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Rodriguez Madrid & Asoc. Ltda.
NIT. 830.038.010-1

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PATENTES

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MAIN NAME

SUPERINDUSTRIA Y COMERCIO

Radicación : 0393678 0020331

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Trámite : 002 PATENTES D 1 REGISTRO/ 329 COMPLETOS

Superindustria 2000 P.V. 191001 DE NUEVOS COMERCIOS

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COM.
DIVISION DE NUEVAS CREACIONES

E. S. D.

REF : EXPEDIENTE No. 000- 93678 de Diciembre 07 de 2000.

PATENTE "METODO NOVEDOSO PARA LA SÍNTESIS
ESTEREOSELECTIVA DE AMINOÁCIDOS CICLICOS"

Estimados señores :

Damos alcance al expediente citado en la referencia, para reivindicar Prioridad de la Patente solicitada, con fundamento jurídico en lo establecido en el Artículo 12 de la Decisión 344 de la comisión del Acuerdo de Cartagena y el Artículo 4 Lit. F del Decreto 117/94 referente a la fuente normativa de reciprocidad, esta se basa en :

- a.- El artículo 4 del convenio de París, aprobado mediante Ley 178/94, declarado exequible por la Corte Constitucional en Sentencia del 18 de Enero/96.
- b.- Ley 170/94 en la cual Colombia aprobó el Acuerdo por el que se establece la Organización Mundial de Comercio (OMC) suscrito en Marrakech (Marruecos) el 15 de Abril de 1994, y sus Acuerdos multilaterales, los cuales incluyen los aspectos de los Derechos de Propiedad Intelectual relacionados con el Comercio; mejor conocido como el Trip'. Dicha Ley 170 de 1997 fue declarada exequible por la Corte Constitucional el 28 de Marzo de 1995.

El Artículo 2, Ord.1, del Trip's establece que la propiedad en el Mundo será reconocida, que los países miembros cumplirán los artículos 1 a 12 y el Artículo 19 del convenio de París. A su vez, el artículo 4 del Convenio de París (es decir, uno de los artículos de cumplimiento obligatorio bajo Trip's) establece que la prioridad sobre la primera solicitud en el mundo será reconocida.

Por lo tanto anexamos:

- 1.- Copia de la Prioridad No.60/169.602 de Diciembre 08 de 1999 Debidamente Legalizada por el Ministerio de Relaciones Exteriores

*Transversal 6a. No. 27-10 "Edificio Antares - Pent House" Teléfax: 283 09 42 * Tel. 334 72 84 - 341 7003
e-mail: rodruci@andinet.com * Santafé de Bogotá, D.C.*

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2.- Traducciones de las reivindicaciones de la primera solicitud de Patente efectuadas por Traductor Oficial avaladas por el Ministerio de Relaciones Exteriores

En consecuencia, ruego a ustedes una vez finiquitada esta diligencia, ordenar lo pertinente para que el expediente siga su curso normal.

Atentamente,

RODOLFO RODRIGUEZ MADRID
C.C. No. 3'792.584-Cartagena
T.P. No. 59.363 del C.S.J

Anexo.- Lo anunciado.



CONSULADO GENERAL DE COLOMBIA

Miami, 20 Noviembre 2000

AUTENTICACION

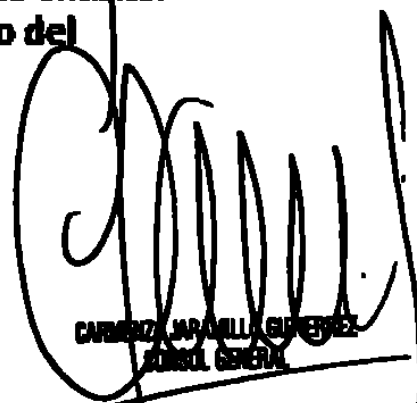
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RESPONSABILIDAD DEL TEXTO

El Cónsul General CERTIFICA que el(la) señor(a) KATHERINE HARRIS que autoriza el documento adjunto, ejercía legalmente en la fecha allí expresada las funciones de SECRETARIO ESTADO y que la firma y sello que aparecen en el documento como suyos son los que usa y acostumbra en sus actos oficiales. El Consulado no asume responsabilidad alguna por el contenido del documento.

Por el Cónsul General,


CARMELO MARILLI GONZALEZ
CÓNsul General



DERECHOS: Timbre US\$ 7.00
Fondo Rot. US\$ 15.00

STATE OF FLORIDA DEPARTMENT OF STATE

SS

Notary Commissions and Certification Section

I, Katherine Harris, Secretary of State, do hereby certify that:

Araceli Matus-Silva

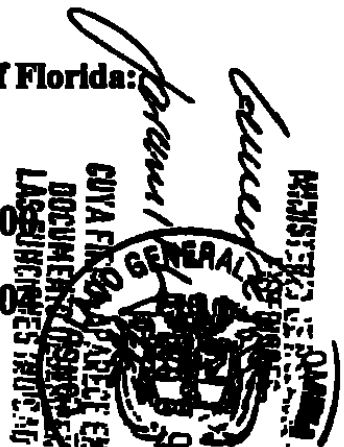
was commissioned as a Notary Public in and for the State of Florida:

Commission number: CC973596

Term beginning: October 27, 2000

Term expiring: October 26, 2001

as shown by the records of this office.



Legal Qualifications and Authority of a Florida Notary Public

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Legal Authority of a Florida Notary Public: A Notary Public may administer an oath and make a certificate thereof when it is necessary for the execution of any writing or document to be published under the seal of a Notary Public. A Notary Public is authorized to take the acknowledgments of deeds and other instruments of writing for record. A Notary Public is authorized to solemnize the rites of matrimony. A Notary Public may supervise the making of a photocopy of an original document and attest to the trueness of the copy.

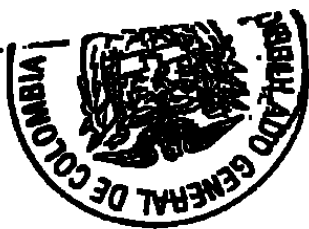
Given under my hand and the Great Seal of the State of Florida, at Tallahassee, the Capital, this the Sixth day of November, A.D., 2000.



Katherine Harris

Secretary of State

DSDE 99 (1-99)



"State of Florida" appears in small letters across the face of this 8 1/2 X 11" document.

Calcutt 516



PA 322268



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME;

UNITED STATES DEPARTMENT OF COMMERCE

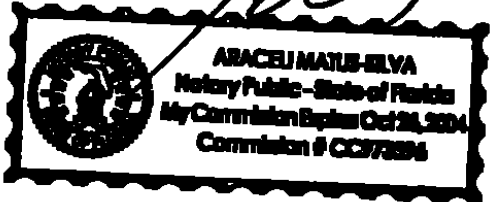
United States Patent and Trademark Office

November 07, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/169,602

FILING DATE: December 08, 1999



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS



L. EDELEN
Certifying Officer

Please type a plus sign (+) inside this box → ☐

Doclet Number: A000128L1-01EMA

PR VISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle if any)	Family Name or Surname	Residence (City and either State or Foreign Country)
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David Olive	Brynes	21 Hulet Road, Cambridge CB1 6TH, United Kingdom
Sophia Caroline	Williams	88 Milne Grove, Cambridge CB1 7TX, United Kingdom

☐ Additional inventors are being named on page 2 attached hereto

TITLE OF THE INVENTION (250 characters max)

NOVEL METHOD FOR THE STEREORELECTIVE SYNTHESIS OF CYCLIC AMINO ACIDS

CORRESPONDENCE ADDRESS

Direct of correspondence to:

☐ Customer Number

Place Customer Number
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State Michigan

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ENCLOSED APPLICATION PARTS (check all that apply)



Specification

Number of Pages

66



Drawing(s)

Number of Sheets



Other (specify)

22 claims on 61 pages
abstract on 1 page

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)



A check or money order is enclosed to cover the filing fee

FILING FEE
AMOUNT (\$)



The Commissioner is hereby authorized to charge filing fee or
credit any overpayment to Deposit Account Number:

23-0488

\$150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.



No.



Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE Elizabeth M. Anderson

DATE December 8, 1999

TYPED or PRINTED NAME Elizabeth M. Anderson

REGISTRATION NO. 31,885
(if appropriate)

TELEPHONE 734-622-7304

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PR VISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

668021-20969109

INVENTOR(S)/APPLICANT(S)		
Given Name (last and middle if any)	Family Name or Surname	Residence (city and either State or Foreign Country)

Certificate of Mailing by Express Mail

I certify that this application and enclosed fee is being deposited on December 8, 1999 with the U.S. Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.
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NOVEL METHOD FOR THE STEREOSELECTIVE SYNTHESIS
OF CYCLIC AMINO ACIDS

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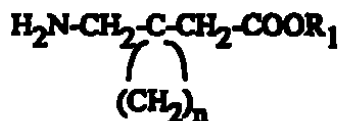
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NOVEL METHOD FOR THE STEREOSELECTIVE SYNTHESIS OF CYCLIC AMINO ACIDS

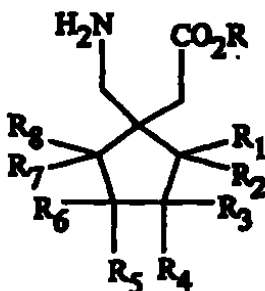
BACKGROUND OF THE INVENTION

Compounds of formula



wherein R_1 is hydrogen or a lower alkyl radical and n is 4, 5, or 6 are known in United States Patent Number 4,024,175 and its divisional United States Patent Number 4,087,544. The uses disclosed are: protective effect against cramp induced by thiosemicarbazide; protective action against cardiazole cramp; the cerebral diseases, epilepsy, faintness attacks, hypokinesia, and cranial traumas; and improvement in cerebral functions. The compounds are useful in geriatric patients. The patents are hereby incorporated by reference.

WO 99/21824 published May 6, 1999, teaches in part compounds of Formula

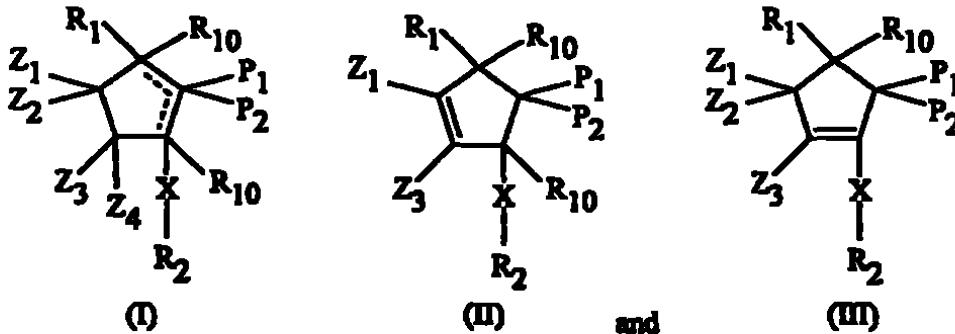


or a pharmaceutically acceptable salt thereof wherein R is hydrogen or a lower alkyl; and R_1 to R_8 are each independently selected from hydrogen, straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, benzyl, fluorine, chlorine, bromine, hydroxy, hydroxymethyl, amino, aminomethyl, trifluoromethyl, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{R}_{15}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{R}_{15}$, $-\text{OR}_{15}$ wherein R_{15} is a straight or

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branched alkyl of from 1 to 6 carbons, phenyl, or benzyl, and R_1 to R_8 are not simultaneously hydrogen. This is hereby incorporated by reference.

WO 94/24084 describes endothelin antagonists of formulas



wherein

R_1 is $-X(CH_2)_nAr$;

R_2 is Ar ;

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-XR_9Y$;

R_3 and R_5 are independently hydrogen, R_{11} , OH , C_{1-8} alkoxy, $S(O)_qR_{11}$,

$N(R_6)_2$, Br , F , I , Cl , CF_3 , $NHCOR_6$, $-R_{11}CO_2R_7$, $-XR_9Y$, or

$-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11} , OH , C_{1-5} alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, $-X(R_{11})$, Br , F , I , Cl ,

or $NHCOR_6$ wherein the C_{1-5} alkoxy may be unsubstituted or substituted by OH , methoxy, or halogen;

R_6 is independently hydrogen or C_{1-4} alkyl;

R_7 is independently hydrogen, C_{1-6} alkyl, or $(CH_2)_nAr$;

R_8 is hydrogen, R_{11} , CO_2R_7 , PO_3H_2 , $SO_2NR_7R_{11}$, $NR_7SO_2R_{11}$, $P(O)(OH)R_7$,

CN , $-C(O)N(R_6)_2$, tetrazole, or OR_6 ;

R_9 is C_{1-10} alkyl, C_{2-10} alkenyl, or phenyl, all of which may be unsubstituted or substituted by one or more OH , $N(R_6)_2$, $COOH$, $>C=O$, halogen, or

XC_{1-5} alkyl;

R_{10} is R_3 or R_4 ;

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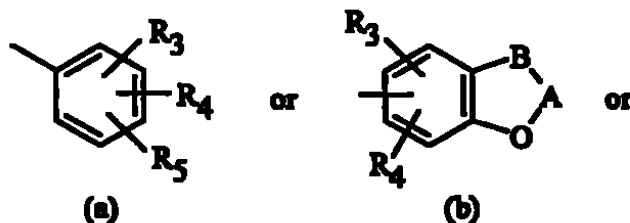
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R_{11} is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, all of which may be unsubstituted or substituted by one or more OH, CH_2OH , $N(R_6)_2$, or halogen;

X is $(CH_2)_n$, O, NR_6 , or $S(O)_q$;

Y is CH_3 or $X(CH_2)_nAr$;

5 Ar is:



naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidiny, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is $>C=O$, or $[C(R_6)_2]_m$;

B is $-CH_2-$ or $-O-$;

Z_1 , Z_2 , Z_3 , and Z_4 are independently hydrogen, C_{1-8} alkyl, C_{2-8} alkenyl,

C_{2-8} alkynyl, OH, C_{1-8} alkoxy, $S(O)_qC_{1-8}$ alkyl, $N(R_6)_2$, Br, F, I, Cl,

$NHCOR_6$, $-X(CH_2)_nR_8$, XR_9Y , phenyl, benzyl, or C_{3-6} cycloalkyl

wherein the C_{1-8} alkyl, C_{2-8} alkenyl, or C_{2-8} alkynyl may be optionally substituted by $COOH$, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen;

q is zero, one, or two;

n is an integer from 0 to 6;

m is 1, 2, or 3;

and the dotted line in Formula (I) indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof; provided that

- when the optional double bond is present, there is only one R_{10} , there is no P_1 , and P_2 is not NR_6R_9Y ;
- X is not NR_6 , and Z_3 is not OH or $N(R_6)_2$ in Formula (III);

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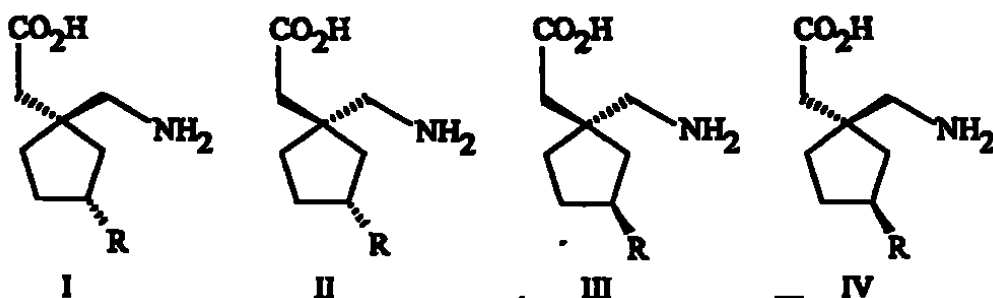
- Z_1 and Z_3 are not OH, $N(R_6)_2$, or Iodine in Formula (II);
- when the optional double bond is present in Formula (I) and $X-R_2$ is attached to the double bond, X is not NR_6 ;
- when the optional double bond is present in Formula (I) and R_1 is attached directly to the double bond, R_1 is not NR_6Ar ;
- when R_3 , R_5 , Z_1 , Z_2 , or Z_3 is $X(CH_2)_nR_8$ and n is not zero, X is oxygen or NR_6 when R_8 is OR_6 or CO_2H .

Also included in the invention are pharmaceutically acceptable salts of the active compounds.

None of the above teach the synthesis of the instant invention.

SUMMARY OF THE INVENTION

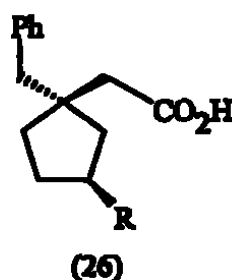
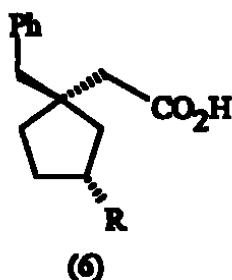
The instant invention encompasses novel synthetic routes for the preparation of 3-substituted cyclopentyl-based analogs of gabapentin and pharmaceutically acceptable salts thereof. Gabapentin, marketed under the trade name Neurontin® for the treatment of seizure disorders, particularly epilepsy, provides well-known medical benefits to patients in need of such treatment. As the instant invention encompasses novel synthetic routes for the preparation of 3-substituted cyclopentyl-based analogs of gabapentin and pharmaceutically acceptable salts thereof, it provides routes that enable the synthesis of each stereoisomer of these analogs with a high degree of stereochemical purity. These routes provide access to pure stereoisomers of Formulas I, II, III, and IV.



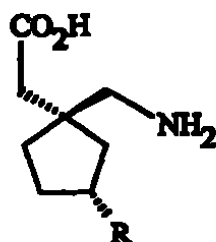
wherein R is C_1 - C_{10} alkyl and C_3 - C_{10} cycloalkyl.

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Further, the invention encompasses the key intermediates of formulas (6) and (26). Still further, the invention provides novel synthetic routes for the preparation of compounds of formulas (6) and (26). The routes enable the synthesis of each stereoisomer of compounds of formulas (6) and (26) with a high degree of stereochemical purity. These routes provide access to pure stereoisomers of formulas (6) and (26) wherein R is C₁-C₁₀ alkyl and C₃-C₁₀ cycloalkyl.



The invention provides a process for the preparation of a compound of Formula I



wherein R is C₁-C₁₀ alkyl and C₃-C₁₀ cycloalkyl, and pharmaceutically acceptable salts thereof, which comprises:

- adding ethyl cyanoacetate to a mixture of a chiral cyclopentanone of formula (1) in a solvent to which a C₁-C₆ carboxylic acid and an amphoteric catalyst were added, and stirring the mixture to produce the alkene of formula (2);
- adding the product of Step a) above to a mixture of benzylmagnesium chloride in a dry solvent to produce the addition product of formula (3);
- adding the product of Step b) above to a mixture of a base in a solvent and stirring the mixture to produce the carboxylic acid of formula (4);

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- d) contacting the product of Step c) above with (S)- α -methyl-benzylamine in a solvent, and recrystallizing the salt so formed to produce the enriched diastereomer of formula (5) as the (S)- α -methyl-benzylamine salt;
- e) adding the product of Step d) to an inorganic acid dissolved in a solvent and stirring to produce the carboxylic acid of formula (6);
- f) adding the product of Step e) to a mixture of iodomethane in a solvent to which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added, and stirring to produce the ester of formula (7);
- g) adding the product of Step f) to a mixture of carbon tetrachloride and acetonitrile to which water, sodium periodate, and ruthenium(III) chloride were added, and stirring to produce the carboxylic acid of formula (8);
- h) adding the product of Step g) to a mixture of an amine base and a solvent to which diphenylphosphoryl azide (DPPA) was added, and stirring to produce the isocyanate of formula (9);
- i) adding the product of Step h) to a solvent to which methanol was added and stirring to produce the carbamate of formula (10);
- j) adding the product of Step i) to a solvent to which aqueous hydrochloric acid was added, and stirring to produce a compound of Formula Ia;
- k) converting the product of Step j) to a compound of Formula I, and further converting, if desired, to a pharmaceutically acceptable salt by known means;