



No. 07-101002- -00005-0000

Fecha: 2008-06-04 16:51:11 Dep. 2020 NUECREACION
Tra. 11 PATENTILYII Lve: 378 FASENACIONAL
Act. 538 PETICION Folios: 2

AS: 105.067

Señores

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

E. S. D.

REF.: Expediente No. 07 101002 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/CA2005/000384

a nombre de **SHIRE CANADA INC.**

Titulada: PROCESOS Y MÉTODOS PARA LA PREPARACIÓN DE CIS-2-HIDROXIMETIL-4-(CITOSIN-1'-IL)-1,3-OXATIOLOANO ÓPTICAMENTE ACTIVAS O SALES ACEPTABLES FARMACÉUTICAMENTE DEL MISMO

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la sociedad **SHIRE CANADA INC.**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 08-28.748 por valor de \$420.000.

De la Señora Jefe atentamente,

JUAN PABLO CADENA SARMIENTO

C.C. No. 80.410.337 de Usaquén

T.P. No. 57492 del C.S.J.

Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 03 de junio de 2008

MEV/JCN/aac

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-101002- -00005-0000

Fecha: 2008-06-04 16:51:11 Dep. 2020 NUECLACIONI
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RECIBO OFICIAL DE CAJA : 08 - 28,748
FECHA : ABRIL 9 DE 2008

***** CONSIGNACION *****

DEBITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3164840	09/04/2008	18,244,000.00

***** CONCEPTO *****

CONCEPTO	TOTAL CONCEPTO
01 SOLICITUDES	
85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
TOTAL :	\$ 420,000.00

CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

250

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
SISTEMA DE TRAMITES-CONSULTA DE RECIBOS
Lunes 21 de Febrero de 2011

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DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-101002

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **591** DE

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

EXPIRA EL **30 DE JULIO 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



US006228860B1

(12) **United States Patent**
Mansour et al.(10) **Patent No.:** **US 6,228,860 B1**
(45) **Date of Patent:** ***May 8, 2001**(54) **SUBSTITUTED 1,3-OXATHIOLANES WITH ANTIVIRAL PROPERTIES**(75) Inventors: **Tarek S. Mansour; Haolun Jin**, both of Montreal (CA)(73) Assignee: **Biochem Pharma Inc.**, Laval (CA)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/718,555**(22) PCT Filed: **Apr. 19, 1995**(86) PCT No.: **PCT/CA95/00212**§ 371 Date: **Nov. 26, 1996**§ 102(e) Date: **Nov. 26, 1996**(87) PCT Pub. No.: **WO95/29176**PCT Pub. Date: **Nov. 2, 1995****Related U.S. Application Data**

(63) Continuation-in-part of application No. 08/230,317, filed on Apr. 20, 1994, now Pat. No. 5,587,480, which is a continuation-in-part of application No. 07/791,441, filed on Nov. 13, 1991, now abandoned, which is a continuation-in-part of application No. 07/612,840, filed on Nov. 13, 1990, now abandoned.

(51) Int. Cl.⁷ **A61P 31/18; A61K 31/4718; C07D 411/04**(52) U.S. Cl. **514/262; 514/274; 544/317**(58) Field of Search **544/317; 514/274, 514/262**(56) **References Cited****U.S. PATENT DOCUMENTS**

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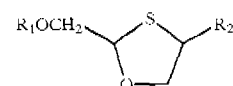
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(List continued on next page.)

Primary Examiner—John M. Ford**Assistant Examiner**—Thomas McKenzie(74) **Attorney, Agent, or Firm**—Millen, White, Zelano & Branigan, P.C.(57) **ABSTRACT**

This invention relates to single enantiomers of novel cis-substituted 1,3-oxathiolanes, of the formula (I):



wherein;

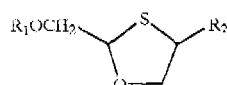
R₁ is hydrogen, and R₂ is cytosine or 5-fluorocytosine, and pharmaceutically acceptable salts and esters thereof. This invention also relates to pharmaceutical compositions containing them and to the use of these compounds as antiviral agents, particularly in combination therapy.**20 Claims, No Drawings**

R. Vince and M. Hua, "Synthesis and anti-HIV activity of carbocyclic 2',3'-didehydro-2',3'-dideoxy 2,6-disubstituted purine nucleosides", *J. Med. Chem.*, 33(1), pp. 17-21 (1990), describe the analogues shown in formulas (F) and (G) as having anti-HIV activity. The unsaturated analogue (F) shows greater selectivity and potency as an inhibitor of HIV replication than the saturated analog (G).

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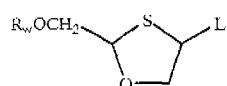
unsubstituted, saturated or unsaturated phosphonates, such as diethylphosphonate; substituted or unsubstituted aliphatic or aromatic sulphonyl group, such as tosylate; or hydrogen.

Oxathiolane compounds of formula (I),



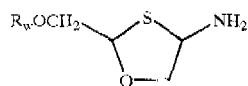
and pharmaceutically acceptable, salts and esters, may be prepared according to the processes discussed herein or by any method known in the art for the preparation of compounds of analogous structure. The compound of this invention can be produced by the methods described by Mansour et al., "Anti-Human Immunodeficiency Virus and Anti-Hepatitis-B Virus Activities and Toxicities of the Enantiomers of 2'-Deoxy-3'-oxa-4'-thiacytidine and Their 5-Fluoro Analogues in vitro", *J. Med. Chem.*, 1995, Vol. 38, No. 1, pp. 1-4, which is incorporated herein by reference.

In one such process for producing oxathiolanes of this invention, a compound of formula (V),



wherein R_w is hydrogen or a hydroxyl protecting group and L is a displaceable atom or group, i.e., a leaving group, is reacted with an appropriate base.

In a second process for producing oxathiolanes of this invention, a compound of formula (VI)



may be converted to a compound of formula (I) by conversion of the anomeric NH_2 group to the required base by methods well known in the art of nucleoside chemistry.

The 1,3-oxathiolanes of formula (I) may also be prepared, for example, by reaction of an aldehyde of formula (VII)



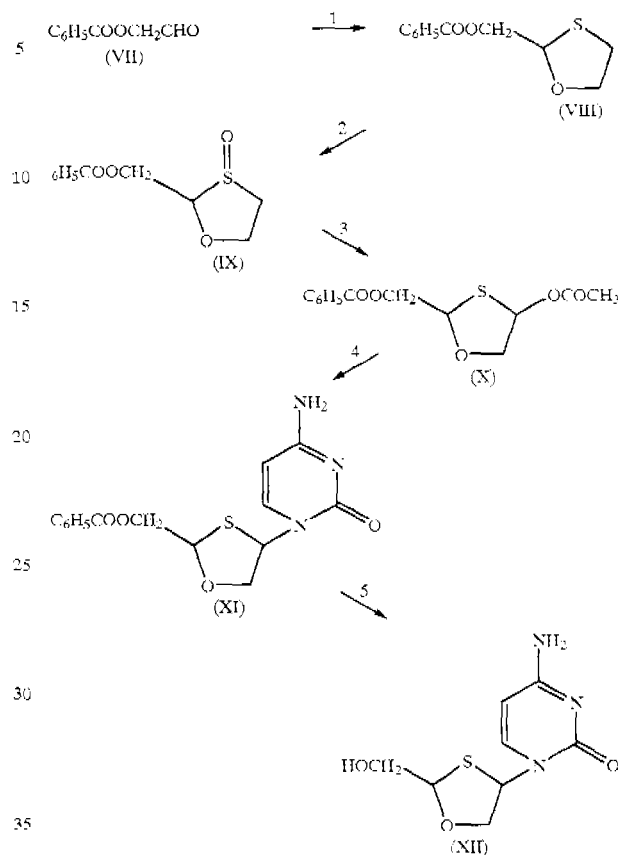
with 2-mercaptoethanol in a compatible organic solvent followed by Pummerer rearrangements as is known in the art (T. Durst, "Dimethylsulfoxide in organic Synthesis", *Adv. Org. Chem.*, E. C. Taylor and B. Wynberg, Eds., 6, pp. 356-365 (1969)) to give 1,3-oxathiolanes of formula (V), which are converted to 1,3-oxathiolanes of formula (I) by methods known in the art of nucleoside chemistry.

Another process for preparing the 1,3-oxathiolanes of formula (I) is illustrated in SCHEME 1.

The various steps involved in the synthesis of 1,3-oxathiolanes of formula (I) as illustrated in SCHEME 1 may be briefly described as follows:

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SCHEME 1



Step 1: Benzoyloxyacetaldehyde of formula (VII) or any aldehyde of the formula R_wOCH_2CHO (C. D. Hurd and E. M. Filiachione, "A new approach to the syntheses of aldehyde sugars", *J. Am. Chem. Soc.*, 61, pp. 1156-1159 (1939)) is condensed with a mercaptoalcohol such as 2-mercaptoethanol in a compatible organic solvent, such as toluene, containing a catalytic amount of a strong acid to give the intermediate shown in formula (VIII).

Step 2: The 1,3-oxathiolane of formula (VIII) is then oxidized with a peracid such as magnesium monoperoxyphthalic acid in a compatible organic solvent such as methylene chloride containing a salt such as tetrabutyl ammonium bromide to give the sulfoxide intermediate shown in formula (IX).

Step 3: The sulfoxide intermediate shown in formula (IX) is treated with an acid anhydride such as acetic anhydride or any other anhydride of the formula $(R_sCO)_2O$ in the presence of a buffer such as tetra-n-butylammonium acetate to give the 2,4-disubstituted-1,3-oxathiolane of formula (X) (T. Durst, *Adv. Org. Chem.*, 6, pp. 356-365 (1969)).

Step 4: The 1,3-oxathiolane of formula (X) is then reacted with a pyrimidine base or analogue thereof, (e.g., cytosine) previously silylated with, for example, hexamethyldisilazane in a compatible solvent using a Lewis acid or trimethylsilyl triflate to give the intermediate of formula (XI) as cis and trans isomers. The isomers may be separated, preferably by chromatography, to give pure cis (XI) and pure trans (XI).

Step 5: The benzoate function of the compound of formula (XI) (cis or trans isomer), is hydrolyzed using a base such as methanolic ammonia to obtain the compound shown

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tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids such as oxalic, while not in themselves pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C₁₋₄ alkyl)₄⁺ salts.

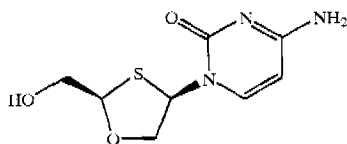
It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable salts and esters thereof, at functional groups in both the cytosine moiety, and at the hydroxymethyl group of the oxathiolane ring, respectively. Modification at all such functional groups is included within the scope of the invention. However, of particular interest are pharmaceutically acceptable salts and esters (e.g., esters or esters of amino acids) obtained by modification of the 2-hydroxymethyl group of the oxathiolane ring.

Preferred esters of the compounds of formula (I) include the compounds in which R₁ is replaced by a carboxyl function R-(CO) in which the non-carbonyl moiety R of the ester grouping is selected from hydrogen, straight or branched chain alkyl (e.g., methyl, ethyl, n-propyl, t-butyl, n-butyl), alkoxyalkyl (e.g., methoxymethyl), aralkyl (e.g., benzyl), aryloxyalkyl (e.g., phenoxymethyl), aryl (e.g., phenyl optionally substituted by halogen, C₁₋₄ alkyl or C₁₋₄ alkoxy); substituted dihydro pyridinyl (e.g., N-methyldihydro pyridinyl); sulphonate esters such as alkyl- or aralkylsulphonyl (e.g., methanesulphonyl); sulfate esters; amino acid esters (e.g., L-valyl or L-isoleucyl) and mono, di- or triphosphate esters.

Also included within the scope of such esters are esters derived from polyfunctional acids such as carboxylic acids containing more than one carboxyl group, for example, dicarboxylic acids HO₂C(CH₂)_nCO₂H where n is an integer of 1 to 10 (for example, succinic acid) or phosphoric acids. Methods for preparing such esters are well known. See, for example, E. Hahn et al., "Nucleotide dimers as anti-human immunodeficiency virus agents", *Nucleotide Analogues As Antiviral Agents*, J. C. Martin, Ed. Symposium Series #401, American Chemical Society, pp. 156-159 (1989) and M. Busso et al., "Nucleotide dimers suppress HIV expression in vitro", *AIDS Research and Human Retroviruses*, 4(6), pp. 449-455 (1988).

Specific compounds of formula (I) include:

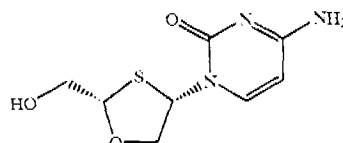
Compound #1



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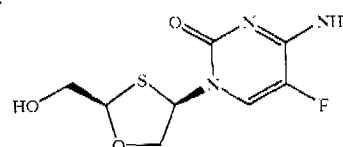
2R-hydroxymethyl-4R-(cytosin-1'-yl)-1,3-oxathiolane;

compound #2:



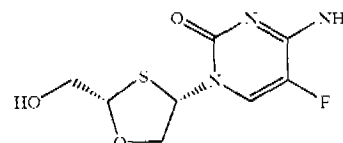
2S-hydroxymethyl-4S-(cytosin-1'-yl)-1,3-oxathiolane;

compound #3:



2R-hydroxymethyl-4R-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane; and

compound #4



2S-hydroxymethyl-4S-(5'-fluorocytosin-1'-yl)-1,3-oxathiolane; and pharmaceutically acceptable salts and esters thereof.

In the processes for preparing the compounds of this invention, the following definitions are used:

R₂ is cytosine or 5-fluorocytosine;

R_w is hydrogen, trisubstituted silyl, C₁₋₆ alkyl, aralkyl such as benzyl or trityl, C₁₋₁₆ acyl, preferably a benzoyl or a benzoyl substituted in any position by at least one halogen (bromine, chlorine, fluorine or iodine), C₁₋₆ alkyl, C₁₋₆ alkoxy, nitro, or trifluoromethyl group;

R_x is C₁₋₆ alkyl; and

L is a "leaving group", i.e., an atom or group which is displaceable upon reaction with an appropriate base, with or without a Lewis acid. Suitable leaving groups include acyloxy groups, alkoxy groups, e.g., alkoxy carbonyl groups such as ethoxy carbonyl; halogens such as iodine, bromine, chlorine, or fluorine; amido; azido; isocyanato; substituted or unsubstituted, saturated or unsaturated thiolates, such as thiomethyl or thiophenyl; substituted or unsubstituted, saturated or unsaturated seleno or selenino compounds, such as phenyl selenide or alkyl selenide; and substituted or unsubstituted, saturated or unsaturated aliphatic or aromatic ketones such as methyl ketone.

A suitable leaving group may also be -OR, where R is a substituted or unsubstituted, saturated or unsaturated alkyl group, e.g., C₁₋₆ alkyl or alkenyl group; a substituted or unsubstituted aliphatic or aromatic acyl group, e.g., a C₁₋₆ aliphatic acyl group such as acetyl and an aromatic acyl group such as benzoyl; a substituted or unsubstituted, saturated or unsaturated alkoxy or aryloxy carbonyl group, such as methyl carbonate and phenyl carbonate; substituted or unsubstituted sulphonyl imidazolidine; substituted or unsubstituted aliphatic or aromatic amino carbonyl group, such as phenyl carbamate; substituted or unsubstituted alkyl imidate group such as trichloroacetimidate; substituted or

in formula (XII) as cis- or trans- isomer, preferably under pressure, to give the product shown in

Many of the reactions in the above-described processes have been extensively reported in the context of pyrimidine nucleoside synthesis, for example, in I. B. Townsend, "Synthesis and reaction of pyrimidine nucleoside", *Chemistry of Nucleoside and Nucleotides* vol. 1, Eds., Plenum Press, New York (1989) at pages 1-95, the text of which is incorporated by reference herein.

In the above-described process, the compounds of formula (I) are generally obtained as a mixture of the cis and trans isomers.

The cis and trans isomers may be separated, for example, by acetylation, e.g., with acetic anhydride followed by separation by physical means, e.g., chromatography on silica gel and deacetylation, e.g., with methanolic ammonia or by fractional crystallization.

Resolution of the final product, or an intermediate or starting material therefore may be effected by any suitable method known in the art: see for example, *Stereochemistry of Carbon Compounds*, by E. L. Eliel (McGraw Hill, 1962) and *Tables of Resolving Agents*, by S. H. Wilen.

Where the compound of formula (I) is desired as a single enantiomer it may be obtained either by resolution of the mixture of the two cis enantiomers (by chiral HPLC) or by stereospecific synthesis from isometrically pure starting material or any convenient intermediate. Thus, the compound of formula (I) or any convenient intermediate may be obtained by chiral HPLC using a suitable stationary phase for example acetylated β -cyclodextrin or cellulose triacetate and a suitable solvent for example an alcohol such as ethanol or an aqueous solution such as triethyl ammonium acetate. Alternatively, the compound of formula (I) or any convenient intermediate may be resolved by enzyme mediated enantioselective catabolism with a suitable enzyme such as cytidine deaminase or selective enzymatic degradation of a suitable derivative using a 5'-nucleotidase for example see Storer et al., "The resolution and Absolute Stereochemistry of the Enantiomers of cis-1[2(Hydroxomethyl)-1,3-Oxathiolan-5-Yl]Cytosine (BCH-189): Equipotent Anti-HIV Agents", *Nucleosides & Nucleotides*, 12(2), 225-236 (1993). When the resolution is effected enzymatically, the enzyme may be employed either in solution or in immobilized form. Enzymes in immobilized form are known in the art for example, by adsorption onto a resin such as Eupergit.

It will be appreciated that the reactions of the above-described processes may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g., benzyl), acyl or aryl (e.g., 2,4-dinitrophenyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J. F. W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1981) which is incorporated by reference herein. Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g., methyl, t-butyl or methoxymethyl), aralkyl (e.g., benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl, (e.g., acetyl or benzoyl) and silyl

groups such as trialkylsilyl (e.g., t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g., by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g., by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved, for example, by treatment with BF_3 /etherate and acetic anhydride followed by removal of acetate groups so formed at an appropriate stage in the synthesis. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

Pharmaceutically acceptable salts of the compounds of the invention may be prepared as described in U.S. Pat. No. 4,383,114, the disclosure of which is incorporated by reference herein. Thus, for example, when it is desired to prepare an acid addition salt of a compound of formula (I), the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods. Pharmaceutically acceptable acid addition salts may be prepared by reacting the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g., ethyl acetate) or an alcohol (e.g., methanol, ethanol or isopropanol). Inorganic basic salts may be prepared by reacting the free base with a suitable base such as an alkoxide (e.g., sodium methoxide) optionally in the presence of a solvent such as an alcohol (e.g., methanol). Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compounds of formula (I) using conventional methods.

A compound of formula (I) may be converted into a pharmaceutically acceptable phosphate or other ester by reaction with a phosphorylating agent, such as POCl_3 , or a suitable esterifying agent, such as an acid halide or anhydride, as appropriate. An ester or salt of a compound of formula (I) may be converted to the parent compound, for example, by hydrolysis.

The compounds of the invention possess anti-viral activity. In particular these compounds are effective in inhibiting the replication of hepatitis B virus and retroviruses, including human retroviruses such as human immunodeficiency viruses (HIV's), the causative agents of AIDS.

There is thus provided as a further aspect of the invention a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use as an active therapeutic agent in particular as an antiviral agent, for example in the treatment of hepatitis B viral and retroviral infections such as HIV infection.

There is also provided in a further or alternative aspect of this invention, use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a viral infection.

Such viral infections may be, in particular HIV and HBV infections.

In a further or alternative aspect there is provided a method for the treatment of a viral infection, in particular an infection caused by hepatitis B virus or a retrovirus such as HIV, in a mammal, including man, comprising administration of an effective amount of an antiviral compound of formula (I) or a pharmaceutically acceptable derivative thereof.

The compounds of the invention are also useful in the treatment of AIDS-related conditions such as AIDS-related complex (ARC), persistent generalized lymphadenopathy

Synthesis and applications of novel, highly efficient HPLC chiral stationary phases: a chiral dimension in drug research analysis

Giovanna Cancelliere, Ilaria D'Acquarica, Francesco Gasparrini, Domenico Misiti and Claudio Villani

This review provides an overview of the synthesis and application of stable and versatile HPLC chiral stationary phases (CSPs), with emphasis placed on the binding strategies developed to anchor several structurally different chiral selectors to silica-gel microparticles. In addition, selected applications relating to the use of these CSPs for the direct resolution of racemates of biological and pharmaceutical relevance will be described. This review discusses enantioselective molecular recognition and dynamic stereochemistry of stereolabile compounds with reference to receptor-based chiral stationary phases (CSPs) and dynamic HPLC on CSPs, respectively.

tem, and high reproducibility and flexibility of the analysis are routinely obtained.

The principle behind the synthesis and functioning of a chiral stationary phase for HPLC is simple: a single enantiomer of a chiral molecule (selector) is immobilized on the surface of a solid support (usually silica microparticles), and it selectively retains the enantiomers of analytes by forming diastereomeric adsorbates of different stabilities with them during the elution process.

Rational design and characteristics of a good CSP

Both thermodynamic (enantioselectivity, α) and kinetic parameters (chromatographic efficiency, N) are important in the rational design of a CSP. Although there is no simple way to determine a priori which is the selector structure that maximizes overall resolution for a given set of enantiomeric solutes, some structural features are common to highly efficient stationary phases:

- 1) A given chiral selector must possess functional groups with high directionality. Single-site or organized arrays of H-bond donor and/or acceptor sites, similar to amide moieties and aromatic rings with electron withdrawing or donating substituents in close proximity to the stereogenic element, are usually found in highly selective receptors. In addition, a certain degree of conformational homogeneity is often associated with high enantioselective recognition ability and loading of the column. This notion stems from the consideration that for a given selector

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▼ The overall biological activity of chiral substances often depends upon their stereochemistry. The enantiomers of chiral drugs show significant differences in their activity, pharmacokinetics, pharmacodynamics and potential adverse drug reaction. Stringent analytical characterization of drug substances, including their isomeric forms, are now required by regulatory agencies. As a result, several enantioselective chromatographic methods based on HPLC have been successfully developed in recent years¹⁻¹¹.

Analytical techniques relying on CSPs are preferred as they offer specific advantages over indirect methods: there is no need to chemically manipulate the samples, the enantiomers under investigation can be directly analysed in complex mixtures, the two enantiomers respond equally with any kind of non-chiroptical detection sys-

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020

Abogado
JUAN PABLO CADENA SARMIENTO

ASUNTO	Radicación	07 101 002
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	09

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐
No. Solicitud Internacional PCT/CA2006/000384			
Fecha de Presentación Internacional 14/Marzo/2005			

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 50 a 84	como se radicó inicialmente.
Reivindicaciones:	Folios 85 a 101	como se radicó inicialmente

2. Análisis de la Prioridad

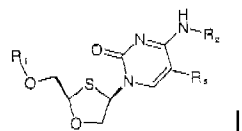
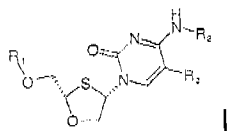
Se acepta la reivindicación de Prioridad porque:
Esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486).
Y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Procesos y métodos para la preparación de cis-2-hidroximetil-4-(citosin-1-il)-1,3-oxatiolano ópticamente activas o sales aceptables farmacéuticamente del mismo".

El problema planteado en esta solicitud es la necesidad de proporcionar formas ópticamente activas del compuesto de formula I y II

Para resolver este problema técnico la solicitud en estudio proporciona un proceso de producción de compuestos ópticamente activos de formula I y II



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El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C 07 D 411/04, A 61 K 31/39 // 31/395, A 61 P 31/12

4. De la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 20, 21, 37, 50, 63 y 68 corresponden al mismo proceso de producción de la reivindicación 1, por lo cual se sugiere establecer la correspondiente dependencia.

El capítulo reivindicatorio no es conciso porque contiene un excesivo número de reivindicaciones independientes, lo cual hace difícil definir cuál es el objeto que se busca proteger.

Se requiere al Solicitante hacer las aclaraciones necesarias.

5. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la

Fecha de Presentación Internacional: Marzo 14 de 2005

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

Item	Documento	Título	Fecha de Publicación
D1	US 6'228.860	Substituted 1,3-oxathiolanes with antiviral properties	08//Mayo/2001

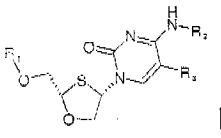
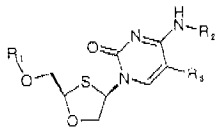
D1 divulga (Columna 1, renglones 11 – 15, folio 252; Esquema 1, columna 8, folio 253) compuestos oxatolanos 1,3 sustituidos con propiedades antivirales y un proceso de obtención.

6. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en un proceso para producir un compuesto ópticamente activo de formula I o II caracterizado por la reacción de un compuesto III en configuración cis con un acido quiral para producir dos sales diastereoméricas; posteriormente la recuperación de una sal diastereomérica y la conversión de esta al compuesto ópticamente activo.

Comparación de las características técnicas **esenciales**, con las del Estado de la Técnica:

Características esenciales	D1
Proceso para producir compuesto I o II	√
 I  II	

<chem>R1OCC1SC2=NC(=O)N(R2)C=C2R3</chem> Reacción entre sales disteroisoméricas	con un ácido quiral para producir dos	-
Recuperación de una sal diasteroisomérica		-
Convertir sal diasteroisomérica al compuestos ópticamente activo.		✓

El documento D1, considerado el estado de la técnica más cercano a la invención definida en la reivindicación 1, divulga un procedimiento de obtención de compuestos de formula I o II, ópticamente activos (Columna 5, compuesto 1; Columna 6, compuesto 2, folio 254; Esquema 1, columna 8, folio 253)

La diferencia entre la invención, definida en la reivindicación 1, y el procedimiento de D1 consiste en que la invención obtiene el compuesto ópticamente activo por la reacción directa del compuesto de partida con un acido quiral para obtener sales diasteroiméricas que se transforman en los correspondientes compuestos ópticamente activos.

No hay evidencia que la obtención del compuesto ópticamente activo a través del proceso reivindicado tenga efectos o propiedades adicionales a lo divulgado por D1

Por lo tanto, el Problema Técnico Objetivo que pretende resolver esta invención se puede formular así: “¿cómo modificar el procedimiento conocido en D1 para tener un procedimiento alternativo de obtención de compuestos de formula I o II ópticamente activos?”.

Sin embargo, la obtención de compuestos de formula I o II ópticamente activos por métodos alternativos como el HPLC quiral ya está divulgada en el documento D1 (columna 9, líneas 23 – 28, folio 255). Es conocido que sobre las columnas de HPLC quiral hay reacciones que generan adsorbatos diasteroisoméricos que posteriormente serán eluidos (Cancellere, G, pàgina 1, folio 256)

En consecuencia, el experto en la materia incluiría la reacción ocurrida sobre una columna de HPLC quiral de obtención de sales diasteroisomèricas en el proceso divulgado por D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Conclusión:
La reivindicación 1 cumple el requisito de novedad (Art. 16), pero no cumple con el requisito de nivel inventivo (Art. 18).

7. Conclusión

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

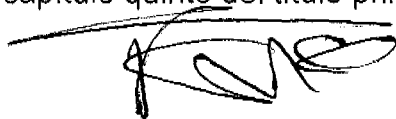
Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 6'228.860	1 - 72	Nivel inventivo

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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 (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 No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

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

CONCEPTO TÉCNICO No. 1119	EXAMINADOR TÉCNICO Código No. 202098
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