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Señores
SUPERINTENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03079612 00000001 Folios: 2
Fecha (AMD): 2004-06-17 09:32:31
Tramite : 011 PCT-PATENT 379 FASE NACI 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref: Expediente No. 03.079.612
Solicitud de patente de invención titulada:
"CONJUGADOS DE PREGABALINA-LACTOSA."
Solicitante: WARNER-LAMBERT COMPANY LLC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTICULO 44 DE LA DECISION 486, GACETA No. 535

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar, que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma. Dando cumplimiento a lo establecido en el articulo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de $177.000 pesos para cubrir la tasa correspondiente, según la Resolución 37323 del año 2003.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo:Recibo por $177.000 pesos
FTT/P2003/000121 040616

69
2

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03079612 00000001 Folios: 2
Fecha (AMD): 2004-06-17 09:32:31
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 46.372
FECHA : JUNIO 9 DE 2004

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LUZ MARINA BULLA	CONSIGNACION	BANCO POPULAR	050-00110-6	27514619	09/06/2004	6.461.000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114	PTC CAP-II EXAMEN DE PATENTIBILID	177.000.00
			TOTAL : $	177.000.00

SON: CIENTO SETENTA Y SIETE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

703.

Industria y Comercio
SUPERINTENDENCIA

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **03- 79612**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION – PCT,** FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **535**, DE FECHA **30** DE **DICIEMBRE** DE **2003**, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **26** DE **MARZO** DE **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 ____ **X** ____

Carrera 13 No. 27-00 Piso 5 y 10
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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/195 — A1

(11) International Publication Number: **WO 00/23067**

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60/104,535 16 October 1998 (16.10.98) US

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: PANDE, Atul, Chandra [US/US]; 3355 Landings Drive, Ann Arbor, MI 48103 (US).

(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, 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).

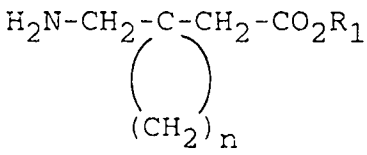
Published
With international search report.

(54) Title: METHOD FOR THE TREATMENT OF MANIA AND BIPOLAR DISORDER

(57) Abstract

The present invention is a novel therapeutic use of pregabalin, its derivatives, and the pharmaceutical salts thereof. The compounds are useful in the treatment of mania in all its various forms whether acute or chronic, single or recurrent, and whether or not it is associated with depression. The invention further includes the preventive treatment of bipolar disorder.

United States Patent Numbers 4,024,175 and 4,087,544 teach cyclic amino acids of formula



wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6 and the pharmaceutically acceptable salts thereof.

The compounds disclosed in the above United States patents are useful for the therapy of certain cerebral diseases, for example, they can be used for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia, and cranial traumas. Additionally, they bring about an improvement of cerebral functions and thus are useful in treating geriatric patients. Particularly valuable is 1-(aminomethyl)-cyclohexane-acetic acid (gabapentin).

United States Patent Number 5,084,479 teaches the compounds of the above formula for therapeutic use in neurodegenerative disorders such as Alzheimer's, Huntington's, Parkinson's, and Amyotrophic Lateral Sclerosis. It also teaches the use of the compounds in the treatment of acute brain injury such as stroke, head trauma, and asphyxia.

United States Patent Number 5,025,035 teaches the use of the compounds of the above formula for depression.

United States Patent Application Serial Number 08/281285 teaches the use of the compounds of the above formula to treat anxiety and/or panic disorders.

SUMMARY OF THE INVENTION

The present invention relates to novel therapeutic uses of a known compound, pregabalin, its derivatives, and pharmaceutically acceptable salts. Pregabalin is (S)-3-(aminomethyl)-5-methylhexanoic acid. The invention concerns a method for treating the symptoms of mania in a human in need of such treatment. This method includes, but is not limited to the treatment of mania in all its various forms whether acute or chronic, single or recurrent episode, and

associated with depression or not. The invention further includes the preventive treatment of bipolar disorder in persons predisposed to this disorder.

Episodes of acute mania are characterized by elevated or irritable mood, disturbed sleep, grandiosity, increased motor activity, pressured thinking, distractibility and poor concentration, impaired judgment, and sometimes psychotic symptoms. The irritability can lead to outbursts of angry or aggressive behavior. Often the episodes are preceded by a period of disturbed sleep. The distractibility makes the patient move endlessly from one activity to another often to the detriment of their physical, occupational, and social well-being. The impact of these behaviors is further aggravated by the lapses of judgment and poor decision-making that is characteristic of this illness.

Episodes of mania occur in patients who suffer from bipolar disorder which is an illness characterized by alternating cycles of depression and mania. This disorder is distinct from the more common form of depression, called Major Depressive Disorder, in which patients only experience recurrent episodes of depression but no mania. Bipolar disorder can be diagnosed by the clinical evaluation of patients using the criteria specified in the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association. In this nomenclature system, bipolar disorder is subsumed under the broader class of Mood Disorders and is clearly distinguished from the Anxiety Disorders and from Organic Mental Disorders.

In studies of healthy subjects and patients suffering from anxiety, pregabalin has been noted to induce sedative and calming effects. These effects will be beneficial in the symptomatic treatment of patients suffering from mania who exhibit irritability, distractibility, and poor judgment. This is a novel use for pregabalin which would not be obvious to a medical practitioner of ordinary skill.

Pregabalin has also been found to enhance sleep. This effect will be beneficial in acute mania and will also lead to reducing the risk for onset of a new episode of mania in a predisposed individual. Thus, the prophylactic use of pregabalin for bipolar disorder is also taught.

Maillard Reaction of Lactose and Fluoxetine Hydrochloride, a Secondary Amine

DAVID D. WIRTH*, STEVEN W. BAERTSCHI, ROSS A. JOHNSON, STEVEN R. MAPLE, MARYBETH S. MILLER, DIANA K. HALLENBECK, AND STEPHEN M. GREGG

Contribution from the *Lilly Research Laboratories, Eli Lilly and Company, Lafayette, Indiana 47905*

Received May 21, 1997. Final revised manuscript received October 20, 1997. Accepted for publication October 23, 1997®.

Abstract □ Analysis of commercially available generic formulations of fluoxetine HCl revealed the presence of lactose as the most common excipient. We show that such formulations are inherently less stable than formulations with starch as the diluent due to the Maillard reaction between the drug, a secondary amine hydrochloride, and lactose. The Amadori rearrangement product was isolated and characterized; the characterization was aided by reduction with sodium borohydride and subsequent characterization of this reduced adduct. The lactose–fluoxetine HCl reaction was examined in aqueous ethanol and in the solid state, in which factors such as water content, lubricant concentration, and temperature were found to influence the degradation. *N*-Formylfluoxetine was identified as a major product of this Maillard reaction and it is proposed that *N*-formyl compounds be used as markers for this drug–excipient interaction since they are easy to prepare synthetically. Many characteristic volatile products of the Maillard reaction have been identified by GC/MS, including furaldehyde, maltol, and 2,3-dihydro-3,5-dihydroxy-6-methyl-4*H*-pyran-4-one. Close similarity between the degradation products of simple mixtures and formulated generic products was found; however, at least one product decomposed at a rate nearly 10 times that predicted from the simple models. Maillard products have also been identified in unstressed capsules. The main conclusion is that drugs which are secondary amines (not just primary amines as sometimes reported) undergo the Maillard reaction with lactose under pharmaceutically relevant conditions. This finding should be considered during the selection of excipients and stability protocols for drugs which are secondary amines or their salts, just as it currently is for primary amines.

Introduction

The Maillard reaction is named after Louis Maillard, who reported over 80 years ago that some amines and reducing carbohydrates react to produce brown pigments.[1] It has been extensively studied and reviewed, especially in the food and nutrition literature.[2] More recent reviews cover not only the chemistry of foods but human physiology as well.[3] The first product of this reaction is a simple glycosylamine,[4] which readily undergoes the Amadori rearrangement to produce 1-amino-1-deoxy-2-ketoses.[5] The large body of literature on these reactions is due to the multitude of possible reaction pathways and products, including fragmentations of the carbohydrates and formation of aromatic compounds from cyclization/dehydration processes.[6] Reducing disaccharides also undergo this reaction,[7] and it is a well-documented process for the degradation of lactose during the heating of milk.[8] Reducing carbohydrates such as glucose, maltose, and lactose are substrates for the Maillard reaction since their cyclic tautomers are in equilibrium with their more reactive aldehyde forms; nonreducing carbohydrates such as mannitol, sucrose, and trehalose are not subject to Maillard reactions. Although early scientists believed that only primary aromatic amines were capable of this reaction, subsequent research has shown that nearly all primary and secondary amines, aromatic or aliphatic, are capable of this reaction.[9] Amino acids and proteins are also substrates for the Maillard reaction.[10] The impact of these reactions on the stability of pharmaceuticals has also been known for some time and was recently reviewed.[11]

Prozac, the world's largest selling antidepressant, is a selective serotonin reuptake inhibitor;[12] it has been used by over 25 million people in more than 90 countries. Its active ingredient is fluoxetine hydrochloride, **1**, and the diluent is starch. Within the past few years, many generic formulations containing fluoxetine HCl have been manufactured and sold in countries lacking patent protection or in which the patents have expired. We have recently examined several dozen of these products and find that a majority of them contain lactose as their primary diluent. Lactose is widely used as a diluent for capsules and tablets due to its low price, high purity, and excellent compression and stability characteristics. Although its ability to undergo nonenzymatic browning (Maillard) reactions has long been known to formulation scientists, some reports have suggested this interaction to be largely restricted to primary amines.[13] The origin of this view is likely founded in early literature reports of the slower browning of glucose mixtures of *N*-methyl glycine as compared to glycine itself[14] and work on the browning of mixtures of lactose and methylated amphetamines.[15] studies which measured optical density only, not characteristic Maillard products. Although these reports showed faster rates of browning of mixtures of reducing carbohydrates with primary amines as compared to secondary ones, they do not support the conclusion that secondary amines should generally be incapable of the Maillard reaction.

The generally accepted mechanism of glycosylation and the Amadori rearrangement are summarized in Scheme 1 for a secondary amine.[16] The imminium ion intermediate can be formed from either primary or secondary amines (but not tertiary ones) and is the key intermediate in both closure to the glycosylamine and deprotonation to the enol version of the Amadori rearrangement product, ARP. The multitude of individual steps in this mechanism allows for considerable variation in the kinetics. For example, the hydrolysis of the glycosylamine of benzylamine and glucose is faster at pH 5 than hydrolysis of the corresponding glycosylamine with piperidine, but the reverse order of reactivity is observed at pH 9.[17] Kinetic studies of the Maillard reaction have been reviewed and will not be explored in depth in this paper.[18] In view of the well-

® Abstract published in *Advance ACS Abstracts*, December 15, 1997.

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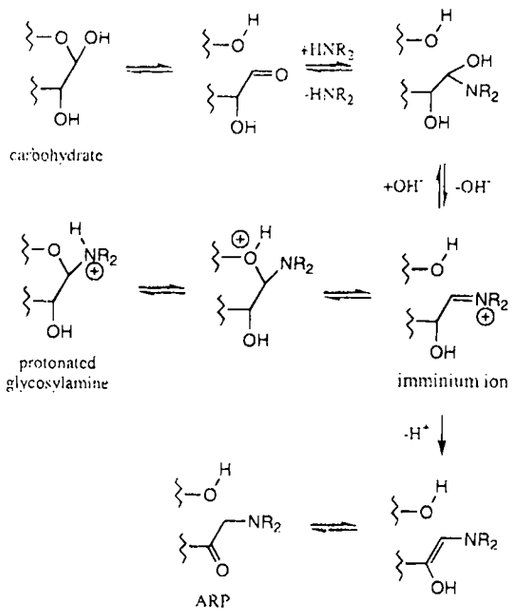

Scheme 1—Mechanism of glycosylation and Amadori rearrangement with secondary amines.

known interaction of reducing carbohydrates and secondary amines, as reported in the carbohydrate and food science literature,[19] we have investigated the Maillard/Amadori reactions of the lactose–fluoxetine system and report our findings here. Detailed mechanistic work such as identification of the rate-determining step and full kinetic analysis as a function of the amine, carbohydrate, and reaction conditions are left for future studies.

Experimental Section

Materials—Fluoxetine HCl and Prozac were obtained from Eli Lilly and Co. generics A, N, O, and Z were obtained in pharmacies outside the United States and were unexpired formulated 20 mg products. Lactose monohydrate was obtained from Aldrich Chemical Co, Milwaukee, WI, and spray-dried lactose was from Foremost Ingredients Group, Baraboo, WI. The anhydrous lactose forms were obtained from Sheffield Products, Norwich, NY. The acetonitrile was spectroscopic grade, obtained from EM Science, Gibbstown, NJ. Reagent grade trifluoroacetic acid was obtained from Aldrich Chemical Co. and was distilled prior to use. Other chemicals and the authentic samples of compounds listed in Table 6 were purchased from Aldrich Chemical Co. and were used as received. Ethanol was anhydrous and denatured with 5% methanol.

NMR—Nuclear magnetic resonance (NMR) spectroscopy for compounds **1**, **2**, **3**, and **6** was carried out on a Bruker AC300 spectrometer with ^{1}H and ^{13}C operating frequencies of 300.13 and 75.46 MHz, respectively. Additional experiments on compound **6** were carried out on a Bruker AMX500 with ^{1}H and ^{13}C operating frequencies of 500.14 and 125.77 MHz, respectively.

GC/MS—Gas chromatography/mass spectrometry was performed on a MicroMass TRIO II quadrapole mass spectrometer controlled using the Masslynx operating system. The instrument was equipped with a Hewlett-Packard Model 5890 gas chromatograph which was fitted with a Scientific Instruments Services short path thermal desorption Model TD 4 system and CryoTrap unit. The mass spectrometer was operated in the EI+ mode and calibrated daily against FC-43. Mass spectral data were obtained in the centroid mode by scanning the mass range from 33 to 600 amu at a rate of 1260 amu/s and using an interscan time delay of 0.05 s.

For the analysis of products from solid-state samples, the contents of one 20 mg capsule of fluoxetine HCl product or mixtures of 20 mg of bulk fluoxetine HCl and 200 mg of lactose were added to a 10 mL glass vial which was crimp sealed with a Teflon-lined rubber septum. The vials were heated at 100 °C for 20 h. A stainless steel GLT short path thermal desorption tube packed with 100 mg of Tenax-TA which had been preconditioned with helium purge at 250 °C and fitted with a needle was inserted into the vial. A second needle connected to a helium source was inserted into the vial and the flow rate set at approximately 7 mL/min. The vial headspace gases were purged onto the Tennax-TA tube for either 5 or 60 min. The GLT tube was then transferred to the short path thermal desorption unit for desorption onto the gas chromatographic column. The following conditions were used for the transfer and chromatographic analysis. Sample transfer: gas purge time, 0.5 min; desorption time, 5 min; GLT desorption temperature, 100 °C initial then 40 °C/min to 200 °C; column cryotrap at −100 °C. GC conditions: injector, 150 °C; transfer line to mass spectrometer, 300 °C; split flow, 7 mL/min or 50 mL/min; the cryotrap was heated rapidly to 250 °C to desorb material onto the GC column; oven temperature program, 40 °C for 3 min then 10 °C/min to 300 °C and hold 3 min; chromatographic column, DB-1, 30 m × 0.25 mm i.d. and 1.0 mm film.

HPLC—High performance liquid chromatography was performed with a Spectra Physics SP8700XR pump, a Spectroflow 757 detector (Anspec) set at 260 nm, a ChromJet integrator by Spectra Physics, and an Alcott 728 autosampler incorporating a Valco injection valve with a 10 μL fixed loop. The column was a Zorbax RX-C8, 25 cm by 4.6 mm, 5 μm particles (Mac-Mod Analytical, Inc., Chadds Ford, PA) maintained at ambient temperature. The flow rate was 1.00 mL min^{-1} throughout. The two eluting solutions used were A = 0.07% trifluoroacetic acid (TFA) in water, v/v; B = 0.07% TFA in acetonitrile. The elution program started at 80:20 A:B for 5 min, ramped linearly to 15:85 A:B at 30 min, held there until 35 min, and returned to 80:20 A:B at 40 min. Injections were made no sooner than every 50 min. The approximate elution times are **1** at 21 min, **2** at 18.4 min, **3** at 27 min, and **4** at 17.9 min. For MS detection, samples were analyzed on MicroMass (formerly Fisons) Quattro II and Platform II LC/MS systems in the positive ion electrospray mode, scanning from 100 to 1000 amu, generating centroid data. Further details and example chromatograms have been published elsewhere.[20] This method allows for the detection and quantitation of impurities which span a wide range of polarities, including nonpolar compounds which are not eluted using the isocratic US Pharmacopeia method.[21]

Lactose–Fluoxetine Amadori Rearrangement Product (ARP, 2)—In a 500 mL round-bottom flask equipped with an overhead stirrer, thermometer, and condenser were combined 20 g of α-D-lactose monohydrate (55.5 mmol), 10 g of fluoxetine HCl (28.9 mmol), 250 mL of ethanol, 120 mL of dimethylacetamide, and 4 mL of triethylamine (28.7 mmol). The nearly homogeneous mixture was stirred at reflux for 24 h. The reaction mixture was filtered at ambient temperature and the wetcake was washed with 50 mL of ethanol. The filtrate was evaporated in vacuo to a thick brown solution (112 g), to which were added 300 mL of ethyl acetate, 300 mL of 20% aqueous sodium chloride, and 30 mL of ether. The pH was adjusted to 11 with 50% sodium hydroxide. White solids which formed during the pH adjustment were filtered and the layers were separated. The bottom layer was discarded and the upper layer was set aside. To the milky middle layer were added 300 mL of ethyl acetate and 30 mL of ether. The layers were separated and the combined organic layers were evaporated in vacuo to a thick brown oil (42.8 g), to which were added 175 mL of 20% aqueous sodium chloride, 400 mL water, and 550 mL chloroform. The pH was adjusted to 1.5 with concentrated HCl. The layers were separated and to the aqueous layer were added 60 g of NaCl, 500 mL of ethyl acetate, and 50 mL of ether. The pH was adjusted to 10.6 with 50% NaOH, and the layers were separated. The ethyl acetate layer was evaporated in vacuo to a residue (4.7 g) which was 85% pure by HPLC analysis at 260 nm. Standard ^{1}H and ^{13}C NMR spectra were acquired on a sample of **2** prepared by dissolving 50–60 mg of the material in DMSO-d_6. A partial list of assignments has been made based on comparison to fluoxetine and is shown in Table 1. Flow-injection mass spectrometry indicated the molecular weight to be 633 (M + H$^+$, *m/z* 634). Accurate mass FAB-MS measurements of the protonated molecular ion (M + H$^+$) indicated the elemental composition to be $C_{29}H_{39}NO_{11}F_3$ (calcd 634.2475, measured 634.2487).

Reduced Adduct (6)—In a 50 mL round-bottom flask equipped with an overhead stirrer, a thermometer, and a condenser were combined 1.5 g of ARP, **2** (2.37 mmol), 15 mL of ethanol, and 1.79

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE

ASUNTO	Radicación	03-79612
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	8338
	Folios	3

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

No. Sol. Internacional PCT/IB02/00647
Fecha de Presentación Internal. 25-02-2002

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: 33 a 58 (como se radicó inicialmente)

1.2. Reivindicaciones: Folios 59 a 61 (como se radicó inicialmente)

1.3. Prioridad: Folio: 1
Fecha: 30-03-2001; país y número: US60/280.176.

2. Objeto de la invención

Título de la solicitud: "CONJUGADOS DE PREGABALINA-LACTOSA".

El objeto de la presente solicitud de patente de invención consiste en compuestos análogos del ácido glutámico y ácido gamma-aminobutírico (GABA)

Reivindicación 1: Un conjugado de pregabalina-lactosa
Reivindicaciones 2-3: Un compuesto producto de la reacción de lactosa con pregabalina
Reivindicación 4: Una formulación farmacéutica.
Reivindicaciones 5-7: Un método para tratar un sujeto.

El problema planteado en esta solicitud es la necesidad de compuestos útiles para tratar trastornos o enfermedades del sistema nervioso central.

Para solucionar este problema técnico la solicitud en estudio proporciona una compuestos producto de la adición de lactosa a la pregabalina.

La invención se catalogó según la Clasificación Internacional de Patentes (IPC.) como: A61K31/7056; A61K47/48.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

La reivindicación 1 utiliza la palabra "conjugado" y las reivindicaciones posteriores se refieren a un compuesto. El término conjugado debe ser retirado de las reivindicaciones ya que le restan claridad a la misma.

La reivindicación 1 carece de concisión ya que no delimita el número de compuestos que se desea proteger, puesto que la expresión "un conjugado pregabalina-lactosa" se refiere a cualquier tipo de compuesto posible que se pueda obtener a partir de estas dos sustancias. Igualmente la descripción no posee información que permita establecer que todos los posibles productos de la adición de lactosa a la pregabalina sean útiles para resolver el problema técnico planteado por el solicitante. Adicionalmente, las expresiones "profármaco", "ésteres", "amidas" y "una de sus sales" deben ser retiradas de la solicitud ya que dentro de la misma no existe soporte que permita establecer la estructura de estos compuestos y que todos ellos sean igualmente útiles para solucionar el problema técnico planteado.

Por lo anterior, la reivindicación 1 no cumple con el requisito de definición, claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)

Las reivindicaciones 5 a 7 corresponden a métodos de tratamiento y por lo tanto no son patentables.

5. 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 30-03-2001

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*
D1	WO 0023067	METHOD FOR THE TREATMENT OF MANIA AND BIPOLAR DISORDER	27-04-2000
D2	Journal of pharmaceutical scieces. Vol. 87, No. 1, January	MAILLARD REACTION OF LACTOSE AND FLUOXETINE HYDROCHLORIDE, A SECONDARY AMINE	January 1998

6. Análisis de patentabilidad (artículo 14 D486)

6.1. Nivel inventivo (artículo18 D486)

El documento del Estado de la Técnica más próximo es D1 que establece la utilidad de la pregabalina, sus derivados y las sales farmacéuticas en el tratamiento de trastornos del sistema nervioso (Ver folios: 71-73)

La única diferencia con D2 es que esta solicitud menciona que los derivados de pregabalina consisten específicamente en productos de degradación que se generan por la reacción de la pregabalina con la lactosa contenida en la forma farmacéutica. Pero esta diferencia no parece conceder un efecto técnico inesperado porque la formación de productos de degradación de aminas secundarias en presencia de lactosa ya se conocía en el estado de la técnica.

El problema técnico planteado en esta solicitud consiste en la necesidad de conjugados de pregabalina útiles para tratar trastornos o enfermedades del sistema nervioso central. Dicho problema sería resuelto fácilmente por el experto en la materia al revisar la información que suministra D2, en donde se establece que las composiciones que contienen lactosa son más inestables y tienden a generar productos de descomposición, debido a que se producen reacciones de Millard entre los fármacos que poseen una amina secundaria y la lactosa (folio 74). Por esta razón se considera que conociendo que la pregabalina posee una amina secundaria, es muy sencillo obtener profármacos de este principio activo mediante reacción de

Millard. Así, una persona conocedora de la materia motivada por tal sugerencia lograría los compuestos de esta solicitud, que son útiles para tratar un trastorno del sistema nervioso central como era de esperarse de un derivado de la pregabalina; de manera que para una persona medianamente versada en la materia sería obvio combinar estos dos documentos y obtener los compuestos que se determinaron inicialmente por la observación de un fenómeno de degradación que se generó en la formulación de pregabalina. Por lo cual, los compuestos producto de la reacción de pregabalina con lactosa de las reivindicaciones1-3 y la composiciones que los comprenden de la reivindicación 4 no poseen Nivel Inventivo.

7. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO 0023067	1-4	Nivel Inventivo
D2	Journal of pharmaceutical scieces. Vol. 87, No. 1, January	1-4	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de 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 27 JUN. 2008

CONCEPTO TÉCNICO No.1303	EXAMINADOR TÉCNICO Código No. 202073