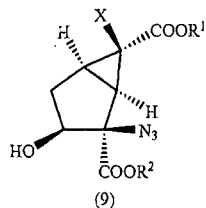
carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile, or a mixture of these solvents, in the presence or absence of organic bases such as triethylamine, N-methylmorpholine, diisopropylethylamine and pyridine or of inorganic bases such as potassium carbonate and sodium hydrogen carbonate, followed by oxidation with a common oxidizing agent such as hydrogen peroxide, OXONE® or ruthenium trichloride-sodium metaperiodate (see M. Hudlicky, "Oxidations in Organic Chemistry") in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane, halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; acetone; water; or a mixture of these solvents. A preferred example of Step 4 is to synthesize compound (5) by reacting compound (4) with thionyl chloride for 0.5 to 2 hours at 0 to 20°C ., in a solvent of dichloromethane, in the presence of triethylamine, followed by oxidation with ruthenium trichloride-sodium metaperiodate as the oxidizing agent, for 0.5 to 2 hours at 0°C . to room temperature, in a mixture of carbon tetrachloride, acetonitrile and water.

[0029] Step 5: Compound (6) may be prepared, for example, by reacting compound (5) with sodium azide in an inert solvent, examples of which include ether type solvents such as tetrahydrofuran; ketones such as acetone; N,N-dimethylformamide; water; or a mixture of these solvents, followed by hydrolysis (see J. Am. Chem. Soc. 110, 7538(1988)). A preferred example of Step 5 is to yield intermediate compound (6) by reacting compound (5) with sodium azide for 1 to 20 hours at room temperature to 50°C ., in a mixture of N,N-dimethylformamide and water, followed by hydrolysis with 20% sulfuric acid for 1 to 2 days, in a mixture of ether and water.

[0030] Compound (9) may be prepared from the obtained synthetic intermediate (6) by inverting the hydroxyl group of compound (7), which has a relative stereo structure represented by formula [II] wherein R^1 and R^2 represents something other than a hydrogen atom, according to Steps 6 and 7 below. Therefore, it is possible to prepare a compound which has the desired relative stereo structure even in the case where the substituent at the 3 position is introduced by means of a stereo inversion on the 3 position carbon atom.



-continued



[0031] Step 6: Compound (8) may be prepared from compound (7) wherein R^1 and R^2 represent something other than a hydrogen atom, for example, by reacting the hydroxyl group of compound (7) with a trifluoromethanesulfonylating agent such as trifluoromethane sulfonic acid anhydride or N-phenyl-bis(trifluoromethanesulfonylimide), or with an alkyl- or aryl sulfonylating agent such as methane sulfonyl chloride, benzene sulfonyl chloride or toluene sulfonyl chloride, in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene, hexane and cyclohexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; amides such as N,N-dimethylformamide and N-methyl-2-pyrrolidinone; dimethylsulfoxide; or a mixture of these solvents, in the presence of inorganic bases such as sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium hydroxide and potassium hydroxide; metal amides such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide and sodium amide; organic bases such as triethylamine, pyridine, diisopropylethylamine, 4-(N,N-dimethylamino)pyridine and 2,6-di-*t*-butylpyridine; bases such as potassium *t*-butoxide. A preferred example of Step 6 is to synthesize compound (8) by reacting compound (7) with trifluoromethane sulfonic acid anhydride for 0.5 to 3 hours at -78°C . to ice-cooled temperature, in a solvent of dichloromethane, in the presence of pyridine.

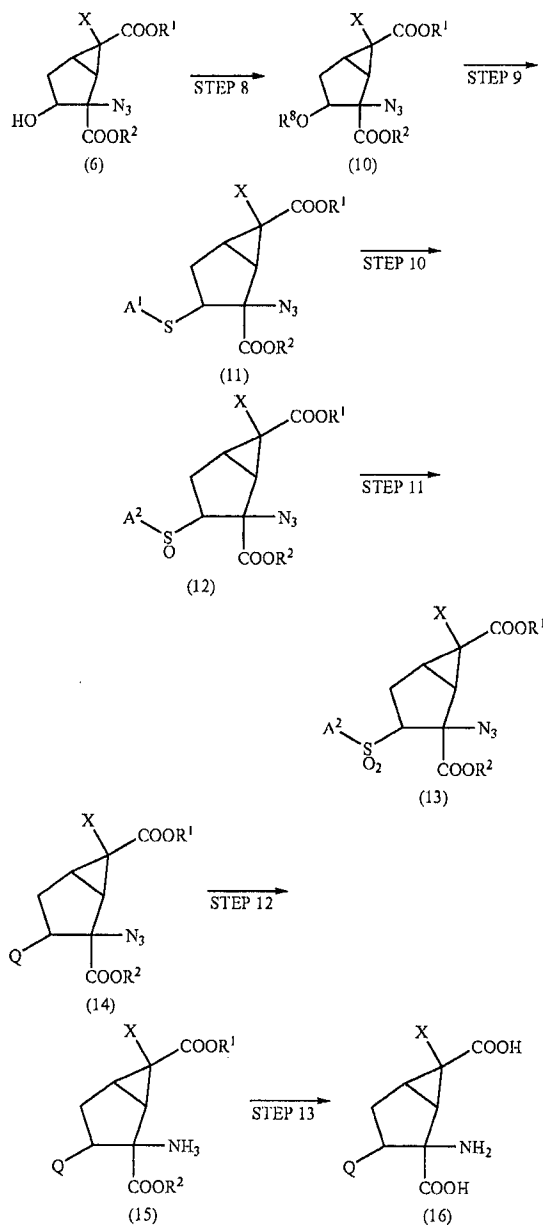
[0032] Step 7: Compound (9) may be prepared, for example, by reacting compound (8) with an alkali hydroxide such as potassium hydroxide or sodium hydroxide; a nitrite salt such as potassium nitrite (see Tetrahedron Lett., 3183 (1975)); or potassium superoxide (see Tetrahedron Lett. 34, 8029 (1993)), in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene, hexane and cyclohexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; amides such as N,N-dimethylformamide, N-methyl-2-pyrrolidinone; alcohol type solvents such as dimethylsulfoxide, methanol and ethanol; water; or a mixture of these solvents, in the presence or absence of crown ether.

[0033] Moreover, it is also possible to prepare compound (9) directly from compound (7) by means of a Mitsunobu reaction with a benzoic acid derivative, in the presence of a dehydrocondensing agent such as diethylazodicarboxylic acid or triphenylphosphine (see D. L. Hughes, OR, 42, 335 (1992)).

[0034] A preferred example of Step 7 is to synthesize compound (9) by reacting compound (8) with potassium

nitrite for 2 to 6 days at room temperature to 45°C ., in N,N-dimethylformamide, in the presence of 18-crown 6-ether.

[0035] Compounds (15) and (16), which are the compounds of the present invention, may be prepared according to Steps 8, 9, 10, 11, 12 and 13 below from synthetic intermediates (6) represented by formula [I] wherein X represents a hydrogen atom or a fluorine atom and Y represents $-\text{SR}^3$, $-\text{S}(\text{O})_n\text{R}^7$, $-\text{SCHR}^3\text{R}^4$ or $-\text{S}(\text{O})_n\text{CHR}^3\text{R}^4$.



X = H, F, Y = SR^3 , $\text{S}(\text{O})_n\text{R}^7$, SCHR^3R^4 , $\text{S}(\text{O})_n\text{CHR}^3\text{R}^4$

[0036] Step 8: Compound (10) may be prepared by means of the same method as the Step 6 by converting the hydroxyl group of compound (6) wherein R^1 and R^2 represent something other than a hydrogen atom. A preferred example of Step 8 is to prepare compound (10) by reacting the hydroxyl group of compound (6) with trifluoromethane sulfonic acid anhydride for 30 minutes to 3 hours at -78°C . to ice-cooled temperature, in dichloromethane, in the presence of pyridine.

[0037] Step 9: Compound (11) may be prepared, for example, by reacting compound (10) with a compound represented by $-A^1\text{SNa}$, $-A^1\text{SK}$, etc, which is prepared from metal alcoholates such as sodium ethoxide and potassium t-butoxide; sodium; potassium; sodium hydride; potassium hydride; and mercaptans or thiophenols represented by $-A^1\text{SH}$, in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; dimethylsulfoxide; N,N -dimethylformamide; or a mixture of these solvents. A preferred example of Step 9 is to prepare compound (11) by reacting compound (10) with a compound represented by $-A^1\text{SNa}$, which is prepared from sodium and a compound represented by $-A^1\text{SH}$, for 10 minutes to 1 hour at room temperature, in dimethylsulfoxide.

[0038] Step 10: Compound (12) may be prepared from compound (11) wherein A^1 represents something other than a hydrogen atom, for example, by means of a common oxidation reaction in which a sulfide is converted into a sulfoxide with sodium periodic acid, peracetic acid, etc (see M. Hudlicky, "Oxidations in Organic Chemistry"), in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; acetone; dimethylsulfoxide; N,N -dimethylformamide; methanol; ethanol; acetic acid; water; or a mixture of these solvents.

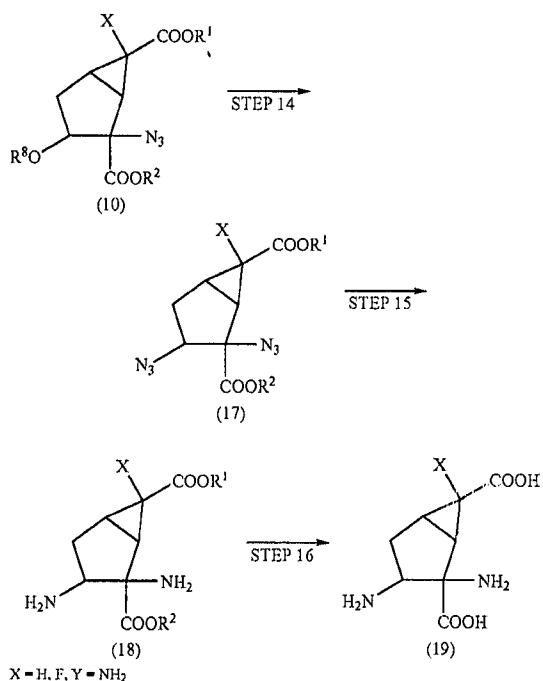
[0039] Step 11: Compound (13) may be prepared from compound (12) or from compound (11) wherein A^1 represents something other than a hydrogen atom, for example, by means of a common oxidation reaction in which a sulfide or a sulfoxide is converted into a sulfone with 3-chloroperbenzoic acid, hydrogen peroxide, etc (see M. Hudlicky, "Oxidations in Organic Chemistry"), in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; acetone; dimethylsulfoxide; N,N -dimethylformamide; water; or a mixture of these solvents. It is also possible to yield a mixture of compound (12) and compound (13) from compound (11) wherein A^1 represents something other than a hydrogen atom, by using a common oxidizing agent such as 3-chloroperbenzoic acid or hydrogen peroxide (see M. Hudlicky, "Oxidations in

Organic Chemistry"), and by controlling the reaction conditions such as the amount, reaction time, reaction temperature and solvent of the oxidizing agent, in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; acetone; dimethylsulfoxide; N,N -dimethylformamide; water; or a mixture of these solvents. A preferred example of Step 11 is to prepare compound (12) and compound (13) by reacting compound (11) with 3-chloroperbenzoic acid for 1 to 24 hours at -78°C . to room temperature, in dichloromethane.

[0040] Step 12: Compound (15) a compound of the present invention, may be prepared from compound (14), for example, by means of a common reduction reaction of an azide group, typical examples of which include: (a) Staudinger reaction with triethyl phosphite, trimethylphosphine, tributyl phosphine, triphenylphosphine, etc (see Bull. Chem. Soc. Fr., 815(1985)), in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; acetone; water; or a mixture of these solvents; (b) hydrogenation in an inert solvent, examples of which include alcohols such as ethanol and methanol; esters such as ethyl acetate; N,N -dimethylformamide; water; or a mixture of these solvents, in the presence of a metal catalyst such as palladium/carbon or palladium black; and (c) hydride reduction with lithium aminoborohydride, etc (see A. F. Abdel-Magid, "Reductions in Organic Synthesis"). A preferred example of Step 12 is to prepare compound (15) by reacting compound (14) by means of a Staudinger reaction with trimethylphosphine for 1 to 2 hours at room temperature, in a mixture of tetrahydrofuran and water.

[0041] Step 13: Compound (16), which is a compound of the present invention, may be prepared from compound (15) wherein at least one of R^1 and R^2 represents something other than a hydrogen atom, for example, by converting the moieties represented by $-\text{COOR}^1$ and $-\text{COOR}^2$ of compound (15) into carboxylic acid by means of a common hydrolysis reaction (see T. W. Greene, P. G. M. Wuts, "Protective Groups in Organic Synthesis"). A preferred example of Step 13 is to prepare compound (16), which is a synthetic intermediate of the compounds of the present invention, by hydrolyzing compound (15) with lithium hydroxide for 5 to 7 days at room temperature to 40°C ., in a mixture of tetrahydrofuran and water. Another preferred example of Step 13 is to prepare compound (16) of the present invention by hydrolyzing compound (15) with 60% sulfuric acid for 1 to 5 days at 100°C . to 150°C .

[0042] Also, compounds (18) and (19), which are compounds of the present invention, may be prepared according to Steps 14, 15 and 16 below from intermediates (10) yielded in Step 8 which are represented by formula [1] wherein X represents a hydrogen atom or a fluorine atom and Y represents $-\text{NH}_2$.



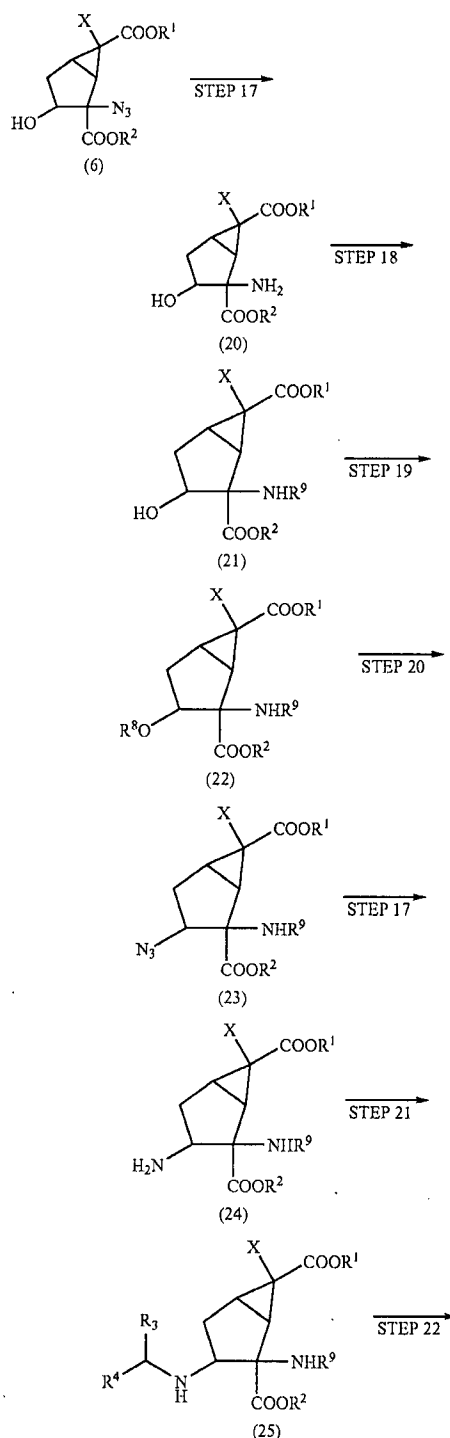
[0043] Step 14: Compound (17) may be prepared by reacting compound (10) with sodium azide in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane; ethyl acetate; acetonitrile; acetone; dimethylsulfoxide; N,N-dimethylformamide; water; or a mixture of these solvents. A preferred example of Step 14 is to prepare compound (17) by reacting compound (10) with sodium azide for 0.5 to 2 hours at room temperature, in N,N-dimethylformamide.

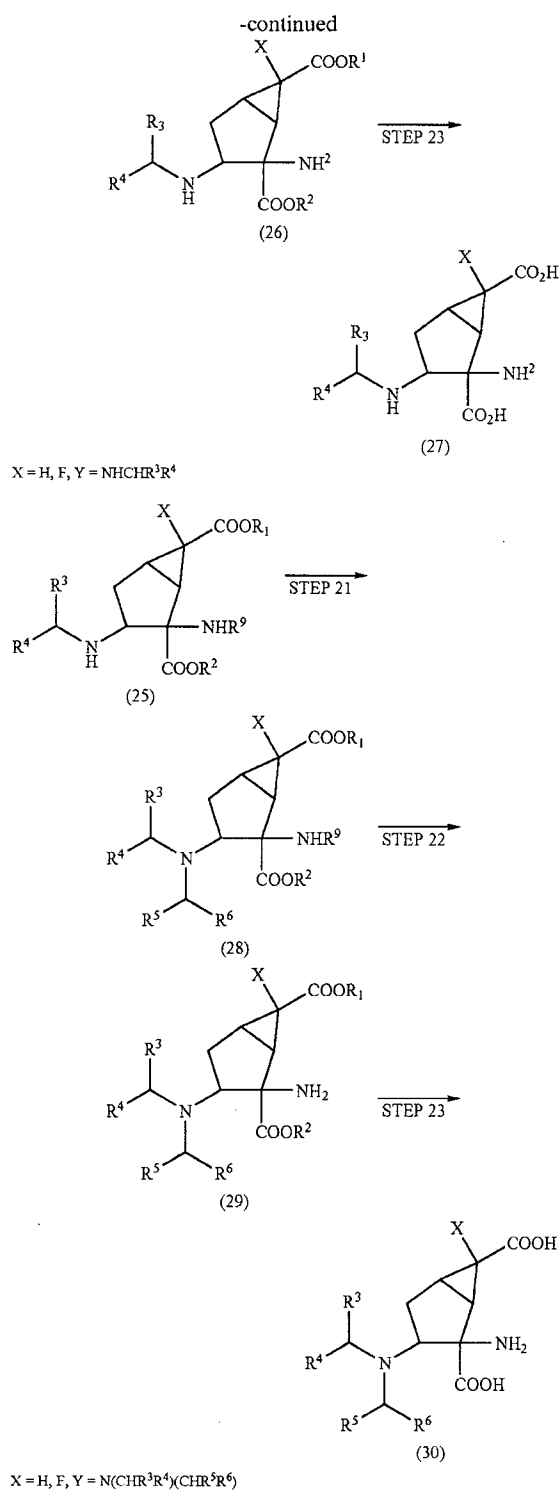
[0044] Step 15: Compound (18), which is a compound of the present invention, may be prepared by hydrolyzing the two azide groups of compound (17) by means of the same method as Step 12. A preferred example of Step 15 is to prepare compound (18) by reacting compound (17) for 1 to 2 days at room temperature, under hydrogen atmosphere, in a mixture of acetic acid and water, in the presence of 10% palladium carbon.

[0045] Step 16: Compound (19), which is a compound of the present invention, may be prepared from compound (18) wherein at least one of R¹ and R² represents something other than a hydrogen atom by hydrolyzing the moieties represented by —COOR¹ and —COOR² of compound (18) by means of the same method as Step 13. A preferred example of Step 16 is to prepare compound (19) of the present invention by hydrolyzing compound (18) with lithium hydroxide for 1 to 7 days at room temperature, in a mixture of tetrahydrofuran and water.

[0046] Compounds (26), (27), (29) and (30), which are the compounds of the present invention, may be prepared from

synthetic intermediate (6) represented by formula [1] wherein X represents a hydrogen atom or a fluorine atom and Y represents —NHCHR³R⁴ or —N(CHR³R⁴)(CHR⁵R⁶), according to Steps 17, 18, 19, 20, 21, 22 and 23 below.





[0047] Step 17: Compounds (20) and (24) may be prepared by reducing the azide groups of compounds (6) and (23), respectively, by means of the same method as Step 12.

A preferred example of Step 17 is to prepare compound (20) and compound (24) by reacting compound (6) and compound (23) by means of a Staudinger reaction with trimethylphosphine for 1 to 12 hours at room temperature, in a mixture of tetrahydrofuran and water.

[0048] Step 18: Compound (21) may be prepared by converting the amino group of compound (20) by means of a common protection reaction of an amino group (see T. W. Greene, P. G. M. Wuts, "Protective Groups in Organic Synthesis"). A preferred example of the protection reaction of an amino group in Step 18 is to prepare compound (21) by reacting compound (20) with di-*t*-butyldicarbonate for 2 to 6 hours at room temperature, in tetrahydrofuran, in the presence of a saturated aqueous solution of sodium hydrogencarbonate.

[0049] Step 19: Compound (22) may be prepared by alkyl- and aryl-sulfonylating the hydroxyl group of compound (21) wherein R¹ and R² represents something other than a hydrogen atom by means of the same method as Step 6. A preferred example of Step 19 is to prepare compound (22) by reacting the hydroxyl group of compound (21) with trifluoromethane sulfonic acid anhydride for 30 minutes to 2 hours at -78° C. to ice-cooled temperature, in dichloromethane, in the presence of pyridine.

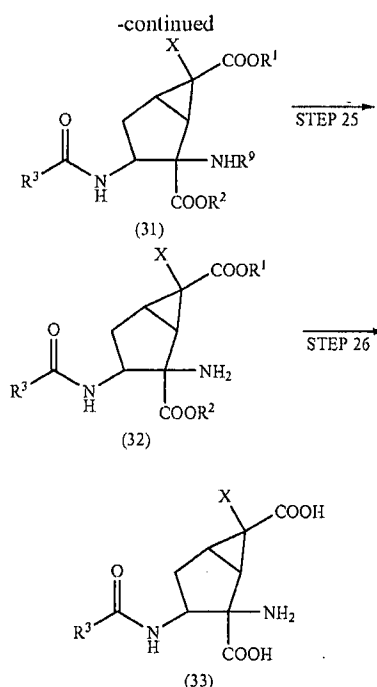
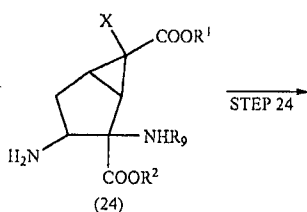
[0050] Step 20: Compound (23) may be prepared, for example, by reacting compound (22) with sodium azide in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; ethyl acetate; acetonitrile; acetone; dimethylsulfoxide; N,N-dimethylformamide; water; or a mixture of these solvents. A preferred example of Step 20 is to prepare compound (23) by reacting compound (22) with sodium azide for 1 to 2 days at room temperature to 35° C., in N,N-dimethylformamide.

[0051] Step 21: Compounds (25) and (28) may be prepared, for example, by reacting the amino groups represented by —NH₂ and —R³R⁴CHNH of compounds (24) and (25), respectively, with a compound represented by R³R⁴CHZ or R⁵R⁶CHZ, in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene, hexane and cyclohexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; amides such as N,N-dimethylformamide and N-methyl-2-pyrrolidinone; dimethylsulfoxide; or a mixture of these solvents, in the presence or absence of inorganic bases such as sodium hydride, potassium hydride, potassium carbonate, sodium carbonate, sodium hydrogen carbonate, sodium hydroxide and potassium hydroxide; metal amides such as lithium bis(trimethylsilyl)amide, lithium diisopropylamide and sodium amide; organic bases such as triethylamine, pyridine, diisopropylethylamine, 4-(N,N-dimethylamino)pyridine and 2,6-di-*t*-butylpyridine; and bases such as potassium *t*-butoxide. In this case, Z represents a leaving group, for example, a halogen atom, tosylsulfonate, trifluoromethanesulfonate or tolylsulfonate. Moreover, it is also possible to prepare compounds (25) and (28), for example, by means of a reductively aminating compounds (24) and (25), respectively, by means of a Borch reaction in which compounds (24) and

(25) are reacted with a compound represented by R^3COR^4 or by R^5COR^6 (see A. F. Abdel-Magid et al., *Tetrahedron Lett.*, 31, 5595 (1990)), in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene, hexane and cyclohexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; amides such as N,N-dimethylformamide and N-methyl-2-pyrrolidinone; dimethylsulfoxide; ethanol; methanol; water; or a mixture of these solvents, in the presence of a reducing agent such as sodium triacetoxy borohydride or sodium cyanotrihydroborate. A preferred example of Step 21 is to prepare compound (25) by reacting compound (24) with a compound represented by R^3R^4CHBr for 1 to 4 days at room temperature, in chloroform, in the presence of pyridine. Another preferred example of Step 21 is to prepare compound (28) by reacting compound (25) with a compound represented by R^5R^6CHI for 1 to 4 days at room temperature, in N,N-dimethylformamide, in the presence of potassium carbonate.

[0052] Step 22: Compounds (26) and (29) may be prepared by deprotecting R^9 , which is the protecting group for the amino group of compound (25) and compound (28), by means of a common deprotection reaction (see T. W. Greene, P. G. M. Wuts, "Protective Groups in Organic Synthesis"), and converting R^9 into an amino group. A preferred example of Step 22 is to prepare compound (26) and compound (29) by deprotecting compound (25) and compound (28) with 4N hydrogen chloride/ethyl acetate for 12 to 36 hours at ice-cooling to room temperature.

[0053] Step 23: Compounds (27) and (30), which are compounds of the present invention, may be prepared from compounds (26) and (29) wherein at least one of R^1 and R^2 represents something other than a hydrogen atom, by hydrolyzing the moieties represented by $COOR^1$ and $COOR^2$ of compounds (26) and (29) by means of the same method as Step 13. A preferred example of Step 23 is to prepare compound (27) and compound (30) of the present invention by hydrolyzing compound (26) and compound (29) with lithium hydroxide for 1 to 7 days at room temperature, in a mixture of tetrahydrofuran and water. Compounds (32) and (33), which are compounds of the present invention, may be prepared from compound (24) represented by formula [I] wherein, X represents a hydrogen atom or a fluorine atom, and Y represents $NHCO R^3$, according to Steps 24, 25 and 26 below.



X = H, F, Y = $NHCO R^3$

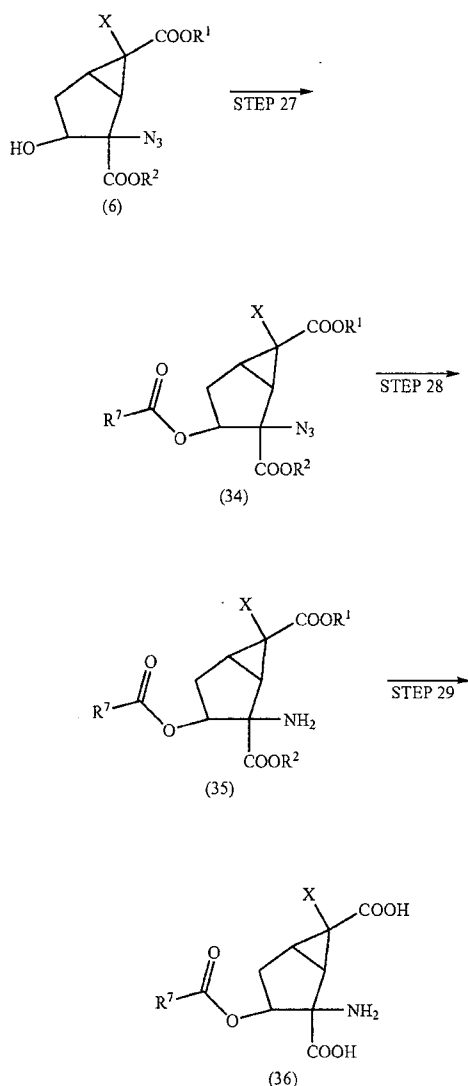
[0054] Step 24: Compound (31) may be prepared, for example, by reacting the 3-position amino group of compound (24) with a compound represented by $ZCOR^7$ or $R^7COOCOR^7$, in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; amides such as N,N-dimethylformamide and N-methyl-2-pyrrolidinone; dimethylsulfoxide; or a mixture of these solvents, in the presence or absence of organic bases such as triethylamine, pyridine, morpholine, diisopropylethylamine, 4-(N,N-dimethylamino)pyridine and 2,6-di-*t*-butylpyridine. In this case, Z represents a leaving group, for example, a halogen atom, an ethoxycarbonyloxy group or a phenoxycarbonyloxy group. Or, in the case where R^3 represents a hydrogen atom, compound (31) may be prepared by means of a common formylation reaction (see T. W. Greene, P. G. M. Wuts, "Protective Groups in Organic Synthesis"). A preferred example of Step 25 is to prepare compound (31) by reacting compound (24) with a compound represented by R^3COCl for 1 to 4 hours at room temperature, in chloroform, in the presence of pyridine.

[0055] Step 25: Compound (32), which is a compound of the present invention, may be prepared from compound (31) by means of the same deprotection reaction of NHR^9 as Step 22. A preferred example of Step 25 is to prepare compound (32) by deprotecting compound (31) with 4N hydrogen chloride/ethyl acetate for 30 minutes to 2 hours at ice-cooled temperature.

[0056] Step 26: Compound (33), which is a compound of the present invention, may be prepared from compound (32) wherein at least one of R^1 and R^2 represents something other

than a hydrogen atom, by means of the same hydrolysis reaction of —COOR^1 and —COOR^2 as Step 13. A preferred example of Step 26 is to prepare compound (33) of the present invention by hydrolyzing compound (32) with lithium hydroxide for 1 to 7 hours at room temperature, in a mixture of tetrahydrofuran and water.

[0057] Compounds (35) and (36) of the present invention may be prepared from synthetic intermediate (6) wherein R^2 represents a benzyl group represented by formula [I] wherein, X represents a hydrogen atom or a fluorine atom and Y represents —OCOR^7 , according to Steps 27, 28 and 29 below.



X = H, F, Y = OCOR⁷, R² = Bn

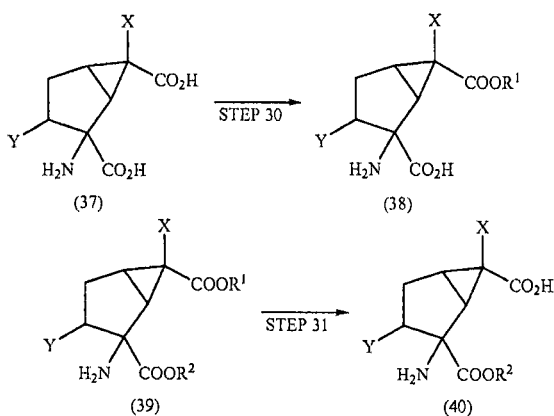
[0058] Step 27: compound (34) may be prepared from compound (6) wherein R^1 represents something other than a hydrogen atom and R^2 represents a benzyl group, for example, by reacting the hydroxyl group of compound (6) with a compound represented by ZCOR^7 or by

$\text{R}^7\text{COOCOR}^7$, in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; amides such as N,N-dimethylformamide and N-methyl-2-pyrrolidinone; dimethylsulfoxide; or a mixture of these solvents, in the presence or absence of organic bases such as triethylamine, pyridine, morpholine, diisopropylethylamine, 4-(N,N-dimethylamino)pyridine and 2,6-di-*t*-butylpyridine. In this case, Z represents a leaving group, for example, a halogen atom, an ethoxycarbonyloxy group or a phenoxycarbonyloxy group. A preferred example of Step 27 is to prepare compound (34) by reacting compound (6) with a compound represented by R^7COCl for 12 to 36 hours at room temperature, in pyridine.

[0059] Step 28: Compound (35), which is a compound of the present invention, may be prepared from compound (34), for example, by yielding an amino body by means of a Staudinger reaction with triethyl phosphite, trimethylphosphine, tributyl phosphine, triphenylphosphine, etc (see Bull. Chem. Soc. Fr., 815(1985)), in an inert solvent, examples of which include hydrocarbon type solvents such as benzene, toluene and hexane; halogen type solvents such as dichloromethane, chloroform and carbon tetrachloride; ether type solvents such as tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane; acetonitrile; acetone; water; or a mixture of these solvents, and then, for example, by further reductively deprotecting the benzyl group of the obtained amino body by means of a hydrogenation reaction in the presence of a metal catalyst such as palladium/carbon or palladium black, in an inert solvent, examples of which include alcohols such as ethanol and methanol; esters such as ethyl acetate; N,N-dimethylformamide; water; or a mixture of these solvents. It is also possible to prepare compound (35) directly from compound (34), for example, by means of a hydrogenation reaction in the presence of a metal catalyst such as palladium/carbon or palladium black, in an inert solvent, examples of which include alcohols such as ethanol and methanol; esters such as ethyl acetate; N,N-dimethylformamide; water; or a mixture of these solvents. A preferred example of Step 28 is to prepare compound (35) as follows: An amine body is prepared by reacting compound (34) by means of a Staudinger reaction with trimethylphosphine for 30 minutes to 2 hours at room temperature, in a mixture of tetrahydrofuran and water. And then compound (35) is prepared by reacting this amine body for 30 minutes to 2 hours at room temperature, in ethanol, in the presence of 5% palladium carbon under hydrogen atmosphere.

[0060] Step 29: Compound (36) of the present invention may be prepared from compound (35) by means of the same method as Step 13. A preferred example of Step 29 is to prepare compound (36) by hydrolyzing compound (35) with lithium hydroxide for 30 minutes to 2 hours at room temperature, in a mixture of tetrahydrofuran and water.

[0061] Also, monoester derivative (38), which is a compound of the present invention, may be prepared from compound (37) of the present invention wherein R^1 and R^2 each represent a hydrogen atom, according to Step 30 below. Moreover, compound (40) of the present invention, which is a monoester derivative, may be prepared from compound (39) wherein R^1 and R^2 each represent something other than a hydrogen atom, according to Step 31 below.



[0062] Step 30: Compound (38), which is a compound of the present invention, may be prepared by esterifying the carboxylic moiety on the 6-position carbon of compound (37) by means of a common esterification reaction (see T. W. Greene, P. G. M. Wuts, "Protective Groups in Organic Synthesis"). A preferred example of Step 30 is to prepare compound (38) of the present invention by reacting compound (37) for 1 to 5 hours at ice-cooling to 50° C., in the presence of R¹OH and thionyl chloride.

[0063] Step 31: Compound (40) of the present invention may be prepared from compound (39) wherein R¹ and R² each represents something other than a hydrogen atom, by converting the moiety represented by —COOR¹ of compound (39) into carboxylic acid by means of a common hydrolysis reaction (see T. W. Greene, P. G. M. Wuts, "Protective Groups in Organic Synthesis"), for a short period of time or at a low temperature. A preferred example of Step 31 is to prepare compound (40) of the present invention by hydrolyzing the moiety represented by —COOR¹ of compound (39) with lithium hydroxide for 30 minutes to 3 hours at 0° C. to room temperature, in a mixture of tetrahydrofuran and water.

[0064] In the present invention, the compound that antagonizes Group II metabotropic glutamate receptors means a compound which shows a concentration-dependant antagonistic effect in a receptor binding test with cells expressing mGluR2 and mGluR3, respectively, by means of the method described in "Mol Pharmacol, 53, 228-233, 1998"; shows the affinity to mGluR2/R3 the same as or higher than that of glutamic acid; and forever shows an antagonistic effect on glutamic acid-induced GTPγS binding, in the GTPγS binding assay. Or, it means a compound which shows an antagonistic effect to the inhibitory action of glutamic acid on the forskolin-stimulated cAMP accumulation.

[0065] The compounds of the present invention may be incorporated into pharmaceutical formulations or pharmaceutical compositions by being combined with one or more pharmaceutically acceptable carriers, excipients or diluents. Examples of the carriers, excipients and diluents include water, lactose, dextrose, fructose, sucrose, sorbitol, mannitol, polyethylene glycol, propylene glycol, starch, gum, gelatin, arginate, calcium silicate, calcium phosphate, cellulose, water syrup, methylcellulose, polyvinyl pyrrolidone,

alkyl parahydroxybenzoate, talc, magnesium stearate, stearic acid, glycerol and oils such as sesame oil, olive oil and soybean oil.

[0066] By means of common formulation procedures the compounds of the present invention may be formulated into drugs for oral or parenteral administrations, in particular, as Group II metabotropic glutamate receptor antagonists, in the form of tablets, pills, capsules, granules, powders, liquids, emulsions, suspensions, ointments, injections and skin plasters by mixing with the above mentioned carriers, excipients or diluents, and, if necessary, further mixing with additives such as commonly used fillers, binders, disintegrants, pH regulators and solubilizers.

[0067] The compounds of the present invention can be administered orally or parenterally to an adult patient in a quantity of 0.01 to 500 mg per day in a single dose or in several doses. Oral administration is preferred from the point of usability and medicinal benefits. The dosage can be increased or decreased as appropriate according to the type of the disease targeted for treatment, and the age, weight and symptoms of the patient.

[0068] In the following are shown examples of the synthesis and the pharmacological tests of the compounds of the present invention in detail. It should be understood that the availability of the compounds of the present invention is not limited to these examples.

REFERENCE EXAMPLE 1

Synthesis of (1R,2R,3R,5R,6R)-2-azido-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester

[0069] (1) 245 mL of a solution of 2.66 M n-butyllithium-hexane was added dropwise to 700 mL of a solution of tetrahydrofuran containing 137 mL of hexamethyldisilazane and stirred for 1 hour at a temperature maintained at -63° C. to -54° C. 340 mL of a solution of tetrahydrofuran containing 101 g of (1R,5R,6R)-6-fluoro-2-oxobicyclo[3.1.0]hexane-6-carboxylic acid ethyl ester was added dropwise thereto at a temperature maintained at -63° C. to -52° C. 700 mL of a solution of tetrahydrofuran containing 213 g of N-phenyl-bis(trifluoromethanesulfonimide) was added thereto 1 hour later at 63° C. to -45° C. The reaction solution was warmed naturally to room temperature and further stirred for 2.5 hours. The reaction solution was diluted with diethyl ether, washed three times with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. After the desiccant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-ethyl acetate=30:1 to 20:1 to 5:1). The obtained 175 g of (1R,5R,6R)-6-fluoro-2-trifluoromethanesulfonyloxybicyclo[3.1.0]hex-2-ene-6-carboxylic acid ethyl ester was dissolved in 875 mL of N,N-dimethylformamide and 875 mL of ethanol, and after 95.1 mL of diisopropylethylamine, 8.65 g of triphenylphosphine and 3.70 g of palladium acetate were added thereto, the mixture was stirred for 5.5 hours at room temperature, under a carbon monoxide atmosphere. 1N hydrochloric acid was added thereto, and the reaction solution was extracted six

times with diethyl ether. The organic layers were combined, washed four times with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. After the desiccant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-ethyl acetate=30:1 to 20:1 to 10:1), thereby yielding 92.6 g of (1R,5R,6R)-6-fluoro-bicyclo[3.1.0]hex-2-ene-2,6-dicarboxylic acid diethyl ester.

[0070] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.31 (t, J=7.0 Hz, 3H), 1.33 (t, J=7.0 Hz, 3H), 2.37-2.51 (m, 1H), 2.65-2.81 (m, 1H), 2.88-3.04 (m, 1H), 3.10 (dd, J=7.5, 2.6 Hz, 1H), 4.12-4.40 (m, 4H), 6.77-6.79 (m, 1H).

[0071] MS(ESI)(Pos)m/z; 265 (M+Na) $^+$

[0072] $[\alpha]_D^{21}=+158.0^\circ$ (CHCl_3 , c=1.5)

[0073] (2) 160 mL of an aqueous solution of 50% N-methylmorpholine N-oxide and 121 mL of an aqueous solution of 4% osmium oxide (VIII) were added to 92.4 g of (1R,5R,6R)-6-fluoro-bicyclo[3.1.0]hex-2-ene-2,6-dicarboxylic acid diethyl ester dissolved in 1.76 L of acetonitrile and 680 mL of water, and the mixture was stirred for 1 hour at room temperature. After sodium sulfite was added thereto at ice-cooled temperature, the reaction solution was stirred for 30 minutes at room temperature and then filtered through celite. A saturated aqueous solution of sodium chloride was added thereto, and the filtrate was extracted twice with ethyl acetate. The organic layers were combined, washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. After the desiccant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel: Wako gel C200, eluent: hexane-ethyl acetate=4:1 to 1:1), thereby yielding 95.6 g of (1R,2S,3R,5R,6R)-6-fluoro-2,3-dihydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0074] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.31 (t, J=7.3 Hz, 6H), 2.03-2.34 (m, 3H), 2.40-2.55 (m, 1H), 2.70 (d, J=9.2 Hz, 1H), 4.09 (s, 1H), 4.18-4.47 (m, 5H).

[0075] MS(ESI)(Nega)m/z; 275 (M-H) $^-$

[0076] $[\alpha]_D^{27}=-69.1^\circ$ (CHCl_3 , c=1.4)

[0077] (3) 106 mL of triethylamine was added to 1.24 L of a solution of dichloromethane containing 95.4 g of (1R,2S,3R,5R,6R)-6-fluoro-2,3-dihydroxybicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester. And after 37.6 mL of thionyl chloride was added dropwise thereto, the mixture was stirred for 30 minutes at ice-cooling. The reaction solution was washed twice with water and with a saturated aqueous solution of sodium chloride, and then dried over anhydrous magnesium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 640 mL of carbon tetrachloride, 640 mL of acetonitrile and 760 mL of water. 96.0 g of sodium metaperiodate and 655 mg of ruthenium trichloride hydrate were added thereto, and the solution was stirred for 1 hour at room temperature. After the mixture was filtered through celite, the filtrate was separated, and the aqueous layer was extracted with diethyl ether. The organic layers were combined, washed with a saturated aqueous solution of

sodium chloride, and then dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel: Wako gel C200, eluent: hexane-ethyl acetate=4:1), thereby yielding 109 g of (1R,1aR,1bS,4aR,5aR)-1-fluoro-3,3-dioxotetrahydro-2,4-dioxo-3

[0078] λ^6 -thiacyclopropa[a]pentalene-1,1b-dicarboxylic acid diethyl ester.

[0079] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.33 (t, J=7.0 Hz, 3H) 1.34 (t, J=7.0 Hz, 3H), 2.52-2.94 (m, 4H), 4.23-4.47 (m, 4H), 5.40-5.53 (m, 1H).

[0080] MS(ESI)(Pos)m/z; 361 (M+Na) $^+$

[0081] $[\alpha]_D^{28}=+18.3^\circ$ (CHCl_3 , c=1.0)

[0082] (4) 37.7 g of sodium azide was added to 109 g of (1R,1aR,1bS,4aR,5aR)-1-fluoro-3,3-dioxotetrahydro-2,4-dioxo-3 λ^6 -thiacyclopropa[a]pentalene-1,1b-dicarboxylic acid diethyl ester dissolved in 1.10 L of N,N-dimethylformamide and 110 mL of water, and the mixture was stirred for 14 hours at 50 $^\circ$ C. The solvent was distilled off under reduced pressure, and after the residue was dissolved in 6.48 L of diethyl ether and 177 mL of water, 516 mL of 20% (V/V) sulfuric acid was added thereto, and the mixture was stirred for 34 hours at room temperature. After the reaction solution was separated, the organic layers were twice washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous magnesium sulfate. After the desiccant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel: Wako gel C200, eluent: hexane-ethyl acetate=4:1), thereby yielding 88.5 g of (1R,2R,3R,5R,6R)-2-azido-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0083] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.33 (t, J=7.0 Hz, 3H), 1.38 (t, J=7.0 Hz, 3H), 2.18-2.61 (m, 5H), 4.21-4.48 (m, 5H).

[0084] MS(ESI)(Pos)m/z; 324 (M+Na) $^+$

[0085] $[\alpha]_D^{22}=-48.7^\circ$ (CHCl_3 , c=1.0)

EXAMPLE 1

Synthesis of (1R,2R,3S,5R,6R)-2-azido-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester

[0086] (1) 48 μL of pyridine and 78 μL of trifluoromethane sulfonic acid anhydride dissolved in 0.4 mL of dichloromethane were added dropwise to 120 mg of (1R,2R,3R,5R,6R)-2-azido-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 20 mL of dichloromethane at -75 $^\circ$ C., and the mixture was stirred for 1.5 hours at ice-cooling under a nitrogen atmosphere. 24 μL of pyridine and 39 μL of trifluoromethane sulfonic acid anhydride dissolved in 0.2 mL of dichloromethane were added dropwise thereto at -75 $^\circ$ C., and the mixture was stirred for 25 minutes at ice-cooling. 10 mL of ether was added thereto, and after the solids were filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel: Wako gel C200, eluent: hexane-ethyl acetate=5:1), thereby

yielding 166 mg of (1R,2R,3R,5R,6R)-2-azido-6-fluoro-3-trifluoromethanesulfonyloxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0087] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm): 1.35 (t, J=7.0 Hz, 3H), 1.38 (t, J=7.0 Hz, 3H), 2.35-2.50 (m, 2H), 2.62-2.86 (m, 2H), 4.31 (q, J=7.0 Hz, 2H), 4.27-4.55 (m, 2H), 4.94-5.10 (m, 1H).

[0088] MS(FAB)(Pos)m/z; 434 (M+H) $^+$

[0089] $[\alpha]_D^{26} = -31.2^\circ$ (CHCl_3 , c=0.4)

[0090] (2) 688 mg of potassium nitrite and 428 mg of 18-crown 6-ether was added to 701 mg of (1R,2R,3R,5R,6R)-2-azido-6-fluoro-3-trifluoromethanesulfonyloxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 6.9 mL of N,N-dimethylformamide, and the mixture was stirred for 1.5 days at room temperature and further stirred for 3.5 days at 45° C., under a nitrogen atmosphere. Water was added thereto, and the mixture was extracted twice with ethyl acetate. The organic layers were combined, washed with a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. After the desiccant was filtered off, the filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel: Wako gel C200, eluent: hexane-ethyl acetate=5:1), thereby yielding 388 mg of (1R,2R,3S,5R,6R)-2-azido-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2,6-diethyl ester.

[0091] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm): 1.34 (t, J=7.0 Hz, 3H), 1.36 (t, J=7.0 Hz, 3H), 2.16 (dd, J=2.9 Hz, 14.9 Hz, 1H), 2.17-2.30 (m, 1H), 2.44 (dd, J=3.1, 8.1 Hz, 1H), 2.61 (dd, J=12.3, 16.0 Hz, 1H), 2.80-2.99 (m, 1H), 4.29 (q, J=7.0 Hz, 2H), 4.34 (q, J=7.0 Hz, 2H), 4.48-4.64 (m, 1H).

[0092] MS(ESI)(Pos)m/z; 324 (M+Na) $^+$

[0093] $[\alpha]_D^{25} = +6.4^\circ$ (CHCl_3 , c=1.0)

EXAMPLE 2

Synthesis of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester, and of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0094] (1) 0.36 mL of trifluoromethane sulfonic acid anhydride dissolved in 1.2 mL of dichloromethane was added dropwise to 364 mg of (1R,2R,3S,5R,6R)-2-azido-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 6.1 mL of dichloromethane and 0.21 mL of pyridine at -77° C. to -69° C., under a nitrogen atmosphere. The mixture was stirred for 30 minutes at -77° C., and further stirred for 30 minutes at ice-cooling. 30 mL of diethyl ether was added thereto, and after the solids were filtered off, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200, eluent: hexane-ethyl acetate=5:1), thereby yielding 487 mg of (1R,2R,3S,5R,6R)-2-azido-6-fluoro-3-trifluoromethanesulfonyloxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0095] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm): 1.36 (t, J=7.0 Hz, 3H), 1.39 (t, J=7.5 Hz, 3H), 2.26-2.63 (m, 3H), 2.91-3.10 (m, 1H), 4.25-4.45 (m, 4H), 5.57 (dd, J=9.0, 2.9 Hz, 1H).

[0096] MS(ESI)(Pos)m/z; 456 (M+Na) $^+$

[0097] $[\alpha]_D^{26} = -41.4^\circ$ (CHCl_3 , c=1.1)

[0098] (2) 2.59 g of 3,4-dichlorobenzylmercaptan was added to 308 mg of sodium dissolved in 18 mL of ethanol, and the mixture was stirred for 5 minutes at room temperature under a nitrogen atmosphere, and then concentrated under reduced pressure. 64 mL of dimethylsulfoxide was added to the residue, and after 3.23 g of (1R,2R,3S,5R,6R)-2-azido-6-fluoro-3-trifluoromethanesulfonyloxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 6.4 mL of dimethylsulfoxide was added thereto, the mixture was stirred for 10 minutes at room temperature. 250 mL of diethyl ether was added thereto, and the upper and lower layers were separated. The lower layer was extracted twice with diethyl ether. The organic layers were combined, washed with cold 1N hydrochloric acid and with a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-ethyl acetate=10:1 to 5:1), thereby yielding 3.35 g of (1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0099] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm): 1.34 (t, J=7.0 Hz, 3H), 1.38 (t, J=7.0 Hz, 3H), 2.20-2.49 (m, 4H), 2.99-3.13 (m, 1H), 3.68 (d, J=13.6 Hz, 1H), 3.84 (d, J=13.6 Hz, 1H), 4.22-4.51 (m, 4H), 7.16 (dd, J=8.1, 2.0 Hz, 1H), 7.34-7.46 (m, 2H).

[0100] MS(ESI)(Pos)m/z; 498 (M+Na) $^+$

[0101] $[\alpha]_D^{24} = +129.9^\circ$ (CHCl_3 , c=0.5)

[0102] (3) 7.7 mL of a solution of 1M trimethylphosphine/tetrahydrofuran was added to 3.35 g of (1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 100 mL of tetrahydrofuran and 10 mL of water, and the mixture was stirred for 1 hour at room temperature. The mixture was diluted with 200 mL of diethyl ether, and after 50 mL of a saturated aqueous solution of sodium hydrogen carbonate was added thereto, the mixture was stirred for 1.5 hours at room temperature. After separation, the organic layers were washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was diluted with chloroform, and then silica gel (Wako gel C200 (made by Wako Pharmaceutical Industries Ltd.)) was added thereto. The mixture was concentrated under reduced pressure, left to stand for 18 hours at room temperature, and then purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-ethyl acetate=2:1), thereby yielding 2.78 g of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0103] (4) 12 mg of lithium hydroxide hydrate was added to 41 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 0.8 mL of tetrahydrofuran and 0.4 mL of water, and the mixture was stirred for 5.5 days at

room temperature. The mixture was adjusted to pH=3 with 1N hydrochloric acid in an ice bath. After 30 mL of water was added thereto, the mixture was stirred for 1 hour at room temperature and then purified by ion exchange resin (AG 50W-X8 Resin (H form), eluent: water, a 40% aqueous solution of tetrahydrofuran, a 10% aqueous solution of pyridine), and the obtained solids were further washed with tetrahydrofuran, thereby yielding 25 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

EXAMPLE 3

Synthesis of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester, and of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0104] (1) 32 mg of 3-chloroperbenzoic acid was added to 73 mg of (1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 1.46 mL of dichloromethane and the mixture was stirred for 1 hour in a dry ice-acetone bath. The mixture was stirred for 3.5 hours in an ice bath, and further stirred for 11 hours at room temperature. 15 mg of 3-chloroperbenzoic acid was further added thereto, and the mixture was stirred for 1 hour in a dry ice-acetone bath, and then stirred for 4 hours in an ice bath. The reaction solution was washed with a saturated aqueous solution of sodium hydrogen carbonate and with a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-ethyl acetate=4:1 to 2:1), thereby yielding 63 mg of (1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester and 12 mg of (1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

(1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester

[0105] ¹H-NMR(200 MHz, CDCl₃)δ(ppm); 1.36 (t, J=7.0 Hz, 3H), 1.38 (t, J=7.0 Hz, 3H), 2.33 (dd, J=14.1, 8.4 Hz, 1H), 2.43-2.61 (m, 2H), 2.80-2.97 (m, 1H), 3.11-3.24 (m, 1H), 3.79 (d, J=13.2 Hz, 1H), 4.09 (d, J=13.2 Hz, 1H), 4.25-4.43 (m, 4H), 7.17 (dd, J=8.4, 2.2 Hz, 1H), 7.40-7.50 (m, 2H).

[0106] MS(ESI)(Pos) m/z; 514 (M+Na)⁺

[0107] [α]_D²⁸=+36.0° (CHCl₃, c=0.5)

(1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester

[0108] ¹H-NMR(200 MHz, CDCl₃)δ(ppm); 1.36 (t, J=7.0 Hz, 3H), 1.39 (t, J=7.0 Hz, 3H), 2.33-2.58 (m, 3H), 2.86-3.05 (m, 1H), 3.53 (dd, J=11.2, 8.1 Hz, 1H), 4.24-4.46 (m, 6H), 7.28 (dd, J=8.4, 2.2 Hz, 1H), 7.44-7.56 (m, 2H).

[0109] MS(ESI)(Pos)m/z; 530 (M+Na)⁺

[0110] [α]_D²⁹=+7.9° (CHCl₃, c=0.7)

[0111] (2) By means of the same method as Example 2 (3), 41 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester was yielded from 61 mg of (1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0112] (3) By means of the same method as Example 2 (4), 17 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid was yielded from 38 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

EXAMPLE 4

Synthesis of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid and of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0113] By means of the same method as Example 2 (3), 169 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester was yielded from 190 mg of (1R,2S,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0114] (2) 108 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester was stirred in 1.08 mL of 60% sulfuric acid (W/V %) for 3 days at 130° C. The reaction solution was ice-cooled and then neutralized in an aqueous solution of 5N sodium hydroxide. The mixture was stirred for 1 hour at room temperature and then purified by ion exchange resin (AG 50W-X8 Resin (H form), eluent: water, a 30% aqueous solution of tetrahydrofuran and a 10% aqueous solution of pyridine), thereby yielding 76 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfonyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

EXAMPLE 5

Synthesis of (1R,2R,3R,5R,6R)-2,3-diamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester and of (1R,2R,3R,5R,6R)-2,3-diamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0115] 56 mg of sodium azide was added to 250 mg of (1R,2R,3S,5R,6R)-2-azido-6-fluoro-3-trifluoromethanesulfonyloxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 5 mL of N,N-dimethylformamide, and the mixture was stirred for 30 minutes at room temperature. After 100 mL of diethyl ether was added to the reaction solution, this ether solution was washed four times with water and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-

ethyl acetate=10:1), thereby yielding 175 mg of (1R,2R,3R,5R,6R)-2,3-diazido-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0116] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.34 (t, J=7.0 Hz, 3H), 1.40 (t, J=7.0 Hz, 3H), 2.25-2.57 (m, 4H), 3.94-4.04 (m, 1H), 4.24-4.45 (m, 4H).

[0117] MS(ESI)(POS)m/z; 349 (M+Na) $^+$

[0118] $[\alpha]_D^{26}=+32.7^\circ$ (CHCl_3 , c=0.59)

[0119] 25 mg of 10% palladium carbon was added to 170 mg of (1R,2R,3R,5R,6R)-2,3-diazido-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in a mixture of 15 mL of acetic acid and 5 mL of water, and the mixture was stirred for 24 hours at room temperature under a hydrogen atmosphere. After celite filtration, the solvent was distilled off at 50° C. under reduced pressure, thereby yielding 42 mg of (1R,2R,3R,5R,6R)-2,3-diamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0120] (3) By means of the same method as Example 2 (4), 14 mg of (1R,2R,3R,5R,6R)-2,3-diamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid was yielded from 42 mg of (1R,2R,3R,5R,6R)-2,3-diamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-ethyl ester.

EXAMPLE 6

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester and of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0121] (1) 0.89 mL of a solution of 1M trimethylphosphine/tetrahydrofuran was added to 245 mg of (1R,2R,3S,5R,6R)-2-azido-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 7.0 mL of tetrahydrofuran and 0.7 mL of water, and the mixture was stirred for 12 hours at room temperature. After the mixture was diluted with 14 mL of diethyl ether, a saturated aqueous solution of sodium hydrogen carbonate was added thereto, and the mixture was stirred for 1 hour at room temperature. After separation, the aqueous layer was extracted twice with chloroform. The organic layers were combined, washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: chloroform-ethanol=50:1), thereby yielding 163 mg of (1R,2R,3S,5R,6R)-2-amino-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0122] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.32 (t, J=7.3 Hz, 6H), 2.07-2.23 (m, 2H), 2.41 (dd, J=8.1, 3.3 Hz, 1H), 2.71-2.91 (m, 1H), 4.10-4.41 (m, 5H).

[0123] MS(ESI)(Pos) m/z; 276 (M+H) $^+$

[0124] $[\alpha]_D^{25}=+2.8^\circ$ (CHCl_3 , c=1.5)

[0125] (2) 0.8 mL of a saturated aqueous solution of sodium hydrogen carbonate and 152 mg of di-*t*-butyldicarbonate were added to 160 mg of (1R,2R,3S,5R,6R)-2-amino-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 0.8 mL of tetrahydrofuran, and the mixture was stirred for 4 hours, at room temperature. The reaction solution was extracted twice with ethyl acetate. The organic layers were combined, washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-ethyl acetate=2:1), thereby yielding 214 mg of (1R,2R,3S,5R,6R)-2-*t*-butoxycarbonylamino-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0126] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.29 (t, J=7.0 Hz, 3H), 1.30 (t, J=7.0 Hz, 3H), 1.44 (s, 9H), 2.20-2.48 (m, 3H), 2.77-2.98 (m, 2H), 4.07-4.48 (m, 5H), 5.57 (s, 1H).

[0127] MS(ESI)(Pos)m/z; 398 (M+Na) $^+$

[0128] $[\alpha]_D^{22}=-14.0$ (CHCl_3 , c=0.9)

[0129] (3) By means of the same method as Example 2 (1), 1.65 g of (1R,2R,3S,5R,6R)-2-*t*-butoxycarbonylamino-6-fluoro-3-trifluoromethanesulfonyloxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester was yielded from 1.47 g of (1R,2R,3S,5R,6R)-2-*t*-butoxycarbonylamino-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0130] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.25-1.41 (m, 6H), 1.44 (s, 9H), 2.13-2.26 (m, 1H), 2.40-2.57 (m, 2H), 2.97-3.20 (m, 1H), 4.14-4.47 (m, 4H), 5.32 (s, 1H), 5.99 (d, J=8.4 Hz, 1H).

[0131] MS(ESI)(Nega)m/z; 506 (M-H) $^-$

[0132] $[\alpha]_D^{28}=+79.8^\circ$ (CHCl_3 , c=0.5)

[0133] (4) 313 mg of sodium azide was added to 1.63 g of (1R,2R,3S,5R,6R)-2-*t*-butoxycarbonylamino-6-fluoro-3-trifluoromethanesulfonyloxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 16.3 mL of *N,N*-dimethylformamide, and the mixture was stirred for 1 hour at room temperature, and then for 20 hours at 35° C. After 104 mg of sodium azide was further added thereto, the mixture was stirred for 18 hours at 35° C. The mixture was diluted with 50 mL of diethyl ether, and then washed twice with water and with a saturated aqueous solution of sodium chloride. The organic layers were dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-ethyl acetate=5:1), thereby yielding 775 mg of (1R,2R,3R,5R,6R)-3-azido-2-*t*-butoxycarbonylamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0134] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.29 (t, J=7.0 Hz, 3H), 1.33 (t, J=7.0 Hz, 3H), 1.45 (s, 9H), 2.21-2.56 (m, 3H), 2.92 (dd, J=7.7, 2.4 Hz, 1H), 3.78-3.88 (m, 1H), 4.17-4.41 (m, 4H), 5.01 (s, 1H).

[0135] MS(ESI)(Pos) m/z; 423 (M+Na)

[0136] $[\alpha]_D^{26}=+0.79^\circ$ (CHCl_3 , c=1.4)

[0137] (5) By means of the same method as Example 6 (1), 553 mg of (1R,2R,3R,5R,6R)-3-amino-2-t-butoxycarbonylamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester was yielded from 725 mg of (1R,2R,3R,5R,6R)-3-azido-2-t-butoxycarbonylamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0138] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.30 (t, J=7.0 Hz, 3H), 1.32 (t, J=7.0 Hz, 3H), 1.44 (s, 9H), 2.06-2.27 (m, 2H), 2.40-2.55 (m, 1H), 2.61-2.72 (m, 1H), 3.28-3.47 (m, 1H), 4.17-4.41 (m, 4H), 5.05 (s, 1H).

[0139] MS(ESI)(Pos) m/z; 397 (M+Na) $^+$

[0140] $[\alpha]_D^{27} = -14.2^\circ$ (CHCl_3 , c=1.4)

[0141] (6) 42 μL of pyridine and 123 mg of 3,4-dichlorobenzylbromide were added to 175 mg of (1R,2R,3R,5R,6R)-3-amino-2-t-butoxycarbonylamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 0.88 mL of chloroform at ice-cooling, and then the mixture was stirred for 3 days at room temperature. A saturated aqueous solution of sodium chloride was added thereto, and the mixture was extracted five times with chloroform. The organic layers were combined and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: chloroform-ethanol=100:1 to 50:1, followed by hexane-ethyl acetate=5:1), thereby yielding 98 mg of (1R,2R,3R,5R,6R)-2-t-butoxycarbonylamino-3-(3,4-dichlorobenzylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0142] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.23-1.34 (m, 6H), 1.44 (s, 9H), 2.03-2.26 (m, 2H), 2.43 (dd, J=13.0, 7.3 Hz, 1H), 2.83-2.93 (m, 1H), 3.02-3.15 (m, 1H), 3.71 (d, J=13.2 Hz, 1H), 3.80 (d, J=13.2 Hz, 1H), 4.12-4.39 (m, 4H), 4.82 (s, 1H), 7.11 (dd, J=8.1, 2.0 Hz, 1H), 7.33-7.45 (m, 2H).

[0143] MS(ESI)(Nega)m/z; 531 (M-H) $^-$

[0144] $[\alpha]_D^{27} = -15.1^\circ$ (CHCl_3 , c=0.5)

[0145] (7) 2.8 mL of a solution of 4N hydrogen chloride/ethyl acetate was added to 28 mg of (1R,2R,3R,5R,6R)-2-t-butoxycarbonylamino-3-(3,4-dichlorobenzylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester, and the mixture was stirred for 6 hours at ice-cooling and further stirred for 18 hours at room temperature. The reaction solution was ice-cooled and then neutralized with a saturated aqueous solution of sodium hydrogen carbonate, followed by separation. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, washed with a saturated aqueous solution of sodium chloride and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure, thereby yielding 21 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0146] (8) By means of the same method as Example 2 (4), 17 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid was yielded from 28 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

EXAMPLE 7

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester and of (1R,2R,3R,5R,6R)-2-amino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0147] (1) 71 mg of potassium carbonate and 64 μL of methyl iodide were added to 136 mg of (1R,2R,3R,5R,6R)-2-t-butoxycarbonylamino-3-(3,4-dichlorobenzylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in 1.36 mL of N,N-dimethylformamide, and the mixture was stirred for 3 days at room temperature. A saturated aqueous solution of sodium thiosulfate was added thereto, and the mixture was extracted twice with ethyl acetate. The organic layers were combined, washed with a saturated aqueous solution of sodium chloride, and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: hexane-ethyl acetate=5:1), thereby yielding 126 mg of (1R,2R,3R,5R,6R)-2-t-butoxycarbonylamino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0148] $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ (ppm); 1.28 (t, J=7.0 Hz, 3H), 1.29 (t, J=7.0 Hz, 3H), 1.43 (s, 9H), 2.11 (s, 3H), 2.16-2.58 (m, 3H), 2.80-3.07 (m, 2H), 3.29 (d, J=13.6 Hz, 1H), 3.78 (d, J=13.6 Hz, 1H), 4.05-4.43 (m, 4H), 4.86 (s, 1H), 7.08 (dd, J=8.4, 1.8 Hz, 1H), 7.31-7.41 (m, 2H).

[0149] MS(ESI)(Pos)m/z; 547 (M+H) $^+$

[0150] $[\alpha]_D^{25} = -51.9^\circ$ (CHCl_3 , c=0.5)

[0151] (2) By means of the same method as Example 6 (7), 96 mg of (1R,2R,3R,5R,6R)-2-amino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester was yielded from 124 mg of (1R,2R,3R,5R,6R)-2-t-butoxycarbonylamino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0152] (3) By means of the same method as Example 2 (4), 62 mg of (1R,2R,3R,5R,6R)-2-amino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid was yielded from 94 mg of (1R,2R,3R,5R,6R)-amino-3-[(3,4-dichlorobenzyl)methylamino]-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

EXAMPLE 8

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester and of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0153] (1) 7.3 μL of pyridine and 14 mg of 3,4-dichlorobenzoyl chloride were added to 17 mg of (1R,2R,3R,5R,6R)-3-amino-2-t-butoxycarbonylamino-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved

in 0.17 mL of chloroform, and the mixture was stirred for 3 hours at room temperature. The reaction solution was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200 (made by Wako Pure Chemical Industries Ltd.), eluent: chloroform-ethanol=100:1), thereby yielding 21 mg of (1R,2R,3R,5R,6R)-2-t-butoxycarbonylamino-3-(3,4-dichlorobenzoylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0154] ¹H-NMR(200 MHz, CDCl₃)δ(ppm); 1.19 (t, J=7.0 Hz, 3H), 1.31 (t, J=7.3 Hz, 3H), 1.41 (s, 9H), 2.21-2.64 (m, 3H), 2.82-2.91 (m, 1H), 4.07-4.37 (m, 4H), 4.58-4.75 (m, 1H), 6.20 (s, 1H), 6.39-6.50 (m, 1H), 7.46-7.57 (m, 2H), 7.80-7.85 (m, 1H).

[0155] MS(ESI)(Neg)m/z; 545 (M-H)⁻

[0156] [α]_D²⁵=+12.1 (CDCl₃, c=0.9)

[0157] (2) By means of the same method as Example 6 (7), 85 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester was yielded from 107 mg of (1R,2R,3R,5R,6R)-2-t-butoxycarbonylamino-3-(3,4-dichlorobenzoylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

[0158] (3) By means of the same method as Example 2 (4), 24 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid was yielded from 48 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester.

EXAMPLE 9

Synthesis of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester and of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid

[0159] (1) 234 mg of 3,4-dichlorobenzoyl chloride was added to 202 mg of (1R,2R,3R,5R,6R)-2-azido-6-fluoro-3-hydroxy-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester dissolved in 3.7 mL of pyridine, and the mixture was stirred for 28 hours at room temperature, under a nitrogen atmosphere. After 100 mL of ethyl acetate was added to the reaction solution, this ethyl acetate solution was washed with a saturated aqueous solution of copper sulfate and with water, and then dried over anhydrous sodium sulfate. The desiccant was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel: Wako gel C200, eluent: hexane-ethyl acetate=10:1), thereby yielding 298 mg of (1R,2R,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzoyloxy)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester.

[0160] ¹H-NMR(200 MHz, CDCl₃)δ(ppm); 1.35 (t, J=7.3 Hz, 3H), 2.35-2.55 (m, 3H), 2.77-2.87 (m, 1H), 4.31 (q, J=7.3 Hz, 2H), 5.24-5.46 (m, 3H), 7.28-7.60 (m, 6H), 7.90-8.20 (m, 2H).

[0161] MS(ESI)(Pos)m/z; 558 (M+Na)⁺

[0162] (2) By means of the same method as Example 2 (3), 218 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester was yielded from 298 mg of (1R,2R,3R,5R,6R)-2-azido-3-(3,4-dichlorobenzoyloxy)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester.

[0163] (3) 15 mg of 5% palladium carbon was added to 218 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester dissolved in 10 mL of ethanol, and the mixture was stirred for 50 minutes at room temperature, under a hydrogen atmosphere. After the palladium carbon was filtered through celite, the filtrate was concentrated under reduced pressure, and the obtained solids were dissolved in a mixture of 2 mL of tetrahydrofuran and 1 mL of water. 10 mg of lithium hydroxide monohydrate was added to this solution, and the mixture was stirred for 30 minutes at ice-cooling. After 0.5 mL of 1N hydrochloric acid was added thereto at ice-cooling, the mixture was diluted with 50 mL of water and then purified by ion exchange resin (AG 50W-X8 Resin (H form), eluent: water, an aqueous solution of 40% tetrahydrofuran and an aqueous solution of 10% pyridine), thereby yielding 25 mg of (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

EXAMPLE 10

Synthesis of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-benzyl ester

[0164] (1) 19 μL of thionyl chloride was added to 26 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid suspended in 0.3 mL of benzyl alcohol at ice-cooling, and then the mixture was stirred for 3.5 hours at 50° C. After standing to cool, the reaction solution was concentrated under reduced pressure, and the residue was purified by reverse phase column chromatography (Wako gel 50C18 (Wako Pharmaceutical Industries Ltd.), eluent: water to an aqueous 70% solution of acetonitrile), thereby yielding 5 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-benzyl ester. 2.19-2.43 (3H, m), 2.47-2.63 (1H, m), 2.96-3.12 (1H, m), 3.75 (1H, d, J=13.2 Hz), 3.81 (1H, d, J=13.2 Hz), 5.22 (2H, s), 7.23-7.54 (8H, m)

[0165] MS(ESI)(Neg)a 482 (M-H)⁻

EXAMPLE 11

Synthesis of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-ethyl ester

[0166] 17 mg of lithium hydroxide monohydrate was added to 150 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester dissolved in a mixture of 3.5 mL tetrahydrofuran and 1.7 mL of water, and the mixture was stirred for 30 minutes at ice-cooling. The mixture was acidified to pH 2 with 1N hydrochloric acid, diluted with 30 mL of water, and then stirred for 30 minutes at ice-cooling. This diluted solution was purified by ion exchange resin (AG 50W-X8 Resin (H form), eluent: water, a 30% aqueous

solution of tetrahydrofuran and a 10% aqueous solution of pyridine), thereby yielding 73 mg of (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluoro-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-ethyl ester.

[0167] The structure and physical data of the compounds described in Examples 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11, as well as those of compounds obtained by means of the same methods are shown in table 1 below.

TABLE 1

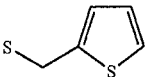
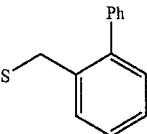
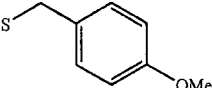
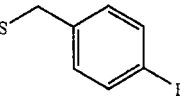
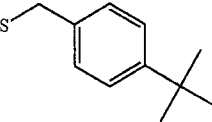
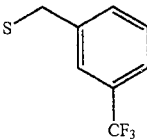
The structure and property data of the compounds obtained in the Examples									
Compound				Y	NMR	MS	Specific rotatory power	m.p. (° C.)	Example
No.	X	R ¹	R ²						
1	F	H	H		(300 MHz, D ₂ O, TMSP) 2.16–2.32(m, 2 H) 2.41–2.50(m, 2H) 3.06–3.18(m, 1H) 4.07(s, 2H) 6.97–7.10(m, 2H) 7.35–7.43(m, 1H)	ESI (Nega) 330 (M – H) [–]	[α] _D ²⁵ +38.7(C = 0.35 1N NaOH)	>230	2
2	F	H	H		(300 MHz, D ₂ O, TMSP) 2.08–2.35(m, 4H) 2.87–3.00(m, 1H) 3.78–4.01(m, 2H) 7.26–7.62(m, 9H)	ESI (Nega) 400 (M – H) [–]	[α] _D ²⁴ +49.3(C = 0.21 1N NaOH)	>230	2
3	F	H	H		(300 MHz, D ₂ O, TMSP) 2.16–2.42(m, 4H) 3.03–3.13(m, 1H) 3.77–3.87(m, 5H) 7.00(d, J=8.7 Hz, 2H) 7.35(d, J=8.7 Hz, 2H)	ESI (Nega) 354 (M – H) [–]	[α] _D ²⁶ +31.0(C = 0.48 1N NaOH)	>240	2
4	F	H	H		(300 MHz, D ₂ O, TMSP) 2.13–2.54(m, 4H) 2.97–3.19(m, 1H) 3.84(s, 2H) 7.03–7.29(m, 2H) 7.33–7.55(m, 2H)	ESI (Nega) 342 (M – H) [–]	[α] _D ²⁵ +25.4(C = 0.20 1N NaOH)	>243	2
5	F	H	H		(300 MHz, D ₂ O, TMSP) 1.31(s, 9H) 2.20–2.47(m, 4H) 3.06–3.20(m, 1H) 3.83(s, 2H) 7.32–7.40(m, 2H) 7.46–7.56(m, 2H)	ESI (Nega) 380 (M – H) [–]	[α] _D ²⁶ –1.14(C = 0.63 1N NaOH)	>271	2
6	F	H	H		(300 MHz, D ₂ O, TMSP) 2.16–2.47(m, 4H) 3.04–3.15(m, 1H) 3.89(d, J=13.2 Hz, 1H) 3.94(d, J=13.2 Hz, 1H) 7.50–7.78(m, 4H)	ESI (Nega) 392 (M – H) [–]	[α] _D ²⁴ +38.9(C = 0.36 1N NaOH)	>271	2

TABLE 1-continued

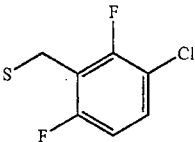
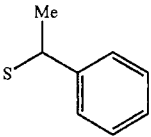
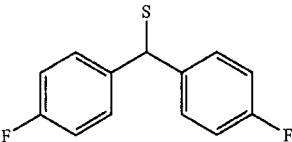
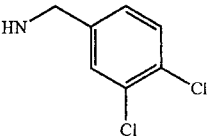
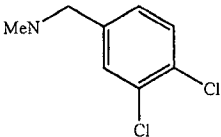
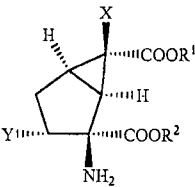
The structure and property data of the compounds obtained in the Examples									
Compound No.	X	R ¹	R ²	Y	NMR	MS	Specific rotatory power	m.p. (° C.)	Example
13	F	H	H		(300 MHz, D ₂ O, TMSP) 2.09–2.62(m, 4H) 3.11–3.40(m, 1H) 3.79–4.11(m, 2H) 6.87–7.23(m, 1H) 7.32–7.61(m, 1H)	ESI (Nega) 394 (M – H) [–]	[α] _D ²⁴ +66.9(C = 0.23 1N NaOH).	>234	2
14	F	H	H	SPr	(300 MHz, D ₂ O, TMSP) 0.79–1.00(m, 3H) 1.20–1.67(m, 4H) 2.22–0.81(m, 6H) 3.08–3.30(m, 1H)	ESI (Nega) 290 (M – H) [–]	[α] _D ²⁴ –5.42 (C = 0.12 1N NaOH)	>261	2
15	F	H	H		(300 MHz, D ₂ O, TMSP) 1.48–1.62(m, 3H) 1.82–1.94(m, 1H) 2.05–2.32(m, 2H) 2.43–2.71(m, 1H) 2.83–3.03(m, 1H) 4.04–4.24(m, 1H) 7.27–7.52(m, 5H)	ESI (Nega) 338 (M – H) [–]	—	>307	2
16	F	H	H		(300 MHz, D ₂ O, TMSP) 2.06–2.60(m, 4H) 2.91–3.08(m, 1H) 5.43(s, 1H) 6.99–7.25(m, 4H) 7.39–7.65(m, 4H)	ESI (Nega) 436 (M – H) [–]	[α] _D ²⁴ +15.4(C = 0.36 1N NaOH)	>243	2
17	F	H	H	NH ₂	(300 MHz, D ₂ O, TMSP) 2.33–2.79(m, 4H) 3.77–3.86(m, 1H)	ESI (Nega) 241 (M + H) ⁺	[α] _D ^{28–} 39.3 (C = 0.14 1N NaOH)	>256	5
18	F	H	H		(300 MHz, D ₂ O, TMSP) 2.31–2.77(m, 4H) 3.59–3.74(m, 1H) 4.06(d, J=13.5 Hz, 1H) 4.15(d, J=13.5 Hz, 1H) 7.35(d, J=7.8 Hz, 1H) 7.58–7.64(m, 2H)	ESI (Nega) 375 (M – H) [–]	[α] _D ²⁷ –14.6(C = 0.29 1N NaOH)	>190	6
19	F	H	H		(300 MHz, D ₂ O, TMSP) 2.31–2.41(m, 1H) 2.45–2.53(m, 1H) 2.64(s, 3H) 2.73–2.82(m, 2H) 3.72–3.82(m, 1H) 4.01 (d, J=13.4 Hz, 1H) 4.27(d, J=13.4 Hz, 1H) 7.35–7.41(m, 1H) 7.61–7.69(m, 2H)	ESI (Nega) 389 (M – H) [–]	[α] _D ²⁴ –35.2(C = 0.51 1N NaOH)	>164	7

TABLE 1-continued

The structure and property data of the compounds obtained in the Examples



Compound				Y	NMR	MS	Specific	m.p.	Example
No.	X	R ¹	R ²				rotatory power		
20	F	H	H		(300 MHz, D ₂ O, TMSP) 2.33–2.42(m, 2H) 2.57–2.67(m, 2H) 4.46–4.55(m, 1H) 7.58–7.68(m, 2H) 7.87–7.90(m, 1H)	ESI (Negn) 389 (M – H) [–]	[α] _D ²⁸ +6.0(C = 0.34 1N NaOH)	>210	8
21	F	H	H		(300 MHz, D ₂ O, TMSP) 2.40–2.45(m, 2H) 2.71–2.77(m, 2H) 5.28–5.36(m, 1H) 7.68(d, J=8.5 Hz, 1H) 7.89(d, J=8.5 Hz, 1H) 8.16(s, 1H)	ESI (Negn) 390 (M – H) [–]	[α] _D ²⁸ +9.2(C = 0.23 MeOH)	>270	9
22	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.30(t, J=7.5 Hz, 3H) 1.35(t, J=7.0 Hz, 3H) 2.04–2.45(m, 4H) 2.87–3.03(m, 1H) 3.93(d, J=14.5 Hz, 1H) 4.14(d, J=14.5 Hz, 1H) 4.14–4.39(m, 4H) 6.86–6.95(m, 2H) 7.19(dd, J=4.8, 1.8 Hz, 1H)	ESI (Pos) 410 (M + Na) ⁺	[α] _D ²² +80.88 (C = 0.61 CHCl ₃)	oil	2
23	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.30(t, J=7.0 Hz, 3H) 1.31(t, J=7.0 Hz, 3H) 2.00–2.36(m, 4H) 2.68–2.84(m, 1H) 3.80(s, 2H) 4.14–4.36(m, 4H) 7.18–7.51(m, 9H)	ESI (Pos) 480 (M + Na) ⁺	[α] _D ²² +46.6 (C = 0.61 CHCl ₃)	oil	2
24	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.30(t, J=7.5 Hz, 3H) 1.34(t, J=7.0 Hz, 3H) 2.03–2.14(m, 1H) 2.21–2.40(m, 3H) 2.77–2.95(m, 1H) 3.72–3.83(m, 5H) 4.16–4.39(m, 4H) 6.79–6.87(m, 2H) 7.17–7.25(m, 2H)	ESI (Pos) 434 (M + Na) ⁺	[α] _D ²² +71.1 (C = 0.18 CHCl ₃)	oil	2

TABLE 1-continued

The structure and property data of the compounds obtained in the Examples

Compound				Y	NMR	MS	Specific rotatory power	m.p. (° C.)	Example
No.	X	R ¹	R ²						

25	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.22–1.44(m, 6H) 2.02–2.19(m, 1H) 2.20–2.43(m, 3H) 2.79–2.98(m, 1H) 3.69–3.93(m, 2H) 4.14–4.42(m, 4H) 6.93–7.09(m, 2H) 7.20–7.37(m, 2H)	ESI (Pos) 422 (M + Na) ⁺	[α] _D ²⁸ +59.3 (C = 0.44 CHCl ₃)	oil	2
26	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.20–1.42(m, 15H) 2.03–2.15(m, 1H) 2.20–2.43(m, 3H) 2.82–2.96(m, 1H) 3.73(d, J=13.2 Hz, 1H) 3.82(d, J13.2 Hz, 1H) 4.15–4.41(m, 4H) 7.15–7.37(m, 4H)	ESI (Pos) 460 (M + Na) ⁺	[α] _D ³⁰ +46.3 (C = 0.50 CHCl ₃)	oil	2
27	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.19–1.42(m, 6H) 2.02–2.43(m, 4H) 2.81–2.95(m, 1H) 3.83(d, J=13.2 Hz, 1H) 3.96(d, J=13.2 Hz, 1H) 4.07–4.41(m, 4H) 7.33–7.65(m, 4H)	ESI (Pos) 450 (M + Na) ⁺	[α] _D ²⁵ +77.3 (C = 0.27 CHCl ₃)	oil	2
28	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.30(t, J=7.0 Hz, 3H) 1.34(t, J=7.0 Hz, 3H) 2.03–2.14(m, 1H) 2.21–2.44(m, 3H) 3.01–3.15(m, 1H) 4.05–4.40(m, 6H) 7.45–7.64(m, 3H) 7.78(t, J=8.1 Hz, 2H) 8.30(d, J=8.3 Hz, 1H)	ESI (Pos) 532 (M + Na) ⁺	[α] _D ²⁸ +101.7 (C = 0.32 CHCl ₃)	oil	2
29	F	Et	Bn		(200 MHz, CDCl ₃ , TMS) 1.24(t, J=7.3 Hz, 3H) 1.77(dd, J=2.3, 2.3 Hz, 1H) 1.80–2.17(m, 4H) 2.46–2.55(m, 1H) 3.65(d, J=13.6 Hz, 1H) 3.82(d, J=13.6 Hz, 1H) 4.09(q, J=7.3 Hz, 2H) 5.23(s, 2H) 7.11–7.16(m, 1H) 7.33–7.44(m, 7H)	ESI (Pos) 516 (M + Na) ⁺	[α] _D ²⁸ +86.35 (C = 0.23 CHCl ₃)	oil	2

TABLE 1-continued

The structure and property data of the compounds obtained in the Examples

Compound				Y	NMR	MS	Specific rotatory power	m.p. (° C.)	Example
No.	X	R ¹	R ²						

30	F	Et	Et		(300 MHz, CDCl ₃ , TMS) 1.31(t, J=7.2 Hz, 3H) 1.35(t, J=7.2 Hz, 3H) 2.08–2.15(m, 1H) 2.24–2.40(m, 3H) 2.86–2.93(m, 1H) 3.73(d, J=13.4 Hz, 1H) 3.88(d, J=13.4 Hz, 1H) 4.21–4.37(m, 4H) 7.15(dd, J=8.2, 2.2 Hz, 1H) 7.36(d, J=8.2 Hz, 1H) 7.42(d, J=2.2 Hz, 1H)	ESI (Pos) 472 (M + Na) ⁺	[α] _D ²⁶ +94.4 (C = 0.25 CHCl ₃)	oil	2
31	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.34(t, J=7.0 Hz, 3H) 1.35(t, J=7.0 Hz, 3H) 2.30–2.43(m, 3H) 2.78–3.12(m, 2H) 3.80(d, J=13.2 Hz, 1H) 4.19–4.36(m, 5H) 7.17(dd, J=8.4, 2.2 Hz, 1H) 7.44(d, J=8.4 Hz, 1H) 7.44(d, J=2.2 Hz, 1H)	ESI (Pos) 488 (M + Na) ⁺	[α] _D ²⁹ +59.1 (C = 0.32 CHCl ₃)	oil	3
32	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.34(t, J=7.0 Hz, 3H) 1.36(t, J=7.0 Hz, 3H) 2.28–2.42(m, 3H) 2.83–3.01(m, 1H) 3.41–3.53(m, 1H) 4.23–4.37(m, 6H) 7.28(dd, J=8.4, 1.8 Hz, 1H) 7.46(d, J=8.4 Hz, 1H) 7.55(d, J=1.8 Hz, 1H)	ESI (Pos) 482 (M + H) ⁺	[α] _D ²⁹ +24.0 (C = 0.86 CHCl ₃)	oil	4
33	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.31(t, J=7.5 Hz, 3H) 1.39(t, J=7.3 Hz, 3H) 2.13–2.35(m, 2H) 2.43–2.74(m, 2H) 3.26–3.41(m, 1H) 4.18–4.46(m, 4H) 7.32(d, J=1.3 Hz, 1H) 7.60–7.61(m, 1H)	ESI (Pos) 458 (M + Na) ⁺	[α] _D ²⁵ +71.2 (C = 0.28 CHCl ₃)	oil	2
34	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.31(t, J=7.0 Hz, 3H) 1.34(t, J=7.0 Hz, 3H) 2.06–2.17(m, 1H) 2.23–2.53(m, 3H) 2.96–3.12(m, 1H) 3.83(d, J=13.2 Hz, 1H) 3.98(d, J=13.2 Hz, 1H) 4.11–4.41(m, 4H) 6.77–6.93(m, 1H) 7.19–7.34(m, 1H)	ESI (Pos) 474 (M + Na) ⁺	[α] _D ²² +81.8 (C = 0.30 CHCl ₃)	oil	2

TABLE 1-continued

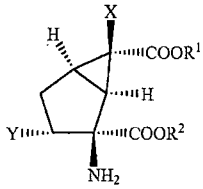
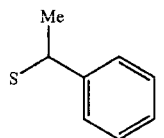
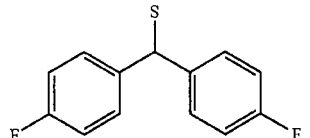
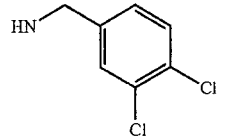
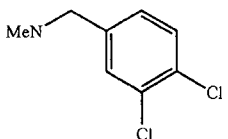
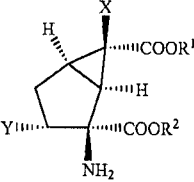
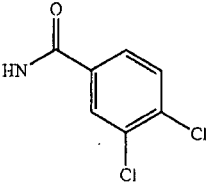
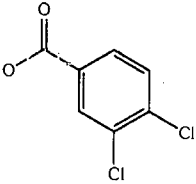
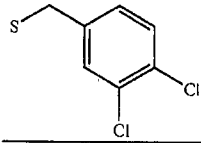
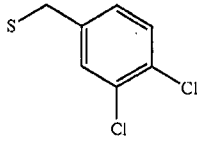
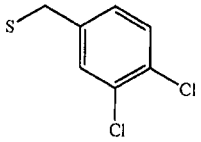
The structure and property data of the compounds obtained in the Examples									
									
Compound No.	X	R¹	R²	Y	NMR	MS	Specific rotatory power	m.p. (° C.)	Example
35	F	Et	Et	SPr	(200 MHz, CDCl₃, TMS) 0.89(t, J=6.8 Hz, 3H) 1.19–1.61(m, 10H) 2.06–2.69(m, 6H) 2.83–3.03(m, 1H) 4.14–4.40(m, 4H)	ESI (Pos) 348 (M + H)⁺	[α] _D ²⁵ +30.5 (C = 0.24 CHCl₃)	oil	2
36	F	Et	Et		(200 MHz, CDCl₃, TMS) 1.20–1.40(m, 6H) 1.49 (d, J=7.0 Hz, 6/5H) 1.57(d, J=7.0 Hz, 9/5H) 1.92–2.25(m, 3H) 2.40–2.78(m, 2H) 4.07–4.39(m, 5H) 7.14–7.38(m, 5H)	ESI (Pos) 418 (M + H)⁺	—	oil	2
37	F	Et	Et		(200 MHz, CDCl₃, TMS) 1.29(t, J=7.0 Hz, 3H) 1.33(t, J=7.0 Hz, 3H) 2.00–2.13(m, 1H) 2.19–2.36(m, 3H) 2.68–2.81(m, 1H) 4.14–4.40(m, 4H) 5.51(s, 1H) 6.90–7.08 (m, 4H) 7.21–7.31(m, 2H) 7.36–7.48(m, 2H)	ESI (Pos) 516 (M + H)⁺	[α] _D ²⁸ +41.2 (C = 0.31 CHCl₃)	oil	2
38	F	Et	Et		(200 MHz, CDCl₃, TMS) 1.31(t, J=7.0 Hz, 3H) 1.34(t, J=6.2 Hz, 3H) 2.03–2.28(m, 3H) 2.35–2.51(m, 1H) 2.94–3.08(m, 1H) 3.77(s, 2H) 4.16–4.40(m, 4H) 7.12(d, J=7.9 Hz, 1H) 7.35(d, J=7.9 Hz, 1H) 7.40(s, 1H)	ESI (Pos) 433 (M + H)⁺	[α] _D ²⁴ –8.4° (C = 0.56 CHCl₃)	oil	6
39	F	Et	Et		(300 MHz, CDCl₃, TMS) 1.33(t, J=7.0 Hz, 3H) 1.35(t, J=7.0 Hz, 3H) 2.06(s, 3H) 2.03–2.21(m, 1H) 2.23–2.60(m, 3H) 2.68–2.84(m, 1H) 3.22(d, J=14.1 Hz, 1H) 3.97(d, J=14.1 Hz, 1H) 4.18–4.32(m, 4H) 7.07(dd, J=8.1, 2.0 Hz, 1H) 7.30–7.39(m, 2H)	ESI (Pos) 447 (M + H)⁺	[α] _D ²³ –24.9° (C = 0.84 CHCl₃)	oil	7

TABLE 1-continued

The structure and property data of the compounds obtained in the Examples									
									
Compound No.	X	R ¹	R ²	Y	NMR	MS	Specific rotatory power	m.p. (° C.)	Example
40	F	Et	Et		(200 MHz, CDCl ₃ , TMS) 1.30(t, J=6.8 Hz, 3H) 1.33(t, J=7.0 Hz, 3H) 2.09–2.43(m, 3H) 2.53–2.38(m, 1H) 4.19–4.38(m, 4H) 4.52–4.71(m, 1H) 7.48–7.55(m, 2H) 7.75–7.84(m, 1H)	ESI (Pos) 469 (M + Na) ⁺	[α] _D ²⁷ +8.3 (C = 0.93 CHCl ₃)	oil	8
41	F	Et	Bn		(200 MHz, CDCl ₃ , TMS) 1.33(t, J=7.3 Hz, 3H) 2.25–2.80(m, 4H) 4.28(q, J=7.3 Hz, 2H) 5.05–5.13(m, 1H) 5.16(d, J=12.3 Hz, 1H) 5.31(d, J=12.3 Hz, 1H) 7.24–7.36(m, 5H) 7.44(d, J=8.4 Hz, 1H) 7.57(dd, J=8.4, 2.20 Hz, 1H) 7.90(d, J=2.2 Hz, 1H)	ESI (Pos) 532 (M + Na) ⁺	[α] _D ²² +31.8 (C = 0.547 CHCl ₃)	oil	9
42	F	Et	Et		(300 MHz, CD ₃ OD, TMS) 1.36(t, J=7.2 Hz, 3H) 2.19–2.48(m, 4H) 2.17–3.31(m, 3H) 4.28–4.45(m, 2H) 7.27(d, J=8.3 Hz, 1H) 7.47(d, J=8.3 Hz, 1H) 7.52(s, 1H)	ESI (Nega) 420 (M – Na) [–]			11
43	F	i-Bu	H		(300 MHz, CD ₃ OD, TMS) 0.94(d, J=6.7 Hz, 6H) 1.86–1.99(m, 1H) 2.23–2.62(m, 4H) 2.99–3.08(m, 1H) 3.76(d, J=13.0 Hz, 1H) 3.81(d, J=13.0 Hz, 1H) 3.96(d, J=6.7 Hz, 2H) 7.27(dd, J=8.4, 1.9 Hz, 1H) 7.45(d, J=8.4 Hz, 1H) 7.52(d, J=2.0 Hz, 1H)	ESI (Pos) 472 (M + Na) ⁺			10
44	F	Bn	H		(300 MHz, CD ₃ OD, TMS) 2.19–2.43(3H, m), 2.47–2.63(1H, m), 2.96–3.12(1H, m), 3.75(1H, d, J=13.2 Hz), 3.81(1H, d, J=13.2 Hz), 5.22(2H, s), 7.23–7.54(8H, m)	ESI (Nega) 482 (M – H) [–]			10

- [0168] The compounds in the table above are as follows:
- [0169] Compound No. 1: (1R,2S,3R,5R,6R)-2-amino-3-(thiophene-2-ylmethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0170] Compound No. 2: (1R,2S,3R,5R,6R)-2-amino-3-(2-phenylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0171] Compound No. 3: (1R,2S,3R,5R,6R)-2-amino-3-(4-methoxybenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0172] Compound No. 4: (1R,2S,3R,5R,6R)-2-amino-3-(4-fluorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0173] Compound No. 5: (1R,2S,3R,5R,6R)-2-amino-3-(4-*t*-butylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0174] Compound No. 6: (1R,2S,3R,5R,6R)-2-amino-3-(3-trifluoromethylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0175] Compound No. 7: (1R,2S,3R,5R,6R)-2-amino-3-(1-bromo-naphthalene-2-ylmethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0176] Compound No. 8: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0177] Compound No. 9: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0178] Compound No. 10: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0179] Compound No. 11: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0180] Compound No. 12: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorophenylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0181] Compound No. 13: (1R,2S,3R,5R,6R)-2-amino-3-(3-chloro-2,6-difluorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0182] Compound No. 14: (1R,2S,3R,5R,6R)-2-amino-3-(propylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0183] Compound No. 15: (1R,2S,3R,5R,6R)-2-amino-3-(1-phenyl-ethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0184] Compound No. 16: (1R,2S,3R,5R,6R)-2-amino-3-[bis-(4-fluorophenyl)methylsulfanyl]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0185] Compound No. 17: (1R,2R,3R,5R,6R)-2,3-diamino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0186] Compound No. 18: (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0187] Compound No. 19: (1R,2R,3R,5R,6R)-2-amino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0188] Compound No. 20: (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0189] Compound No. 21: (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;
- [0190] Compound No. 22: (1R,2S,3R,5R,6R)-2-amino-3-(thiophene-2-ylmethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0191] Compound No. 23: (1R,2S,3R,5R,6R)-2-amino-3-(2-phenylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0192] Compound No. 24: (1R,2S,3R,5R,6R)-2-amino-3-(4-methoxybenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0193] Compound No. 25: (1R,2S,3R,5R,6R)-2-amino-3-(4-fluorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0194] Compound No. 26: (1R,2S,3R,5R,6R)-2-amino-3-(4-*t*-butylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0195] Compound No. 27: (1R,2S,3R,5R,6R)-2-amino-3-(3-trifluoromethylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0196] Compound No. 28: (1R,2S,3R,5R,6R)-2-amino-3-(1-bromo-naphthalene-2-ylmethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0197] Compound No. 29: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester;
- [0198] Compound No. 30: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0199] Compound No. 31: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0200] Compound No. 32: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0201] Compound No. 33: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorophenylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0202] Compound No. 34: (1R,2S,3R,5R,6R)-2-amino-3-(3-chloro-2,6-difluorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0203] Compound No. 35: (1R,2S,3R,5R,6R)-2-amino-3-(propylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;
- [0204] Compound No. 36: (1R,2S,3R,5R,6R)-2-amino-3-(1-phenyl-ethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

[0205] Compound No. 37: (1R,2S,3R,5R,6R)-2-amino-3-[bis-(4-fluorophenyl)methylsulfanyl]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

[0206] Compound No. 38: (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

[0207] Compound No. 39: (1R,2R,3R,5R,6R)-2-amino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

[0208] Compound No. 40: (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

[0209] Compound No. 41: (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester;

[0210] Compound No. 42: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-ethyl ester;

[0211] Compound No. 43: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-isobutyl ester; and

[0212] Compound No. 44: (1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-benzyl ester.

Pharmacological Test 1

Effects (or Antagonistic Action) of the Test Compound the on cAMP Accumulation in CHO Cells Modified to Stably Express Metabotropic Glutamate Receptor mGluR2

[0213] CHO cells modified to stably express metabotropic glutamate receptor mGluR2 were seeded in a 96-well plate 1.26×10^4 cells/well/0.32 cm²/150 μ L using Dulbecco's modified Eagle medium containing 10% dialyzed fetal bovine serum [1% proline, 50 units/mL penicillin, 50 μ g/mL streptomycin, 2 mM L-glutamine (added before use)], and were cultured for 2 days at 37° C., under 5% CO₂. The medium was then exchanged with a L-glutamine free medium, the supernatant was removed by suction 4 hours later, and the late was washed with 150 μ L of PBS(+)-IBMX (10 mM PBS(-), 1 mM MgCl₂, 1 mM CaCl₂, 1 mM IBMX), and after 100 μ L of PBS(+)-IBMX containing the test compound at the final concentration of 0.3 mM to 100 μ M was added, the cells were incubated for 20 minutes at 37° C., under 5% CO₂. After 2 μ L of 500 μ M forskolin (the final concentration 10 μ M) was added, the cells were incubated for 15 minutes at 37° C. under 5% CO₂, and the effect of the test compound on the inhibitory action of glutamic acid to the forskolin-stimulated cAMP accumulation was examined (for the control, the test compounds were not added in the above procedure) (Tanabe et al, Neuron, 8, 169-179 (1992)). After 200 μ L of ice-cooled ethanol was added to halt the reaction, all of the supernatant was collected into a separate plate, evaporated to dryness with an evaporator at room temperature, and stored at -20° C. The cAMP level of the dried up sample was determined with a cAMP EIA kit (Amersham Biosciences Corp.). The cAMP level of the control was subtracted from each of the cAMP levels these determined. The IC₅₀ of the test compound was determined, as the concentrations of the test compound antagonizes by

50% of the inhibitory action of 30 μ M glutamic acid against the 10 μ M forskolin-stimulated cAMP accumulation.

[0214] Among the compounds of the present invention represented by formula [II] those having hydrogen atom at R¹ and R² showed low IC₅₀ values, in the above pharmacological test.

Pharmacological Test 2

Effects of the Test Compound of the [³H]MGS0008 Binding to Receptors in CHO Cells Modified to Stably Express Metabotropic Glutamate Receptor mGluR2

[0215] CHO cells modified to stably express metabotropic glutamate receptor mGluR2 were seeded in a T-225 flask using Dulbecco's modified Eagle medium containing 10% dialyzed fetal bovine serum [1% proline, 50 units/mL penicillin, 50 μ g/mL streptomycin, 2 mM L-glutamine (added before use)], and were cultured for 2 days at 37° C., under 5% CO₂. In a state of confluency, the cells were washed twice with PBS(-), exfoliated with a cell scraper, centrifuged at 1000 $\times$ g for 15 minutes at 4° C. and collected. The obtained pellet was stored at -80° C. The frozen pellet was dissolved before use and suspended in a 50 mM Tris-HCl buffer solution (pH 7.4). The buffer solution was homogenized with a homogenizer for 20 seconds and then centrifuged for 20 minutes at 4° C., 48,000 $\times$ g. The pellet was again suspended and homogenized in the above buffer solution, and after being, incubated for 15 minutes at 37° C., and then centrifuged for 20 minutes at 4° C., 48,000 $\times$ g. The obtained pellet was further washed twice by centrifugation and homogenized with a 50 mM Tris-HCl buffer (2 mM MgCl₂, pH 7.4), to obtain a membrane fraction. The receptor-binding assay was carried out at a membrane concentration between 50 to 200 μ g/0.5 mL. The test compound and 3 nM [³H]MGS0008 were added to the membrane fraction, followed by 1 hour of incubation at 25° C. The reaction was halted by filtering the mixture by suction with a Brandel cell harvester onto a Whatman GF/C filterer pre-soaked in 0.3% polyethylenimine. After the suction, the filter was washed three times with 3 mL of an ice-cooled buffer solution of 50 mM Tris-HCl (2 mM MgCl₂, pH 7.4). Then the filter thus obtain were soaked in 10 mL of Aquasol-2. After the filter was left to stand for over 6 hours, the fluorescence activity was measured with a Beckman LS6000 liquid scintillation counter. Non-specific binding was determined by similar fluorescence measurements in the presence of 10 μ M LY354740, and the fluorescence value was subtracted from each of the binding level. The IC₅₀ of the test compound was determined as the concentration of the test compound showing a 50% inhibitory effect on the [³H]MGS0008 binding.

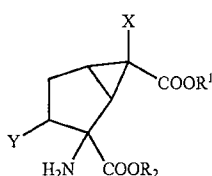
[0216] The compounds of the present invention represented by formula [I] wherein R¹ and R² each represents a hydroxyl group and R³ represents a hydrogen atom, therefore meaning compounds 1 to 58 described in table 1 above, showed a low IC₅₀ value of below 200 nM, which indicates a strong binding action on mGluR2 receptors, when measured as described in the pharmacological test of the present invention.

INDUSTRIAL APPLICABILITY

[0217] As shown above, compounds of the present invention may be used as metabotropic glutamate receptor antagonists. Therefore, the present invention makes it possible to

provide a drug which is effective for the treatment and prevention of psychiatric disorders such as schizophrenia, anxiety and related ailments, depression, bipolar disorder and epilepsy; for the treatment and prevention of neurological diseases such as drug dependence, cognitive disorder, Alzheimer's disease, Huntington's chorea, Parkinson's disease, dyskinesia associated with muscular rigidity, cerebral ischaemia, cerebral failure, myelopathy and head trauma; and also for relieving spasms, pain, nausea and the like.

1. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [I]



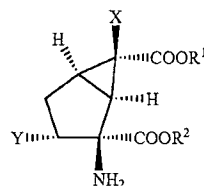
[wherein R^1 and R^2 are the same or different, and each represents a hydrogen atom, a C_{1-10} alkyl group, a phenyl group, a naphthyl group, a C_{1-10} alkyl group substituted by one or two phenyl groups, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group, a hydroxyl C_{2-10} alkyl group, a C_{1-10} alkoxycarbonyl C_{1-10} alkyl group, an amino C_{2-10} alkyl group or a C_{1-10} alkoxy C_{1-10} alkyl group;

X represents a hydrogen atom or a fluorine atom;

Y represents an amino group, $-SR^3$, $-S(O)_nR^7$, $-SCHR^3R^4$, $-S(O)_nCHR^3R^4$, $-NHCHR^3R^4$, $-N(CHR^3R^4)(CHR^5R^6)$, $-NHCOR^3$ or $-OCOR^7$ (wherein R^3 , R^4 , R^5 and R^6 are the same or different, and each represents a hydrogen atom, a C_{1-10} alkyl group, a phenyl group, a naphthyl group, a naphthyl group substituted by one to seven halogen atoms or a hetroaromatic group, or represents "a phenyl group substituted by one to five substituents selected from a group consisting of a halogen atom, a phenyl group, a C_{1-10} alkyl group, a C_{1-10} alkoxy group and a trifluoromethyl group";

R^7 represents a C_{1-10} alkyl group, a phenyl group, a naphthyl group, a naphthyl group substituted by one to seven halogen atoms or a hetroaromatic group, or represents "a phenyl group substituted by one to five substituents selected from a group consisting of a halogen atom, a phenyl group, a C_{1-10} alkyl group, a C_{1-10} alkoxy group and a trifluoromethyl group"; and n represents integer 1 or 2].

2. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II]



[Wherein R^1 and R^2 are the same or different, and each represents a hydrogen atom, a C_{1-10} alkyl group, a phenyl group, a naphthyl group, a C_{1-10} alkyl group substituted by one or two phenyl groups, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group, a hydroxyl C_{2-10} alkyl group, a C_{1-10} alkoxycarbonyl C_{1-10} alkyl group, an amino C_{2-10} alkyl group or a C_{1-10} alkoxy C_{1-10} alkyl group;

X represents a hydrogen atom or a fluorine atom;

Y represents an amino group, $-SR^3$, $-S(O)_nR^7$, $-SCHR^3R^4$, $-S(O)_nCHR^3R^4$, $-NHCHR^3R^4$, $-N(CHR^3R^4)(CHR^5R^6)$, $-NHCOR^3$ or $-OCOR^7$ (wherein R^3 , R^4 , R^5 and R^6 are the same or different, and each represents a hydrogen atom, a C_{1-10} alkyl group, a phenyl group, a naphthyl group, a naphthyl group substituted by one to seven halogen atoms or a hetroaromatic group, or represents "a phenyl group substituted by one to five substituents selected from a group consisting of a halogen atom, a phenyl group, a C_{1-10} alkyl group, a C_{1-10} alkoxy group and a trifluoromethyl group";

R^7 represents a C_{1-10} alkyl group, a phenyl group, a naphthyl group, a naphthyl group substituted by one to seven halogen atoms or a hetroaromatic group or represents "a phenyl group substituted by one to five substituents selected from a group consisting of a halogen atom, a phenyl group, a C_{1-10} alkyl group, a C_{1-10} alkoxy group and a trifluoromethyl group"; and n represents integer 1 or 2].

3. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^2 represents a hydrogen atom.

4. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom.

5. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom; and

X represents a fluorine atom.

6. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom; and

X represents a hydrogen atom.

7. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a fluorine atom; and

Y represents $-SR^3$ ($-SR^3$ is the same as mentioned above).

8. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a fluorine atom; and

Y represents $-S(O)_nR^7$ ($-S(O)_nR^7$ is the same as mentioned above).

9. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a fluorine atom; and

Y represents $-SCHR^3R^4$ ($-SCHR^3R^4$ is the same as mentioned above).

10. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a fluorine atom; and

Y represents $-S(O)_nCHR^3R^4$ ($-S(O)_nCHR^3R^4$ is the same as described above).

11. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a fluorine atom; and

Y represents $-NHCHR^3R^4$ ($-NHCHR^3R^4$ is the same as mentioned above).

12. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a fluorine atom; and

Y represents $-N(CHR^3R^4)(CHR^5R^6)(-N(CHR^3R^4)(CHR^5R^6)$ is the same as mentioned above).

13. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a fluorine atom; and

Y represents $-NHCOR^3$ ($-NHCOR^3$ is the same as mentioned above).

14. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically

acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a fluorine atom; and

Y represents $-OCOR^7$ ($-OCOR^7$ is the same as mentioned above).

15. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a hydrogen atom; and

Y represents $-SR^3$ ($-SR^3$ is the same as mentioned above).

16. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a hydrogen atom; and

Y represents $-S(O)_nR^7$ ($-S(O)_nR^7$ is the same as mentioned above).

17. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a hydrogen atom; and

Y represents $-SCHR^3R^4$ ($-SCHR^3R^4$ is the same as mentioned above).

18. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a hydrogen atom; and

Y represents $-S(O)_nCHR^3R^4$ ($-S(O)_nCHR^3R^4$ is the same as mentioned above).

19. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a hydrogen atom; and

Y represents $-NHCHR^3R^4$ ($-NHCHR^3R^4$ is the same as mentioned above).

20. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R^1 and R^2 each represents a hydrogen atom;

X represents a hydrogen atom; and

Y represents $-N(CHR^3R^4)(CHR^5R^6)(-N(CHR^3R^4)(CHR^5R^6)$ is the same as mentioned above).

21. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically

acceptable salt thereof or a hydrate thereof, represented by formula [II], wherein R¹ and R² each represents a hydrogen atom;

X represents a hydrogen atom; and

Y represents —NHCOR³ (—NHCOR³ is the same as mentioned above).

22. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, such a compound of formula [II] being:

(1R,2S,3R,5R,6R)-2-amino-3-(thiophene-2-ylmethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(2-phenylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(4-methoxybenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(4-fluorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(4-*t*-butylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(3-trifluoromethylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(1-bromo-naphthalene-2-ylmethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorophenylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(3-chloro-2,6-difluorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(propylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-(1-phenyl-ethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2S,3R,5R,6R)-2-amino-3-[bis-(4-fluorophenyl)methylsulfanyl]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2R,3R,5R,6R)-2,3-diamino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2R,3R,5R,6R)-2-amino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

(1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid; or

(1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid.

23. A 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 2, a pharmaceutically acceptable salt thereof or a hydrate thereof, such a compound of formula [II] being:

(1R,2R,3R,5R,6R)-2,3-diamino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(thiophene-2-ylmethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(2-phenylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(4-methoxybenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(4-fluorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(4-*t*-butylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3-trifluoromethylbenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(1-bromo-naphthalene-2-ylmethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorophenylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3-chloro-2,6-difluorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(propylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(1-phenyl-ethylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-[bis-(4-fluorophenyl)methylsulfanyl]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylamino)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2R,3R,5R,6R)-2-amino-3-[N,N-(3,4-dichlorobenzyl)methylamino]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoylamino)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid diethyl ester;

(1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzoyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-benzyl ester 6-ethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 2-ethyl ester;

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-isobutyl ester; or

(1R,2S,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzylsulfanyl)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid 6-benzyl ester.

24. A drug comprising the 2-amino-bicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivative according to claim 1, the pharmaceutically acceptable salt thereof or the hydrate thereof as an active ingredient.

25. The drug according to claim 24 wherein the drug is a Group II metabotropic glutamate receptor antagonist.

* * * * *



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NOTARÍA 75 - BOGOTÁ D. C.
REPUBLICA DE COLOMBIA

ESCRITURA: **75**
SETENTA Y CINCO

Fecha: **ENERO - 23 - 2013**

ACTO: **PODER GENERAL**

DE: Laboratorio Franco Colombiano LAFRANCOL S.A.S. Sigla: LAFRANCOL S.A.S., Nit. 890.301.463-8.

Representante legal: Juan Camilo Palacio Ramírez, cc. 19.455.622 de Bogotá.

A FAVOR DE: Tito Noe Parra Murillo, cc. 79.579.680 de Bogotá
T.P. 71.168 C. S. de la J.

VIGENCIA: **TÉRMINO INDEFINIDO.**

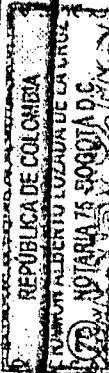
En Bogotá, Distrito Capital, República de Colombia, a los veintitrés (23) días del mes de enero de dos mil trece (2013), ante mí, **MIGUEL ÁNGEL LOZADA URREGO, NOTARIO SETENTA Y CINCO (75) DEL CÍRCULO DE BOGOTÁ - ENCARGADO**, se otorgó escritura en los siguientes términos:

OTORGANTE COMPARECIENTE CON MINUTA:

JUAN CAMILO PALACIO RAMÍREZ, varón, colombiano, mayor de edad, domiciliado y residente en esta ciudad e identificado con cédula de ciudadanía 19.455.622 de Bogotá y manifestó:

PRIMERO.- Que obra en su carácter de representante legal de **LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.** Sigla: **LAFRANCOL S.A.S.**, Nit. 890.301.463-8, sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Cali (Valle), constituida mediante escritura mil cuatrocientos treinta y cuatro (1.434) de la Notaría Cuarta (4ª) del

Papel notarial para uso exclusivo en la escritura pública - No tiene costo para el notario



República de Colombia

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Ca037148489

1.001.34.11757582-05

07-Ene-2013

Cadena S.A. No. 890.301.463-8

Cadena S.A. No. 890.301.463-8

49

Círculo de Cali del veintinueve (29) de septiembre de mil novecientos cincuenta y ocho (1958), reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali.-----

SEGUNDO.- Que en tal carácter, por este público instrumento concede **PODER GENERAL, AMPLIO Y SUFICIENTE** a **TITO NOE PARRA MURILLO**, varón, colombiano, mayor de edad, domiciliado y residente en esta ciudad e identificado con cédula de ciudadanía 79.579.680 de Bogotá, abogado en ejercicio, portador de la Tarjeta Profesional 71.168 del Consejo Superior de la Judicatura, domiciliado en Bogotá, D.C., República de Colombia con dirección en la Diagonal 108 número 51-45 de la misma ciudad, como su representante con poder general amplio y suficiente, para obtener la protección de los derechos de propiedad industrial, protección a la competencia y asuntos jurisdiccionales en materia de competencia desleal y protección al consumidor de **LAFRANCOL S.A.S**, a cuyo efecto lo autorizo, para que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las del orden administrativo, contencioso administrativo y judicial, en todo lo concerniente a los siguientes asuntos:-----

a) En cuanto a marcas, lemas, enseñas comerciales, depósito de nombres comerciales, diseños industriales y modelos de utilidad, patentes de invención y derechos de autor para que solicite su registro o depósito, lleve los procesos respectivos hasta su culminación, haga solicitudes, solicite traspasos, cesiones, modificaciones o correcciones, solicite prórrogas, preste caución, solicite renovaciones, inscriba afectaciones, acuerdo comercialización y licencias de uso, desista de solicitudes, presente derechos de petición, responda cualquier requerimiento o auto, presente recursos, presente demandas, intervenga en procesos administrativos y jurisdiccionales, asista audiencias, presente y solicite pruebas, conteste demandas, proteja en general los derechos y prioridades, formule observaciones, presente acciones de oposición, de cancelación, de nulidad, de medidas cautelares y en general intervenga e procesos civiles, penales, administrativos, o contenciosos – administrativos relacionados con estos derechos u otros de similar naturaleza, que promueva **LAFRANCOL S.A.S**, o se promuevan contra ésta. -----

b) En cuanto a procesos jurisdiccionales, en materia de competencia desleal y en materia de protección al consumidor, lleve los mismos hasta su culminación,



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A0001312473

presentando demandas y respondiendo a las mismas, actuando en todo lo atinente con la naturaleza de dichos procesos. Así mismo, represente a la sociedad poderdante en todos los trámites relativos a protección de la competencia que la entidad encargada pueda adelantar. En general, faculto a mi apoderado a realizar todos aquellos trámites en materia de protección al consumidor, protección de la competencia, reglamentos técnicos y metrología legal, incluso aquellas investigaciones administrativas por reporte de precios, protección de datos personales, asuntos relacionados con propiedad industrial y asuntos jurisdiccionales en materia de protección al consumidor y competencia desleal. -----

c) Para que en todos los asuntos arriba determinados, tanto en los términos señalados por los artículos 42 y complementarios de la Decisión 486 de la Comunidad Andina de Naciones como del artículo 70 del C.P.C., y normas pertinentes del Código Contencioso Administrativo, pueda sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos, de todos los asuntos antes mencionados que se deban tramitar ante la Superintendencia de Industria y Comercio, los Tribunales Contencioso Administrativos, Consejo de Estado y jurisdicción penal, civil o comercial. -----

NOTA.- Manifiesto que de la veracidad de las declaraciones y autenticidad de los documentos anexos en este instrumento público solo responde la parte compareciente. -----

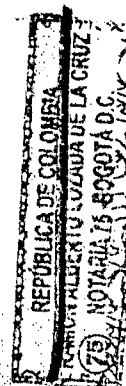
DECLARACIÓN DEL REPRESENTANTE LEGAL DE LA PODERDANTE: -----

El representante legal declara bajo juramento: -----

- a) Que la sociedad a la cual representa, no ha sido disuelta a la fecha. -----
- b) Que las facultades que sirven de fundamento para el otorgamiento de la presente escritura se encuentran vigentes y se hace responsable conforme a la Ley. -----
- c) Que no existe impedimento legal alguno para ejercer el presente mandato. -----

Presente **TITO NOE PARRA MURILLO**, de condiciones civiles indicadas, declaró que acepta el poder que por esta escritura se le otorga. -----

HASTA AQUÍ EL CONTENIDO DE LA MINUTA PRESENTADA PREVIAMENTE ELABORADA, REVISADA, APROBADA Y ACEPTADA ✓ -----



LOS COMPARECIENTES HACEN CONSTAR QUE: -----

1. Han verificado cuidadosamente sus nombres y apellidos, su real estado civil, números correcto de sus documentos de identificación y aprueban este instrumento sin reserva alguna, en la forma como quedó redactado. -----

Por consiguiente, sólo solicitarán correcciones, aclaraciones o modificaciones al texto de la presente escritura en la forma y en los casos previstos por la Ley. -----

2. Las declaraciones consignadas en este instrumento corresponden a la verdad y los otorgantes las aprueban totalmente, sin reserva alguna.-----

3. Conocen la ley y saben que el Notario Encargado responde de la regularidad formal de los instrumentos que autoriza, pero no de la veracidad de las declaraciones de los otorgantes, ni de la autenticidad de los documentos que forman parte de este instrumento.-----

Política de privacidad: Los otorgantes, expresamente declaran que **NO** autorizan la divulgación, ni comercialización, ni publicación por ningún medio, sin excepción alguna, de su imagen personal y/o fotografía tomada en la Notaría 75 - Bogotá, ni su huella digital, ni de sus documentos de identidad, ni su dirección electrónica ni física, ni teléfonos, salvo lo relacionado con el presente instrumento y demás actos notariales que personalmente o por intermedio de apoderado soliciten por escrito, conforme a la Ley. -----

OTORGAMIENTO Y AUTORIZACIÓN

LEIDO, APROBADO TOTALMENTE SIN OBJECION ALGUNA Y FIRMADO por los otorgantes este instrumento, que se elaboró conforme a su voluntad, declaraciones e instrucciones, se les hicieron las advertencias de Ley. El Notario Encargado lo autoriza y da fe de ello. -----

Instrumento elaborado papel notarial números: Aa001312464, Aa001312473, Aa001312498.-✓

Enmendado: "Aa001312473". SI VALE.-✓



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4a001312498

ESTA HOJA CORRESPONDE A LA ESCRITURA: **75**
DE FECHA: **ENERO - 23 - 2013**
OTORGADA EN LA NOTARIA SETENTA Y CINCO (75) DEL CÍRCULO DE BOGOTÁ

ESCRITURACIÓN

RECIBIÓ MARCELA RADICÓ MARCELA
DIGITÓ [Firma] Vo.Bo. MARCELA
IDENTIFICÓ [Firma] FELLAS/FOTO P.C. — 0 —
LIQUIDÓ 1 ALEJANDRO LIQUIDÓ 2 GEORVAN?
REV./LEGAL GEORVAN? CERRO [Firma]
ORGANIZÓ [Firma]

Derechos notariales:	\$45.320
Total gastos de escrituración	\$58.842
IVA:	\$16.666
Superintendencia de Notariado y registro:	\$4.250
Cuenta especial para el Notariado:	\$4.250

Cuentas Palacios

JUAN CAMILO PALACIO RAMÍREZ

C.C. 19478622

DIRECCION.

TELEFONO.

CELULAR

E-MAIL:

Representante legal de LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S., sigla: LAFRANCOL S.A.S.

REPÚBLICA
RAMÓN ALBERTO

75 NOTARIA 75

TITO NOE PARRA MURILLO

CC

T.P.

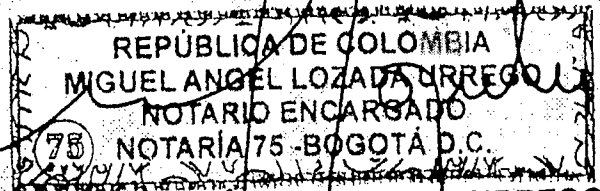
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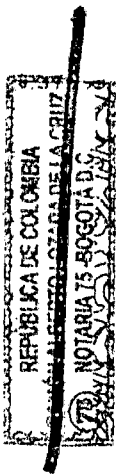
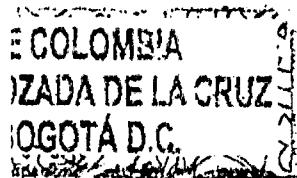


MIGUEL ANGEL LOZADA URREGO

NOTARIO SETENTA Y CINCO (75) DEL CÍRCULO DE BOGOTÁ - ENCARGADO

Avenida Suba No. 106-52
Teléfono 2716446 ♦ Cel. 320 8565019
E-mail: notaria75@gmail.com
Preparó: Johanna Rojas - 87B/13.-

0075/13



ES FIEL Y DOSCIENTOS NOVENTA (290) COPIA,
DE LA ESCRITURA 75 DE ENERO 23 DE 2013,
TOMADA DE SU ORIGINAL EN CUATRO (4)
HOJAS (INCLUIDA ESTA). DEC. 960/70 ART. 80 - MODIFICADO ART.
42 DEC. 2163/70 - ART. 41 DEC. 2148/83 -

HOY 28/10/2013, SIENDO LAS 11:30 A.M.; LA
PRESENTE ESCRITURA NO TIENE NOTA DE
REVOCACIÓN O SUSTITUCIÓN DE PODER.

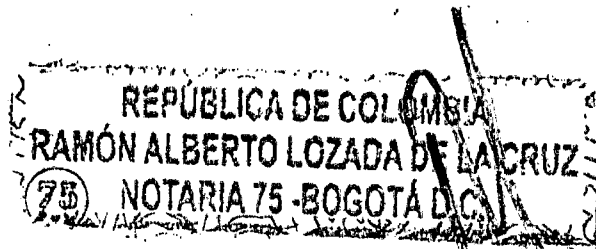
NOTA: Según lo dispuesto por el artículo 2189 del Código
Civil el poder termina, entre otras causas, por:

- 1.- La muerte o interdicción del poderdante,
- 2.- La quiebra o insolvencia del poderdante o apoderado.

SE EXPIDE CON DESTINO A:

NUESTRO USUARIO

BOGOTÁ D.C., 28/10/2013



RAMÓN ALBERTO LOZADA DE LA CRUZ
NOTARIO 75 - BOGOTÁ





01



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2013/12/13

HORA: 08:22:54

OPERACION: 02LJS1213021

PAGINA: 1

REPUBLICA DE COLOMBIA

CERTIFICADO DE EXISTENCIA Y REPRESENTACION DE SOCIEDADES

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE CALI

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.

SIGLA : LAFRANCOL S.A.S.

DOMICILIO: CALI VALLE

DIRECCION DOMICILIO PRINCIPAL: CRA. 1 NRO. 46 84

DIRECCION NOTIFICACION JUDICIAL: CRA. 1 NRO. 46 84

CIUDAD: CALI

MATRICULA MERCANTIL NRO. 5233-16 FECHA MATRICULA : 02 DE OCTUBRE DE 1958

DIRECCION ELECTRONICA : lafrancolsa@lafrancol.co

DIRECCION WEB : www.lafrancol.com

AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX ,SE CONSTITUYO LABORATORIO FRANCO COLOMBIANO LAFRANCOL S. A.

CERTIFICA:

QUE POR ESCRITURA NRO. 3672 DEL 24 DE AGOSTO DE 2009 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 27 DE AGOSTO DE 2009 BAJO EL NRO. 9876 DEL LIBRO IX ,CAMBIO SU NOMBRE DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. . POR EL DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. SIGLA: LAFRANCOL S. A. .

CERTIFICA:

QUE POR ACTA NRO. 124 DEL 30 DE MARZO DE 2012 ASAMBLEA GENERAL , INSCRITA EN LA CAMARA DE COMERCIO EL 31 DE MAYO DE 2012 BAJO EL NRO. 6645 DEL LIBRO IX ,SE TRANSFORMO DE SOCIEDAD ANÓNIMA EN SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. SIGLA: LAFRANCOL S.A. S. .

CERTIFICA:

QUE POR ACTA NRO. 124 DEL 30 DE MARZO DE 2012 ASAMBLEA DE ACCIONISTAS ,

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INSCRITA EN LA CAMARA DE COMERCIO EL 03 DE DICIEMBRE DE 2012 BAJO EL NRO. 14136 DEL LIBRO IX ,SE APROBO LA ESCISION ENTRE (ESCINDENTE) AMERICAN GENERICS S.A.S. Y (BENEFICIARIA(S)) LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. .

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
INS LIBRO				
E.P. 1104 19467	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	
E.P. 2309 20089	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	
E.P. 1725 24528	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	
E.P. 1824 26360	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	
E.P. 2422 26717	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963	
E.P. 1720 28406	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964	
E.P. 101 31039	31/01/1966	NOTARIA CUARTA DE CALI	01/02/1966	
E.P. 552 35711	21/03/1968	NOTARIA CUARTA DE CALI	01/04/1968	
E.P. 4964 2975 IX	12/12/1972	NOTARIA CUARTA DE CALI	16/01/1973	
E.P. 1956 4337 IX	30/05/1973	NOTARIA CUARTA DE CALI	13/06/1973	
E.P. 4964 5994 IX	12/12/1972	NOTARIA CUARTA DE CALI	28/11/1973	
E.P. 5579 5995 IX	12/11/1973	NOTARIA CUARTA DE CALI	28/11/1973	
E.P. 4406 10887 IX	30/09/1974	NOTARIA CUARTA DE CALI	28/11/1974	
E.P. 192 25355 IX	03/02/1978	NOTARIA CUARTA DE CALI	14/02/1978	

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E.P. 3479 34204 IX	07/09/1979	NOTARIA CUARTA DE CALI	19/09/1979
E.P. 4274 73088 IX	12/12/1984	NOTARIA NOVENA DE CALI	19/12/1984
E.P. 1155 76917 IX	21/05/1985	NOTARIA SEPTIMA DE CALI	03/06/1985
E.P. 1553 85997 IX	20/06/1986	NOTARIA SEPTIMA DE CALI	08/07/1986
E.P. 1458 3508 IX	09/06/1987	NOTARIA SEPTIMA DE CALI	24/12/1987
E.P. 7222 13847 IX	14/12/1988	NOTARIA TERCERA DE CALI	19/12/1988
E.P. 4530 21508 IX	04/09/1989	NOTARIA TERCERA DE CALI	07/09/1989
E.P. 3865 31708 IX	02/08/1990	NOTARIA TERCERA DE CALI	13/08/1990
E.P. 8305 557 IX	13/12/1995	NOTARIA TERCERA DE CALI	23/01/1996
E.P. 4559 7911 IX	16/11/1999	NOTARIA TERCERA DE CALI	26/11/1999
E.P. 6.004 13371 IX	02/12/2004	NOTARIA TERCERA DE CALI	14/12/2004
E.P. 6241 625 IX	27/12/2006	NOTARIA TERCERA DE CALI	19/01/2007
E.P. 389 1880 IX	07/02/2008	NOTARIA TERCERA DE CALI	19/02/2008
E.P. 1907 5950 IX	11/05/2009	NOTARIA TERCERA DE CALI	26/05/2009
E.P. 3672 9876 IX	24/08/2009	NOTARIA TERCERA DE CALI	27/08/2009
ACT 116 5470 IX	04/03/2010	ASAMBLEA GRAL ORDINARIA	11/05/2010
E.P. 4421 12622 IX	21/10/2010	NOTARIA TERCERA DE CALI	26/10/2010
E.P. 1786	16/05/2011	NOTARIA TERCERA DE CALI	24/05/2011

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6318	IX			
ACT 124		30/03/2012	ASAMBLEA GENERAL	31/05/2012
6645	IX			
ACT 125		27/07/2012	ASAMBLEA GENERAL DE ACCIONISTAS	23/08/2012
10177	IX			
ACT 127		12/12/2012	ASAMBLEA GENERAL DE ACCIONISTAS	13/12/2012
14600	IX			
ACT 131		17/06/2013	ASAMBLEA GENERAL DE ACCIONISTAS	24/06/2013
7217	IX			

CERTIFICA:

VIGENCIA:

INDEFINIDA

CERTIFICA:

OBJETO SOCIAL. LA SOCIEDAD EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ REALIZAR, ENTRE OTROS, LAS SIGUIENTES ACTIVIDADES COMERCIALES Y EMPRESARIALES: 2.1) FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES. 2.2) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. 2.3) FABRICACIÓN, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPO DE PRODUCTOS VETERINARIOS. 2.4) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. 2.5) IMPORTAR CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES Y/O PRODUCTOS INTERMEDIOS O A GRANEL. PARÁGRAFO UNO: EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAÍCES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAÍCES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR EN MUTUO DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN O NO LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS, O CUALESQUIERA OTRAS EMPRESAS DE OTROS OBJETOS SOCIALES. PARÁGRAFO DOS: ADEMÁS DE LAS ACTIVIDADES REFERIDAS EN ESTE ARTICULO, Y LAS ENUNCIADAS EN EL

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PARÁGRAFO UNO, COMO SOCIEDAD POR ACCIONES SIMPLIFICADA, PODRÁ REALIZAR CUALQUIER ACTIVIDAD LICITA DE COMERCIO EN EL PAÍS O EN EL EXTERIOR, POR EJEMPLO, Y DE MANERA ILUSTRATIVA MÁS NO LIMITATIVA, GESTIÓN DE LICENCIAS, REGISTROS DE EXPORTACIÓN O IMPORTACIÓN, CONVENIOS RELATIVOS A ESAS ACTIVIDADES Y LOS ACTOS RELACIONADOS CON EL MISMO. PARÁGRAFO TRES: POR RAZÓN DE SU OBJETO SOCIAL, LA SOCIEDAD NO PODRÁ CONSTITUIRSE GARANTE NI FIADORA DE OBLIGACIONES DISTINTAS DE LAS PROPIAS NI GARANTIZAR CON SUS BIENES OBLIGACIONES DE TERCEROS, A MENOS QUE LO AUTORICE EN CADA CASO LA ASAMBLEA GENERAL DE ACCIONISTAS CON EL VOTO DE LA TOTALIDAD DE LOS MIEMBROS PRESENTES EN LA REUNIÓN CORRESPONDIENTE.

CERTIFICA:

DIRECCIÓN Y ADMINISTRACIÓN. LA DIRECCIÓN Y ADMINISTRACIÓN DE LA SOCIEDAD ESTARÁ A CARGO DE: A) LA ASAMBLEA GENERAL DE ACCIONISTAS; Y B) LOS REPRESENTANTES LEGALES COMO SE DESCRIBEN EN SUS CARGOS Y FUNCIONES EN LOS PRESENTES ESTATUTOS.

REPRESENTACIÓN LEGAL. ADMINISTRACIÓN. LA ADMINISTRACIÓN DE LA SOCIEDAD CORRESPONDE AL REPRESENTANTE LEGAL, EL CUAL SE CLASIFICARÁ EN TRES TIPOS, TIPO A, TIPO B Y TIPO C, ASÍ COMO LA GESTIÓN Y EJECUCIÓN DE LOS NEGOCIOS Y ASUNTOS SOCIALES. LOS REPRESENTANTES LEGALES SERÁN DESIGNADOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS POR UN TÉRMINO INDEFINIDO Y SE MANTENDRÁN VIGENTES HASTA TANTO NO SEAN REMOVIDOS DE SUS CARGOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS. ADICIONALMENTE SE CREA EL CARGO DE REPRESENTANTE LEGAL PARA ASUNTOS LEGALES, ADMINISTRATIVOS Y JUDICIALES EN TODAS LAS JURISDICCIONES, EL CUAL SERÁ IGUALMENTE DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS Y CUYAS FUNCIONES SE DESCRIBEN EN EL ARTÍCULO SIGUIENTE DE ESTOS ESTATUTOS.

FUNCIONES DEL REPRESENTANTE LEGAL.- EL REPRESENTANTE LEGAL DE LA SOCIEDAD, SEA REPRESENTANTE TIPO A, B O C, ES UN MANDATARIO CON REPRESENTACIÓN, INVESTIDO DE FACULTADES EJECUTIVAS Y ADMINISTRATIVAS, Y COMO TAL, TIENE A SU CARGO LA REPRESENTACIÓN LEGAL, LA GESTIÓN COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCIÓN ADMINISTRATIVA, LA

COORDINACIÓN Y SUPERVISIÓN GENERAL DE LA EMPRESA, LAS CUALES CUMPLIRÁ CON ARREGLO A LAS NORMAS DE ESTOS ESTATUTOS Y LAS DISPOSICIONES LEGALES, Y CON SUJECCIÓN A LAS ÓRDENES E INSTRUCCIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. AL REPRESENTANTE LEGAL LE CORRESPONDE: 1) REPRESENTAR A LA SOCIEDAD EN LOS NEGOCIOS SOCIALES SIN LÍMITE DE CUANTÍA Y ACTUACIÓN, SIEMPRE Y CUANDO ACTÚEN

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DE MANERA CONJUNTA DOS REPRESENTANTES TIPO A, O UN REPRESENTANTE TIPO A CONJUNTAMENTE CON UN REPRESENTANTE TIPO B; 2) COMPROMETER A LA SOCIEDAD HASTA UNA CUANTÍA DE DOS MILLONES DE DÓLARES DE ESTADOS UNIDOS DE AMÉRICA (US\$2.000.000), SIEMPRE Y CUANDO ACTÚEN DE MANERA CONJUNTA DOS REPRESENTANTES TIPO B, O UN REPRESENTANTE TIPO B CON UN REPRESENTANTE TIPO C, O DOS REPRESENTANTES TIPO C. LOS REPRESENTANTES LEGALES CUALQUIERA SEA SU TIPO, DONDE ACTÚEN DE MANERA CONJUNTA AL MENOS DOS DE ELLOS Y SIN LÍMITE DE CUANTÍA PODRÁN (I) SUSCRIBIR EN NOMBRE DE LA SOCIEDAD CONTRATOS DE DISTRIBUCIÓN DE LOS PRODUCTOS FABRICADOS, IMPORTADOS O DE TITULARIDAD DE LA SOCIEDAD, (II) PRESENTAR EN NOMBRE DE LA SOCIEDAD PROPUESTAS U OFERTAS DENTRO DE PROCESOS LICITATORIOS, INVITACIONES DIRECTAS O CUALQUIER PROCESO CONTRACTUAL. ASIMISMO, PODRÁ SUSCRIBIR LOS DOCUMENTOS QUE SE REQUIERAN PARA FORMALIZAR EL CONTRATO EN CASO DE SER ADJUDICADO A LA SOCIEDAD, (III) OTORGAR PODERES. LA OTORGACIÓN DE PODERES DE MANERA PARCIAL Y TOTAL EN NINGÚN CASO PODRÁ EXCEDER LAS CUANTÍAS ESTABLECIDAS PARA LOS DIFERENTES TIPOS DE REPRESENTANTES A, B Y C. EL OTORGAMIENTO DE PODERES ESTARÁ SUJETO A LAS REGLAS DE COMBINACIONES Y FIRMAS ESTABLECIDAS ANTERIORMENTE.

NO OBSTANTE LO ANTERIOR, EL REPRESENTANTE LEGAL CUALQUIERA SEA SU TIPO, DE FORMA INDIVIDUAL Y SIN LÍMITE DE CUANTÍA, PODRÁ FIRMAR DECLARACIONES DE CAMBIO Y DECLARACIONES DE IMPUESTOS DEL ORDEN NACIONAL Y DISTRITAL.

DE IGUAL MANERA EL REPRESENTANTE LEGAL PARA ASUNTOS LEGALES, ADMINISTRATIVOS, JUDICIALES Y EN TODAS LAS JURISDICCIONES TENDRÁ LAS SIGUIENTES FUNCIONES Y ASÍ MISMO PODRÁ OTORGAR PODERES PARA LOS SIGUIENTES ASUNTOS: 1) REPRESENTAR A LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE EN TODOS LOS ASUNTOS LEGALES, JUDICIALES, ADMINISTRATIVOS, LABORALES, CIVILES, PENALES, CONTENCIOSOS ADMINISTRATIVOS Y DEMÁS ASUNTOS RELACIONADOS; 2) ADELANTAR TODO TIPO DE TRÁMITES ANTE CUALQUIER AUTORIDAD O ENTIDAD PÚBLICA; 3) REPRESENTAR A LA SOCIEDAD EN AUDIENCIAS JUDICIALES, CONCILIAR, RECIBIR, TRANSIGIR, DESISTIR Y CONFERIR PODERES EN RELACIÓN CON LAS ATRIBUCIONES AQUÍ DESCRITAS PARA DICHO REPRESENTANTE.

ADICIONALMENTE, Y CON LAS LIMITACIONES DE MONTOS ANTES EXPUESTAS, EL REPRESENTANTE LEGAL PODRÁ

- 1) CUMPLIR Y HACER CUMPLIR LAS DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y HACER USO DE LA RAZÓN SOCIAL;
- 2) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS

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AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICÍAS ADUANALES, POSTALES, Y DEMÁS APLICABLES.

3) ORGANIZAR LOS SERVICIOS Y LAS OFICINAS DE LA SOCIEDAD, LA CONTABILIDAD Y APLICAR LOS ESTATUTOS Y REGLAMENTOS;

4) LLEVAR A CABO LA GESTIÓN COMERCIAL Y FINANCIERA;

5) TENDRÁ LA PLENA RESPONSABILIDAD DE LA ACCIÓN ADMINISTRATIVA, LA COORDINACIÓN Y LA SUPERVISIÓN GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRÁ CON ARREGLO A LAS NORMAS DE ESTOS ESTATUTOS;

6) COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALESQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GÉNERO DE RECURSOS Y CONSTITUIR APODERADO QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE.

7) HACER DEPÓSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARÉS, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASÍ COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS Y PAGARLOS, DESCARGARLOS, ETC.;

8) NOMBRAR Y REMOVER LIBREMENTE A LOS EMPLEADOS DISTINTOS DE LOS QUE LA ASAMBLEA GENERAL DE ACCIONISTAS TENGA ATRIBUCIONES; DE ACUERDO AL REGLAMENTO INTERNO DE LA COMPAÑÍA.

9) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS EN SUS REUNIONES ORDINARIAS, EL INFORME SOBRE LA FORMA COMO HAYA LLEVADO A CABO SU GESTIÓN E INNOVACIONES QUE CONVENGA INTRODUCIR PARA EL MEJOR SERVICIO DE SUS INTERESES;

10) SUSCRIBIR TODA CLASE DE DOCUMENTOS PÚBLICOS O PRIVADOS CON EL PROPÓSITO DE INSTRUMENTAR CUALQUIER TIPO DE ACTOS, NEGOCIOS JURÍDICOS, OPERACIONES DE CUALQUIER ÍNDOLE, Y SIEMPRE Y CUANDO NO SUPERE LA CUANTÍA PREVISTA EN ESTOS ESTATUTOS COMO LÍMITE DEL EJERCICIO DE SUS FUNCIONES Y CUANTÍAS, Y POR ENCIMA DE LA CUAL REQUIERE AUTORIZACIÓN DE LA ASAMBLEA DE ACCIONISTAS;

11) PODRÁ EJERCER LA REPRESENTACIÓN LEGAL SIN PERJUICIO DE LA MISMA FUNCIÓN ASIGNADA A LOS OTROS REPRESENTANTES LEGALES PARA OTORGAR PODERES A TERCEROS, NOMBRAR ABOGADOS Y PROCURADORES, INTERPONER RECLAMACIONES EN LA VÍA GUBERNATIVA, ANTE TRIBUNALES, JURISDICCIONES ORDINARIAS, LABORALES Y ESPECIALES, REPRESENTAR A LA SOCIEDAD ANTE ADMINISTRACIONES O HACIENDAS PÚBLICAS, PRIVADAS, NACIONALES, INTERNACIONALES Y AUTONÓMICAS, CONCURRIR A TODA CLASE DE SUBASTAS, CONCURSOS O SUMINISTROS OFICIALES O PARTICULARES, PUDIENDO POR TANTO REDACTAR, SUSCRIBIR, PRESENTAR Y, EN SU CASO, MEJORAR EN LICITACIÓN VERBAL O ESCRITA LAS OFERTAS O PROPOSICIONES PERTINENTES, ACEPTAR DONACIONES PARA LA SOCIEDAD Y ACEPTAR CON BENEFICIO DE INVENTARIO, LEGADOS,

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EJERCITAR ACCIONES O PONER EXCEPCIONES, PARA ACTUAR EN CALIDAD DE DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE;

12) RESOLVER SOBRE LAS RENUNCIAS Y LICENCIAS DE LOS EMPLEADOS DE LA COMPAÑÍA, CUYO NOMBRAMIENTO LE CORRESPONDA.

13) ORDENAR LOS PAGOS A REALIZAR POR LA SOCIEDAD PARA QUE EL TESORERO O QUIEN HAGA SUS VECES, EXPIDA LAS ÓRDENES DE PAGO USANDO EL MEDIO MÁS EXPEDITO PARA CONTAR CON LA CELERIDAD QUE LOS NEGOCIOS SOCIALES EXIGEN; TODO ELLO DENTRO DE LAS LIMITACIONES ESTABLECIDAS EN ESTOS ESTATUTOS.

14) LOS REPRESENTANTES TIPO B Y C NO PODRÁN VENDER O AUTORIZAR LA VENTA DE LOS INTANGIBLES DE LA COMPAÑÍA.

15) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A LOS ESTATUTOS. SON FUNCIONES DEL REPRESENTANTE LEGAL PARA ASUNTOS LEGALES, ADMINISTRATIVOS Y JUDICIALES EN TODAS LAS JURISDICCIONES LAS SIGUIENTES: 1) REPRESENTAR A LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE EN TODOS LOS ASUNTOS JUDICIALES, ADMINISTRATIVOS, LABORALES, CIVILES, PENALES, CONTENCIOSOS ADMINISTRATIVOS, Y DEMÁS ASUNTOS RELACIONADOS; 2) ADELANTAR TODO TIPO DE TRÁMITES ANTE CUALQUIER AUTORIDAD O ENTIDAD PÚBLICA; 3) REPRESENTAR A LA SOCIEDAD EN AUDIENCIAS JUDICIALES, CONCILIAR, RECIBIR, TRANSIGIR, DESISTIR Y CONFERIR PODERES EN RELACIÓN CON LAS ATRIBUCIONES AQUÍ DESCRITAS.

CERTIFICA:

DOCUMENTO: ACTA No. 127 DEL 12 DE DICIEMBRE DE 2012

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 14 DE DICIEMBRE DE 2012 No. 14639 DEL LIBRO IX

FUE(ON) NOMBRADO(S):

REPRESENTANTE LEGAL TIPO A

ALEJANDRO WEINSTEIN MANIEU

PPTE.5920870-5

REPRESENTANTE LEGAL TIPO A

ALEJANDRO WEINSTEIN CRENOVICH

PPTE.2228962-4

REPRESENTANTE LEGAL TIPO A

NICOLAS WEINSTEIN MANIEU

PPTE.5920871-3

REPRESENTANTE LEGAL TIPO A

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NICOLAS WEINSTEIN DIAZ
PPTE.15376690-8
REPRESENTANTE LEGAL TIPO B
PATRICIO VARGAS MUÑOZ
PPTE.12232715-9
REPRESENTANTE LEGAL TIPO B
VICTOR JULIO CHUNCO
C.E.439831
REPRESENTANTE LEGAL TIPO B
AGUSTIN EGUIGUREN
PPTE.11472453-K
REPRESENTANTE LEGAL TIPO C
LUIS PALACIOS
C.C.319788
REPRESENTANTE LEGAL TIPO C
FRANCISCO JAVIER PICART LAURENZ
C.E.399661
REPRESENTANTE LEGAL TIPO C
JULIO ESPINOZA OVALLE
PPTE.10931698-9

CERTIFICA:

DOCUMENTO: ACTA No. 131 DEL 17 DE JUNIO DE 2013
ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS
INSCRIPCION: 24 DE JUNIO DE 2013 No. 7218 DEL LIBRO IX
FUE(ON) NOMBRADO(S):
REPRESENTANTE LEGAL PARA ASUNTOS LEGALES, ADMINISTRATIVOS Y JUDICIALES
TITO NOE PARRA MURILLO
C.C.79579680

CERTIFICA:

DOCUMENTO: ACTA No. 129 DEL 21 DE MARZO DE 2013
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 29 DE AGOSTO DE 2013 No. 10088 DEL LIBRO IX
FUE(ON) NOMBRADO(S):
REPRESENTANTE LEGAL TIPO C
VICTOR JULIO CHUNCO

*** CONTINUA ***

57

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2013/12/13

HORA: 08:22:54

OPERACION: 02LJS1213021

PAGINA: 10

C.E.439831

CERTIFICA:

DOCUMENTO: ACTA No. 130 DEL 15 DE MAYO DE 2013

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 28 DE MAYO DE 2013 No. 6165 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

REVISOR FISCAL FIRMA

BDO AUDIT S.A.

NIT.860600063-9

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 21 DE MAYO DE 2013

ORIGEN: BDO AUDIT S.A.

INSCRIPCION: 28 DE MAYO DE 2013 No. 6166 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL

GIOVANNI MOSQUERA RAYO

C.C.16739734

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 06 DE NOVIEMBRE DE 2013

ORIGEN: BDO AUDIT S.A.

INSCRIPCION: 20 DE NOVIEMBRE DE 2013 No. 13443 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

REVISOR FISCAL SUPLENTE

CARLOS ANDRES BUENO PORTILLA

C.C.16506322

CERTIFICA:

CAPITAL AUTORIZADO: \$40,000,000,224

NUMERO DE ACCIONES: 3,333,333,352

VALOR NOMINAL: \$12

CAPITAL SUSCRITO: \$24,140,480,940

NUMERO DE ACCIONES: 2,011,706,745

VALOR NOMINAL: \$12

CAPITAL PAGADO: \$24,140,480,940

NUMERO DE ACCIONES: 2,011,706,745

VALOR NOMINAL: \$12

*** CONTINUA ***



01

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2013/12/13

HORA: 08:22:54

OPERACION: 02LJS1213021

PAGINA: 11

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 03 DE DICIEMBRE DE 2009
INSCRIPCIÓN: 28 DE DICIEMBRE DE 2009 BAJO EL NRO. 14869 DEL LIBRO IX
CONSTA LA SITUACIÓN DE CONTROL:
CONTROLANTE: DORAL INVESTMENTS INTERNATIONAL INC
DOMICILIO: PROVINCIA DE PANAMA
ACTIVIDAD: OTRAS ACTIVIDADES EMPRESARIALES
CONTROLADA: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S.
NIT: 890301463-8
DOMICILIO: CALI VALLE
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: LA FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA
REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS,
PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTOS FUNCIONALES, COSMÉTICOS Y
FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS
DIETÉTICOS, COLORANTES DE PERFUMERÍA Y AFINES.
PRESUPUESTO DE CONTROL: POSEE PARTICIPACIÓN ACCIONARIA MAYOR AL 50% A PARTIR
DEL 10 DE NOVIEMBRE DE 2009.

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 30 DE ABRIL DE 2004
INSCRIPCIÓN: 03 DE MAYO DE 2004 No. 4859 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 29 DE ABRIL DE 2005
INSCRIPCIÓN: 06 DE MAYO DE 2005 No. 4983 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 15 DE JUNIO DE 2006
INSCRIPCIÓN: 21 DE JUNIO DE 2006 No. 7526 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 01 DE NOVIEMBRE DE 2006
INSCRIPCIÓN: 28 DE NOVIEMBRE DE 2006 No. 13380 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE DICIEMBRE DE 2006
INSCRIPCIÓN: 21 DE DICIEMBRE DE 2006 No. 14301 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE DICIEMBRE DE 2007
INSCRIPCIÓN: 21 DE DICIEMBRE DE 2007 No. 13604 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE OCTUBRE DE 2009
INSCRIPCIÓN: 22 DE OCTUBRE DE 2009 No. 12216 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 23 DE FEBRERO DE 2010
INSCRIPCIÓN: 25 DE FEBRERO DE 2010 No. 2203 DEL LIBRO IX

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2013/12/13

HORA: 08:22:54

OPERACION: 02LJS1213021

PAGINA: 12

DOCUMENTO: DOCUMENTO PRIVADO DEL 27 DE ABRIL DE 2010
INSCRIPCIÓN: 28 DE ABRIL DE 2010 NRO. 4911 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 10 DE JUNIO DE 2010
INSCRIPCION: 17 DE JUNIO DE 2010 NRO. 7195 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 25 DE AGOSTO DE 2010
INSCRIPCION: 07 DE SEPTIEMBRE DE 2010 BAJO EL NRO. 10541 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 14 DE JUNIO DEL 2011
INSCRIPCION: 22 DE JUNIO DE 2011 BAJO EL NRO. 7772 LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 02 DE MAYO DE 2012
INSCRIPCION: 03 DE MAYO DEL 2012 NRO. 5421 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 01 DE JUNIO DE 2012
INSCRIPCIÓN: 05 DE JUNIO DEL 2012 NRO. 6825 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 22 DE AGOSTO DE 2012
INSCRIPCIÓN: 31 DE AGOSTO DEL 2012 NRO. 10510 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 15 DE NOVIEMBRE DE 2012
INSCRIPCION: 21 DE NOVIEMBRE DE 2012 No. 13665 DEL LIBRO IX
CONSTA EL SIGUIENTE GRUPO EMPRESARIAL:

CONTROLANTE

LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S

NIT. 890301463-8

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

ACTIVIDAD: A) LA FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES DE PERFUMERÍA Y AFINES. B) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACIÓN, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PUEDE LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAÍCES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAÍCES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD, DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS

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01

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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OPERACION: 02LJS1213021

PAGINA: 13

CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

SUBORDINADA

AMERICAN GENERICS S A S

NIT. 800223214-9

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTÍCULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LAFRANCOL INTERNACIONAL S.A.S.

NIT. 815003912-2

DOMICILIO: PALMIRA VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: LA SOCIEDAD EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ REALIZAR, ENTRE OTROS, LAS SIGUIENTES ACTIVIDADES COMERCIALES Y EMPRESARIALES DESDE LA ZONA FRANCA CUMPLIENDO LAS NORMAS DEL RÉGIMEN FRANCO: 1) LA PRESTACIÓN DE TODO TIPO DE SERVICIOS ASI COMO FABRICAR, DISTRIBUIR, VENDER, COMPRAR, IMPORTAR Y EXPORTAR TODO TIPO DE MATERIAS PRIMAS, PRODUCTOS TERMINADOS Y SEMITERMINADOS RELACIONADOS CON LA INDUSTRIA DE ALIMENTOS FUNCIONALES, COSMÉTICA Y FARMACÉUTICA. 2) DESARROLLAR Y EJECUTAR EN CUALQUIER FORMA O MODO SERVICIOS LOGÍSTICOS, CONTRATAR DIRECTAMENTE O MEDIANTE CONTRATO EXTERNO TODAS Y CADA UNA DE SUS ACTIVIDADES O SERVICIOS. 3) CELEBRAR CUALQUIER TIPO DE CONTRATO DE FABRICACIÓN DE MAQUILA CON ENTIDADES COLOMBIANAS O EXTRANJERAS.

SUBORDINADA

LAFRANCOL PERÚ S.R.L.

DOMICILIO: LIMA

NACIONALIDAD: PERU

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LABORATORIOS PAULY PHARMACEUTICAL S.A.S.

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2013/12/13

HORA: 08:22:54

OPERACION: 02LJS1213021

PAGINA: 14

NIT. 800097402-6

DOMICILIO:CALI VALLE

NACIONALIDAD:COLOMBIA

PRESUPUESTO DE CONTROL:NUMERAL 1, ARTÍCULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LAFRANCOL GUATEMALA S.A.

NIT. 4088707

DOMICILIO:GUATEMALA

NACIONALIDAD:GUATEMALA

PRESUPUESTO DE CONTROL:NUMERAL 1, ARTÍCULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: PRODUCCIÓN, FABRICACIÓN, EXPORTACIÓN Y DISTRIBUCIÓN DE PRODUCTOS FARMACÉUTICOS Y/O ALIMENTICIOS Y NATURALES DE CONSUMO HUMANO Y LA COMERCIALIZACIÓN DE TODA CLASE DE MERCANCÍAS POR CUENTA PROPIA O EN NOMBRE DE TERCEROS.

SUBORDINADA

DISTRIBUCIONES UQUIFA S A S

NIT. 800182021-7

DOMICILIO:CALI VALLE

NACIONALIDAD:COLOMBIA

PRESUPUESTO DE CONTROL:NUMERAL 1, ARTÍCULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS Y ALIMENTOS FUNCIONALES DE CONSUMO HUMANO.

SUBORDINADA

LABORATORIOS NATURMEDIK S A S

NIT. 800226363-1

DOMICILIO:CALI VALLE

NACIONALIDAD:COLOMBIA

PRESUPUESTO DE CONTROL:NUMERAL 1, ARTÍCULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LAFRANCOL DOMINICANA S.A.S.

DOMICILIO:SANTO DOMINGO REPÚBLICA DOMINICANA

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01



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2013/12/13

HORA: 08:22:54

OPERACION: 02LJS1213021

PAGINA: 15

NACIONALIDAD: REPÚBLICA DOMINICANA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTÍCULO 27 DE LA LEY 222.

ACTIVIDAD: FABRICACIÓN DE PRODUCTOS FARMACÉUTICOS.

SUBORDINADA

FOCUS PHARMACEUTICAL S.A.S.

NIT: 900.104.555-8

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995. LA FECHA DE LA PRIMERA TRANSACCION COMERCIAL FUE EN ENERO DE 2010 Y LA CAPITALIZACION SE HIZO EN ENERO DE 2010.

ACTIVIDAD: EL OBJETO PRINCIPAL DE LA SOCIEDAD ES EL DESARROLLO, FABRICACIÓN O PRODUCCIÓN, DIRECTAMENTE O A TRAVÉS DE TERCEROS EN CUALQUIER MODALIDAD NEGOCIAL, LA COMERCIALIZACIÓN Y DISTRIBUCIÓN, NACIONAL O INTERNACIONAL, DE TODA CLASE DE ARTÍCULOS DE GÉNERO FARMACÉUTICO, ESPECÍFICAMENTE DE MEDICAMENTOS ESA ACTIVIDAD PRINCIPAL CONLLEVA LA HABILITACIÓN PARA DESARROLLAR TODA OTRA CONEXA O NECESARIA, INCLUYENDO DE MANERA ESPECIAL PERO NO LIMITATIVA, LA INVESTIGACIÓN FARMACÉUTICA, EL DESARROLLO DE PRODUCTOS MÉDICOS Y FARMACÉUTICOS, EQUIPOS MÉDICOS, TRATAMIENTOS ALTERNATIVOS Y EN GENERAL, TODO AQUELLO VINCULADO A LA PROTECCIÓN DE LA SALUD HUMANA.

PODRÁ EFECTUAR LA INVERSIÓN EN BIENES INMUEBLES, URBANOS O RURALES Y LA ADQUISICIÓN, ADMINISTRACIÓN, ARRENDAMIENTO, GRAVAMEN Y ENAJENACIÓN DE LOS MISMOS.

LA INVERSIÓN DE FONDOS PROPIOS, EN BIENES INMUEBLES, BONOS, VALORES BURSÁTILES Y PARTES DE INTERÉS EN SOCIEDADES COMERCIALES, ASÍ COMO LA NEGOCIACIÓN DE TODA CLASE DE DERECHOS DE CRÉDITO.

CERTIFICA:

SE DEJA CONSTANCIA ASI MISMO, QUE LOS REPRESENTANTES LEGALES TIPO C ANTES DESIGNADOS DEBERÁN ACTUAR SIEMPRE DE LA SIGUIENTE FORMA:

JUAN CAMILO PALACIO CON JAVIER PICART; O

LUIS PALACIOS CON ROBERTO VENTURA; O

JULIO ESPINOZA CON JUAN CAMILO PALACIO; O

JULIO ESPINOZA CON LUIS PALACIOS; O

JULIO

ESPINOZA

CON

JAVIER

PICART

CERTIFICA:

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60

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2013/12/13

HORA: 08:22:54

OPERACION: 02LJS1213021

PAGINA: 16

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL

UBICADO EN: ---K 1 46 84 DE CALI

RENOVO : POR EL AÑO 2013

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.870576- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS FRANCO COLOMBIANO
LAFRANCOL SAS

UBICADO EN: CL. 36A NRO. 4 05 DE CALI

FECHA MATRICULA : 02 DE MAYO DE 2013

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 19 DE
MARZO DE 2013 .

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL
PRESENTE CERTIFICADO.

LOS ACTOS ADMINISTRATIVOS DE REGISTRO QUEDAN EN FIRME DIEZ (10) DIAS HABILES
DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO
TERMINO NO SEAN OBJETO DE RECURSOS.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR
LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A
CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 13 DIAS DEL MES DE DICIEMBRE DEL AÑO 2013 HORA: 08:56:56
AM

