

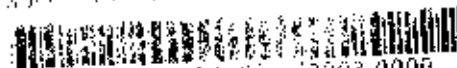
SEÑORES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Superintendencia de Industria y Comercio



Nº. 06-122.667-40003-0000

Expediente de Patente de Invención
Nº. 06-122.667-40003-0000
AUTORIDAD NACIONAL DE INTELIGENCIA TECNOLÓGICA

Ref.: Expediente N°. 06-122.667

Solicitud de Patente de Invención titulada: "NUCLEOSIDOS DE 3 β -D-RIBOFURANOSILTIAZOLO [4, 5-d]PIRIDIMINA Y USOS DE LOS MISMOS".

Solicitante: ANADYS PHARMACEUTICALS, INC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 583

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 de la sociedad de la referencia, 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. Adjunto recibo por el monto de \$420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 de 26 de diciembre 2007.

Atentamente,

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

Anexo: Recibo por \$420.000 pesos

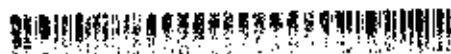
412 400
2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 15,371
FECHA : FEBRERO 21 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARTE RAISBECK	CONSIGNACION	BANCO DE BOGOTA	062754387	1403221	21/02/2008	22,239,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50065-01-01	SOLICITUDES	
		25 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. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-122667

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO 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.

SI _____

NO X

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
5 June 2003 (05.06.2003)

PCT

(10) International Publication Number
WO 03/045968 A1

(51) International Patent Classification: C07H 19/24, A61K 31/7052, A61P 37/02

(74) Agent: DAIGNAULT, Ronald, A.; Merchant & Gould P.C., P.O. Box 2903, Minneapolis, MN 55402-0903 (US).

(21) International Application Number: PCT/US02/38001

(81) Designated States (national): 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, GR, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date:
27 November 2002 (27.11.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/333,460 27 November 2001 (27.11.2001) US

(84) Designated States (regional): ARIPO patent (GI, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

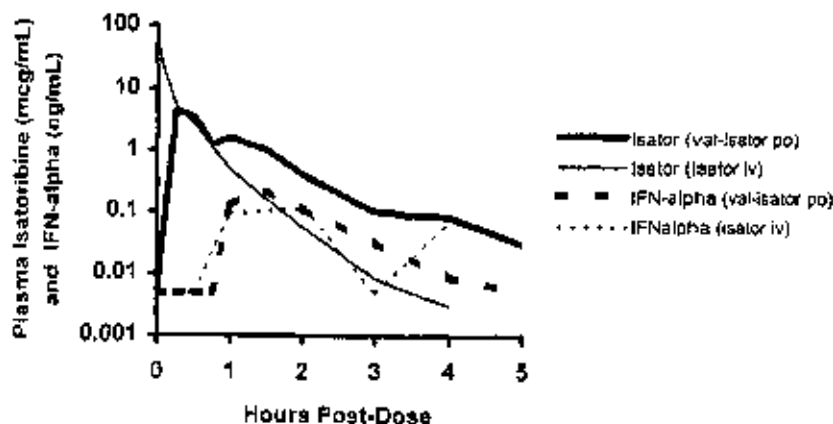
(71) Applicant: ANADYS PHARMACEUTICALS, INC. [US/US]; 9050 Camino Santa Fe, San Diego, CA 92121 (US).

Published:
— with international search report

[Continued on next page]

(54) Title: 3- β -D-RIBOFURANOSYLTHIAZOL[4,5-d]PYRIDIMINE NUCLEOSIDES AND USES THEREOF

Murine Interferon-alpha Response
Isatoribine 25 mg/kg i.v. vs Val-Isatoribine 50 mg/kg p.o.



(57) Abstract: The invention is directed to 3- β -D-ribofuranosylthiazolo[4,5-d]pyridimine nucleosides and pharmaceutical compositions containing such compounds that have immunomodulatory activity. The invention is also directed to the therapeutic or prophylactic use of such compounds and compositions, and to methods of treating diseases and disorders described herein, by administering effective amounts of such compounds.

**3- β -D-RIBOFURANOSYLTHIAZOLO[4,5-*d*]PYRIDIMINE
NUCLEOSIDES AND USES THEREOF**

This application is being filed as a PCT international patent application in the
5 names of Devron R. Averett and Stephen E. Webber, both citizens and residents of
the U.S., on 27 November 2002, designating all countries except the U.S.

FIELD OF THE INVENTION

The invention is directed to 3- β -D-ribofuranosylthiazolo[4,5-*d*]pyridimine
10 nucleosides and pharmaceutical compositions containing such compounds that have
immunomodulatory activity. The invention is also directed to the therapeutic or
prophylactic use of such compounds and compositions, and to methods of treating
diseases and disorders described herein, by administering effective amounts of such
compounds.

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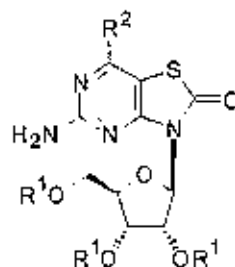
BACKGROUND OF THE INVENTION

The last few decades have seen significant efforts expended in exploring
possible therapeutic uses of D- and L-purine nucleoside analogs. A number of
nucleoside analogs are currently being marketed as antiviral drugs, including the
20 HIV reverse transcriptase inhibitors (AZT, ddI, ddC, d4T, and 3TC).

A variety of D- and L-purine nucleoside analogs have also been explored
in search of immunomodulators. Guanosine analogs having substituents at the
7-and/or 8-positions, for example, have been shown to stimulate the immune
system. See Reitz et al, *J. Med. Chem.*, 37, 3561-78 (1994); Michael et al., *J.*
25 *Med. Chem.*, 36, 3431-36 (1993). In other research, U.S. Patent No. 5,821,236
to Krenitsky et al. discloses 6-alkoxy derivatives of arabinofuranosyl purine
derivatives that are useful for tumor therapy. Also reported in U.S. Patent No.
5,539,098 to Krenitsky et al. are inhibitors of varicella zoster virus, including 5'-
O-propionyl and 5'-O-butyryl esters of 2-amino-6-methoxy-9-(β -D-
30 arabinofuranosyl)-9H-purine. 7-Deazaguanosine and analogs have been shown
to exhibit antiviral activity in mice against a variety of RNA viruses, even
though the compound lacks antiviral properties in cell culture. 3-Deazaguanine

What is claimed is:

1. A compound represented by Formula I:



I

wherein:

- 5 R^1 is independently H, $-C(O)R^3$, or a racemic, L-, or D- amino acid group $-C(O)CHNH_2R^4$, wherein R^3 is a substituted or unsubstituted alkyl, and R^4 is H, or a substituted or unsubstituted alkyl;
- R^2 is H, OR^5 , or $N(R^6)_2$, wherein R^5 is independently H or alkyl, and wherein R^6 is independently H, substituted or unsubstituted alkyl, cycloalkyl, or together
- 10 with nitrogen forms a substituted or unsubstituted heterocycloalkyl ring; and
- wherein if R^2 is $-OH$, at least one of the R^1 groups is a racemic, L-, or D- amino acid group $-C(O)CHNH_2R^4$;
- or a pharmaceutically acceptable salt.
- 15 2. The compound or pharmaceutically acceptable salt according to claim 1, wherein at least one of the R^1 groups is a racemic, L-, or D- amino acid group $-C(O)CHNH_2R^4$, wherein R^4 is a substituted or unsubstituted alkyl, and wherein the remaining R^1 groups are H; R^2 is OR^5 or $N(R^6)_2$, wherein R^5 is independently
- selected from H or alkyl, and wherein R^6 is independently H, substituted or
- 20 unsubstituted alkyl, cycloalkyl, or together with nitrogen forms a substituted or unsubstituted heterocycloalkyl ring.
3. The compound or pharmaceutically acceptable salt according to claim 2, wherein at least one of the R^1 groups is a L- amino acid group $-C(O)CHNH_2R^4$,
- 25 wherein R^4 is a substituted or unsubstituted alkyl, and wherein the remaining R^1 groups are H; R^2 is OR^5 or $N(R^6)_2$, wherein R^5 is a substituted alkyl, and wherein R^6 is independently H or substituted or unsubstituted alkyl.

United States Patent [19]

Robins et al.

[11] Patent Number: 5,041,426

[45] Date of Patent: * Aug. 20, 1991

[54] IMMUNE SYSTEM ENHANCING
3-β-D-RIBOFURANOSYLTHIAZOLO[4,5-
D]PYRIDIMINE NUCLEOSIDES AND
NUCLEOTIDES

[75] Inventors: Roland K. Robins, Irvine; Howard B.
Cottam, Fallbrook, both of Calif.

[73] Assignee: Brigham Young University, Provo,
Utah

[*] Notice: The portion of the term of this patent
subsequent to Nov. 14, 2006 has been
disclaimed.

[21] Appl. No.: 236,366

[22] Filed: Aug. 25, 1988

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 136,020, Dec. 21,
1987, Pat. No. 4,880,784.

[51] Int. Cl.³ A61K 31/70

[52] U.S. Cl. 514/43; 514/48;

536/24; 536/28

[58] Field of Search 514/43, 45-48;
536/24, 26-29

References Cited

U.S. PATENT DOCUMENTS

4,746,651 5/1988 Goodman 514/43

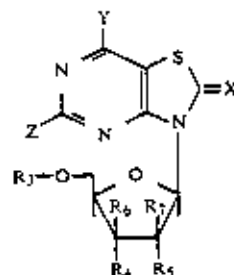
Primary Examiner—Johnnie R. Brown

Assistant Examiner—L. Eric Crane

Attorney, Agent, or Firm—Herb Boswell

[57] ABSTRACT

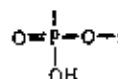
Compounds of the structure:



wherein R₄, R₅, R₆ and R₇ individually are H, OH or
C₁-C₁₈ O-acyl and R₃ is H, C₁-C₁₈ acyl or



or R₅ and R₇ are H or OH, R₆ is H and together R₃ and
R₄ are



and X is =O or =S; Y is —OH, —SH, —NH₂ or halo-
gen; and Z is H, —NH₂, —OH or halogen; wherein
halogen is Cl or Br; or pharmaceutically acceptable salt
thereof are useful as antivirals, antitumors, antimetastat-
ics and as immune system enhancers.

23 Claims, No Drawings

EXAMPLE 51

Tumoricidal Activity of Macrophages In Mice

The activity of compound 7 with respect to its ability to activate macrophages was tested by injecting CBA/-CaJ mice with a single dose of compound 7 (2 mg per mouse) and after 24 hours the cytotoxicity of the spleen cells (SC), non adherent SC and adherent SC was determined. The results are shown in Table 23.

TABLE 23

Effector Cells	Activation of Macrophages following Single Injection of Compound 7 in Mice ^a		
	Dose (mg) of Compound 7/mouse	% Cytotoxicity Assay	
		4 hrs.	20 hrs.
Spleen Cells (SC)	None	13	41
Nonadherent (SC)	2	45	70
Adherent cells	2	37	69

^aA group of four mice (CBA/CaJ) were injected with 2 mg/mouse of compound 7 solution. Control group received saline. After 24 hours of injection, spleens were harvested. Adherent and nonadherent cells were separated by incubation of spleen cells on plastic plates for one hour. Cell suspension of spleen cells, nonadherent cells (NC) and adherent cells (AC) were prepared in complete medium. Cytotoxicity of SC, NC and AC was then measured against P815 tumor target cells in 4 hrs and 20 hrs chromium release assay.

As is evident from Table 23 compound 7 was able to activate both natural killer and adherent (macrophage) cells as evidenced by the ability of these cells to exert augmented cytotoxicity against tumor target cells.

In examples 52 and 53 the combination activity of compounds of the invention with the known antiviral agent Ribavirin against San Angelo Virus and Banzi Virus were measured utilizing compound 7 in a prophylactic protocol. The Ribavirin served as a further antiviral agent for use in combination with the compounds of the invention.

EXAMPLE 52

Combination Chemotherapy Against San Angelo Virus In Mice

The combination chemotherapy results against San Angelo Virus in Mice are shown in Table 24.

TABLE 24

Combination Chemotherapy Against San Angelo Virus			
Treatment ^a	Survivors/Total (%)	Mean Survival Time ^b (Days)	
- 24 Hrs	Days 0-6		
Saline	Saline	1/16 (6)	8.3 ± 1.8 ^c
Compound 7 (5) ^d	Saline	7/16 (44) ^e	9.6 ± 1.6
Saline	Ribavirin (50)	6/16 (38)	9.0 ± 1.2
Saline	Ribavirin (25)	9/16 (56) ^e	8.1 ± 0.7
Compound 7 (5)	Ribavirin (50)	8/16 (50) ^e	8.9 ± 2.2
Compound 7 (5)	Ribavirin (25)	6/16 (38)	10.1 ± 3.6

^aA single injection of saline or compound 7 was given 24 hours before virus inoculation. Treatments on days 0-6 were twice a day for 7 days starting 2 hours pre-virus inoculation.

^bOf mice that died.

^cStandard Deviation.

^dThe dose in mg/kg/day is in parentheses.

^eStatistically significant ($p < .05$), determined by the two-tailed Fisher exact test.

EXAMPLE 53

Combination Chemotherapy Against Banzi Virus Infection In Mice

The combination chemotherapy results against Banzi Virus infection in mice are shown in Table 25.

TABLE 25

Combination Chemotherapy Against Banzi Virus Infection			
Treatment ^a	Treatment ^b	Survivors/Total (%)	Mean Survival Time ^c (days)
- 24 hours	days 0-6		
Placebo ^d	Saline	0/12 (0)	7.7 ± 0.5
Placebo	Ribavirin	0/12 (0)	8.5 ± 1.0 ^e
	100 mg/kg		
Placebo	Ribavirin	0/12 (0)	9.1 ± 0.8 ^e
	200 mg/kg		
Compound 7	Saline	0/12 (0)	9.3 ± 1.0 ^e
100 mg/kg			
Compound 7	Ribavirin	0/12 (0)	10.2 ± 0.9 ^e
100 mg/kg	100 mg/kg		
Compound 7	Ribavirin	3/12 (25)	12.4 ± 3.5 ^e

^aSingle injection given 24 hours before virus inoculation.

^bHalf-daily doses given twice a day for 7 days starting 2 hours pre-virus inoculation.

^cOf mice that died. Survivors lived 21 days.

^dA 2% sodium bicarbonate solution was the placebo and diluent for compound 7. Ribavirin was dissolved in saline.

^eStatistically significant ($p < .05$), determined by a two-tailed t-test.

As is evident from Tables 24 and 25, compound 7 in a prophylactic mode in combination with the known antiviral Ribavirin, exhibited efficacy against the test viruses.

Compounds of the invention have further shown the ability to suppress metastasis in host mammals bearing metastatic tumors and in artificially induced metastasis in such hosts.

Utilizing the protocol of Alessandri, G., Giavazzi, R., Falautano, P., Spreafico, F., Garattini, S., and Mantovani, A., *European J. Cancer*, 17:651-658, 1981, the antimetastatic activity of Compound 7 is seen in a sarcoma M5076 tumor system.

EXAMPLE 54

Reduction of Reticulum-cell Sarcoma Metastatic Foci

Fragments of reticulum-cell sarcoma M5076 were introduced into mice. The animals were treated with compound 7 for 20 days at various dosages. After treatment, the required tissues were collected, fixed in Bouin's solution and subjected to microscopic observation to enumerate metastatic foci. The results are shown in table 26 as the number of metastatic foci and table 27 as the number of mice with metastatic foci. In table 26 both the range and the median number of foci for each test group is indicated.

TABLE 26

Metastatic Foci Formed in Lungs And Liver In Response to Reticulum-cell Sarcoma M5076 ^a				
Number of Metastatic Foci				
Drug ^c (mg/kg)	In Lung		In Liver	
	Median	Range	Median	Range
0	18	(6-30)	154	(61-275)
37	6 ($p < 0.01$) ^b	(1-11)	1 ($p < 0.005$) ^b	(0-17)
62	2 ($p < 0.09$) ^b	(0-29)	0 ($p < 0.005$) ^b	(0-1)
104	0 ($p < 0.002$) ^b	(0-4)	0 ($p < 0.0009$) ^b	(0-0)

^aFragments of reticulum-cell sarcoma M5076 (≈ 14 mg) were implanted subcutaneously in the left flank of BDF₁ female mice and ip bolus injections of drug were initiated 24 hrs later. The drug was delivered on the basis of 0.01 ml/g mouse weight. Control mice received a 0.9% solution of NaCl delivered on the same basis. Seven mice were used per treatment group. Treatment gave qd for days 1-20.

^bStudent t-test.

^cCompound 7.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado:

✓ **CARLOS REINALDO OLARTE GARCIA**

ASUNTO:	Radicación No.	06 12 2667
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	3078
	Folios	

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:

Documentos estudiados:

Descripción:	Folios 144 a 346 como se radicó inicialmente.
Reivindicaciones:	Folios 347 a 355 como se radicó inicialmente.
Prioridad:	Junio, 7, 2004

Objeto de la Invención

Título de la invención: "Nucleósidos de 3- beta-D-ribofuranosiltiazolo[4,5-d]pirimidina y usos de los mismos."

Problema Técnico Planteado: "Necesidad de análogos de nucleósidos de purina con disponibilidad oral, tolerabilidad y administración mejoradas, que sean utilizados para que sean utilizados para modular aspectos del sistema inmune."

Solución: "Proveer nucleósidos de 3- beta-D-ribofuranosiltiazolo[4,5-D]pirimidina de acuerdo a la formula I, profármacos, metabolitos, solvatos farmacéuticamente aceptables de los mismos "

IPC: C07H 19/24, A61K 31/7052

Excepciones a la Patentabilidad (Art 20 D 486 literal d)

Las reivindicaciones 15 - 20 se refieren a método de tratamiento, deben ser retiradas del capítulo reivindicatorio.

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Claridad y concisión: La reivindicación 1 reclama compuestos de acuerdo a la fórmula I sin definir claramente algunas porciones de la molécula.

En el folio 347 y 348, es evidente que las porciones de algunos radicales no se han definido concisamente. Tal es el caso de R5, el cual es definido claramente pero los grupos que a su vez no sustituyen a dicho radical no son definidos por el número de átomos carbonos que contienen, como ejemplo se citan: -NH-alquilo, -N(alquilo)₂, -SO₂ arilo.

Es necesario que el solicitante restrinja debidamente el alcance de las definiciones dadas para la fórmula I en la reivindicación 1.

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de prioridad: Junio, 7, 2004 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

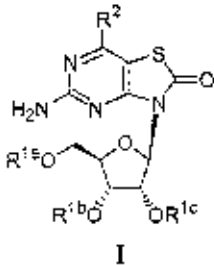
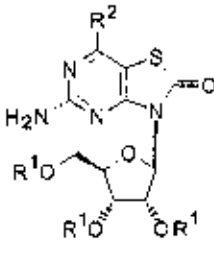
Item	Documento	Título	Fecha de Publicación
D1	WO03/045968	#-beta-ribofuranosylthiazolo[4-5,d]pyrimidine nucleosides and uses thereof	Jun 5, 2003
D2	US5041426	Immune system enhancing 3-beta-D-ribofuraznosylthiazolo[4,5d]pyrimidine nucleosides and nucleotides.	Ago 20, 1991

Análisis de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

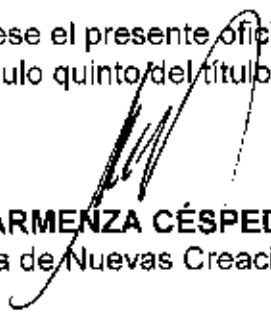
La reivindicación 1 presenta compuestos de acuerdo a la fórmula I, en donde R1a, R1b y R1c son independientemente H, -C(O)R3, un grupo de aminoácido racémico, L-, D- o -C(O)CH₂NHR₄, -C(O)CH(C1-6alquil)NHR₄, o R1b y R1c son colectivamente -C(O)-, los cuales junto con los átomos de oxígeno forman un anillo de carbonato de cinco miembros; lo demás como en el folio 347.

D1 revela nucleósidos de acuerdo a la fórmula I y composiciones farmacéuticas que los contienen, en donde se define concisamente cada uno de los sustituyentes R1 y R2 de esta molécula. (Reivindicación 1)

Características esenciales de la Solicitud	D1
	US 5.395.356
 I	 I
R2 es H, OR5 ó N(R6)2	SI (reivindicación 1, página 47)
R1a, R1b y R1c son H, -C(O)R3, grupo de	SI (reivindicación 1, páginas 47)

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.


ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

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

CONCEPTO TÉCNICO NUMERO: 564	EXAMINADOR TÉCNICO Código: 202092
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