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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

COMERCIO

CREACIONES
NACIONALES

Ref: Expediente No. 05-103.293

Solicitud de patente de invención titulada:

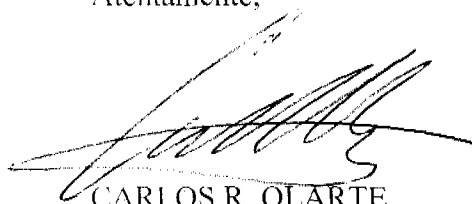
“COMPUESTOS N-HETEROCÍCLICOS CONDENSADOS Y SU USO COMO ANTAGONISTAS DE RECEPTORES DEL FACTOR LIBERADOR DE CORTICOTROPINA.”.

Solicitante: SB PHARMCO PUERTO RICO y NEUROCRINE BIOSCIENCE INC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 576

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 artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$202.000 pesos para cubrir la tasa correspondiente, según la Resolución 36155 del año 2006.

Atentamente,



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

Anexo: Recibo por \$202.000 pesos

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 000120007-2

RECIBO OFICIAL DE CAJA : 07 - 89,002
FECHA : OCTUBRE 31 DE 2007

***** DEPOSITACION *****

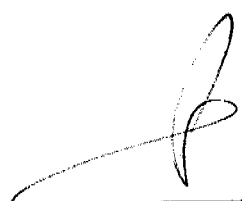
DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGC	V. PAGO
CLARTE SAISBEY	CONSIGNACION	BANCO POPULAR	050-00110-6	67033753	31/10/2007	4,394,000.00

***** CONCEPTO *****

CANT.	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	
	114 PTC CAP-II EXAMEN DE PATENTIBILIDAD	202,000.00
	TOTAL :	202,000.00

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE :



DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-103293

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **576** DE

FECHA **31 DE MAYO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **31 DE AGOSTO DE 2007**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO _____ X _____

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- halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, $-C(O)R_5$, nitro, $-NR_6R_7$, cyano, and a group R_8 ;
- 5 R_1 is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, halogen, NR_6R_7 or cyano;
- R_2 is hydrogen, C3-C7 cycloalkyl, or a group R_9 ;
- R_3 is C3-C7 cycloalkyl, or a group R_9 , or
- R_2 and R_3 together with N form a 5-14 membered heterocycle, which may be substituted by 1 to 3 R_{10} groups;
- 10 R_4 is hydrogen, C1-C6 alkyl, halogen or halo C1-C6 alkyl;
- R_5 is a C1-C4 alkyl, $-OR_6$ or $-NR_6R_7$;
- R_6 is hydrogen or C1-C6 alkyl;
- R_7 is hydrogen or C1-C6 alkyl;
- 15 R_8 is a 5-6 membered heterocycle, which may be saturated or may contain one to three double bonds, and which may be substituted by 1 or more R_{11} groups;
- R_9 is a C1-C6 alkyl that may be substituted by one or more groups selected from: C3-C7 cycloalkyl, C1-C6 alkoxy, halo C1-C6 alkoxy, hydroxy, halo C1-C6 alkyl;
- 20 R_{10} is a group R_8 , C3-C7 cycloalkyl, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, hydroxy, halogen, nitro, cyano, $C(O)NR_6R_7$, phenyl which may be substituted by 1 to 4 R_{11} groups;
- 25 R_{11} is C3-C7 cycloalkyl, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, hydroxy, halogen, nitro, cyano, or $C(O)NR_6R_7$;
- X is carbon or nitrogen;
- n is 1 or 2.

- 30 Acid addition salts of the free base amino compounds of the present invention may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, malic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, p-toluenesulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Thus, the term "pharmaceutically acceptable salt" of structure (I) is intended to encompass any and all acceptable salt forms.

40 The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

- In addition, prodrugs are also included within the context of this invention. Prodrugs are any covalently bonded carriers that release a compound of structure (I) in vivo when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or in vivo, yielding the parent compound. Prodrugs include, for example, compounds of this invention wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a patient, cleaves to form the hydroxy, amine or sulfhydryl groups. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of alcohol, sulfhydryl and amine functional groups of the compounds of structure (I). Further, in the case of a carboxylic acid ($-COOH$), esters may be employed, such as methyl esters, ethyl esters, and the like.

- With regard to stereoisomers, the compounds of structure (I) may have chiral centers and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers.
- 15 All such isomeric forms are included within the present invention, including mixtures thereof. Furthermore, some of the crystalline forms of the compounds of structure (I) may exist as polymorphs, which are included in the present invention.

- The term C1-C6 alkyl as used herein as a group or a part of the group refers to a linear or branched alkyl group containing from 1 to 6 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert butyl, pentyl or hexyl.

- The term C3-C7 cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl; while unsaturated cycloalkyls include cyclopentenyl and cyclohexenyl, and the like.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

- 30 The term halo C1-C6 alkyl, or halo C1-C2 alkyl means an alkyl group having one or more carbon atoms and wherein at least one hydrogen atom is replaced with halogen such as for example a trifluoromethyl group and the like.

- The term C2-C6 alkenyl defines straight or branched chain hydrocarbon radicals containing one or more double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl or 3-hexenyl and the like.

- The term C1-C6 alkoxy group may be a linear or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy and the like.

The term halo C1-C6 alkoxy group may be a C1-C6 alkoxy group as defined before substituted with at least one halogen, preferably fluorine, such as $OCHF_2$, or OCF_3 .

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The term C2-C6 alkynyl defines straight or branched chain hydrocarbon radicals containing one or more triple bond and having from 2 to 6 carbon atoms including acetylenyl, propynyl, 1-butylnyl, 1-pentylnyl, 3-methyl-1-butylnyl and the like.

5 The term aryl means an aromatic carbocyclic moiety such as phenyl, biphenyl or naphthyl.

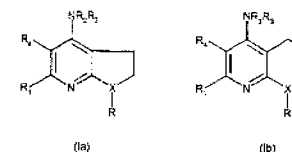
The term heteroaryl means an aromatic heterocycle ring of 5 to 10 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including both mono- and bicyclic ring systems.

10 Representative heteroaryls include (but are not limited to) furyl, benzofuranyl, thiophenyl, benzothiophenyl, pyrrolyl, indolyl, isoindolyl, azaindolyl, pyridyl, quinolyl, isoquinolyl, oxazolyl, isooxazolyl, benzoxazolyl, pyrazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolyl, phthalazinyl, triazolyl, tetrazolyl, and quinazolyl.

15 The term 5-14 membered heterocycle means a 5 to 7-membered monocyclic, or 7-to 14-membered polycyclic, heterocycle ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized, including bicyclic rings in which any of the above heterocycles are fused to a benzene ring as well as tricyclic (and higher) heterocyclic rings. The heterocycle may be attached via any heteroatom or carbon atom. Heterocycles include heteroaryls as defined above. Thus, in addition to the aromatic heteroaryls listed above, heterocycles also include (but are not limited to) morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

20 The term 5-6 membered heterocycle means, according to the above definition, a 5-6 monocyclic heterocyclic ring which is either saturated, unsaturated or aromatic, and which contains from 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, and wherein the nitrogen and sulfur heteroatoms may be optionally oxidized, and the nitrogen heteroatom may be optionally quaternized. Heterocycles include heteroaryls as defined above. The heterocycle may be attached via any heteroatom or carbon atom. Thus, the term include (but are not limited to) morpholinyl, pyridinyl, pyrazinyl, pyrazolyl, thiazolyl, triazolyl, imidazolyl, oxadiazolyl, oxazolyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like.

Representative compounds of this invention include the following structure (Ia) and (Ib)

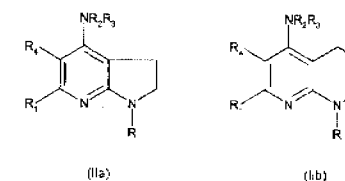


In one preferred embodiment in which n is 1, according to the definition of the compounds of formula (I) above, the CRF receptor antagonists of this invention have structure (Ia), and, when n is 2, then the CRF receptor antagonists of this invention have structure (Ib), wherein R, R₁, R₂ and R₃ are defined as above.

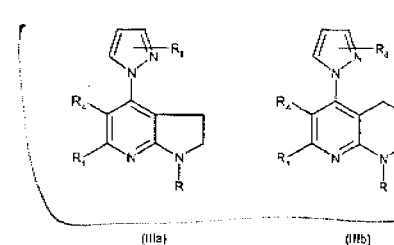
Further representative compounds of this invention include compounds of general formula (I) in which

10 R₂ and R₃ together with N form a 5-14 membered heterocyclic group, which may be substituted by 1 to 3 R₁₀ groups; such R₁₀ groups are defined as above.

Depending upon the choice of X, the CRF receptor antagonists of this invention include compounds of formula (IIa) and (IIb), in which the group NR₂R₃ represents a 5-6 membered heterocyclic group, which may be substituted by 1 to 3 R₈ groups.



20 In particular compounds of formula (IIIa) and (IIIb) are included



in which R₁, R and R₃ have the meanings as defined before.

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Examples of such compounds are reported in the Experimental Part.

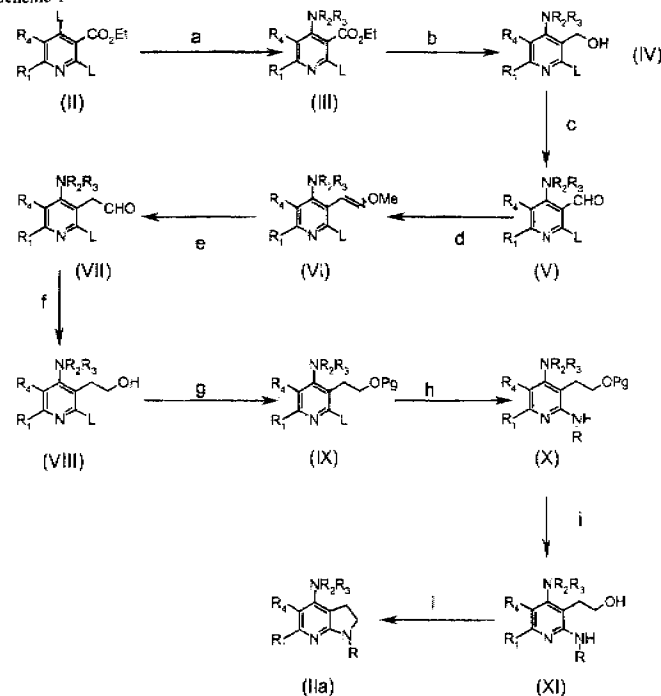
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Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined herein. In the following description, the groups R, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, and n have the meanings as previously defined for compounds of formula (I) unless otherwise stated.

5

Compounds of formula (IIa) may be conveniently prepared according to the following Scheme 1:

Scheme 1



10 in which

- step a stands for conversion of the leaving group L, selected in a group consisting from: halogen or reactive residue of sulphonic acid (e.g. mesylate, tosylate), preferably chloride, in the amino group of compounds (II), by reaction with the suitable amine NR₂R₃ in basic conditions;
- step b stands for reduction of the ester group with a suitable reducing agent (such as DIBAL-H) to hydroxy group of compounds (IV);
- step c stands for oxidation of the hydroxy group with a suitable oxidising agent (such as Dess-Martin periodinane) to aldehyde group of compound (V);

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- step d stands for formation of the aldehyde group of compounds (VII) by Wittig reaction in the usual conditions, through formation of enol ether followed by acid hydrolysis (step e);
- step f stands for reduction of the aldehyde group with a suitable reducing agent (such as NaBH₄) to hydroxy group of compounds (VIII);
- step g stands for conversion of the hydroxy group in the suitable protecting group of compounds (IX) (such as TBS: *tert*-butyldimethylsilyl);
- step h stands for Buchwald reaction by coupling with the suitable amine RNH₂;
- step i stands for deprotection reaction to give the hydroxy group of compounds (XI);
- step l stands for intramolecular cyclisation by heating after conversion of the hydroxy group of compounds (XI) in a suitable leaving group (such as bromide, by reaction with CBr₄ and PPh₃) to give the final compounds (IIa).

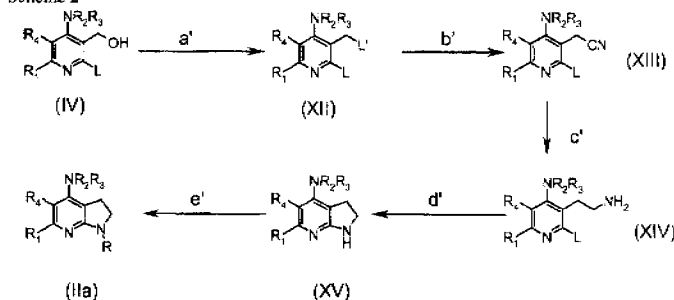
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Alternatively, compounds of formula (IIa) may be conveniently prepared according to the following Scheme 2:

Scheme 2



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in which

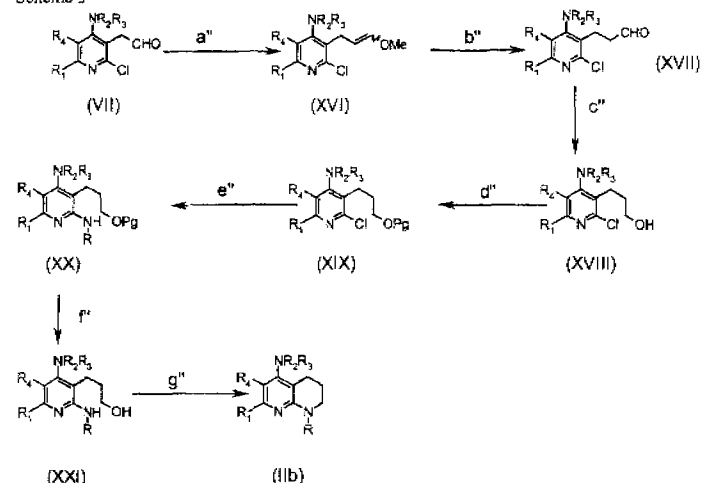
- step a' stands for conversion of the hydroxy group in a suitable leaving group L' of compounds (XII), which, independently from L, has the same definition (e.g. mesylate, by reaction with MsCl in Et₃N);
- step b' stands for conversion of L' in the cyano derivative of compounds (XIII) by reaction with, e.g. KCN in an aprotic dipolar solvent, like DMF;
- step c' stands for reduction of the cyano group with a suitable reducing agent (such as BH₃-THF) to the amino group of compound (XIV);
- step d' stands for intramolecular cyclisation of compounds (XIV) by heating in a suitable solvent (such as NMP) at high temperature;
- step e' stands for reduction of the aldehyde group with a suitable reducing agent (such as NaBH₄) to hydroxy group of compounds (VIII);
- step f' corresponds to previous step h.

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Compounds of formula (IIb) may be conveniently prepared according to the following Scheme 3:

Scheme 3



5 in which:

- step a'' corresponds to previous step d;
 step b'' corresponds to previous step e;
 step c'' corresponds to previous step f;
 step d'' corresponds to previous step g;
 step e'' corresponds to previous step h;
 step f'' corresponds to previous step i;
 step g'' corresponds to previous step j;

15 Compounds of formula (II) are known compounds or may be prepared according to known methods in the literature.

20 Compounds of formula (IIIa) and (IIIb) may be prepared according to the previous Schemes 1, 2 and 3, once prepared the heterocyclic reactive residue according to known methods to the skilled in the art.

25 Examples of suitable hydroxy protecting group include trihydroacetyl silyl ethers such as the trimethylsilyl or t-butyl dimethylsilyl ether. The hydroxyl protecting groups may be removed by well-known standard procedures (such as those described in Protective Groups in Organic Chemistry, pages 46-119, Edited by J F W McOmie (Plenum Press, 1973)). For example when Pg is a t-butyl dimethylsilyl group, this may be removed by treatment with triethylamine trihydrofluoride.

Pharmaceutical acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compound of formula (I) using conventional methods.

5 The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation or evaporation of an appropriate solvent to give the corresponding solvates.

10 When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods. Thus the required enantiomer may be obtained from the racemic compound of formula (I) by use of chiral HPLC procedure.

15 The subject invention also includes isotopically-labeled compounds, which are identical to those recited in formulas I and following, 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, iodine, and chlorine, such as ^3H , ^{11}C , ^{14}C , ^{18}F , ^{123}I and ^{125}I .

20 Compounds of the present invention and pharmaceutically acceptable salts of said compounds that contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H , ^{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.
 25 ^{11}C and ^{18}F isotopes are particularly useful in PET (positron emission tomography), and ^{125}I isotopes are particularly useful in SPECT (single photon emission computerized tomography), all useful in brain imaging. 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 labeled compounds of formula I and following of this invention can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

35 The CRF receptor antagonists of the present invention demonstrate activity at the CRF receptor site including CRF 1 and CRF 2 receptors and may be used in the treatment of conditions mediated by CRF or CRF receptors.

40 The effectiveness of a compound as a CRF receptor antagonist may be determined by various assay methods. Suitable CRF antagonists of this invention are capable of inhibiting the specific binding of CRF to its receptor and antagonizing activities associated with CRF. A compound of structure (I) may be assessed for activity as a CRF antagonist by one or more generally accepted assays for this purpose, including (but not limited to) the assays disclosed by DeSouza et al. (J. Neuroscience 7: 88, 1987) and Battaglia et al. (Synapse 1: 572, 1987).

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The CRF receptors-binding assay was performed by using the homogeneous technique of scintillation proximity (SPA). The ligand binds to recombinant membrane preparation expressing the CRF receptors which in turn bind to wheatgerm agglutinin coated SPA beads. In the Experimental Part will be disclosed the details of the experiments.

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With reference to CRF receptor binding affinities, CRF receptor antagonists of this invention have a K_i less than 10 μM .

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Compounds of the invention are useful in the treatment of central nervous system disorders where CRF receptors are involved. In particular in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

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Compounds of the invention are also useful in the treatment or prevention of schizophrenic disorders including paranoid schizophrenia, disorganised schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, residual schizophrenia.

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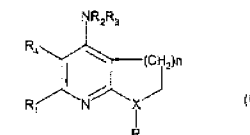
Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmenorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondylitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful for the treatment of dysfunction of appetite and food intake and in circumstances such as anorexia, anorexia nervosa and bulimia.

Claims

1. Compounds of formula (I) including stereoisomers, prodrugs and pharmaceutically acceptable salts or solvates thereof

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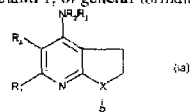
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- R is aryl or heteroaryl, each of which may be substituted by 1 to 4 groups selected from:
halogen, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, $-\text{C}(\text{O})\text{R}_5$, nitro, $-\text{NR}_6\text{R}_7$, cyano, and a group R_8 ;
- R_1 is hydrogen, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkyl, halo C1-C6 alkoxy, halogen, NR_6R_7 or cyano;
- R_2 is hydrogen, C3-C7 cycloalkyl, or a group R_9 ;
- R_3 is C3-C7 cycloalkyl, or a group R_9 ; or
 R_2 and R_3 together with N form a 5-14 membered heterocycle, which may be substituted by 1 to 3 R_{10} groups;
- R_4 is hydrogen, C1-C6 alkyl, halogen or halo C1-C6 alkyl;
- R_5 is a C1-C4 alkyl, $-\text{OR}_6$ or $-\text{NR}_6\text{R}_7$;
- R_6 is hydrogen or C1-C6 alkyl;
- R_7 is hydrogen or C1-C6 alkyl;
- R_8 is a 5-6 membered heterocycle, which may be saturated or may contain one to three double bonds, and which may be substituted by 1 or more R_{11} groups;
- R_9 is a C1-C6 alkyl that may be substituted by one or more groups selected from: C3-C7 cycloalkyl, C1-C6 alkoxy, halo C1-C6 alkoxy, hydroxy, halo C1-C6 alkyl;
- R_{10} is a group R_4 , C3-C7 cycloalkyl, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, hydroxy, halogen, nitro, cyano, $\text{C}(\text{O})\text{NR}_6\text{R}_7$, phenyl which may be substituted by 1 to 4 R_{11} groups;
- R_{11} is C3-C7 cycloalkyl, C1-C6 alkyl, C1-C6 alkoxy, halo C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, halo C1-C6 alkoxy, hydroxy, halogen, nitro, cyano, or $\text{C}(\text{O})\text{NR}_6\text{R}_7$;
- X is carbon or nitrogen;
- n is 1 or 2.
2. Compounds, according to claim 1, in which
 R_2 and R_3 together with N form a 5-14 membered heterocyclic group, which may be substituted by 1 to 3 R_{10} groups.

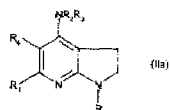
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3. Compounds, according to claim 1, of general formula (Ia)



in which R, R₁, R₂, R₃, R₄ and X are defined as in claim 1.

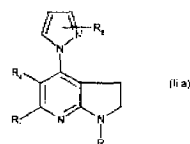
4. Compounds, according to claim 3, of general formula (IIa)



in which R, R₁, R₂, R₄ and R₃ are defined as in claim 1.

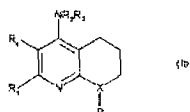
5. Compounds, according to claim 4, in which the group NR₂R₃ represents a 5-6 membered heterocyclic group, which may be substituted by 1 to 3 R₄ groups.

6. Compounds, according to claim 5, of general formula (IIa)



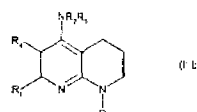
in which R, R₁, R₄ and R₃ are defined as in claim 1.

7. Compounds, according to claim 1, of general formula (Ib)



in which R, R₁, R₂, R₃, R₄ and X are defined as in claim 1.

8. Compounds, according to claim 7, of general formula (IIIb)



in which R, R₁, R₂, R₄ and R₃ are defined as in claim 1.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE

ASUNTO	Radicación	05103293
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	000
	Folios	013

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

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

No. Sol. Internacional PCT/IB2004/001350
Fecha de Presentación Internat. 07-04-2004.

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

Documentos estudiados

Descripción: Folios: 139 a 353 (como se radicó inicialmente)

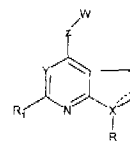
Reivindicaciones: Folios: 354 a 373 (como se radicó inicialmente)

Prioridad: Folio 1 (09-04-2003, GB 0308208.8).
(07-07-2003, US60/485,322).

Objeto de la invención

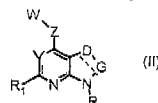
Título de la solicitud: COMPUESTOS N-HETEROCÍCLICOS CONDENSADOS Y SU USO COMO ANTAGONISTAS DE RECEPTORES DEL FACTOR LIBERADOR DE CORTICOTROPINA.

El objeto de la presente solicitud de patente de invención consiste en:
Compuestos derivados bicíclicos.



Reivindicaciones 1-25,30-32 : Un Compuesto de fórmula I.

Reivindicación 26: Un procedimiento para preparar los compuestos de fórmula II



Reivindicaciones 27-29: De uso.

Reivindicación 33: Una composición farmacéutica que contiene el compuesto I.

Reivindicaciones 34-36: Un método de tratamiento.

El problema planteado en esta solicitud es la necesidad de compuestos caracterizados por ser antagonistas potentes y específicos de los receptores CRF.

Para solucionar este problema técnico la solicitud en estudio proporciona compuestos de fórmula I, sus procesos de preparación y composiciones farmacéuticas que las contienen.

El objeto de la invención definido anteriormente se clasificó de acuerdo con la Clasificación Internacional de Patentes (IPC): C07D471/04, C07D487/04.

De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

- La reivindicación 1 no es concisa ya que hay términos muy generales. Por este motivo se obtienen un número indefinido de compuestos. Por tal motivo se obtiene un número indefinido de compuestos lo cual hace que no se pueda determinar que todos los que se obtienen finalmente, presenten la actividad reclamada. Estos términos son:
 - Un grupo arilo o heteroarilo para el radical R ya que no se especifica el número de carbonos que los conforman, no se define su tamaño y adicionalmente en el caso de heteroarilo no se define el número y clase de heteroátomos que lo conforman. Tampoco especifica si dichos grupos pueden estar sustituidos o no. Para el grupo heterociclo de 5-6 miembros del radical Z, no se especifica los heteroátomos que lo pueden conformar.
- Los términos prodrogas y solvatos deben ser eliminados, ya que los grupos estructurales que los conforman no pueden ser claramente identificados. Y no encuentran sustento en la descripción.
- Las reivindicaciones 30-32, no son claras ya que se reclama el compuesto ya reclamado anteriormente, sin aportar alguna característica técnica adicional.

Unidad de invención (artículo 25 D 486)

Se aclara que, de acuerdo al Art 25, en las reivindicaciones 1-26,30-33 (Folios 354 a 373), carecen de unidad de invención por lo siguiente:

Se distinguen los siguientes grupos de invención a posteriori:

1. Compuestos de fórmula I donde Y es CR7 (derivados de pirrolo[2,3-*b*]piridina, composiciones farmacéuticas que los contienen y procedimiento para prepararlos.
2. Compuestos de fórmula I donde Y es N (derivados de pirrolo[2,3-*d*]pirimidina., composiciones farmacéuticas que los contienen y procedimiento para prepararlos.

Cada una de estas invenciones , es una invención distinta caracterizada por su propia característica técnica y no se encuentran tan unidas como para formar un concepto general inventivo único, por las siguientes razones.

Se realizó la búsqueda de anterioridades , donde se encontró un documento relevante para la evaluación de patentabilidad del grupo que corresponde específicamente a cuando Y es CR7. Al ser este documento tan específico para una de las estructuras reclamadas por el solicitante y observar que dichas estructuras no cumplen con el requisito de patentabilidad (nivel inventivo), las características técnicas para cuando Y es N , ya no están unidas por un concepto inventivo único común.

En consecuencia, esta Dependencia recomienda realizar las modificaciones correspondientes y/o seleccionar el o los grupos que son relevantes para la invención.

Excepción a la patentabilidad (artículo 20 D486 literal a)-d))

Se aclara que, de acuerdo al Art 20 literal d) el método de tratamiento de las reivindicaciones 34-36, no es patentable

Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

Se aclara que, de acuerdo con el Art 14, el uso de las reivindicaciones 27-29 , no es patentable.

Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 09-04-2003, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

N°	Documento	Título	Fecha de Publicación*
D1	WO03/008412	CHEMICAL COMPOUNDS	30-01-2003

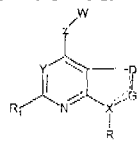
Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo18 D486)

Para el grupo inventivo 1

Respecto a la solicitud en estudio.

La reivindicación 1 dice “ Compuestos de fórmula I , incluyendo estereoisómeros, profármacos, y sales farmacéuticamente aceptables o solvatos de los mismos



Respecto al estado de la técnica:

D1 (folios 399-405) divulga compuestos derivados de pirrolo[2,3-b]piridina, caracterizados por ser antagonistas potentes y específicos de los receptores CRF.

SOLICITUD		D1	
 Compuesto 1-1 Compuesto 2-1 Compuesto 3-1	R₁ es alquilo C₁₋₆ (metilo) Y es CR₇ y R₇ es hidrógeno. Z es un heterociclo de 5-6- miembros. (pirazol) W es un anillo de 4-8 miembros , el cual puede estar saturado o puede contener uno a tres enlaces dobles y en el cual: - un átomo de carbono se reemplaza por un carbonilo o S(O)m, y - de 1 a 4 átomos de carbono se pueden reemplazar por oxígeno, nitrógeno o NR₁₂, S(O)m, carbonilo. (imidazolinina, pirrolidinona, tetrahidropirimidinona) D es CR₈R₉ R₈ y R₉ son hidrogeno,	 (IIa) 	R₁ es alquilo C₁₋₆ (metilo) R₄ es hidrógeno. R₂ y R₃ juntos forman con el nitrógeno que los une un heterociclo de 5-14 miembros (pirazol) El anillo formado por R₂ y R₃ se encuentra sustituido por grupos R₁₀ , R₁₀ es R₈ el cual es un anillo heterociclo 5-6 miembros el cual puede estar saturado o puede contener de uno a tres dobles enlaces (imidazolil, pirrolidinil, tetrahidropirimidinil, n es 1. X es C o N. R es arilo o heteroarilo. Fenilo sustituido por metilo y metoxi

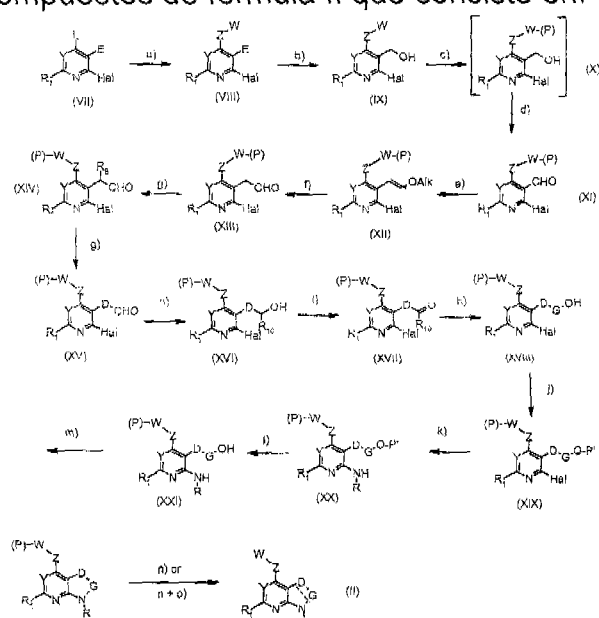
La solicitud se diferencia de D1 en que el anillo denominado W, se reemplaza un átomo de carbono por un carbonilo o S(O)m, y- de 1 a 4 átomos de carbono se pueden reemplazar por oxígeno, nitrógeno o NR₁₂, S(O)m, carbonilo.

Esta diferencia no parece conceder un efecto técnico inesperado ó una ventaja a las

El Problema Técnico Objetivo de esta solicitud es la necesidad de compuestos derivados de pirrolo[2,3-b]piridina caracterizados por ser agentes antagonistas de los receptores CFR alternativos a los ya conocidos en el estado del arte.

De manera que la solución propuesta por esta solicitud en las reivindicaciones 1-25.30-32 es obvia y no tiene Nivel Inventivo.

Para la reivindicación 26 en donde se reclama un proceso de preparación de los compuestos de fórmula II que consiste en:



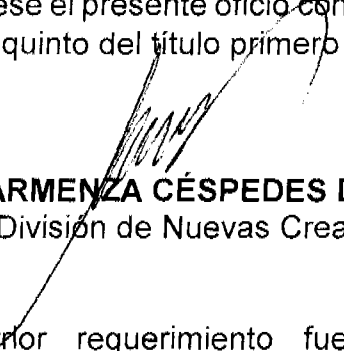
Conclusión:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO03/008412	1-26,30-33	Nivel inventivo.

111

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 _____

CONCEPTO TÉCNICO No. 2935	EXAMINADOR TÉCNICO Código No. 202075
-------------------------------------	--

1. Condensed N-heterocyclic compounds and their use as CRF receptor antagonists en mi lista de patentes
Información de publicación: AU2004/32551 (A1) — 2004-11-04
2. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: BR-10409117 (A) — 2006-03-28
3. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: CA2521929 (A1) — 2004-11-04
4. Condensed N-heterocyclic compounds and their use as CRF receptor antagonists en mi lista de patentes
Información de publicación: CN1805958 (A) — 2006-07-19
5. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: EP1611133 (A1) — 2006-01-04
6. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: EP1618107 (A1) — 2006-01-25
7. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: ES8119 (A) — 2005-11-08
8. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: JP2006522798 (T) — 2006-10-05
9. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: JP2006522799 (T) — 2006-10-05
10. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: KR20060021826 (A) — 2006-03-08
11. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: MA27796 (A1) — 2006-03-01
12. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: MXPA05010874 (A) — 2006-03-21
13. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: NO20055238 (A) — 2006-01-09
14. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: PL378755 (A1) — 2006-05-15
15. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: RU2005134652 (A) — 2006-05-10
16. Condensed n-heterocyclic compounds and their use as crf receptor antagonists en mi lista de patentes
Información de publicación: US2007004708 (A1) — 2007-01-04
17. Condensed n-heterocyclic compounds and their use as crf receptor antagonists en mi lista de patentes
Información de publicación: US2007021429 (A1) — 2007-01-25
18. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: WO2004094419 (A1) — 2004-11-04
19. CONDENSED N-HETEROCYCLIC COMPOUNDS AND THEIR USE AS CRF RECEPTOR ANTAGONISTS en mi lista de patentes
Información de publicación: WO2004094420 (A1) — 2004-11-04

EXAMEN TÉCNICO DE FONDO

Nº Radicación	05103293	Fecha de presentación	10-10-2005
Nº Solicitud Internacional	PCT/IB2004/001350	Fecha Solicitud Internacional	07-04-2004
Nº Prioridad	GB 0308208.8	Fecha de Prioridad	09-04-2003

Palabras clave

Heterocyclic compounds, 1H-pyrrolo[2,3-b]pyridine, antagonist of corticotrophin releasing factor CRF.

CLASIFICACIONES INTERNACIONALES DE BUSQUEDA

C07D471/04, C07D487/04

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES

Ver hoja anexa

Patente Original

BASES DE DATOS CONSULTADAS

EPOLINE	COLOMBIANA	japonesa	Patent family
ESPACENET	SINGAPUR	scirus	SURECHEM
uspto	depatinet	Universidad nacional	CHEMSPIDER

INFORMES DE EXÁMENES EN OTRAS OFICINAS

Oficina	Fecha	Rev. afectadas
EUROPEA	27-11-2006	1-53
uspto	26-06-2006	1-52

ANTERIORIDADES ENCONTRADAS

Documento	Rev. afectadas	Relevancia
WO03/008412	1-26,30-33	Nivel inventivo.

LITERATURA NO PATENTES

Documento	Relevancia	Rev. afectadas

Observaciones

Fecha del examen

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 15549

Por la cual se niega una patente de invención

Rad. PCT/05-103293

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "COMPUESTOS N-HETEROCICLICOS CONDENSADOS Y SU USO COMO ANTAGONISTAS DE RECEPTORES DEL FACTOR LIBERADOR DE CORTICOTROPINA", que corresponde a la solicitud internacional PCT/IB2004/001350 de fecha 07 de abril del 2004, fue radicada en esta Superintendencia el 10 de octubre del 2005 bajo el número 05-103293 -00000-0000, para que se dé comienzo a la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales.(...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente"*.

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 399 a 411 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del solicitante, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION ^{Nº} 15549

Por la cual se niega una patente de invención

Rad. PCT/05-103293

RESUELVE:

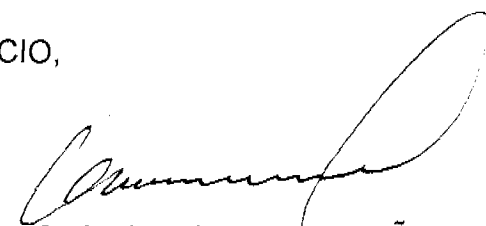
ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPUESTOS N-HETEROCICLICOS CONDENSADOS Y SU USO COMO ANTAGONISTAS DE RECEPTORES DEL FACTOR LIBERADOR DE CORTICOTROPINA", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Carlos Reinaldo Olarte García, en su calidad de apoderado de SB PHARMCO PUERTO RICO INC. y NEUROCRINE BIOSCIENCES INC., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 23 MAR. 2010.

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


GUSTAVO VALBUENA QUIÑONES

Doctor
CARLOS REINALDO OLARTE GARCIA
Diagonal 34 No. 5-28
Bogotá D.C.

