

ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

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132

As. 2528/PCT.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Ref.: Expediente No. 03-009.952
Solicitud de Patente a nombre de
Ortho-McNeil Pharmaceutical, Inc.

SUPERINDUSTRIA Y COMERCIO	
Radicacion : 03009952 00000004	Folios: 2
Fecha (AND): 2004-06-08 16:03:35	
Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION	
Dependencia: PARA ATENCION DE NUEVAS CREACIONES	

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad **Ortho-McNeil Pharmaceutical, Inc.**, domiciliada en Raritan, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 04 - 38,507 de mayo 14, 2004, por la suma de \$353.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


JIMENA ESCOBAR URIBE
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T.P. 68.228
Cod. 5376
JEU/ra.

NIT : 000176004-2

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03009952 00000004

Folios: 2

Fecha (AMH): 2004-06-08 16:03:35

Tramite : 011 PCI-PATENT 379 FASE HACI 530 PETICION

Residencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 38,307

FECHA : MAYO 14 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4992973	13/05/2004	2,790,000.00

***** CONCEPTO *****

CANT. CONTISTICO	CONCEPTO	TOTAL CONCEPTO
1 00005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	353,000.00
	TOTAL :	\$ 353,000.00

SON: TRESCIENTOS CINCUENTA Y TRES MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

134

2020
Bogotá, D.C.,

Doctora:
Jimena Escobar Uribe
Apoderada
Ortho-McNeil Pharmaceutical, Inc.

Oficio N° 888

ASUNTO:	Radicación N°	03-9952
	Solicitud internacional	PCT/US01/41565
	Trámite	011
	Evento	379
	Actuación	416
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones, para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá D.C.,

10 DIC. 2003


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

202021



PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: 2004 / 06 / 08 / AAAA MM DD 16:03:35	Recorrido:
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐		
Radicator:		Planilla:

ID	No. Radicación	Consecutivo	Item
1	03009952	135-140	6
2			
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Item	Unidad de Conservación
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Toma
6	Otro
Item	Soporte Documental
7	CD
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

[illegible]

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-9952

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 536

DE FECHA 30 DE ENERO DE 2004 EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL 28 DE ABRIL DEL 2004

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO ☒ _____

Bogotá D.C, 2007

(19)  **Europäisches Patentamt**
European Patent Office
Office européen des brevets



(11) **EP 0 949 242 A1**

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 published in accordance with Art. 158(3) EPC

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 C07C 209/10, C07D 239/42,
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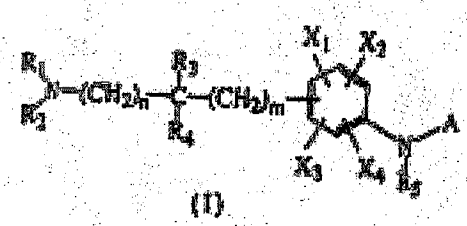
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(54) **AROMATIC AMINE DERIVATIVES HAVING NOS INHIBITORY EFFECT**

(57) Compounds represented by the general formula (1):



(where R₁ and R₂ are typically a hydrogen atom; R₃ and R₄ are typically a hydrogen atom or a lower alkyl group; R₅ is typically a hydrogen atom; X₁, X₂, X₃ and X₄ are typically a hydrogen atom or a lower alkoxy group; A is typically an optionally substituted pyridine ring; m and n are each 0 or 1) have an NOS inhibiting activity and are useful as therapeutics of cerebrovascular diseases and other pharmaceuticals.

EP 0 949 242 A1

Description

TECHNICAL FIELD

8 [0001] This invention relates to N-substituted aniline derivatives, more particularly to compounds represented by the general formula (I) that have a nitric oxide synthase (NOS) inhibiting action to suppress the production of nitric oxide (NO) and thereby prove effective against disorders and diseases in which excessive NO or NO metabolites are supposedly involved, namely, cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothrombotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus. The invention also relates to possible tautomers, stereoisomers and optically active forms of said compounds, as well as pharmaceutically acceptable salts thereof. The invention further relates to preventives and therapeutics that contain said compounds, derivatives or pharmaceutically acceptable salts as active ingredients.

BACKGROUND ART

20 [0002] The number of deaths from cerebrovascular diseases in Japan had increased until 1970 when it began to decline mostly due to the improvement in their acute-phase therapy. Nevertheless, cerebrovascular diseases remain the second leading cause of death among adult diseases, next only to cancers. As for the incidence of cerebrovascular diseases, many statistical surveys indicate that it is generally constant and in view of the fact that the number of elderly persons will increase at an uncomparably faster speed in Japan than any other country in the world, the number of patients suffering from cerebrovascular diseases is estimated to increase rather than decrease in the future. The declining mortality and the growing population of aged people combine to increase the cases of cerebrovascular diseases in the chronic phase and this has presented with a national problem not only from the aspects of individual patients and society at large but also from the viewpoint of medical economics since patients with chronic cerebrovascular disease are inevitably involved in long-term care. In cerebral infarction that accounts for most cases of cerebrovascular diseases, cerebral arteries are occluded and blood deficit starting at the blocked site extends to the peripheral site, causing an ischemic state. The symptoms of cerebral infarction in the chronic phase are in almost all cases derived from the loss of neurons and it would be extremely difficult to develop medications or established therapeutic methods for achieving complete recovery from those symptoms. Therefore, it is no exaggeration that the improvement in the performance of treatments for cerebral infarction depends on how patients in an acute phase can be treated with a specific view to protecting neurons and how far their symptoms can be ameliorated in the acute phase. However, most of the medications currently in clinical use are antiplatelet drugs, anticoagulants and thrombolytics and none of these have a direct nerve protecting action (see Kazuo MINEMATSU et al., "MEDICINA", published by Igaku Shoin, 32, 1995 and Hideniro MIZUSAWA et al., published by Nankodo, "Naika" 79, 1997). Therefore, it is desired to develop a drug that provides an effective therapy for cerebrovascular diseases, in particular cerebral infarction, by working in an entirely novel and different mechanism of action from the conventional medications.

40 [0003] A presently dominant theory based on genetic DNA analyses holds that NOS exists in at least three isoforms, namely, calcium-dependent nNOS (type 1) which is present constitutively in neurons, calcium-dependent eNOS (type 3) which is present constitutively in vascular endothelial cells, and apparently calcium-independent iNOS (type 2) which is induced and synthesized by stimulation with cytokines and/or lipopolysaccharides (LPS) in macrophages and many other cells (Nathan et al., FASEB J. 16, 3051-3064, 1992; Nagafuji et al., Mol. Chem. Neuropathol. 25, 107-157, 1995).

45 [0004] A mechanism that has been proposed as being most probable for explaining the brain tissue damage which accompanies cerebral ischemia is a pathway comprising the sequence of elevation in the extracellular glutamic acid level, hyperactivation of glutamic acid receptors on the post-synapses, elevation in the intracellular calcium level and activation of calcium-dependant enzymes (Siesjö, J. Cereb. Blood Flow Metab. 1, 155-185, 1981; Siesjö, J. Neurosurg. 60, 883-908, 1984; Choi, Trends Neurosci. 11, 465-469, 1988; Siesjö and Bengtsson, J. Cereb. Blood Flow Metab. 9, 127-140, 1989). As already mentioned, nNOS is calcium-dependent, so the inhibition of hyperactivation of this type of NOS isoforms would contribute to the neuro-protective effects of NOS inhibitors (Dawson et al., Annals Neurol. 32, 297-311, 1992).

50 [0005] As a matter of fact, the mRNA level of nNOS and the number of nNOS containing neurons start to increase early after focal cerebral ischemia in rats and their temporal alterations coincide with the development of infarction (Zhang et al., Brain Res. 654, 85-95, 1994). In addition, in a mouse model of focal cerebral ischemia, the percent inhibition of nNOS activity and the percent reduction of infarct volume correlate to each other at least in a dose range of N^G-nitro-L-arginine (L-NA) that produces a recognizable infarct volume reductive action (Carreau et al., Eur. J. Pharmacol. 255, 241-249, 1994). Further in addition, it has been reported that in nNOS knockout mice, the infarct volume

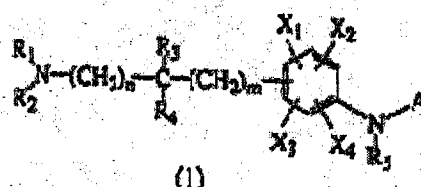
J. Biol. Chem. 37, 885-887, 1994; Furtine et al. J. Biol. Chem. 269, 26577-26583, 1994; WO95/09619; Narayanan et al., J. Biol. Chem. 270, 11103-11110, 1995; Nagaiji et al., Neuroreport 6, 1541-1545, 1995). S-ethyl-L-thiocitrulline (L-EIN) (Furtine et al., J. Biol. Chem. 269, 26577-26583, 1994; WO95/09619; Narayanan et al., J. Biol. Chem. 270, 11103-11110, 1995), and ARL 17477 (Gentile et al., WO95/05363; Zhang et al., J. Cereb. Blood Flow Metab., 16, 598-604, 1996).

[0012] In addition, the inhibitors that have been reported to have a certain degree of selectivity for iNOS are N^G-nitroethyl-L-ornithine (L-NIO) (McCall et al., Br. J. Pharmacol. 102, 234-238, 1991) and aminoguanidine (AO) (Griffith et al., Br. J. Pharmacol. 110, 963-968, 1993; Hasan et al. Eur. J. Pharmacol. 249, 101-106, 1993).

DISCLOSURE OF INVENTION

[0013] An object of the present invention is to provide novel compounds that have an inhibitory effect on calcium-dependent nNOS which is present constitutively in the brain, particularly in neurons or an inducible and apparently calcium-independent iNOS and which are useful as therapeutics of cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothrombotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus.

[0014] As a result of the intensive studies made in order to attain the stated object, the present inventors found that aromatic amine derivatives represented by the general formula (1), or possible tautomers, stereoisomers and optically active forms of said compounds, as well as pharmaceutically acceptable salts thereof have an inhibitory action on type 1 NOS and so forth, thereby exhibiting marked effectiveness as therapeutics of cerebrovascular diseases (especially as therapeutics of occlusive cerebrovascular diseases):



[where R₁ and R₂ which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group or a lower alkoxy carbonyl group, or R₁ and R₂ may combine together to form a 3- to 8-membered ring;

R₃ and R₄ which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or R₃ and R₄ may combine together to form a monocyclic or fused ring having 3 - 10 carbon atoms;

R₅ is a hydrogen atom, a lower alkyl group, an acyl group or a lower alkoxy carbonyl group;

X₁, X₂, X₃, and X₄, which may be the same or different are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl group, an optionally substituted lower alkyl group, a lower alkenyl group, a lower alkynyl group, an optionally substituted lower alkoxy group, an optionally substituted lower alkylthio group, a phenyl group optionally substituted by a halogen atom and/or a lower alkyl group, NX₅X₆ or C(=O)X₇;

where X₅ and X₆ which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxy carbonyl group, or X₅ and X₆ may combine together to form a 3- to 8-membered ring;

X₇ is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, or NX₈X₉;

where X₈ and X₉ which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X₈ and X₉ may combine together to form a 3- to 8-membered ring;

A is an optionally substituted benzene ring or a 5- or 6-membered aromatic hetero ring which is optionally substituted and which contains at least one nitrogen atom as a hetero atom;

n and m are each an integer of 0 or 1).

[0015] The present invention has been accomplished on the basis of this finding.

[0016] The present invention also provides a process for producing a compound of the general formula (1) which is

1,4-dioxane or methylene chloride or without using any solvent at all, with the aid of a deprotecting agent such as trifluoroacetic acid, hydrochloric acid, sulfuric acid or methanesulfonic acid at a temperature between 0°C and room temperature, with the use of anhydrous conditions, room temperature and trifluoroacetic acid being particularly preferred.

6 [0047] If the compounds of the invention which are represented by the general formula (1) have asymmetric carbons in their structure, the pure forms of their stereoisomers and optically active forms can be obtained by known techniques in the art, such as chromatography or optical isomer separating columns and fractional crystallization.

10 [0048] Pharmaceutically acceptable salts of the compounds of the invention which are represented by the general formula (1) may be of any types as long as they are pharmaceutically acceptable salts and typical examples include salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobromic acid and hydroiodic acid, salts with organic acids such as formic acid, acetic acid, oxalic acid and tartaric acid, salts with alkali metals such as sodium and potassium, and salts with alkaline earth metals such as calcium and magnesium.

15 [0049] The compounds of the invention or salts thereof may be formulated with suitable excipients, adjuvants, lubricants, antiseptics, disintegrators, buffering agents, binders, stabilizers, wetting agents, emulsifiers, coloring agents, flavoring agents, fragrances, etc. to form tablets, granules, sublingual granules, powders, capsules, syrups, elixirs, suspensions, emulsions, injections, etc. for oral or parenteral administration. When the cerebrovascular diseases to be treated are in a hyperacute phase (immediately after the stroke), an acute phase (from the stroke to 2 or 3 days later) or in a subacute phase (2 or 3 days up to 2 weeks after the stroke), administration is effected primarily by intramuscular or intravenous injection. In addition, oral administration may be performed in a chronic phase (the third week after stroke and onward) if the patient admits ingestion.

20 [0050] The compounds of the invention or salts thereof may be administered in doses that vary with the physical constitution of the patient, his or her age, physical condition, the severity of the disease, the time of lapse after the onset of the disease and other factors; typical daily doses range from 0.5 to 5 mg/body for oral administration and from 1 to 10 mg/body for parenteral administration. It should generally be noted that even if the same dose is administered, the plasma concentration may sometimes vary considerably between patients; hence, an optimal dose of the drug should ideally be determined for each patient on the basis of a monitored plasma concentration of the drug.

25 [0051] If the compounds of the invention or salts thereof are to be formulated as preparations for internal application, lactose, sucrose, sorbitol, mannitol, starches such as potato starch or corn starch, starch derivatives and common additives such as cellulose derivatives or gelatin are suitably used as vehicles, with lubricants such as magnesium stearate, carbowaxes and polyethylene glycol being optionally added concurrently; the resulting mixtures may be formulated in the usual manner into granules, tablets, capsules or other forms suitable for internal application.

30 [0052] If the compounds of the invention or salts thereof are to be formulated as aqueous preparations, effective amounts of the principal ingredients may be dissolved in distilled water for injection, with antioxidants, stabilizers, dissolution aids, buffering agents, preservatives, etc. added as required and, after complete solutions are formed, they are filtered, filled into ampules and sealed in the usual manner and sterilized by a suitable medium such as high-pressure vapor or dry heat so as to prepare injections.

35 [0053] If the compounds of the invention or salts thereof are to be formulated as lyophilized preparations, aqueous solutions having the principal ingredients dissolved in distilled water for injection may be freeze-dried in the usual manner; depending on the need, excipients that provide for easy lyophilization, such as sugars (e.g. lactose, maltose and sucrose), sugar alcohols (e.g. mannitol and inositol), glycine and the like, may be added before freeze-drying is performed in the usual manner to make the intended preparations.

Examples

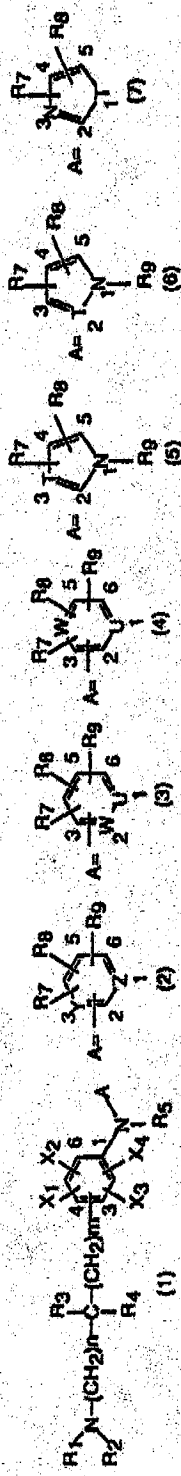
40 [0054] Lists of the compounds prepared in the Examples of the invention are given in Tables 1 - 37 below.

Table 60

Example	Reagent	Product	Spectral data
495			¹ H-NMR (DMSO-d ₆) δ 2.19 (3H, s), 3.79 (3H, s), 3.94 (2H, q, J=5.6 Hz), 6.16 (1H, d, J=7.6 Hz), 7.03 (1H, d, J=7.9 Hz), 7.29 (1H, dd, J=7.9, 7.9 Hz), 7.36 (1H, d, J=7.6 Hz), 7.64 (1H, d, J=7.9 Hz), 7.82 (1H, s), 7.95 (1H, brs), 8.35 (3H, brs)
496			¹ H-NMR (DMSO-d ₆) δ 3.74 (3H, s), 3.88 (3H, s), 4.00 (2H, q, J=5.3 Hz), 6.35 (1H, d, J=2.3 Hz), 6.46 (1H, dd, J=9.6, 2.3 Hz), 7.15 (1H, d, J=8.6 Hz), 7.40 (1H, d, J=8.6 Hz), 7.43 (1H, s), 8.13 (1H, d, J=9.6 Hz), 8.18 (3H, brs), 9.60 (1H, s)
501			¹ H-NMR (DMSO-d ₆) δ 2.25 (3H, s), 4.21 (2H, q, J=5.6 Hz), 7.26-7.50 (4H, m), 7.62 (1H, s), 7.88 (1H, d, J=10.2 Hz), 7.95 (1H, s), 8.57 (3H, brs), 10.77 (1H, brs)
502			¹ H-NMR (DMSO-d ₆) δ 2.40 (3H, s), 4.04 (2H, q, J=5.6 Hz), 7.42 (1H, dd, J=6.6, 6.6 Hz), 7.40-7.57 (3H, m), 7.66 (1H, s), 7.90-7.99 (2H, m), 8.65 (3H, brs), 9.77 (1H, brs)

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Table 36



Ex. No.	A	Y	Z	R6	Substitution position of A	R7 ¹	R8 ¹	R9 ¹	X1 ²	X2 ²	X3 ²	X4 ²	Substitution position of B	R1	R2	R3	R4	m	R5
526	(2)	CR6	N	H	2	4-H	5-CN	6-H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
527	(2)	CR6	N	CN	2	4-CO2Et	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
528	(2)	CR6	N	H	2	4-CO2H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
529	(2)	CR6	N	H	2	4-H	5-CO2H	6-H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
530	(2)	CR6	N	Cl	2	4-H	5-CO2H	6-H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
531	(2)	CR6	N	H	2	4-CO2H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
532	(2)	CR6	N	H	2	4-H	5-H	6-CO2H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
533	(2)	CR6	N	CONH2	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
534	(2)	CR6	N	CONH2	2	4-H	5-Cl	6-H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
535	(2)	CR6	N	H	2	4-CONH2	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
536	(2)	CR6	N	CONH2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
537	(2)	CR6	N	H	2	4-H	5-Br	6-H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
538	(2)	CR6	N	Cl	2	4-H	5-Cl	6-H	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
539	(2)	CR6	N	H	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	H	H	0	H
540	(2)	CR6	N	H	2	4-Me	5-H	6-H	2-OMe	4-H	5-H	6-H	3	CO2Bu	CO2Bu	H	H	0	H

*1: Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2: Numerals represent substitution positions on the benzene ring.



**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C., 8/11/2007

Abogada
JIMENA ESCOBAR URIBE
Apoderada

ASUNTO	Radicación	03009952
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	15363
	Folios	154

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒
No. Sol. Internacional	PCT/US01/41565		
Fecha de Presentación Internal.	6/08/2001		

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

1. Documentos estudiados

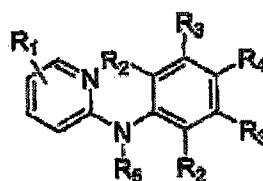
- 1.1. Descripción: Folios: 30 a 94
- 1.2. Reivindicaciones: Folios 98 a 105
- 1.3. Prioridad: Fecha: 8/8/2000, país: US, número: 60/223,795

2. Objeto de la invención

- Título de la solicitud: **Composiciones de 2-piridinamina y métodos relacionados.** Número de folio: 1.

El objeto de la presente solicitud de patente de invención consiste en composiciones farmacéuticas neuroprotectoras que comprenden 2-piridinaminas, métodos de uso de estas composiciones para prevenir y reducir la muerte celular isquémica neuronal ocasionada por un evento traumático y un aparato para administrar a un sujeto las presentes composiciones farmacéuticas.

Reivindicaciones 1 - 28: Composición farmacéutica que comprende un vehículo y un compuesto de la fórmula general (I) con sus respectivos sustituyentes y diferentes posibilidades estructurales.



Reivindicaciones 29 - 30: Método para reducir la muerte por isquemia en una población de células con una cantidad profilácticamente efectiva el compuesto de la reivindicación 1.

Reivindicaciones 31 - 43: Método para reducir la muerte de células neuronales en respuesta a un evento traumático con una cantidad profilácticamente efectiva el compuesto de la reivindicación 1.

Reivindicaciones 44 - 45: Aparato para administrar a un sujeto la composición farmacéutica de la reivindicación 1 que comprende un contenedor y la composición farmacéutica en donde el contenedor tiene un dispositivo para liberar al sujeto la dosis profiláctica de la composición.

El problema planteado en esta solicitud es la necesidad de composiciones útiles para la prevención de la muerte de células neuronales y los desórdenes que ella ocasiona.

Para solucionar este problema técnico la solicitud en estudio proporciona composiciones farmacéuticas que comprenden 2-piridinaminas, métodos de uso y un aparato para administrar las composiciones.

Clasificación Internacional de Patentes (IPC.): A61K 31/44

3. De la solicitud de Patente (según el caso)

3.1. Descripción (artículo 28 D. 486)

- La descripción no es explícita y concreta al explicar o detallar las ventajas o al salto tecnológico de la solicitud con respecto al estado de la técnica.
- No es clara en cuanto a los conceptos vagos expresados como: "reducir la muerte por isquemia", "reducir la muerte celular en respuesta a un evento traumático", "un desorden médico", "un trauma físico", "un trauma químico", "un trauma biológico".
- Se requiere al solicitante aclarar cuáles son los compuestos a los cuáles se refieren las marcas comerciales o nomenclaturas listadas contra los cuáles se está comparando actividad.

3.2. Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

instrucciones, etc.) pertenecen a diferentes campos técnicos de manera que no dan cabida al principio de unidad de invención.

5. Excepción a la patentabilidad (artículo 20 D486 literal a)-d)) (según causal)

Reivindicaciones 29-30: Se refiere a un método para reducir la muerte por isquemia en una población de células con una cantidad profilácticamente efectiva el compuesto de la reivindicación 1 por lo tanto no se acepta según la legislación vigente.

Reivindicaciones 31 - 43: Se refiere a un método para reducir la muerte de células neuronales en respuesta a un evento traumático con una cantidad profilácticamente efectiva el compuesto de la reivindicación 1 por lo tanto no se acepta según la legislación vigente.

6. Determinación del Estado de la Técnica

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

Fecha de presentación de la solicitud prioritaria 8/8/2000

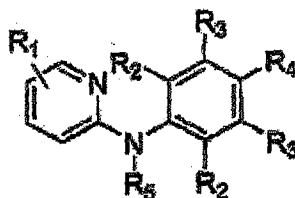
Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	EP0949242	AROMATIC AMINE DERIVATIVES HAVING NOS INHIBITORY EFFECT	13/10/1999

7. Análisis de patentabilidad (según requisito) (artículo 14 D486)

7.1 Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica (de 1 - 28) una composición farmacéutica con el siguiente compuesto de fórmula general I:

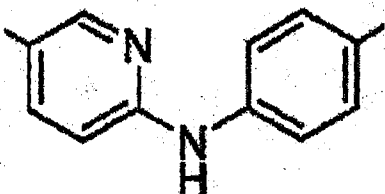
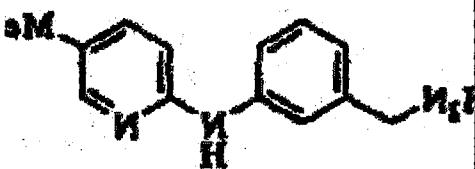
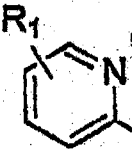
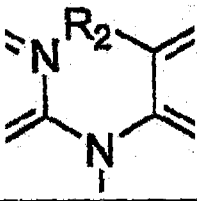
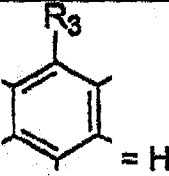
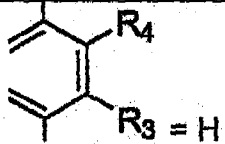
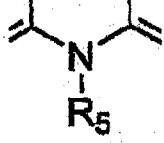


Dicho compuesto se ve afectado por el siguiente documento más cercano del Estado de la Técnica:

D₁ que enseña compuestos derivados de anilina N-sustituídos (2-piridinaminas) con actividad inhibitoria NOS (sintetasa oxido nítrico) y útiles para terapias en enfermedades cerebrovasculares (hemorragia cerebral, hemorragia

subaracnoidea, infarto cerebral, ataque isquémico, edema cerebral, daño cerebral traumático, enfermedad de parkinson) y otras que pueden ser administrados parenteralmente durante las fases hiperaguda, aguda o postaguda. (Ver folios: 143-146).

TABLA 1

SOLICITUD		ANTERIORIDAD (D1)	Estado comparativo
(I)	 Ej 1 folios 53-56	 Ej 501 folio 147 (se invierte para observar equivalencias)	
R ₁	 = H o un sustituyente alquilo, alquenoilo, alquinilo	H, Me	Equivalente
R ₂	 = H	H	Equivalente
R ₃	 = H R₃ = H, alquilo, amino, alquilamino, dialquilamino, alcoxi	H, amino	Equivalente
R ₄	 R₃ = H	H	Equivalente
R ₅	 = H o alquilo	H	Equivalente

La única diferencia con D₁ para este ejemplo es que el N de la piridina se ubica en una posición diferente pero esta diferencia no parece conceder un efecto técnico inesperado o una ventaja que otorgue un salto tecnológico ventajoso excepcional.

De esta forma no puede determinarse un efecto técnico que logre la diferencia con la anterioridad encontrada porque la descripción no presenta datos en tal sentido ya que se presentan datos que representan una actividad mayor al 80% contra las anterioridades que allí se listan (folios 68 y 69) pero no se observan las diferencias o comparaciones con respecto a la anterioridad estudiada en el presente examen.

No es posible hacer una evaluación para los demás compuestos debido a las inexactitudes y la amplitud de las reivindicaciones explicada en el ítem 3. Se requiere al solicitante hacer las precisiones necesarias.

Por consiguiente, de acuerdo a las consideraciones expuestas anteriormente, resultaría obvio el diseño de este tipo de composiciones y para un experto en la materia y sus compuestos habrían sido ya conocidos en el estado de la técnica.

De esta forma el Problema Técnico Objetivo fundamental de la Invención Reivindicada no puede definirse y los compuestos y composiciones reivindicados se consideran tan solo una alternativa, sin algún salto tecnológico que lo haga superior a lo previamente conocido.

13. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	EP 0949242	1 - 28	Nivel inventivo

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

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

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
30 NOV. 2007

CONCEPTO TÉCNICO No. 2214	EXAMINADOR TÉCNICO Código No. 202087
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