

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-089705- -00004-0000

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Tra 11 PATENTEIYII Eve: 378 FASLNACIONALI
Act. 538 PETICION Folios: 2

Señora

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Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. _____ S. _____ D. _____

Referencia: Expediente No. 07.089.705

Solicitud de Patente de Invención titulada: "Formas cristalinas y amorfas del
clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-
piperazin-1-il]-propil)-n-piridin-2-il-benzamina"

Solicitante: Wyeth

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISIÓN**486. GACETA NO. 587**

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad arriba mencionada, solicito que se examine la invención de la referencia según los requisitos de patentabilidad previstos en la Decisión 486 de la Comisión de la Comunidad Andina de Naciones. Adjunto recibo de caja por valor de \$420.000 para cubrir la tasa correspondiente según la Resolución 44372 del 26 de diciembre de 2007.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ

C.C.No.79.143.366 de Usaquén

T.P.20.281

Anexo: Recibo de caja por valor de \$420.000

2008/012/72

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : JUNIO 24 DE 2008

***** CONSIGNACION *****

DEBITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	7445085	23/06/2008	61,32,800.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

171

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-89705

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **592** DE

FECHA **30 DE MAYO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **28 DE AGOSTO DE 2008**

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.

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P 0202213 10 July 2002 (10.07.2002) HU(71) Applicant (for all designated States except US):
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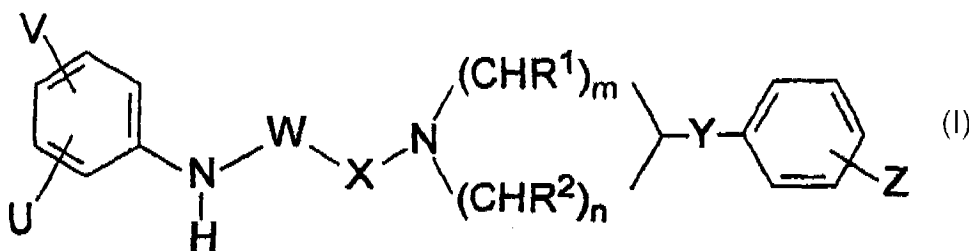
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dapest (HU).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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VN, YU, ZA, ZM, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW),
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(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).

Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,

[Continued on next page]

(54) Title: PIPERIDINE DERIVATIVES AS NMDA RECEPTOR ANTAGONISTS

(57) Abstract: The present invention relates to new carboxylic acid amide derivatives of formula (I), wherein U, V, W, X, Y, Z, n and m are as defined as in Claim 1. A further object of the invention are the processes for producing of carboxylic acid amide compounds of formula (I), and the pharmaceutical manufacture of medicaments containing these compounds, as well as the process of treat-
ments with these compounds, which means administering to a mammal to be treated including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament. The new carboxylic acid amide derivatives of formula (I) of the present invention are highly effective and selective antagonists of NMDA receptor, and moreover most of the compounds are selective antagonist of NR2B subtype of NMDA receptor.

5 Detailed description of the invention

$$\begin{array}{c}
 \text{V} \\
 | \\
 \text{C}_6\text{H}_3 \\
 | \\
 \text{N} - \text{W} - \text{X} - \text{N} \begin{array}{l} \text{(CHR}^1\text{)}_m \\ \text{(CHR}^2\text{)}_n \end{array} \\
 | \qquad \qquad \qquad | \\
 \text{H} \qquad \qquad \qquad \text{C} - \text{Y} - \text{C}_6\text{H}_4 - \text{Z} \\
 \qquad \qquad \qquad | \\
 \qquad \qquad \qquad \text{H}
 \end{array}$$

(1)

10 V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C₁-C₄ alkylamino optionally substituted by a halogen atom or halogen atoms, arylamino optionally substituted by a halogen atom or halogen atoms, aralkylamino optionally substituted by a halogen atom or halogen atoms, C₁-C₄ alkylsulfonamido optionally substituted by a halogen atom or halogen atoms, C₁-C₄ alkanoylamido optionally substituted by a halogen atom or halogen atoms, arylsulfonamido, C₁-C₄ alkylsulfonyloxy, carboxyl, trifluoromethyl, trifluoromethoxy, C₁-C₄ alkyl-SO₂-NH-CH₂-, NH₂-(CH₂)₁₋₄-SO₂-NH-, NH₂-(CH₂)₁₋₄-(CO)-NH-, sulfamoyl [NH₂-SO₂-], formyl [-CHO], amino-methyl [-CH₂-NH₂], hydroxymethyl, C₁-C₄ alkyl, C₁-C₄ alkoxymethyl, halogenmethyl, tetrazolyl group, or C₁-C₄ alkoxy, C₁-C₄ alkoxycarbonyl, C₁-C₆ alkanoyloxy, phenyl or C₁-C₄ alkoxy groups, optionally substituted by amino group, or

the neighboring V and U groups in given case together with one or more identical or different additional hetero atom and -CH= and/or -CH₂- groups can form an optionally substituted 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole,

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imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

W and X independently are -CO-, -CH₂- or -CH(-alkyl)- groups - wherein alkyl is a C₁-C₄ alkyl group groups - with the restriction, that the meaning of W and X can not be methylene at the same time

Y is oxygen atom, as well as C₁-C₄ alkylene, C₁-C₄ alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)-, -CH₂O-, -CH(OH)-, -OCH₂- group, - wherein alkyl is a C₁-C₄ alkyl group -,

Z is hydrogen or halogen atom, nitro, amino, C₁-C₄ alkyl, C₁-C₄ alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

R¹ and R² independently are hydrogen atom or alkyl group, or R¹ and R² together form an optionally substituted C₁-C₃ bridge and

n and m independently are 0-3, with the restriction, that n and m can not be 0 at the same time, and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases with the proviso that

when Z means hydrogen atom, Y means -CH₂- group, both of m and n mean 2, both of R¹ and R² mean hydrogen atom, W means -CO- group, X means -CH₂- group and V means hydrogen atom, then the meaning of U is other than a 4-bromo substituent and

when Z means hydrogen atom, Y means -CH₂- group, both of m and n mean 2, both of R¹ and R² mean hydrogen atom, both of W and X mean -CO- group and V means hydrogen atom, then the meaning of U is other than a 4-carboxyl or 4-etoxy carbonyl substituent.

Furthermore objects of the present invention are the pharmaceutical compositions containing carboxylic acid amide compounds of formula (I) or optical antipodes or racemates or the salts thereof as active ingredients.

A further object of the invention are the processes for producing of carboxylic acid amide compounds of formula (I), and the pharmaceutical manufacture of medicaments containing these compounds, as well as the process of treatments with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

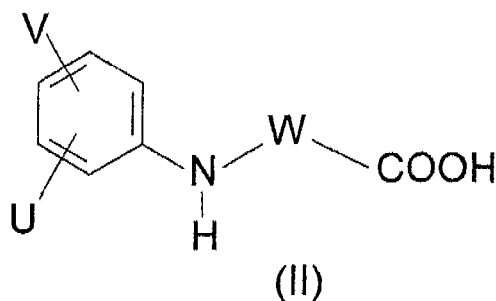
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- 5 -

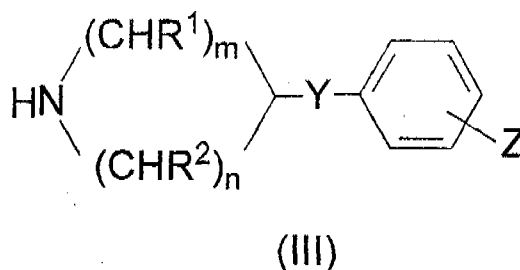
The new carboxylic acid amide derivatives of formula (I) of the present invention are highly effective and selective antagonists of NMDA receptor, and moreover most of the compounds are selective antagonist of NR2B subtype of NMDA receptor.

According to the invention the carboxylic acid amide compounds of formula (I) can be prepared by the following processes

a.) for producing of compounds of formula (I) having -CO- group in place of X - wherein the meaning of R^1 , R^2 , Y, Z, U, V, W, n and m are as given before for the formula of (I) - a carboxylic acid of formula (II)



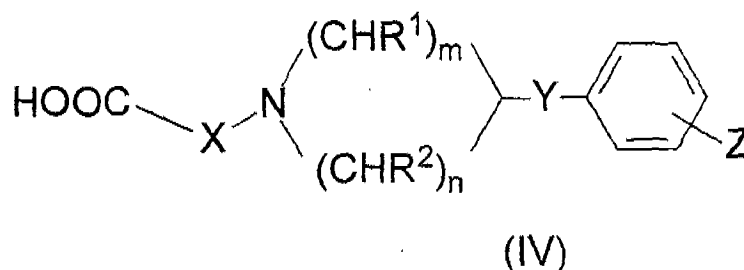
- wherein the meaning of U, V and W are as given for the formula of (I) - or a reactive derivative of it is reacted with an amine of formula (III)



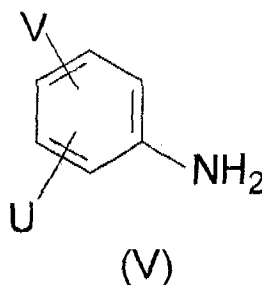
- wherein the meaning of R^1 , R^2 , Y, Z, n and m are as given before for the formula of (I) - , or

b.) for producing of compounds of formula (I) having -CO- group in place of W - wherein the meaning of R^1 , R^2 , Y, Z, U, V, X, n and m are as given before for the formula of (I) - a carboxylic acid of formula (IV)

- 6 -

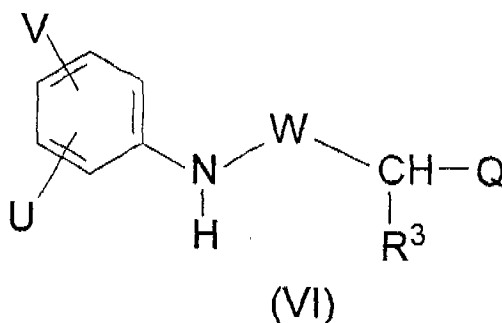


- wherein the meaning of X, R¹, R², Y, Z, n and m are as described above for the formula of (I) - or a reactive derivative of it is reacted with an amine of formula (V)



5 - wherein the meaning of U and V are as given before for the formula of (I) -, or

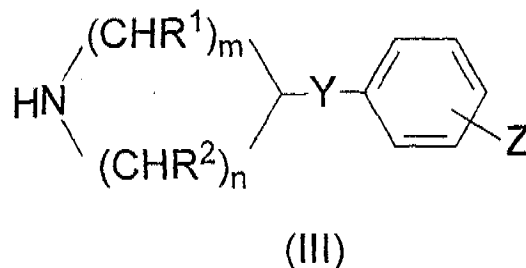
c.) for producing of compounds of formula (I) having -CH₂- or -CH(-alkyl)- group in place of X - wherein alkyl is a C₁-C₄ alkyl group and the meaning of R¹, R², Y, Z, U, V, W, n and m are as given before for the formula of (I) - a halogene derivative of a compound of formula (VI)



10

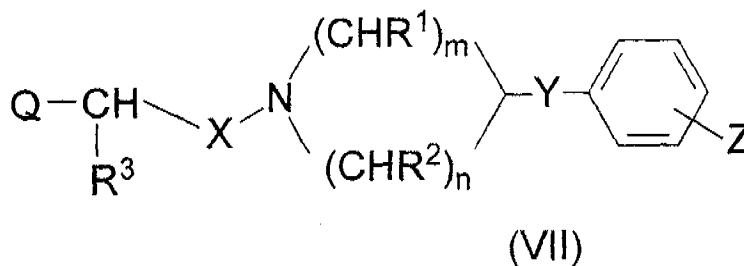
- wherein the meaning of Q is halogen atom, R³ is hydrogen atom or a C₁-C₄ alkyl group and U, V and W are as described above for the formula of (I) - is reacted with an amine of formula (III)

- 7 -

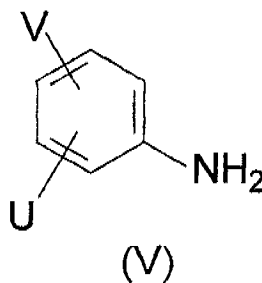


- wherein the meaning of R^1 , R^2 , Y, Z, n and m are as given before for the formula of (I) -, or

- d.) for producing of compounds of formula (I) having $-\text{CH}_2-$ or $-\text{CH}(\text{-alkyl})-$ group in place of W - wherein alkyl is a C_1 - C_4 alkyl group and the meaning of R^1 , R^2 , Y, Z, U, V, X, n and m are as given before for the formula of (I) - a halogene derivative of a compound of formula (VII)



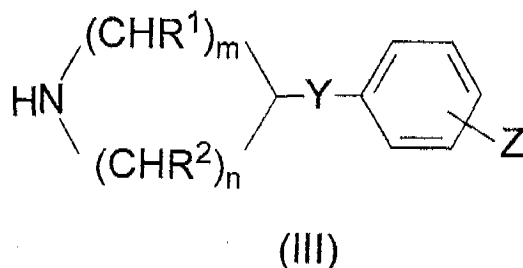
- wherein the meaning of Q is halogen atom, R^3 is hydrogen atom or a C_1 - C_4 alkyl group and X, R^1 , R^2 , Y, Z, n and m are as described above for the formula of (I) - is reacted with an amine of formula (V)



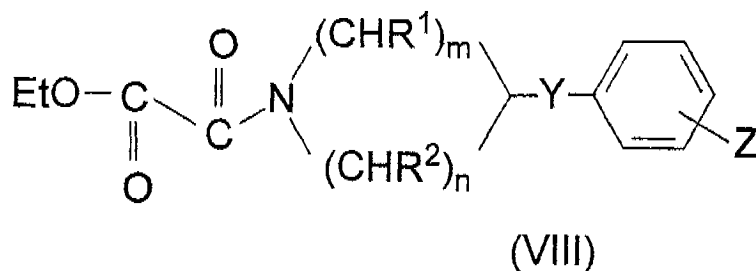
- wherein the meaning of U and V are as given before for the formula of (I) -, or

- process e e.) for producing compound of formula (I), where X mean $-\text{CO}-$ group and R^1 , R^2 , Y, Z, U, V, n and m are as defined for the formula (I), a secondary amine of formula (III)

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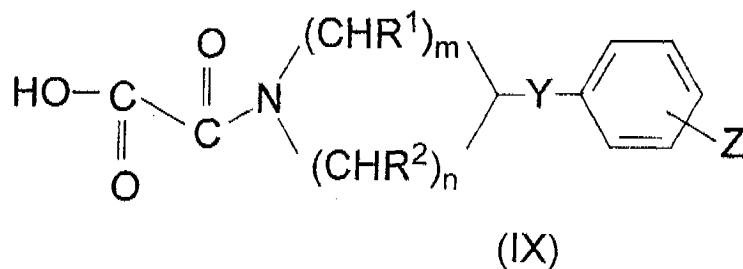


- where R^1 , R^2 , m, n, Y and Z have the same meaning as given for formula (I) - is reacted with ethyl oxalylchloride in the presence of solid-supported base in dichloromethane,
the obtained ester compound of formula (VIII)



5

- where R^1 , R^2 , m, n, Y and Z have the same meaning as given for formula (I) - is saponified with a strongly basic ion exchange resin in ethanol and
the obtained oxalamid acid of formula (IX)

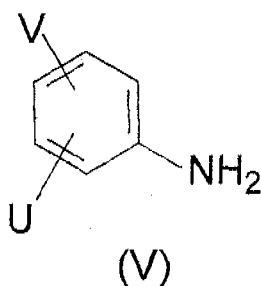


10

where R^1 , R^2 , m, n, Y and Z have the same meaning as given for formula (I) is reacted with an amide of formula (V)

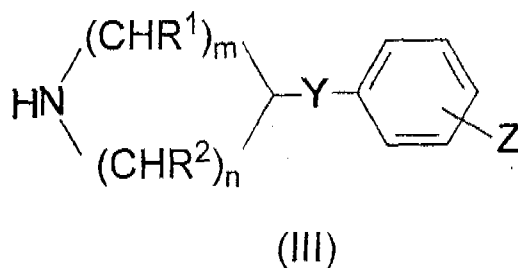
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- 9 -

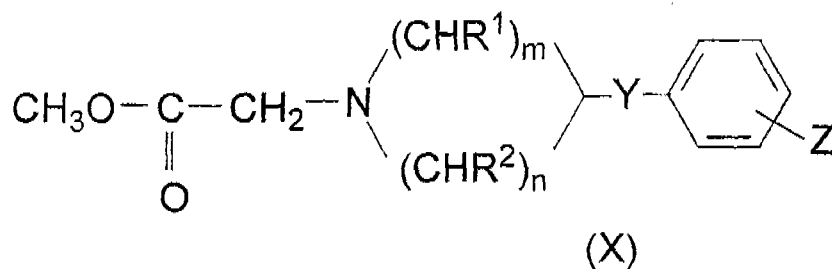


- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in the presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide, or

- 5 f.) for producing compound of formula (I), where X mean $-\text{CH}_2-$ group and R^1 , R^2 , Y, Z, U, V, n and m are as defined for the formula (I), a secondary amine of formula (III)



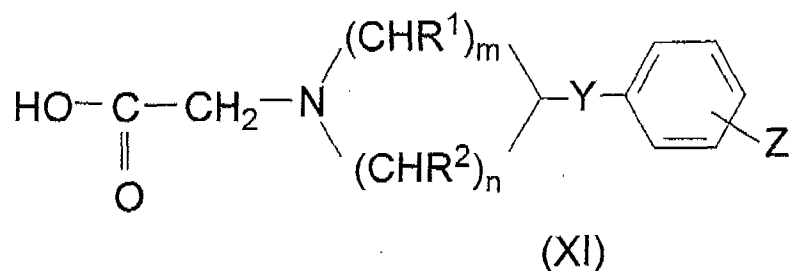
- 10 - where R^1 , R^2 , m, n, Y and Z have the same meaning as given for formula (I) - is reacted with methyl bromoacetate in the presence of potassium carbonate in dimethylformamide, the obtained ester compound of formula (X)



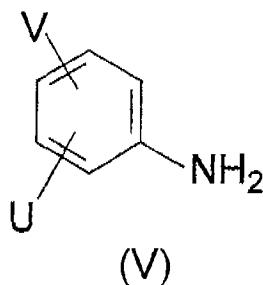
- 15 where R^1 , R^2 , m, n, Y and Z have the same meaning as given for formula (I) is saponified with a strongly basic ion exchange resin in ethanol and the obtained substituted glycine of formula (XI)

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- 10 -



where R^1 , R^2 , m , n , Y and Z have the same meaning as given for formula (I) is reacted with an amide of formula (V)



5

- wherein the meaning of U and V are as given before for the formula of (I) - in dichloromethan/dimethylformamide mixture in presence of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide,

and the obtained compounds of formula (I) - where R^1 , R^2 , Y , Z , U , V , X , W , n and m are as defined above - in given case are transformed into an other compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or formation of salts with acids and/or liberating the carboxylic acid amide derivative of formula (I) from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid amide derivative of formula (I) can be transformed into a salt by treatment with a base and/or are resolved into their optical antipodes.

The amide bond formation is preferably carried out by preparing an active derivative from a carboxylic acid of formula (II) or (IV) which is reacted with an amine of formula (III) or (V) preferably in the presence of a base.

The transformation of a carboxylic acid into an active derivative can be carried out in situ during the amide bond formation in a proper solvent (for example dimethylformamide, acetonitrile, chlorinated hydrocarbons or hydrocarbons). The active derivatives can be acid chlorides (for example prepared from carboxylic acid with thionyl chloride), mixed anhydrides

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The title compound is prepared from 4-amino-benzonitrile (Aldrich) and (4-benzyl-piperidin-1-yl)-oxo-acetic acid according to the method described in Example 2. Mp.: 166-169 °C (diethylether)

Example 6

5 2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-indol-5-yl)-acetamide (45
70001823)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 5-amino-1,3-dihydro-indol-2-one according to the method described in Example 2. Mp.: 115-118 °C (water)

10

Example 7

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)-acetamide
(45 70001824)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example 5b) and 5-amino-1,3-dihydro-benzimidazol-2-one according to the method described in Example
15 2. Mp.: > 260 °C (water)

Example 8

2-(4-Benzyl-piperidin-1-yl)-2-oxo-N-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-acetamide (45
70001861)

The title compound is prepared from (4-benzyl-piperidin-1-yl)-oxo-acetic acid (Example
20 5b) and 6-amino-3H-benzoxazol-2-one according to the method described in Example 1c.
Mp.: 190-193 °C (diethylether)

Example 9

N-(4-Cyano-phenyl)-2-[4-(4-fluoro-benzyl)-piperidin-1-yl]-2-oxo-acetamide (45 70001946)

The title compound is prepared from 4-amino-benzonitrile and [4-(4-fluoro-benzyl)-
25 piperidin-1-yl]-oxo-acetic acid (Example 1b) according to the method described in Example 1c.
Mp.: 167-169 °C (diethylether)

Example 10

2-(4-Benzyl-piperidin-1-yl)-N-(3-nitro-phenyl)-2-oxo-acetamide (45 70001862)
10a) N-(3-Nitro-phenyl)-oxalamic acid

30 The title compound is prepared from N-(3-nitro-phenyl)-oxalamic acid ethyl ester
[J.Chem. Soc., 121, 1501. (1922)] according to the method described in Example 1b. Mp.: > 270
°C (ethanol-water)

eluent and processing to 55% B eluent in 30 minutes for those compounds where the capacity factor was less than 2.5. The collected fractions were qualified by the above detailed analytical method and the solvent was evaporated by Speed Vac (Savant, USA).

The compounds prepared as described above in procedures "A" and "B" are shown in
5 Tables 3, 4, 5 and 6, respectively.

Table 3

Compounds of formula (I) prepared by procedure "A" described in Example 259
where X means -CO- group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, Y, Z,
U and V are as given below:

10

No.	V	U	Y	Z	MW _c	MW _f	k'
1.	4- Ac-NH-	H-	-CH ₂ -	4-F-	397.45	398.5	3.421
2.	4- Ac-NH-	H-	-CH ₂ -	4-Cl-	413.905	414.5	3.202
3.	4- CH ₃ -SO ₂ -NH-	H-	-O-	4-CH ₃ -	431.507	432.5	3.349
4.	4- Ac-NH-	H-	-O-	4-CH ₃ -	395.459	396.4	3.306
5.	4- CH ₃ -SO ₂ -NH-	H-	-O-	4-Cl-	451.925	452.5	3.545
6.	4- CH ₃ -SO ₂ -NH-	H-	-CH ₂ -	4-Cl-	449.953	450.4	3.67
7.	4- Ac-NH-	H-	-O-	4-Cl-	415.877	416.5	3.518
8.	4- CH ₃ -SO ₂ -NH-	H-	CH ₃ -N<	4-Cl-	464.968	465.5	2.304
9.	4- Ac-NH-	H-	CH ₃ -N<	4-Cl-	428.92	429.5	2.259
10.	4- CH ₃ -SO ₂ -NH-	H-	-CH ₂ -CH ₂ -	4-F-	447.525	448.5	3.57
11.	4- Ac-NH-	H-	-CH ₂ -CH ₂ -	4-F-	411.477	412.5	3.555
12.	4- CH ₃ -SO ₂ -NH-	H-	CH ₃ -N<	4-CH ₃ -	444.55	445.5	1.155
13.	4- CH ₃ -SO ₂ -NH-	H-	-CH ₂ -N(CH ₃)-	H-	444.55	445.4	1.776
14.	4- Ac-NH-	H-	CH ₃ -N<	4-Br-	473.371	474.4	2.33
15.	4- Ac-NH-	H-	CH ₃ -N<	4-CH ₃ -	408.502	409.5	2.169

Table 4

Compounds of formula (I) prepared by procedure "A" described in Example 259
where X means -CO- group, both of $-(CHR^1)_m-$ and $-(CHR^2)_n-$ are $-CH_2-CH_2-$ groups, U
15 **and V form together a bivalente group and Y and Z are as given below:**

from the obtained acid addition salts by treatment with a base and/or the free carboxylic acid amide derivative of formula (I) can be transformed into a salt by treatment with a base.

For example cleaving the methyl and benzyl groups from methoxy and benzyloxy groups, which stands for U,V and Z, leads to phenol derivatives. The removal of the benzyl group can be carried out for example with catalytic hydrogenation or with hydrogen bromide in acetic acid solution, the cleavage of methyl group can be carried out with boron tribromide in dichloromethane solution. The compounds of formula (I) containing free phenolic hydroxy group can be transformed into acyloxy or sulfoxy derivatives with different acylating or sulfonylating agents. The reactions are carried out at room temperature in chlorinated hydrocarbons using acid chloride or acid anhydride as acylating agent in the presence of a base (for example triethylamine or sodium carbonate). The carboxylic acid amide derivatives of formula (I) containing a nitro group (I) can be transformed into amines by catalytic hydrogenation and the amines can be further reacted to give acid amides as described for the acylation of phenolic hydroxy groups. Free hydroxy groups can be esterified by acid anhydrides or acid halogenides in the presence of a base.

The carboxylic acids of formula (II) or (IV), the primary or secondary amines of formula (III) or (V) and the halogene compounds of formula (VI) or (VII) are either commercially available or can be synthesized by different known methods. The syntheses of some commercially not available carboxylic acids of formula (II) or (IV) or halogen compounds of (VI) or (VII) are described in the Examples. Following these procedures the other commercially not available carboxylic acids of formula (II) or (IV) or halogen compounds of formula (VI) or (VII) can also be prepared.

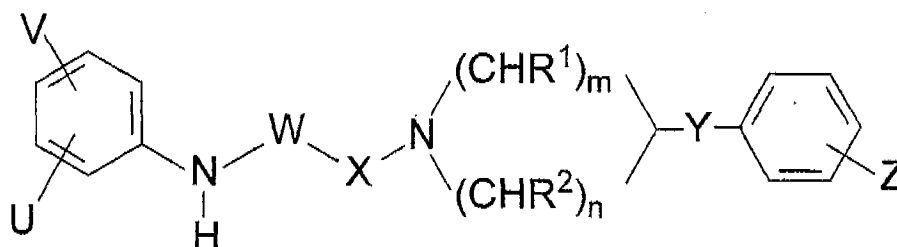
Experimental protocols

Assessing the functional NMDA antagonist potency of compounds in primary cultures of rat cortical neurons based on measuring the intracellular calcium concentration using a fluorimeter plate reader

It is known that during postnatal development the subunit composition of neuronal NMDA receptors is changing. Similar change has been detected in neuronal cell cultures [Eur. J. Neurosci., **10**, 1704-1715 (1998)]. According to data in the literature and to our own immunocytochemical examinations neuronal cells cultured for 4-7 days *in vitro* predominantly express the NR2B subunit, together with NR1 subunit. Therefore, functional test of NMDA antagonism in these cells reflects mainly an action on NR2B subunit containing receptors. Since

What we claim is:

1. New carboxylic acid amide derivatives of formula (I)



(I)

5 - wherein

V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C₁-C₄ alkylamino optionally substituted by a halogen atom or halogen atoms, arylamino optionally substituted by a halogen atom or halogen atoms, aralkylamino optionally substituted by a halogen atom or halogen atoms, C₁-C₄ alkylsulfonamido optionally substituted by a halogen atom or halogen atoms, C₁-C₄ alkanoylamido optionally substituted by a halogen atom or halogen atoms, arylsulfonamido, C₁-C₄ alkylsulfonyloxy, carboxyl, trifluoromethyl, trifluoromethoxy, C₁-C₄ alkyl-SO₂-NH-CH₂-, NH₂-(CH₂)₁₋₄-SO₂-NH-, NH₂-(CH₂)₁₋₄-(CO)-NH-, sulfamoyl [NH₂-SO₂-], formyl [-CHO], amino-methyl [-CH₂-NH₂], hydroxymethyl, C₁-C₄ alkyl, C₁-C₄ alkoxymethyl, halogenmethyl, tetrazolyl group, or C₁-C₄ alkoxy, C₁-C₄ alkoxycarbonyl, C₁-C₆ alkanoyloxy, phenyl or C₁-C₄ alkoxy groups, optionally substituted by amino group, or

the neighboring V and U groups form together and with one or more identical or different additional hetero atom and -CH= and/or -CH₂- groups an optionally substituted 4-7 membered homo- or heterocyclic ring, preferably morpholine, pyrrole, pyrrolidine, oxo- or thioxo-pyrrolidine, pyrazole, pyrazolidine, imidazole, imidazolidine, oxo- or thioxo-imidazole or imidazolidine, 1,4-oxazine, oxazole, oxazolidine, oxo- or thioxo-oxazolidine, or 3-oxo-1,4-oxazine ring,

W and X independently are -CO-, -CH₂- or -CH(-alkyl)- groups - wherein alkyl is a C₁-C₄ alkyl group groups - with the restriction, that the meaning of W and X can not be methylene at the same time

Y is oxygen atom, as well as C₁-C₄ alkylene, C₁-C₄ alkynylene, cycloalkylene, aminocarbonyl, -NH-, -N(alkyl)-, -CH₂O-, -CH(OH)-, -OCH₂- group, - wherein alkyl is a C₁-C₄ alkyl group -

Z is hydrogen or halogen atom, nitro, amino, C₁-C₄ alkyl, C₁-C₄ alkoxy, cyano, trifluoromethyl, hydroxyl or carboxyl group,

R¹ and R² independently are hydrogen atom or alkyl group, or R¹ and R² together form an optionally substituted C₁-C₃ bridge and

n and m independently are 0-3, with the restriction, that n and m can not be 0 at the same time, and optical antipodes or racemates and/or pharmaceutically acceptable salts thereof formed with acids and bases with the proviso that

when Z means hydrogen atom, Y means -CH₂- group, both of m and n mean 2, both of R¹ and R² mean hydrogen atom, W means -CO- group, X means -CH₂- group and V means hydrogen atom, then the meaning of U is other than a 4-bromo substituent and

when Z means hydrogen atom, Y means -CH₂- group, both of m and n mean 2, both of R¹ and R² mean hydrogen atom, both of W and X mean -CO- group and V means hydrogen atom, then the meaning of U is other than a 4-carboxyl or 4-etoxy carbonyl substituent.

2. Compounds of claim 1, where both of -(CHR¹)_m- and -(CHR²)_n- are -CH₂-CH₂- groups and W, X, V, U, Y and Z have the meanings as defined for formula (I).

3. Compounds of claim 2, where W means -CO- group, X means -CH₂- group, and V, U, Y and Z have the meanings as defined for formula (I).

4. Compounds of claim 2, where X means -CO- group, and W means -CH₂- group, and V, U, Y and Z have the meanings as defined for formula (I).

5. Compounds of claim 2, where both of X and W mean -CO- groups, and V, U, Y and Z have the meanings as defined for formula (I).

6. Compounds of claim 2, where V and U independently are hydrogen or halogen atom, hydroxyl, cyano, nitro, amino, C₁-C₄ alkylamino optionally substituted by a halogen atom or halogen atoms, arylamino optionally substituted by a halogen atom or halogen atoms, aralkylamino optionally substituted by a halogen atom or halogen atoms, C₁-C₄ alkylsulfonamido

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 02 de Febrero de 2011

Abogad
ALVARO CORREA ORDOÑEZ

ASUNTO	Radicación	07 089 705
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	004028
	Folios	20

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐
No. Solicitud Internacional PCT/US2006/006802			
Fecha de Presentación Internacional 27/Febrero/2006			

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 comunica:

1. Documentos estudiados

Descripción:	Folios 69 a 120	como se radicó inicialmente.
Reivindicaciones:	Folios 121 a 144	como se radicó inicialmente

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque:
Esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486).
Y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "FORMAS CRISTALINAS Y AMORFAS DEL CLORHIDRATO 4-CIANO-N-((2R)-2-[4-(2,3-DIHIDRO-BENZO[1,4]DIOXIN-5-IL)-PIPERAZIN-1-IL]-PROPI)-N-PIRIDIN-2-IL-BENZAMIDA".

El problema planteado en esta solicitud es la necesidad de formas cristalinas y amorfas nuevas del clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida que muestren mejor biodisponibilidad o mejor estabilidad.

Para resolver este problema técnico la solicitud en estudio proporciona formas cristalinas y amorfas del clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida

Clasificación Internacional de Patentes (CIP): C 07D 405/12, A 61K 31/495, A 61P 13/00, A 61P 15/00, A 61P 25/06

4. Excepción a la Patentabilidad (Art 20 D 486 literal d)

El objeto de las reivindicaciones 50 – 54 y 64 – 68 no es patentable de acuerdo con el Art citado.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 55 – 63 y 69 – 77 no es patentable de acuerdo con los Art citados.

6. De la Solicitud de Patente

Título

El título corresponde con el objeto de la solicitud porque se refiere al contenido de la solicitud

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las Reivindicaciones 5, 9, 13, 34 y 79 no son claras porque hacen referencia a la descripción o a los dibujos, según la expresión, "de acuerdo a la tabla H", "tal como se indica en la Fig. 1". Se sugiere eliminar la referencia a la descripción o a los dibujos si esta no es estrictamente necesaria.

La reivindicación 1 y 32 no son claras porque el término: "sustancialmente libre" es impreciso y no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto.

La reivindicación 27 no es clara porque el término: "esencialmente" es impreciso por lo cual no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto.

La reivindicación 32 corresponde a la misma forma cristalina de la reivindicación 1, por lo cual se sugiere establecer la correspondiente dependencia.

La reivindicación 45 corresponde al procedimiento de preparación de la misma forma cristalina de la reivindicación 24, por lo cual se sugiere establecer la correspondiente dependencia.

Se requiere al Solicitante hacer las aclaraciones necesarias.

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la

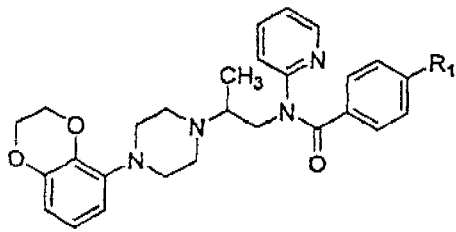
Fecha de Presentación de la Solicitud de Prioridad: Marzo 01 de 2005

y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Expediente 07 089 705 1er Art 45

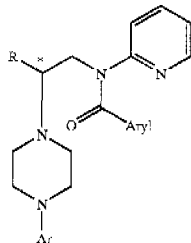
Item	Documento	Título	Fecha de Publicación
D1	WO/2002/044142A	Piperazin Derivates, their preparation and their use for treating central nervous system (CNS) disorders	06/Junio/2002
D2	US 2004/230056 A1	Process for synthesizing N-aryl piperazines with chiral N'-1-[benzoyl(2-pyridyl)amino]-2-propane substitution	18/Noviembre/2004

D1 divulga (página 2, renglones 12 – 19, folio 212A; página 7, renglones 1 – 9, folio 217; Ejemplo 1) un compuesto de fórmula



En donde R1 es un grupo ciano, nitro, trifluorometilo o halógeno, o sus sales de adición, que son útiles como antagonistas de receptor 5HT1A en el tratamiento de enfermedades del Sistema Nervioso Central. El Ejemplo 1 divulga el 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-n-piridin-2-il-benzamida.

D2 divulga (Abstract, folio 218; Ejemplo 7, folio 225) un proceso para la obtención de N-aryl piperazines con carbono quiral N'-1-benzoil(2-pyridyl)amino]-2-propane con estructura



* = chiral

Incluyendo 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-n-piridin-2-il-benzamida. La quiralidad se introduce por la formación del anillo piperazina y la sustitución 2-aminopiridil. Estos derivados son útiles como antagonistas de receptores 5HT.

12. Análisis de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una forma cristalina del clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-n-piridin-2-il-benzamida caracterizada por un patrón de difracción de rayos X en polvo que comprende picos, expresados en términos de 2θ, alrededor de 16.8° y alrededor de 21.8°, en donde la forma cristalina es libre de solvente hidrocarburo

Comparación de las características técnicas **esenciales** de la reivindicación 1, con las del estado de la Técnica:

Características esenciales	D1	D2
Forma cristalina del clorhidrato de 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida	-	-
Picos de difracción de rayos X, expresados en términos de 2θ, alrededor de 16.8° y alrededor de 21,8°	-	-
Libre de solvente hidrocarburo	√	√

Comparando las características esenciales de la reivindicación 1 con lo divulgado en el documento D1 y D2, se considera novedosa, porque D1 y D2 no contemplan formas cristalinas de la molécula clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida con los parámetros de difracción de rayos X registrados en la invención.

La reivindicación 78 consiste en una forma amorfa del clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida caractaerizada porque tiene un patrón de difracción de rayos X desprovisto de picos característicos, expresados en términos 2θ.

Comparación de las características técnicas **esenciales de la reivindicación 78**, con las del estado de la Técnica:

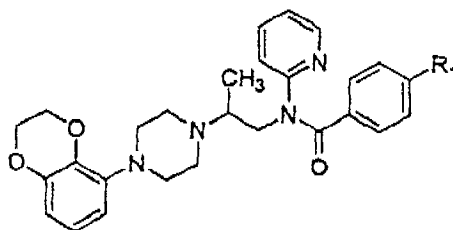
Características esenciales	D1	D2
Forma amorfa del clorhidrato de 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida	-	-
difracción de rayos X desprovistos de picos característicos	-	-
Libre de solvente hidrocarburo	√	√

Comparando las características esenciales de la reivindicación 78 con lo divulgado en el documento D1 y D2, se considera novedosa, porque D1 y D2 no contemplan formas amorfas de la molécula clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida con los parámetros de difracción de rayos X registrados en la invención.

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en una forma cristalina del clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida caracterizada por un patrón de difracción de rayos X en polvos que comprende picos, expresados en términos de 2θ, alrededor de 16.8° y alrededor de 21,8°, en donde la forma cristalina es libre de solvente hidrocarburo

El documento D1, considerado el estado de la técnica más cercano a la invención definida en la reivindicación 1, divulga (página 2, renglones 12 – 19, folio 212A; página 7, renglones 1 – 9, folio 217; Ejemplo 1) un compuesto de fórmula



En donde R1 es un grupo ciano, nitro, trifluorometilo o halógeno, o sus sales de adición, que son útiles como antagonistas de receptor 5HT1A en el tratamiento de enfermedades del Sistema Nervioso Central. El Ejemplo 1 divulga el 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida.

La diferencia entre la invención, definida en la reivindicación 1 y la molécula de D1 consiste en que la invención es la sal clorhidrato del compuesto dado a conocer en D1 y registra parámetros de difracción de rayos X característicos que D1 no tiene.

No hay evidencia de que la sal clorhidrato en forma cristalina presente efectos o propiedades adicionales a las divulgadas en D1.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: "¿cómo modificar el 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida conocido en D1 para desarrollar sales en formas cristalinas alternativas de la molécula?"

Sin embargo, se debe considerar que D1 divulga la obtención de la molécula base en forma cristalina (ejemplo 1, paginas 11 – 12). Del mismo modo, D1 divulga sales farmacéuticamente aceptables que indican la sal clorhidrato en la página 3 renglones 27 – 30 y en la pagina 4 renglones 1 – 4

De esta manera, la reivindicación 1 se considera obvia, porque el Experto en la Materia enfrentado al problema de modificar la molécula conocida en D1 para desarrollar sales en formas cristalinas alternativas, incluiría la sal clorhidrato y la forma cristalina que se revelan en D1, logrando así la forma cristalina objeto de esta solicitud.

De la misma manera, la reivindicación 78 carece de nivel inventivo porque D2 divulga la obtención de un solido blanco de 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida (ejemplo 7) y D1 divulga la utilización de la sal clorhidrato de la molécula (página 3 renglones 27 – 30 y en la pagina 4 renglones 1 – 4), por lo que el Estado de la Técnica sugiere al Experto en la Materia la forma en que se resuelve el problema en esta reivindicación. Por lo cual se considera obvia.

La reivindicación 24 consiste en un procedimiento para preparar una forma cristalina del clorhidrato 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil)-n-piridin-2-il-benzamida caracterizada por un patrón de difracción de rayos X en polvos que comprende picos, expresados en términos de 2θ, alrededor de 16,8° y alrededor de 21,8°, y comprende precipitar la forma cristalina a partir de un solución de la molécula en un solvente para cristalización.

El documento D1 divulga (página 7, líneas 20 – 26, folio 217) un método de cristalización por antisolvente del 4-ciano-n-((2r)-2-[4-(2,3-dihidro-

benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-n-piridin-2-il-benzamida, que comprende la utilización de un solvente para cristalización.

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: “¿cómo modificar el procedimiento de preparación el 4-ciano-n-((2r)-2-[4-(2,3-dihidro-benzo[1,4]dioxin-5-il)-piperazin-1-il]-propil}-n-piridin-2-il-benzamida conocido en D1 para desarrollar procedimiento de preparación de sales en formas cristalinas nuevas de la molécula?”

Sin embargo, se debe considerar que D1 divulga el procedimiento de obtención de la molécula base en forma cristalina utilizando un solvente para cristalización (ejemplo 1, paginas 11 – 12).

De esta manera, la reivindicación 24 se considera obvia, porque el Experto en la Materia enfrentado al problema de modificar el procedimiento de obtención de la molécula conocida en D1 para desarrollar el procedimiento de preparación de sales en formas cristalinas nuevas, incluiría el proceso de precipitación a partir de la solución de la molécula en un solvente para cristalización.

Conclusión:
Las reivindicaciones 1, 24 y 78, cumplen el requisito de novedad (Art. 16), pero no cumplen con el requisito de nivel inventivo (Art. 18).

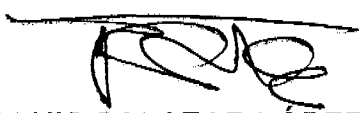
8. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO/2002/044142A	1 – 49, 78 – 82	Nivel Inventivo
D2	US 2004/230056 A1	1 – 49, 78 – 82	Nivel nventivo

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 60 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.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 04 MAR. 2001

CONCEPTO TÉCNICO No. 407	EXAMINADOR TÉCNICO Código No. 202098
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