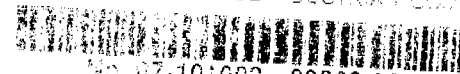


PETITORIO

AS: 105.067



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-101002-00000-0000

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

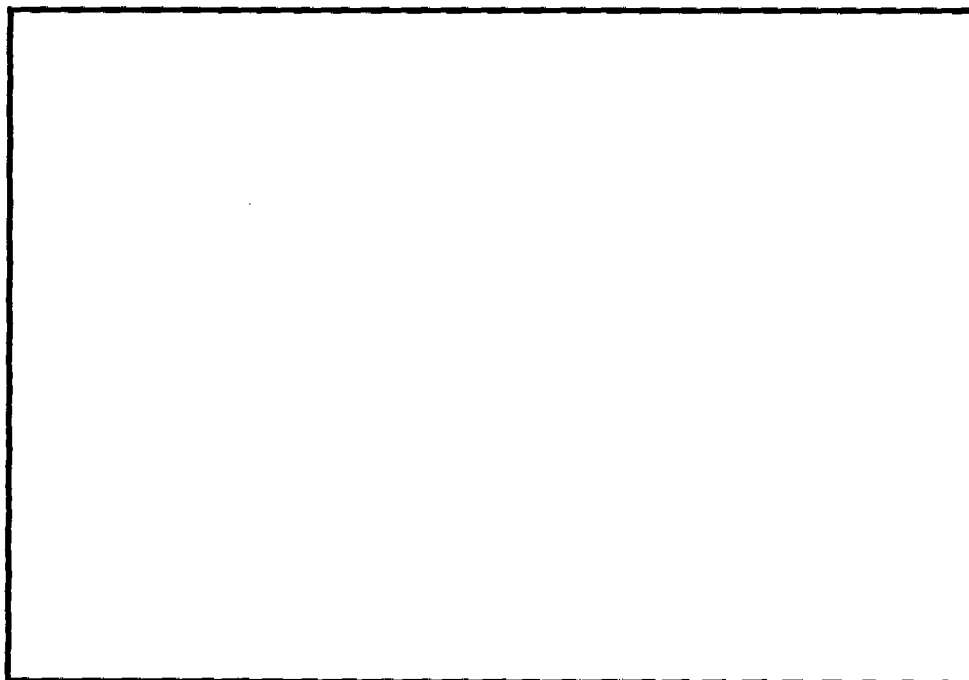
1 SOLICITUD DE:			
☒ Patente de Invención.		☐ Patente de Modelo de Utilidad.	
☒ Capítulo I.		☐ Capítulo II.	
2 SOLICITANTE (71)	Nombre: SHIRE BIOCHEM INC. Dirección: Suite 500, 2250 Alfred-Nobel Boulevard, Ville St-Laurent, Québec H4S 2C9, Canada Nacionalidad o Domicilio: Canada Lugar de Constitución: Canada Teléfono: Fax: E-mail:		IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: JUAN PABLO CADENA SARMIENTO Dirección: Cra. 7 No. 71-21 Torre B – Piso 4, Bogotá, Colombia. Teléfono: 744-2200 Fax: 742-2200 E-mail:		IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 80.410.337 TP 57492
4 INVENTOR (ES) (72)	Nombre: Ioana SIMION, Alex CIMPOIA. Dirección: 147 River Bend Road East, Edmonton, Alberta T6R 1N5, Canada; 290 Elgar, Apt. 204, Verdun, Québec H3E 1C9, Canada. (Respectivamente). Nacionalidad o Domicilio: Canada (Respectivamente).		
5 PCT (86)			
Solicitud Internacional No. PCT/CA2005/000384		Fecha 14-03-2005	
Publicación Internacional No. WO 2006/096954 A1		Fecha 21-09-2006	
6 Título (54): PROCESOS Y MÉTODOS PARA LA PREPARACIÓN DE CIS-2-HIDROXIMETIL-4-(CITOSIN-1-IL)-1,3-OXATIOLANO OPTICAMENTE ACTIVAS O SALES ACEPTABLES FARMACÉUTICAMENTE DEL MISMO.			
7 Clasificación Internacional (51): (67D) 411/04; A61K 31/39, 31/495; A61P 31/12.			
8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☐ NO ☒			
9 Comprobante de pago No. 07-62,574		Fecha 26-09-2007	
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.			

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$482 000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: Tarjeta de Propietarios
Documentos PCT

11 FIGURA CARACTERÍSTICA:



12

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 62,574
 FECHA : AGOSTO 3 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07 101002-00000-0000

Fecha: 2007-08-03 16:40:01 Dep. 2020 NUECREACION
 No. 07 101002-00000-0000 Eje: 378 PASSE NACIONAL
 Act. 41 PRESENTACION Folios: 184

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	51181691	03/08/2007	45,240,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
	TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



11



4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

PATENTE ☒ PCT/CA2005/000384 MODELO DE UTILIDAD ☐ DISEÑO INDUSTRIAL ☐

SOLICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES SHIRE BIOCHEM INC.

DOMICILIO QUÉBEC, CANADA.

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO PROCESOS Y MÉTODOS PARA LA PREPARACIÓN DE CIS-2-HIDROXIMETIL-4-(CITOSIN-1-IL)
-1,3-OXATIOLANO ...

CLASIFICACION

EXPEDIENTE No. FECHA DE SOLICITUD ROLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR (ES) IOANA SIMION, ALEX CIMPOIA.

OTROS

OFICINA DE COMUNICACIONES

PATENT COOPERATION TREATY

PCT/CA2005/000384

CORRECTED VERSION

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

BORDEN LADNER GERVAIS LLP
World Exchange Plaza
100 Queen Street, Suite 1100
Ottawa, Ontario K1P 1J9
CANADADate of mailing (day/month/year)
17 September 2007 (17.09.2007)Applicant's or agent's file reference
PAT 3813W-90International application No.
PCT/CA2005/000384

IMPORTANT NOTIFICATION

International filing date (day/month/year)
14 March 2005 (14.03.2005)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

SIMION, Ioana
147 River Bend Road East
Edmonton, Alberta T6R 1N5
Canada

State of Nationality

CA

State of Residence

CA

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

SIMION, Ioana
147 River Bend Road East
Edmonton, Alberta T6R 1N5
Canada

State of Nationality

CA

State of Residence

CA

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person indicated above has been recorded as applicant for US only (legal representative of the deceased inventor SIMION, Dan).

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Faust Céline

Facsimile No. +41 22 338 89 95

e-mail pt04.pct@wipo.int

Telephone No. +41 22 338 74 04

Form PCT/IB/306 (October 2005)

I/DD2M6RP00

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

BRITT, Katherine
BCF LLP
1100 René-Lévesque Blvd. West
25th Floor
Montréal, Québec H3B 5C9
CANADA

Date of mailing (day/month/year)

26 September 2006 (26.09.2006)

Applicant's or agent's file reference

10680-002

IMPORTANT NOTIFICATION

International application No.

PCT/CA2005/000384

International filing date (day/month/year)

14 March 2005 (14.03.2005)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address

State of Nationality

State of Residence

SIMION, Ioana
147 River Bend Road East
Edmonton, Alberta T6R 1N5
Canada

CA

CA

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The person indicated in Box 2 has been recorded as additional applicant for all designated States (legal representative of the deceased inventor)

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Devillard Marie-José

Facsimile No. +41 22 338 82 70

Facsimile No. +41 22 338 89 95

Telephone No. +41 22 338 94 39

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 September 2006 (21.09.2006)

PCT

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(71) Applicant (for all designated States except US): **SHIRE BIOCHEM INC.** [CA/CA]; Suite 500, 2250 Alfred-Nobel Boulevard, Ville St-Laurent, Québec H4S 2C9 (CA).

(72) Inventor: **SIMION, Dan** (deceased).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **CIMPOIA, Alex** [CA/CA]; 290 Elgar, Apt. 204, Verdun, Québec H3E 1C9 (CA).

(74) Agents: **BRITT, Katherine et al.**; BCF LLP, 1100 René-Lévesque Blvd. West, 25th Floor, Montréal, Québec H3B 5C9 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

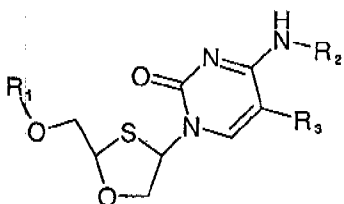
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

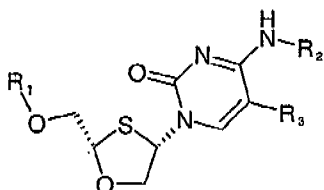
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

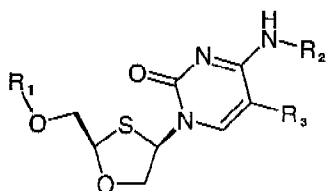
(54) Title: PROCESS AND METHODS FOR THE PREPARATION OF OPTICALLY ACTIVE CIS-2-HYDROXYMETHYL-4-(CYTOSIN-1'-YL)-1,3-OXATHIOLANE OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF



(I)



(II)



(III)

(57) Abstract: There is provided a method for resolving a compound of formula (III), in the cis configuration: There is also provided a process for producing optically active compound of formula (I) or (II): wherein: R₁, R₂, R₃ are as defined herein, the method and process involving the production, recovery and conversion of diastereomeric salts.

WO 2006/096954 A1

Process and methods for the preparation of optically active
cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane or
pharmaceutically acceptable salts thereof.

5 FIELD OF INVENTION

The present invention relates to the field of making optically active compounds, particularly the preparation of optically active oxathiolane nucleosides.

10 BACKGROUND

Classes of compounds known as 2-substituted-4-substituted-1,3-oxathiolanes have been found to have potent antiviral activity. In particular, these compounds have been found to act as potent inhibitors of HIV-1 replication in T-lymphocytes over a

15 prolonged period of time with less cytotoxic side effects than compounds known in the art. These compounds have also been found active against 3TC-resistant HIV strains. These compounds are also useful in prophylaxis and treatment of hepatitis B virus infections.

20

Cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane 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'-
25 oxa-4'-thiacytidine and Their 5-Fluoro Analogues in vitro", *J. Med. Chem.*, (1995), Vol. 38, No. 1, pp. 1-4, as well as US 6,228,860 or *Nucleosides and Nucleotides*, (1995) 14(3-5) pp. 627-735 which are incorporated herein by reference.

30 Typically, when compounds are desired as a single enantiomer they 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. A complete review of known technology
35 may be found in "Enantiomers, Racemates and Resolutions" by J. Jacques, A. Collet & S.H. Wilen (John Wiley & Sons, 1981). Alternatively, compounds or any convenient intermediate may be resolved by enzymatic resolution with a suitable enzyme such as cytidine deaminase or selective enzymatic degradation of a

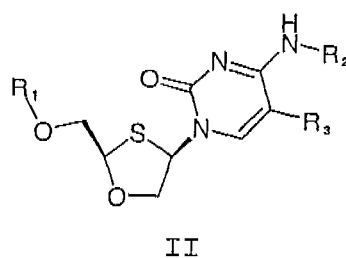
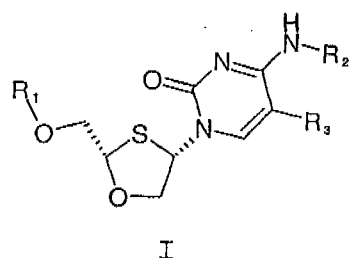
suitable derivative. See for example Storer et al., "The resolution and Absolute Stereochemistry of the Enantiomers of cis-1[2(Hydroxymethyl)-1,3-Oxathiolan-5-Yl]Cytosine (BCH-189): Equipotent Anti-HIV Agents", *Nucleosides & Nucleotides*, 12(2), 5:225-236 (1993).

Another process known as resolution by formation of diastereomeric compounds require intervention of chiral agents. Unlike enantiomers, diastereomers may have significantly different physico-chemical properties that may allow for the separation from one another. One variation of such technique involves the formation and separation of diastereomeric salts between a racemic substance and an optically active resolving acid or base. Pasteur first reported the resolution of a racemic acid using an optically active base (Pasteur, L., *C.R Acad. Sci.* (1853) 37 p.162; Pasteur, L., *Ann. Chim* (Paris) (1853) 3, 38 p. 437). A resolution using nonstoichiometric quantities of chiral agents was studied by Marckwald 1896 and later referred to as "method of half-quantity" (Marckwald, W., *Ber.* (1896), 29, p. 42; Marckwald, W., *Ber.* (1896), 29, p. 43). The process for the resolution of tartaric acid through crystallization of its salt of cinchonine was improved by Marckwald while using only half of the cinchonine necessary for formation of the tartrate salt. The resolution is based on the separation of one of the diastereomers and one of the enantiomers rather than the separation of two diastereomeric salts formed in equal quantities. When using the method of half-quantity, the racemate is partially neutralized by the optically active resolving agent. In the process described by Pope & Peachey (Pope, W.J., Peachey, S.J. *J. Chem. Soc.* (1899) 75, p.1066) the excess of racemate not neutralized by the resolving agent is neutralized by the addition of the necessary quantity of an achiral acid or base (depending on whether the resolving agent was an acid or base).

35

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a process for producing optically active compound of formula I or II:



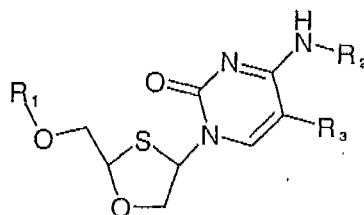
wherein:

R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl (e.g., C₇₋₁₂ arylalkyl), (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl (e.g., (CO)C₇₋₁₂ arylalkyl);

R₂ is H, C₁₋₆ alkyl or CO-R₅; wherein R₅ is H or C₁₋₆ alkyl;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or CF₃; comprising:

a) reacting a compound of formula III in the cis configuration:



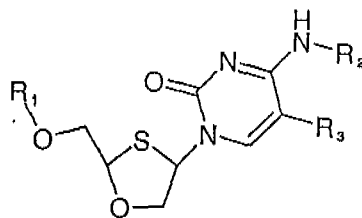
III

with a chiral acid to produce two diastereomeric salts;

b) recovering substantially one diastereomeric salt;

c) converting said one diastereomeric salt into said optically active compound.

In another aspect, there is provided a method for resolving a compound of formula III, in the cis configuration:



III

wherein:

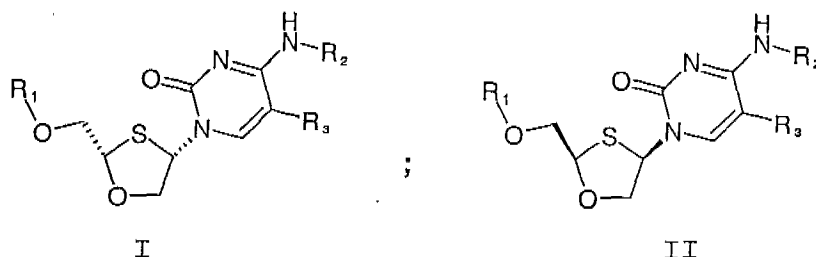
R_1 is H, C_{1-6} alkyl, C_{6-12} aryl, C_{6-12} arylalkyl (e.g., C_{7-12} arylalkyl), $(CO)C_{1-6}$ alkyl, $(CO)O-C_{1-6}$ alkyl, $(CO)O-C_{6-12}$ aryl, or $(CO)-C_{6-12}$ arylalkyl (e.g., $(CO)C_{7-12}$ arylalkyl);

R_2 is chosen from H, C_{1-6} alkyl, C_{1-6} acyl and $CO-R_5$;

5 wherein R_5 is H or C_{1-6} alkyl;

R_3 is H, C_{1-6} alkyl, bromide, chloride, fluoride, iodide or CF_3 ; comprising:

- a) reacting said compound of formula III with a chiral acid to produce two diastereomeric salts;
- 10 b) recovering substantially one diastereomeric salt;
- c) converting said one diastereomeric salt into compound of formula I or II:



15

In a further aspect, the present invention provides a process for producing optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:

- a) reacting a chiral acid with cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane to produce two diastereomeric salts;
- 20 b) recovering substantially one diastereomeric salt;
- c) converting said one diastereomeric salt into said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

25

In still a further aspect, there is provided a process for producing (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane comprising:

- a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a half quantity molar amount of a chiral acid to substantially produce (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt, said molar ratio being with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane;
- 30

- In still a further aspect, there is provided a process for producing optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:

- In a further aspect, the present invention further provides novel cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane salts.

Accordingly, the present invention relates to a process for producing optically active compound of formula I or II:

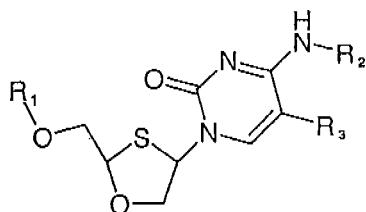


R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl (e.g., C₇₋₁₂ arylalkyl), (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl (e.g., (CO)C₇₋₁₂ arylalkyl);

wherein R₅ is H or C₁₋₆ alkyl;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or CF₃; comprising:

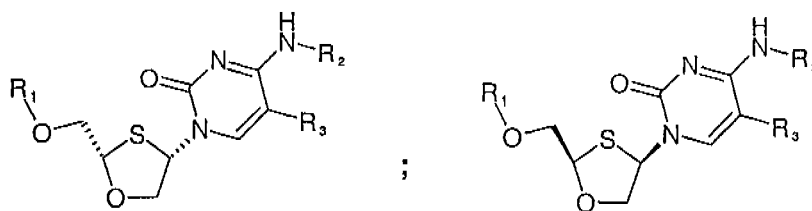
- a) reacting a compound of formula III in the cis configuration:



III

- 5 with a chiral acid to produce two diastereomeric salts;
 b) recovering substantially one diastereomeric salt;
 c) converting said one diastereomeric salt into said optically active compound.
- 10 The scope the present invention includes a process as described above wherein the over-all yield of the desired enantiomer is equal to or greater than 25% (100g of racemate would produce at least 25g of the desired enantiomer).
- 15 An embodiment of the present invention relates to a process which generates a final product which is substantially in the form of a single enantiomer. Additionally, an embodiment of the present invention includes a process described above which results in a product having an enantiomeric excess of 99% or
- 20 higher.

An embodiment of the present invention relates to a process for producing optically active compound of formula I or II:



I

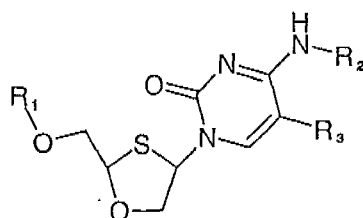
II

25

wherein: R_1 , R_2 , R_3 are as defined above, comprising:

- a) reacting a compound of formula III in the cis configuration:

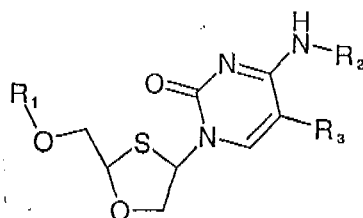
14



III

- with a chiral acid to produce two diastereomeric salts;
- b) recovering substantially one diastereomeric salt;
- 5 c) converting said one diastereomeric salt into said optically active compound.

There is also provided a method for resolving a compound of formula III, in the cis configuration:

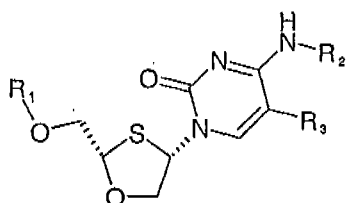


III

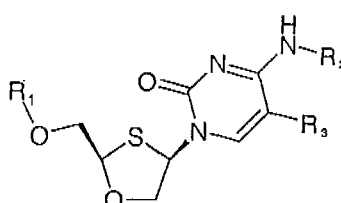
10

wherein: R_1 , R_2 , R_3 are as defined above, comprising:

- a) reacting said compound of formula III with a chiral acid to produce two diastereomeric salts;
- 15 b) recovering substantially one diastereomeric salt;
- c) converting said one diastereomeric salt into a compound of formula I or II:



I



II

20

In one embodiment, R_1 is H, C_{1-6} alkyl, $(CO)C_{1-6}$ alkyl, $(CO)O-C_{1-6}$ alkyl or $(CO)C_{6-12}$ aryl.

In further embodiments:

- 25 R_1 is H, $(CO)C_{1-6}$ alkyl or $(CO)C_{6-12}$ aryl,
- R_1 is H,

R_1 is (CO)C₆₋₁₂ aryl.

Still in further embodiments:

R_2 is H or C₁₋₆ alkyl,

R_2 is CO- R_5 , wherein R_5 is H or C₁₋₆ alkyl,

5 R_2 is formyl or acetyl.

In one embodiment, R_3 is H, C₁₋₆ alkyl or fluoride.

In further embodiments:

R_3 is H or fluoride,

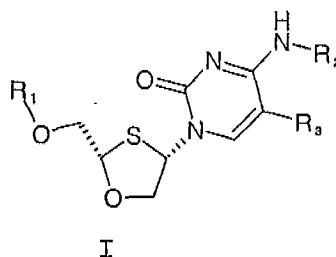
10 R_3 is H,

R_3 is fluoride.

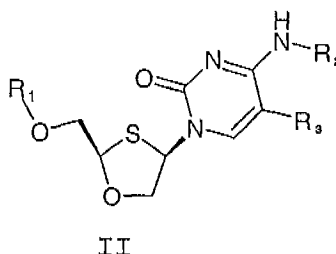
In one embodiment, the chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.

In one embodiment, the chiral acid is (1R)-(-)-10-camphorsulfonic acid.

20 In another embodiment, the optically active compound is



In another embodiment, the optically active compound is



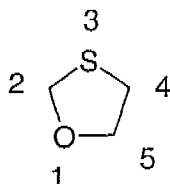
25

In one embodiment, the two diastereomeric salts comprise a first more soluble diastereomeric salt and a second less soluble diastereomeric salt.

30

In one embodiment, said enantiomeric salt is (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane hydrochloric acid salt.

- 5 An "oxathiolane ring" is any substituted or unsubstituted five member monocyclic ring that has an oxygen atom in position 1 and a sulfur atom in position 3 of the ring as illustrated below:



- 10 It will be apparent to a skilled person in the field that the reaction conditions described in these examples may be modified and still achieve successful results.

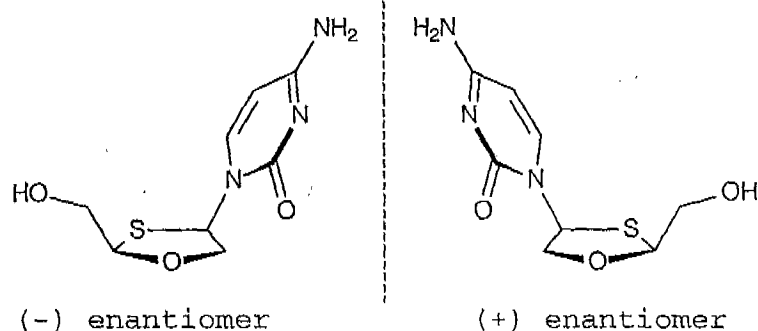
Typically, solvents, temperature and time of reaction may be varied. A suitable solvent will allow the process to occur under the reaction conditions without adversely affecting the reaction. The solvent may be one or more solvents and may be organic (e.g., methanol, ethanol, propanol, isopropanol, dichloromethane, dichloroethane, tetrahydrofuran, hexane, pentane, ether spirit, ethyl ether), water or aqueous/organic (e.g., methanol-water, isopropanol-water). The solvents may also be present in various ratios (for example 1:1, 2:1, 5:1, 10:1 or 1:1:1, 1:2:1).

- 25 The temperature may be varied and will allow the process to occur under the reaction conditions. The suitable temperature will provide the desired product without adversely affecting the reaction.
- 30 It will be appreciated by a person of skill in the art that a suitable period of time is a time for obtaining a sufficient chemical transformation of the starting material, obtaining the desired purity or the desired yield of the reaction product or

a combination of those. The reaction can typically be monitored, if desired, by thin layer chromatography, light absorption (e.g., U.V.) of reaction medium, gas chromatography or high performance liquid chromatography (HPLC).

5

Cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane exist as enantiomers which may be in various ratios.



- 10 For example the enantiomers may be present as racemate (i.e. in equal proportions) or any alternative ratio of the enantiomers such as for example 1:1, 2:1, 5:1, 10:1, 100:1 or 1:2, 1:5, 1:10, 1:100. References hereinafter to cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane according to the invention
- 15 includes all such possible ratios of enantiomers.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

- 20 All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not
- 25 intended to be limiting.

- As used in this application, the term "alkyl" represents a straight chain or branched chain hydrocarbon moiety which may optionally be substituted by one or more of halogen, nitro,
- 30 nitroso, sulfate, sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl (e.g., C₇₋₁₂

aralkyl), C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl (e.g., C(O)C₇₋₁₂ aralkyl), heterocycle having 3-10 ring-members, hydroxyl, amino, ester, cyano, azido, amidino or guanido. Useful examples of alkyl include isopropyl, propyl, ethyl, methyl, hexyl or cyclopropyl, which in each case is unsubstituted or substituted one or more times by, for example, halogen, nitro, nitroso, sulfate, sulfonate, amide, hydroxyl, amino, ester, cyano, azido, amidino or guanido. The term alkyl is also meant to include alkyl in which one or more hydrogen atoms are each replaced by a halogen, preferably fluoro (e.g., CF₃- or CF₃CH₂-).

The term "aryl" represents a carbocyclic moiety containing at least one benzenoid-type ring which may optionally be substituted by one or more of halogen, nitro, nitroso, sulfate, sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl, heterocycle having 3-10 ring-members, hydroxyl, amino, ester, cyano, azido, amidino or guanido. Examples of aryl include phenyl and naphthyl, which in each case is unsubstituted or substituted one or more times by, for example, halogen, nitro, nitroso, sulfate, sulfonate, amide, hydroxyl, amino, ester, cyano, azido, amidino or guanido.

The term "aralkyl" represents an aryl group attached to the adjacent atom by an alkyl. Useful examples include benzyl which is unsubstituted or substituted one or more times by, for example, halogen, nitro, nitroso, sulfate, sulfonate, amide, hydroxyl, amino, ester, cyano, azido, amidino or guanido.

The term "heterocycle" represents a saturated or unsaturated, cyclic moiety wherein said cyclic moiety is interrupted by at least one heteroatom, (e.g., oxygen, sulfur or nitrogen) which may optionally be substituted by one or more of halogen, nitro, nitroso, sulfate, sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl,

24
27

C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl, hydroxyl, amino, ester, cyano, azido, amidino or guanido. It is understood that the term heterocyclic ring represents a mono or polycyclic (e.g., bicyclic) ring. Examples of heterocyclic rings include but are not limited to epoxide; furan; benzofuran; isobenzofuran; oxathiolane; dithiolane; dioxolane; pyrrole; pyrrolidine; imidazole; pyridine; pyrimidine; indole; piperidine; morpholine; thiophene and thiomorpholine, which in each case is unsubstituted or substituted one or more times by, for example, halogen, nitro, nitroso, sulfate, sulfonate, amide, hydroxyl, amino, ester, cyano, azido, amidino or guanido.

The term "independently" means that a substituent can be the same or different definition for each item.

The term "optically active" means that the enantiomeric excess is greater than zero.

The optical purity is numerically equivalent to the "enantiomeric excess". The term "enantiomeric excess" or "ee" is defined in percentage (%) value as follows: [mole fraction (major enantiomer) - mole fraction (minor enantiomer)] x 100. (for example, an ee of 99% represent a ratio of 99.5% of one enantiomer and 0.5% of the opposite enantiomer).

The term "chiral acid" means an optically active acidic compound able to form a diastereomer with a compound of formula III, such as 2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane. Examples of such acids include without limitation: tartaric acid, O,O'-dibenzoyltartaric acid, O,O'-di-p-toluoyltartaric acid, 2-nitrotartranilic acid, mandelic acid, malic acid, 2-phenoxypropionic acid, 10-camphorsulfonic acid, hydratropic acid, N-acetylleucine, N-(α -methylbenzyl)succinamic acid, N-(α -methylbenzyl)phthamic acid, 3-bromocamphor-9-sulfonic acid, camphor-3-sulfonic acid, quinic acid, di-O-isopropylidene-2-oxo-L-gulonic acid, lasalocid, 1,1'-binaphthyl-2,2/-phosphoric acid, cholestenonesulfonic acid. Further examples include (1R)-

(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid and (-)-L-malic acid.

A person of ordinary skill will understand that the term
5 "achiral acid" includes a variety of acids such as inorganic acids (e.g., HCl, HBr, H₂SO₄, HBF₄); sulfonic acids (e.g., methanesulfonic, benzenesulfonic, p-toluenesulfonic, p-hydroxytoluenesulfonic, sulfanilic, p-chlorobenzenesulfonic); substituted acetic acids (e.g., glycolic, chloro-, dichloro-,
10 trichloroacetic); polycarboxylic and oxy acids (e.g., succinic, adipic, maleic, fumaric, citric, pyruvic).

There are also provided pharmaceutically acceptable salts of the compounds of the present invention. By the term
15 "pharmaceutically acceptable salts" is meant salts derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycollic, lactic, salicylic, succinic,
20 toluene-p-sulphonic, tartaric, acetic, trifluoroacetic, citric, methanesulphonic, formic, benzoic, malonic, naphthalene-2-sulphonic, cysteic acid and benzenesulphonic acids. Other acids such as oxalic, while not themselves pharmaceutically acceptable, may be useful as intermediates in
25 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 NR₄⁺ (where R is C₁₋₄ alkyl) salts.

30 References hereinafter to a compound according to the invention include the compound and its pharmaceutically acceptable salts.

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35

In one aspect, the present invention provides novel compounds as described in table 1:

TABLE 1

	(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonate
	(+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonate
	(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1S)-(+)-10-camphorsulfonate
	(+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1S)-(+)-10-camphorsulfonate

5.

In one embodiment, the process and method of the present invention comprises those wherein the following embodiments are present, either independently or in combination.

10 The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

EXAMPLES

15

The following examples are provided to illustrate various embodiments of the present invention and shall not be considered as limiting in scope.

Example 1: Screening of chiral resolving agents

Experimental conditions:

100 mg of cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane
5 is combined with 1 equivalent of the resolving agent, in 1 ml
of solvent (95% ethanol- 5% water). The solid is isolated and
weighed. A significant test requires that the weight of
crystals does not exceed 50% of the overall diastereomer
amount. If this condition is not fulfilled the amount or type
10 of solvent is changed.

TABLE 2

Chiral Resolving Agent	No crystal Observed	Crystal Observed
(-)-L-Malic acid		x
(-)-L-Lactic acid	X (oil)	
(+)-L-Tartaric acid		x
(-)-2,3-Dibenzoyl-L-Tartaric acid		x
(1R)-(-)-10-Camphorsulfonic acid		x

15 Example 2: Resolution experimentationsGeneral experimental conditions:

cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, and a
chiral acid were dissolved with stirring in a solvent at a
20 temperature of about room temperature to about 50 °C and then
cooled at a temperature of between about room temperature to -
10°C for 2-4 hours. The solid product was collected by
filtration. The composition was determined by Chiral HPLC, the
aqueous buffer was prepared by diluting 0.5 ml triethylamine in
25 1L HPLC water, the pH adjusted to 6.88 with glacial acetic
acid,. The mobile phase was prepared by combining the aqueous
buffer and methanol in a ratio of 90:10 and the gas was
removed. The following conditions were used:

Column: Astec Cyclobond I 2000 RSP, 5 micron, 250 x 4.5 mm.

Guard column: Astec Cyclobond I 2000 RSP, 20 x 4.0 mm

Flow: 0.6 ml/min.

- 5 Sample preparation: prepare solution of 0.5 mg/ml in mobile phase.

Injection volume: 5 μ L.

Mode: isocratic.

UV-Vis detector at: 270 nm.

- 10 Column temperature: 0°C.

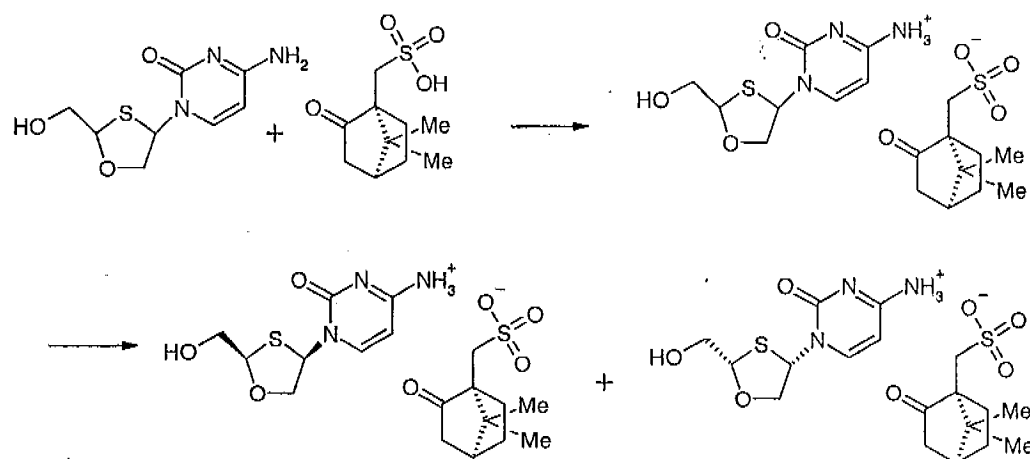
Run time: 40 min.

TABLE 3

	Chiral resolving agent/ achiral acid	Solvent	Experimental Conditions	Enantiomeric Ratio (yield %)
1	L-tartaric acid (0.5 eq)/ HCl (0.5eq.)	Isopropyl alcohol and water 1:1 (v/v)	100g scale. Magnetic stirring.	45.2:52.1 (63%)
2	(R)- Camphorsulfonic Acid (0.5 eq)/ HCl (0.5eq.)	Isopropyl alcohol and water 1:1 (v/v)	5g scale. Heated @50°C to dissolve solids Magnetic stirring	92.4:7.6 (36%)
3	(-)-2,3-Dibenzoyl-L-Tartaric acid (0.25eq)/ HCl (0.5eq.)	Water	5g scale. Magnetic stirring	47.6:45.7 (41.7%)
4	(R)- Camphorsulfonic Acid (0.5 eq)/ HCl (0.5eq.)	Isopropyl alcohol and water 1:1 (v/v)	25g scale. Mechanical stirring	90.9:9.1 (52.6%)
5	(R)- Camphorsulfonic Acid (0.5 eq)/ HCl (0.5eq.)	Water Methanol 17% water in methanol (v/v)	5g scale. Heated at reflux. Magnetic stirring	78.7:21.3 (72%)
6	(R)- Camphorsulfonic Acid (1 eq)/ no achiral acid	Isopropyl alcohol and water 1:1 (v/v)	5g scale. Heated @50°C to dissolve solids Magnetic stirring	53.6:46.4 (60.6%)

Scheme 1

5



10

Example 3: Diastereomeric salt optical resolution of cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane (1.03g, 15 4.3 mmol), and (1R)-(-)-10-Camphorsulfonic acid (1.03g, 4.3 mmol) were dissolved in 32 mL of a 1:1 isopropyl alcohol and water (v/v) at 50 °C. The solution was cooled at 0 °C. The solid was filtered to provide 0.55g of dry crystals. The diastereomeric composition was determined by HPLC to be 87:13 20 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt : (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt)].

25 The mother liquor was concentrated to dryness giving 1.38 g of dry solids with a diastereomeric composition of 35:65 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt : (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt)]. The 30 composition was analyzed as shown in Example 2.

Example 4: Recrystallization to increase the diastereomeric ratio of (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt with regard to (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-Camphorsulfonic salt.

The crude cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonate salt generated in entry 4 of table 3 in example 2 having an enantiomeric ratio of 90.9: 9.1 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt : (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt] was dissolved in isopropyl alcohol-water 1:1 (v/v) at 70°C. After cooling, the crystals were recovered with a yield of 76% and an enantiomeric ratio of 99.1: 0.9 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt : (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt].

20

Example 5: Kilogram-scale Diastereomeric salt optical resolution

A mixture of isopropanol (2274 kg), distilled water (2905 kg), cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane (193.7 kg) were introduced into the reactor (model R06 5700L GLMS). Dilute hydrochloric acid (prepared as 41.57 kg in 380 kg of water) was introduced followed by (1R)-(-)-10-camphorsulfonic acid (100 kg). The temperature of the resulting slurry was adjusted to 50 °C and agitated until all solid dissolved. The solution was then cooled to about -10°C (-13°C to -7°C) and agitated for 4-6 hours.

The resulting slurry is filtered, rinsing forward with 60 L of 1:1 isopropyl alcohol and water (v/v). The product is pulled dry with enantiomeric ratio of 91:9 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic

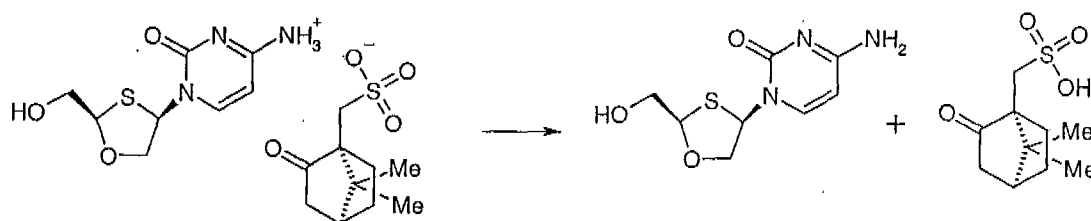
salt : (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt)].

Isopropanol (228 kg) and water (291 kg) are added to the wet crude product then the temperature of the resulting solution was adjusted to 70°C and agitated until all solid dissolved the slurry is heated and agitated until all the solids dissolve. The solution is then cooled to about 22°C (19°C to 25°C) and then to 0°C (-3°C to 3°C).

10

The resulting slurry is filtered, rinsing forward with two portions of 70 L of 1:1 isopropyl alcohol and water (v/v). The product is spin-dried until the flow of filtrate essentially stops. 90.8 kg of product recovered (87% yield, corrected for loss on dryness of a sample) with an enantiomeric purity higher than 98%.

20 Scheme 2



Example 6: (1R)-(-)-10-camphorsulfonic acid removal from (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt

5

(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-Camphorsulfonic salt (90.8 kg) is dissolved in methanol (601 kg) by heating the mixture at 40°C and agitating until a solution is achieved.

10

The warm solution is circulated through an ion exchange column containing Dowex® Marathon A-OH (133.6 kg) and methanol (200 kg) of while maintaining the temperature at 40°C until no residual camphorsulfonic acid is detected by NMR analysis and
15 pH is greater than 7 (measured using water-wet pH paper).

The eluent is filtered, rinsing forward with methanol (200 kg).

The filtrate is partially concentrated under vacuum to about
20 140L.

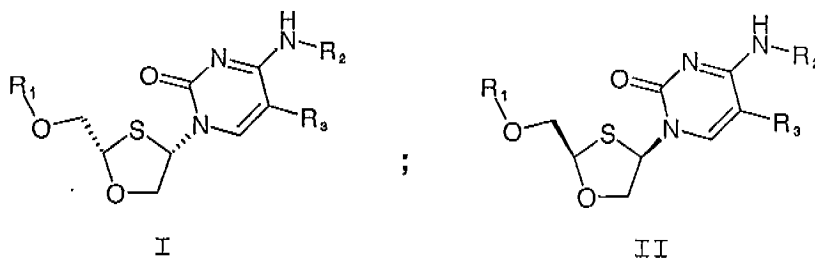
The concentrate is cooled to about -10°C for one hour and agitated. The resulting slurry is filtered, rinsing forward with 2 portions of 18 kg of cold methanol (-10°C). The product
25 is dried under vacuum while heating to 35-40°C.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for
30 those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope
35 thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

We Claims:

1. A process for producing an optically active compound of
5 formula I or II;



wherein:

10 R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl, (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl;

R_2 is H, C_{1-6} alkyl or $CO-R_5$;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or CF₃; and

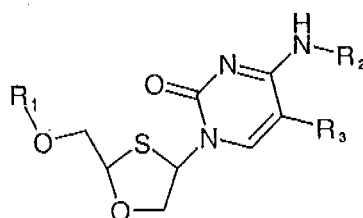
R₅ is H or C₁₋₆ alkyl;

15 wherein in the definitions of R₁, R₂, R₃, and R₅ "alkyl" is,
in each case, unsubstituted or substituted by one or more
of halogen, nitro, nitroso, sulfate, sulfate ester,
sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆
alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy,
20 C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl,
heterocycle having 3-10 ring-members, hydroxyl, amino,
ester, cyano, azido, amidino or guanido; and

in the definitions of R₁, R₂, R₃, and R₅ "aryl" is, in each case, unsubstituted or substituted by one or more of
25 halogen, nitro, nitroso, sulfate, sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl, heterocycle having 3-10 ring-members, hydroxyl, amino,
30 ester, cyano, azido, amidino or guanido;

said process comprising:

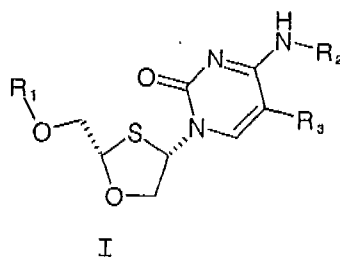
- a) reacting a compound of formula III in the cis configuration:



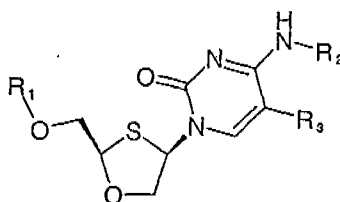
III

- 5 with a chiral acid to produce two diastereomeric salts;
 - b) recovering substantially one diastereomeric salt;
 - c) converting said one diastereomeric salt into said optically active compound.
- 10 2. A process according to claim 1, wherein
 - R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl, (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl;
 - R₂ is H, C₁₋₆ alkyl or CO-R₅;
 - 15 R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or CF₃; and
 - R₅ is H or C₁₋₆ alkyl.
 3. A process according to claim 1, wherein R₁ is H, C₁₋₆ alkyl,
 20 (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl or (CO)C₆₋₁₂ aryl.
 4. A process according to claim 1, wherein R₁ is H, (CO)C₁₋₆ alkyl or (CO)C₆₋₁₂ aryl.
 - 25 5. A process according to claim 1, wherein R₁ is H.
 6. A process according to claim 1, wherein R₁ is (CO)C₆₋₁₂ aryl.
 7. A process according to claim 1, wherein R₂ is H or C₁₋₆
 30 alkyl.
 8. A process according to claim 1, wherein R₂ is CO-R₅, wherein R₅ is H or C₁₋₆ alkyl.

9. A process according to claim 1, wherein R_2 is formyl or acetyl.
- 5 10. A process according to claim 1, wherein R_3 is H, C_{1-6} alkyl or fluoride.
11. A process according to claim 1, wherein R_3 is H or fluoride.
- 10 12. A process according to claim 1, wherein R_3 is H.
13. A process according to claim 1, wherein R_3 is fluoride.
- 15 14. A process according to anyone of claims 1 to 13, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.
- 20 15. A process according to anyone of claims 1 to 13, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.
16. A process according to claim 1, wherein said optically active compound is



- 25 17. A process according to claim 1, wherein said optically active compound is

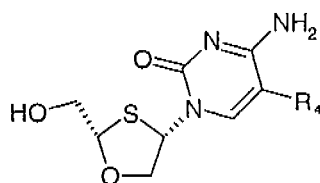


II

18. A process according to anyone of claims 1 to 17, wherein
 said two diastereomeric salts comprise a first more
 5 soluble diastereomeric salt and a second less soluble
 diastereomeric salt.

19. A process according to anyone of claims 1 to 17, wherein
 said step b) further comprise recovering a second
 10 diastereomeric salt.

20. A process for producing optically active compound of
 formula IV:

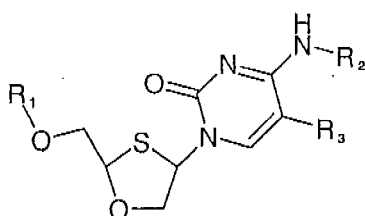


IV

wherein:

R₄ is H or fluoride; comprising:

a) reacting a compound of formula III in the cis
 configuration:



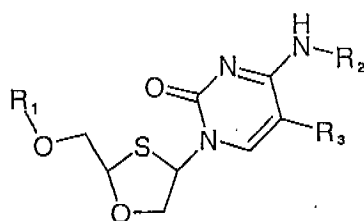
III

with a chiral acid selected from (1R)-(-)-10-
 camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid,
 (+)-L-tartaric acid or (-)-L-malic acid, to produce two
 25 diastereomeric salts;

b) recovering substantially one diastereomeric salt;

c) converting said one diastereomeric salt into said
 optically active compound.

30 21. A method for resolving a compound of formula III, in the
 cis configuration:



III

wherein:

R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl, (CO)C₁₋₆ alkyl,
 5 (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl;

R₂ is H, C₁₋₆ alkyl or CO-R₅;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or
 CF₃; and

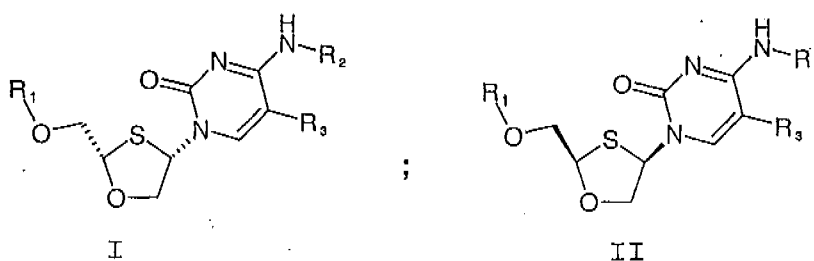
R₅ is H or C₁₋₆ alkyl;

10 wherein "alkyl," in each case, is unsubstituted or
 substituted by one or more of halogen, nitro, nitroso,
 sulfate, sulfate ester, sulfonate, sulfonate ester,
 phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂
 aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂
 15 aryl, C(O)C₆₋₁₂ aralkyl, heterocycle having 3-10 ring-
 members, hydroxyl, amino, ester, cyano, azido, amidino or
 guanido; and

"aryl," in each case, is unsubstituted or substituted by
 one or more of halogen, nitro, nitroso, sulfate, sulfate
 20 ester, sulfonate, sulfonate ester, phosphonate ester,
 amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy,
 C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂
 aralkyl, heterocycle having 3-10 ring-members, hydroxyl,
 amino, ester, cyano, azido, amidino or guanido;

25 said process comprising:

- a) reacting said compound of formula III with a
 chiral acid to produce two diastereomeric salts;
- b) recovering substantially one diastereomeric salt;
- 30 c) converting said one diastereomeric salt into
 compound of formula I or II:



22. A method according to claim 21, wherein R_1 is H, C_{1-6} alkyl,
5 (CO) C_{1-6} alkyl, (CO)O- C_{1-6} alkyl or (CO) C_{6-12} aryl.
23. A method according to claim 21, wherein R_1 is H, (CO) C_{1-6}
alkyl or (CO) C_{6-12} aryl.
- 10 24. A method according to claim 21, wherein R_1 is H.
25. A method according to claim 21, wherein R_1 is (CO) C_{6-12}
aryl.
- 15 26. A method according to claim 21, wherein R_2 is H or C_{1-6}
alkyl.
27. A method according to claim 21, wherein R_2 is CO- R_5 ,
wherein R_5 is H or C_{1-6} alkyl.
- 20 28. A method according to claim 21, wherein R_2 is formyl or
acetyl.
29. A method according to claim 21, wherein R_3 is H, C_{1-6} alkyl
25 or fluoride.
30. A method according to claim 21, wherein R_3 is H or
fluoride.
31. A method according to claim 21, wherein R_3 is H.
- 30 32. A method according to claim 21, wherein R_3 is fluoride.

33. A method according to claim 21, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.
- 5 34. A method according to claim 21, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.
- 10 35. A method according to anyone of claims 21 to 34, wherein said two diastereomeric salts comprise a first more soluble diastereomeric salt and a second less soluble diastereomeric salt.
- 15 36. A method according to anyone of claims 21 to 34, wherein said step b) further comprise recovering a second diastereomeric salt.
- 20 37. A process for producing optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:
a) reacting a chiral acid with cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane to produce two diastereomeric salts;
b) recovering substantially one diastereomeric salt;
c) converting said one diastereomeric salt into said
25 optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.
- 30 38. A process according to claim 37, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is crystalline.
- 35 39. A process according to anyone of claims 37 to 38, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is (-) enantiomer.
40. A process according to anyone of claims 37 to 38, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is (+) enantiomer.

41. A process according to anyone of claims 37 to 40, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.
- 5
42. A method according to anyone of claims 37 to 40, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.
43. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 60% or higher.
- 10
44. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 70% or higher.
- 15
45. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 80% or higher.
- 20
46. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 90% or higher.
- 25
47. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 95% or higher.
- 30
48. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 98% or higher.
- 35
49. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 99% or higher.
- 40

yl)-1,3-oxathiolane has an enantiomeric excess of 99% or higher.

50. A process for producing (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt, comprising:
- a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a chiral acid to produce (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt and (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid salt;
- b) recovering said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt.
51. A process according to claim 50, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.
52. A method according to claim 50, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.
53. A process according to anyone of claims 50 to 52, wherein said step b) further comprise recovering (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt.
54. A process according to anyone of claims 50 to 52, wherein said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt contains less than 30% of (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid addition salt.
55. A process according to anyone of claims 50 to 52, wherein said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt contains less than 20% of (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid addition salt.
56. A process according to anyone of claims 50 to 52, wherein said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-

oxathiolane.chiral acid salt contains less than 10% of
(+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral resolving acid addition salt.

- 5 57. A process according to anyone of claims 50 to 52, wherein
said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral acid salt contains less than 5% of (+)-
cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral resolving acid addition salt.
- 10 58. A process according to anyone of claims 50 to 52, wherein
said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral acid salt contains less than 1% of (+)-
cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
15 oxathiolane.chiral resolving acid addition salt.
59. A process according to anyone of claims 50 to 52, wherein
said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral acid salt is substantially free of (+)-
20 cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral resolving acid addition salt.
60. A process according to anyone of claims 50 to 59, further
comprising recrystallizing said (-)-cis-2-hydroxymethyl-4-
25 (cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid
addition salt.
61. A process according to anyone of claims 50 to 59, wherein
said chiral acid is in stoichiometric molar ratio with
30 regard cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.
62. A process according to anyone of claims 50 to 59, wherein
said chiral acid is in nonstoichiometric molar ratio with
35 regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.
63. A process for producing (-)-cis-2-hydroxymethyl-4-
(cytosin-1'-yl)-1,3-oxathiolane comprising:

- 44
- 5 a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a half quantity molar amount of a chiral acid to substantially produce (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt, said molar ratio being with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane;
- 10 b) recovering said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt;
- c) converting said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt into said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

- 15 64. A process according to claim 62, wherein said step a) further comprise adding a half-quantity molar amount of achiral acid to substantially produce (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.achiral acid salt, said molar ratio being with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

- 20 65. A process according to anyone of claims 63 to 64, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.

- 25 66. A process according to anyone of claims 63 to 64, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.

67. A process according to anyone of claims 63 to 66, wherein said achiral acid is hydrochloric acid.

- 30 68. A process for producing crystalline optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:

- 35 a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a chiral acid and an achiral acid to produce substantially one diastereomeric salt and substantially one enantiomeric salt;
- b) recovering said diastereomeric salt;

c) converting said diastereomeric salt into optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

- 5 69. A process according to claim 68, wherein said chiral salt
is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-
tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.
- 10 70. A process according to claim 68, wherein said chiral acid
is (1R)-(-)-10-camphorsulfonic acid.
- 15 71. A process according to claim 68, wherein said
diastereomeric salt is (-)-cis-2-hydroxymethyl-4-(cytosin-
1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonate.
- 20 72. A compound selected from:
(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.(1R)-(-)-10-camphorsulfonate;
(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.(1S)-(+)-10-camphorsulfonate;
(+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.(1R)-(-)-10-camphorsulfonate; or
(+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.(1S)-(+)-10-camphorsulfonate.
- 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/000384

A. CLASSIFICATION OF SUBJECT MATTER IPC(7): C07D 411/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(7): C07D 411/04; US: 544/317

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Delphion: (IPC(7): C07D 411/04; US: 544/317 and oxathiolan*); Canadian Patent Database: (IPC(7): C07D 411/04); STN: Structure search based on formula (III)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Tetrahedron Letters, 1994, 35 (27), 4739-4742 (WANG, W. et al.) (BIOCHEM THERAPEUTIC INC.), 4 July 1994 (04-07-1994) *see whole document*	
A	Bioorg. Med. Chem. Let., 1993, 3(8), 1723-1728 (BELLEAU, B. et al.) (BIOCHEM PHARMA INC.) August 1993 (08-1993) *see whole document*	
A	CA 2188283 A (MANSOUR, T. S. et al.) (BIOCHEM PHARMA INC.) 02.November 1995 (02-11-1995) *see pages 5-13, 23-48 and claims 1-6* cited in the application as US 6228860	
A	CA 2095613 A (BELLEAU, B. et al.) (BIOCHEM PHARMA INC.) 14 May 1992 (14-05-1992) *see pages 5-6, 38 and claims 1-4, 6-7, 9-10, 12, 20-23*	

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"P" document published prior to the international filing date but later than the priority date claimed	

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Karla Randell (819) 956-6118

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/CA2005/000384

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2188283	02-11-1995	AT143016T T	15-10-1996
		AT214066T T	15-03-2002
		AT275144T T	15-09-2004
		AU693884 B2	09-07-1998
		AU2211895 A	16-11-1995
		AU8864191 A	11-06-1992
		CA2095613 A1	14-05-1992
		DE69122264D D1	24-10-1996
		DE69122264T T2	06-02-1997
		DE69525742D D1	11-04-2002
		DE69525742T T2	26-09-2002
		DE69533458D D1	07-10-2004
		DK560794T T3	23-12-1996
		DK756595T T3	17-06-2002
		DK1153924T T3	27-12-2004
		DK1224940T T3	27-12-2004
		EP0560794 A1	22-09-1993
		EP0756595 A1	05-02-1997
		EP1153924 A2	14-11-2001
		EP1473294 A2	03-11-2004
		ES2091948T T3	16-11-1996
		ES2172580T T3	01-10-2002
		ES2228714T T3	16-04-2005
		GR3021074T T3	31-12-1996
		HK12597 A	14-02-1997
		HK1005544 A1	07-06-2002
		HK1041487 A1	07-01-2005
		JP2960164B2 B2	06-10-1999
		JP6504266T T	19-05-1994
		JP9512526T T	16-12-1997
		PT756595T T	30-08-2002
		US5587480 A	24-12-1996
		US6228860 B1	08-05-2001
		US6369066 B1	09-04-2002
		WO9208717 A1	29-05-1992
		WO9529176 A1	02-11-1995
CA2095613	14-05-1992	AT143016T T	15-10-1996
		AT214066T T	15-03-2002
		AT275144T T	15-09-2004
		AU693884 B2	09-07-1998
		AU2211895 A	16-11-1995
		AU8864191 A	11-06-1992
		CA2188283 A1	02-11-1995
		DE69122264D D1	24-10-1996
		DE69122264T T2	06-02-1997
		DE69525742D D1	11-04-2002
		DE69525742T T2	26-09-2002
		DE69533458D D1	07-10-2004
		DK560794T T3	23-12-1996
		DK756595T T3	17-06-2002
		DK1153924T T3	27-12-2004
		DK1224940T T3	27-12-2004
		EP0560794 A1	22-09-1993
		EP0756595 A1	05-02-1997
		EP1153924 A2	14-11-2001
		EP1473294 A2	03-11-2004
		ES2091948T T3	16-11-1996
		ES2172580T T3	01-10-2002
		ES2228714T T3	16-04-2005
		GR3021074T T3	31-12-1996
		HK12597 A	14-02-1997
		HK1005544 A1	07-06-2002
		HK1041487 A1	07-01-2005

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/000384

JP2960164B2 B2	06-10-1999
JP6504266T T	19-05-1994
JP9512526T T	16-12-1997
PT756595T T	30-08-2002
US5587480 A	24-12-1996
US6228860 B1	08-05-2001
US6369066 B1	09-04-2002
WO9208717 A1	29-05-1992
WO9529176 A1	02-11-1995

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- (71) Solicitante (para todos los estados designados excepto US): SHIRE BIOCHEM INC. [CA/CA]; Suite 500, 2250 Alfred-Nobel Boulevard, Ville St-Laurent, Québec H4S 2C9 (CA).
- (72) Inventor: SIMION, Dan (fallecido)
- (72) Inventores; e
- (75) Inventores/solicitantes (solo para EU): CIMPOIA, Alex [CA/CA]; 290 Elgar, Apt. 204, Verdun, Québec H3E 1C9 (CA).
- (74) Agentes: BRITT, Katherine et al; BCF LLP, 1100 René Lévesque Blvd. West, 25th Floor, Montréal, Québec H3B 5C9 (CA).

(81) Estados Designados (a menos que se indique lo contrario, para todo tipo de protección nacional disponible): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

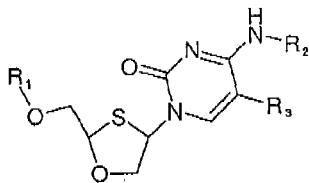
(84) Estados Designados (a menos que se indique lo contrario, para todo tipo de protección regional disponible): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:

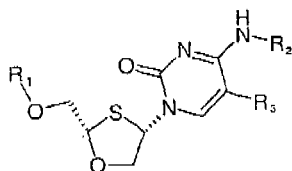
— con el informe de búsqueda internacional

Para códigos de dos letras y otras abreviaciones, referirse a las "Notas de guía sobre Códigos y Abreviaturas" que aparecen al comienzo de cada edición de la Gaceta del PCT

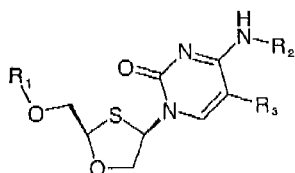
(54) Título: PROCESOS Y MÉTODOS PARA LA PREPARACIÓN DE CIS-2-HIDROXIMETIL-4-(CITOSIN-1-IL)-1,3-OXATOLANO OPTICAMENTE ACTIVAS O SALES ACEPTABLES FARMACÉUTICAMENTE DEL MISMO.



(I)



(II)



(III)

(57) Resumen: Se proporciona un método para resolver un compuesto de fórmula (III), en la configuración cis: También se proporciona un proceso para producir un compuesto ópticamente activo de fórmula (I) o (II): donde: R1, R2, R3 se definen aquí, el método y proceso que involucran la producción, recuperación y conversión de sales diastereoméricas.

PROCESOS Y MÉTODOS PARA LA PREPARACIÓN DE CIS-2-HIDROXIMETIL-4-(CITOSIN-1-IL)-1,3-OXATIOLOANO OPTICAMENTE ACTIVAS O SALES

ACEPTABLES FARMACÉUTICAMENTE DEL MISMO

CAMPO DE LA INVENCION

5 La presente invención es concerniente con el campo de fabricación de compuestos ópticamente activos, particularmente la preparación de nucleósidos de oxatiolano ópticamente activos.

ANTECEDENTES DE LA INVENCION

10

Se ha encontrado que las clases de compuestos conocidos como 1,3-oxatíolanos 2-sustituídos-4-sustituídos tienen potente actividad antiviral. En particular, se ha encontrado que estos compuestos actúan como potentes inhibidores de replicación de HIV-1 en T-linfocitos en un período de tiempo prolongado con menos efectos secundarios citotóxicos que los compuestos conocidos en el arte. También se ha encontrado que estos compuestos son activos contra cepas de HIV 3TC-resistentes. Estos compuestos también son útiles en profilaxis y tratamiento de infecciones de virus de hepatitis B.

20

El cis-2-hidroxi metil-4-(citosin-1'-il)-1,3-oxatiolano puede ser producido mediante los métodos descritos por Mansour et al., "Anti-Human Immunodeficiency Virus and Anti-Hepatitis Virus Activities and Toxicities of the Enantiomers of 2'-Deoxy-3'-oxa-4'-thiacytidine and Their 5-

25

Fluoro Analogues in vitro", J. Med. Chem., (1995), Vol. 38, No. 1, pp. 1-4, también como patente estadounidense 6,228,860 o Nucleosides and Nucleotides, (1995) 14(3-5) pp. 627-735 que son incorporados por referencia en la presente.

5 Comúnmente, cuando los compuestos son deseados como un solo enantiómero pueden ser obtenidos ya sea mediante resolución de la mezcla de los dos enantiómeros cis mediante HPLC quiral o mediante síntesis estereoespecífica a partir de un material de partida isométricamente puro o cualquier
10 intermediario conveniente. Una revisión completa de la tecnología conocida puede ser encontrada en "Enantiomers, Racemates and Resolutions" por J. Jacques, A. Collet & S. H. Wilen (John Wiley & Sons, 1981). Alternativamente, los compuestos o cualquier intermediario conveniente pueden ser
15 resueltos mediante resolución enzimática con una enzima apropiada tal como citidina desaminasa o degradación enzimática selectiva de un derivado apropiado. Véase por ejemplo Storer et al., "The resolution and Absolute Stereochemistry of the Enantiomers of cis-1[2(Hydroxymethyl)-1,3-Oxathiolan-5-yl)Cytosine (BCH-189): Equipotent Anti-HIV Agents", Nucleosides
20 & Nucleotides, 12(2), 225-236 (1993).

Otro proceso conocido como resolución mediante formación de compuestos diastereoméricos requiere la intervención de agentes quirales. A diferencia de los
25 enantiómeros, los diastereómeros pueden tener propiedades

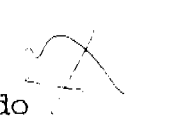
físico-químicas significativamente diferentes que pueden permitir la separación entre sí. Una variación de tal técnica involucra la formación y separación de sales diastereoméricas entre una sustancia racémica y un ácido o base de resolución ópticamente activo. Pasteur reportó por primera vez la resolución de un ácido racémico utilizando una base ópticamente activa (Pasteur, L., C.R Acad. Sci. (1853) 37 p.162; Pasteur, L., Ann. Chim (París) (1853) 3, 38 p. 437). Una resolución utilizando cantidades no estequiométricas de agentes quirales fue estudiada por Marckwald en 1896 y referida más tarde como "método de cantidad media" (Marckwald, W., Ber. (1896), 29, p. 42; Marckwald, W., Ber. (1896), 29, p. 43). El proceso para la resolución de ácido tartárico por medio de cristalización de su sal de quinchonina fue mejorado mediante Marckwald en tanto que usa solamente la mitad de la quinchonina necesaria para la formación de la sal de tartrato. La resolución está basada en la separación de uno de los diastereómeros y uno de los enantiómeros en lugar de la separación de las dos sales diastereoméricas formadas en iguales cantidades. Cuando se usa el método la mitad de la cantidad, el racemato es neutralizado parcialmente por el agente de resolución ópticamente activo. En el proceso descrito por Pope & Peachey (Pope, W.J., Peachey, S.J. J, Chem. Soc. (1899) 75, p.1066) el exceso de racemato no neutralizado por el agente de resolución es neutralizado mediante la adición de la cantidad necesaria de un ácido o base



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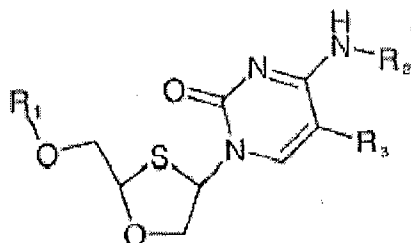
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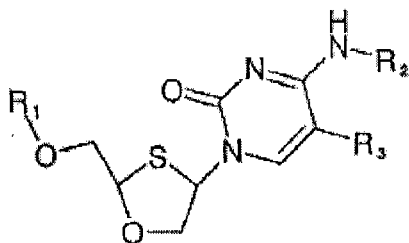
III

con un ácido quiral para producir dos sales
10 diastereoméricas;

(b) recuperar sustancialmente una sal
diastereomérica;

(c) convertir la sal diastereomérica al compuesto
ópticamente activo.

15 En otro aspecto, se proporciona un método para
resolver un compuesto de fórmula III, en configuración cis:



III

en donde:

R₁ es H, C₁₋₆ alquilo, C₆₋₁₂ arilo, C₆₋₁₂ arilalquilo (por
ejemplo, C₇₋₁₂ arilalquilo), (CO)C₁₋₆ alquilo, (CO)O-C₁₋₆ alquilo,
25 (CO)O-C₆₋₁₂ arilo o (CO)-C₆₋₁₂ arilalquilo (por ejemplo, (CO)C₇₋₁₂

arilalquilo);

R_2 es escogido de H, C_{1-6} alquilo, C_{1-6} acilo y $CO-R_5$;

en donde R_5 es H o C_{1-6} alquilo;

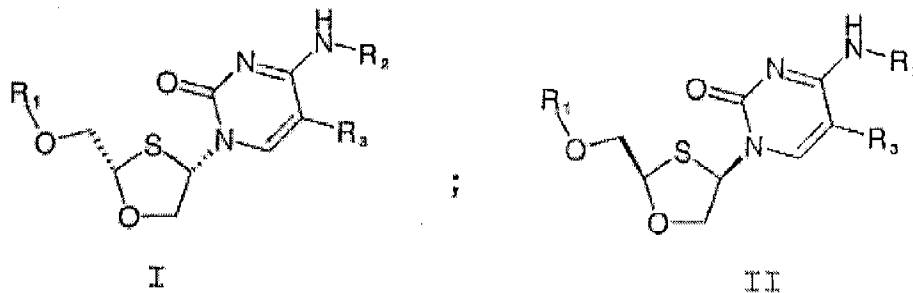
R_3 es H, C_{1-6} alquilo, bromuro, cloruro, fluoruro,

5 yoduro o CF_3 ; que comprende:

(a) hacer reaccionar el compuesto de fórmula III con un ácido quirral para producir dos sales diastereoméricas;

(b) recuperar sustancialmente una sal diastereomérica;

10 (c) convertir una sal diastereomérica al compuesto de fórmula I o II:



15

En un aspecto adicional, la presente invención proporciona un proceso para producir cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo que

20 comprende:

(a) hacer reaccionar un ácido quirral con cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano para producir dos sales diastereoméricas;

(b) recuperar sustancialmente una sal diastereomérica;

25

(c) convertir la sal diastereomérica al cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo.

En todavía un aspecto adicional, se proporciona un proceso para producir (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano que comprende:

(a) hacer reaccionar el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano con una mitad de la cantidad molar de un ácido quiral para producir sustancialmente sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano. quiral, la proporción molar es con respecto al cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano;

(b) recuperar la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano. quiral;

(c) convertir la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano. quiral al (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.

En todavía un aspecto adicional, se proporciona un proceso para producir cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo, que comprende:

(a) hacer reaccionar el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano con un ácido quiral y un ácido aquiral para producir sustancialmente una sal diastereomérica y sustancialmente una sal enantiomérica;

(b) recuperar la sal diastereomérica;

En un aspecto adicional, la presente invención
5 proporciona además nuevas sales cis-2-hidroximetil-4-(citosin-
1'-il)-1,3-oxatiolano.

Así, La presente invención es concerniente con un
10 proceso para producir el compuesto ópticamente activo de
fórmula I o II:

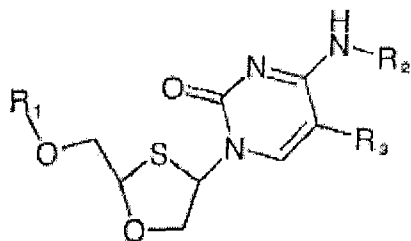


R₁ es H, C₁₋₆ alquilo, C₆₋₁₂ arilo, C₆₋₁₂ arilalquilo (por ejemplo, C₇₋₁₂ arilalquilo), (CO)C₁₋₆ alquilo, (CO)O-C₁₋₆ alquilo, (CO)C₆₋₁₂ arilo, o (CO)C₆₋₁₂ arilalquilo (por ejemplo, (CO)C₇₋₁₂ arilalquilo);

en donde R_5 es H o C_{1-6} alquilo;

R₃ es H, C₁₋₆ alquilo, bromuro, cloruro, fluoruro,
25 yoduro o CF₃; que comprende:

(a) hacer reaccionar un compuesto de fórmula III en configuración cis:



III

con un ácido quiral para producir dos sales diastereoméricas;

(b) recuperar sustancialmente una sal diastereomérica;

(c) convertir la sal diastereomérica al compuesto ópticamente activo.

El alcance la presente invención incluye un proceso como se describe anteriormente en donde el rendimiento global del enantiómero deseado es igual o mayor de 25% (100 g de racemato produciría por lo menos 25 g del enantiómero deseado).

Una modalidad de la presente invención es concerniente con un proceso que genera un producto final que está sustancialmente en forma de un solo enantiómero. Adicionalmente, una modalidad de la presente invención incluye un proceso descrito anteriormente que da como resultado un producto que tiene un exceso enantiomérico de 99% o más alto.

Una modalidad de la presente invención es concerniente con un proceso para producir el compuesto

5



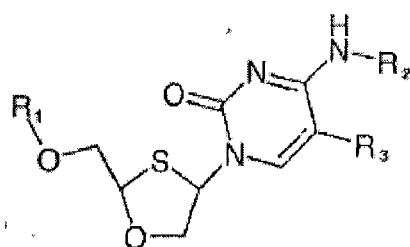
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También se proporciona un método para resolver un compuesto de fórmula III, en configuración cis:



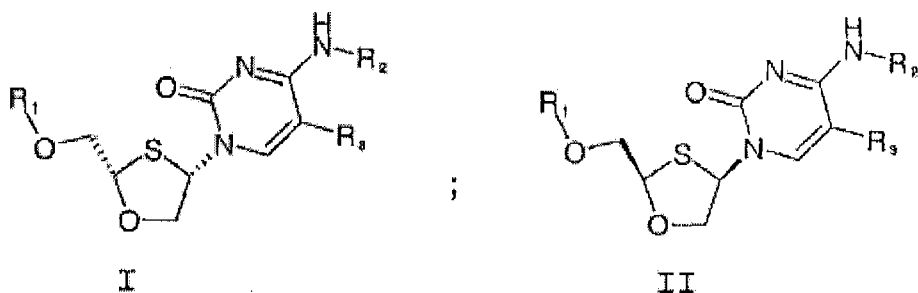
III

en donde: R_1 , R_2 , R_3 son como se definen anteriormente, que comprende:

(a) hacer reaccionar el compuesto de fórmula III con un ácido quiral para producir dos sales diastereoméricas;

(b) recuperar sustancialmente una sal diastereomérica;

(c) convertir la sal diastereomérica a un compuesto de fórmula I o II:



I

II

En una modalidad, R_1 es H, C_{1-6} alquilo, $(CO)C_{1-6}$ alquilo, $(CO)O-C_{1-6}$ alquilo o $(CO)C_{6-12}$ arilo.

En modalidades adicionales:

R_1 es H, $(CO)C_{1-6}$ alquilo o $(CO)C_{6-12}$ arilo,

R_1 es H,

R_1 es $(CO)C_{6-12}$ arilo.

Todavía en modalidades adicionales:

R_2 es H o C_{6-12} alquilo,

R_2 es $CO-R_5$, en donde R_5 es H o C_{1-6} alquilo,

R_2 es formilo o acetilo.

5 En una modalidad, R_3 es H, C_{1-6} alquilo o fluoruro.

En modalidades adicionales:

R_3 es H o fluoruro,

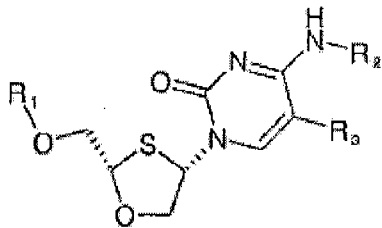
R_3 es H,

R_3 es fluoruro.

10 En una modalidad, el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L- tartárico o ácido (-)-L-málico.

En una modalidad, el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico.

15 En otra modalidad, el compuesto ópticamente activo es

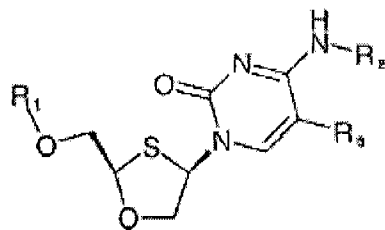


I

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En otra modalidad, el compuesto ópticamente activo es

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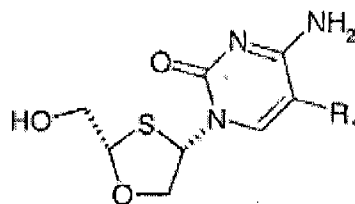


II

En una modalidad, los dos sales diastereoméricas comprenden una primera sal diastereomérica más soluble y una segunda sal diastereomérica menos soluble.

En una modalidad adicional, la etapa (b) descrita anteriormente comprende además recuperar una segunda sal diastereomérica.

La presente invención proporciona además un proceso para producir el compuesto ópticamente activo de fórmula IV:

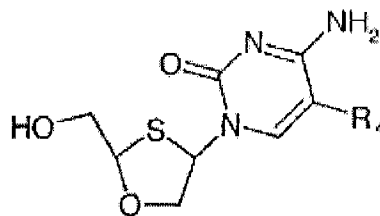


en donde:

IV

R₄ es H o fluoruro; que comprende:

(a) hacer reaccionar un compuesto de fórmula III en configuración cis:



III

con un ácido quiral seleccionado de ácido (1R)-(-)-

10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico o ácido (-)-L-málico, para producir dos sales diastereoméricas;

(b) recuperar sustancialmente una sal
5 diastereomérica;

(c) convertir la sal diastereomérica al compuesto ópticamente activo.

En un aspecto, se proporciona un proceso para producir cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano
10 ópticamente activo, que comprende:

(a) hacer reaccionar un ácido quirál con cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano para producir dos sales diastereoméricas;

(b) recuperar sustancialmente una sal
15 diastereomérica;

(c) convertir la sal diastereomérica al cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo.

En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo es cristalino.
20

En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo es el enantiómero (-).

En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo es el enantiómero (+).

25 En una modalidad, el ácido quirál es ácido (1R)-(-)-

10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico o ácido (-)-L-málico.

En una modalidad, el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico.

5 En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso enantiomérico de 60% o más alto.

En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso
10 enantiomérico de 70% o más alto.

En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso enantiomérico de 80% o mayor.

En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso
15 enantiomérico de 90% o mayor.

En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso enantiomérico de 95% o mayor.

20 En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso enantiomérico de 98% o más alto.

En una modalidad, el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso
25 enantiomérico de 99% o mayor.

En un aspecto, se proporciona un proceso para producir sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral, que comprende:

(a) hacer reaccionar el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano con un ácido quirar para producir sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral y sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral;

(b) recuperar la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

En una modalidad, la etapa (b) comprende además recuperar la sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

En una modalidad, la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano quirar contiene menos de 30% de sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

En modalidades adicionales:

La sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral contiene menos de 20% de sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral; la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral contiene menos de 10% de la sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral;

la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3- oxatiolano.quiral contiene menos de 5% de la sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.quiral;

5 la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3- oxatiolano.quiral contiene menos de 1% de la sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano quiral;

10 la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3- oxatiolano.quiral está sustancialmente libre de la sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.quiral.

En una modalidad, el proceso comprende además recristalización de esta sal de adición de ácido de resolución de (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.quiral.

En una modalidad, el ácido quiraral está en proporción molar estequiométrica con respecto al cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.

20 En una modalidad, el ácido quiraral está en proporción molar no estequiométrica con respecto al cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.

En un aspecto, se proporciona un proceso para la producción de (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano que comprende:

67

(a) hacer reaccionar el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano con la mitad de la cantidad molar de un ácido quiral para producir sustancialmente sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral, la proporción molar es con respecto al cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano;

(b) recuperar la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral;

(c) convertir la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral al (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.

En una modalidad, la etapa (a) comprende además agregar la mitad de la cantidad molar de un ácido aquiral para producir sustancialmente la sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano quiral, la proporción molar es con respecto al cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.

En una modalidad, el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico o ácido (-)-L-málico.

En una modalidad, el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico.

En una modalidad, el ácido aquiral es ácido clorhídrico.

En un aspecto adicional, se proporciona un proceso

para la producción de cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo cristalino, que comprende:

(a) hacer reaccionar el cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano con un ácido quiral y un ácido
5 aquiral para producir sustancialmente una sal diastereomérica y sustancialmente una sal enantiomérica;

(b) recuperar la sal diastereomérica;

(c) convertir la sal diastereomérica al cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente
10 activo.

Una modalidad del proceso de la presente invención genera un rendimiento global o mayor de 25% del enantiómero deseado.

Una modalidad adicional del proceso de la presente
15 invención genera el enantiómero deseado con un exceso enantiomérico de 95% o mayor.

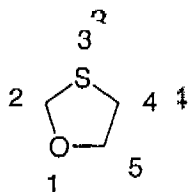
Otra modalidad del proceso de la presente invención genera un rendimiento global mayor o igual al 25% del enantiómero deseado en exceso enantiomérico de 99% o mayor.

20 En una modalidad, la sal diastereomérica es (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano. (1R)-(-)-10-alcanforsulfonato.

En una modalidad, la sal enantiomérica es sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano
25 clorhídrico.

Un "anillo de oxatiolano" es cualquier anillo monocíclico de cinco miembros sustituidos o sin sustituir que tiene un átomo de oxígeno posición 1 y un átomo de azufre en posición 3 del anillo como se ilustra posteriormente en la

5 presente:



10 Será evidente para el experimentado en el arte que las condiciones de reacción descritas en estos ejemplos pueden ser modificadas y todavía obtener resultados exitosos.

Comúnmente, los solventes, temperatura y tiempo de reacción se pueden hacer variar. Un solvente apropiado

15 permitirá que el proceso ocurra bajo las condiciones de reacción sin afectar adversamente la reacción. El solvente puede ser uno o más solventes y puede ser orgánico (por ejemplo, metanol, etanol, propanol, isopropanol, diclorometano, dicloroetano, tetrahidrofurano, hexano, pentano, espíritu de

20 éter, éter etílico), agua o acuoso/orgánico (por ejemplo, metanol-agua, isopropanol-agua). Los solventes pueden también estar presentes en varias proporciones (por ejemplo 1:1, 2:1, 5:1, 10:1 ó 1:1:1, 1:2:1).

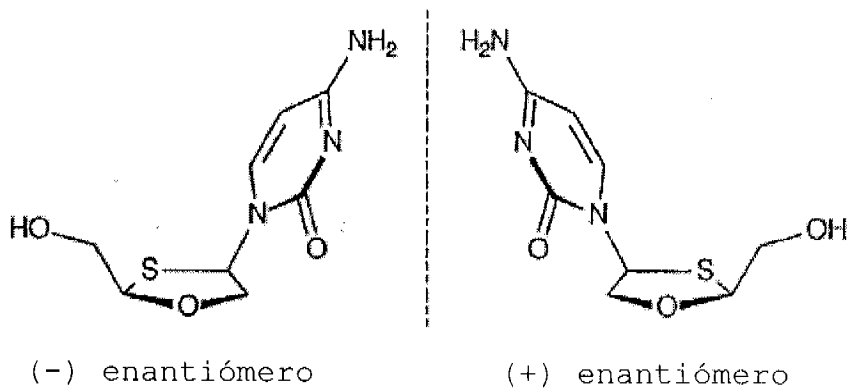
La temperatura puede ser variada y permitirá que el

25 proceso ocurra bajo las condiciones de reacción. La temperatura

apropiada proporcionará el producto deseado sin afectar adversamente la reacción.

Se apreciará por la persona de habilidad en el arte que un período de tiempo apropiado es un tiempo para obtener una transformación química suficiente del material de partida, obteniendo la pureza deseada o el rendimiento deseado del producto de reacción o una combinación de aquellos. La reacción puede comúnmente ser monitoreada, si se desea, mediante cromatografía de capa delgada o capa fina, absorción de luz (por ejemplo, U.V.) del medio de reacción, cromatografía de gases o cromatografía líquida de alto desempeño (HPLC).

El cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano existe como enantiómeros que pueden estar en varias proporciones.



20 Por ejemplo los enantiómeros pueden estar presentes como racematos (esto es, en proporciones igual) o cualquier proporción alternativa de los enantiómeros tales como por ejemplo 1:1, 2:1, 5:1, 10:1, 100:1 ó 1:2, 1:5, 1:10, 1:100. Las referencias posteriormente en la presente a cis-2-hidroximetil-

25

4-(citosin-1'-il)-1,3-oxatíolano de acuerdo con la invención incluye todas las proporciones posibles de enantiómeros.

A no ser que se defina de otra manera, todos los términos técnicos y científicos usados en la presente tienen el mismo significado como se entiende comúnmente por aquel de habilidad ordinaria en el arte con la cual esta invención pertenece. Todas las publicaciones, solicitudes de patente, patentes y otras referencias mencionadas en la presente son incorporadas por referencia en su totalidad. En caso de conflicto, la presente especificación, en las que se incluyen definiciones, controlarán. Además, los materiales, métodos y ejemplos son ilustrativos solamente y no pretende ser limitantes.

Como usa en esta solicitud, el término "alquilo" representa una entidad de hidrocarburo de cadena recta o cadena ramificada que puede opcionalmente estar sustituida por uno o más de halógeno, nitro, nitroso, sulfato, éster de sulfato, sulfonato, éster de sulfonato, éster de fosfonato, amida, C₁₋₆ alquilo, C₆₋₁₂ aralquilo (por ejemplo, C₇₋₁₂ aralquilo), C₆₋₁₂ arilo, C₁₋₆ alquiloxi, C₆₋₁₂ ariloxi, C(O)-C₁₋₆ alquilo, C(O)-C₆₋₁₂ arilo, C(O)C₆₋₁₂ aralquilo (por ejemplo, C(O)C₇₋₁₂ aralquilo), heterociclo que tiene 3-10 miembros del anillo, hidroxilo, amino, éster, ciano, azido, amidino o guanido. Ejemplos útiles de alquilo incluyen isopropilo, propilo, etilo, metilo, hexilo o ciclopropilo, que en cada caso está sin sustituir o

sustituido por una o más veces por ejemplo, halógeno, nitro, nitroso, sulfato, sulfonato, amida, hidroxilo, amino, éster, ciano, azido, amidino o guanido. El término alquilo también se propone incluir alquilo en cual uno o más átomos de hidrógeno
 5 están cada uno reemplazado por un halógeno, preferiblemente fluoro (por ejemplo, CF_3 - o CF_3CH_2 -).

El término "arilo" representa una entidad carbocíclica que contiene por lo menos un anillo tipo bencenoide que puede opcionalmente estar sustituido por uno o
 10 más de halógeno, nitro, nitroso, sulfato, éster de sulfato, sulfonato, éster de sulfonato, éster de fosfonato, amida, C_{1-6} alquilo, C_{6-12} aralquilo, C_{6-12} arilo, C_{1-6} alquiloxi, C_{6-12} ariloxi, $\text{C}(\text{O})-\text{C}_{1-6}$ alquilo, $\text{C}(\text{O})-\text{C}_{6-12}$ arilo, $\text{C}(\text{O})\text{C}_{6-12}$ aralquilo, heterociclo que tiene 3-10 miembros del anillo, hidroxilo,
 15 amino, éster, ciano, azido, amidino o guanido. Ejemplos de arilo incluyen fenilo y naftilo, que en cada caso está sin sustituir o sustituido uno o más veces por, por ejemplo, halógeno, nitro, nitroso, sulfato, sulfonato, amida, hidroxilo, amino, éster, ciano, azido, amidino o guanido.

El término "aralquilo" representa un grupo arilo anexado al átomo adyacente por un alquilo. Ejemplos útiles incluyen bencilo que está sin sustituir o sustituido una o más veces por, por ejemplo, halógeno, nitro, nitroso, sulfato, sulfonato, amida, hidroxilo, amino, éster, ciano, azido,
 25 amidino o guanido.

El término "heterociclo" representa una entidad cíclica saturada o insaturada, en donde la entidad cíclica está interrumpida por al menos un heteroátomo (por ejemplo, oxígeno, azufre o nitrógeno) que puede opcionalmente estar sustituido por uno o más de halógeno, nitro, nitroso, sulfato, éster de sulfato, sulfonato, éster de sulfonato, éster de fosfonato, amida, C₁₋₆ alquilo, C₆₋₁₂ aralquilo, C₆₋₁₂ arilo, C₁₋₆ alquiloxi, C₆₋₁₂ ariloxi, C(O)-C₁₋₆ alquilo, C(O)-C₆₋₁₂ arilo, C(O)C₆₋₁₂ aralquilo, hidroxilo, amino, éster, ciano, azido, amidino o guanido. Se comprenderá que el término anillo heterocíclico representa un anillo mono o policíclico (por ejemplo, bicíclico). Ejemplos de anillos heterocíclicos incluyen pero no están limitados a epóxido; furano; benzofurano; isobenzofurano; oxatiolano; ditiolano; dioxolano; pirrol; pirrolidina; imidazol; piridina; pirimidina; indol; piperidina; morfolina; tiofeno y tiomorfolina, que en cada caso está sin sustituir o sustituido una o más veces por, por ejemplo, halógeno, nitro, nitroso, sulfato, sulfonato, amida, hidroxilo, amino, éster, ciano, azido, amidino o guanido.

El término "independientemente" significa que un sustituyente puede ser el mismo o de diferente definición para cada ítem.

El término "ópticamente activo" significa que el exceso enantiomérico es mayor de cero.

La pureza óptica es numéricamente al "exceso

enantiomérico". El término "exceso enantiomérico" o "ee" es definido en valor de porcentaje (%) como sigue: [fracción molar (enantiómero mayor)-fracción molar (enantiómero menor)] x 100. (Por ejemplo, un ee de 99% representa una proporción de 99.5% de un enantiómero y 0.5% del enantiómero opuesto).

El término "ácido quirral" significa un compuesto ácido ópticamente activo apto de formar un diastereómero con un compuesto de fórmula III, tal como 2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano. Ejemplos de tales ácidos incluyen sin limitación: ácido tartárico, ácido O,O'-dibenzoil tartárico, ácido O,O'-di-p-toluil tartárico, ácido 2-nitrotartranílico, ácido mandélico, ácido málico, ácido 2-fenoxi propiónico, ácido 10-alcanforsulfónico, ácido hidratrópico, N-acetilleucina, ácido N-(α -metilbencil)succinámico, ácido N-(α -metilbencil)ftámico, ácido 3-bromoalcanfor-9-sulfónico, ácido alcanfor-3-sulfónico, ácido quínico, ácido di-O-isopropiliden-2-oxo-L-gulónico, lasalocid, ácido 1,1'-binaftil-2,2/-fosfórico, ácido colestén sulfónico. Ejemplos adicionales incluyen ácido (IR)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico y ácido (-)-L-málico.

La persona de habilidad ordinaria entenderá que el término "ácido aquiral" incluye una variedad de ácidos tales como ácidos inorgánicos (por ejemplo, HCl, HBr, H₂SO₄, HBF₄); ácidos sulfónicos (por ejemplo, ácido metansulfónico,

bencensulfónico, p-toluensulfónico, p-hidroxitoluensulfónico, sulfanílico, p-clorobencensulfónico); ácidos acéticos sustituidos (por ejemplo, glicólico, cloro-, dicloro-, tricloroacético); ácidos policarboxílicos y oxiácidos (por ejemplo, succínico, adípico, maleico, fumárico, cítrico, pirúvico):

También se proporcionan sales aceptables farmacéuticamente de los compuestos de la presente invención. El término "sales aceptables farmacéuticamente" significa sales derivadas de ácidos y bases inorgánicos y orgánicos aceptables farmacéuticamente. Ejemplos de ácidos apropiados incluyen ácido clorhídrico, bromhídrico, sulfúrico, nítrico, perclórico, fumárico, maleico, fosfórico, glicólico, láctico, salicílico, succínico, toluen-p-sulfónico, tartárico, acético, trifluoroacético, cítrico, metansulfónico, fórmico, benzoico, malónico, naftalen-2-sulfónico, ácido cisteico y ácido bencensulfónico. Otros ácidos tales como oxálico, en tanto que no son por sí mismos aceptables farmacéuticamente, pueden ser útiles como intermediarios para obtener los compuestos de la invención y sus sales de adición de ácido aceptables farmacéuticamente. Sales derivadas de bases apropiadas incluyen sales de metal alcalino (por ejemplo, sodio), metal alcalino térreo (por ejemplo, magnesio), sales de amonio y NR_4^+ (en donde R es C_{1-4} alquilo).

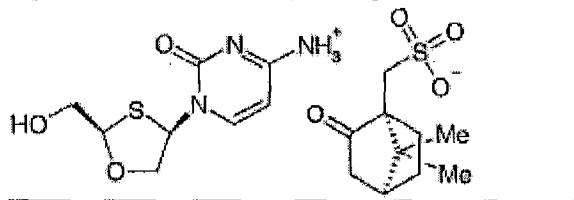
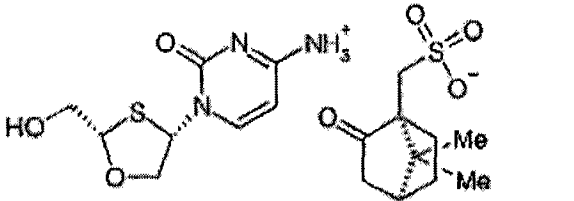
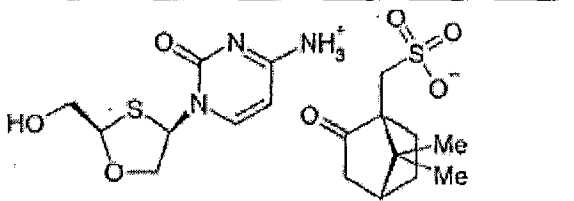
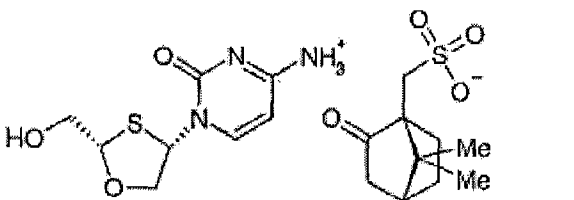
Las referencias posteriormente en la presente a un

compuesto de acuerdo con la invención incluyen el compuesto y sus sales aceptables farmacéuticamente.

Dowex® Marathon A-OH es una marca de DOW Chemical Company.

En un aspecto, la presente invención proporciona nuevos compuestos como se describe en tabla 1:

TABLA 1

10		(-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano. (1R)-(-)-10-alcanforsulfonato
		(+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano. (1R)-(-)-10-alcanforsulfonato
15		(-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano. (1S)-(+)-10-alcanforsulfonato
20		(+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano. (1S)-(+)-10-alcanforsulfonato

En una modalidad, el proceso y método de la presente invención comprende aquellos en donde las siguientes modalidades están presentes, ya sea independientemente o en combinación.

Las revelaciones enteras de todas las solicitudes, patentes y publicaciones, citadas anterior y posteriormente en la presente, son incorporadas en la presente por referencia.

5 EJEMPLOS

Los siguientes ejemplos son proporcionados para ilustrar varias modalidades de la presente invención y no serán considerados como limitantes del alcance.

Ejemplo 1: Selección de agentes de resolución quiral

10 Condiciones experimentales:

100 mg de cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano son combinados con 1 equivalente del agente de resolución, en 1 ml de solvente (95% de etanol - 5% de agua). El sólido es aislado y pesado. Una prueba significativa
15 requiere que el peso de los cristales no exceda el 50% de la cantidad del diastereómero global. Si esta condición no se satisface, la cantidad o tipo de solvente es cambiado.

TABLA 2

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Agente de Resolución Quiral	Ningún cristal observado	Cristal observado
Ácido (-)-L-málico		X
Ácido (-)-L-láctico	X (aceite)	
Ácido (+)-L-tartárico		X
Ácido (-)-2,3-dibenzoil-L-tartárico		X
Ácido (1R)-(-)-10-alcanforsulfónico		X

Ejemplo 2: Experimentaciones de resolución

Condiciones experimentales generales:

cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano y un ácido quirál fueron disueltos con agitación en un solvente a una temperatura de aproximadamente temperatura ambiente a aproximadamente 50°C y luego enfriados a una temperatura de entre aproximadamente la temperatura ambiente a - 10°C por 2-4 horas. El producto sólido fue recolectado mediante filtración. La composición fue determinada mediante HPLC quirál, la solución reguladora del pH acuosa fue preparada al diluir 0.5 ml de trietilamina en Agua HPLC 1 litro, el pH ajustado a 6.88 con ácido acético glacial. La fase móvil fue preparada al combinar la solución reguladora del pH acuosa y metanol en una proporción de 90:10 y el gas fue removido. Las siguientes condiciones fueron usadas:

Columna: Astec Cyclobond I 2000 RSP, 5 micras, 250 x 4.5 mm.

Columna de protección: Astec Cyclobond I 2000 RSP, 20 x 4.0 mm

Flujo: 0.6 ml/min.

Preparación de muestra: se prepara una solución de 0.5 mg/ml en fase móvil.

Volumen de inyección: 5 µL.

Modo: isocrático.

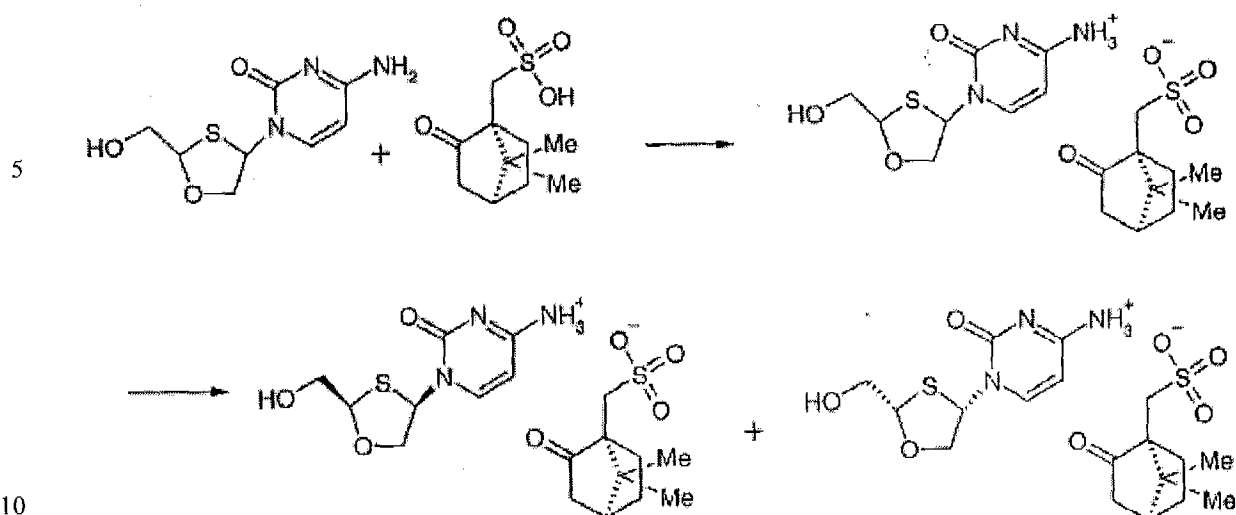
Detector UV-Vis a: 270 nm.

Temperatura de columna: 0°C.

Tiempo de corrida: 40 min.

TABLA 3

	Agente de resolución quiral / ácido aquiral	Solvente	Condiciones experimentales	Proporción enantiomérica (% de rendimiento)
1	Ácido L-tartárico (0.5 eq.) / HCl (0.5 eq.)	Alcohol isopropílico y agua 1:1 (v/v)	Balanza de 100 g Agitación magnética	45.2:52.1 (63%)
2	(R)- Ácido alcanforsulfónico (0.5 eq)/ HCl (0.5 eq.)	Alcohol isopropílico y agua 1:1 (v/v)	Balanza de 5 g Calentada @50°C para disolver los sólidos agitación magnética	92.4:7.6 (36%)
3	Ácido (-)-2,3-dibenzoil- L-tartárico (0.25 eq.) / HCl (0.5 eq.)	Agua	Balanza de 5 g Agitación magnética	47.6:45.7 (41.7%)
4	Ácido (R)- alcanforsulfónico (0.5 eq.) / HCl (0.5 eq.)	Alcohol isopropílico y agua 1:1 (v/v)	Balanza de 25 g Agitación mecánica	90.9:9.1 (52.6%)
5	Ácido (R)- alcanforsulfónico (0.5 eq.) / HCl (0.5 eq.)	Agua Metanol 17% de agua en metanol (v/v)	Balanza de 5 g Calentada a reflujo Agitación magnética	78.7:21.3 (72%)
6	Ácido (R)- alcanforsulfónico (1 eq.) / sin ácido aquiral	Alcohol isopropílico y agua 1:1 (v/v)	Balanza de 5 g Calentada @50°C para disolver los sólidos Agitación magnética	53.6:46.4 (60.6%)

Esquema de Reacción 1

Ejemplo 3: Resolución óptica de sal diastereomérica de cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatiolano

15 cis-2-hidroxi-metil-4-(citosin-1'-il)-1,3-oxatiolano
(1.03 g, 4.3 mmoles) y ácido (1R)-(-)-10-alcanforsulfónico
(1.03 g, 4.3 mmoles) fueron disueltos en 32 ml de alcohol
isopropílico 1:1 y agua (v/v) a 50°C. La solución fue enfriada
a 0°C. El sólido fue filtrado para proporcionar 0.55 g de
20 cristales anhidros. Se determinó mediante HPLC que la
composición diastereomérica era de 87:13 de sal de [(-)-cis-2-
hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-
alcanforsulfónico: sal de (+)-cis-2-hidroxi-metil-4-(citosin-1'-
il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfónico)].

25 El licor madre fue concentrado a sequedad para dar

1.38 g de sólidos anhidros con una composición diastereomérica de 35:65 sal de [(-)-cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfónico: sal de (+)-cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfónico)]. La composición fue analizada como se muestra en el Ejemplo 2.

Ejemplo 4: Recristalización para incrementar la proporción diastereomérica de sal de (-)-cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfónico con respecto a la sal de (+)-cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfónico

La sal de cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfonato cruda generada en la entrada 4 de la tabla 3 en ejemplo 2 que tiene una proporción enantiomérica de 90.9:9.1 de sal de [(-)-cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfónico: sal de (+)-cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfónico] fue disuelta en alcohol isopropilo-agua 1:1 (v/v) a 70°C. Después del enfriamiento, los cristales fueron recuperados con un rendimiento de 76% y una proporción enantiomérica de 99.1:0.9 de sal de [(-)-cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-alcanforsulfónico: sal de (+)-cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatiolano.(1R)-(-)-10-

alcanforsulfónico].

Ejemplo 5: Resolución óptica de la sal diastereomérica a escala de kilogramos

5 Una mezcla de isopropanol (2274 Kg), agua destilada (2905 Kg), cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano (193.7 Kg) fueron introducidos al reactor (modelo RO6 5700L GLMS). Ácido clorhídrico diluido (preparado como 41.57 Kg en 380 Kg de agua) fue introducido seguido por ácido (1R)-(-)-10-
10 alcanforsulfónico (100 Kg). La temperatura de la suspensión resultante fue ajustada a 50°C y fue agitada esta que todos los sólidos se disolvieron. La solución fue luego enfriada a aproximadamente -10°C (-13°C a -7°C) y agitada durante 4-6 horas.

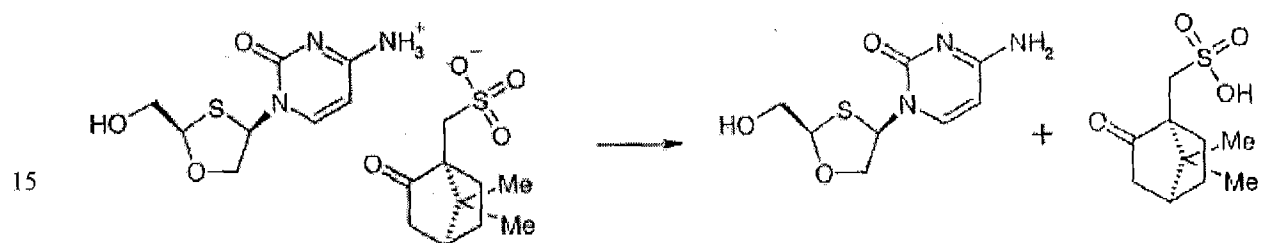
15 La suspensión resultante es filtrada, enjuagando hacia adelante con 60 litros de alcohol isopropílico y agua 1:1 (v/v). El producto es extraído anhidro con proporción enantiomérica de 91:9 sal de [(-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano. (1R)-(-)-10-alcanforsulfónico:
20 sal de (+)-cis-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano. (1R)-(-)-10-alcanforsulfónico)].

Isopropanol (228 Kg) y agua (291 Kg) son agregados al producto crudo húmedo y luego la temperatura de la solución resultante fue ajustada a 70°C y agitada hasta que todos los
25 sólidos se disolvieron, la solución es calentada y agitada

hasta que todos los sólidos se disuelven. Luego la solución es enfriada a aproximadamente 22°C (19°C a 25°C) y luego a 0°C (-3°C a 3°C).

La suspensión resultante es filtrada, enjuagando hacia adelante con dos porciones de 70 litros de alcohol isopropilo y agua 1:1 (v/v). El producto es secado por centrifugación hasta que el flujo del filtrado esencialmente se detiene. 90.8 Kg de producto recuperado (rendimiento de 87%, corregido por perdido en la sequedad de una muestra) con una pureza enantiomérica mayor de 98%.

Esquema de Reacción 2



Ejemplo 6: Remoción del ácido (1R)-(-)-10-alcanforsulfónico a partir de la sal de (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.(1R)-(-)-10-alcanforsulfónico

Sal de (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.(1R)-(-)-10-alcanforsulfónico (90.8 Kg) es disuelta en metanol (601 Kg) mediante calentamiento de la mezcla a 40°C y agitación hasta que se obtiene una solución.

La solución caliente se hace circular a través de una

columna de intercambio iónico que contiene Dowex® Marathon A-OH (133.6 Kg) y metanol (200 Kg) en tanto que se mantiene la temperatura a 40°C hasta que no se detecta algún ácido alcanforsulfónico residual mediante análisis de RMN y el pH es mayor de 7 (medido utilizando papel pH humectado por agua).

El eluyente es filtrado, enjuagado hacia adelante con metanol (200 Kg).

El filtrado es parcialmente concentrado bajo vacío a aproximadamente 140 litros.

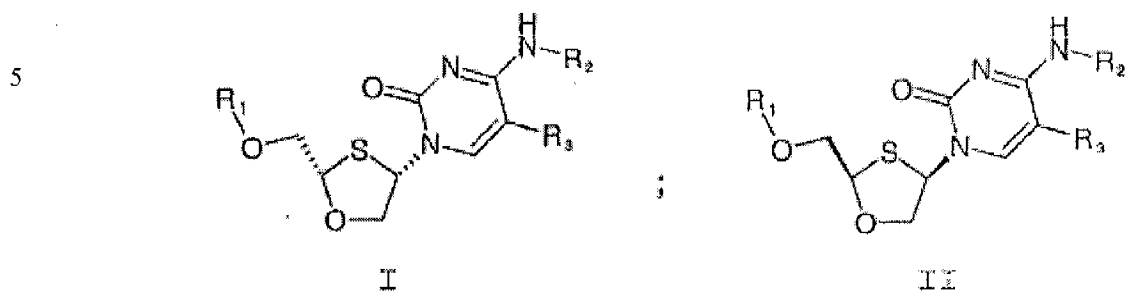
El concentrado es enfriado a una temperatura de aproximadamente -10°C por una hora y agitado. La suspensión resultante es filtrada, enjuagando hacia adelante con 2 porciones de 18 Kg de metanol frío (-10°C). El producto es secado bajo vacío en tanto que se calienta a 35-40°C.

Los ejemplos precedentes pueden ser repetidos con éxito similar al sustituir los reactivos y/o condiciones de operación descritas genérica o específicamente de esta invención para aquellos usados en los ejemplos precedentes.

A partir de la descripción anterior, el experimentado en el arte puede determinar fácilmente las características esenciales de esta invención y sin desviarse del espíritu y alcance de la misma, puede efectuar varios cambios y modificaciones de la invención para adaptarla a varios usos y condiciones.

REIVINDICACIONES

1. Un proceso para producir un compuesto ópticamente activo de fórmula I ó II:



caracterizado porque:

10 R₁ es H, C₁₋₆ alquilo, C₆₋₁₂ arilo, C₆₋₁₂ arilalquilo,
(CO)C₁₋₆ alquilo, (CO)O-C₁₋₆ alquilo, (CO)C₆₋₁₂ arilo o (CO)C₆₋₁₂
arilalquilo;

R₂ es H, C₁₋₆ alquilo o CO-R₅;

R₃ es H, C₁₋₆ alquilo, bromuro, cloruro, fluoruro,
15 yoduro o CF₃; y

R₅ es H o C₁₋₆ alquilo;

en donde en las definiciones de R₁, R₂, R₃ y R₅, "alquilo" está, en cada caso, sin sustituir o sustituido por uno o más de halógeno, nitro, nitroso, sulfato, éster de sulfato, sulfonato, éster de sulfonato, éster de fosfonato, amida, C₁₋₆ alquilo, C₆₋₁₂ aralquilo, C₆₋₁₂ arilo, C₁₋₆ alquilo, C₆₋₁₂ arilo, C(O)-C₁₋₆ alquilo, C(O)-C₆₋₁₂ arilo, C(O)C₆₋₁₂ aralquilo, heterociclo que tiene 3-10 miembros en el anillo, hidroxilo, amino, éster, ciano, azido, amidino o guanido; y en las definiciones de R₁, R₂, R₃ y R₅ "arilo" está, en cada caso,

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12. El proceso de conformidad con la reivindicación 1, caracterizado porque R_3 es H.

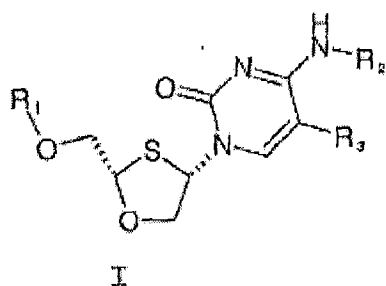
13. El proceso de conformidad con la reivindicación 1, caracterizado porque R_3 es fluoruro.

5 14. El proceso de conformidad con cualquiera de las reivindicaciones 1 a 13, caracterizado porque el ácido quirál es ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico o ácido (-)-L-málico.

10 15. El proceso de conformidad con cualquiera de las reivindicaciones 1 a 13, caracterizado porque el ácido quirál es ácido (1R)-(-)-10-alcanforsulfónico.

16. El proceso de conformidad con la reivindicación 1, caracterizado porque el compuesto ópticamente activo es

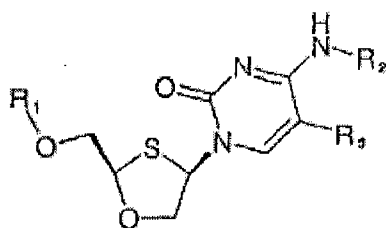
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17. El proceso de conformidad con la reivindicación 1, caracterizado porque el compuesto ópticamente activo es

25

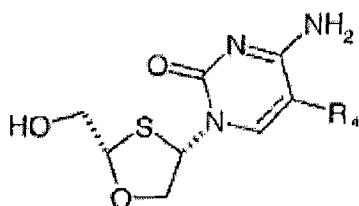


II

18. El proceso de conformidad con cualquiera de las reivindicaciones 1 a 17, caracterizado porque las dos sales diastereoméricas comprenden una primera sal diastereomérica más soluble y una segunda sal diastereomérica menos soluble.

19. El proceso de conformidad con cualquiera de las reivindicaciones 1 a 17, caracterizado porque la etapa (b) comprende además recuperar una segunda sal diastereomérica.

20. Un proceso para producir el compuesto ópticamente activo de fórmula IV:



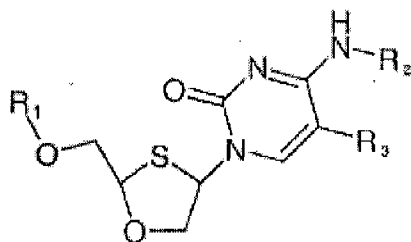
IV

en donde:

R_4 es H o fluoruro; caracterizado porque comprende:

(a) hacer reaccionar un compuesto de fórmula III en configuración cis:

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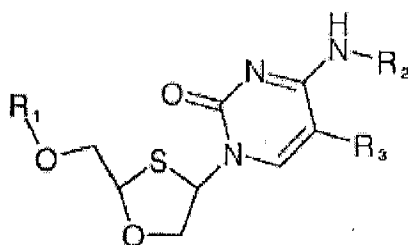
III

con un ácido quiral seleccionado de ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico o ácido (-)-L-málico, para producir dos sales diastereoméricas;

(b) recuperar sustancialmente una sal diastereomérica;

(c) convertir la sal diastereomérica al compuesto ópticamente activo.

21. Un método para resolver un compuesto de fórmula III, en configuración cis:



20

III

en donde:

R₁ es H, C₁₋₆ alquilo, C₆₋₁₂ arilo, C₆₋₁₂ arilalquilo, (CO)C₁₋₆ alquilo, (CO)O-C₁₋₆ alquilo, (CO)C₆₋₁₂ arilo o (CO) C₆₋₁₂ arilalquilo;

25

21, caracterizado porque R_2 es formilo o acetilo.

29. El método de conformidad con la reivindicación 21, caracterizado porque R_3 es H, C_{1-6} alquilo ó fluoruro.

30. El método de conformidad con la reivindicación 5 21, caracterizado porque R_3 es H o fluoruro.

31. El método de conformidad con la reivindicación 21, caracterizado porque R_3 es H.

32. El método de conformidad con la reivindicación 21, caracterizado porque R_3 es fluoruro.

10 33. El método de conformidad con la reivindicación 21, caracterizado porque el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico o ácido (-)-L-málico.

15 34. El método de conformidad con la reivindicación 21, caracterizado porque el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico.

20 35. El método de conformidad con cualquiera de las reivindicaciones 21 a 34, caracterizado porque las dos sales diastereoméricas comprenden una primera sal diastereomérica más soluble y una segunda sal diastereomérica menos soluble.

36. El método de conformidad con cualquiera de las reivindicaciones 21 a 34, caracterizado porque la etapa (b) comprende además recuperar una segunda sal diastereomérica.

25 37. Un proceso para producir cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo,

caracterizado porque comprende:

(a) hacer reaccionar un ácido quiral con cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano para producir dos sales diastereoméricas;

5 (b) recuperar sustancialmente una sal diastereomérica;

(c) convertir la sal diastereomérica al cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo.

10 38. El proceso de conformidad con la reivindicación 37, caracterizado porque el cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo es cristalino.

39. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 38, caracterizado porque el cis-2-
15 hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo es enantiómero (-).

40. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 38, caracterizado porque el cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente
20 activo es enantiómero (+).

41. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico o ácido (-)-L-
25 málico.

42. El método de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico.

5 43. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo tiene un exceso enantiomérico de 60% o mayor.

10 44. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo tiene un exceso enantiomérico de 70% o mayor.

15 45. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo tiene un exceso enantiomérico de 80% o mayor.

46. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo tiene un exceso enantiomérico de 90% o mayor.

20 47. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el cis-2-hidroxiometil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo tiene un exceso enantiomérico de 95% o mayor.

25 48. El proceso de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el cis-2-

hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso enantiomérico de 98% o mayor.

49. Un proceso de conformidad con cualquiera de las reivindicaciones 37 a 40, caracterizado porque el cis-2-
5 hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano ópticamente activo tiene un exceso enantiomérico de 99% o mayor.

50. Un proceso para producir sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.quiral, caracterizado porque comprende:

10 (a) hacer reaccionar cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano con un ácido quirral para producir sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.quiral y sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.quiral;

15 (b) recuperar la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatiolano.quiral.

51. El proceso de conformidad con la reivindicación 50, caracterizado porque el ácido quirral es ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido
20 (+)-L-tartárico o ácido (-)-L-málico.

52. El método de conformidad con la reivindicación 50, caracterizado porque el ácido quirral es ácido (1R)-(-)-10-alcanforsulfónico.

53. El proceso de conformidad con cualquiera de las
25 reivindicaciones 50 a 52, caracterizado porque la etapa (b)

comprende además recuperar la sal de ácido (+)-cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

54. El proceso de conformidad con cualquiera de las
reivindicaciones 50 a 52, caracterizado porque la sal de ácido
5 (-)-cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quiral
contiene menos de 30% sal de adición de ácido que resuelve
(+)-cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

55. El proceso de conformidad con cualquiera de las
reivindicaciones 50 a 52, caracterizado porque la sal de ácido
10 (-)-cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quiral
contiene menos de 20% de sal de adición de ácido que resuelve
(+)-cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

56. Un proceso de conformidad con cualquiera de las
reivindicaciones 50 a 52, caracterizado porque la sal de ácido
15 (-)-cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quiral
contiene menos de 10% de sal de ácido que resuelve (+)-cis-2-
hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

57. El proceso de conformidad con cualquiera de las
reivindicaciones 50 a 52, caracterizado porque la sal de ácido
20 (-)-cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quiral
contiene menos de 5% de sal de adición de ácido que resuelve
(+)- cis-2-hidroxi-
metil-4-(citosin-1'-il)-1,3-oxatolano.quir-
al.

58. El proceso de conformidad con cualquiera de las
25 reivindicaciones 50 a 52, caracterizado porque la sal de ácido

(-)-cis-2-hidroxitimetil-4-(citosin-1'-il)-1,3-oxatolano.quiral
contiene menos de 1% de sal de adición de ácido que resuelve
(+)- cis-2-hidroxitimetil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

5 59. El proceso de conformidad con cualquiera de las
reivindicaciones 50 a 52, caracterizado porque la sal de ácido
(-)-cis-2-hidroxitimetil-4-(citosin-1'-il)-1,3-oxatolano.quiral
está sustancialmente libre de sal de adición de ácido que
resuelve (+)-cis-2-hidroxitimetil-4-(citosin-1'-il)-1,3-oxatio-
10 lano.quiral.

60. El proceso de conformidad con cualquiera de las
reivindicaciones 50 a 59, caracterizado porque comprende además
recristalizar la sal de adición de ácido que resuelve (-)-cis-
2-hidroxitimetil-4-(citosin-1'-il)-1,3-oxatolano.quiral.

15 61. El proceso de conformidad con cualquiera de las
reivindicaciones 50 a 59, caracterizado porque el ácido quirar
está en una proporción molar estequiométrica con respecto a
cis-2-hidroxitimetil-4-(citosin-1'-il)-1,3-oxatolano.

62. El proceso de conformidad con cualquiera de las
20 reivindicaciones 50 a 59, caracterizado porque el ácido quirar
está en una proporción molar no estequiométrica con respecto a
cis-2-hidroxitimetil-4-(citosin-1'-il)-1,3-oxatolano.

63. Un proceso para producir (-)-cis-2-hidroxitimetil-
4-(citosin-1'-il)-1,3-oxatolano caracterizado porque
25 comprende:

(a) hacer reaccionar cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano con una cantidad molar de media cantidad de ácido quiral para producir sustancialmente sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral, la
5 proporción molar es con respecto a cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano;

(b) recuperar la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral;

(c) convertir la sal de ácido (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.quiral en (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.
10

64. El proceso de conformidad con la reivindicación 62, caracterizado porque la etapa (a) comprende además agregar una cantidad molar de media cantidad de ácido aquiral para
15 producir sustancialmente sal de ácido (+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.aquiral, la proporción molar es con respecto a cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.

65. El proceso de conformidad con cualquiera de las
20 reivindicaciones 63 a 64, caracterizado porque el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L-tartárico, ácido (+)-L-tartárico o ácido (-)-L-málico.

66. El proceso de conformidad con cualquiera de las
25 reivindicaciones 63 a 64, caracterizado porque el ácido quiral

100
~~100~~

es ácido (1R)-(-)-10-alcanforsulfónico.

67. El proceso de conformidad con cualquiera de las reivindicaciones 63 a 66, caracterizado porque el ácido quiral es ácido clorhídrico.

5 68. Un proceso para producir cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano ópticamente activo cristalino, caracterizado porque comprende:

 (a) hacer reaccionar cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano con un ácido quiral y un ácido quiral
10 para producir sustancialmente una sal diastereomérica y una sal sustancialmente enantiomérica;

 (b) recuperar la sal diastereomérica;

 (c) convertir la sal diastereomérica en cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano ópticamente
15 activo.

69. El proceso de conformidad con la reivindicación 68, caracterizado porque la sal quiral es ácido (1R)-(-)-10-alcanforsulfónico, ácido (-)-2,3-dibenzoil-L- tartárico, ácido (+)-L-tartárico o ácido (-)-L-málico.

20 70. El proceso de conformidad con la reivindicación 68, caracterizado porque el ácido quiral es ácido (1R)-(-)-10-alcanforsulfónico.

 71. El proceso de conformidad con la reivindicación 68, caracterizado porque la sal diastereomérica es (-)-cis-2-
25 hidroximetil-4-(citosin-1'-il)-1,3-oxatolano. (1R)-(-)-10-

top 101

alcanforsulfonato.

72. Un compuesto seleccionado de:

(-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.(1R)-(-)-10-alcanforsulfonato;

5 (-)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.(1S)-(+)-10-alcanforsulfonato;

(+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.(1R)-(-)-10-alcanforsulfonato; o

(+)-cis-2-hidroximetil-4-(citosin-1'-il)-1,3-oxatolano.(1S)-(+)-10-alcanforsulfonato.

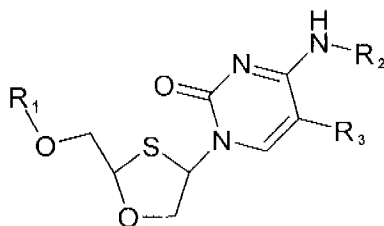
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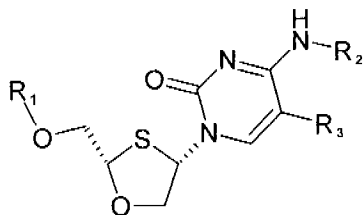
RESUMEN DE LA INVENCION

Se proporciona un método para la resolución de un compuesto de fórmula (III), en configuración cis:

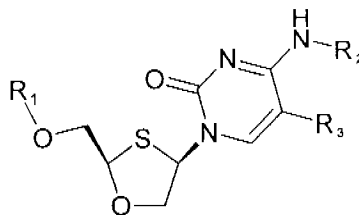


(III)

También se proporciona un proceso para producir el compuesto óptimamente activo de fórmula (I) o (II):



(I)



(II)

en donde: R_1 , R_2 , R_3 son como se define en la presente, el método y proceso involucran la producción, recuperación y conversión de sales diastereoméricas.

PATENT COOPERATION TREATY

REQU / RECEIVED

25 AOUT 2005

PCT BCF S.E.N.C.R.L. / LLP

From the INTERNATIONAL SEARCHING AUTHORITY

To:
BCF LLP
1100, Rene-Levesque Blvd. West
25th Floor
MONTREAL, Quebec
Canada, H3B 5C9

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing 23 August 2005 (23-08-2005)
(day/month/year)

Applicant's or agent's file reference
10680-002

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/CA2005/000384

International filing date 14 March 2005 (14-03-2005)
(day/month/year)

Applicant
SHIRE BIOCHEM INC. ET AL

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19 :

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46) :

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that :

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for the international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer
Lucille Leonard (819) 953-1737

NOTES TO FORM PCT/ISA/220

These Notes are intended to give instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)) :

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

10

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter :

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

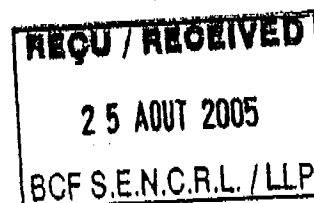
If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43bis.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY
PCT
INTERNATIONAL SEARCH REPORT
(PCT Article 18 and Rules 43 and 44)



Applicant's or agent's file reference 10680-002	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below	
International application No. PCT/CA2005/000384	International filing date (day/month/year) 14 March 2005 (14-03-2005)	(Earliest) Priority date (day/month/year)
Applicant SHIRE BIOCHEM INC. ET AL		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I

2. ☐ **Certain claims were found unsearchable** (see Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows :

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant

☐ as selected by this Authority, because the applicant failed to suggest a figure

☐ as selected by this Authority, because this figure better characterizes the invention

b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/000384A. CLASSIFICATION OF SUBJECT MATTER
IPC(7): C07D 411/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(7): C07D 411/04; US: 544/317

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Delphion: (IPC(7): C07D 411/04; US: 544/317 and oxathiolan*); Canadian Patent Database: (IPC(7): C07D 411/04); STN: Structure search based on formula (III)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Tetrahedron Letters, 1994, 35 (27), 4739-4742 (WANG, W. et al.) (BIOCHEM THERAPEUTIC INC.), 4 July 1994 (04-07-1994) *see whole document*	
A	Bioorg. Med. Chem. Let., 1993, 3(8), 1723-1728 (BELLEAU, B. et al.) (BIOCHEM PHARMA INC.) August 1993 (08-1993) *see whole document*	
A	CA 2188283 A (MANSOUR, T. S. et al.) (BIOCHEM PHARMA INC.) 02 November 1995 (02-11-1995) *see pages 5-13, 23-48 and claims 1-6* cited in the application as US 6228860	
A	CA 2095613 A (BELLEAU, B. et al.) (BIOCHEM PHARMA INC.) 14 May 1992 (14-05-1992) *see pages 5-6, 38 and claims 1-4, 6-7, 9-10, 12, 20-23*	

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

6 July 2005 (06-07-2005)

Date of mailing of the international search report

23 August 2005 (23-08-2005)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Authorized officer

Karla Randell (819) 956-6118

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2005/000384

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2188283	02-11-1995	AT143016T T	15-10-1996
		AT214066T T	15-03-2002
		AT275144T T	15-09-2004
		AU693884 B2	09-07-1998
		AU2211895 A	16-11-1995
		AU8864191 A	11-06-1992
		CA2095613 A1	14-05-1992
		DE69122264D D1	24-10-1996
		DE69122264T T2	06-02-1997
		DE69525742D D1	11-04-2002
		DE69525742T T2	26-09-2002
		DE69533458D D1	07-10-2004
		DK560794T T3	23-12-1996
		DK756595T T3	17-06-2002
		DK1153924T T3	27-12-2004
		DK1224940T T3	27-12-2004
		EP0560794 A1	22-09-1993
		EP0756595 A1	05-02-1997
		EP1153924 A2	14-11-2001
		EP1473294 A2	03-11-2004
		ES2091948T T3	16-11-1996
		ES2172580T T3	01-10-2002
		ES2228714T T3	16-04-2005
		GR3021074T T3	31-12-1996
		HK12597 A	14-02-1997
		HK1005544 A1	07-06-2002
		HK1041487 A1	07-01-2005
		JP2960164B2 B2	06-10-1999
		JP6504266T T	19-05-1994
		JP9512526T T	16-12-1997
		PT756595T T	30-08-2002
		US5587480 A	24-12-1996
		US6228860 B1	08-05-2001
		US6369066 B1	09-04-2002
		WO9208717 A1	29-05-1992
		WO9529176 A1	02-11-1995
CA2095613	14-05-1992	AT143016T T	15-10-1996
		AT214066T T	15-03-2002
		AT275144T T	15-09-2004
		AU693884 B2	09-07-1998
		AU2211895 A	16-11-1995
		AU8864191 A	11-06-1992
		CA2188283 A1	02-11-1995
		DE69122264D D1	24-10-1996
		DE69122264T T2	06-02-1997
		DE69525742D D1	11-04-2002
		DE69525742T T2	26-09-2002
		DE69533458D D1	07-10-2004
		DK560794T T3	23-12-1996
		DK756595T T3	17-06-2002
		DK1153924T T3	27-12-2004
		DK1224940T T3	27-12-2004
		EP0560794 A1	22-09-1993
		EP0756595 A1	05-02-1997
		EP1153924 A2	14-11-2001
		EP1473294 A2	03-11-2004
		ES2091948T T3	16-11-1996
		ES2172580T T3	01-10-2002
		ES2228714T T3	16-04-2005
		GR3021074T T3	31-12-1996
		HK12597 A	14-02-1997
		HK1005544 A1	07-06-2002
		HK1041487 A1	07-01-2005

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2005/000384

JP2960164B2 B2	06-10-1999
JP6504266T T	19-05-1994
JP9512526T T	16-12-1997
PT756595T T	30-08-2002
US5587480 A	24-12-1996
US6228860 B1	08-05-2001
US6369066 B1	09-04-2002
WO9208717 A1	29-05-1992
WO9529176 A1	02-11-1995

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

RECEIVED

25 AOUT 2005

PCT

BCF S.E.N.C.R.L. / LLP

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
BCF LLP
1100, Rene-Levesque Blvd. West
25th Floor
MONTREAL, Quebec
Canada, H3B 5C9

Date of mailing 23 August 2005 (23-08-2005)
(day/month/year)

Applicant's or agent's file reference
10680-002

FOR FURTHER ACTION
See paragraph 2 below

International application No.

PCT/CA2005/000384

International filing date (day/month/year)
14 March 2005 (14-03-2005)

Priority date (day/month/year)

International Patent Classification (IPC) or both national classification and IPC
IPC(7): C07D 411/04

Applicant

SHIRE BIOCHEM INC. ET AL

1. This opinion contains indications relating to the following items :

- | | |
|--|--|
| ☒ Box No. I | Basis of the opinion |
| ☐ Box No. II | Priority |
| ☐ Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ Box No. IV | Lack of unity of invention |
| ☒ Box No. V | Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ Box No. VI | Certain documents cited |
| ☐ Box No. VII | Certain defects in the international application |
| ☒ Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001(819)953-2476

Date of completion of this opinion
11 July 2005 (11-07-2005)

Authorized officer

Karla Randell (819) 956-6118

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form

☐ furnished subsequently to this Authority for the purposes of search.

3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statement that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments :

Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>1-72</u>	YES
	Claims <u>NONE</u>	NO
Inventive step (IS)	Claims <u>1-72</u>	YES
	Claims <u>NONE</u>	NO
Industrial applicability (IA)	Claims <u>1-72</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations :

D1: Tetrahedron Letters, 1994, 35 (27), 4739-4742 (WANG, W. et al.) 4 July 1994 (04-07-1994)
D2: Bioorg. Med. Chem. Let., 1993, 3 (8), 1723-1728 (BELLEAU, B. et al.) August 1993 (08-1993)
D3: CA 2188283 A (MANSOUR, T. S. et al.) 02 November 1995 (02-11-1995)
D4: CA 2095613 A (BELLEAU, B. et al.) 14 May 1992 (14-05-1992)

Novelty (N)

The subject matter of this application is considered to be novel and thus fulfills the requirements of PCT Article 33(2). The prior art does not disclose the separation of the two cis-isomers of 1,3-oxathiolane derivatives using a chiral acid. This process produces two diastereomeric salts that are separated and converted to the pure, optically active compounds.

D1 teaches the synthesis of 1,3-oxathiolane derivatives to yield a mixture of cis- and trans- isomers that are separated by preparative TLC.

D2 teaches the separation of 1,3-oxathiolane derivatives using chiral HPLC or enzymatic resolution.

D3 teaches the separation of 1,3-oxathiolane derivatives using chiral HPLC, enzymatic resolution or stereospecific synthesis from isomerically pure starting material or any convenient intermediate.

D4 teaches the synthesis of oxathiolane derivatives and references separation by any suitable method known in the art.

Inventive Step (IS)

The subject matter of this application is considered to involve an inventive step since, having regard to the prior art, it is not, at the prescribed relevant date, obvious to a person skilled in the art and thus fulfills the requirements of PCT Article 33(3).

Industrial Applicability (IA)

The subject matter of this application is considered to be industrially applicable and thus fulfills the requirements of PCT Article 33(4).

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

The description does not comply with PCT Article 5 for the following reasons:

A statement in an application, such as found on page 1, line 28, page 15, line 21, and page 19, lines 10-12, which incorporates by reference any other document, does not fully describe the invention. The description shall be complete in and on itself. A person should be able to understand the patent specification without reference to any other document.

The representation of a compound of formula III on page 9 is not consistent with the other depictions of formula III.

A statement, such as found on page 15, lines 17-25, page 19, lines 16-18, and page 26, lines 32-36, which implies that the protection sought may be expanded to cover the "spirit" of the invention, does not comply with PCT Article 6 and should be removed.

Claims 1, 2, 20, 21, 37, 42, 50, 52, 54-60, 64, 67, 68 and 69 do not comply with PCT Article 6. The claim or claims shall define the subject matter for which protection is sought. The claims shall be clear and concise. They shall be fully supported by the description.

In claims 1, 20, 21, 37, 64 and 68, the term "substantially" causes a lack of clarity.

Claim 2 does not define any additional characteristics over claim 1.

In claim 20, the variables R1-R3 are not defined, R1 is H, R2 is H, and R3 is H or F.

There is no antecedent in claim 20 for "said process" as claimed in claim 21.

Claim 42 is directed to a method, but is dependent on claims 37-40 which are directed towards a process.

In claims 50 and 54-60 the characteristic "resolving acid salt" is not found in the description.

Claim 52 is directed to a method, but is dependent on claim 50 which is directed towards a process.

There is no antecedent in claim 63 for "said achiral acid" as claimed in claim 67.

There is no antecedent in claim 68 for "said chiral salt" as claimed in claim 69.

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

BORDEN LADNER GERVAIS LLP
World Exchange Plaza
100 Queen Street, Suite 1100
Ottawa, Ontario K1P 1J9
CANADA

Date of mailing (day/month/year)
19 July 2007 (19.07.2007)

Applicant's or agent's file reference
PAT 3813W-90

IMPORTANT NOTICE

International application No.
PCT/CA2005/000384

International filing date (day/month/year)
14 March 2005 (14.03.2005)

Priority date (day/month/year)

Applicant

SHIRE BIOCHEM INC. et al

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does not apply**, please see Form PCT/IB/308(First Notice) issued previously.
2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
21 September 2006 (21.09.2006)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SG, SK, SL, SM, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZM, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **30 MONTHS** from the priority date.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For **regular updates on the applicable time limits** (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Athina Nickitas-Etienne

Facsimile No. +41 22 338 82 70

e-mail: pt04.pct@wipo.int

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

BCF S.E.N.C.R.L./LLP PCT

25 MAY 2005 NOTIFICATION OF RECEIPT OF
RECORD COPY

REQU/RECEIVED (PCT Rule 24.2(a))

To:

BRITT, Katherine
BCF LLP
1100 René-Lévesque Blvd. West
25th Floor
Montréal, Québec H3B 5C9
Canada

Date of mailing (day/month/year) 18 May 2005 (18.05.2005)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 10680-002	International application No. PCT/CA2005/000384

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

SHIRE BIOCHEM INC. (for all designated States except US)
CIMPOIA, Alex (for US)

International filing date : 14 March 2005 (14.03.2005)

Priority date(s) claimed :

Date of receipt of the record copy
by the International Bureau : 22 April 2005 (22.04.2005)

List of designated Offices :

AP : BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.95	Authorized officer: T. Vernhes (Fax 338-8995) Telephone No. (41-22) 338 8133
--	--

116
PHAR-144-002 P

#10680-002

ASSIGNMENT OF INVENTION

UNIVERSAL

WHEREAS, I/We Alex CIMPOIA

whose full addresses is 290 Elgar, apt. 204, Verdun, Québec, H3E 1C9, CANADA

(hereinafter referred to as the assignor) in consideration of \$1.00 and other good and valuable consideration, the receipt of which is hereby acknowledged and for which a full release and discharge is given, do hereby sell and assign to SHIRE BIOCHEM INC.

whose full post office address is 2250 Alfred-Nobel Blvd., Suite 500, Ville St-Laurent, Québec, CANADA, H4S 2C9

(hereinafter referred to as the assignee), all of my/our rights, titles and interests in each and every country in the world in and to the invention entitled: PROCESS AND METHODS FOR THE PREPARATION OF OPTICALLY ACTIVE CIS-2-HYDROXYMETHYL-4-(CYTOSIN-1'-YL)-1,3-OXATHIOLANE OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

as described in the International PCT Patent Application filed on March 14, 2005 with the Canadian PCT Receiving Office, including without limitation the right to claim, any and all of the benefit(s) of the International Convention relating to priority associated with the said invention and all of my corresponding rights, titles and interests in and to any and all patents, registrations and the like which may issue therefor anywhere in the world including, without limitation, in the United States and Canada, including any rights, titles and interest in any reissues and extensions thereof to be obtained in any country and any divisional, continuation, continuation-in-part, substitute application(s) or supplementary disclosure(s) which may be filed in any country and which pertains to the said invention.

I/We further agree without any further payment by said assignee other than reasonable expenses incurred by the undersigned, to communicate to said assignee, its representatives or agents, any facts relating to said invention or inventions, including evidence for interference purposes or for other proceedings, whenever requested; testify in any interference, litigation or other proceedings, whenever requested; and execute and deliver, on request, all lawful papers required to make any of the foregoing provisions effective, and likewise make these provisions binding upon my/our heirs, legal representatives, administrators and assigns.

I/We hereby authorize the firm of BCF LLP to correct errors in this assignment or to insert any further identification or other information necessary or desirable to make this assignment suitable for recordal.

Le(s) soussigné(s) désire(nt) que la présente cession soit rédigée en anglais. The undersigned request(s) that the present assignment be in English.

IN WITNESS WHEREOF, I/We have hereunto set my/our hand(s) and seal this 22ND day of APRIL 2005.

Witness

Assignor : Alex CIMPOIA

ASSIGNMENT OF INVENTION

UNIVERSAL

WHEREAS, I/We Dan Simion (deceased) by The Estate of Dan SIMION, by its Executrix, Ioana R. Simion, whose full addresses is 147 Rhatigan Road, Edmonton, Alberta T6R 1N5

(hereinafter referred to as the assignor) in consideration of \$1.00 and other good and valuable consideration, the receipt of which is hereby acknowledged and for which a full release and discharge is given, do hereby sell and assign to SHIRE BIOCHEM INC.

whose full post office address is 2250 Alfred-Nobel Blvd., Suite 500, Ville St-Laurent, Québec, CANADA, H4S 2C9

(hereinafter referred to as the assignee), all of my/our rights, titles and interests in each and every country in the world in and to the invention entitled: PROCESS AND METHODS FOR THE PREPARATION OF OPTICALLY ACTIVE CIS-2-HYDROXYMETHYL-4-(CYTOSIN-1'-YL)-1,3-OXATHIOLANE OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

as described in the International PCT Patent Application filed on March 14, 2005 with the Canadian PCT Receiving Office, including without limitation the right to claim, any and all of the benefit(s) of the International Convention relating to priority associated with the said invention and all of my corresponding rights, titles and interests in and to any and all patents, registrations and the like which may issue therefor anywhere in the world including, without limitation, in the United States and Canada, including any rights, titles and interest in any reissues and extensions thereof to be obtained in any country and any divisional, continuation, continuation-in-part, substitute application(s) or supplementary disclosure(s) which may be filed in any country and which pertains to the said invention.

I/We further agree without any further payment by said assignee other than reasonable expenses incurred by the undersigned, to communicate to said assignee, its representatives or agents, any facts relating to said invention or inventions, including evidence for interference purposes or for other proceedings, whenever requested; testify in any interference, litigation or other proceedings, whenever requested; and execute and deliver, on request, all lawful papers required to make any of the foregoing provisions effective, and likewise make these provisions binding upon my/our heirs, legal representatives, administrators and assigns.

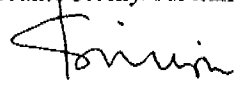
I/We hereby authorize the firm of BCF LLP to correct errors in this assignment or to insert any further identification or other information necessary or desirable to make this assignment suitable for recordal.

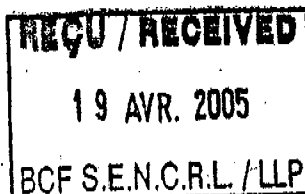
Le(s) soussigné(s) désire(nt) que la présente cession soit rédigée en anglais. The undersigned request(s) that the present assignment be in English.

IN WITNESS WHEREOF, I/We have hereunto set my/our hand(s) and seal this 13 day of September 2005.

Witness

SIMON R. FOXCROFT
BARRISTER & SOLICITOR


The Estate of Dan Simion, by its Executrix,
Ioana R. Simion



PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only	
PCT/CA 2005/000384	
International Application No.	
14 MARCH 2005	14.03.05
International Filing Date	
RO/CA	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired) (12 characters maximum) 10680-002	

Box No. I TITLE OF INVENTION Process and methods for the preparation of optically active cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane or pharmaceutically acceptable salts thereof	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) SHIRE BIOCHEM INC. 2250 Alfred-Nobel Blvd. Suite 500 Ville St-Laurent, Québec H4S 2C9 CANADA	
Telephone No. 514-787-2319	
Facsimile No. 514-787-2423	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: CA	State (that is, country) of residence: CA
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) SIMION, Dan (deceased)	
This person is: ☐ applicant only ☒ applicant and inventor ☒ inventor only (If this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) BRITT, Katherine; PRINCE, Gaétan; KOSIE, Ronald S.; FOURNIER, Claude BCF LLP 1100 René-Lévesque Blvd. West, 25th Floor Montréal, Québec H3B 5C9 CANADA	
Telephone No. 514-397-6705	
Facsimile No. 514-397-8515	
Teleprinter No.	
Agent's registration No. with the Office	
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

44 DELETED RO/CA

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

CIMPOIA, Alex
290 Elgar, apt. 204
Verdun, Québec H3E 1C9
CANADA

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

CA

State (that is, country) of residence:

CA

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ KR Republic of Korea is not designated for any kind of national protection
- ☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1)				
item (2)				
item (3)				

- ☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

- ☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / CA

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

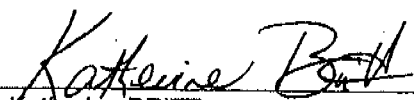
Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | |
|---|--|---|
| ☐ Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| ☐ Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| ☐ Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| ☐ Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| ☐ Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

Box No. IX CHECK LIST; LANGUAGE OF FILING	
This international application contains: (a) In paper form , the following number of sheets: request (including declaration sheets) : 4 description (excluding sequence listing and/or tables related thereto) : 26 claims : 12 abstract : 1 drawings : Sub-total number of sheets : 43 sequence listing : tables related thereto : <i>(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)</i> Total number of sheets : 43 (b) ☐ only in computer readable form (Section 801(a)(i)) (i) ☐ sequence listing (ii) ☐ tables related thereto (c) ☐ also in computer readable form (Section 801(a)(ii)) (i) ☐ sequence listing (ii) ☐ tables related thereto Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the ☐ sequence listing : ☐ tables related thereto : <i>(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)</i>	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): 1. ☒ fee calculation sheet : 1 2. ☐ original separate power of attorney : 3. ☐ original general power of attorney : 4. ☐ copy of general power of attorney; reference number, if any: : 5. ☐ statement explaining lack of signature : 6. ☐ priority document(s) identified in Box No. VI as item(s): : 7. ☐ translation of international application into (language): : 8. ☐ separate indications concerning deposited microorganism or other biological material : 9. ☐ sequence listing in computer readable form (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column : 10. ☐ tables in computer readable form related to sequence listing (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column : 11. ☐ other (specify): : Figure of the drawings which should accompany the abstract: Language of filing of the international application: ENGLISH
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i> BCF LLP by:  Katherine BRITT	

For receiving Office use only	
1. Date of actual receipt of the purported international application: 14 MARCH 2005 14.03.05	2. Drawings: ☐ received: ☒ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA/CA	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

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122

**Process and methods for the preparation of optically active
cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane or
pharmaceutically acceptable salts thereof.**

5 FIELD OF INVENTION

The present invention relates to the field of making optically active compounds, particularly the preparation of optically active oxathiolane nucleosides.

10 BACKGROUND

Classes of compounds known as 2-substituted-4-substituted-1,3-oxathiolanes have been found to have potent antiviral activity. In particular, these compounds have been found to act as potent inhibitors of HIV-1 replication in T-lymphocytes over a

15 prolonged period of time with less cytotoxic side effects than compounds known in the art. These compounds have also been found active against 3TC-resistant HIV strains. These compounds are also useful in prophylaxis and treatment of hepatitis B virus infections.

20

Cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane 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'-
25 oxa-4'-thiacytidine and Their 5-Fluoro Analogues in vitro", *J. Med. Chem.*, (1995), Vol. 38, No. 1, pp. 1-4, as well as US 6,228,860 or *Nucleosides and Nucleotides*, (1995) 14(3-5) pp. 627-735 which are incorporated herein by reference.

30 Typically, when compounds are desired as a single enantiomer they 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. A complete review of known technology
35 may be found in "Enantiomers, Racemates and Resolutions" by J.

123

Jacques, A. Collet & S.H. Wilen (John Wiley & Sons, 1981).
Alternatively, compounds or any convenient intermediate may be
resolved by enzymatic resolution with a suitable enzyme such as
cytidine deaminase or selective enzymatic degradation of a
5 suitable derivative. See for example Storer et al., "The
resolution and Absolute Stereochemistry of the Enantiomers of
cis-1[2(Hydroxymethyl)-1,3-Oxathiolan-5-Yl]Cytosine (BCH-189):
Equipotent Anti-HIV Agents", *Nucleosides & Nucleotides*, 12(2),
225-236 (1993).

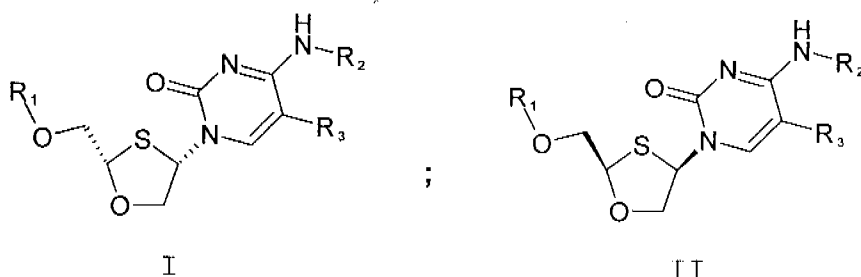
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Another process known as resolution by formation of
diastereomeric compounds require intervention of chiral agents.
Unlike enantiomers, diastereomers may have significantly
different physico-chemical properties that may allow for the
15 separation from one another. One variation of such technique
involves the formation and separation of diastereomeric salts
between a racemic substance and an optically active resolving
acid or base. Pasteur first reported the resolution of a
racemic acid using an optically active base (Pasteur, L., *C.R.*
20 *Acad. Sci.* (1853) 37 p.162; Pasteur, L., *Ann. Chim* (Paris)
(1853) 3, 38 p. 437). A resolution using nonstoichiometric
quantities of chiral agents was studied by Marckwald 1896 and
later referred to as "method of half-quantity" (Marckwald, W.,
Ber. (1896), 29, p. 42; Marckwald, W., *Ber.* (1896), 29, p. 43).
25 The process for the resolution of tartaric acid through
crystallization of its salt of cinchonine was improved by
Marckwald while using only half of the cinchonine necessary for
formation of the tartrate salt. The resolution is based on the
separation of one of the diastereomers and one of the
30 enantiomers rather than the separation of two diastereomeric
salts formed in equal quantities. When using the method of
half-quantity, the racemate is partially neutralized by the
optically active resolving agent. In the process described by
Pope & Peachey (Pope, W.J., Peachey, S.J. *J. Chem. Soc.* (1899)
35 75, p.1066) the excess of racemate not neutralized by the

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5 SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a process for producing optically active compound of formula I or II:

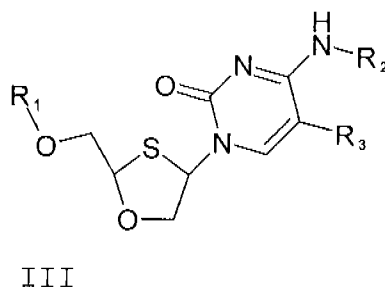


10 wherein:

R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl (e.g., C₇₋₁₂ arylalkyl), (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl (e.g., (CO)C₇₋₁₂ arylalkyl);

15 R₂ is H, C₁₋₆ alkyl or CO-R₅; wherein R₅ is H or C₁₋₆ alkyl;
R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or
CF₃; comprising:

a) reacting a compound of formula III in the cis configuration:

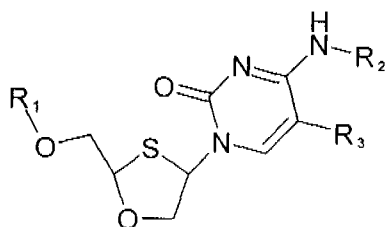


with a chiral acid to produce two diastereomeric salts;

b) recovering substantially one diastereomeric salt;
c) converting said one diastereomeric salt into said optically active compound.

(125)

In another aspect, there is provided a method for resolving a compound of formula III, in the cis configuration:



III

5 wherein:

R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl (e.g., C₇₋₁₂ arylalkyl), (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)O-C₆₋₁₂ aryl, or (CO)-C₆₋₁₂ arylalkyl (e.g., (CO)C₇₋₁₂ arylalkyl);

R₂ is chosen from H, C₁₋₆ alkyl, C₁₋₆ acyl and CO-R₅;

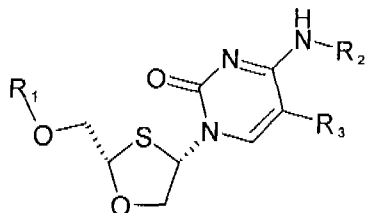
10 wherein R₅ is H or C₁₋₆ alkyl;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or CF₃; comprising:

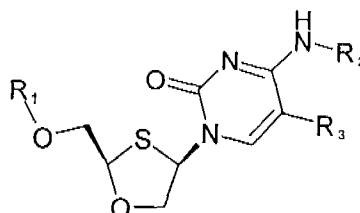
a) reacting said compound of formula III with a chiral acid to produce two diastereomeric salts;

15 b) recovering substantially one diastereomeric salt;

c) converting said one diastereomeric salt into compound of formula I or II:



I



II

20

In a further aspect, the present invention provides a process for producing optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:

a) reacting a chiral acid with cis-2-hydroxymethyl-4-(cytosin-

25 1'-yl)-1,3-oxathiolane to produce two diastereomeric salts;

b) recovering substantially one diastereomeric salt;

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c) converting said one diastereomeric salt into said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

5 In still a further aspect, there is provided a process for producing (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane comprising:

- a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a half quantity molar amount of a chiral acid to substantially produce (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt, said molar ratio being with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane;
- 10
- b) recovering said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt;
- 15
- c) converting said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt into said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

20 In still a further aspect, there is provided a process for producing optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:

- a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a chiral acid and an achiral acid to produce substantially one diastereomeric salt and substantially one enantiomeric salt;
- 25
- b) recovering said diastereomeric salt;
- c) converting said diastereomeric salt into optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

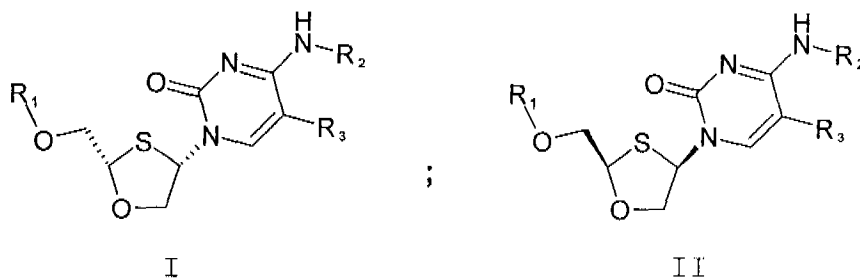
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In a further aspect, the present invention further provides novel cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane salts.

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DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to a process for producing optically active compound of formula I or II:



wherein:

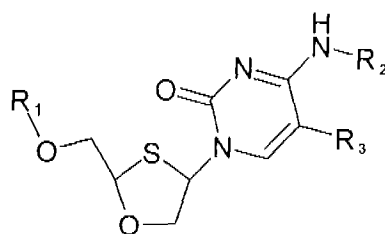
R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl (e.g., C₇₋₁₂ arylalkyl), (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or
10 (CO)C₆₋₁₂ arylalkyl (e.g., (CO)C₇₋₁₂ arylalkyl);

R₂ is H, C₁₋₆ alkyl or CO-R₅;

wherein R₅ is H or C₁₋₆ alkyl;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or CF₃; comprising:

15 a) reacting a compound of formula III in the cis configuration:



III

with a chiral acid to produce two diastereomeric salts;

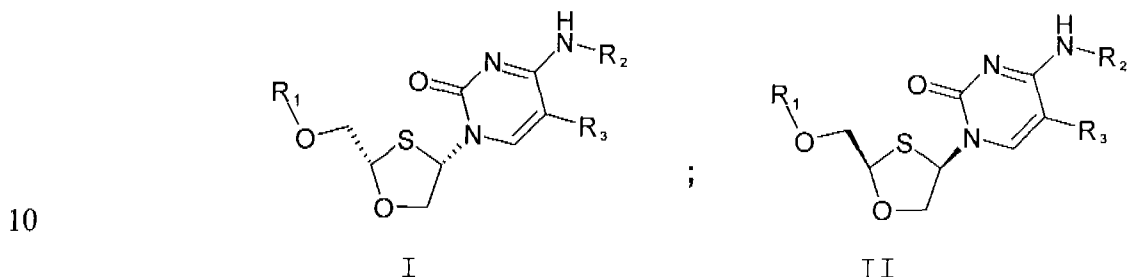
20 b) recovering substantially one diastereomeric salt;
c) converting said one diastereomeric salt into said optically active compound.

The scope the present invention includes a process as described
25 above wherein the over-all yield of the desired enantiomer is equal to or greater than 25% (100g of racemate would produce at least 25g of the desired enantiomer).

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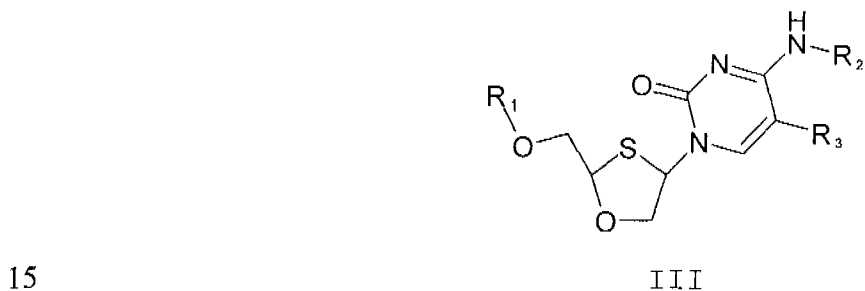
An embodiment of the present invention relates to a process which generates a final product which is substantially in the form of a single enantiomer. Additionally, an embodiment of the present invention includes a process described above which
5 results in a product having an enantiomeric excess of 99% or higher.

An embodiment of the present invention relates to a process for producing optically active compound of formula I or II:



wherein: R₁, R₂, R₃ are as defined above, comprising:

a) reacting a compound of formula III in the cis configuration:

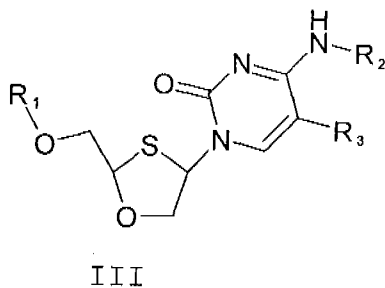


with a chiral acid to produce two diastereomeric salts;

b) recovering substantially one diastereomeric salt;

c) converting said one diastereomeric salt into said optically active compound.

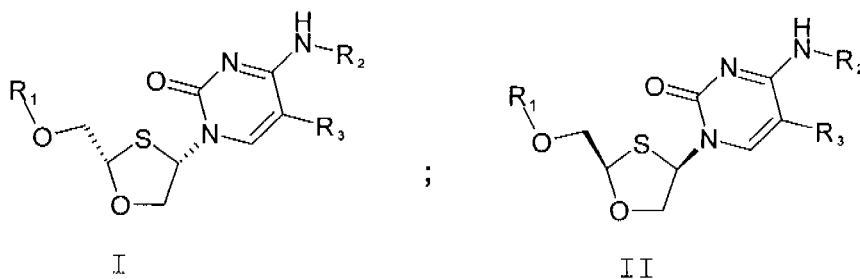
20 There is also provided a method for resolving a compound of formula III, in the cis configuration:



124 129

wherein: R_1 , R_2 , R_3 are as defined above, comprising:

- a) reacting said compound of formula III with a chiral acid to produce two diastereomeric salts;
- b) recovering substantially one diastereomeric salt;
- 5 c) converting said one diastereomeric salt into a compound of formula I or II:



- 10 In one embodiment, R_1 is H, C_{1-6} alkyl, $(CO)C_{1-6}$ alkyl, $(CO)O-C_{1-6}$ alkyl or $(CO)C_{6-12}$ aryl.

In further embodiments:

- R_1 is H, $(CO)C_{1-6}$ alkyl or $(CO)C_{6-12}$ aryl,
- 15 R_1 is H,
- R_1 is $(CO)C_{6-12}$ aryl.

Still in further embodiments:

- R_2 is H or C_{1-6} alkyl,
- R_2 is $CO-R_5$, wherein R_5 is H or C_{1-6} alkyl,
- 20 R_2 is formyl or acetyl.

In one embodiment, R_3 is H, C_{1-6} alkyl or fluoride.

In further embodiments:

- R_3 is H or fluoride,
- 25 R_3 is H,
- R_3 is fluoride.

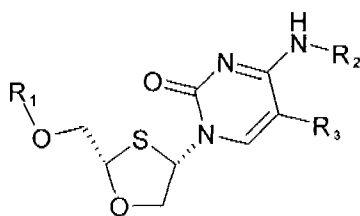
In one embodiment, the chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.

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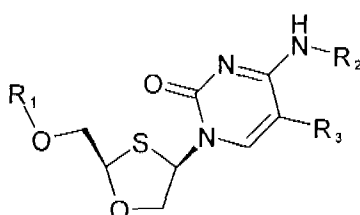
In one embodiment, the chiral acid is (1R)-(-)-10-camphorsulfonic acid.

In another embodiment, the optically active compound is



I

In another embodiment, the optically active compound is



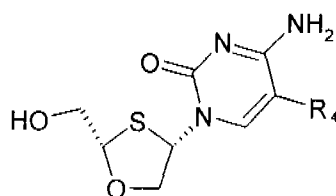
II

In one embodiment, the two diastereomeric salts comprise a first more soluble diastereomeric salt and a second less soluble diastereomeric salt.

15

In a further embodiment, step b) described above further comprises recovering a second diastereomeric salt.

The present invention further provides a process for producing
20 optically active compound of formula IV:



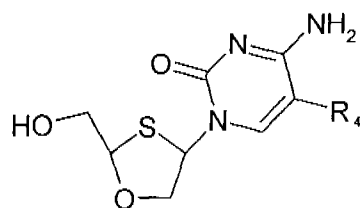
IV

wherein:

R₄ is H or fluoride; comprising:

25 a) reacting a compound of formula III in the cis configuration:

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III

- with a chiral acid selected from (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or
- 5 (-)-L-malic acid, to produce two diastereomeric salts;
- b) recovering substantially one diastereomeric salt;
- c) converting said one diastereomeric salt into said optically active compound.
- 10 In one aspect, there is provided a process for producing optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:
- a) reacting a chiral acid with cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane to produce two diastereomeric
- 15 salts;
- b) recovering substantially one diastereomeric salt;
- c) converting said one diastereomeric salt into said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.
- 20 In one embodiment, the optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is crystalline.
- In one embodiment, the optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is the (-) enantiomer.
- 25 In one embodiment, the optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is the (+) enantiomer.
- 30 In one embodiment, the chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.

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In one embodiment, the chiral acid is (1R)-(-)-10-camphorsulfonic acid.

5 In one embodiment, the optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 60% or higher.

In one embodiment, the optically active cis-2-hydroxymethyl-4-
10 (cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 70% or higher.

In one embodiment, the optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of
15 80% or higher.

In one embodiment, the optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 90% or higher.
20

In one embodiment, the optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 95% or higher.

25 In one embodiment, the optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 98% or higher.

In one embodiment, the optically active cis-2-hydroxymethyl-4-
30 (cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 99% or higher.

In one aspect, there is provided a process for producing (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral
35 acid salt, comprising:

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- a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a chiral acid to produce (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt and (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt;
- b) recovering said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt.

In one embodiment, said step b) further comprises recovering (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt.

In one embodiment, said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt contains less than 30% of (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt.

In further embodiments:

(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt contains less than 20% of (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt;

(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt contains less than 10% of (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt;

(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt contains less than 5% of (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt;

(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt contains less than 1% of (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt;

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(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt is substantially free of (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt.

5

In one embodiment, the process further comprises recrystallizing said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral resolving acid addition salt.

10 In one embodiment, said chiral acid is in stoichiometric molar ratio with regard cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

In one embodiment, said chiral acid is in nonstoichiometric
15 molar ratio with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

In one aspect, there is provided a process for producing (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane

20 comprising:

- a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a half-quantity molar amount of a chiral acid to substantially produce (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt, said molar
25 ratio being with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane;
- b) recovering said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane•chiral acid salt;
- c) converting said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-
30 1,3-oxathiolane•chiral acid salt into said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

In one embodiment, said step a) further comprise adding a half-quantity molar amount of achiral acid to substantially produce
35 (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-

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oxathiolane.achiral acid salt, said molar ratio being with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

- 5 In one embodiment, said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.

In one embodiment, said chiral acid is (1R)-(-)-10-
10 camphorsulfonic acid.

In one embodiment, said achiral acid is hydrochloric acid.

In a further aspect, there is provided a process for producing
15 crystalline optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:

- a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a chiral acid and an achiral acid to produce substantially one diastereomeric salt and substantially one
20 enantiomeric salt;
b) recovering said diastereomeric salt;
c) converting said diastereomeric salt into optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

- 25 An embodiment of the process of the present invention generates an over-all yield equal to or greater than 25% of the desired enantiomer.

An additional embodiment of the process of the present
30 invention generates the desired enantiomer with an enantiomeric excess of 95% or higher.

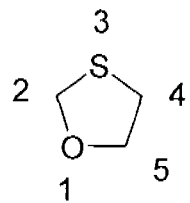
Another embodiment of the process of the present invention generates an over-all yield equal to or greater than 25% of the
35 desired enantiomer and an enantiomeric excess of 99% or higher.

In one embodiment, said diastereomeric salt is (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonate.

5

In one embodiment, said enantiomeric salt is (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.hydrochloric acid salt.

10 An "oxathiolane ring" is any substituted or unsubstituted five member monocyclic ring that has an oxygen atom in position 1 and a sulfur atom in position 3 of the ring as illustrated below:



15 It will be apparent to a skilled person in the field that the reaction conditions described in these examples may be modified and still achieve successful results.

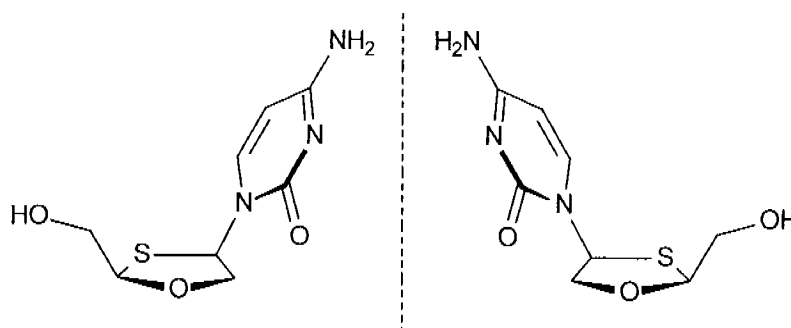
Typically, solvents, temperature and time of reaction may be varied. A suitable solvent will allow the process to occur under the reaction conditions without adversely affecting the reaction. The solvent may be one or more solvents and may be organic (e.g., methanol, ethanol, propanol, isopropanol, dichloromethane, dichloroethane, tetrahydrofuran, hexane, pentane, ether spirit, ethyl ether), water or aqueous/organic (e.g., methanol-water, isopropanol-water). The solvents may also be present in various ratios (for example 1:1, 2:1, 5:1, 10:1 or 1:1:1, 1:2:1).

30 The temperature may be varied and will allow the process to occur under the reaction conditions. The suitable temperature

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will provide the desired product without adversely affecting the reaction.

It will be appreciated by a person of skill in the art that a
5 suitable period of time is a time for obtaining a sufficient
chemical transformation of the starting material, obtaining the
desired purity or the desired yield of the reaction product or
a combination of those. The reaction can typically be
monitored, if desired, by thin layer chromatography, light
10 absorption (e.g., U.V.) of reaction medium, gas chromatography



or high performance liquid chromatography (HPLC).

Cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane exist as enantiomers which may be in various ratios.

15 (-) enantiomer (+) enantiomer

For example the enantiomers may be present as racemate (i.e. in
equal proportions) or any alternative ratio of the enantiomers
such as for example 1:1, 2:1, 5:1, 10:1, 100:1 or 1:2, 1:5,
20 1:10, 1:100. References hereinafter to cis-2-Hydroxymethyl-4-
(cytosin-1'-yl)-1,3-oxathiolane according to the invention
includes all such possible ratios of enantiomers.

Unless otherwise defined, all technical and scientific terms
25 used herein have the same meaning as commonly understood by one
of ordinary skill in the art to which this invention belongs.
All publications, patent applications, patents, and other
references mentioned herein are incorporated by reference in
their entirety. In case of conflict, the present specification,

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including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

5 As used in this application, the term "alkyl" represents a straight chain or branched chain hydrocarbon moiety which may optionally be substituted by one or more of halogen, nitro, nitroso, sulfate, sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl (e.g., C₇₋₁₂
10 aralkyl), C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl (e.g., C(O)C₇₋₁₂ aralkyl), heterocycle having 3-10 ring-members, hydroxyl, amino, ester, cyano, azido, amidino or guanido. Useful examples of alkyl include isopropyl, propyl, ethyl, methyl, hexyl or cyclopropyl,
15 which in each case is unsubstituted or substituted one or more times by, for example, halogen, nitro, nitroso, sulfate, sulfonate, amide, hydroxyl, amino, ester, cyano, azido, amidino or guanido. The term alkyl is also meant to include alkyl in which one or more hydrogen atoms are each replaced by a
20 halogen, preferably fluoro (e.g., CF₃- or CF₃CH₂-).

The term "aryl" represents a carbocyclic moiety containing at least one benzenoid-type ring which may optionally be substituted by one or more of halogen, nitro, nitroso, sulfate,
25 sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl, heterocycle having 3-10 ring-members, hydroxyl, amino, ester, cyano, azido, amidino or guanido. Examples of aryl include
30 phenyl and naphthyl, which in each case is unsubstituted or substituted one or more times by, for example, halogen, nitro, nitroso, sulfate, sulfonate, amide, hydroxyl, amino, ester, cyano, azido, amidino or guanido.

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The term "aralkyl" represents an aryl group attached to the adjacent atom by an alkyl. Useful examples include benzyl which is unsubstituted or substituted one or more times by, for example, halogen, nitro, nitroso, sulfate, sulfonate, amide, 5 hydroxyl, amino, ester, cyano, azido, amidino or guanido.

The term "heterocycle" represents a saturated or unsaturated, cyclic moiety wherein said cyclic moiety is interrupted by at least one heteroatom, (e.g., oxygen, sulfur or nitrogen) which 10 may optionally be substituted by one or more of halogen, nitro, nitroso, sulfate, sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl, hydroxyl, amino, ester, cyano, azido, amidino 15 or guanido. It is understood that the term heterocyclic ring represents a mono or polycyclic (e.g., bicyclic) ring. Examples of heterocyclic rings include but are not limited to epoxide; furan; benzofuran; isobenzofuran; oxathiolane; dithiolane; dioxolane; pyrrole; pyrrolidine; imidazole; pyridine; 20 pyrimidine; indole; piperidine; morpholine; thiophene and thiomorpholine, which in each case is unsubstituted or substituted one or more times by, for example, halogen, nitro, nitroso, sulfate, sulfonate, amide, hydroxyl, amino, ester, cyano, azido, amidino or guanido.

25

The term "independently" means that a substituent can be the same or different definition for each item.

The term "optically active" means that the enantiomeric excess 30 is greater than zero.

The optical purity is numerically equivalent to the "enantiomeric excess". The term "enantiomeric excess" or "ee" is defined in percentage (%) value as follows: [mole fraction 35 (major enantiomer) - mole fraction (minor enantiomer)] x 100.

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(for example, an ee of 99% represent a ratio of 99.5% of one enantiomer and 0.5% of the opposite enantiomer).

The term "chiral acid" means an optically active acidic compound able to form a diastereomer with a compound of formula III, such as 2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane. Examples of such acids include without limitation: tartaric acid, O,O'-dibenzoyltartaric acid, O,O'-di-p-toluoyltartaric acid, 2-nitrotartronic acid, mandelic acid, malic acid, 2-phenoxypropionic acid, 10-camphorsulfonic acid, hydratropic acid, N-acetylleucine, N-(α -methylbenzyl)succinamic acid, N-(α -methylbenzyl)phthamic acid, 3-bromocamphor-9-sulfonic acid, camphor-3-sulfonic acid, quinic acid, di-O-isopropylidene-2-oxo-L-gulonic acid, lasalocid, 1,1'-binaphthyl-2,2/-phosphoric acid, cholestenonesulfonic acid. Further examples include (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid and (-)-L-malic acid.

A person of ordinary skill will understand that the term "achiral acid" includes a variety of acids such as inorganic acids (e.g., HCl, HBr, H₂SO₄, HBF₄); sulfonic acids (e.g., methanesulfonic, benzenesulfonic, p-toluenesulfonic, p-hydroxytoluenesulfonic, sulfanilic, p-chlorobenzenesulfonic); substituted acetic acids (e.g., glycolic, chloro-, dichloro-, trichloroacetic); polycarboxylic and oxy acids (e.g., succinic, adipic, maleic, fumaric, citric, pyruvic).

There are also provided pharmaceutically acceptable salts of the compounds of the present invention. By the term "pharmaceutically acceptable salts" is meant salts derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulphuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulphonic, tartaric, acetic, trifluoroacetic, citric,

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methanesulphonic, formic, benzoic, malonic,
 naphthalene-2-sulphonic, cysteic acid and benzenesulphonic
 acids. Other acids such as oxalic, while not themselves
 pharmaceutically acceptable, may be useful as intermediates in
 5 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 NR_4^+ (where R is C_{1-4} alkyl) salts.

10

References hereinafter to a compound according to the invention
 include the compound and its pharmaceutically acceptable salts.

Dowex® Marathon A-OH is a mark of DOW Chemical Company.

15

In one aspect, the present invention provides novel compounds
 as described in table 1:

TABLE 1

	(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.1R-(-)-10-camphorsulfonate
	(+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.1R-(-)-10-camphorsulfonate
	(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.1S-(+)-10-camphorsulfonate
	(+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.1S-(+)-10-camphorsulfonate

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In one embodiment, the process and method of the present invention comprises those wherein the following embodiments are present, either independently or in combination.

5

The entire disclosures of all applications, patents and publications, cited above and below, are hereby incorporated by reference.

10 EXAMPLES

The following examples are provided to illustrate various embodiments of the present invention and shall not be considered as limiting in scope.

15

Example 1: Screening of chiral resolving agents

Experimental conditions:
100 mg of cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane
20 is combined with 1 equivalent of the resolving agent, in 1 ml of solvent (95% ethanol- 5% water). The solid is isolated and weighed. A significant test requires that the weight of crystals does not exceed 50% of the overall diastereomer amount. If this condition is not fulfilled the amount or type
25 of solvent is changed.

TABLE 2

Chiral Resolving Agent	No crystal Observed	Crystal Observed
(-)-L-Malic acid		x
(-)-L-Lactic acid	X (oil)	
(+)-L-Tartaric acid		x

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(-)-2,3-Dibenzoyl-L-Tartaric acid		x
(1R)-(-)-10-Camphorsulfonic acid		x

Example 2: Resolution experimentations

5 General experimental conditions:

cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, and a chiral acid were dissolved with stirring in a solvent at a temperature of about room temperature to about 50 °C and then cooled at a temperature of between about room temperature to -

10 10°C for 2-4 hours. The solid product was collected by filtration. The composition was determined by Chiral HPLC, the aqueous buffer was prepared by diluting 0.5 ml triethylamine in 1L HPLC water, the pH adjusted to 6.88 with glacial acetic acid,. The mobile phase was prepared by combining the aqueous

15 buffer and methanol in a ratio of 90:10 and the gas was removed. The following conditions were used:

Column: Astec Cyclobond I 2000 RSP, 5 micron, 250 x 4.5 mm.

20 Guard column: Astec Cyclobond I 2000 RSP, 20 x 4.0 mm
Flow: 0.6 ml/min.

Sample preparation: prepare solution of 0.5 mg/ml in mobile phase.

Injection volume: 5 µL.

25 Mode: isocratic.

UV-Vis detector at: 270 nm.

Column temperature: 0°C.

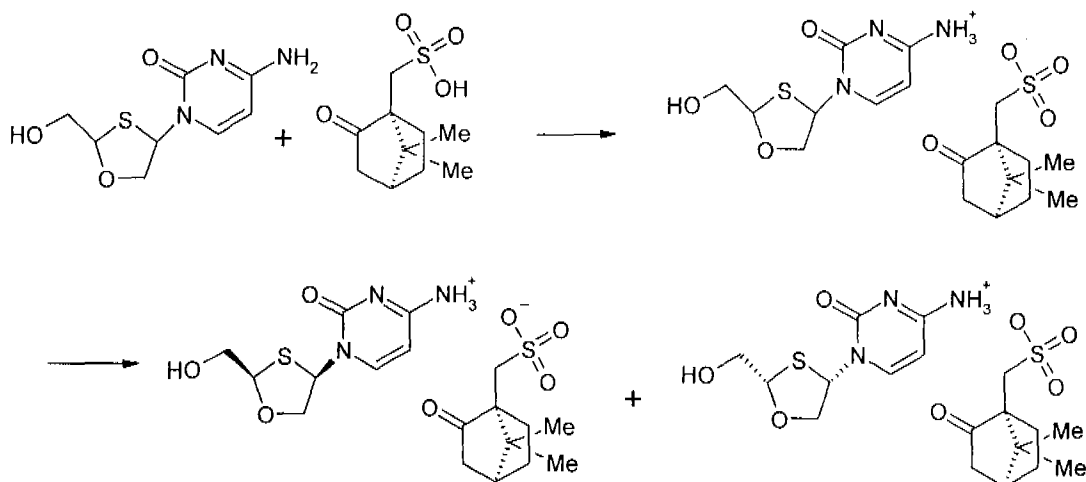
Run time: 40 min.

TABLE 3

	Chiral resolving agent/ achiral acid	Solvent	Experimental Conditions	Enantiomeric Ratio (yield %)
1	L-tartaric acid (0.5 eq)/ HCl (0.5eq.)	Isopropyl alcohol and water 1:1 (v/v)	100g scale. Magnetic stirring.	45.2:52.1 (63%)
2	(R) - Camphorsulfonic Acid (0.5 eq)/ HCl (0.5eq.)	Isopropyl alcohol and water 1:1 (v/v)	5g scale. Heated @50°C to dissolve solids Magnetic stirring	92.4:7.6 (36%)
3	(-) -2,3- Dibenzoyl-L-Tartaric acid (0.25eq)/ HCl (0.5eq.)	Water	5g scale. Magnetic stirring	47.6:45.7 (41.7%)
4	(R) - Camphorsulfonic Acid (0.5 eq)/ HCl (0.5eq.)	Isopropyl alcohol and water 1:1 (v/v)	25g scale. Mechanical stirring	90.9:9.1 (52.6%)
5	(R) - Camphorsulfonic Acid (0.5 eq)/ HCl (0.5eq.)	Water Methanol 17% water in methanol (v/v)	5g scale. Heated at reflux. Magnetic stirring	78.7:21.3 (72%)
6	(R) - Camphorsulfonic Acid (1 eq)/ no achiral acid	Isopropyl alcohol and water 1:1 (v/v)	5g scale. Heated @50°C to dissolve solids Magnetic stirring	53.6:46.4 (60.6%)

Scheme 1

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Example 3: Diastereomeric salt optical resolution of cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane (1.03g, 4.3 mmol), and (1R)-(-)-10-Camphorsulfonic acid (1.03g, 4.3 mmol) were dissolved in 32 mL of a 1:1 isopropyl alcohol and water (v/v) at 50 °C. The solution was cooled at 0 °C. The solid was filtered to provide 0.55g of dry crystals. The diastereomeric composition was determined by HPLC to be 87:13 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt : (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt)].

The mother liquor was concentrated to dryness giving 1.38 g of dry solids with a diastereomeric composition of 35:65 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt : (+)-cis-2-hydroxymethyl-4-(cytosin-

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1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt)] The composition was analyzed as shown in Example 2.

Example 4: Recrystallization to increase the diastereomeric

5 ratio of (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt with regard to (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-Camphorsulfonic salt.

- 10 The crude cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonate salt generated in entry 4 of table 3 in example 2 having an enantiomeric ratio of 90.9: 9.1 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt : (+)-cis-2-
- 15 hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt] was dissolved in isopropyl alcohol-water 1:1 (v/v) at 70°C. After cooling, the crystals were recovered with a yield of 76% and an enantiomeric ratio of 99.1: 0.9 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
- 20 oxathiolane.(1R)- (-)-10-camphorsulfonic salt : (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt].

25 Example 5: Kilogram-scale Diastereomeric salt optical resolution

- A mixture of isopropanol (2274 kg), distilled water (2905 kg), cis-2-Hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane (193.7
- 30 kg) were introduced into the reactor (model R06 5700L GLMS). Dilute hydrochloric acid (prepared as 41.57 kg in 380 kg of water) was introduced followed by (1R)-(-)-10-camphorsulfonic acid (100 kg). The temperature of the resulting slurry was adjusted to 50 °C and agitated until all solid dissolved. The

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solution was then cooled to about -10°C (-13°C to -7°C) and agitated for 4-6 hours.

The resulting slurry is filtered, rinsing forward with 60 L of 1:1 isopropyl alcohol and water (v/v). The product is pulled dry with enantiomeric ratio of 91:9 [(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt : (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt)].

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Isopropanol (228 kg) and water (291 kg) are added to the wet crude product then the temperature of the resulting solution was adjusted to 70°C and agitated until all solid dissolved the slurry is heated and agitated until all the solids dissolve.

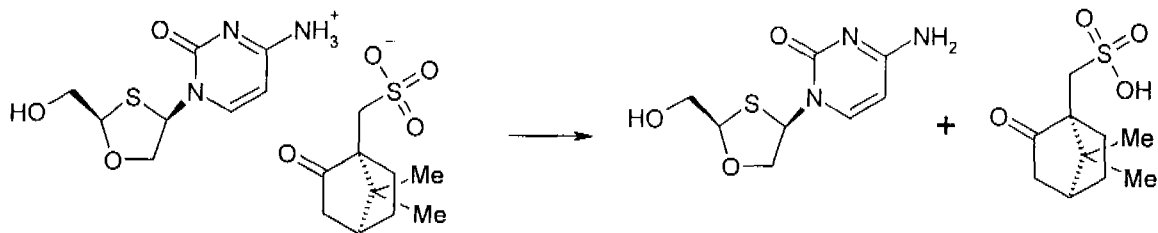
15 The solution is then cooled to about 22°C (19°C to 25°C) and then to 0°C (-3°C to 3°C).

The resulting slurry is filtered, rinsing forward with two portions of 70 L of 1:1 isopropyl alcohol and water (v/v). The product is spin-dried until the flow of filtrate essentially stops. 90.8 kg of product recovered (87% yield, corrected for loss on dryness of a sample) with an enantiomeric purity higher than 98%.

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Scheme 2

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Example 6: (1R)-(-)-10-camphorsulfonic acid removal from (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonic salt

5

(-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-Camphorsulfonic salt (90.8 kg) is dissolved in methanol (601 kg) by heating the mixture at 40°C and agitating until a solution is achieved.

10

The warm solution is circulated through an ion exchange column containing Dowex® Marathon A-OH (133.6 kg) and methanol (200 kg) of while maintaining the temperature at 40°C until no residual camphorsulfonic acid is detected by NMR analysis and
15 pH is greater than 7 (measured using water-wet pH paper).

The eluent is filtered, rinsing forward with methanol (200 kg).

The filtrate is partially concentrated under vacuum to about
20 140L.

The concentrate is cooled to about -10°C for one hour and agitated. The resulting slurry is filtered, rinsing forward with 2 portions of 18 kg of cold methanol (-10°C). The product
25 is dried under vacuum while heating to 35-40°C.

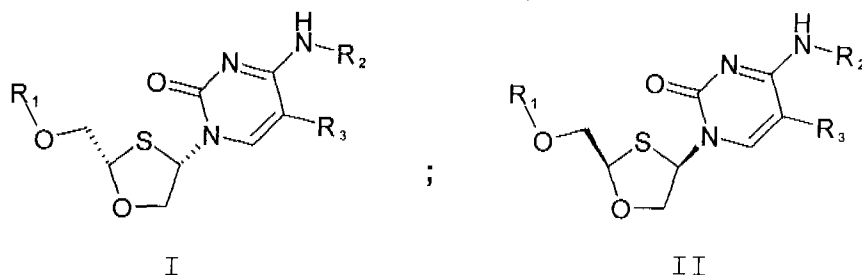
The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for
30 those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope

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We Claims:

1. A process for producing an optically active compound of
5 formula I or II:



wherein:

10 R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl, (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl;

R₂ is H, C₁₋₆ alkyl or CO-R₅;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or CF₃; and

R₅ is H or C₁₋₆ alkyl;

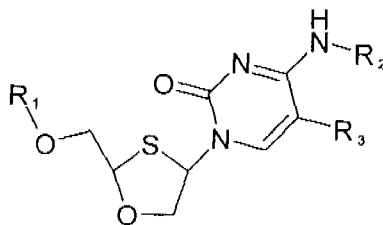
15 wherein in the definitions of R₁, R₂, R₃, and R₅ "alkyl" is, in each case, unsubstituted or substituted by one or more of halogen, nitro, nitroso, sulfate, sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl, 20 heterocycle having 3-10 ring-members, hydroxyl, amino, ester, cyano, azido, amidino or guanido; and

25 in the definitions of R₁, R₂, R₃, and R₅ "aryl" is, in each case, unsubstituted or substituted by one or more of halogen, nitro, nitroso, sulfate, sulfate ester, sulfonate, sulfonate ester, phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂ aralkyl, 30 heterocycle having 3-10 ring-members, hydroxyl, amino, ester, cyano, azido, amidino or guanido;

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said process comprising:

- a) reacting a compound of formula III in the cis configuration:



III

5

with a chiral acid to produce two diastereomeric salts;

- b) recovering substantially one diastereomeric salt;
c) converting said one diastereomeric salt into said optically active compound.

10

2. A process according to claim 1, wherein

R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl, (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl;

15

R₂ is H, C₁₋₆ alkyl or CO-R₅;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or CF₃; and

R₅ is H or C₁₋₆ alkyl.

20

3. A process according to claim 1, wherein R₁ is H, C₁₋₆ alkyl, (CO)C₁₋₆ alkyl, (CO)O-C₁₋₆ alkyl or (CO)C₆₋₁₂ aryl.

4. A process according to claim 1, wherein R₁ is H, (CO)C₁₋₆ alkyl or (CO)C₆₋₁₂ aryl.

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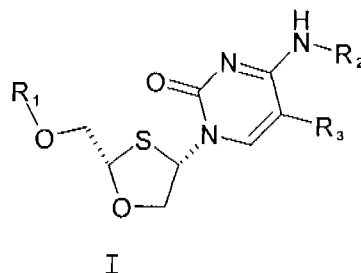
5. A process according to claim 1, wherein R₁ is H.

6. A process according to claim 1, wherein R₁ is (CO)C₆₋₁₂ aryl.

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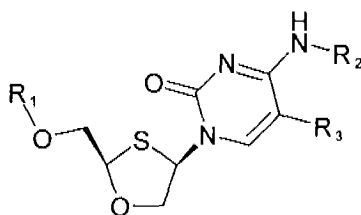
7. A process according to claim 1, wherein R₂ is H or C₁₋₆ alkyl.

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8. A process according to claim 1, wherein R_2 is CO-R_5 ,
wherein R_5 is H or C_{1-6} alkyl.
9. A process according to claim 1, wherein R_2 is formyl or
5 acetyl.
10. A process according to claim 1, wherein R_3 is H, C_{1-6} alkyl
or fluoride.
- 10 11. A process according to claim 1, wherein R_3 is H or
fluoride.
12. A process according to claim 1, wherein R_3 is H.
- 15 13. A process according to claim 1, wherein R_3 is fluoride.
14. A process according to anyone of claims 1 to 13, wherein
said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-
2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-
20 L-malic acid.
15. A process according to anyone of claims 1 to 13, wherein
said chiral acid is (1R)-(-)-10-camphorsulfonic acid.
- 25 16. A process according to claim 1, wherein said optically
active compound is



- 30 17. A process according to claim 1, wherein said optically
active compound is

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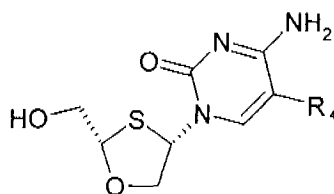


II

18. A process according to anyone of claims 1 to 17, wherein
5 said two diastereomeric salts comprise a first more
soluble diastereomeric salt and a second less soluble
diastereomeric salt.

19. A process according to anyone of claims 1 to 17, wherein
10 said step b) further comprise recovering a second
diastereomeric salt.

20. A process for producing optically active compound of
formula IV:

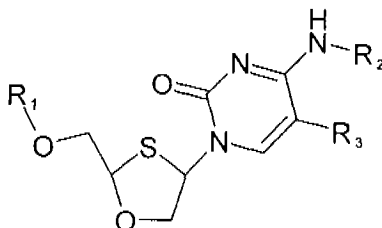


IV

wherein:

R₄ is H or fluoride; comprising:

20 a) reacting a compound of formula III in the cis
configuration:



III

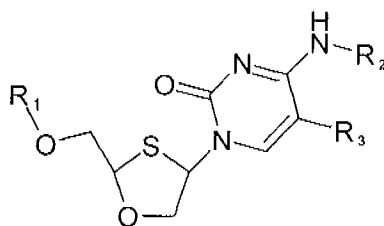
with a chiral acid selected from (1R)-(-)-10-
camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric

acid, (+)-L-tartaric acid or (-)-L-malic acid, to
produce two diastereomeric salts;

b) recovering substantially one diastereomeric salt;

c) converting said one diastereomeric salt into said
optically active compound.

21. A method for resolving a compound of formula III, in the
cis configuration:



III

wherein:

R₁ is H, C₁₋₆ alkyl, C₆₋₁₂ aryl, C₆₋₁₂ arylalkyl, (CO)C₁₋₆ alkyl,
(CO)O-C₁₋₆ alkyl, (CO)C₆₋₁₂ aryl, or (CO)C₆₋₁₂ arylalkyl;

R₂ is H, C₁₋₆ alkyl or CO-R₅;

R₃ is H, C₁₋₆ alkyl, bromide, chloride, fluoride, iodide or
CF₃; and

R₅ is H or C₁₋₆ alkyl;

wherein "alkyl," in each case, is unsubstituted or
substituted by one or more of halogen, nitro, nitroso,
sulfate, sulfate ester, sulfonate, sulfonate ester,
phosphonate ester, amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂
aryl, C₁₋₆ alkyloxy, C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂
aryl, C(O)C₆₋₁₂ aralkyl, heterocycle having 3-10 ring-
members, hydroxyl, amino, ester, cyano, azido, amidino or
guanido; and

"aryl," in each case, is unsubstituted or substituted by
one or more of halogen, nitro, nitroso, sulfate, sulfate
ester, sulfonate, sulfonate ester, phosphonate ester,
amide, C₁₋₆ alkyl, C₆₋₁₂ aralkyl, C₆₋₁₂ aryl, C₁₋₆ alkyloxy,
C₆₋₁₂ aryloxy, C(O)-C₁₋₆ alkyl, C(O)-C₆₋₁₂ aryl, C(O)C₆₋₁₂

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28. A method according to claim 21, wherein R₂ is formyl or acetyl.
29. A method according to claim 21, wherein R₃ is H, C₁₋₆ alkyl or fluoride.
30. A method according to claim 21, wherein R₃ is H or fluoride.
31. A method according to claim 21, wherein R₃ is H.
32. A method according to claim 21, wherein R₃ is fluoride.
33. A method according to claim 21, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.
34. A method according to claim 21, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.
35. A method according to anyone of claims 21 to 34, wherein said two diastereomeric salts comprise a first more soluble diastereomeric salt and a second less soluble diastereomeric salt.
36. A method according to anyone of claims 21 to 34, wherein said step b) further comprise recovering a second diastereomeric salt.
37. A process for producing optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:
- a) reacting a chiral acid with cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane to produce two diastereomeric salts;
 - b) recovering substantially one diastereomeric salt;

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c) converting said one diastereomeric salt into said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

5 38. A process according to claim 37, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is crystalline.

10 39. A process according to anyone of claims 37 to 38, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is (-) enantiomer.

15 40. A process according to anyone of claims 37 to 38, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane is (+) enantiomer.

20 41. A process according to anyone of claims 37 to 40, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.

42. A method according to anyone of claims 37 to 40, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.

25 43. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 60% or higher.

30 44. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 70% or higher.

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45. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 80% or higher.
- 5
46. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 90% or higher.
- 10
47. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 95% or higher.
- 15
48. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 98% or higher.
- 20
49. A process according to anyone of claims 37 to 40, wherein said optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane has an enantiomeric excess of 99% or higher.
- 25
50. A process for producing (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt, comprising:
- 30
- a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a chiral acid to produce (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt and (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid salt;

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b) recovering said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt.

51. A process according to claim 50, wherein said chiral acid
5 is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.
52. A method according to claim 50, wherein said chiral acid
10 is (1R)-(-)-10-camphorsulfonic acid.
53. A process according to anyone of claims 50 to 52, wherein
said step b) further comprise recovering (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral
acid salt.
- 15 54. A process according to anyone of claims 50 to 52, wherein
said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt contains less than 30% of
(+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid addition salt.
- 20 55. A process according to anyone of claims 50 to 52, wherein
said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt contains less than 20% of
25 (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid addition salt.
56. A process according to anyone of claims 50 to 52, wherein
said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt contains less than 10% of
30 (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid addition salt.
57. A process according to anyone of claims 50 to 52, wherein
35 said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-

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oxathiolane.chiral acid salt contains less than 5% of (+)-
cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral resolving acid addition salt.

- 5 58. A process according to anyone of claims 50 to 52, wherein
said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral acid salt contains less than 1% of (+)-
cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral resolving acid addition salt.

10

59. A process according to anyone of claims 50 to 52, wherein
said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
oxathiolane.chiral acid salt is substantially free of (+)-
cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
15 oxathiolane.chiral resolving acid addition salt.

60. A process according to anyone of claims 50 to 59, further
comprising recrystallizing said (-)-cis-2-hydroxymethyl-4-
(cytosin-1'-yl)-1,3-oxathiolane.chiral resolving acid
20 addition salt.

61. A process according to anyone of claims 50 to 59, wherein
said chiral acid is in stoichiometric molar ratio with
regard cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
25 oxathiolane.

62. A process according to anyone of claims 50 to 59, wherein
said chiral acid is in nonstoichiometric molar ratio with
regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
30 oxathiolane.

63. A process for producing (-)-cis-2-hydroxymethyl-4-
(cytosin-1'-yl)-1,3-oxathiolane comprising:
a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
35 oxathiolane with a half quantity molar amount of a

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chiral acid to substantially produce (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt, said molar ratio being with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane;

5 b) recovering said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt;

c) converting said (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.chiral acid salt into said

10 (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

64. A process according to claim 62, wherein said step a) further comprise adding a half-quantity molar amount of

15 achiral acid to substantially produce (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.achiral acid salt, said molar ratio being with regard to cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.

20 65. A process according to anyone of claims 63 to 64, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.

25 66. A process according to anyone of claims 63 to 64, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.

67. A process according to anyone of claims 63 to 66, wherein said achiral acid is hydrochloric acid.

30 68. A process for producing crystalline optically active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane, comprising:

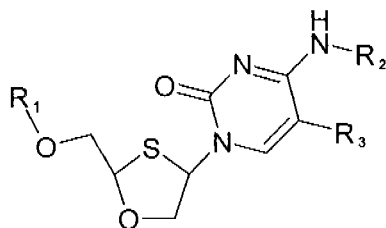
a) reacting cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane with a chiral acid and an achiral acid to

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- produce substantially one diastereomeric salt and substantially one enantiomeric salt;
- b) recovering said diastereomeric salt;
- c) converting said diastereomeric salt into optically
- 5 active cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.
69. A process according to claim 68, wherein said chiral salt is (1R)-(-)-10-camphorsulfonic acid, (-)-2,3-dibenzoyl-L-
- 10 tartaric acid, (+)-L-tartaric acid or (-)-L-malic acid.
70. A process according to claim 68, wherein said chiral acid is (1R)-(-)-10-camphorsulfonic acid.
- 15 71. A process according to claim 68, wherein said diastereomeric salt is (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonate.
72. A compound selected from:
- 20 (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1R)-(-)-10-camphorsulfonate;
- (-)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1S)-(+)-10-camphorsulfonate;
- (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-
- 25 oxathiolane.(1R)-(-)-10-camphorsulfonate; or
- (+)-cis-2-hydroxymethyl-4-(cytosin-1'-yl)-1,3-oxathiolane.(1S)-(+)-10-camphorsulfonate.

Abstract

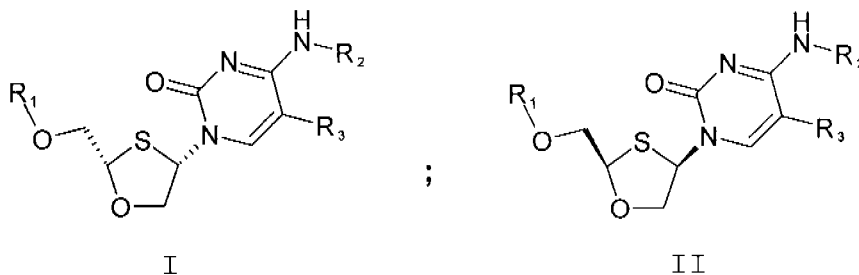
There is provided a method for resolving a compound of formula III, in the cis configuration:



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III

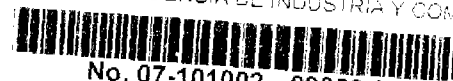
There is also provided a process for producing optically active compound of formula I or II:



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wherein: R_1 , R_2 , R_3 are as defined herein, the method and process involving the production, recovery and conversion of diastereomeric salts.

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No. 07-101002-00000-0000

Fecha: 2007-09-27 16:41:01 Dep. 2020 NUECREACION
 Tra 01 PATENTE/II Eje: 378 FASENACION-
 Act 411 PRESENTACION Folia: 164

Industria y Comercio
 SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION []

MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Descripción de la invención []
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Fdo. BEJNANO
 Firma Responsable

Fecha 27-SEP-07

Carrera 13 No. 27-00 Piso 5, 7 y 10
 Conmutador: 3 82 08 40
 Fax: 350 52 20
 E-mail: Info@sic.gov.co
www.sic.gov.co
 Bogotá, D.C., Colombia

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO

REFERENCIA	Radicación No.	7 101002
	Solicitud internacional	PCT/CA2005/000384
	Fecha inicio fase nacional	14/10/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	13822

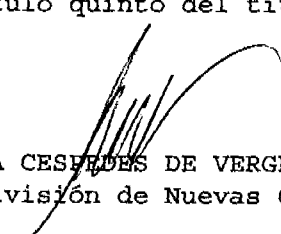
Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha _____
adpall