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Señora

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Solicitud de Patente de Invención titulada: "Derivados de la piridazina y su uso como agentes terapéuticos."

Solicitante: Xenon Pharmaceuticals Inc

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISIÓN
486. GACETA No. 577

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 \$404.000 para cubrir la tasa correspondiente según la Resolución 36155 del 28 de diciembre de 2006.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ

C.C.No.79.143.366 de Usaquén

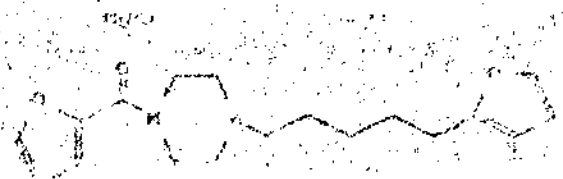
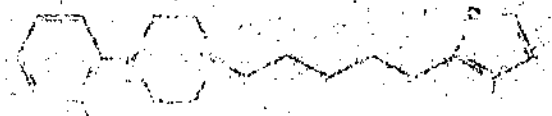
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Anexo: Recibo de caja por valor de \$404.000

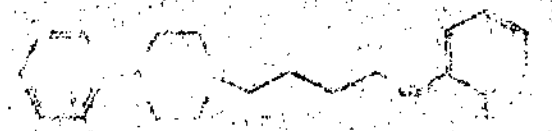
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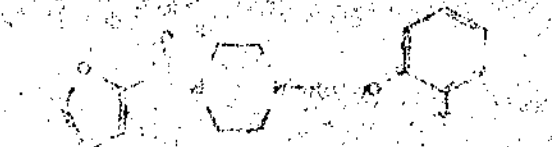
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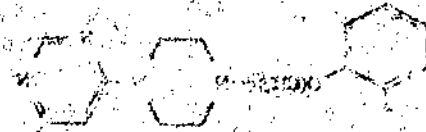
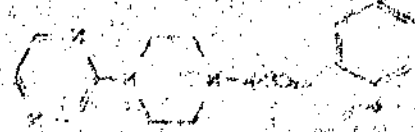
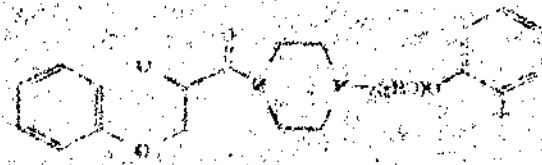
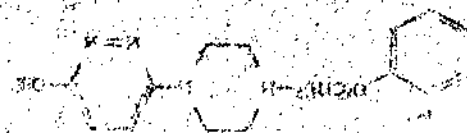
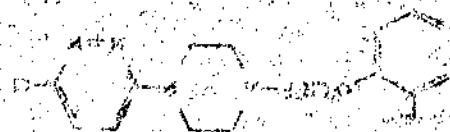
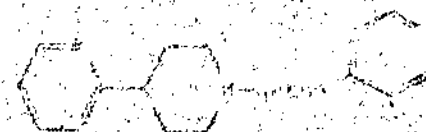


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Chemical Structures



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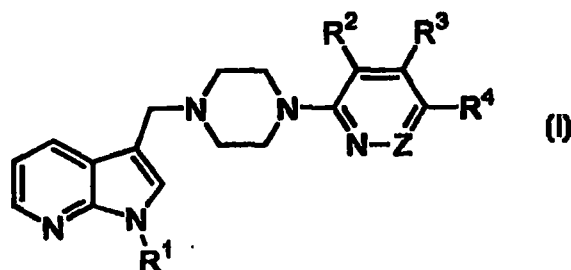
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(51) International Patent Classification ⁶ : C07D 471/04, A61K 31/44, 31/555, 51/04, C07F 7/22 // (C07D 471/04, 221:00, 209:00)		A1	(11) International Publication Number: WO 99/00386 (43) International Publication Date: 7 January 1999 (07.01.99)
(21) International Application Number: PCT/CA98/00615 (22) International Filing Date: 26 June 1998 (26.06.98) (30) Priority Data: 08/884,551 27 June 1997 (27.06.97) US 08/905,546 4 August 1997 (04.08.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications US 08/884,551 (CIP) Filed on 27 June 1997 (27.06.97) US 08/905,546 (CIP) Filed on 4 August 1997 (04.08.97) (71) Applicant (for all designated States except US): RESOLUTION PHARMACEUTICALS INC. [CA/CA]; 6850 Goreway Drive, Mississauga, Ontario L4V 1V7 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): POLLAK, Alfred [CA/CA]; Apartment 1400, 135 Marlee Avenue, Toronto, Ontario M6B 4C6 (CA). DUNN-DUFAULT, Robert [CA/CA]; 30 Markson Road, Guelph, Ontario N1H 1X2		(CA). ROE, David [GB/CA]; 100 Inkerman Street #7, Rockwood, Ontario N0B 2K0 (CA). (74) Agent: DEETH WILLIAMS WALL; National Bank Building, Suite 400, 150 York Street, Toronto, Ontario M5H 3S5 (CA). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	

(54) Title: DOPAMINE D4 RECEPTOR LIGANDS

(57) Abstract

Described herein are D4 receptor-selective compounds of formula (I) wherein Z is selected from N and C(R⁵); R¹ is selected from H and an acid labile protecting group; R², R³, R⁴ and R⁵ are independently selected from H, hydroxy, loweralkyl, loweralkyl optionally substituted with one or more groups selected from halo, hydroxy and loweralkoxy; loweralkyl-S-, halo, radioisotopic halo, loweralkoxy, trifluoromethylsulfonyl, cycloalkyl, aryl and tri(loweralkyl)tin; with the proviso that when Z is C(R⁵) then at least one of R², R³, R⁴ and R⁵ are selected from radioisotopic halo and tri(loweralkyl)tin; and salts, solvates or hydrates thereof. Also described is the use of these compounds as pharmaceuticals to treat indications for which a dopamine D4 receptor antagonist is indicated. Radiolabeled compounds are useful particularly to image localization of D4 receptor in the human brain, and can therefore aid in the diagnosis of schizophrenia and other medial conditions in which the D4 receptor is implicated.



INFORMATION REPORT

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9. Recommendations: [illegible]

10. Other comments: [illegible]

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8. Conclusion: [illegible]

9. Recommendations: [illegible]

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A mixture of 1-*t*-butoxycarbonyl-3-[4-(6-iodopyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo[2,3-*b*]pyridine (52 mg, 0.1 mmol), hexamethylditin (30 OL, 47 mg, 0.145 mmol), and tetrakis triphenylphosphine palladium (0) (23 mg, 0.02 mmol) in toluene (2 mL) under argon was heated at reflux for 1.5 h during which time the solution darkened to a very dark brown. The heating was discontinued and the mixture allowed to cool to room temperature. The reaction was then filtered through a short pad of celite and the pad washed with ethyl acetate. The solvents were then removed under reduced pressure. The residue was partitioned between ethyl acetate and a saturated aqueous solution of KF (7 mL) for 2h with stirring. The mixture was extracted with dichloromethane (2 x 30 mL). The combined organic layers were then concentrated under reduced pressure to give semi-pure title compound. δ H (CDCl₃) 0.34 (5H, s, Sn(CH₃)₃); 1.66 (9H, s, C(CH₃)₃); 2.59 (4H, m, piperaziny CH₂); 3.66 (4H, m, piperaziny CH₂); 3.73 (2H, s, CH₂); 6.75 (1H, d, J = 9.5); 7.17 (2H, m); 7.54 (1H, s); 8.08 (1H, d, J = 7.6); 8.51 (1H, d, J = 4.5): ESMS 557.04 (M⁺): other impurities consist of PPh₃.

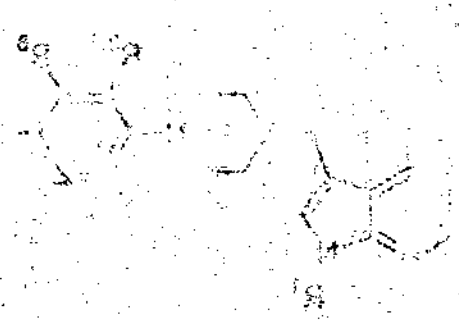
Example 5: Preparation of 3-[4-(6-methoxypyridazin-3-yl)-piperazin-1-yl]methyl-1H-pyrrolo-[2,3-*b*]pyridine

A solution of 1-(6-methoxypyridazin-3-yl)-piperazine (100 mg, 0.515 mmol) and 3-(N,N-dimethylaminomethyl)-1H-pyrrolo[2,3-*b*]pyridine (87 mg, 0.47 mmol) (prepared in example 3(a)) in toluene (3 mL) was heated at reflux for 15 h. The heating was discontinued and the solution allowed to cool to room temperature during which time a colourless solid precipitated out of solution. The solid was collected by filtration and dried in vacuo to yield the title compound as a colourless solid (147 mg, 94%). δ H (CDCl₃) 2.63 (4H, m, piperaziny CH₂); 3.52 (4H, m, piperaziny CH₂); 3.75 (2H, s, CH₂); 4.02 (3H, s, OCH₃); 6.81 (1H, d, J = 9.6); 6.99 (1H, d, J = 9.7); 7.09 (1H, dd, J = 4.9 and 7.6); 7.28 (1H, s); 8.10 (1H, d, J = 7.5); 8.32 (1H, d, J = 4.6); 9.62 (1H br s, NH).

A mixture of 1,4-dioxane, 7.4 g (0.05 mole) and 1,2-dichloroethane, 10 ml, was added to a solution of 0.5 g (0.01 mole) of 1,2-dichloroethane in 10 ml of 1,4-dioxane. The mixture was stirred for 1 hour at room temperature. The mixture was then poured into 100 ml of water. The organic layer was separated and dried over anhydrous calcium chloride. The solvent was removed by distillation under reduced pressure. The residue was a white solid, mp 10-12°C. The mother liquor was dried and distilled under reduced pressure. The residue was a white solid, mp 10-12°C. The total yield was 0.8 g (80%).

ANAL. Calcd for $C_4H_8Cl_2$: C, 44.0%; H, 6.7%; Cl, 49.3%. Found: C, 44.0%; H, 6.7%; Cl, 49.3%.

A solution of 1.0 g (0.01 mole) of 1,2-dichloroethane in 10 ml of 1,4-dioxane was added to a solution of 0.5 g (0.01 mole) of 1,2-dichloroethane in 10 ml of 1,4-dioxane. The mixture was stirred for 1 hour at room temperature. The mixture was then poured into 100 ml of water. The organic layer was separated and dried over anhydrous calcium chloride. The solvent was removed by distillation under reduced pressure. The residue was a white solid, mp 10-12°C. The mother liquor was dried and distilled under reduced pressure. The residue was a white solid, mp 10-12°C. The total yield was 0.8 g (80%).



Structure 1 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 2 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 3 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 4 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 5 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 6 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 7 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 8 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 9 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 10 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 11 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 12 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 13 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 14 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 15 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 16 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 17 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 18 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 19 is a substituted benzene ring with a substituent at the 1-position and a double bond at the 2-position.

Structure 20 is a substituted cyclohexane ring with a substituent at the 1-position and a double bond at the 2-position.

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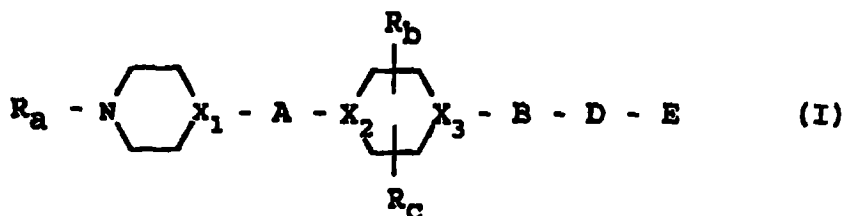


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INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

(51) Internationale Patentklassifikation ⁶ : C07D 211/22, 211/26, 211/46, 211/58, A61K 31/445		A1	(11) Internationale Veröffentlichungsnummer: WO 97/37975 (43) Internationales Veröffentlichungsdatum: 16. Oktober 1997 (16.10.97)
(21) Internationales Aktenzeichen: PCT/EP97/01698 (22) Internationales Anmeldedatum: 4. April 1997 (04.04.97) (30) Prioritätsdaten: 196 14 204.0 10. April 1996 (10.04.96) DE (71) Anmelder: DR. KARL THOMAE GMBH [DE/DE]; Patentstelle, Birkendorfer Strasse 65, D-88397 Biberach (DE). (72) Erfinder: PIEPER, Helmut; Kapellenweg 5, D-88400 Biberach (DE). LINZ, Günter; Eschenweg 6, D-88441 Mittlbiberach (DE). AUSTEL, Volkhard; Kapellenweg 7, D-88400 Biberach (DE). HIMMELSBACH, Frank; Ahornweg 16, D-88441 Mittlbiberach (DE). GUTH, Brian; Am Schlegel- berg 24, D-88447 Warthausen (DE). WEISENBERGER, Johannes; Haydnweg 5, D-88400 Biberach (DE).		(81) Bestimmungsstaaten: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO Patent (GH, KE, LS, MW, SD, SZ, UG), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Veröffentlicht Mit internationalem Recherchenbericht.	

(54) Title: **CARBOXYLIC ACID DERIVATIVES WITH AN AGGREGATION-INHIBITING ACTION**

(54) Bezeichnung: **CARBONSÄUREDERIVATE MIT AGGREGATIONSHemmENDER WIRKUNG**



(57) Abstract

The invention concerns carboxylic acid derivatives of the general formula (I), in which R_a to R_c , A, B, D, E and X_1 to X_3 are as defined in claim 1, their stereoisomers, including mixtures and salts, in particular physiologically tolerated salts, with inorganic or organic acids or bases, which exhibit useful pharmacological properties, preferably an aggregation-inhibiting action. The invention also concerns drugs containing such compounds, their use and methods of preparing them.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft Carbonsäurederivate der allgemeinen Formel (I), in der R_a bis R_c , A, B, D, E und X_1 bis X_3 wie im Anspruch 1 definiert sind, deren Tautomere, deren Stereoisomere einschließlich deren Gemische und deren Salze, insbesondere deren physiologisch verträgliche Salze mit anorganischen oder organischen Säuren oder Basen, welche wertvolle pharmakologische Eigenschaften aufweisen, vorzugsweise aggregationshemmende Wirkungen, diese Verbindungen enthaltende Arzneimittel, deren Verwendung und Verfahren zu ihrer Herstellung.

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(27) trans-1-(4-Carboxymethyloxy-piperidino)-4-[(piperidin-4-yl)-methyloxy]-cyclohexan-ditrifluoracetat

Hergestellt aus trans-1-(4-tert. Butyloxycarbonylmethyloxy-piperidino)-4-[(1-tert. butyloxycarbonyl-piperidin-4-yl)-methyloxy]-cyclohexan und Trifluoressigsäure.

Ausbeute: quantitativ, Harz

Massenspektrum: $M^+ = 354$

R_f -Wert: 0.10 (Kieselgel; Methylenchlorid/Methanol/konz. Ammoniak = 2:1:0.2)

(28) 1-(3-Carboxymethyloxy-pyridazin-6-yl)-4-[2-(piperidin-4-yl)-ethyl]-piperazin-dihydrochlorid

Hergestellt aus 4-[2-(1-tert. Butyloxycarbonyl-piperidin-4-yl)-ethyl]-1-(3-methoxycarbonylmethyloxy-pyridazin-6-yl)-piperazin.

Ausbeute: 6 % der Theorie,

Schmelzpunkt: 265-270°C

Massenspektrum: $(M+H)^+ = 350$

R_f -Wert: 0.20 (Kieselgel; Methylenchlorid/Methanol/konz. Ammoniak = 2:1:0.2)

(29) cis/trans-1-(4-Carboxymethyl-piperazino)-4-[(piperidin-4-yl)-methyloxy]-cyclohexan-trihydrochlorid

Hergestellt aus cis/trans-1-(4-Methoxycarbonylmethyl-piperazino)-4-[(piperidin-4-yl)-methyloxy]-cyclohexan-trihydrochlorid.

Ausbeute: quantitativ,

Massenspektrum: $(M+H)^+ = 340$

R_f -Wert: 0.13 (Kieselgel; Methylenchlorid/Methanol/konz. Ammoniak = 2:1:0.2)

(30) cis/trans-1-[4-(1-Carboxyprop-2-yl)-piperazino]-4-[(piperidin-4-yl)-methyloxy]-cyclohexan-trihydrochlorid

Hergestellt aus cis/trans-1-[4-(1-Methoxycarbonylprop-2-yl)-piperazino]-4-[(piperidin-4-yl)-methyloxy]-cyclohexan-trihydrochlorid.

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Example 2

A mixture of 22 parts of ethyl 4-(6-chloro-5-methyl-3-pyridazinyl)-1-piperazinecarboxylate, 28 parts of potassium hydroxide and 160 parts of 1-butanol was stirred overnight at reflux temperature. The reaction mixture was evaporated. Water was added. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. 2,2'-Oxybispropane was added. The product was filtered off and dried, yielding 17 parts (100%) of 3-chloro-4-methyl-6-(1-piperazinyl)-pyridazine (7).

Example 3

A mixture of 15.3 parts of (E)-(3-chloro-1-propenyl)benzene, 12 parts of 2-methylpiperazine, 28.5 parts of sodium carbonate and 225 parts of N,N-dimethylformamide was stirred overnight at 65°C. The reaction mixture was poured into ice water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (96:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in 2-propanol. The salt was filtered off and dried, yielding 8.27 parts - (28.6%) of (E)-3-methyl-1-(3-phenyl-2-propenyl)-piperazine dihydrochloride; mp. 202°C (8).

B. Preparation of Final compounds

Example 4

A mixture of 3.8 parts of 3,6-dichloropyridazine, 4.1 parts of 1-(3-phenyl-2-propenyl)piperazine, 6.4 parts of sodium carbonate and 180 parts of N,N-dimethylformamide was stirred overnight at 65°C. The reaction mixture was poured into ice water. The product was filtered off and dissolved in dichloromethane. The organic layer was washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 3.7 parts - (58.8%) of (E)-3-chloro-6-[4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine; mp. 129.0°C (1).

In a similar manner there was also prepared:

(E)-3-chloro-6-[2-methyl-4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine monohydrochloride.hemihydrate; mp.138.4°C (2).

Example 5

A mixture of 6 parts of 3,6-dibromopyridazine, 4.1 parts of 1-(3-phenyl-2-propenyl)piperazine, 6.4 parts of sodium carbonate and 180 parts of N,N-dimethylacetamide was stirred overnight at 65°C. The reaction mixture was poured into ice water. The product was filtered off and dissolved in dichloromethane. The solution was washed with water, dried, filtered and evaporated. The residue was crystallized from a mixture of ethanol and 2-propanol. The product was filtered off and dried, yielding 2.9 parts (40.3%) of (E)-3-bromo-6-[4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine; mp. 134.6°C (3).

Example 6

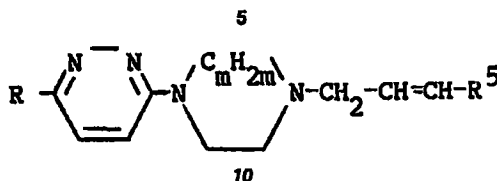
A mixture of 3 parts of (3-chloro-1-propenyl)benzene, 3 parts of 3-methoxy-6-(1-piperazinyl)pyridazine, 3.2 parts of sodium carbonate and 90 parts of N,N-dimethylacetamide was stirred overnight at 60°C. The reaction mixture was poured into water. The product was filtered off and taken up in trichloromethane. The solution was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (97:3 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 1 part (21%) of (E)-3-methoxy-6-[4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine; mp. 135.0°C (4).

Example 7

A mixture of 4.7 parts of 4-chloro-1-(3-chloro-1-propenyl)benzene, 4 parts of 3-chloro-6-(1-piperazinyl)pyridazine, 5.3 parts of sodium carbonate and 72 parts of N,N-dimethylformamide was stirred overnight at 65°C. The reaction mixture was evaporated. Water was added. The product was filtered off, washed with water and dissolved in trichloromethane. The organic layer was dried, filtered and evaporated. The residue was crystallized from a mixture of methanol and 2-propanol. The

product was filtered off and dried, yielding 4.5 parts (64%) of (E)-3-chloro-6-[4-[3-(4-chlorophenyl)-2-propenyl]-1-piperazinyl]pyridazine; mp. 177.9°C - (5).

In a similar manner there were also prepared:



No.	R	m	R ⁵	isomeric base/ form salt	mp. (°C)
6	C ₆ H ₅ -	2	C ₆ H ₅ -	E base	176.8
7	Cl-	3	C ₆ H ₅ -	E base	130.9
8	H-	2	C ₆ H ₅ -	E 2HCl.1/2H ₂ O	225.2
9	CH ₃ O-	2	4-F-C ₆ H ₄ -	E base	143.1
10	Cl-	2	4-F-C ₆ H ₄ -	E base	165.7
11	H-	2	4-F-C ₆ H ₄ -	E base	127.1
12	Cl-	2	2-thienyl	E base	127.1
13	Cl-	2	4-CH ₃ -C ₆ H ₄ -	E base	164.0
14	Cl-	2	4-CH ₃ O-C ₆ H ₄ -	E base	146.8
15	C ₆ H ₅ -	3	2-thienyl	E base	124.9
16	H	2	4-CH ₃ -C ₆ H ₄ -	E base	125.2
17	C ₆ H ₅ -	2	4F-C ₆ H ₄ -	E base	197.3
18	H	2	4CH ₃ O-C ₆ H ₄ -	E 2HCl.1/2H ₂ O	200.6
19	C ₆ H ₅ -	3	C ₆ H ₅ -	E base	104.1

Example 8

A mixture of 6.9 parts of 3-phenyl-2-propynol methanesulfonate (ester), 6 parts of 3-chloro-6-(1-piperazinyl)pyridazine, 9.54 parts of sodium carbonate and 180 parts of N,N-dimethylformamide was stirred overnight at ±85°C. The reaction mixture was poured into ice water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized from 2-propanol. The product was fil-

tered off and dried, yielding 7.8 parts (83.1%) of 3-chloro-6-[4-(3-phenyl-2-propynyl)-1-piperazinyl]pyridazine; mp. 123.2°C (20).

Example 9

A mixture of 3.5 parts of (E)-(3-chloro-1-propenyl)benzene, 4.8 parts of 3-chloro-6-(3-methyl-1-piperazinyl)pyridazine, 6.4 parts of sodium carbonate and 200 parts of 4-methyl-2-pentanone was stirred over weekend at reflux temperature using a water separator. After cooling, water was added and the layers were separated. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica

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123
188

gel using a mixture of trichloromethane and methanol (98.5:1.5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 1 part (13.5%) of (E)-3-chloro-6-[3-methyl-4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine; mp. 117.2°C (21).

In a similar manner there were also prepared:

(E)-3-chloro-6-[2-methyl-4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine (22);

(E)-3-chloro-6-[2,3-dimethyl-4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine (23);

(cis)-(E)-3-chloro-6-[2,5-dimethyl-4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine monohydrochloride; mp. 123.0°C (24);

(E)-3-chloro-6-[3,5-dimethyl-4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine; mp. 129.8°C; and

(E)-3-chloro-6-[2,6-dimethyl-4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine (26);

Example 10

A solution of 7.2 parts of 3-phenyl-6-(1-piperazinyl)pyridazine in 200 parts of 2-propanol was acidified with 2-propanol, saturated with hydrogen chloride. 4.3 Parts of 1-phenylethanone and 0.9 parts of poly(oxymethylene) were added and the whole was stirred for 3 hours. Another portion of 0.9 parts of poly(oxymethylene) was added and stirring was continued for 8 hours at reflux. After the addition of 0.9 parts of poly(oxymethylene), the whole was stirred and refluxed over weekend. The product was filtered off and dried, yielding 6.9 parts (51.6%) of 1-phenyl-3-[4-(6-phenyl-3-pyridazinyl)-1-piperazinyl]-1-propanone dihydrochloride; mp. 191°C (27).

Following the same procedure and using equivalent amounts of the appropriate starting materials, there were also prepared:

3-[4-(6-chloro-3-pyridazinyl)-1-piperazinyl]-1-phenyl-1-propanone; mp. 138.2°C (28); and

3-[4-(6-chloro-5-methyl-3-pyridazinyl)-1-piperazinyl]-1-phenyl-1-propanone; mp. 131.3°C - (29).

Example 11

To a stirred mixture of 3 parts of 3-[4-(6-chloro-3-pyridazinyl)-1-piperazinyl]-1-phenyl-1-propanone and 80 parts of methanol were added portionwise 0.76 parts of sodium borohydride. Upon completion, stirring was continued for 20 hours at room temperature. The reaction mixture was evaporated. Water was added. The product was extracted with trichloromethane. The extract was dried, filtered and evaporated. The residue was crystallized from a mixture of 2-propanol and 2,2'-oxybispropane. The product was filtered off and dried, yielding 2.5 parts (83%) of 4-(6-chloro-3-pyridazinyl)- α -phenyl-1-piperazinepropanol; mp. 144.5°C (30).

Following the same procedure and using equivalent amounts of the appropriate starting materials, there was also prepared:

α -phenyl-4-(6-phenyl-3-pyridazinyl)-1-piperazinepropanol; mp. 162.9°C (31).

Example 12

A mixture of 6.3 parts of 3-chloro-6-[4-(3-phenyl-2-propynyl)-1-piperazinyl]pyridazine, 3 parts of a solution of thiophene in methanol 4% and 120 parts of methanol was hydrogenated at normal pressure and at room temperature with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and acetonitrile (70:30 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanol. The product was filtered off and dried, yielding 1.6 parts (25.4%) of (Z)-3-chloro-6-[4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine; mp. 118.0°C (32).

Example 13

To a stirred solution of 1.2 parts of sodium in 30 parts of benzenemethanol were added 7.9 parts of (E)-3-chloro-6-[4-(3-phenyl-2-propenyl)-1-piperazinyl]pyridazine and stirring was continued for 6 hours at $\pm 170^\circ\text{C}$. After cooling, water and dichloromethane were added. The separated organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (98.5:1.5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-

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6. Вопросы, связанные с деятельностью органов государственной власти

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CONFIDENTIAL

El objeto de la presente solicitud se refiere a inhibidores de la estearoil-CoA desaturasa, tales como los derivados de la piridazina, y con los usos de dichos compuestos en el tratamiento y/o prevención de diversas enfermedades humanas, incluso de aquellas mediadas por las enzimas estearoil-CoA desaturasas (SCD), preferentemente SCD1, especialmente las enfermedades relacionadas con elevados niveles de lípidos, la enfermedad cardiovascular, la diabetes, la obesidad, el síndrome metabólico y similares.

Según la descripción, las enzimas acil desaturasas catalizan la formación de enlaces dobles en los ácidos grasos derivados de fuentes dietéticas o sintetizados de novo en el hígado. Las estearoil-CoA desaturasas (SCD) introducen un doble enlace en la posición C9-10 de los ácidos grasos saturados.

A la fecha, no se conoce ningún compuesto de molécula pequeña similar a un fármaco que específicamente inhiba o module la actividad SCD. Se han utilizado históricamente ciertos hidrocarburos de cadena larga para estudiar la actividad SCD. Ninguno de los compuestos inhibidores de la SCD, conocidos son selectivos para las SCD o las delta-9 desaturasas, ya que también inhiben otras desaturasas y enzimas.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 9, 36 (folios: 114 a 116, 122): un método para inhibir la actividad de la estearoil-CoA desaturasa humana (hSCD) que comprende contactar una fuente de hSCD con un compuesto de la fórmula (I), un estereoisómero, enantiómero o tautómero del mismo, una sal farmacéuticamente aceptable del mismo, una composición farmacéutica del mismo o una prodroga del mismo.

Reivindicaciones 10 a 35 (folios: 116 a 122): un compuesto de la fórmula (Ia), un estereoisómero, enantiómero o tautómero del mismo, una sal farmacéuticamente aceptable del mismo, una composición farmacéutica del mismo o una prodroga del mismo.

Reivindicación 37 (folio: 122): una composición farmacéutica que comprende un excipiente farmacéuticamente aceptable y una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 10.

El problema planteado en esta solicitud es la necesidad de inhibidores de SCD selectivos para regular los niveles de lípidos, especialmente lípidos plasmáticos, y para el tratamiento de enfermedades relacionadas con dislipidemia, cardiovascular, diabetes, obesidad, síndrome metabólico y similares.

La solución propuesta por la presente solicitud consiste en compuestos derivados de (piridazin-3-il)-(piperazin-1-il)-sustituidos, un estereoisómero, enantiómero o tautómero del mismo, una sal farmacéuticamente aceptable del mismo, una composición farmacéutica del mismo o una prodroga del mismo.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/00, 31/496, 31/501; A61P 3/06; C07D 295/00.

4. De la solicitud de Patente

4.1. Descripción (artículo 28 D. 486)

De acuerdo con lo revelado en la descripción, el título de la solicitud debe especificar

1. The purpose of this study is to determine the effect of the use of the computer on the learning of the English language. The study was conducted in a classroom of 20 students, 10 of whom were using the computer and 10 were not. The results of the study showed that the students who used the computer had a significantly higher score on the English language test than the students who did not use the computer. This suggests that the use of the computer can be an effective tool for learning the English language.

1. The first step in the process of identifying a problem is to define the problem. This involves identifying the symptoms of the problem and determining the scope of the problem. Once the problem has been defined, the next step is to identify the causes of the problem. This involves identifying the factors that are contributing to the problem and determining the root cause of the problem. Once the causes of the problem have been identified, the next step is to develop a plan to address the problem. This involves identifying the actions that need to be taken to address the problem and determining the resources that will be needed to implement the plan. Once a plan has been developed, the next step is to implement the plan. This involves taking the actions that have been identified in the plan and monitoring the progress of the plan. Finally, the last step in the process is to evaluate the results of the plan. This involves determining whether the plan has been successful in addressing the problem and identifying any lessons learned from the process.

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1. The first part of the report is a summary of the work done during the year. It is a brief statement of the results of the work, and is intended to give a general impression of the progress made.

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(1) of each type, as shown in the table below, is to be used in the following manner:

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Reference to the Bureau report in this file will be made by memorandum dated 12-27

aun más los compuestos que se están reclamando y no se debe hacer alusión a su uso farmacológico y/o terapéutico.

4.2. Reivindicaciones (artículo 30 D 486)

De acuerdo con lo revelado en el capítulo reivindicatorio, la reivindicación 10 y sus dependientes (ver folios: 116 y 117) que se relacionan con un compuesto de fórmula la, también mencionan composiciones farmacéuticas que los contienen y "prodrogas" del mismo, lo cual no es claro, puesto que una reivindicación de compuesto se debe caracterizar por su estructura química (núcleo principal y sustituyentes) que la hagan diferente de lo que se encuentra en el estado de la técnica y no por las composiciones farmacéuticas que lo puedan contener ni por sus profármacos.

Hay términos que no están escritos correctamente o tienen mala traducción y no están empleando la terminología técnica adecuada, por ejemplo "prodroga".

Se encuentran sustituyentes que no son concisos, y al hacer los reemplazos en la fórmula la, resulta un número elevado de compuestos que se desean proteger y que ni siquiera se contemplan en los ejemplos que están en la descripción. Por ejemplo, los significados para R2, especialmente cuando este R2 es "una estructura de múltiples anillos con 2 a 4 anillos que se caracteriza porque los anillos se seleccionan del grupo que consiste en cicloalquilo, heterociclo, arilo y heteroarilo...", no se aclara cómo están unidos tales múltiples anillos, ni cuántos carbonos tienen los heterociclos y heteroarilos, ni heteroátomos, puntos de unión al núcleo central, etc.

5. **Unidad de Invención** (artículo 25 D 486)

Según lo anterior la (s) reivindicación (es) 10 (folios: 116 y 117), que se refiere(n) a compuestos de fórmula la, no conforma un único concepto inventivo con los profármacos (prodrogas como aparece escrito en dicha reivindicación) que se mencionan allí.

6. **Excepciones de Patentabilidad** (artículo 20 D486 literal a)-d))

De acuerdo con lo anterior, la(s) reivindicación(es): 1 a 9, 36 (folios: 114 a 116), que se refiere(n) a un método para inhibir la actividad de la esteroil-CoA desaturasa humana (hSCD) que comprende contactar una fuente de hSCD con un compuesto de la fórmula (I), un estereoisómero, enantiómero o tautómero del mismo, una sal farmacéuticamente aceptable del mismo, una composición farmacéutica del mismo o una prodroga del mismo, no es (son) patentable(s) porque es un método de tratamiento el cual está excluido de patentabilidad.

7. **Determinación del Estado de la Técnica:**

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

Fecha de presentación de la solicitud prioritaria 30-07-2003

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

1. The first of these is the fact that the...

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Nº	Documento	Título	Fecha de Publicación
D1	US 5166147	4-heteroaryl-and 4-aryl-1,4-dihydropyridine, derivatives with calcium, agonist and alpha ₁ -antagonist activity	24 de noviembre de 1992
D2	WO 99/00386	Dopamine D4 receptor ligands	7 de enero de 1999
D3	WO 97/37975	Carboxylic acid derivatives with an aggregation-inhibiting action	16 de octubre de 1997
D4	EP 0211457	Novel (4-substituted-piperaziny)pyridazines	25 de febrero de 1987

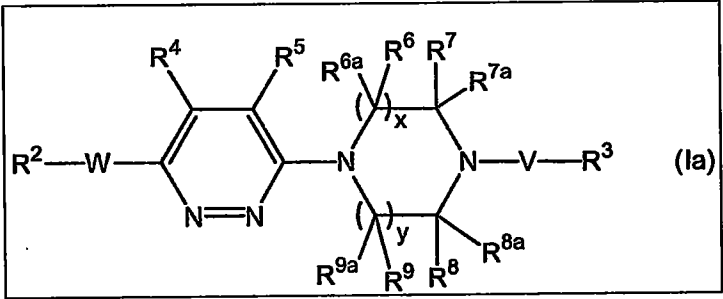
8. Análisis de patentabilidad (artículo 14 D486)

8.1. Novedad (artículo 16 D486)

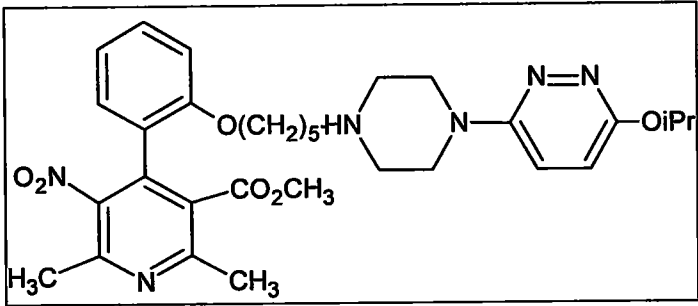
Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No. 0607906, se refiere a:

Un compuesto de fórmula Ia, derivado de (piridazin-3-il)-(piperazin-1-il)-sustituido:



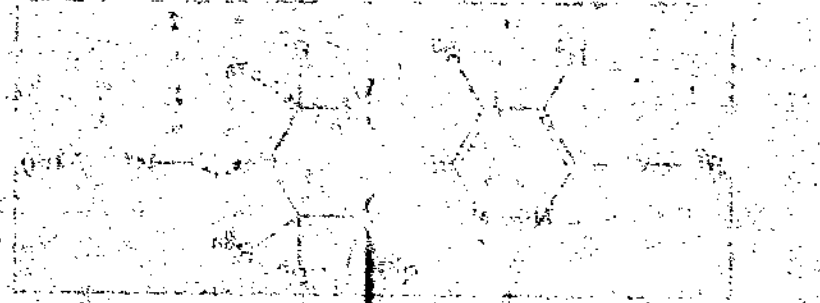
La anterioridad: US 5166147 (folios: 177 a 179), se relaciona con: derivados de dihidropiridinas de fórmula:



La anterioridad: WO 99/00386 (folios: 180 a 182), trata sobre: ligandos de dopamina D4, en donde se pueden ver compuestos específicos que son iguales a compuestos de la presente solicitud, como por ejemplo: 3-[4-(6-metoxipiridazin-3-il)-piperazin-1-il]metil-1H-pirrolo-[2,3-b]piridina.

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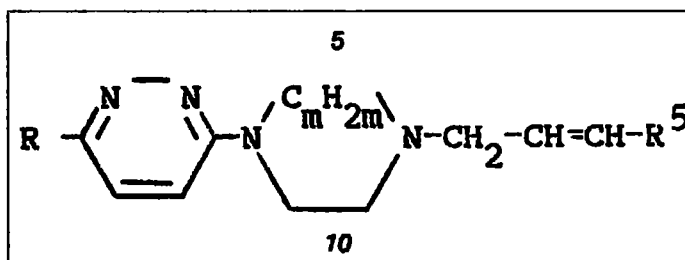
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El documento WO 97/37975 (folios: 183 y 184) menciona compuestos derivados de ácido carboxílico, donde se revela el compuestos específico de la presente solicitud: 1-(3-carboximetiloxi-piridazin-6-il)-4-[2-(piperidin-4-il)-etil]-piperazin-dicloro.

El documento EP 0211457 (folios: 185 a 188), se relaciona con compuestos derivados de piridazina, menciona en sus ejemplos, compuestos específicos de la presente solicitud, al hacer los reemplazos de sustituyentes correspondientes (ver ejemplos: 6, 7 y 9 de dicha anterioridad, folios: 186 y 187).



El elemento característico de los derivados (piridazin)-(piperazin)-sustituidos reivindicados, ya era conocido en los documentos D1 a D4; por lo cual los compuestos de fórmula la de las reivindicaciones 10 a 35 y 37 no pueden considerarse nuevos.

8.2. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: derivados de (piridazin-3-il)-(piperazin-1-il)-sustituidos que son inhibidores de SCD selectivos para regular los niveles de lípidos, tienen actividad contra la diabetes, obesidad, dislipidemia, etc.

Las anterioridades D1 a D4 muestran compuestos específicos de la presente solicitud, por lo cual es de esperarse que la persona medianamente versada en la materia los puede emplear para investigación de otras enfermedades.

El problema técnico planteado en esta solicitud: la necesidad de inhibidores de SCD selectivos para regular los niveles de lípidos, especialmente lípidos plasmáticos, y para el tratamiento de enfermedades relacionadas con dislipidemia, cardiovascular, diabetes, obesidad, síndrome metabólico y similares, se había resuelto previamente mediante derivados de (piridazin-3-il)-(piperazin-1-il)-sustituidos ya conocidos(as). Por esta razón se considera que las sustituciones de los compuestos de fórmula la reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

Las reivindicaciones 10 y sus dependientes de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a los compuestos, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1 a D4 divulgaban previamente compuestos específicos derivados de (piridazin-3-il)-(piperazin-1-il)-sustituidos (folios: 177 a 188), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud es decir, derivados de (piridazin-3-il)-(piperazin-1-il)-sustituidos; de manera que para una persona medianamente versada en la materia sería obvio utilizar estos documentos para continuar sus investigaciones de nuevos tratamientos. Por lo cual puede no haber Nivel Inventivo.

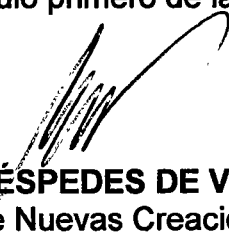
9. Conclusión:

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

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	US 5166147	10 a 35, 37	Novedad y Nivel Inventivo
D2	WO 99/00386	10 a 35, 37	Novedad y Nivel Inventivo
D3	WO 97/37975	10 a 35, 37	Novedad y Nivel Inventivo
D4	EP 0211457	10 a 35, 37	Novedad y Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la 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 Nº 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 07 MAR 2008

CONCEPTO TÉCNICO No. 634	EXAMINADOR TÉCNICO Código No. 202005
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