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**PCT**

SOLICITUD

**PATENTE DE INVENCION**

**04-2061**

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54. TÍTULO

METODO ESTEREOSELECTIVO PARA LA PREPARACION DE ANALOGOS DE NUCLEOSIDO.

51. CLASIFICACIÓN INTERNACIONAL

C07D 409/04

71. SOLICITANTE

SHIRE BIOCHEM INC.

DOMICILIO

Laval, Québec, Canadá

74. APODERADO

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**FORMULARIO UNICO DE SOLICITUD DE PATENTE**  
**PCT**  
**ENTRADA EN FASE NACIONAL**

|                                                                                                                                                                                                        |                                                                                                                                                                                                                            |                                                         |                                                                                                                                                                                                                                  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>1</b> SOLICITUD DE:                                                                                                                                                                                 |                                                                                                                                                                                                                            |                                                         |                                                                                                                                                                                                                                  |
| <input checked="" type="checkbox"/> Patente de Invención.                                                                                                                                              |                                                                                                                                                                                                                            | <input type="checkbox"/> Patente de Modelo de Utilidad. |                                                                                                                                                                                                                                  |
| <input type="checkbox"/> Capítulo I.                                                                                                                                                                   |                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> Capítulo II.        |                                                                                                                                                                                                                                  |
| <b>2</b><br><b>SOLICITANTE</b><br>(71)                                                                                                                                                                 | Nombre: <b>SHIRE BIOCHEM INC.</b><br>sociedad constituida y existente bajo las leyes de Canadá<br><br>Dirección: 275 Armand Frappier Boulevard,<br>Laval, Québec H7V 4A7<br>Canadá<br><br>Domicilio: Laval, Québec, Canadá |                                                         | <b>IDENTIFICACION</b><br><br>C.C. <input type="checkbox"/> NIT <input type="checkbox"/><br><br>C.E. <input type="checkbox"/> Otro <input type="checkbox"/><br>Cual _____<br>Número: _____                                        |
| <b>3</b><br><b>REPRESENTANTE</b><br><b>O APODERADO</b>                                                                                                                                                 | Nombre: <b>EMILIO FERRERO</b><br><br>Dirección: Carrera 4ª. No. 72-35<br>Teléfono: 347 36 11<br>Fax:: 217 92 11<br>E-mail: <u>clientes@camyp.com.</u><br>Domicilio: Bogotá, Colombia.                                      |                                                         | <b>IDENTIFICACION</b><br><br>C.C. <input checked="" type="checkbox"/> NIT <input type="checkbox"/><br><br>C.E. <input type="checkbox"/> Otro <input type="checkbox"/><br>Cual _____<br>Número: <u>438.019</u> T.P. <u>31.929</u> |
| <b>4</b><br><b>INVENTOR (ES)</b><br>(72)                                                                                                                                                               | Qing YU<br>58 Concorde Ouest,<br>Laval, Québec H7N 1H6<br>Canadá                                                                                                                                                           |                                                         |                                                                                                                                                                                                                                  |
| <b>5</b> PCT (88)<br>Solicitud Internacional No. <u>PCT/CA02/00899</u> Fecha: <u>14 de junio de 2002</u><br>Publicación Internacional No. <u>WO 02/102796 A1</u> Fecha: <u>27 de diciembre de 2002</u> |                                                                                                                                                                                                                            |                                                         |                                                                                                                                                                                                                                  |
| <b>6</b> Título (54)<br><b>MÉTODO ESTEREOSELECTIVO PARA LA PREPARACIÓN DE ANÁLOGOS DE NUCLEÓSIDO</b>                                                                                                   |                                                                                                                                                                                                                            |                                                         |                                                                                                                                                                                                                                  |
| <b>7</b> Clasificación Internacional (51) <u>C07D 409/04</u>                                                                                                                                           |                                                                                                                                                                                                                            |                                                         |                                                                                                                                                                                                                                  |
| <b>8</b><br><b>Prioridad</b><br><br>SI <input checked="" type="checkbox"/> NO <input type="checkbox"/>                                                                                                 | (33) País de Origen                                                                                                                                                                                                        | (32) Fecha                                              | (31) Número de Solicitud                                                                                                                                                                                                         |
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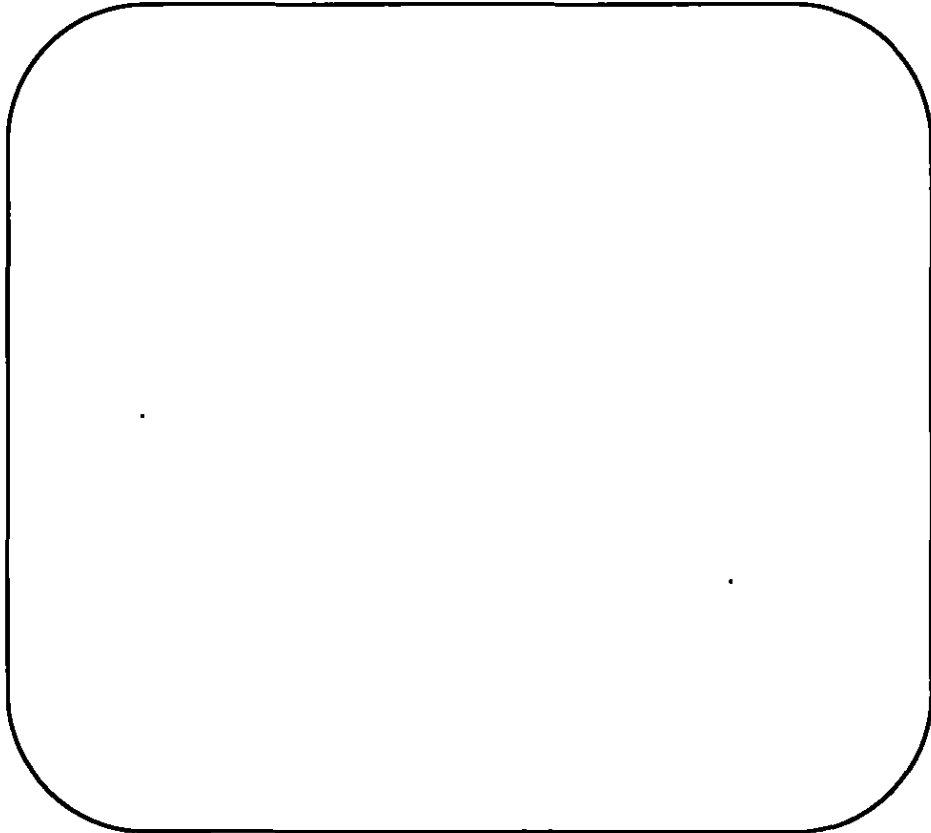
## Anexos:

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por \$ 422.000.00.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☐ Documento que acredita 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

11

## FIGURA CARACTERISTICA:



12

Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA:

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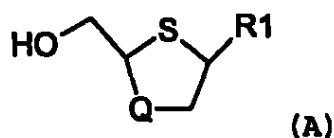
(54) Title: STERBOSELECTIVE METHOD FOR THE PREPARATION OF NUCLEOSIDE ANALOGUES

(57) Abstract: A process for producing predominantly *cis* nucleosides or nucleoside analogues and derivatives of formula (A): wherein R1 is a pyrimidine base or a pharmaceutically acceptable derivative thereof and Q is oxygen, carbon or sulphur, comprising a coupling step of the pyrimidine base with a molecule of formula (B) described herein in a suitable coupling solvent, in the presence of catalytic amounts of an element or combination of elements of groups 1B or 11B of the periodic table, a tertiary amine and a Lewis acid to obtained an intermediate of formula (D) which is deprotected in the subsequent step to generate the product of formula (A).

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## ATEROSELECTIVE METHOD FOR THE PREPARATION OF NUCLEOSIDE ANALOGUES

The present invention relates to a novel process for producing *cis* nucleosides or nucleoside analogues and derivatives of formula (A):



wherein R1 is a pyrimidine base or a pharmaceutically acceptable derivative thereof and Q is oxygen, carbon or sulphur.

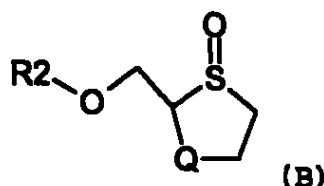
Classes of compounds of formula (A), particularly the 2-substituted 4-substituted 1,3-oxathiolanes have been found to have potent antiviral activity. In particular, these compounds have been found to act as potent inhibitors of HIV-1 replication in T-lymphocytes over a prolonged period of time with less cytotoxic side effects than compounds known in the art (see Belleau et al (1993) Bioorg. Med. Chem. Lett. Vol. 3, No. 8, pp. 1723-1728). These compounds have also been found active against 3TC-resistant HIV strains (see Taylor et al (2000) Antiviral Chem. Chemother. Vol 11, No. 4, pp. 291-301; Stoddart et al (2000) Antimicrob. Agents Chemother. Vol. 44, No. 3, pp. 783-786). These compounds are also useful in prophylaxis and treatment of hepatitis B virus infections.

Methods for the preparation of these compounds have been disclosed in PCT publications WO 92/08717 and WO 95/29176 as well as in publications by Belleau et al (1993) Bioorg. Med. Chem. Lett. Vol. 3, No. 8, pp. 1723-1728; Wang et al (1994) Tetrahedron Lett. Vol. 35, No.27, pp. 4739 -

4742; Mansour et al , (1995) J. of Med. Chem. Vol. 38, No. 1, pp. 1-4 and Caputo et al in Eur. J. Org. Chem. Vol. 6, pp. 1455-1458 (1999). These processes involve a multitude of steps that increase the cost of production and reduce the  
 5 yield of the desired compounds.

#### Summary of the Invention

The process object of the present invention comprise the step of coupling the intermediate of formula (B):



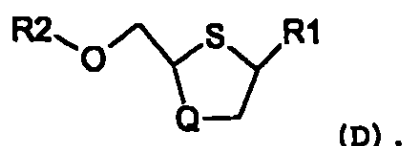
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wherein

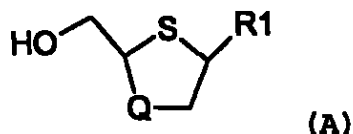
R2 is hydrogen or a hydroxyl protecting group such as C<sub>7-10</sub> arylalkyl, C<sub>1-16</sub> acyl or Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), where Z<sup>1</sup>, Z<sup>2</sup> and Z<sup>3</sup> are independently selected from the group consisting  
 15 of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-6</sub> alkoxy or C<sub>6-20</sub> aryloxy; C<sub>7-20</sub> aralkyl optionally substituted by halogen, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; C<sub>6-20</sub> aryl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; trialkylsilyl;  
 20 fluoro; bromo; chloro and iodo; and

Q is carbon, oxygen or sulfur; with

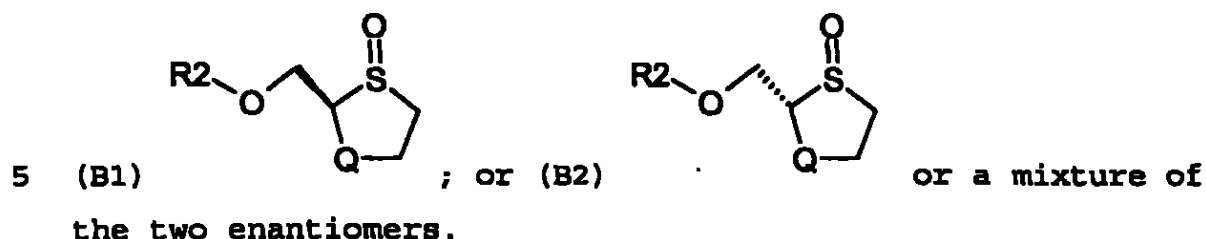
R1, a pyrimidine base or a pharmaceutically acceptable derivative thereof in the presence of a catalytic amount of an element or combination of elements of group 1B  
 25 or 11B, a Lewis acid and a tertiary amine. The resulting intermediate of formula (D)



is deprotected to obtain the *cis* nucleoside of formula (A):



The compound of formula (B) may be either :



In an alternative embodiment of the present invention the deprotection of intermediate of formula (D) is achieved by dissolving said intermediate in a suitable solvent in the presence of a deprotection agent.

In an alternative embodiment of the present invention a simple two step preparation method for *cis* nucleosides of formula (A) wherein the coupling step results in a product wherein the ratio of *cis* to *trans* is greater than 2 to 1 is provided.

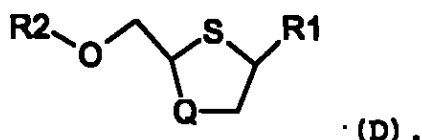
In a further embodiment the *cis* to *trans* ratio of the intermediate product of formula (D) is inversely proportional to the reaction temperature of the coupling step.

In an alternate embodiment of the present invention, the deprotection step results in the selective

aryloxy; C<sub>7-20</sub> aralkyl optionally substituted by halogen, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; C<sub>6-20</sub> aryl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; trialkylsilyl; fluoro; bromo; chloro and iodo; and

- 5 R7 is selected from the group consisting of fluoro; bromo; chloro; iodo; C<sub>1-20</sub> sulphonate esters, optionally substituted by fluoro, bromo, chloro or iodo; C<sub>1-20</sub> alkyl esters optionally substituted by fluoro, bromo, chloro or iodo; triiodide; a silyl group of the general formula
- 10 (R4)(R5)(R6)Si (wherein R4, R5, and R6 are as defined above); C<sub>6-20</sub> arylselenenyl; C<sub>6-20</sub> arylsulfenyl; C<sub>6-20</sub> alkoxyalkyl; and trialkylsiloxo;

to yield an intermediate of formula (D):



- 15 The coupling step is followed by a deprotection step to yield the *cis* nucleosides or nucleoside analogues or derivatives of formula (A).

In an alternative embodiment of the present invention a simple two step preparation method for *cis* nucleosides of formula (A) wherein the process results in a product of formula (A) wherein the ratio of *cis* to *trans* is greater than 2 to 1. The invention includes a process wherein the ratio of *cis* to *trans* is greater than or equal to 3 to 1.

- 25 The term "alkyl", as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of C<sub>1-30</sub>.

particularly C<sub>1-6</sub>, unsubstituted or optionally mono- or di-substituted by hydroxy, N<sub>3</sub>, CN, SH, amino, halogen (F, Cl, Br, I), C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl, C<sub>2-12</sub> alkoxyalkyl or nitro. It specifically includes methyl, ethyl, cyclopropyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl.

The term "acyl", as used hereinafter refers to a functional group derived from an aliphatic carboxylic acid, by removal of the -OH group of 1 to 30 carbon atoms, particularly 1 to 6 carbon atoms. Like the acid to which it is related, an aliphatic acyl radical may be substituted (by a hydroxy, N<sub>3</sub>, CN, halogen (F, Cl, Br, I), C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl, C<sub>2-12</sub> alkoxyalkyl or nitro) or unsubstituted, and whatever the structure of the rest of the molecule may be, the properties of the functional group remain essentially the same (e.g., acetyl, propionyl, isobutanoyl, pivaloyl, hexanoyl, butyryl, pentanoyl, 3-methylbutyryl, hydrogen succinate, mesylate, valeryl, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, oleic, 3-chlorobenzoate, trifluoroacetyl, chloroacetyl, and cyclohexanoyl).

The terms "alkenyl" and "alkynyl" represent substituted (by a N<sub>3</sub>, CN, halogen, hydroxyl or C<sub>6-20</sub> aryl) or unsubstituted straight, branched or cyclic hydrocarbon chains having 2 to 30 carbon atoms and preferably from 2 to 6 carbon atoms and containing at least one unsaturated group (e.g. allyl).

The term "alkoxy" represents a substituted or unsubstituted alkyl group containing from 1 to 30 carbon atoms and preferably from 1 to 6 carbon atoms, wherein the alkyl group is covalently bonded to an oxygen atom (e.g., methoxy and ethoxy).

The term "aryl" represents a aromatic moiety which may be mono, bi, tri, tetra or penta-substituted by hydroxy, nitro, N<sub>3</sub>, CN, halogen (F, Cl, Br, I) or combinations thereof and containing at least one benzenoid-type ring, the group may contain from 6 to 14 carbon atoms (e.g., phenyl and naphthyl), particularly 6 to 10 carbon atoms.

The term "aryloxy" represents a substituted (by a halogen, trifluoromethyl or C<sub>1-5</sub> alkoxy) or unsubstituted aryl moiety, having 6 to 14 carbon atoms, covalently bonded through an oxygen atom (e.g., benzyloxy, phenoxy).

The term "aralkyl" represents a substituent comprising an aryl moiety attached via an alkyl chain (e.g. benzyl, phenylethyl) wherein the sum total of carbon atoms for the aryl moiety and the alkyl chain is 7 to 21. The aryl or chain portion of the group is optionally mono- or di-substituted with OH, SH, amino, halogen or C<sub>1-6</sub> alkyl.

The term "thiol" represents C<sub>1-6</sub> alkyl, C<sub>6-15</sub> aryl, C<sub>7-21</sub> aralkyl, C<sub>2-6</sub> alkenyl or C<sub>2-6</sub> alkynyl groups covalently bonded to an adjacent sulfur atom bearing a hydrogen.

The terms "alkylthio" (e.g. thiomethy, thioethyl) and "arylthio" (e.g. thiophenyl, thiobenzyl), refers to C<sub>1-6</sub> alkyl or C<sub>6-10</sub> aryl groups, unsubstituted or optionally mono- or di-substituted by hydroxy, halogen (F, Cl, Br, I),

C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl, C<sub>2-12</sub> alkoxyalkyl or nitro, covalently bonded to an adjacent sulfur atom.

The terms "acyloxy" and "alkoxycarbonyl" refer to 1 to 30 carbon atoms chains, particularly 1 to 6 carbon atoms, that are either saturated or unsaturated and may also be straight or branched (e.g.: acetyloxy). The chains may be unsubstituted or optionally mono- or di-substituted by hydroxy, N<sub>3</sub>, CN, SH, amino, halogen (F, Cl, Br, I), C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl, C<sub>2-12</sub> alkoxyalkyl or nitro.

10 The term "alkoxyalkyl" represents a C<sub>1-6</sub> alkoxy group attached to an adjacent C<sub>1-6</sub> alkyl group (e.g., methoxymethyl, ethoxymethyl). They may be unsubstituted or optionally mono- or di-substituted by hydroxy, N<sub>3</sub>, CN, SH, amino, halogen (F, Cl, Br, I), C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl, C<sub>2-12</sub> alkoxyalkyl or nitro.

The term "heterocycle" represents a saturated or unsaturated mono- or polycyclic (i.e. bicyclic) ring incorporating 1 or more (i.e. 1-4) heteroatoms selected from N, O and S. It is understood that a heterocycle is optionally mono- or di-substituted with OH, SH, amino, halogen, CF<sub>3</sub>, oxo or C<sub>1-6</sub> alkyl. Examples of suitable monocyclic heterocycles include but are not limited to pyridine, piperidine, pyrazine, piperazine, pyrimidine, imidazole, thiazole, oxazole, furan, pyran and thiophene. 20 Examples of suitable bicyclic heterocycles include but are not limited to indole, benzimidazole, quinoline, isoquinoline, purine, and carbazole.

The term "aralkyl" represents a substituent comprising a C<sub>6-10</sub> aryl moiety attached via a C<sub>1-6</sub> alkyl

chain (e.g. benzyl, phenethyl). The aryl or chain portion of the group is unsubstituted or optionally mono- or di-substituted by hydroxy, N<sub>3</sub>, CN, SH, amino, halogen (F, Cl, Br, I), C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl, C<sub>2-12</sub> alkoxyalkyl or nitro.

5           The term "amino" represents C<sub>1-6</sub> alkyl, C<sub>6-10</sub> aryl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, or C<sub>7-12</sub> aralkyl groups, unsubstituted or optionally mono- or di-substituted by hydroxy, N<sub>3</sub>, CN, SH, amino, halogen (F, Cl, Br, I), C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl, C<sub>2-12</sub> alkoxyalkyl or nitro, wherein the  
10 carbon atoms are covalently bonded to an adjacent element through a nitrogen atom (e.g., pyrrolidine). They include primary, secondary and tertiary amines and quaternary ammonium salts.

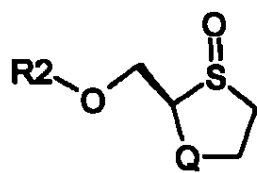
          The term "protected" as used herein and unless  
15 otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis. Suitable protecting groups are  
20 described, for example, in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference.

          By pyrimidine base derivative or analogue is meant a pyrimidine base found in nucleoside or an analogue thereof  
25 which mimics such bases in that their structures (the kinds of atoms and their arrangement) are similar to the normal bases but may possess additional or lack certain of the functional properties of the normal bases. Derivatives of such bases or analogues include those obtained by  
30 replacement of a CH moiety by a nitrogen atom (for example,

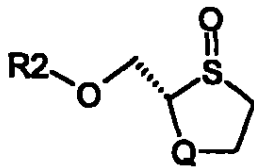
5-azapyrimidines such as 5-azacytosine) or may have ring substituted by halogen, hydroxyl, azido, cyano, amino, substituted amino, thiol, C<sub>1-6</sub> alkyl and C<sub>6-10</sub> aryl.

By the term "pharmaceutically acceptable derivative" of a pyrimidine is meant any pyrimidine base which may give rise to a pharmaceutically acceptable salt, ester, or salt of such ester of a compound of formula (A), or any other compound which, upon administration to the recipient, is capable of providing (directly or indirectly) a compound of formula (A) or an antivirally active metabolite or residue thereof. It will be appreciated by those skilled in the art that the compounds of formula (A) may be modified to provide pharmaceutically acceptable derivatives thereof, at functional groups in the base moiety.

The compound of formula (B) may be either :



(B1); or



(B2) or a mixture of

the two enantiomers. The sulfoxide may be a single enantiomer or a mixture of enantiomers including but not limited to a racemic mixture.

The coupling step of the process object of the present invention includes the addition of one or more elements of group 1B or 11B. The element or combination of elements used may be in their oxidized state. This element or combination of elements of group 1B or 11B catalyzes the coupling step. The chosen element or combination of elements of group 1B or 11B are present in amounts between about 0.25 molar % and about 100 molar %. In another

embodiment, the concentration of the element or combination of elements of group 1B or 11B may be between about 5% to about 35%.

The process object of the present invention  
5 includes a coupling step wherein the element or combination of elements of group 1B or 11B are selected from the group comprising  $\text{Cu}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Ag}^+$ ,  $\text{Au}^+$ ,  $\text{Au}^{3+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$  and combinations thereof.

The process object of the present invention  
.0 includes a coupling step wherein the element or combination of elements of group 1B or 11B are selected from  $\text{Cu}^+$ ,  $\text{Cu}^{2+}$  or  $\text{Zn}^{2+}$ .

The term tertiary amine includes tertiary amines with high basicity. The tertiary amine is of the form  
.5  $\text{N}(\text{Z}^4)(\text{Z}^5)(\text{Z}^6)$  wherein  $(\text{Z}^4)$ ,  $(\text{Z}^5)$ ,  $(\text{Z}^6)$  are independently selected from the group consisting  $\text{C}_{1-6}$  alkyl optionally substituted with  $\text{C}_{1-3}$  alkyl,  $\text{C}_{6-10}$  aryl, halogen. Examples of the tertiary amine include triethylamine,  
diethylcyclohexylamine, diethylmethylaniline,  
20 dimethylethylamine, dimethylisopropylamine,  
dimethylbutylamine, dimethylcyclohexylamine, tributylamine, diethylmethylaniline, dimethylisopropylamine and diisopropylethylamine.

The amount of tertiary amine can vary between  
25 about 1 eq to about 4 eq. The amount of tertiary amine used may vary between about 1 eq and 2 eq.

The coupling step of the process object of the present invention is preformed in a suitable coupling solvent. A suitable coupling solvent includes  $\text{C}_{1-10}$   
30 chlorinated organic solvents. Suitable coupling solvents

9

also include C<sub>1-8</sub> chloroalkyls, C<sub>1-8</sub> chloroalkenyls, C<sub>6-10</sub> chloroaryls, C<sub>1-8</sub> alkylonitriles and combinations thereof. The coupling solvents may be selected from chloromethanes, chloroethanes, methanonitriles or mixtures thereof. The

5 coupling solvents of interest include dichloromethane, chloroform, acetonitrile, dichloroethane, chlorobenzene and combinations thereof.

The amount of coupling solvent used may vary between about 5 mL per g of sulfoxide to 50 mL per gram of

10 sulfoxide. In an alternate embodiment of the invention the amount of coupling solvent is between 10 mL per g of sulfoxide to 30 mL per gram of sulfoxide.

The coupling step of the process object of the present invention is affected by the temperature of the

15 reaction. The cis to trans ratio of the product of formula (D) is inversely proportional to the reaction temperature. The coupling step is preformed at a temperature between about 40 degrees C and about - 40 degrees C. In an alternate embodiment, the coupling step reaction temperature

20 is between about 30 degrees C and about - 50 degrees C.

The second step in the process object of the present invention is a deprotection step. The deprotection crystallization step is preformed in a suitable solvent. Of particular interest are solvents that favor the

25 crystallization of the product of formula (A). Suitable solvents include water, methanol, ethanol, toluene, tert-butyl methyl ether or combinations thereof.

The deprotection may also include the presence of adequate amounts a deprotection agent. Of particular

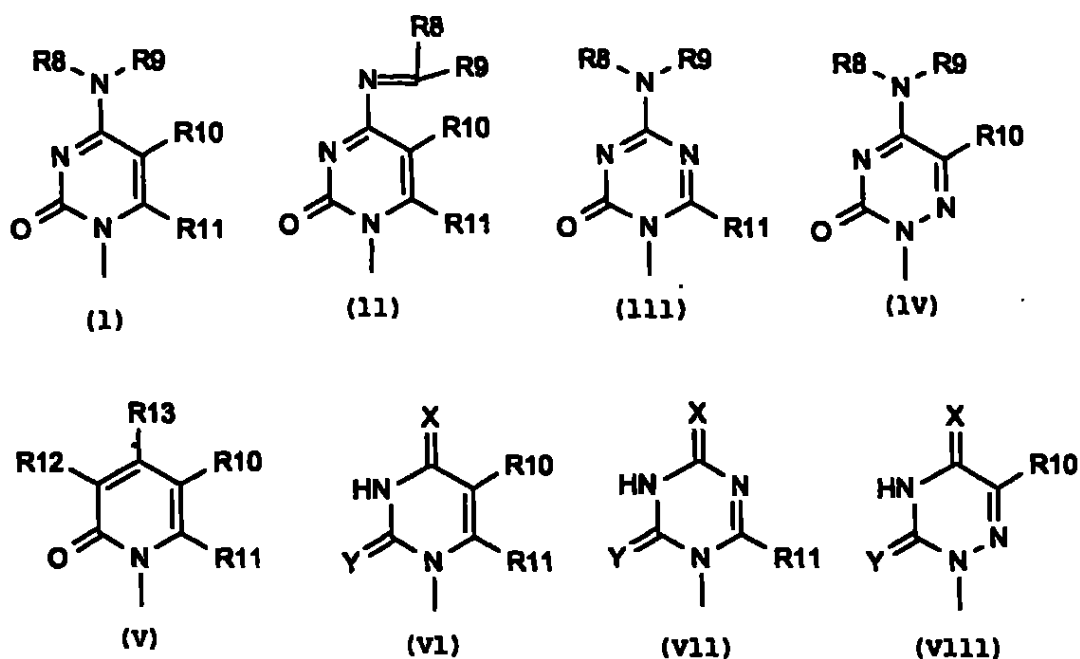
30 interest are deprotection agents that will aid in the separation of the cis product of formula (A). Suitable

deprotection agents are selected according to the identity of the protecting group on the intermediate of formula (D) as shown in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991.

- 5 Deprotection agents may be alkaline. Deprotection agents include sodium hydroxide, sodium methoxide, ammonium hydroxide, potassium hydroxide, lithium hydroxide and methanolic ammonia.

In another embodiment of the present invention,  
 10 the deprotection agent is present in catalytic amounts. In another embodiment the deprotection agent is present in concentrations between about 0.1 molar percentage and about 50 molar percentage. An alternative embodiment includes deprotection agent concentrations between about 5 to about  
 15 20 molar percentage of the deprotection agent.

Conveniently, the base R1 is selected from:



wherein:

20 x is oxygen, NH or sulfur.

y is oxygen, NH or sulfur.

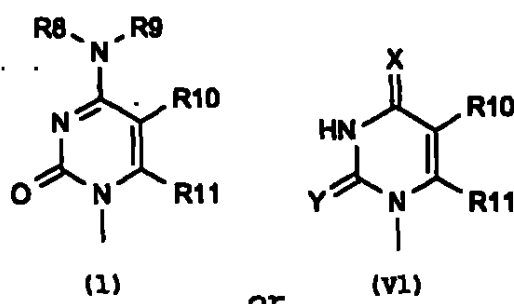
R8 and R9 are independently selected from hydrogen, hydroxyl, amino, C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-10</sub> acyl, C<sub>6-10</sub> aryl, C<sub>6-11</sub> carbonylaryl, C<sub>1-7</sub> carbonyloxyalkyl, C<sub>6-11</sub> carbonyloxyaryl, C<sub>2-7</sub> carbonylaminoalkyl, or amino acids.

R8 may be a saturated or unsaturated C<sub>3-8</sub> carbocyclic ring optionally substituted with COOH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, halogen, C(O)R<sub>14</sub> wherein R<sub>14</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C(O)OR<sub>15</sub> wherein R<sub>15</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl; and R9 is chosen from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl and C<sub>2-6</sub> alkynyl.

R<sub>8</sub>R<sub>9</sub> can also be connected to the nitrogen atom to form a saturated or unsaturated C<sub>3-8</sub> heterocyclic ring optionally substituted with C(O)OH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, halogen, C(O)R<sub>14</sub> wherein R<sub>14</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C(O)OR<sub>15</sub> wherein R<sub>15</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl.

R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub> and R<sub>13</sub> are each independently selected from hydrogen, halogen, hydroxyl, amino, cyano, carboxyl, carbamoyl, C<sub>2-7</sub> alkoxy carbonyl, hydroxymethyl, trifluoromethyl, C<sub>6-10</sub> arylthio, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl substituted or unsubstituted with halogen or azido, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> acyloxy, thiocarboxy, thiocarbamoyl, carbamate, ureido, amidino, or C<sub>6-10</sub> aryloxy.

In another embodiment of the present invention R<sub>1</sub> is



wherein R8 and R9 are independently selected from hydrogen, hydroxyl, amino, C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>1-10</sub> acyl, C<sub>6-10</sub> aryl, C<sub>6-16</sub> carbonylaryl, C<sub>1-10</sub> carbonyloxyalkyl, C<sub>6-16</sub> carbonyloxyaryl, C<sub>2-12</sub> carbonylaminoalkyl, or amino acids; R10 and R11 are each independently selected from hydrogen, halogen, hydroxyl, hydroxymethyl, trifluoromethyl, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl substituted or unsubstituted with halogen, azido, C<sub>2-6</sub> alkynyl, or C<sub>6-10</sub> aryloxy; and

X and Y are independently selected from O or S.

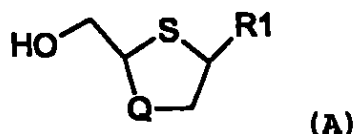
In an alternate embodiment R1 is a pyrimidine base selected from N<sup>4</sup>-alkylpyrimidines, N<sup>4</sup>-acylpyrimidines, 4-halopyrimidines, N<sup>4</sup>-acetylenic pyrimidines, 4-amino and N<sup>4</sup>-acyl pyrimidines, 4-hydroxyalkyl pyrimidines, 4-thioalkyl pyrimidines, thymine, cytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrimidine, uracil, C<sup>5</sup>-alkylpyrimidines, C<sup>5</sup>-benzylpyrimidines, C<sup>5</sup> halopyrimidines, C<sup>5</sup>-vinylpyrimidine, C<sup>5</sup>-acetylenic pyrimidine, C<sup>5</sup>-acyl pyrimidine, C<sup>5</sup>-amidopyrimidine, C<sup>5</sup>-cyanopyrimidine, C<sup>5</sup>-nitropyrimidine, C<sup>5</sup>-aminopyrimidine, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl or pyrazolopyrimidinyl.

The functional oxygen and nitrogen groups on R1 can be protected as necessary or desired. Suitable

protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, t-butyl dimethylsilyl, and t-butyl diphenylsilyl, trityl, C<sub>1-12</sub> alkyl groups, C<sub>1-12</sub> acyl groups such as acetyl and propionyl, benzoyl, methanesulfonyl, and p-toluenesulfonyl.

In an additional embodiment of the present invention R<sub>1</sub> is selected from cytosine, uracil, thymine, 5-fluoropyrimidine or protected analogs of these bases.

Another embodiment of the present invention includes a stereoselective process for making predominantly cis nucleosides or nucleoside analogues and derivatives of formula (A):

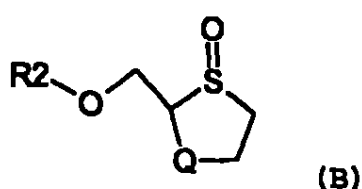


wherein

R<sub>1</sub> is a pyrimidine base selected from N<sup>4</sup> -alkylpyrimidines, N<sup>4</sup> -acylpyrimidines, 4-halopyrimidines, N<sup>4</sup> -acetylenic pyrimidines, 4-amino and N<sup>4</sup> -acyl pyrimidines, 4-hydroxyalkyl pyrimidines, 4-thioalkyl pyrimidines, thymine, cytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrimidine, uracil, C<sup>5</sup> -alkylpyrimidines, C<sup>5</sup> -benzylpyrimidines, C<sup>5</sup> halopyrimidines, C<sup>5</sup> -vinylpyrimidine, C<sup>5</sup> -acetylenic pyrimidine, C<sup>5</sup> -acyl pyrimidine, C<sup>5</sup> -amidopyrimidine, C<sup>5</sup> -cyanopyrimidine, C<sup>5</sup> -nitropyrimidine, C<sup>5</sup> -aminopyrimidine, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl. or a pharmaceutically acceptable derivative thereof; and

Q is oxygen ,

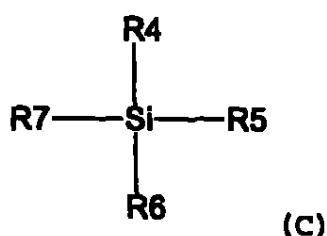
consisting of coupling step of the a compound of formula (B):



5 wherein

R2 is C<sub>7-10</sub> aralkyl, C<sub>1-16</sub> acyl or Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), where Z<sup>1</sup>, Z<sup>2</sup> and Z<sup>3</sup> are independently selected from the group consisting of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-6</sub> alkoxy or C<sub>6-20</sub> aryloxy; C<sub>7-10</sub> aralkyl optionally substituted by halogen, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; C<sub>6-20</sub> aryl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; trialkylsilyl; fluoro; bromo; chloro and iodo;

with a base R1, as defined above, in a suitable coupling solvent in the presence of a catalytic amount of an element or combination of elements of group 1B or 11B ; a tertiary amine and a Lewis acid of formula (C):



wherein

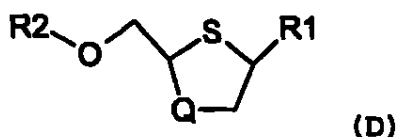
R4, R5 and R6 are independently selected from the group consisting of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluor , bromo, chlor , iodo, C<sub>1-6</sub> alkoxy or C<sub>6-</sub>

12

20 aryloxy; C<sub>7-20</sub> aralkyl optionally substituted by halogen, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; C<sub>6-20</sub> aryl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; trialkylsilyl; fluoro; bromo; chloro and iodo; and

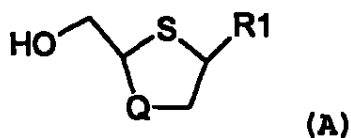
5 R<sub>7</sub> is selected from the group consisting of fluoro; bromo; chloro; iodo; C<sub>1-20</sub> sulphonate esters, optionally substituted by fluoro, bromo, chloro or iodo; C<sub>1-20</sub> alkyl esters optionally substituted by fluoro, bromo, chloro or iodo; triiodide; a silyl group of the general formula  
 10 (R<sub>4</sub>)(R<sub>5</sub>)(R<sub>6</sub>)Si (wherein R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are as defined above); C<sub>6-20</sub> arylselenenyl; C<sub>6-20</sub> arylsulfenyl; C<sub>6-20</sub> alkoxyalkyl; and trialkylsiloxyl;

to yield an intermediate of formula (D):



15 wherein Q, R<sub>1</sub> and R<sub>2</sub> are as defined above. The coupling step is followed by a deprotection step wherein said intermediate (D) is dissolved in a suitable solvent in the presence of appropriate amounts of a deprotection agent to yield the *cis* nucleosides or nucleoside analogues or  
 20 derivatives of formula (A).

The present invention includes the embodiment wherein the stereoselective process for making predominantly *cis* nucleosides or nucleoside analogues and derivatives of formula (A):

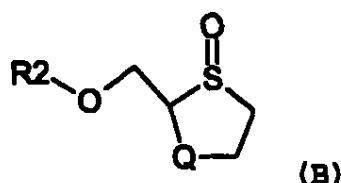


wherein

R1 is a pyrimidine base selected from cytosine, uracil, thymine, 5-fluoropyrimidine or a pharmaceutically acceptable derivative thereof; and

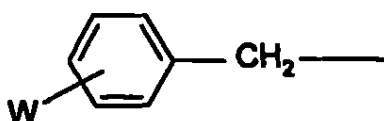
5 Q is oxygen ,

consisting of coupling step of the a compound of formula (B) :

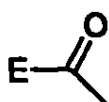


wherein

10 R2 is



wherein W is halogen, C<sub>1-16</sub> alkyl, C<sub>2-16</sub> alkoxyalkyl, C<sub>6-10</sub> aryl, C<sub>1-16</sub> alkoxy or nitro; or

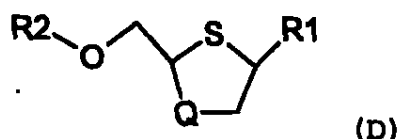


15 wherein E is C<sub>6-10</sub> aryl, C<sub>1-16</sub> alkoxy, C<sub>2-16</sub> alkoxyalkyl or C<sub>1-16</sub> alkyl; or

Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), where Z<sup>1</sup>, Z<sup>2</sup> and Z<sup>3</sup> are independently selected from the group consisting of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo,  
20 chloro, iodo; C<sub>7-10</sub> aralalkyl optionally substituted by

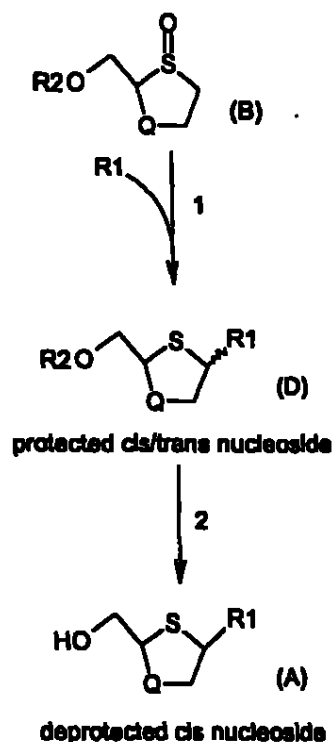
fluoro, bromo, chloro or iodo; and C<sub>6-10</sub> aryl optionally substituted by fluoro, bromo, chloro or iodo; with

a base R<sub>1</sub>, as defined above, in a suitable coupling solvent in the presence of a catalytic amount of Cu or Zn or mixtures thereof; a tertiary amine and a Lewis acid selected from trimethylsilyl triflate bromotrimethylsilane or iodotrimethylsilane; to yield an intermediate of formula (D):



wherein Q, R<sub>1</sub> and R<sub>2</sub> are as defined above. The coupling step is followed by a deprotection step wherein said intermediate (D) is dissolved in a suitable solvent in the presence of appropriate amounts of a deprotection agent to yield the *cis* nucleosides or nucleoside analogues or derivatives of formula (A).

The process object of the present invention includes the reaction scheme shown in Scheme 1:

Scheme 1

The various steps as illustrated in Scheme 1 may be briefly described as follows:

- 5            Step 1: The sulfoxide of formula (B) may be obtained using several methods including those disclosed in PCT publications WO 92/08717 and WO 95/29176, J. Med. Chem. 38(1) 1-4 (1995), Tetrahedron Lett. 35(27) 4739-4742 (1994), Bioorg. Med. Chem. Lett. 3 (8) 1723-1728 (1993) and Eur. J.
- 10 Org. Chem. 6:1455-1458 (1999). The sulfoxide may be a single enantiomer or a mixture of enantiomers including but not limited to a racemic mixture.

The sulfoxide of formula (B) is coupled with base R1. The base R1 may be previously protected, for example

15 silylated (or silylated in situ) pyrimidine base or pharmaceutically acceptable derivative may be used. The coupling reaction takes place in the presence of a tertiary amine, a Lewis acid of formula (C) and catalytic amounts of

an element of groups IB or IIB in a suitable coupling solvent to give the cis/trans pyrimidine nucleoside of formula (D). In the resulting intermediate of formula (D), the cis isomer predominates over the trans isomer in a ratio equal to greater than 2 to 1. The ratio of cis to trans isomer is inversely proportional to the temperature of the reaction temperature. The coupling reaction may be preformed at or below room temperature. The temperature of the coupling step may be between about 0 degrees C and about .0 - 50 degrees C.

If a silylated base is used, adequate silylating agent may include t-butyldimethylsilyl triflate 1,1,1,3,3,3 hexamethyldisilazane, TMSI, N,O,bis(TMS) acetone and trimethylsilyl triflate. Additional protective agents are .5 disclosed in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991.

The tertiary amine used in step 1 include triethylamine, diethylcyclohexylamine, diethylmethylaniline, dimethylethylamine, dimethylisopropylamine, 20 dimethylbutylamine, dimethylcyclohexylamine, tributylamine, diethylmethylaniline, dimethylisopropylamine and diisopropylethylamine and combinations thereof.

The element or combination of elements of groups IB or IIB used in step 1 include Cu, Ag, Au, Zn, or Cd in 25 oxidized state.

The suitable coupling solvent is an organic solvent with one to ten carbons. The suitable coupling solvents include  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{CN}$  and mixtures thereof.

Suitable Lewis acids include trimethylsilyl 30 triflate bromotrimethylsilane iodotrimethylsilane and

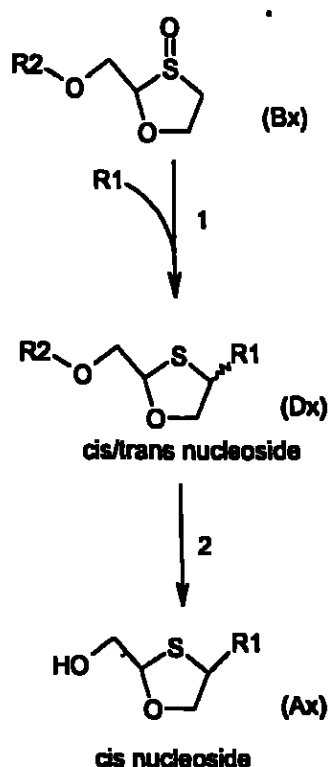
combinations thereof. The amount of the Lewis acid may be between about 2 eq to about 5 eq.

Step 2: The *cis/trans* pyrimidine 1,3-oxathiolane nucleoside of formula (D) is dissolved in a suitable deprotection solvent in the presence of adequate amounts of a deprotection agent to yield the *cis* nucleosides or nucleoside analogues or derivatives of formula (A). The deprotection step is preformed at a temperature below the boiling point of the suitable deprotection solvent. The reaction temperature of the deprotection step may be between - 30 degrees C and 60 degrees C. The reaction may be preformed at a temperature between about 0 degrees C to about 35 degrees C.

A deprotection suitable solvent favors the crystallization of the product of formula (A). Suitable solvents include water, methanol, ethanol, toluene, tert-butyl methyl ether or combinations thereof.

Suitable deprotection agents include sodium hydroxide, sodium methoxide, ammonium hydroxide, potassium hydroxide, lithium hydroxide and methanolic ammonia. Of particular interest are deprotection agents which will aid in the separation of the product of formula (A).

Scheme 1a



The various steps as illustrated in Schemes 1a may be briefly described as follows:

- 5            Step 1: The sulfoxide of the 1,3 oxathiolane of formula (Bx) may be obtained using several methods including those disclosed in PCT publications WO 92/08717 and WO 95/29176, J. Med. Chem. 38(1) 1-4 (1995), Tetrahedron Lett. 35(27) 4739-4742 (1994), Bioorg. Med. Chem. Lett. 3 (8) 1723-1728 (1993). The asymmetric synthesis of the sulfoxide of formula (Bx) is disclosed by Caputo et al in Eur. J. Org. Chem. 6:1455-1458 (1999).
- 10

The sulfoxide of the 1,3 oxathiolane of formula (Bx) is coupled with base R1. The base R1 may be previously 15 protected, for example silylated (or silylated in situ) pyrimidine base or pharmaceutically acceptable derivative. The coupling reaction takes place in the presence of a tertiary amine, a Lewis acid of formula (C) and catalytic

amounts of an element of groups IB or IIB in a suitable coupling solvent to give the cis/trans pyrimidine 1,3 oxathiolane nucleoside of formula (Dx). In the resulting intermediate of formula (Dx), the cis isomer predominates over the trans isomer in a ratio equal to greater than 2 to 1. The ratio of cis to trans isomer is inversely proportional to the temperature of the reaction temperature. The reaction may be preformed at or below room temperature.

The silylating agent that may be used for the protection of R1 include t-butyldimethylsilyl triflate, 1,1,1,3,3,3 hexamethyldisilazane, TMSI, N,O,bisTMS acetone and trimethylsilyl triflate.

The tertiary amine used in step 1 include triethylamine, diethylcyclohexylamine, diethylmethylaniline, dimethylethylamine, dimethylisopropylamine, dimethylbutylamine, dimethylcyclohexylamine, tributylamine, diethylmethylaniline, dimethylisopropylamine and diisopropylethylamine and combinations thereof.

The element or combination of elements of groups IB or IIB used in step 1 include Cu, Ag, Au, Zn, or Cd in oxidized state.

The suitable coupling solvent is an organic solvent. The suitable coupling solvents include  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{CN}$  or mixtures thereof.

The Lewis acid that may be used in this step include trimethylsilyl triflate bromotrimethylsilane iodotrimethylsilane and mixtures thereof. The amount of the Lewis acid may be between about 2 eq to about 5 eq.

Step 2: The cis/trans pyrimidine nucleoside of formula (Dx) is dissolved in a suitable deprotection solvent

in the presence of adequate amounts of a deprotection agent to yield the *cis* nucleosides or nucleoside analogues or derivatives of formula (Ax).

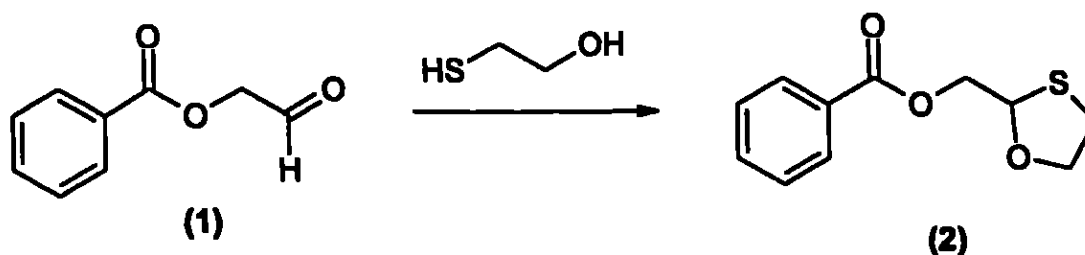
A suitable deprotection solvent favors the  
5 crystallization of the product of formula (A). Suitable solvents include water, methanol, ethanol, toluene, tert-butyl methyl ether or combinations thereof. Suitable combinations of solvents include methanol and water, methanol and toluene, methanol and tert-butyl methyl ether  
10 mixtures.

Suitable deprotection agents include sodium hydroxide, sodium methoxide, ammonium hydroxide, potassium hydroxide, lithium hydroxide and methanolic ammonia. Of particular interest are deprotection agents that will aid in  
15 the separation of the product of formula (A).

The deprotection step is preformed at a temperature below the boiling point of the suitable deprotection solvent

The following examples illustrate the present  
20 invention in a manner of which it can be practiced but, as such, should not be construed as limitations upon the overall scope of the processes of this invention.

1) 2-benzoyloxymethyl-1, 3-oxathiolane



Compound (1) was dissolved in toluene and the solution was heated up to 90-100°C. Catalyst was added followed by mercaptoethanol (portionwise). 5 molar % of catalyst were used. Reactions were carried out on 15g scale at 0.3M concentration of (1). The reaction mixture was refluxed with water removal by Dean-Stark trap. Results for this step are shown in Table 1.

Table 1

| Catalyst                         | Reaction after 20 min |                | Reaction after 40 min |                |
|----------------------------------|-----------------------|----------------|-----------------------|----------------|
|                                  | Conversion %          | Yield of (2) % | Conversion %          | Yield of (2) % |
| BF <sub>3</sub> OEt <sub>2</sub> | 100                   | 79             | 100                   | 71             |
| pTsOH                            | 100                   | 82             | 100                   | 80             |

Compound (2) was identified by <sup>1</sup>H- and <sup>13</sup>C-NMR.

0 R<sub>f</sub>: 0.39 (hexane: ethyl acetate)

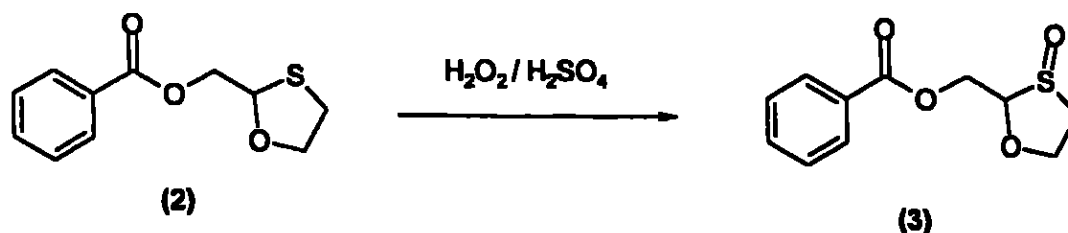
<sup>1</sup>H-NMR: δ (ppm in CDCl<sub>3</sub>)

8.03 (m, 2H, aromatic)  
7.53 (m, 1H, aromatic)  
7.39 (m, 2H, aromatic)  
5.41 (dd, 1H, C<sub>2</sub>-H)  
4.43 (m, 2H, C<sub>2</sub>-CH<sub>2</sub>OCC<sub>6</sub>H<sub>5</sub>)  
4.21 (m, 1H, C<sub>5</sub>-H)  
3.96 (m, 1H, C<sub>5</sub>-H)  
2.98 (m, 2H, C<sub>4</sub>-H)

20 <sup>13</sup>C-NMR: δ (ppm in CDCl<sub>3</sub>)

166.82, 133.74, 130.35, 128.97, 83.58, 71.87,  
66.62 and 32.74

2) 2-benzoyloxymethyl-1,3-oxathiolane-S-oxide



- 5 Cold 30% hydrogen peroxide (46ml, 0.44 mol) was added to (2)  
(82g, 0.366 mol) in toluene (8 ml). 10M sulfuric acid  
(4.5ml, 0.044 mol, 10 mol %) was added dropwise (addition  
time approximately 1 min). The reaction mixture was  
vigorously stirred at 25-30 °C for 2 h followed by 1 h  
10 string at 30 °C. Water (100ml) was added followed by sodium  
bicarbonate (3.7 g 0.044 mol) followed by sodium  
metabisulfite (8g). Organic layer was separated and aqueous  
phase was extracted with dichloromethane (3x20 ml). The  
combined organic extracts were dried over sodium sulfite,  
15 concentrated to dryness and triturated with hexane to form a  
solid. 83g

(94% ) of target compound (3) was obtained.

m.p.: 70-72°

<sup>1</sup>H-NMR: δ(ppm in CDCl<sub>3</sub>)

- |    |                                                                                                                          |
|----|--------------------------------------------------------------------------------------------------------------------------|
| 20 | 8.05 (m, 2H, aromatic, <i>cis</i> -isomer)                                                                               |
|    | 7.95 (m, 2H, aromatic, <i>trans</i> -isomer)                                                                             |
|    | 7.56 (m, aromatic)                                                                                                       |
|    | 7.23 (m, aromatic)                                                                                                       |
|    | 4.77 (m, 4H, C <sub>2</sub> -H, C <sub>5</sub> -H, and C <sub>2</sub> -CH <sub>2</sub> OCC <sub>6</sub> H <sub>5</sub> ) |
| 25 | 4.43 (m, 1H, C <sub>5</sub> -H, <i>trans</i> -isomer)                                                                    |

4.09 (m, 1H, C<sub>5</sub>-H, *cis*-isomer)  
 3.11 (m, 2H, C<sub>4</sub>-H, *trans*-isomer)  
 2.75 (m, 2H, C<sub>4</sub>-H, *cis*-isomer)

<sup>13</sup>C-NMR: δ(ppm in CDCl<sub>3</sub>)

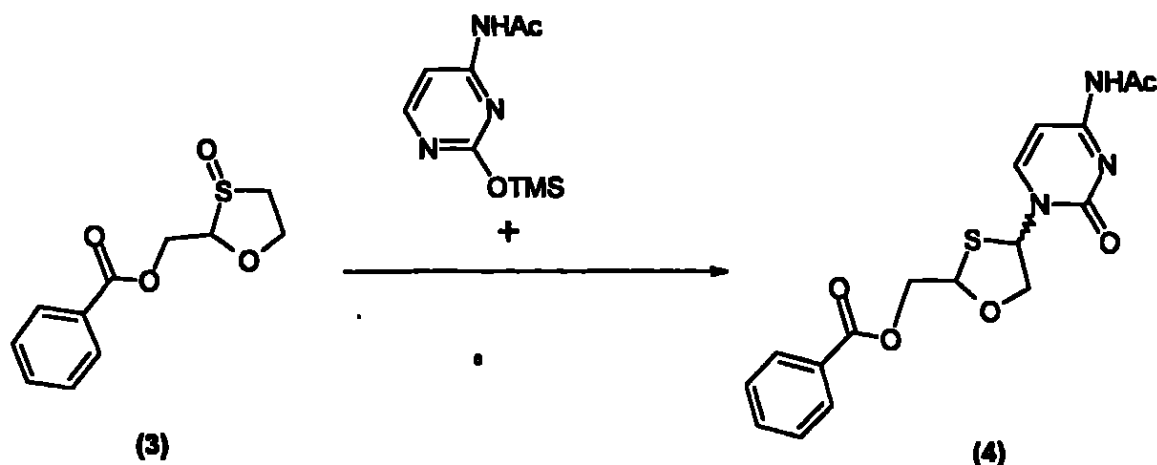
5 *cis*-isomer:

166.64, 134.02, 130.42, 129.88, 129.06, 96.16,  
 68.83, 59.47 and 54.30

*trans*-isomer:

166.36, 134.12, 130.29, 129.68, 129.15, 108.07,  
 10 70.09, 61.83 and 53.47

3) (+/-)-*Cis, trans*-2benzoylmethyl-4-(*N*-acetylcytosine-1'-yl)-1,3-oxathiolane



Compound (3) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (20mL/g) and  
 15 cooled to -15 °C. The amine (between 1 and 2 eq) was added  
 followed by addition of TMSI (between 2 and 5 eq) while  
 keeping the internal temperature below -5°C. stirred at -5°C  
 to -10°C until the compound (3) disappeared. The CuCl (20%)  
 and the pyrimidine (1.1eq) was added. The reaction mix was  
 20 warmed up and kept between 5-10°C until TLC indicated the

reaction is complete. The reaction mixture was poured into 5%  $\text{NH}_4\text{OH}$  and stirred for 10 minutes until no solid precipitate was detected. The organic layer was separated and aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with water, 2%  $\text{HCl}$ , dilute  $\text{Na}_2\text{S}_2\text{O}_3$ . The washed organic layer was evaporated to give the product, compound (4). Results for this step are shown in Table 2.

These were characterized by  $^1\text{H}$  and  $^{13}\text{C}$ -NMR.

*cis*-isomer:

10  $^1\text{H}$ -NMR:  $\delta$ (ppm in  $\text{CDCl}_3$ )

|    |                                                                              |
|----|------------------------------------------------------------------------------|
|    | 9.61 (b, 1H, $\text{C}_4$ -NHCOCH <sub>3</sub> )                             |
|    | 8.29 (d, 1H, $\text{C}_6$ -H)                                                |
|    | 8.06 (m, 2H, aromatic)                                                       |
|    | 7.65 (m, 1H, aromatic)                                                       |
| 15 | 7.51 (m, 2H, aromatic)                                                       |
|    | 7.25 (d, 1H, $\text{C}_5$ -H)                                                |
|    | 6.61 (d, 1H, $\text{C}_4$ -H)                                                |
|    | 5.50 (t, 1H, $\text{C}_2$ -H)                                                |
|    | 4.80 (m, 2H, $\text{C}_2$ -CH <sub>2</sub> OCC <sub>6</sub> H <sub>5</sub> ) |
| 20 | 4.48 (d, 1H, $\text{C}_5$ -H)                                                |
|    | 4.05 (dd, 1H, $\text{C}_5$ -H)                                               |
|    | 2.25 (s, 3H, CH <sub>3</sub> )                                               |

$^{13}\text{C}$ -NMR:  $\delta$ (ppm in  $\text{CDCl}_3$ )

170.93, 166.28, 162.80, 155.76, 146.06, 133.91,  
25 129.90, 128.84, 97.45, 85.88, 78.25, 64.60, 63.53 and 24.71.

*trans*-isomer:

<sup>1</sup>H-NMR: δ(ppm in DMSO d<sub>6</sub>)

|    |                                                                                       |
|----|---------------------------------------------------------------------------------------|
|    | 10.88 (s, 1H, C <sub>4</sub> '-NHCOCH <sub>3</sub> )                                  |
|    | 8.13 (d, 1H, C <sub>6</sub> '-H)                                                      |
| 5  | 7.96 (m, 2H, aromatic)                                                                |
|    | 7.68 (m, 1H, aromatic)                                                                |
|    | 7.52 (m, 2H, aromatic)                                                                |
|    | 7.20 (d, 1H, C <sub>5</sub> '-H)                                                      |
|    | 6.35 (d, 1H, C <sub>4</sub> -H)                                                       |
| 10 | 5.96 (dd, 1H, C <sub>2</sub> -H)                                                      |
|    | 4.58 (dd, 1H, C <sub>2</sub> -CH <sub>2</sub> OOCC <sub>6</sub> H <sub>5</sub> )      |
|    | 4.44 (d, 1H, C <sub>5</sub> -H)                                                       |
|    | 4.29 (m, 2H, C <sub>5</sub> -H and CH <sub>2</sub> OOCC <sub>6</sub> H <sub>5</sub> ) |
|    | 2.07 (s, 3H, CH <sub>3</sub> )                                                        |

15 <sup>13</sup>C-NMR: δ(ppm in DMSO d<sub>6</sub>)

171.53, 165.84, 162.76, 155.21, 146.59, 134.00,  
129.64, 129.23, 96.54, 83.78, 74.24, 64.58, 64.01 and 24.35

Table 2

| Pyrimidine       | Base           | Catalyst<br>(molar eq)         | Conditions                                              | Yield<br>(Cis +<br>Trans) | Cis/<br>Trans | Yield<br>% Cis |
|------------------|----------------|--------------------------------|---------------------------------------------------------|---------------------------|---------------|----------------|
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq |                                | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C<br>RT, O/N     | 80%                       | 2.0 : 1       | 53             |
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>3h RT, O/N | 91%                       | 3.9 : 1       | 72             |
| N-Ac-Cy<br>1.1eq | TEA<br>1.2eq   | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 75%                       | 3.8 : 1       | 59             |
| N-Ac-Cy<br>1.1eq | DMCA<br>1.2eq  | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 80%                       | 3.4 : 1       | 62             |
| N-Ac-Cy<br>1.1eq | DECA<br>1.2eq  | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C<br>RT, O/N     | 71%                       | 3.9 : 1       | 57             |
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq | CuCl <sub>2</sub> (2%)         | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>3h RT, O/N | 80%                       | 2.4 : 1       | 56             |
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq | CuBr <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 80%                       | 3.7 : 1       | 63             |
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq | Cu(acac) <sub>2</sub><br>(20%) | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 85%                       | 3.7 : 1       | 67             |
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq | CuCl (20%)                     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 80%                       | 3.6 : 1       | 63             |
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq | CuI (20%)                      | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 74%                       | 3.5 : 1       | 58             |
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq | CuSCN<br>(20%)                 | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 70%                       | 3.1:1         | 53             |
| N-Ac-Cy<br>1.1eq | DIPEA<br>1.2eq | ZnBr <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 53%                       | 3.1: 1        | 40             |
| Cy<br>1.1eq      | DIPEA<br>1.2eq | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 72%                       | 2.4:1         | 51             |

Cy = cytosine

DIPEA = diisopropylethylamine

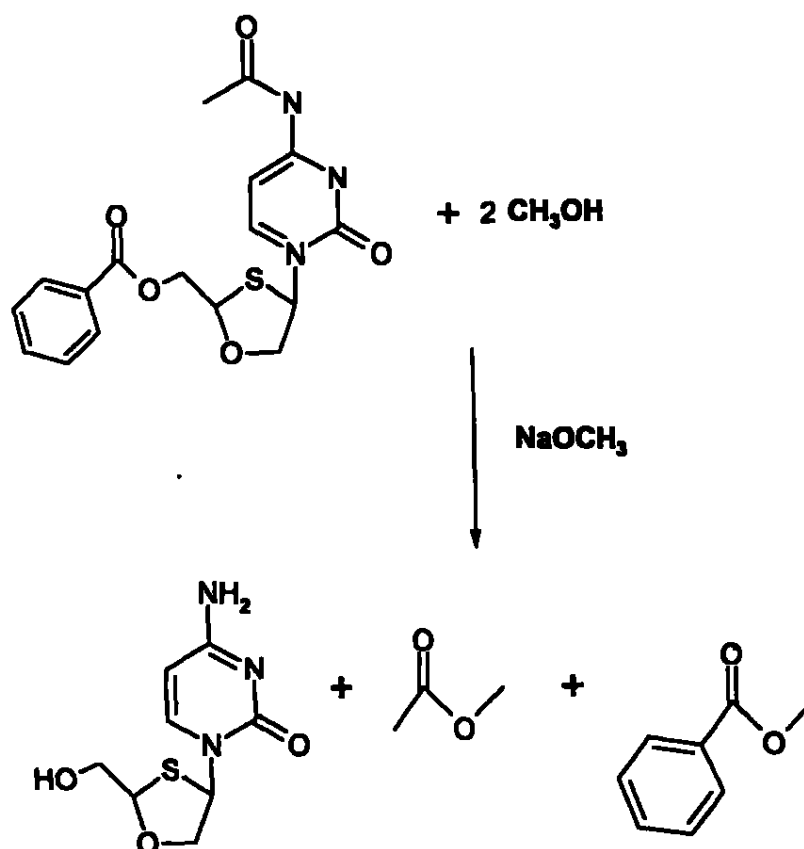
5 TEA = Triethylamine

DECA = diethylcyclohexylamine

DMCA = dimethylcyclohexylamine

$\text{Cu}(\text{acac})_2$  = Copper (II) acetylacetonate

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

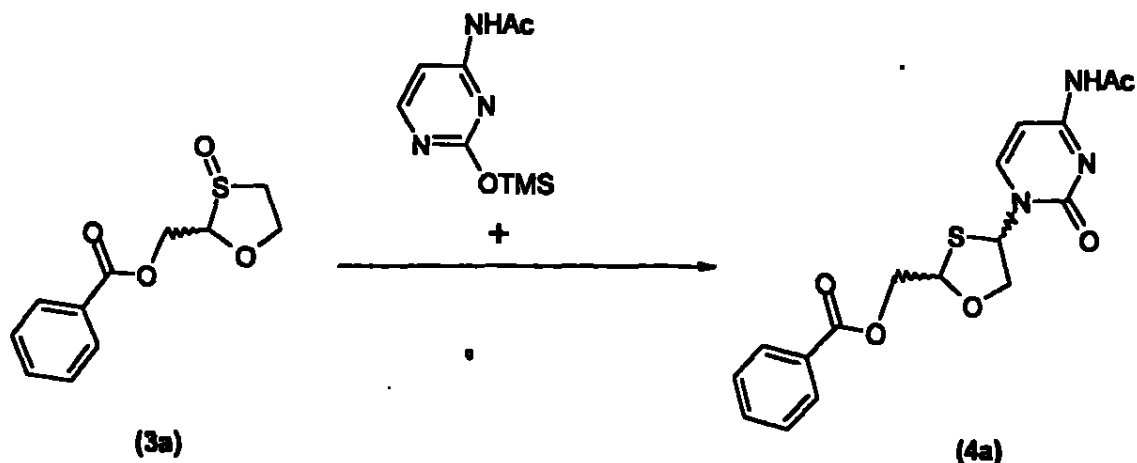


A suspension of the substrate, sodium methoxide, 5 10 mole percentage, and the appropriate solvent was stirred at RT for 2 h before it was filtered. The filter cake was dried and weighed before checking the C/T ratio (by  $^1\text{H}$  NMR ) and yield. Results for this step are shown in table 3.

Table 3

| Weight of<br>Cis/Trans<br>mix (g) | Cis/<br>Trans<br>ratio | Solvent                          | Strong<br>base | Conditions            | % of<br>trans<br>(NMR) | Recovery<br>of Cis<br>(%) |
|-----------------------------------|------------------------|----------------------------------|----------------|-----------------------|------------------------|---------------------------|
| 4                                 | 3.4 :<br>1             | MeOH,                            | MeONa          | Mix and stir<br>at RT | 0                      | 89                        |
| 10                                | 3.4 :<br>1             | MeOH                             | MeONa          | Mix and stir<br>at RT | 0                      | 88.5                      |
|                                   |                        |                                  |                |                       |                        |                           |
| 4                                 | 3.4 :<br>1             | MeOH/tBME<br>(7 :3)              | MeONa          | Mix and stir<br>at RT | 0                      | 90                        |
| 25                                | 3.4 :<br>1             | MeOH/tBME<br>(7 :3)              | MeONa          | Mix and stir<br>at RT | traces                 | 91                        |
|                                   |                        |                                  |                |                       |                        |                           |
| 1                                 | 3.4 :<br>1             | MeOH/EtOH<br>(1 :1)              | MeONa          | RT                    | 0                      | 98                        |
| 4                                 | 3.4 :<br>1             | MeOH/EtOH<br>(1 :1)              | MeONa          | Mix and stir<br>at RT | traces                 | 92.5                      |
| 25                                | 3.4 :<br>1             | MeOH/EtOH<br>(1 :1), 150<br>mL   | MeONa          | Mix and stir<br>at RT | traces                 | 93                        |
| 1                                 | 3.4 :<br>1             | MeOH/Toluene<br>(6 :4)           | MeONa          | RT                    | traces                 | 92.5                      |
| 4                                 | 3.4 :<br>1             | MeOH :Toluene<br>(6 :4)          | MeONa          | Mix and stir<br>at RT | traces                 | 90                        |
| 25                                | 3.4 :<br>1             | MeOH/Toluene<br>(6 :4) L         | MeONa          | Mix and stir<br>at RT | traces                 | 91                        |
|                                   |                        |                                  |                |                       |                        |                           |
| 1                                 | 3.4 :<br>1             | MeOH/H <sub>2</sub> O<br>(95 :5) | NaOH           | RT                    | 20                     | 90                        |
| 1                                 | 3.4 :<br>1             | MeOH/H <sub>2</sub> O<br>(95 :5) | NaOH           | At 50 °C              | 20                     | 90                        |

5) Synthesis of 2benzoylmethyl-4-(N-acetylcytosine-1'-yl)-1,3-oxathiolane using (-) or (+) 2-benzoyloxymethyl-1,3-oxathiolane-S-oxide



- 5           The enantiomerically pure Compound (3a) was dissolved in  $\text{CH}_2\text{Cl}_2$  (10mL/g) and cooled to reaction temperature. The amine was added followed by addition of TMSI while keeping the internal temperature below  $-5^\circ\text{C}$ . stirred at  $-5^\circ\text{C}$  to  $-40^\circ\text{C}$  until the compound (3a) disappeared.
- 10   The  $\text{CuCl}$  (20%) and the pyrimidine (1.1eq) was added. The reaction mix was warmed up and kept between  $-40$  to  $30^\circ\text{C}$  until TLC indicated the reaction is complete. The reaction was cooled to  $0^\circ\text{C}$ - $5^\circ\text{C}$ . Celite (12g, 100% w/w) was added to the suspension and stirred. Concentrated ammonium hydroxyde
- 15   (was added slowly and the suspension temperature was kept between  $0^\circ\text{C}$  -  $10^\circ\text{C}$ . Stirred at  $0^\circ\text{C}$ - $5^\circ\text{C}$ . The suspension was filtered and the cake was resuspended in dichloromethane. Stirred then filtered. The phases were separated and the aqueous was extracted with dichloromethane. The combined
- 20   organic layers were washed with a 2% solution of ammonium hydroxyde, water, 2% hydrochloric solution, 2% sodium metabisulfite solution and saturated sodium bicarbonate solution. The organic phase was dried over magnesium sulfate, filtered then reduced in volume in vacuo to give

crude base-coupled material as a beige solid. The solids were dissolved in EtOAc and allowed to crystallize. The suspension was stirred at 0-5°C then filtered. The solids were dried in vacuo to give pure base-coupled product as a pale beige solid. Results for this step are shown in Table 4 and Table 5.

<sup>1</sup>H NMR (300MHz) (CDCl<sub>3</sub>) δ: 2.27 (s, 3H, CH<sub>3</sub> cis), 2.29 (s, 3H, CH<sub>3</sub> trans), 4.06 (dd, J= 4.5 Hz & J=10.8 Hz, 1H, C5 cis), 4.30 (dd, J= 3.4 Hz & J=12.4 Hz, 1H, C5 trans), 4.49 (dd, J=3.1 Hz & J=10.8 Hz, 1H, C5 cis) 4.72 (dd, J=8.3 Hz & J=12.4 Hz, 1H, C5 trans), 4.77, (AB, J=4.5 Hz, 2H, CH<sub>2</sub>OBz cis), 4.84 (AB, J=2.3 Hz, 2H, CH<sub>2</sub>OBz trans), 5.50 (dd, J= 3.1 Hz & J=4.5 Hz, 1H, C4 cis), 5.92 (dd, J= 3.4 Hz & J=8.3 Hz, 1H, C4 trans), 6.61 (dd, J= 2.3 Hz trans & J=4.5 Hz cis, 1H, C2), 7.25 (d, J=7.5 Hz, 1H, C5'), 7.5-8.1 (m, 10H, aromatic cis & trans), 8.30 (d, J=7.5 Hz, 1H, C6'), 9.50 (s 1H, NH).

<sup>13</sup>C NMR (300MHz) (CDCl<sub>3</sub>) δ: 25.9 (cis & trans), 64.3 (cis), 65.1 (trans), 65.3 (cis & trans), 76.1 (trans), 78.7 (cis), 84.7 (trans), 86.2 (cis), 97.9 (cis), 98.1 (trans), 128.6 (cis & trans), 128.7 (cis & trans), 129.2 (cis & trans), 129.4 (cis & trans), 129.8 (cis & trans), 133.5 (trans), 133.7 (cis), 145.3 (trans), 145.6 (cis), 155.2 (trans), 155.3 (cis), 162.5 (cis & trans), 162.6 (trans), 165.7 (cis), 171.0 (cis), 171.1 (trans).

Table 4

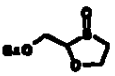
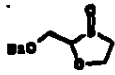
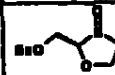
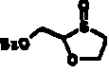
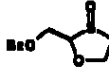
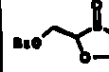
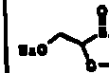
| Sulfoxide                                                                           | Base  | Reaction Temp. (°C)                                                      | (-)Cis (%) | (+)Cis (%)  | (-)Trans (%) | (+)trans (%) | Cis/Trans (%) |
|-------------------------------------------------------------------------------------|-------|--------------------------------------------------------------------------|------------|-------------|--------------|--------------|---------------|
|    | DIPEA | -15                                                                      | 48.9       | <u>27.4</u> | 6.7          | 17           | 3.2 :1        |
|  | TEA   | -15                                                                      | 70.4       | 5.2         | 1.6          | 22.8         | 3.1 :1        |
|  | TEA   | -15                                                                      | <u>4.9</u> | 73.6        | 20           | 1.5          | 3.6 :1        |
|  | DMCA  | -25                                                                      | 72.4       | <u>4.5</u>  | 1.25         | 21.8         | 3.3 :1        |
|  | TEA   | - 30<br>(internal temp),<br>warm up to RT after<br>adding silylated base | 1          | <u>74.4</u> | 24.6         | 0            | 3 :1          |

Table 5

| Sulfoxide                                                                           | Base                        | Reaction Temperature<br>°C | Yield % | Cis/Trans (%) |
|-------------------------------------------------------------------------------------|-----------------------------|----------------------------|---------|---------------|
|    | TEA<br>+DIPEA               | -20                        | 74      | 3.3 : 1       |
|    | (i-pro)<br>NMe <sub>2</sub> | -20                        | 72      | 3.7 : 1       |
|  | TEA                         | -20                        | 63      | 4 : 1         |
|  | (i-pro)<br>NMe <sub>2</sub> | -20                        | 72      | 3.3 : 1       |
|  | TEA                         | -20                        | 70      | 3.3 : 1       |

TEA = Triethylamine

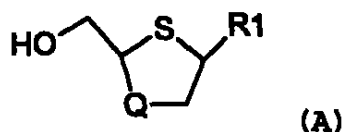
DIPEA = Diisopropylethylamine

5 DMCA = Dimethylcyclohexylamine

(i-pro)NMe<sub>2</sub> = Isopropyl dimethylamine

CLAIMS:

1) A stereoselective process for making predominantly cis nucleosides or nucleoside analogues and derivatives of formula (A):

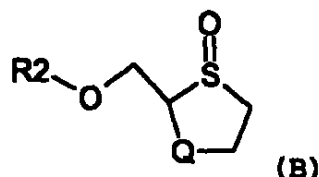


wherein

R1 is a pyrimidine base or a pharmaceutically acceptable derivative thereof; and

Q is carbon, oxygen or sulfur;

10 consisting of coupling step of the a compound of formula (B):

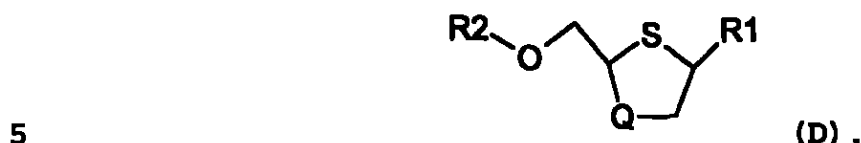


wherein

15 R2 is C<sub>7-10</sub> aralkyl, C<sub>1-16</sub> acyl or Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), where Z<sup>1</sup>, Z<sup>2</sup> and Z<sup>3</sup> are independently selected from the group consisting of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-6</sub> alkoxy or C<sub>6-20</sub> aryloxy; C<sub>7-20</sub> aralkyl optionally substituted by halogen, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; C<sub>6-20</sub> aryl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; 20 trialkylsilyl; fluoro; bromo; chloro and iodo;

with a base R1, wherein R1 is a pyrimidine base or a pharmaceutically acceptable derivative thereof;

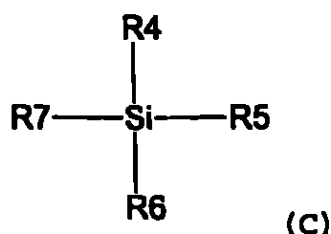
in a C<sub>1-10</sub> coupling solvent in the presence of a catalytic amount of an element or combination of elements of group 1B or 11B of the periodic table; a tertiary amine and a Lewis acid to yield an intermediate of formula (D):



wherein R1, R2 and Q are defined above; and

a second step to deprotect the intermediate for formula (D) to yield of the *cis* nucleosides or nucleoside analogues or derivatives of formula (A).

- 10 2) A process according to claim 1 wherein the Lewis acid is a compound of formula (C):



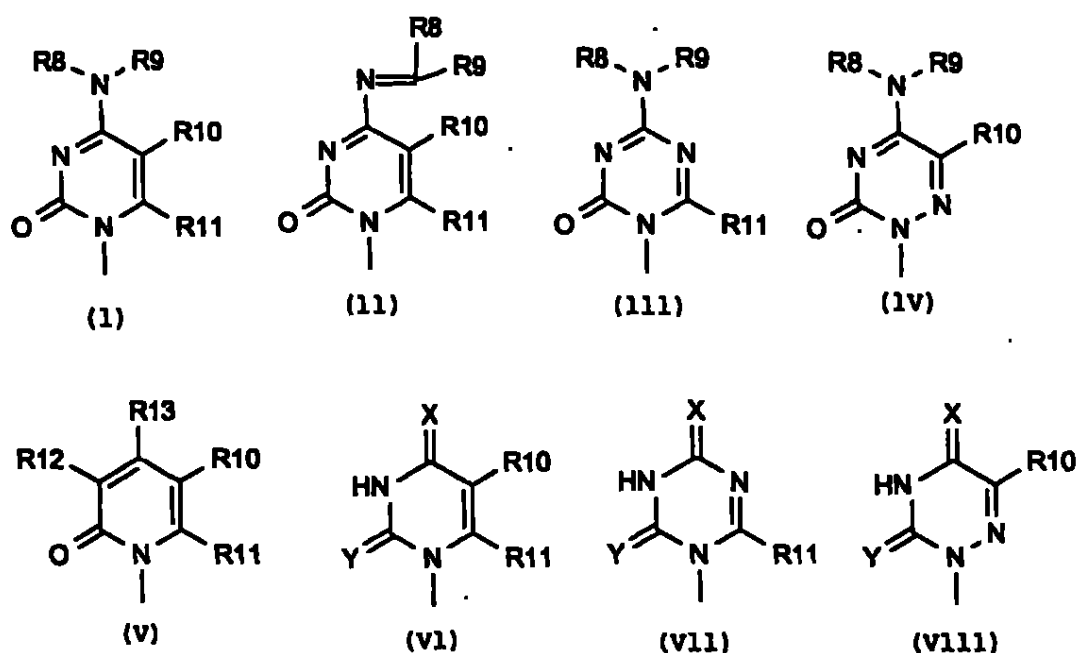
wherein

- 15 R4, R5 and R6 are independently selected from the group consisting of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-6</sub> alkoxy or C<sub>6-20</sub> aryloxy; C<sub>7-20</sub> aralkyl optionally substituted by halogen, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; C<sub>6-20</sub> aryl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy;
- 20 trialkylsilyl; fluoro; bromo; chloro and iodo; and

R7 is selected from the group consisting of fluoro; bromo; chloro; iodo; C<sub>1-20</sub> sulphonate esters, optionally substituted by fluoro, bromo, chloro or iodo; C<sub>1-20</sub>

alkyl esters optionally substituted by fluoro, bromo, chloro or iodo; triiodide; a silyl group of the general formula (R4)(R5)(R6)Si (wherein R4, R5, and R6 are as defined above); C<sub>6-20</sub> arylselenenyl; C<sub>6-20</sub> arylsulfenyl; C<sub>6-20</sub> alkoxyalkyl; and trialkylsiloxy.

3) A process according to claim 1 wherein R1 is selected from:



10 wherein:

x is oxygen, NH or sulfur;

y is oxygen, NH or sulfur;

R8 and R9 are independently selected from hydrogen, hydroxyl, amino, C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-10</sub> acyl, C<sub>6-10</sub> aryl, C<sub>6-11</sub> carbonylaryl, C<sub>1-7</sub> carbonyloxyalkyl, C<sub>6-11</sub> carbonyloxyaryl, C<sub>2-7</sub> carbonylaminoalkyl, or amino acids;

R8 may be a saturated or unsaturated C<sub>3-8</sub> carbocyclic ring optionally substituted with COOH, C(O)NH<sub>2</sub>,

OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, halogen, C(O)R<sub>14</sub> wherein R<sub>14</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C(O)OR<sub>15</sub> wherein R<sub>15</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl; and R<sub>9</sub> is chosen from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl and C<sub>2-6</sub> alkynyl;

R<sub>8</sub>R<sub>9</sub> can also be connected to the nitrogen atom to form a saturated or unsaturated C<sub>3-8</sub> heterocyclic ring optionally substituted with C(O)OH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, halogen, C(O)R<sub>14</sub> wherein R<sub>14</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C(O)OR<sub>15</sub> wherein R<sub>15</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl; and

R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub> and R<sub>13</sub> are each independently selected from hydrogen, halogen, hydroxyl, amino, cyano, carboxyl, carbamoyl, C<sub>2-7</sub> alkoxycarbonyl, hydroxymethyl, trifluoromethyl, C<sub>6-10</sub> arylthio, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl substituted or unsubstituted with halogen or azido, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> acyloxy, thiocarboxy, thiocarbamoyl, carbamate, ureido, amidino, or C<sub>6-10</sub> aryloxy.

4) A process according to claim 1 wherein the element or combination of elements of groups IB or IIB is Cu, Ag, Au, Zn or Cd.

5) A process according to claim 1 wherein the tertiary amine is of the form N(Z<sup>4</sup>)(Z<sup>5</sup>)(Z<sup>6</sup>) wherein (Z<sup>4</sup>), (Z<sup>5</sup>), (Z<sup>6</sup>) are independently selected from the group consisting C<sub>1-6</sub> alkyl optionally substituted with C<sub>1-3</sub> alkyl, C<sub>6-10</sub> aryl or halogen.

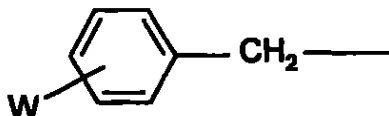
- 6) A process according to claim 1 wherein the organic solvent is a. C<sub>1-8</sub> chloroalkyl, a C<sub>1-8</sub> chloroalkenyls, a C<sub>6-10</sub> chloroaryl, C<sub>1-8</sub> alkylonitrile or mixtures thereof.
- 7) A process according to claim 6 wherein the organic solvent is selected from the group consisting of chloromethanes, chloroethanes, methanonitriles and mixtures thereof.
- 8) A process according to claim 5 wherein the tertiary amine is triethylamine, diethylcyclohexylamine, diethylmethylaniline, dimethylethylamine, dimethylisopropylamine, dimethylbutylamine, dimethylcyclohexylamine, tributylamine, diethylmethylaniline, dimethylisopropylamine, diisopropylethylamine or combinations thereof.
- 9) A process according to claim 4 wherein the element r combination of elements of groups IB or IIB is Cu, Zn or combinations thereof.
- 10) A process according to claim 1 wherein Q is oxygen.
- 11) A process according to claim 1 wherein the coupling step is preformed at a temperature equal to or less than 30 degrees Celsius.
- 12) A process according to claim 1 wherein the deprotection step is preformed in the presence of a deprotecting agent and a deprotecting solvent which favors the crystallization of the *cis* nucleosides or nucleoside analogues or derivatives of formula (A).
- 13) A process according to claim 12 wherein the deprotection agent is alkaline.

14) A process according to claim 13 wherein the deprotection agent is sodium hydroxide, sodium methoxide, ammonium hydroxide, potassium hydroxide, lithium hydroxide, methanolic ammonia or combinations thereof.

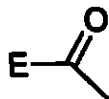
5 15) A process according to claim 12 wherein the deprotecting solvent is water, methanol, ethanol, toluene, tert-butyl methyl ether or combinations thereof.

16) A process according to claim 3 wherein R1 is selected from N<sup>4</sup> -alkylpyrimidines, N<sup>4</sup> -acylpyrimidines, 4-halopyrimidines, N<sup>4</sup> -acetylenic pyrimidines, 4-amino and N<sup>4</sup> -acyl pyrimidines, 4-hydroxyalkyl pyrimidines, 4-thioalkyl pyrimidines, thymine, cytosine, 6-azapyrimidine, 2- mercaptopyrimidine, 4-mercaptopyrimidine, uracil, C<sup>5</sup> -alkylpyrimidines, C<sup>5</sup> -benzylpyrimidines, C<sup>5</sup> halopyrimidines, C<sup>5</sup>-vinylpyrimidine, C<sup>5</sup> -acetylenic pyrimidine, C<sup>5</sup> -acyl pyrimidine, C<sup>5</sup> -amidopyrimidine, C<sup>5</sup> -cyanopyrimidine, C<sup>5</sup> -nitropyrimidine, C<sup>5</sup> -aminopyrimidine, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl  
 15  
 20 or a pharmaceutically acceptable derivative thereof.

17) A process according to claim 3 wherein R2 is



wherein W is halogen, C<sub>1-16</sub> alkyl, C<sub>2-16</sub> alkoxyalkyl, C<sub>6-18</sub> aryl, C<sub>1-16</sub> alkoxy or nitro; or

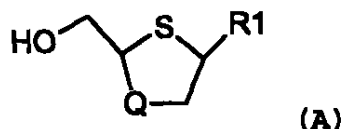


wherein E is C<sub>6-10</sub> aryl, C<sub>1-16</sub> alkoxy, C<sub>2-16</sub> alkoxyalkyl or C<sub>1-16</sub> alkyl; or

Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), where Z<sup>1</sup>, Z<sup>2</sup> and Z<sup>3</sup> are independently selected from the group consisting of  
5 hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo, chloro, iodo; C<sub>7-10</sub> aralkyl optionally substituted by fluoro, bromo, chloro or iodo; and C<sub>6-10</sub> aryl optionally substituted by fluoro, bromo, chloro or iodo.

AMENDED CLAIMS (December 17, 2003)

1) A stereoselective process for making predominantly cis nucleosides or nucleoside analogues and derivatives of formula (A) :

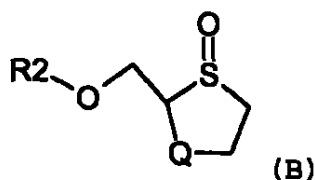


wherein

R1 is a pyrimidine base or a pharmaceutically acceptable derivative thereof; and

Q is carbon, oxygen or sulfur;

consisting of the step of coupling a compound of formula (B) :

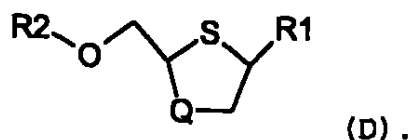


wherein

R2 is C<sub>7-10</sub> aralkyl, C<sub>1-16</sub> acyl or Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), where Z<sup>1</sup>, Z<sup>2</sup> and Z<sup>3</sup> are independently selected from the group consisting of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-6</sub> alkoxy or C<sub>6-20</sub> aryloxy; C<sub>7-20</sub> aralkyl optionally substituted by halogen, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; C<sub>6-20</sub> aryl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; trialkylsilyl; fluoro; bromo; chloro and iodo;

with a base R1, wherein R1 is a pyrimidine base or a pharmaceutically acceptable derivative thereof;

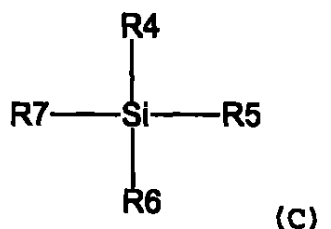
in a C<sub>1-10</sub> coupling solvent in the presence of a catalytic amount of an element or combination of elements of group 1B or 11B of the periodic table; a tertiary amine and a Lewis acid to yield an intermediate of formula (D) :



wherein R1, R2 and Q are defined above; and

a second step to deprotect the intermediate for formula (D) to yield of the *cis* nucleosides or nucleoside analogues or derivatives of formula (A).

2) A process according to claim 1 wherein the Lewis acid is a compound of formula (C):

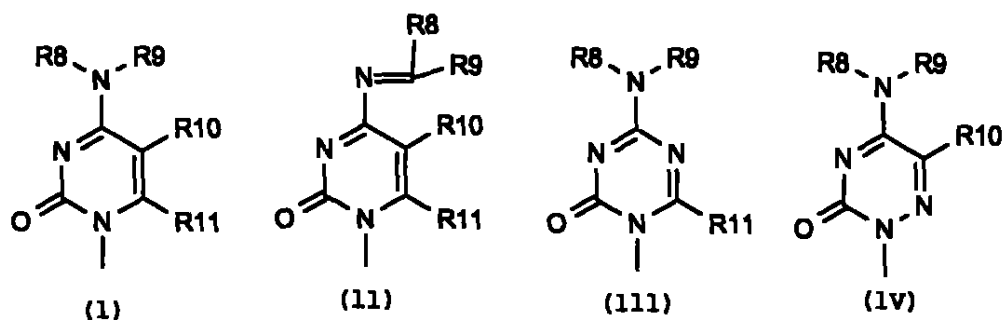


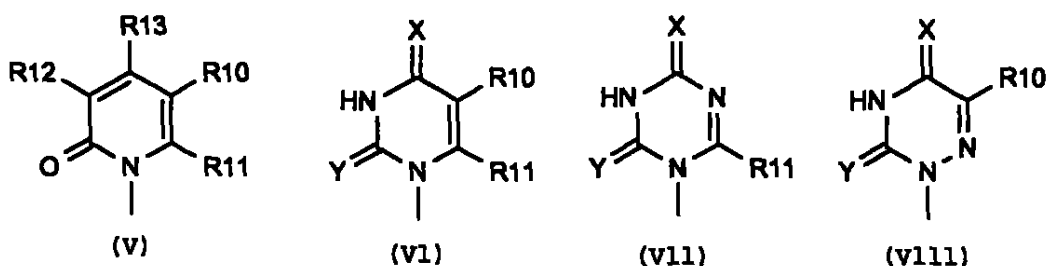
wherein

R4, R5 and R6 are independently selected from the group consisting of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-6</sub> alkoxy or C<sub>6-20</sub> aryloxy; C<sub>7-20</sub> aralkyl optionally substituted by halogen, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; C<sub>6-20</sub> aryl optionally substituted by fluoro, bromo, chloro, iodo, C<sub>1-20</sub> alkyl or C<sub>1-20</sub> alkoxy; trialkylsilyl; fluoro; bromo; chloro and iodo; and

R7 is selected from the group consisting of fluoro; bromo; chloro; iodo; C<sub>1-20</sub> sulphonate esters, optionally substituted by fluoro, bromo, chloro or iodo; C<sub>1-20</sub> alkyl esters optionally substituted by fluoro, bromo, chloro or iodo; triiodide; a silyl group of the general formula (R4)(R5)(R6)Si (wherein R4, R5, and R6 are as defined above); C<sub>6-20</sub> arylselenenyl; C<sub>6-20</sub> arylsulfenyl; C<sub>6-20</sub> alkoxyalkyl; and trialkylsiloxy.

3) A process according to claim 1 wherein R1 is selected from:





wherein:

x is oxygen, NH or sulfur;

y is oxygen, NH or sulfur;

R8 and R9 are independently selected from hydrogen, hydroxyl, amino, C<sub>1-6</sub> alkyl or C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-10</sub> acyl, C<sub>6-10</sub> aryl, C<sub>6-11</sub> carbonylaryl, C<sub>1-7</sub> carbonyloxyalkyl, C<sub>6-11</sub> carbonyloxyaryl, C<sub>2-7</sub> carbonylaminoalkyl, or amino acids;

R8 may be a saturated or unsaturated C<sub>3-8</sub> carbocyclic ring optionally substituted with COOH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, halogen, C(O)R<sub>14</sub> wherein R<sub>14</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C(O)OR<sub>15</sub> wherein R<sub>15</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl; and R9 is chosen from H, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl and C<sub>2-6</sub> alkynyl;

R<sub>8</sub>R<sub>9</sub> can also be connected to the nitrogen atom to form a saturated or unsaturated C<sub>3-8</sub> heterocyclic ring optionally substituted with C(O)OH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, halogen, C(O)R<sub>14</sub> wherein R<sub>14</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl and C(O)OR<sub>15</sub> wherein R<sub>15</sub> is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl; and

R<sub>10</sub>, R<sub>11</sub>, R<sub>12</sub> and R<sub>13</sub> are each independently selected from hydrogen, halogen, hydroxyl, amino, cyano, carboxyl, carbamoyl, C<sub>2-7</sub> alkoxy carbonyl, hydroxymethyl, trifluoromethyl, C<sub>6-10</sub> arylthio, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl substituted or unsubstituted with halogen or azido, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> acyloxy, thiocarboxy, thiocarbamoyl, carbamate, ureido, amidino, or C<sub>6-10</sub> aryloxy.

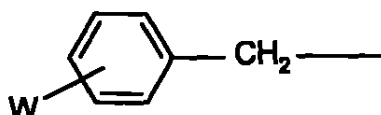
4) A process according to claim 1 wherein the element or combination of elements of groups IB or IIB is Cu, Ag, Au, Zn or Cd.

- 5) A process according to claim 1 wherein the tertiary amine is of the form  $N(Z^4)(Z^5)(Z^6)$  wherein  $(Z^4)$ ,  $(Z^5)$ ,  $(Z^6)$  are independently selected from the group consisting of  $C_{1-6}$  alkyl optionally substituted with  $C_{1-3}$  alkyl,  $C_{6-10}$  aryl or halogen.
- 6) A process according to claim 1 wherein the organic solvent is a  $C_{1-8}$  chloroalkyl, a  $C_{1-8}$  chloroalkenyls, a  $C_{6-10}$  chloroaryl,  $C_{1-8}$  alkylonitrile or mixtures thereof.
- 7) A process according to claim 6 wherein the organic solvent is selected from the group consisting of chloromethanes, chloroethanes, methanonitriles and mixtures thereof.
- 8) A process according to claim 5 wherein the tertiary amine is triethylamine, diethylcyclohexylamine, diethylmethylamine, dimethylethylamine, dimethylisopropylamine, dimethylbutylamine, dimethylcyclohexylamine, tributylamine, diethylmethylamine, dimethylisopropylamine, diisopropylethylamine or combinations thereof.
- 9) A process according to claim 4 wherein the element or combination of elements of groups IB or IIB is Cu, Zn or combinations thereof.
- 10) A process according to claim 1 wherein Q is oxygen.
- 11) A process according to claim 1 wherein the coupling step is performed at a temperature equal to or less than 30 degrees Celsius.
- 12) A process according to claim 1 wherein the deprotection step is performed in the presence of a deprotecting agent and a deprotecting solvent which favors the crystallization of the *cis* nucleosides or nucleoside analogues or derivatives of formula (A).
- 13) A process according to claim 12 wherein the deprotection agent is alkaline.
- 14) A process according to claim 13 wherein the deprotection agent is sodium hydroxide, sodium methoxide, ammonium hydroxide, potassium hydroxide, lithium hydroxide, methanolic ammonia or combinations thereof.

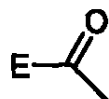
15) A process according to claim 12 wherein the deprotecting solvent is water, methanol, ethanol, toluene, tert-butyl methyl ether or combinations thereof.

16) A process according to claim 3 wherein R1 is selected from N<sup>4</sup> -alkylpyrimidines, N<sup>4</sup> -acylpyrimidines, 4-halopyrimidines, N<sup>4</sup> -acetylenic pyrimidines, 4-amino and N<sup>4</sup> -acyl pyrimidines, 4-hydroxyalkyl pyrimidines, 4-thioalkyl pyrimidines, thymine, cytosine, 6-azapyrimidine, 2- mercaptopyrimidine, 4-mercaptopyrimidine, uracil, C<sup>5</sup> -alkylpyrimidines, C<sup>5</sup> -benzylpyrimidines, C<sup>5</sup> halopyrimidines, C<sup>5</sup>-vinylpyrimidine, C<sup>5</sup> -acetylenic pyrimidine, C<sup>5</sup> -acyl pyrimidine, C<sup>5</sup> -amidopyrimidine, C<sup>5</sup> -cyanopyrimidine, C<sup>5</sup> -nitropyrimidine, C<sup>5</sup> -aminopyrimidine, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl or a pharmaceutically acceptable derivative thereof.

17) A process according to claim 3 wherein R2 is



wherein W is halogen, C<sub>1-16</sub> alkyl, C<sub>2-16</sub> alkoxyalkyl, C<sub>6-10</sub> aryl, C<sub>1-16</sub> alkoxy or nitro; or



wherein E is C<sub>6-10</sub> aryl, C<sub>1-16</sub> alkoxy, C<sub>2-16</sub> alkoxyalkyl or C<sub>1-16</sub> alkyl; or

Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), where Z<sup>1</sup>, Z<sup>2</sup> and Z<sup>3</sup> are independently selected from the group consisting of hydrogen; C<sub>1-20</sub> alkyl optionally substituted by fluoro, bromo, chloro, iodo; C<sub>7-10</sub> arylalkyl optionally substituted by fluoro, bromo, chloro or iodo; and C<sub>6-10</sub> aryl optionally substituted by fluoro, bromo, chloro or iodo.

## PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING  
SUBMISSION OR TRANSMITTAL  
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

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2002 NOV 13 A 9 16

WHEELER, Michael, E.  
Smart & Biggar  
P.O. Box 2999, Station D  
900-55 Metcalfe Street  
Ottawa, Ontario K1P 5X6  
Canada

|                                                                      |                                                                       |
|----------------------------------------------------------------------|-----------------------------------------------------------------------|
| Date of mailing (day/month/year)<br>29 October 2002 (29.10.02)       |                                                                       |
| Applicant's or agent's file reference<br>74872-82                    | IMPORTANT NOTIFICATION                                                |
| International application No.<br>PCT/CA02/00899                      | International filing date (day/month/year)<br>14 June 2002 (14.06.02) |
| International publication date (day/month/year)<br>Not yet published | Priority date (day/month/year)<br>15 June 2001 (15.06.01)             |
| Applicant<br>SHIRE BIOCHEM INC. et al                                |                                                                       |

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(\*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denotes a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| Priority date           | Priority application No. | Country or regional Office<br>or PCT receiving Office | Date of receipt<br>of priority document |
|-------------------------|--------------------------|-------------------------------------------------------|-----------------------------------------|
| 15 June 2001 (15.06.01) | 60/298,079               | US                                                    | 25 Octo 2002 (25.10.02)                 |

|                                                                                               |                                                        |
|-----------------------------------------------------------------------------------------------|--------------------------------------------------------|
| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>François BAECHLER (Fax 338-8995) |
| Facsimile No. (41-22) 740.14.35                                                               | Telephone No. (41-22) 338.83.38                        |

Form PCT/IB/304 (July 1998)

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## PCT

## REQUEST

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

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) 74872-82

Box No. I TITLE OF INVENTION  
STEREOSELECTIVE METHOD FOR THE PREPARATION OF NUCLEOSIDES

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.  
275 Armand Frappier Boulevard  
Laval, Quebec  
H7V 4A7 Canada

Telephone No.

Facsimile No.

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.)

YU, Qing  
58 Concorde Ouest  
Laval, Quebec  
H7N 1H6 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

☐ 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.)

WHEELER, Michael E.; HIRAMA, Tokuo; MORROW, Joy D.;  
SCHWARTZ, David E.; and NGUYEN, Thuy Huong  
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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.

Box No.V DESIGNATION OF STATES Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

**Regional Patent**

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Cote d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

**National Patent (if other kind of protection or treatment desired, specify on dotted line):**

- |                                                                           |                                                                                  |                                                                    |
|---------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <input checked="" type="checkbox"/> AE United Arab Emirates               | <input checked="" type="checkbox"/> GM Gambia                                    | <input checked="" type="checkbox"/> NZ New Zealand                 |
| <input checked="" type="checkbox"/> AG Antigua and Barbuda                | <input checked="" type="checkbox"/> HR Croatia                                   | <input checked="" type="checkbox"/> OM Oman                        |
| <input checked="" type="checkbox"/> AL Albania                            | <input checked="" type="checkbox"/> HU Hungary                                   | <input checked="" type="checkbox"/> PH Philippines                 |
| <input checked="" type="checkbox"/> AM Armenia                            | <input checked="" type="checkbox"/> ID Indonesia                                 | <input checked="" type="checkbox"/> PL Poland                      |
| <input checked="" type="checkbox"/> AT Austria                            | <input checked="" type="checkbox"/> IL Israel                                    | <input checked="" type="checkbox"/> PT Portugal                    |
| <input checked="" type="checkbox"/> AU Australia                          | <input checked="" type="checkbox"/> IN India                                     | <input checked="" type="checkbox"/> RO Romania                     |
| <input checked="" type="checkbox"/> AZ Azerbaijan                         | <input checked="" type="checkbox"/> IS Iceland                                   | <input checked="" type="checkbox"/> RU Russian Federation          |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina             | <input checked="" type="checkbox"/> JP Japan                                     | <input checked="" type="checkbox"/> SD Sudan                       |
| <input checked="" type="checkbox"/> BB Barbados                           | <input checked="" type="checkbox"/> KE Kenya                                     | <input checked="" type="checkbox"/> SE Sweden                      |
| <input checked="" type="checkbox"/> BG Bulgaria                           | <input checked="" type="checkbox"/> KG Kyrgyzstan                                | <input checked="" type="checkbox"/> SG Singapore                   |
| <input checked="" type="checkbox"/> BR Brazil                             | <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea     | <input checked="" type="checkbox"/> SI Slovenia                    |
| <input checked="" type="checkbox"/> BY Belarus                            | <input checked="" type="checkbox"/> KR Republic of Korea                         | <input checked="" type="checkbox"/> SK Slovakia                    |
| <input checked="" type="checkbox"/> BZ Belize                             | <input checked="" type="checkbox"/> KZ Kazakhstan                                | <input checked="" type="checkbox"/> SL Sierra Leone                |
| <input checked="" type="checkbox"/> CA Canada                             | <input checked="" type="checkbox"/> LC Saint Lucia                               | <input checked="" type="checkbox"/> TJ Tajikistan                  |
| <input checked="" type="checkbox"/> CH & LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> LK Sri Lanka                                 | <input checked="" type="checkbox"/> TM Turkmenistan                |
| <input checked="" type="checkbox"/> CN China                              | <input checked="" type="checkbox"/> LR Liberia                                   | <input checked="" type="checkbox"/> TN Tunisia                     |
| <input checked="" type="checkbox"/> CO Colombia                           | <input checked="" type="checkbox"/> LS Lesotho                                   | <input checked="" type="checkbox"/> TR Turkey                      |
| <input checked="" type="checkbox"/> CR Costa Rica                         | <input checked="" type="checkbox"/> LT Lithuania                                 | <input checked="" type="checkbox"/> TT Trinidad and Tobago         |
| <input checked="" type="checkbox"/> CU Cuba                               | <input checked="" type="checkbox"/> LU Luxembourg                                | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> CZ Czech Republic                     | <input checked="" type="checkbox"/> LV Latvia                                    | <input checked="" type="checkbox"/> UA Ukraine                     |
| <input checked="" type="checkbox"/> DE Germany                            | <input checked="" type="checkbox"/> MA Morocco                                   | <input checked="" type="checkbox"/> UG Uganda                      |
| <input checked="" type="checkbox"/> DK Denmark                            | <input checked="" type="checkbox"/> MD Republic of Moldova                       | <input checked="" type="checkbox"/> US United States of America    |
| <input checked="" type="checkbox"/> DM Dominica                           | <input checked="" type="checkbox"/> MG Madagascar                                | <input checked="" type="checkbox"/> UZ Uzbekistan                  |
| <input checked="" type="checkbox"/> DZ Algeria                            | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia | <input checked="" type="checkbox"/> VN Viet Nam                    |
| <input checked="" type="checkbox"/> EC Ecuador                            | <input checked="" type="checkbox"/> MN Mongolia                                  | <input checked="" type="checkbox"/> YU Yugoslavia                  |
| <input checked="" type="checkbox"/> EE Estonia                            | <input checked="" type="checkbox"/> MW Malawi                                    | <input checked="" type="checkbox"/> ZA South Africa                |
| <input checked="" type="checkbox"/> ES Spain                              | <input checked="" type="checkbox"/> MX Mexico                                    | <input checked="" type="checkbox"/> ZM Zambia                      |
| <input checked="" type="checkbox"/> FI Finland                            | <input checked="" type="checkbox"/> MZ Mozambique                                | <input checked="" type="checkbox"/> ZW Zimbabwe                    |
| <input checked="" type="checkbox"/> GB United Kingdom                     | <input checked="" type="checkbox"/> NO Norway                                    |                                                                    |
| <input checked="" type="checkbox"/> GD Grenada                            |                                                                                  |                                                                    |
| <input checked="" type="checkbox"/> GE Georgia                            |                                                                                  |                                                                    |
| <input checked="" type="checkbox"/> GH Ghana                              |                                                                                  |                                                                    |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

|                          |                          |                          |
|--------------------------|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

**Box No. VI PRIORITY CLAIM**

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

| Filing date<br>of earlier application<br>(day/month/year) | Number<br>of earlier application | Where earlier application is:    |                                          |                                                |
|-----------------------------------------------------------|----------------------------------|----------------------------------|------------------------------------------|------------------------------------------------|
|                                                           |                                  | national application:<br>country | regional application:<br>regional Office | international application:<br>receiving Office |
| item (1)<br>15 June 2001<br>(15/06/01)                    | 60/298,079                       | US                               |                                          |                                                |
| item (2)                                                  |                                  |                                  |                                          |                                                |
| item (3)                                                  |                                  |                                  |                                          |                                                |
| item (4)                                                  |                                  |                                  |                                          |                                                |
| item (5)                                                  |                                  |                                  |                                          |                                                |

☐ 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)    ☐ item (4)    ☐ item (5)    ☐ 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/ EPO

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

- |                                             |                                                                                                                                      |   |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|---|
| <input type="checkbox"/> Box No. VIII (i)   | Declaration as to the identity of the inventor                                                                                       | : |
| <input type="checkbox"/> 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             | : |
| <input type="checkbox"/> 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 | : |
| <input type="checkbox"/> Box No. VIII (iv)  | Declaration of inventorship (only for the purposes of the designation of the United States of America)                               | : |
| <input type="checkbox"/> Box No. VIII (v)   | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty                                                       | : |

| Box No. IX CHECK LIST; LANGUAGE OF FILING                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| <b>This international application contains:</b><br>(a) the following number of sheets in paper form:<br>request (including declaration sheets) : 4<br>description (excluding sequence listing part) : 39<br>claims : 7<br>abstract : 1<br>drawings :<br>Sub-total number of sheets : 51<br>sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) :<br>Total number of sheets : 51<br>(b) sequence listing part of description filed in computer readable form<br>(i) <input type="checkbox"/> only (under Section 801 (a)(i))<br>(ii) <input type="checkbox"/> in addition to being filed in paper form (under Section 801 (a)(ii))<br>Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column): | <b>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):</b><br>1. <input checked="" type="checkbox"/> fee calculation sheet : 1<br>2. <input type="checkbox"/> original separate power of attorney :<br>3. <input type="checkbox"/> original general power of attorney :<br>4. <input type="checkbox"/> copy of general power of attorney; reference number, if any: :<br>5. <input type="checkbox"/> statement explaining lack of signature :<br>6. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): :<br>7. <input type="checkbox"/> translation of international application into (language): :<br>8. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material :<br>9. <input type="checkbox"/> sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))<br>(i) <input type="checkbox"/> copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :<br>(ii) <input type="checkbox"/> (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :<br>(iii) <input type="checkbox"/> together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column :<br>10. <input type="checkbox"/> other (specify): : | <b>Number of items</b> |
| <b>Figure of the drawings which should accompany the abstract:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Language of filing of the international application:</b> 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><br><br><div style="text-align: center;"><br/>Michael E. Wheeler<br/>(for Smart &amp; Biggar)</div> |

| For receiving Office use only                                                                                                               |                                                                                                  |
|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| 1. Date of actual receipt of the purported international application:                                                                       | 2. Drawings:<br><input type="checkbox"/> received:<br><br><input type="checkbox"/> 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/                                                                   | 6. <input type="checkbox"/> 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: |

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's  
file reference

74872-82

Applicant

SHIRE BIOCHEM INC., ET AL

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE .....

200.00

T

2. SEARCH FEE .....

1,380.00

S

International search to be carried out by EPO

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets

51

Where item (b) of Box No. IX does not apply, enter Total number of sheets

b1 first 30 sheets

839.00

b1

b2 21  
number of sheets

x 15.00  
fee per sheet

=

315.00

b2

b3 additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):

400

x  
fee per sheet

=

b3

Add amounts entered at b1, b2 and b3 and enter total at B . . .

954.00

B

Designation Fees

The international application contains 93 designations.

5

x 138.00

number of designation fees  
payable (maximum 5)

amount of designation fee

=

690.00

D

Add amounts entered at B and D and enter total at I . . . . .

1,644.00

I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the

4. FEE FOR PRIORITY DOCUMENT (if applicable) . . . . .

P

5. TOTAL FEES PAYABLE . . . . .

3,204.00

TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge

☐ postal money order

☐ cash

☐ coupons

☒ cheque

☐ bank draft

☐ revenue stamps

☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

☐ Authorization to charge the total fees indicated above.

☐ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

☐ Authorization to charge the fee for priority document.

Receiving Office: RO/ CA

Deposit Account No.: 27F13

Date: June 14, 2002

Name: Michael E. Wheeler

Signature: Michael E. Wheeler

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

## PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

To:  
SMART & BIGGAR  
Attn. Wheeler, Michael E.  
900-55 Metcalfe Street  
P.O. Box 2999, Station D  
Ottawa, Ontario K1P 5Y6  
CANADA

Date of mailing  
(day/month/year) 04/09/2002

Applicant's or agent's file reference  
74872-82

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.  
PCT/CA 02/ 00899

International filing date  
(day/month/year) 14/06/2002

Applicant  
SHIRE BIOCHEM INC.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

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 is 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. Further action(s): The applicant is reminded of the following:

Shortly after 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 International publication.

Within 19 months from the priority date, 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).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  
 European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer  
Véronique Baillou

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic 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, 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 letter 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.

ON DOCKET  
P5H  
DUE  
Nov. 4/02.

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 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 18 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 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 (Administrative Instructions, 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.

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 48.4)**

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 under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

**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, where 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 Office, 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 Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

|                                                          |                                                                                                                                                         |                                                                |
|----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Applicant's or agent's file reference<br><b>74872-82</b> | <b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below. |                                                                |
| International application No.<br><b>PCT/CA 02/ 00899</b> | International filing date (day/month/year)<br><b>14/06/2002</b>                                                                                         | (Earliest) Priority Date (day/month/year)<br><b>15/06/2001</b> |
| Applicant<br><b>SHIRE BIOCHEM INC.</b>                   |                                                                                                                                                         |                                                                |

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 3 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, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

## 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:

**STERESELECTIVE METHOD FOR THE PREPARATION OF NUCLEOSIDE ANALOGUES**

## 5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 35.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

## 6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CA 02/00899A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D409/04 C07D411/04

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

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

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                     | Relevant to claim No. |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A          | CAPUTO ET AL.: "A new strategy for the asymmetric synthesis of 1,3-oxathiolane-based nucleoside analogues"<br>EUROPEAN JOURNAL OF ORGANIC CHEMISTRY,<br>WILEY-VCH VERLAG, WEINHEIM, DE,<br>1999, pages 1455-1458, XP002210506<br>ISSN: 1434-193X<br>cited in the application<br>page 1456, left-hand column<br><br>-/- | 1-17                  |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

21 August 2002

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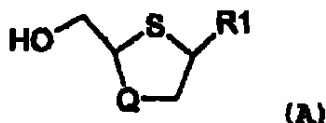
Gohlke, P

Form PCTISA/210 (second sheet) (July 1992)

Form PCTISA/210 (patent family annex) (July 1992)

**MÉTODO ESTEREOSELECTIVO PARA LA PREPARACIÓN DE**  
**ANÁLOGOS DE NUCLEÓSIDO**

La presente invención se refiere a un proceso novedoso  
5 para producir cis-nucleósidos o análogos de nucleósido y derivados  
de la fórmula (A):



10 en la que R<sub>1</sub> es una base de pirimidina, o un derivado aceptable para  
uso farmacéutico, y Q es oxígeno, carbono o azufre.

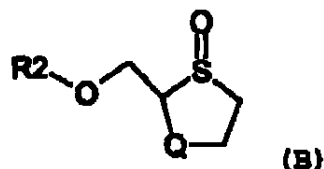
Se ha descubierto que las clases de compuestos de la  
fórmula (A), en particular los 1,3-oxatíolanos 2-sustituidos, 4-  
sustituidos, tienen actividad antiviral potente. En particular se ha  
15 descubierto que esos compuestos actúan como inhibidores potentes  
de la reproducción de VIH-1 en linfocitos T, durante un periodo  
prolongado de tiempo, con menos efectos colaterales citotóxicos que  
los compuestos conocidos en la técnica (véase Belleau y coautores  
(1993) *Bioorg. Med. Chem. Lett.*, tomo 3, No. 8, páginas 1723-1728).  
20 Se ha encontrado que esos compuestos también son activos contra  
cepas de VIH resistentes a 3TC (véase Taylor y coautores (2000)  
*Antiviral Chem. Chemother.*, tomo 11, No. 4, páginas 291-301;  
Stoddart y coautores (2000) *Antimicrob. Agents Chemother.*, tomo 44,  
No. 3, páginas 783-786). Esos compuestos también son útiles en la  
25 profilaxis y el tratamiento de infecciones por virus de hepatitis B.

Se han descrito métodos para la preparación de esos  
compuestos en las publicaciones del TCP No. WO 92/08717 y WO  
95/29176, así como en publicaciones por Belleau y coautores (1993),  
*Bioorg. Med. Chem. Lett.*, tomo 3, No. 8, páginas 1723-1728; Wang y  
30 coautores (1994) *Tetrahedron Lett.*, tomo 35, No. 27, páginas 4739-

4742; Mansour y coautores (1995), *J. of Med. Chem.*, tomo 38, No. 1, páginas 1-4; y Caputo y coautores, en *Eur. J. Org. Chem.*, tomo 6, páginas 1455-1458 (1999). Estos procesos involucran una multitud de pasos que aumentan los costos de producción y reducen el  
 5 rendimiento de los compuestos deseados.

### **BREVE DESCRIPCIÓN DE LA INVENCION**

El proceso que constituye el objetivo de la presente  
 10 invención comprende el paso de acoplar el intermediario de la fórmula (B):



15

en la que:

R2 es hidrógeno o un grupo protector de hidroxilo, tal como arilalquilo de 7 a 10 átomos de carbono, acilo de 1 a 16 átomos de carbono o  $\text{Si}(\text{Z}^1)(\text{Z}^2)(\text{Z}^3)$ , donde  $\text{Z}^1$ ,  $\text{Z}^2$  y  $\text{Z}^3$  están seleccionados  
 20 independientemente del grupo que consiste de hidrógeno, alquilo de 1 a 20 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro, yodo, alcoxi de 1 a 6 átomos de carbono o ariloxi de 6 a 20 átomos de carbono; aralquilo de 7 a 20 átomos de carbono, opcionalmente sustituido con halógeno, alquilo de 1 a 20 átomos de  
 25 carbono o alcoxi de 1 a 20 átomos de carbono; arilo de 6 a 20 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro, yodo, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; trialquilsililo; flúor; bromo; cloro y yodo; y

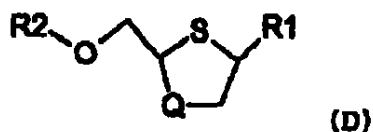
Q es carbono, oxígeno o azufre; con

30

R1, una base de pirimidina o un derivado aceptable para uso

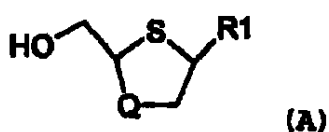
farmacéutico, en presencia de una cantidad catalítica de un elemento, o de una combinación de elementos del grupo IB o IIB, un ácido de Lewis y una amina terciaria. Se desprotege el intermediario resultante, de la fórmula (D):

5



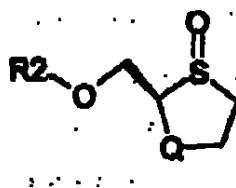
para obtener el cis-nucleósido de la fórmula (A)

10

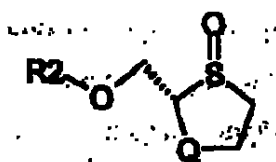


El compuesto de la fórmula (B) puede ser (B1):

15



20 o bien (B2):



25 o una mezcla de los dos enantiómeros.

En una modalidad alternativa de la presente invención, se obtiene la desprotección del intermediario de la fórmula (D) disolviendo dicho intermediario en un solvente adecuado, en presencia de un agente de desprotección.

30

En una modalidad alternativa de la presente invención se

provee un simple método de preparación de dos pasos para los cis-nucleósidos de la fórmula (A), donde el paso de acoplamiento da por resultado un producto en el que la razón cis a trans es mayor que 2 a 1.

5 En otra modalidad, la razón cis a trans del producto intermediario de la fórmula (D) es inversamente proporcional a la temperatura de reacción en el paso de acoplamiento.

En una modalidad alternativa de la presente invención el paso de desprotección da por resultado la precipitación selectiva del  
10 cis-nucleósido de la fórmula (A) mediante la selección de un agente de desprotección apropiado y un solvente.

Los procesos de la presente invención tienen las ventajas de permitir la preparación de un nucleósido de la fórmula (A), sus análogos o sus derivados, sin el uso de materiales de partida  
15 costosos, de etapas de protección y desprotección dificultosas, ni de adiciones ni eliminación de los sustituyentes en 2' o 3'.

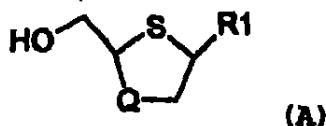
El proceso de la presente invención produce cis-nucleósidos de la fórmula (A) en rendimientos elevados, con gran pureza y elevada estereoselectividad.

20 El proceso de la presente invención tiene la ventaja adicional de generar nucleósidos cuya configuración estereoquímica puede ser controlada fácilmente, de manera simple, mediante la selección de las condiciones de partida apropiadas.

## 25 DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención describe un proceso estereoselectivo para preparar predominantemente cis-nucleósidos o análogos y derivados de nucleósido de la fórmula (A):

30

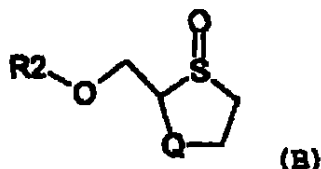


en la que:

R1 es una base de pirimidina o un derivado de ella aceptable para uso farmacéutico; y

Q es carbono, oxígeno o azufre;

5 que consiste del paso de acoplamiento de un compuesto de la fórmula (B):

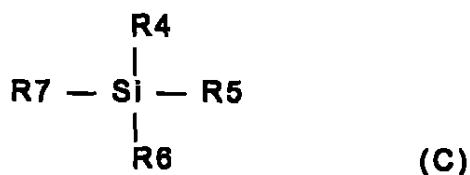


10

en la que:

R2 es hidrógeno o un grupo protector de hidroxilo, tal como aralquilo de 7 a 10 átomos de carbono, acilo de 1 a 16 átomos de carbono o  $\text{Si}(\text{Z}^1)(\text{Z}^2)(\text{Z}^3)$ , donde  $\text{Z}^1$ ,  $\text{Z}^2$  y  $\text{Z}^3$  están seleccionados  
 15 independientemente del grupo que consiste de hidrógeno; alquilo de 1 a 20 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro, yodo, alcoxi de 1 a 6 átomos de carbono o ariloxi de 6 a 20 átomos de carbono; aralquilo de 7 a 20 átomos de carbono, opcionalmente sustituido con halógeno, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; arilo de 6 a 20 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro, yodo, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; trialkilsililo; flúor; bromo; cloro y yodo;

con una base R1, donde R1 es una base de pirimidina o un  
 25 derivado de ella aceptable para uso farmacéutico; en un solvente de acoplamiento adecuado, en presencia de una cantidad catalítica de un elemento o de una combinación de elementos del grupo IB o IIB; una amina terciaria y un ácido de Lewis de la fórmula (C):

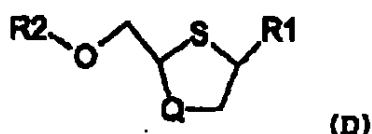


30

en la que:

R4, R5 y R6 están seleccionados independientemente del grupo que consiste de hidrógeno; alquilo de 1 a 20 átomos de carbono, sustituido opcionalmente con flúor, bromo, cloro, yodo, alcoxi de 1 a  
 5 6 átomos de carbono o ariloxi de 6 a 20 átomos de carbono; aralquilo de 7 a 20 átomos de carbono, sustituido opcionalmente con halógeno, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; arilo de 6 a 20 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro, yodo, alquilo de 1 a  
 10 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; trialquilsililo; flúor; bromo; cloro y yodo; y

R7 está seleccionado del grupo que consiste de flúor; bromo; cloro; yodo; ésteres sulfonato de 1 a 20 átomos de carbono, opcionalmente sustituidos con flúor, bromo, cloro o yodo; ésteres de  
 15 alquilo de 1 a 20 átomos de carbono, opcionalmente sustituidos con flúor, bromo, cloro o yodo; triyoduro; un grupo sililo de la fórmula general (R4)(R5)(R6)Si (donde R4, R5 y R6 son como se definió aquí con anterioridad); arilselenenilo de 6 a 20 átomos de carbono; arilsulfenilo de 6 a 20 átomos de carbono; alcoxi alquilo de 6 a 20  
 20 átomos de carbono; y trialquilsiloxi;  
 para producir un intermediario de la fórmula (D):



25 El paso de acoplamiento va seguido de un paso de desprotección para producir los cis-nucleósidos o los análogos o derivados de nucleósido de la fórmula (A).

En una modalidad alternativa, la presente invención contempla un método simple de preparación, de dos pasos, para  
 30 preparar nucleósidos de la fórmula (A), donde el proceso da por

resultado un producto de la fórmula (A) en el que la razón cis a trans es mayor que 2 a 1. La invención incluye un proceso en el que la razón cis a trans es mayor que, o igual a, 3 a 1.

El término "alquilo, cuando se usa en la presente, a menos que se especifique de otra manera, se refiere a un hidrocarburo primario, secundario o terciario saturado, de cadena recta, ramificado o cíclico, de 1 a 30 átomos de carbono, particularmente de 1 a 6 átomos de carbono, no sustituido o monosustituido o disustituido opcionalmente con hidroxilo,  $N_3$ , CN, SH, amino, halógeno (F, Cl, Br, I), arilo de 6 a 12 átomos de carbono, alquilo de 1 a 6 átomos de carbono, alcoxilalquilo de 2 a 12 átomos de carbono o nitrógeno. Incluye específicamente: metilo, etilo, ciclopropilo, propilo, isopropilo, butilo, isobutilo, butilo terciario, pentilo, ciclopentilo, isopentilo, neopentilo, hexilo, isohexilo, ciclohexilo, ciclohexilmetilo, 3-metilpentilo, 2,2-dimetilbutilo y 2,3-dimetilbutilo.

El término "acilo, cuando se usa en lo que viene a continuación, se refiere a un grupo funcional derivado de un ácido carboxílico alifático, por eliminación del grupo -OH, de 1 a 30 átomos de carbono, particularmente de 1 a 6 átomos de carbono. Como el ácido al que está relacionado, el radical acilo alifático puede estar sustituido (con un hidroxilo,  $N_3$ , CN, halógeno (F, Cl, Br, I), arilo de 6 a 12 átomos de carbono, alquilo de 1 a 6 átomos de carbono, alcoxilalquilo de 2 a 12 átomos de carbono o nitrógeno), o no sustituido; y cualquiera que pueda ser la estructura del resto de la molécula, las propiedades del grupo funcional permanecen esencialmente invariables (por ejemplo, acetilo, propionilo, isobutanilo, pivalilo, hexanilo, butirilo, pentanilo, 3-metilbutirilo, bisuccinato, mesitato, valerilo, caproico, caprílico, cáprico, láurico, mirístico, palmítico, esteárico, oleico, 3-clorobenzoato,

trifluoroacetilo, cloroacetilo y ciclohexanóilo).

Los términos "alquenilo" y "alquinilo" representan cadenas de hidrocarburo rectas, ramificadas o cíclicas, sustituidas (con  $N_3$ , CN, halógeno, hidroxilo o arilo de 6 a 20 átomos de carbono), que  
5 tienen de 2 a 30 átomos de carbono y, de preferencia, de 2 a 6 átomos de carbono, y que contienen por lo menos un grupo insaturado (por ejemplo, alilo).

El término "alcoxi" representa un grupo alquilo sustituido o no sustituido, de 1 a 30 átomos de carbono y, de preferencia, de 1  
10 a 6 átomos de carbono, en el que el grupo alquilo está unido covalentemente a un átomo de oxígeno (por ejemplo, metoxi o etoxi).

El término "arilo" representa una porción aromática que puede estar mono-, bi-, tri-, tetra- o penta-sustituida por hidroxilo, nitro,  $N_3$ , CN, halógeno (F, Cl, Br, I) o sus combinaciones, y que  
15 contiene por lo menos un anillo del tipo bencenoide; el grupo puede contener de 6 a 14 átomos de carbono (por ejemplo, fenilo y naftilo), en particular, de 6 a 10 átomos de carbono.

El término "ariloxi" representa una porción arilo sustituida (con un halógeno, trifluorometilo o alcoxi de 1 a 5 átomos de  
20 carbono) o no sustituida, que tiene de 6 a 14 átomos de carbono, unida covalentemente a un átomo de oxígeno (por ejemplo, benciloxi, fenoxi).

El término "aralalquilo" representa un sustituyente que comprende una porción arilo fijada por medio de una cadena alquilo  
25 (por ejemplo, bencilo, feniletilo), donde la suma total de los átomos de carbono de la porción arilo y de la cadena de alquilo es de 7 a 21. La porción arilo o la cadena, del grupo, opcionalmente está sustituida una o dos veces con OH, SH, amino, halógeno o alquilo de 1 a 6 átomos de carbono.

30 El término "tíol" representa grupos alquilo de 1 a 6

átomos de carbono, arilo de 6 a 15 átomos de carbono, aralquilo de 7 a 21 átomos de carbono, alquenilo de 2 a 6 átomos de carbono o alquinilo de 2 a 6 átomos de carbono, unidos covalentemente a un átomo de azufre adyacente que contiene un hidrógeno.

5 Los términos "alquiltio" (por ejemplo, metiltio, etiltio) y "ariltio" (por ejemplo, feniltio, benciltio), se refieren a grupos alquilo de 1 a 6 átomos de carbono o arilo de 6 a 10 átomos de carbono, no sustituido o monosustituidos o disustituidos opcionalmente con hidroxilo, halógeno (F, Cl, Br, I), arilo de 6 a 12 átomos de carbono,  
10 alquilo de 1 a 6 átomos de carbono, alcoxialquilo de 2 a 12 átomos de carbono o nitro; unidos covalentemente a un átomo de azufre adyacente.

Los términos "aciloxi" y "alcoxycarbonilo" se refieren a cadenas de 1 a 30 átomos de carbono, en particular de 1 a 6 átomos  
15 de carbono, que están saturadas o insaturadas, y que también pueden ser rectas o ramificadas (por ejemplo, acetiloxi). Las cadenas pueden estar no sustituidas u opcionalmente monosustituidas o disustituidas con hidroxilo, N<sub>3</sub>, CN, SH, amino, halógeno (F, Cl, Br, I), arilo de 6 a 12 átomos de carbono, alquilo de  
20 1 a 6 átomos de carbono, alcoxialquilo de 2 a 12 átomos de carbono, o nitro.

El término "alcoxialquilo" representa un grupo alcoxi de 1 a 6 átomos de carbono, fijado a un grupo alquilo adyacente, de 1 a 6 átomos de carbono (por ejemplo, metoximetilo, etoximetilo). Pueden  
25 estar no sustituidos u opcionalmente monosustituidos o disustituidos con hidroxilo, N<sub>3</sub>, CN, SH, amino, halógeno (F, Cl, Br, I), arilo de 6 a 12 átomos de carbono, alquilo de 1 a 6 átomos de carbono, alcoxialquilo de 2 a 12 átomos de carbono o nitro.

El término "heterociclo" representa un anillo monocíclico  
30 o policíclico (es decir, bicíclico), saturado o no saturado, que

incorpora uno o más heteroátomos (es decir, de 1 a 4), seleccionados de N, O y S. Se debe entender que un heterociclo está opcionalmente monosustituido o disustituido con OH, SH, amino, halógeno, CF<sub>3</sub>, oxo o alquilo de 1 a 6 átomos de carbono. Los  
5 ejemplos de heterociclos monocíclicos adecuados incluyen, aunque no están limitados a ellos: piridina, piperidina, pirazina, piperazina, pirimidina, imidazol, triazol, oxazol, furano, pirano y tiofeno. Los ejemplos de heterociclos bicíclicos adecuados incluyen, aunque no están limitados a ellos: indol, bencimidazol, quinolina, isoquinolina,  
10 purina y carbazol.

El término "aralquilo" representa un sustituyente que comprende una porción arilo de 6 a 10 átomos de carbono, fijado por medio de una cadena de alquilo de 1 a 6 átomos de carbono (por ejemplo, bencilo, fenetilo). La porción arilo o de cadena del grupo  
15 está no sustituida u opcionalmente está monosustituida o disustituida con hidroxí, N<sub>3</sub>, CN, SH, amino, halógeno (F, Cl, Br, I), arilo de 6 a 12 átomos de carbono, alquilo de 1 a 6 átomos de carbono, alquiloalquilo de 2 a 12 átomos de carbono o nitro.

El término "amino" representa grupos alquilo de 1 a 6  
20 átomos de carbono, arilo de 6 a 10 átomos de carbono, alqueno de 2 a 6 átomos de carbono, alquino de 2 a 6 átomos de carbono o aralquilo de 7 a 12 átomos de carbono, no sustituidos u opcionalmente monosustituidos o disustituidos con hidroxí, N<sub>3</sub>, CN, SH, amino, halógeno (F, Cl, Br, I), arilo de 6 a 12 átomos de  
25 carbono, alquilo de 1 a 6 átomos de carbono, alcohalquilo de 2 a 12 átomos de carbono o nitro; donde los átomos de carbono están unidos covalentemente a un elemento adyacente, a través de un átomo de nitrógeno (por ejemplo, pirrolidina). Incluyen aminas primarias, secundarias y terciarias, y sales de amonio cuaternario.

30 El término "protegido", cuando se usa en la presente, y a

menos que se defina de otra manera, se refiere a un grupo que se añade a un átomo de oxígeno, de nitrógeno o de fósforo para prevenir su reacción ulterior o para otros propósitos. Quienes sean expertos en la materia de las síntesis orgánicas conocerán una gran  
5 variedad de grupos protectores de oxígeno y de nitrógeno. Los grupos protectores adecuados están descritos, por ejemplo, en Greene y coautores *Protective Groups in Organic Synthesis*, John Wiley and Sons, segunda edición, 1991, que queda incorporado aquí por medio de esta referencia.

10 Por base de piridina, su derivado o su análogo se quiere decir una base de piridina encontrada en el nucleósido o un análogo suyo, que imite aquellas bases por cuanto sus estructuras (las clases de átomos y su disposición) son similares a las bases normales, pero pueden poseer otras propiedades funcionales adicionales o pueden  
15 carecer de ciertas propiedades funcionales, de las bases normales. Los derivados de dichas bases o sus análogos incluyen aquellos que son obtenidos por reemplazo de una porción CH con un átomo de nitrógeno (por ejemplo, 5-azapirimidinas, tales como 5-azacitosina), o pueden un anillo sustituido con halógeno, hidroxilo, azido, ciano,  
20 amino, amino sustituido, tiol, alquilo de 1 a 6 átomos de carbono y arilo de 6 a 10 átomos de carbono.

Mediante el término "derivado aceptable para uso farmacéutico" de una pirimidina, se quiere decir cualquier base de pirimidina que pueda dar lugar a la formación de una sal, un éster,  
25 aceptables para uso farmacéutico, o una sal de dicho éster, de un compuesto de la fórmula (A), o cualquier otro compuesto que, al ser administrado a un receptor, es capaz de proveer (directa o indirectamente) un compuesto de la fórmula (A) o un metabolito o residuo suyo, antiviralmente activo. Quienes sean expertos en la  
30 materia apreciarán que los compuestos de la fórmula (A) pueden ser

modificados para proveer sus derivados aceptables para uso farmacéutico, en los grupos funcionales, en la porción de base.

El compuesto de la fórmula (B) puede ser (B1):



o bien (B2):



o una mezcla de ambos enantiómeros. El sulfóxido puede ser un enantiómero individual o una mezcla de enantiómeros, incluyendo, pero sin limitación, una mezcla racémica.

El paso de acoplamiento del proceso que forma el objetivo de la presente invención incluye la adición de uno o más elementos del grupo IB o IIB. El elemento, o la combinación de elementos, usados, pueden estar en su estado oxidado. Este elemento o esta combinación de elementos del grupo IB o IIB, cataliza el paso de acoplamiento. El elemento seleccionado, o la combinación de elementos del grupo IB o del grupo IIB, están presentes en cantidades de entre alrededor de 0.25 por ciento molar y 100 por ciento molar. En otra modalidad, la concentración del elemento o la combinación de elementos del grupo IB o del grupo IIB puede estar entre alrededor de 5 por ciento y alrededor de 35 por ciento.

El proceso que forma el objetivo de la presente invención incluye un paso de acoplamiento, en el que el elemento o la combinación de elementos del grupo IB o del grupo IIB están seleccionados del grupo que comprende  $\text{Cu}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Ag}^+$ ,  $\text{Au}^+$ ,  $\text{Au}^{3+}$ ,

$\text{Zn}^{2+}$ ,  $\text{Cd}^{2+}$  y combinaciones de ellos.

El proceso que forma el objetivo de la presente invención incluye un paso de acoplamiento, en el que el elemento o la combinación de elementos del grupo IB o del grupo IIB están  
5 seleccionados de  $\text{Cu}^+$ ,  $\text{Cu}^{2+}$  o  $\text{Zn}^{2+}$ .

El término "amina terciaria" incluye aminas terciarias con elevada basicidad. La amina terciaria tiene la forma  $\text{N}(\text{Z}^4)(\text{Z}^5)(\text{Z}^6)$ , en la que  $(\text{Z}^4)$ ,  $(\text{Z}^5)$ ,  $(\text{Z}^6)$  están seleccionados independientemente del grupo que consiste de alquilo de 1 a 6 átomos de carbono,  
10 opcionalmente sustituido con alquilo de 1 a 3 átomos de carbono, arilo de 6 a 10 átomos de carbono, halógeno. Los ejemplos de la amina terciaria incluyen: trietilamina, dietilciclohexilamina, dietilmetilamina, dimetiletilamina, dimetilisopropilamina, dimetilbutilamina, dimetilciclohexilamina, tributilamina, dietilmetilamina,  
15 dimetilisopropilamina y diisopropiletilamina.

La cantidad de amina terciaria puede variar entre aproximadamente un equivalente y aproximadamente cuatro equivalentes. La cantidad de amina terciaria usada puede variar entre aproximadamente un equivalente y dos equivalentes.

20 El paso de acoplamiento del proceso que forma el objetivo de la presente invención se efectúa en un solvente de acoplamiento adecuado. Un solvente de acoplamiento adecuado incluye los solventes orgánicos clorados de 1 a 10 átomos de carbono. Los solventes de acoplamiento adecuados incluyen también: cloroalquilos  
25 de 1 a 8 átomos de carbono, cloroalquénilos de 1 a 8 átomos de carbono, cloroarilos de 6 a 10 átomos de carbono, alquilonitrilos de 1 a 8 átomos de carbono, y sus combinaciones. Se puede seleccionar los solventes de acoplamiento de: clorometanos, cloroetanos, metanonitrilos, o sus mezclas. Los solventes de acoplamiento de  
30 interés incluyen: diclorometano, cloroformo, acetonitrilo,

dicloroetano, clorobenceno y sus combinaciones.

La cantidad de solvente de acoplamiento usada puede variar entre alrededor de 5 mL por gramo de sulfóxido y 50 mL por gramo de sulfóxido. En una modalidad alternativa de la invención la  
5 cantidad de solvente de acoplamiento está entre 10 mL por gramo de sulfóxido y 30 mL por gramo de sulfóxido.

El paso de acoplamiento del proceso que forma el objetivo de la presente invención es afectado por la temperatura de la reacción. La razón cis a trans del producto de la fórmula (D) es  
10 inversamente proporcional a la temperatura de la reacción. Se lleva a cabo el paso de acoplamiento a una temperatura entre alrededor de 40 grados C y aproximadamente -40°C. En una modalidad alternativa, la temperatura de reacción del paso de acoplamiento está entre alrededor de 30°C y alrededor de -50°C.

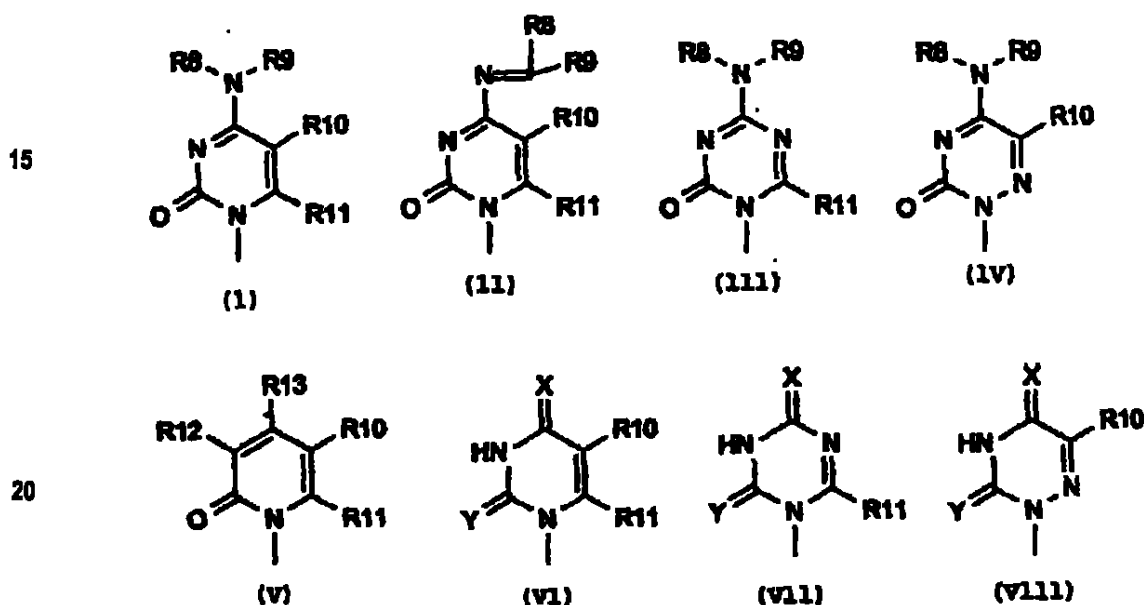
15 El segundo paso en el proceso que forma el objetivo de la presente invención es un paso de desprotección. El paso de cristalización con desprotección es efectuado en un solvente adecuado. Son particularmente interesantes los solventes que favorecen la cristalización del producto de la fórmula (A). Los  
20 solventes adecuados incluyen: agua, metanol, etanol, tolueno, éter terbutilmetílico, o combinaciones de ellos.

La desprotección también puede incluir la presencia de cantidades adecuadas de un agente de desprotección. Son de interés particular los agentes de desprotección que ayuden a la  
25 separación del producto cis de la fórmula (A). Los agentes de desprotección adecuados son seleccionados de acuerdo con la identidad del grupo protector en el intermediario de la fórmula (D) como está mostrado en Greene y coautores: *Protective Groups in Organic Synthesis*, John Wiley and Sons, segunda edición, 1991.  
30 Los agentes de desprotección pueden ser alcalinos. Los agentes de

desprotección incluyen: hidróxido de sodio, metóxido de sodio, hidróxido de amonio, hidróxido de potasio, hidróxido de litio y amoniaco metanólico.

En otra modalidad de la presente invención está presente  
5 el agente de desprotección en cantidades catalíticas. En otra  
modalidad, el agente de desprotección está presente en  
concentraciones que van desde alrededor de 0.1 por ciento molar  
hasta alrededor de 50 por ciento molar. Una modalidad alternativa  
incluye concentraciones del agente de desprotección que van desde  
10 alrededor de 5 por ciento molar hasta alrededor de 20 por ciento  
molar del agente de desprotección.

Convenientemente, la base R1 está seleccionada de:



en las que:

x es oxígeno, NH o azufre;

25 y es oxígeno, NH o azufre;

R8 y R9 están seleccionados independientemente de hidrógeno, hidroxilo, amino, alquilo de 1 a 6 átomos de carbono o alquénilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, acilo de 1 a 10 átomos de carbono, arilo de 6 a 10 átomos de carbono,  
30 carbonilarilo de 6 a 11 átomos de carbono, carboniloxialquilo de 1 a

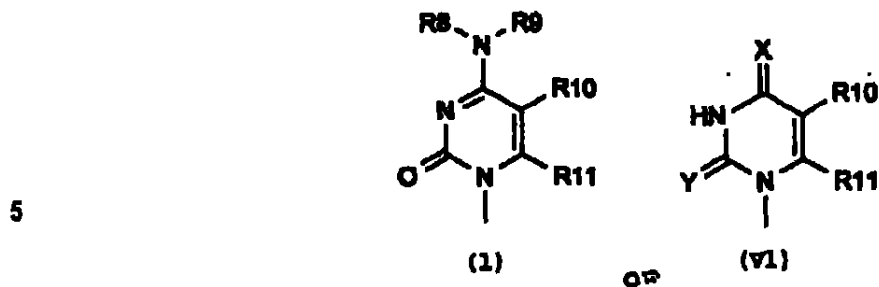
7 átomos de carbono, carboniloxiarilo de 6 a 11 átomos de carbono, carbonilaminoalquilo de 2 a 7 átomos de carbono, o aminoácidos;

R8 puede ser un anillo carbocíclico de 3 a 8 átomos de carbono, saturado o insaturado, opcionalmente sustituido con COOH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, halógeno, C(O)R14, donde R14 es un alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono; y R9 está seleccionado de H, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono y alquinilo de 2 a 6 átomos de carbono;

R8R9 también pueden estar conectados al átomo de nitrógeno para formar un anillo heterocíclico saturado o insaturado, de 3 a 8 átomos de carbono, opcionalmente sustituido con C(O)OH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, halógeno, C(O)R14, donde R14 es un alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono y C(O)OR15, donde R15 es un alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono;

R10 R11, R12 y R13 están seleccionados, cada uno independientemente, de hidrógeno, halógeno, hidroxilo, amino, ciano, carboxilo, carbamilo, alcóxicarbonilo de 2 a 7 átomos de carbono, hidroximetilo, trifluorometilo, ariltio de 6 a 10 átomos de carbono, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, sustituidos o no sustituidos con halógeno o azido, alquinilo de 2 a 6 átomos de carbono, aciloxi de 1 a 6 átomos de carbono, tiocarboxi, tiocarbamilo, carbamato, ureído, amidino o ariloxi de 6 a 10 átomos de carbono.

En otra modalidad de la presente invención, R1 es:



donde R8 y R9 están seleccionados independientemente de hidrógeno, hidroxilo, amino, alquilo de 1 a 10 átomos de carbono o  
 10 alquenilo de 2 a 10 átomos de carbono, alquinilo de 2 a 10 átomos de carbono, acilo de 1 a 10 átomos de carbono, arilo de 6 a 10 átomos de carbono, carbonilarilo de 6 a 16 átomos de carbono, carboniloxialquilo de 1 a 10 átomos de carbono, carboniloxiarilo de 6 a 16 átomos de carbono, carbonilaminoalquilo de 2 a 12 átomos de  
 15 carbono, o aminoácidos; R10 y R11 están seleccionados, cada uno independientemente, de hidrógeno, halógeno, hidroxilo, hidroximetilo, trifluorometilo, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, sustituidos o no sustituidos con halógeno, azido, alquinilo de 2 a 6 átomos de carbono, o ariloxi  
 20 de 6 a 10 átomos de carbono; y  
 X y Y están seleccionados independientemente de O ó S.

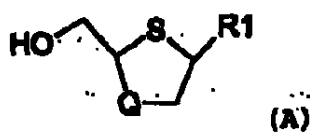
En una modalidad alternativa, R1 es una base de pirimidina, seleccionada de N<sup>4</sup>-alquilpirimidinas, N<sup>4</sup>-acilpirimidina, 4-halopirimidina, pirimidinas N<sup>4</sup>-acetilénicas, 4-amino y N<sup>4</sup>-  
 25 acilpirimidina, 4-hidroxialquilpirimidina, 4-tioalquilpirimidina, timina, citosina, 6-azapirimidina, incluyendo 6-azacitosina, 2- y/o 4-mercaptopirimidina, uracilo, C<sup>5</sup>-alquilpirimidinas, C<sup>5</sup>-bencilpirimidina, C<sup>5</sup>-halopirimidina, C<sup>5</sup>-vinilpirimidina, pirimidina C<sup>5</sup>-acetilénica, C<sup>5</sup>-acilpirimidina, C<sup>5</sup>-amidopirimidina, C<sup>5</sup>-cianopirimidina, C<sup>5</sup>-  
 30 nitropirimidina, C<sup>5</sup>-aminopirimidina, 5-azacitidinilo, 5-azauracililo,

triazolopiridinilo, imidazolopiridinilo, pirrolopirimidinilo o pirazolopirimidinilo.

Los grupos oxígeno funcional y nitrógeno, en R1, pueden estar protegidos cuando sea necesario o conveniente. Los grupos protectores adecuados son bien conocidos por los expertos en la materia, e incluyen: trimetilsililo, dimetilhexilsililo, terbutildimetilsililo y terbutildifenilsililo, tritilo, grupos alquilo de 1 a 12 átomos de carbono, grupos acilo de 1 a 12 átomos de carbono, tales como acetilo y propionilo, benzilo, metansulfonilo y p-toluensulfonilo.

En una modalidad adicional de la presente invención, se selecciona R1 de: citosina, uracilo, timina, 5-fluoropirimidina o análogos protegidos de esas bases.

Otra modalidad de la presente invención incluye un proceso estereoselectivo para formar predominantemente cis-nucleósidos o análogos y derivados de nucleósido de la fórmula (A):



20

en la que:

R1 es una base de pirimidina, seleccionada de N<sup>4</sup>-alquilpirimidinas, N<sup>4</sup>-acilpirimidina, 4-halopirimidina, pirimidinas N<sup>4</sup>-acetilénicas, 4-amino y N<sup>4</sup>-acilpirimidina, 4-hidroxialquilpirimidina, 4-tioalquilpirimidinas, timina, citosina, 6-azapirimidina, incluyendo 6-azacitosina, 2- y/o 4-mercaptopirimidina, uracilo, C<sup>5</sup>-alquilpirimidina, C<sup>5</sup>-bencilpirimidinas, C<sup>5</sup>-halopirimidinas, C<sup>5</sup>-vinilpirimidina, pirimidina C<sup>5</sup>-acetilénica, C<sup>5</sup>-acilpirimidina, C<sup>5</sup>-amidopirimidina, C<sup>5</sup>-cianopirimidina, C<sup>5</sup>-nitropirimidina, C<sup>5</sup>-aminopirimidina, 5-azacitidinilo, 5-azauracililo, triazolopiridinilo, imidazolopiridinilo,

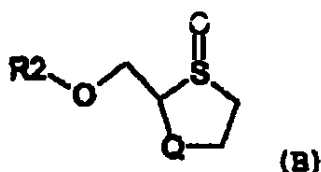
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pirrolopirimidinilo, pirazolopirimidinilo o un derivado suyo aceptable para uso farmacéutico; y

Q es oxígeno;

que consiste del paso de acoplar un compuesto de la fórmula

5 (B):



10 en la que:

R2 es aralquilo de 7 a 10 átomos de carbono, acilo de 1 a 16 átomos de carbono o  $\text{Si}(\text{Z}^1)(\text{Z}^2)(\text{Z}^3)$ , donde  $\text{Z}^1$ ,  $\text{Z}^2$  y  $\text{Z}^3$  están seleccionados independientemente del grupo que consiste de hidrógeno, alquilo de 1 a 20 átomos de carbono, opcionalmente  
 15 sustituido con flúor, bromo, cloro, yodo, alcoxi de 1 a 6 átomos de carbono o arilo de 6 a 20 átomos de carbono; aralquilo de 7 a 20 átomos de carbono, sustituido opcionalmente con halógeno, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; arilo de 6 a 20 átomos de carbono, sustituido opcionalmente con  
 20 flúor, bromo, cloro, yodo, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; trialkilsililo, flúor, bromo, cloro y yodo;

con una base R1, como se definió más atrás, en un solvente de acoplamiento adecuado, en presencia de una cantidad catalítica de  
 25 un elemento, o de una combinación de elementos del grupo IB o del grupo IIB; una amina terciaria o un ácido de Lewis de la fórmula (C):

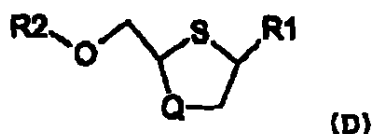


en la que:

R4, R5 y R6 están seleccionados independientemente del grupo que consiste de hidrógeno; alquilo de 1 a 20 átomos de carbono, sustituido opcionalmente con flúor, bromo, cloro, yodo, alcoxi de 1 a 5 6 átomos de carbono o arilo de 6 a 20 átomos de carbono; aralquilo de 7 a 20 átomos de carbono, sustituido opcionalmente con halógeno, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; arilo de 6 a 20 átomos de carbono, sustituido opcionalmente con flúor, bromo, cloro, yodo, alquilo de 1 a 20 10 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; trialquilsililo; flúor; bromo; cloro y yodo; y

R7 está seleccionado del grupo que consiste de flúor; bromo; cloro; yodo; ésteres sulfonato de 1 a 20 átomos de carbono, opcionalmente sustituidos con flúor, bromo, cloro o yodo; ésteres de 15 alquilo de 1 a 20 átomos de carbono, sustituidos opcionalmente con flúor, bromo, cloro o yodo; triyoduro; un grupo sililo de la fórmula general (R4)(R5)(R6)Si (donde R4, R5 y R6 son como se definió aquí con anterioridad); arilselenenilo de 6 a 20 átomos de carbono; arilsulfenilo de 6 a 20 átomos de carbono; alcoxi alquilo de 6 a 20 20 átomos de carbono; y trialquilsiloxi;

para producir un intermediario de la fórmula (D):



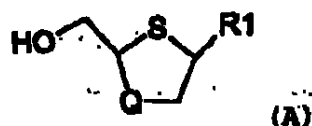
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en la que Q, R1 y R2 son como se definió aquí con anterioridad. El paso de acoplamiento va seguido de un paso de desprotección, en el que se disuelve el intermediario (D) en un solvente adecuado, en presencia de cantidades apropiadas de un agente de desprotección, 30 para producir los cis-nucleósidos o análogos o derivados de

nucleósido de la fórmula (A).

La presente invención incluye la modalidad en la cual el proceso estereoselectivo de formar predominantemente cis-nucleósidos o análogos y derivados de nucleósido de la fórmula (A):

5



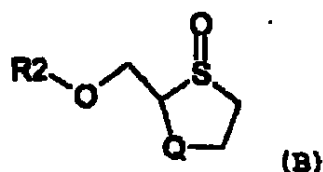
en la que:

R1 es una base de pirimidina, seleccionada de citosina, uracilo, timina, 5-fluoropirimidina, o un derivado de ella, aceptable para uso farmacéutico; y

Q es oxígeno;

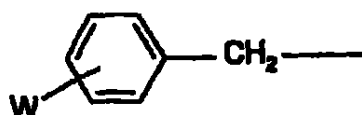
que consiste del paso de acoplar un compuesto de la fórmula (B):

15

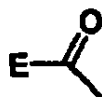


20 en la que:

R2 es:



25 donde W es halógeno, alquilo de 1 a 16 átomos de carbono, alcoxialquilo de 2 a 16 átomos de carbono, arilo de 6 a 10 átomos de carbono, alcoxi de 1 a 16 átomos de carbono o nitro; o

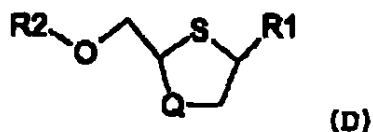


30

donde E es arilo de 6 a 10 átomos de carbono, alcoxi de 1 a 16 átomos de carbono, alcoxialquilo de 2 a 16 átomos de carbono o alquilo de 1 a 16 átomos de carbono; o

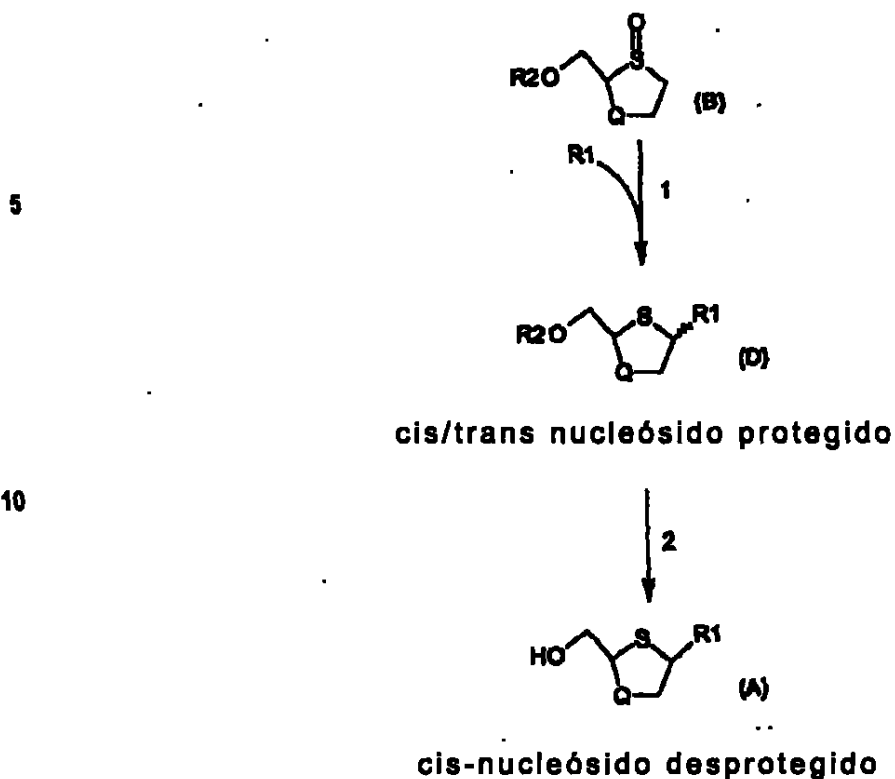
Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), donde Z<sup>1</sup>, Z<sup>2</sup> y Z<sup>3</sup> están seleccionados  
 5 independientemente del grupo que consiste de hidrógeno, alquilo de 1 a 20 átomos de carbono, sustituido opcionalmente con flúor, bromo, cloro, yodo; aralalquilo de 7 a 10 átomos de carbono, sustituido con flúor, bromo, cloro o yodo; y arilo de 6 a 10 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro o yodo;  
 10 con

una base R<sub>1</sub>, como se definió aquí con anterioridad, en un solvente de acoplamiento adecuado, en presencia de una cantidad catalítica de Cu o Zn, o mezclas de ellos; una amina terciaria y un ácido de Lewis, seleccionado de triflato de trimetilsililo,  
 15 bromotrimetilsilano o yodotrimetilsilano; para producir un intermediario de la fórmula (D):



20 en la que Q, R<sub>1</sub> y R<sub>2</sub> son tal como se definió con anterioridad. El paso de acoplamiento va seguido de un paso de desprotección, en el que se disuelve el intermediario (D) en un solvente adecuado, en presencia de cantidades apropiadas de un agente de desprotección para producir los cis-nucleósidos o los análogos o derivados de  
 25 nucleósido de la fórmula (A).

El proceso que constituye el objetivo de la presente invención incluye el esquema de reacción mostrado en el esquema 1:

**ESQUEMA 1**

15 Los diversos pasos que están ilustrados en el esquema 1 pueden ser descritos brevemente de la siguiente manera:

**Paso 1:** Se puede obtener el sulfóxido de la fórmula (B) usando diversos métodos, incluyendo aquellos que están descritos en las publicaciones del TCP WO 92/08717 y WO 96/29176; en *J. Med. Chem.*, 38(1) 1-4 (1995); *Tetrahedron Lett.*, 35(27, 4739-4742 (1994); *Bioorg. Med. Chem. Lett.*, 3(8) 1723-1728 (1993) y *Eur. J. Org. Chem.*, 6:1455-1458 (1999). El sulfóxido puede ser un enantiómero individual o una mezcla de enantiómeros, incluyendo, pero sin limitación a ella, una mezcla racémica.

25 Se acopla el sulfóxido de la fórmula (B) con la base R1. La base R1 puede estar previamente protegida, por ejemplo, puede ser una base de pirimidina siliada (o siliada *in situ*), o se puede usar un derivado aceptable para uso farmacéutico. La reacción de acoplamiento tiene lugar en presencia de una amina terciaria, un

30 ácido de Lewis de la fórmula (C) y cantidades catalíticas de un

elemento de los grupos IB o IIB, en un solvente de acoplamiento adecuado, para dar el nucleósido de cis/trans-pirimidina de la fórmula (D). En el intermediario resultante de la fórmula (D), predomina el isómero cis sobre el isómero trans, en una razón igual  
5 a o mayor que 2 a 1. La razón de isómero cis a trans es inversamente proporcional a la temperatura de reacción. Se puede llevar a cabo la reacción de acoplamiento a la temperatura ambiente o por debajo de ella. La temperatura del paso de acoplamiento puede estar entre alrededor de 0°C y alrededor de -50°C.

10 Si se usa una base sililada, el agente sililante adecuado puede incluir: triflato de terbutildimetilsililo, 1,1,1,3,3,3-hexametildisilazano, TMSI, N,O,bis(TMS)acetono y triflato de trimetilsililo. Están descritos agentes protectores adicionales en Greene y coautores, *Protective Groups in Organic Synthesis*, John  
15 Wiley and Sons, segunda edición, 1991.

La amina terciaria usada en el paso 1 incluye: trietilamina, dietilciclohexilamina, dietilmetilamina, dimetiletilamina, dimetilisopropilamina, dimetilbutilamina, dimetilciclohexilamina, tributilamina, dietilmetilamina, dimetilisopropilamina y  
20 diisopropiletilamina, y sus combinaciones.

El elemento, o la combinación de elementos, de los grupos IB o IIB, usados en el paso 1, incluyen: Cu, Ag, Au, Zn o Cd, en estado oxidado.

El solvente de acoplamiento adecuado es un solvente  
25 orgánico que tiene de uno a diez átomos de carbono. Los solventes de acoplamiento adecuados incluyen: cloruro de metileno, acetonitrilo y mezclas de ellos.

Los ácidos de Lewis adecuados incluyen: triflato de trimetilsililo, bromotrimetilsilano, yodotrimetilsilano y sus  
30 combinaciones. La cantidad de ácido de Lewis puede estar entre

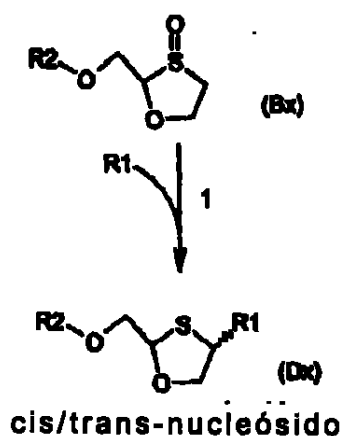
alrededor de 2 equivalentes y alrededor de 5 equivalentes.

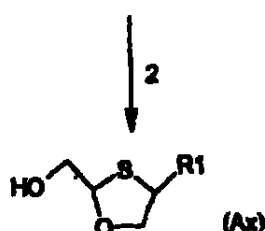
**Paso 2:** Se disuelve el nucleósido cis/trans-pirimidin-1,3-oxatolano de la fórmula (D) en un solvente de desprotección adecuado, en presencia de cantidades adecuadas de un agente de desprotección, para producir los cis-nucleósidos o análogos o derivados de nucleósido de la fórmula (A). Se lleva a cabo el paso de desprotección a una temperatura inferior al punto de ebullición del solvente de desprotección adecuado. La temperatura de reacción del paso de desprotección puede estar entre -30°C y 60°C. Se puede efectuar la reacción a una temperatura aproximada de entre 0°C y 35°C.

Un solvente de desprotección adecuado favorece la cristalización del producto de la fórmula (A). Los solventes adecuados incluyen: agua, metanol, etanol, tolueno, éter terbutilmetílico, o combinaciones de ellos.

Los agentes de desprotección adecuados incluyen: hidróxido de sodio, metóxido de sodio, hidróxido de amonio, hidróxido de potasio, hidróxido de litio y amoniaco metanólico. Son de interés particular los agentes de desprotección que ayudan a la separación del producto de la fórmula (A).

#### ESQUEMA 1a





5

### cis-nucleósido

Los diversos pasos que están ilustrados en el esquema 1a pueden ser descritos brevemente de la siguiente manera:

10        **Paso 1:** Se puede obtener el sulfóxido del 1,3-oxatolano de la fórmula (Bx) usando diversos métodos, incluyendo los que están descritos en las publicaciones del TCP WO 92/08717 y WO 95/29176; en *J. Med. Chem.*, 38(1) 1-4 (1995), *Tetrahedron Lett.*, 35(27) 4739-4742 (1994); *Bioorg. Med. Chem. Lett.*, 3(8) 1723-1728  
15        (1993). La síntesis asimétrica del sulfóxido de la fórmula (Bx) está descrito por Caputo y coautores en *Eur. J. Org. Chem.*, 6:1455-1458 (1999).

Se acopla el sulfóxido del 1,3-oxatolano de la fórmula (Bx) con la base R1. La base R1 puede estar protegida previamente,  
20        por ejemplo, puede ser una base de pirimidina sililada (o se puede sililar *in situ*), o un derivado aceptable para uso farmacéutico. Se efectúa la reacción de acoplamiento en presencia de una amina terciaria, un ácido de Lewis de la fórmula (C) y una cantidad catalítica de un elemento de los grupos IB o IIB, en un solvente de  
25        acoplamiento adecuado, para dar el nucleósido cis/trans-pirimidin-1,3-oxatolano de la fórmula (Dx). En el intermediario resultante de la fórmula (Dx) predomina el isómero cis sobre el isómero trans, en una razón igual a o mayor que 2 a 1. La razón de isómero cis a trans es inversamente proporcional a la temperatura de la reacción.  
30        Se puede efectuar la reacción a la temperatura ambiente o por debajo de ella.

El agente sililante que puede ser usado para la protección de R1 incluye triflato de terbutildimetilsililo, 1,1,1,3,3,3-hexametildisilazano, TMSI, N,O,bisTMS-acetonuro y triflato de trimetilsililo.

5           La amina terciaria usada en el paso 1 incluye: trietilamina, dietilciclohexilamina, dietilmetilamina, dimetiletilamina, dimetilisopropilamina, dimetilbutilamina, dimetilciclohexilamina, tributilamina, dietilmetilamina, dimetilisopropilamina y diisopropiletilamina, y sus combinaciones.

10           El elemento, o la combinación de elementos de los grupos IB o IIB usados en el paso 1 Incluyen: Cu, Ag, Au, Zn o Cd, en estado oxidado.

El solvente de acoplamiento adecuado es un solvente orgánico. Los solventes de acoplamiento adecuados incluyen:  
15   cloruro de metileno, acetonitrilo o mezclas de ellos.

El ácido de Lewis que puede ser usado en este paso incluye: triflato de trimetilsililo, bromotrimetilsilano, yodotrimetilsilano y mezclas de ellos. La cantidad de ácido de Lewis puede estar entre alrededor de 2 equivalentes y alrededor de 5  
20   equivalentes.

Paso 2: Se disuelve el nucleósido cis/trans-pirimidina de la fórmula (Dx) en un solvente de desprotección adecuado, en presencia de cantidades adecuadas de un agente de desprotección, para dar los cis-nucleósidos o los análogos o derivados de  
25   nucleósido de la fórmula (Ax).

Un solvente de desprotección adecuado favorece la cristalización del producto de la fórmula (A). Los solventes adecuados incluyen: agua, metanol, etanol, tolueno, éter terbutilmetílico, o combinaciones de ellos. Las combinaciones  
30   adecuadas de solventes incluyen: mezclas de metanol y agua,

metanol y tolueno, metanol y éter terbutilmetílico.

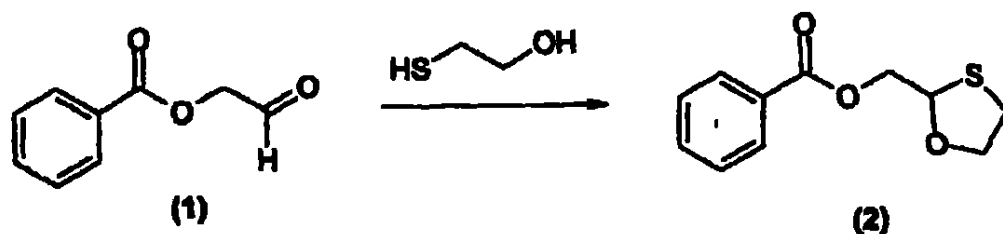
Los agentes de desprotección adecuados incluyen: hidróxido de sodio, metóxido de sodio, hidróxido de amonio, hidróxido de potasio, hidróxido de litio y amoniaco metanólico. Son particularmente interesantes los agentes de desprotección que ayudan a la separación del producto de la fórmula (A).

Se lleva a cabo el paso de desprotección a una temperatura inferior al punto de ebullición del solvente de desprotección adecuado.

Los siguientes ejemplos ilustran la presente invención de una manera en la que puede ser puesta en práctica; pero como tal, no se deben considerar como limitaciones al alcance de los procesos de la presente invención.

15

1) 2-BENZOILOXIMETIL-1,3-OXATIOLANO



20

Se disolvió el compuesto (1) en tolueno, y se calentó la solución hasta 90-100°C. Se añadió catalizador, seguido por mercaptoetanol (en porciones). Se usó 5 por ciento molar de catalizador. Se llevó a cabo las reacciones a escala de 15 g, a concentración de 0.3 M de (1). Se dejó al reflujo la mezcla de reacción, con separación de agua mediante una trampa de Dean-Stark. Los resultados para este paso están mostrados en la Tabla 1.

30

TABLA 1

| Catalizador                      | Reacción después de 20 min. |                         | Reacción después de 40 min. |                         |
|----------------------------------|-----------------------------|-------------------------|-----------------------------|-------------------------|
|                                  | % de conversión             | % de rendimiento de (2) | % de conversión             | % de rendimiento de (2) |
| BF <sub>3</sub> OEt <sub>2</sub> | 100                         | 79                      | 100                         | 71                      |
| pTsOH                            | 100                         | 82                      | 100                         | 80                      |

Se identificó el compuesto (2) mediante RMN con <sup>1</sup>H y con <sup>13</sup>C.

R<sub>f</sub>: 0.39 (hexano:acetato de etilo).

RMN con <sup>1</sup>H: δ (ppm en CDCl<sub>3</sub>):

8.03 (m, 2H, aromático)

7.53 (m, 1H, aromático)

7.39 (m, 2H, aromático)

5.41 (dd, 1H, C<sub>2</sub>-H)

4.43 (m, 2H, C<sub>2</sub>-CH<sub>2</sub>OCC<sub>6</sub>H<sub>5</sub>)

4.21 (m, 1H, C<sub>5</sub>-H)

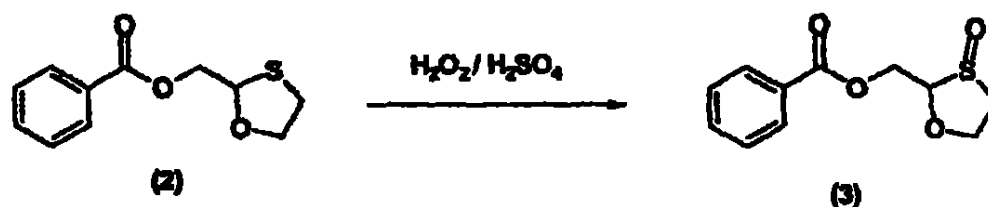
3.96 (m, 1H, C<sub>6</sub>-H)

2.98 (m, 2H, C<sub>4</sub>-H).

RMN con <sup>13</sup>C δ (ppm en CDCl<sub>3</sub>):

166.82, 133.74, 130.35, 128.97, 83.58, 71.87, 66.62 y 32.74.

## 2) S-ÓXIDO DE 2-BENZOILOXIMETIL-1,3-OXATIOLANO



Se añadió 46 mL (0.44 mol) de peróxido de hidrógeno frío

al 30 por ciento a 82 g (0.366 mol) de (2) en 8 mL de tolueno. Se  
añadió a gotas 4.5 mL (0.044 mol, 10 por ciento molar) de ácido  
sulfúrico 10 M (tiempo de adición, aproximadamente 1 minuto). Se  
agitó vigorosamente la mezcla de reacción a 25-30°C durante dos  
5 horas, y luego una hora a 30°C. Se añadió 100 mL de agua, y a  
continuación 3.7 g (0.044 mol) de bicarbonato de sodio, seguidos por  
8 g de metabisulfito de sodio. Se separó la capa orgánica y se  
extrajo la fase acuosa con 3 x 20 mL de diclorometano. Se secó  
sobre sulfito de sodio los extractos combinados, se concentró hasta  
10 sequedad y se trituró con hexano para formar 83 g de un sólido.

Se obtuvo 94 por ciento del compuesto (3) buscado; p. f.  
70-72°.

RMN con  $^1\text{H}$ :  $\delta$  (ppm en  $\text{CDCl}_3$ ):

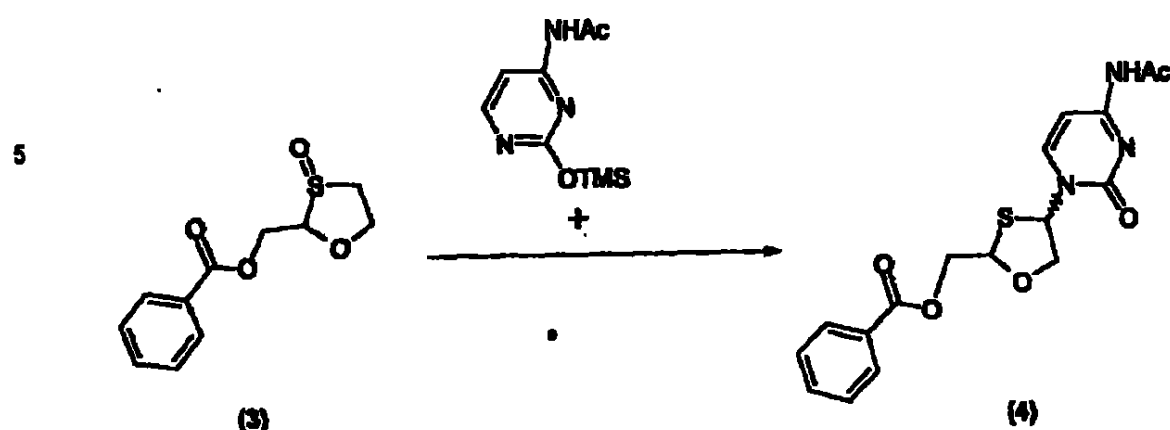
8.05 (m, 2H, aromático, isómero cis)  
15 7.95 (m, 2H, aromático, isómero trans)  
7.56 (m, aromático)  
7.23 (m, aromático)  
4.77 (m, 4H,  $\text{C}_2\text{-H}$ ,  $\text{C}_5\text{-H}$  y  $\text{C}_2\text{-CH}_2\text{OOC}\text{C}_6\text{H}_5$ )  
4.43 (m, 1H,  $\text{C}_6\text{-H}$ , isómero trans)  
20 4.09 (m, 1H,  $\text{C}_5\text{-H}$ , isómero cis)  
3.11 (m, 2H,  $\text{C}_4\text{-H}$ , isómero trans)  
2.75 (m, 2H,  $\text{C}_4\text{-H}$ , isómero cis.

RMN con  $^{13}\text{C}$ :  $\delta$  (ppm en  $\text{CDCl}_3$ ):

isómero cis:  
25 166.64, 134.02, 130.42, 129.88, 129.06, 96.16, 68.83,  
59.47 y 54.30.

isómero trans:  
166.36, 134.12, 130.29, 129.68, 129.15, 108.07, 70.09,  
61.83 y 53.47

**3) (±)-CIS.TRANS-2-BENZOILMETIL-4-(N-ACETILCITOSINA-1'-IL)-**  
**1,3-OXATIOLOANO**



10

Se disolvió el compuesto (3) en 20 mL/g de cloruro de metileno y se enfrió a  $-15^{\circ}\text{C}$ . Se añadió entre 1 y 2 equivalentes de la amina, seguidos por la adición de entre 2 y 5 equivalentes de TMSI, mientras se mantenía la temperatura interna por debajo de  $-5^{\circ}\text{C}$ . Se agitó a  $-5^{\circ}\text{C}$  hasta  $-10^{\circ}\text{C}$ , hasta que desapareció el compuesto (3). Se añadió CuCl al 20 por ciento y 1.1 equivalentes de pirimidina. Se calentó la mezcla de reacción y se mantuvo entre  $5-10^{\circ}\text{C}$  hasta que la TLC indicó que la reacción estaba completa. Se vertió la mezcla de reacción en  $\text{NH}_4\text{OH}$  al 5 por ciento y se agitó durante diez minutos, hasta que no se detectó ningún precipitado sólido. Se separó la capa orgánica y se extrajo la capa acuosa con cloruro de metileno. Se lavó con agua la capa orgánica, con HCl al 2 por ciento y con  $\text{Na}_2\text{S}_2\text{O}_3$  diluido. Se evaporó la capa orgánica lavada para dar el producto, compuesto (4). Los resultados de este

25 paso están mostrados en la tabla 2.

Se caracterizaron mediante RMN con  $^1\text{H}$  y con  $^{13}\text{C}$ .

isómero cis:

RMN con  $^1\text{H}$ :  $\delta$  (ppm en  $\text{CDCl}_3$ )

9.61 (b, 1H,  $\text{C}_4\text{-NHCOCH}_3$ )

8.29 (d, 1H,  $\text{C}_6\text{-H}$ )

30

- 8.06 (m, 2H, aromático)  
 7.65 (m, 1H, aromático)  
 7.51 (m, 2H, aromático)  
 7.25 (d, 1H, C<sub>6</sub>-H)  
 5 6.61 (d, 1H, C<sub>4</sub>-H)  
 5.50 (t, 1H, C<sub>2</sub>-H)  
 4.80 (m, 2H, C<sub>2</sub>-CH<sub>2</sub>OOCC<sub>6</sub>H<sub>5</sub>)  
 4.48 (d, 1H, C<sub>5</sub>-H)  
 4.05 (dd, 1H, C<sub>5</sub>-H)  
 10 2.25 (s, 3H, CH<sub>3</sub>).

RMN con <sup>13</sup>C: δ (ppm en CDCl<sub>3</sub>)

170.93, 166.28, 162.80, 155.76, 146.06, 133.91, 129.90,  
 128.84, 97.45, 85.88, 78.25, 84.60, 63.53 y 24.71.

isómero trans:

- 15 RMN con <sup>1</sup>H: δ (ppm en DMSO d<sub>6</sub>):

- 10.88 (s, 1H, C<sub>4</sub>-NHCOCH<sub>3</sub>)  
 8.13 (d, 1H, C<sub>6</sub>-H)  
 7.96 (m, 2H, aromático)  
 7.68 (m, 1H, aromático)  
 20 7.52 (m, 2H, aromático)  
 7.20 (d, 1H, C<sub>6</sub>-H)  
 6.35 (d, 1H, C<sub>4</sub>-H)  
 5.96 (dd, 1H, C<sub>2</sub>-H)  
 4.58 (dd, 1H, C<sub>2</sub>-CH<sub>2</sub>OOCC<sub>6</sub>H<sub>5</sub>)  
 25 4.44 (d, 1H, C<sub>5</sub>-H)  
 4.29 (m, 2H, C<sub>5</sub>-H y CH<sub>2</sub>OOCC<sub>6</sub>H<sub>5</sub>)  
 2.07 (s, 3H, CH<sub>3</sub>)

RMN con <sup>13</sup>C: δ (ppm en DMSO d<sub>6</sub>):

- 171.53, 165.84, 162.76, 155.21, 146.59, 134.00, 129.64,  
 30 129.23, 96.54, 83.78, 74.24, 64.58, 64.01 y 24.35.

**TABLA 2**

|    | Pirimidina       | Base           | Catalizador<br>(eq. molar)     | Condiciones                                             | Rendim.<br>(cis-trans) | Cis/trans | Rendim.<br>% de<br>cis |
|----|------------------|----------------|--------------------------------|---------------------------------------------------------|------------------------|-----------|------------------------|
|    | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq |                                | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C<br>RT, O/N     | 80%                    | 2.0 : 1   | 53                     |
| 5  | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>3h RT, O/N | 91%                    | 3.9 : 1   | 72                     |
|    | N-Ac-Cy<br>1.1eq | TEA<br>1.2eq   | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 75%                    | 3.8 : 1   | 59                     |
|    | N-Ac-Cy<br>1.1eq | DMCA<br>1.2eq  | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 80%                    | 3.4 : 1   | 62                     |
|    | N-Ac-Cy<br>1.1eq | DECA<br>1.2eq  | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C<br>RT, O/N     | 71%                    | 3.9 : 1   | 57                     |
| 10 | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq | CuCl <sub>2</sub> (2%)         | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>3h RT, O/N | 80%                    | 2.4 : 1   | 56                     |
|    | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq | CuBr <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 80%                    | 3.7 : 1   | 63                     |
|    | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq | Cu(acac) <sub>2</sub><br>(20%) | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 85%                    | 3.7 : 1   | 67                     |
|    | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq | CuCl (20%)                     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 80%                    | 3.6 : 1   | 63                     |
| 15 | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq | CuI (20%)                      | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 74%                    | 3.5 : 1   | 58                     |
|    | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq | CuSCN<br>(20%)                 | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 70%                    | 3.1:1     | 53                     |
|    | N-Ac-Cy<br>1.1eq | DIPHA<br>1.2eq | ZnBr <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 53%                    | 3.1: 1    | 40                     |
| 20 | Cy<br>1.1eq      | DIPHA<br>1.2eq | CuCl <sub>2</sub><br>(20%)     | CH <sub>2</sub> Cl <sub>2</sub> , -15 °C,<br>5h RT, O/N | 72%                    | 2.4:1     | 51                     |

Cy = citosina

DIPEA = diisopropiletilamina

TEA = trietilamina

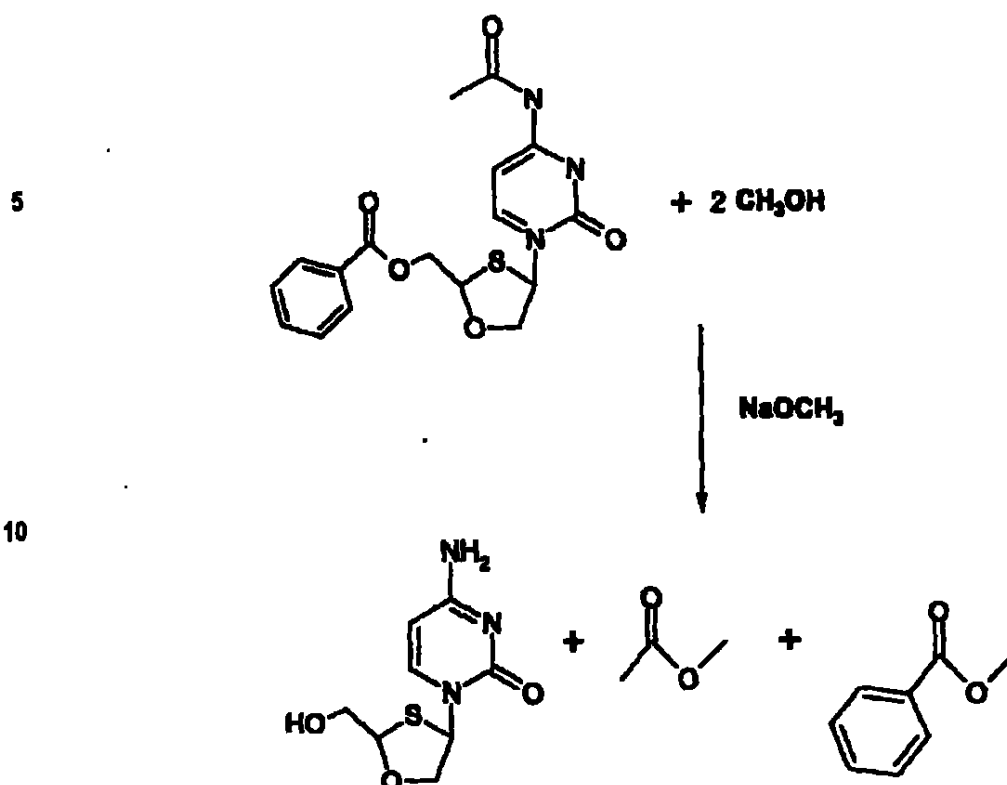
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DECA = dietilciclohexilamina

DMCA = dimetilciclohexilamina

Cu(acac)<sub>2</sub> = acetilacetonato de cobre (II)

30

**4) 2-HIDROXIMETIL-4-(CITOSIN-1'-IL)-1,3-OXATIOLOANO**

15            Se agitó una suspensión del substrato, metóxido de sodio, 10 por ciento molar, y el solvente apropiado, a la temperatura ambiente, durante dos horas, antes de ser filtrada. Se secó la torta de filtro y se pesó, antes de comprobar la razón C/T (mediante RMN con  $^1\text{H}$ ) y el rendimiento. Los resultados de este paso están

20    mostrados en la tabla 3.

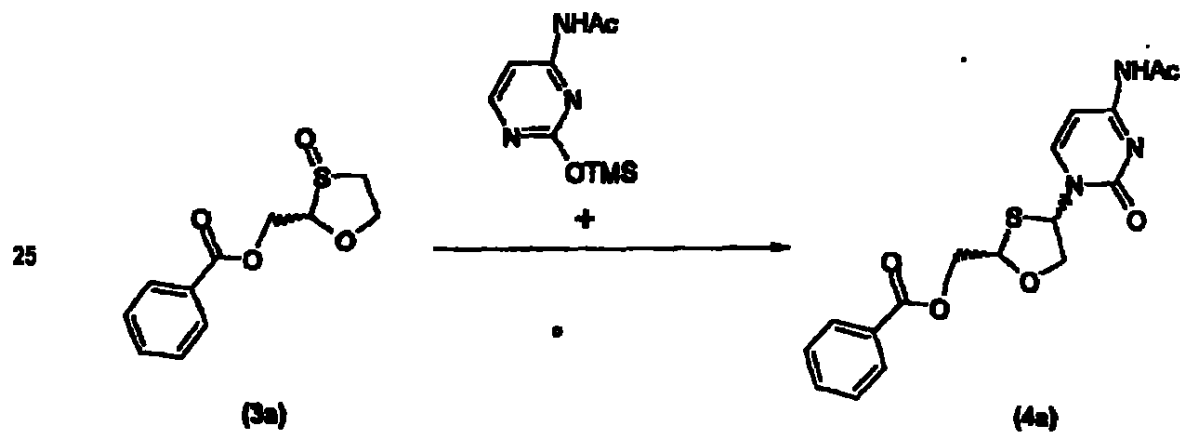
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TABLA 3

|                           | Peso de la mezcla cis/ trans (g). | Razón cis/ trans | Solvente                     | Base fuerte | Condiciones           | % de trans (RMN) | Recuperación de cis (%) |
|---------------------------|-----------------------------------|------------------|------------------------------|-------------|-----------------------|------------------|-------------------------|
| 5                         | 4                                 | 3.4:1            | MeOH                         | MeONa       | mezclar y agitar a TA | 0                | 89                      |
|                           | 10                                | 3.4:1            | MeOH                         | MeONa       | mezclar y agitar a TA | 0                | 88.5                    |
|                           | 4                                 | 3.4:1            | MeOH/tBME (7:3)              | MeONa       | mezclar y agitar a TA | 0                | 90                      |
|                           | 25                                | 3.4:1            | MeOH/tBME (7:3)              | MeONa       | mezclar y agitar a TA | huellas          | 91                      |
| 10                        | 1                                 | 3.4:1            | MeOH/EtOH (1:1)              | MeONa       | TA                    | 0                | 98                      |
|                           | 4                                 | 3.4:1            | MeOH/EtOH (1:1)              | MeONa       | mezclar y agitar a TA | huellas          | 92.5                    |
|                           | 25                                | 3.4:1            | MeOH/EtOH (1:1), 150 mL      | MeONa       | mezclar y agitar a TA | huellas          | 93                      |
|                           | 1                                 | 3.4:1            | MeOH/tolueno (8:4)           | MeONa       | TA                    | huellas          | 92.5                    |
|                           | 4                                 | 3.4:1            | MeOH/tolueno (8:4)           | MeONa       | mezclar y agitar a TA | huellas          | 90                      |
|                           | 25                                | 3.4:1            | MeOH/tolueno (6:4) L         | MeONa       | mezclar y agitar a TA | huellas          | 91                      |
| 15                        | 1                                 | 3.4:1            | MeOH/H <sub>2</sub> O (95:5) | NaOH        | TA                    | 20               | 90                      |
| TA = temperatura ambiente | 4                                 | 3.4:1            | MeOH/H <sub>2</sub> O (95:5) | NaOH        | a 50°C                | 20               | 90                      |

5) SÍNTESIS DE 2-BENZOILMETIL-4-(N-ACETILCITOSINA-1'-IL)-1,3-OXATIOLOANO USANDO S-ÓXIDO DE (-) O (+)-2-BENZOILOXIMETIL-1,3-OXATIOLOANO



Se disolvió el compuesto (3a), enantioméricamente puro, en 10 mL/g de cloruro de metileno y se enfrió a la temperatura de la

reacción. Se añadió la amina, seguida por la adición de TMSI, mientras se mantenía la temperatura interna por debajo de  $-5^{\circ}\text{C}$ . Se agitó a  $-5^{\circ}\text{C}$  hasta  $-40^{\circ}\text{C}$  hasta que desapareció el compuesto (3a). Se añadió CuCl (al 20 por ciento) y 1.1 equivalentes de pirimidina.

5 Se calentó la mezcla de reacción y se mantuvo entre  $-40$  y  $30^{\circ}\text{C}$  hasta que la TLC indicó que estaba completa la reacción. Se enfrió la reacción a  $0^{\circ}\text{C}$ - $5^{\circ}\text{C}$ . Se añadió a la suspensión 12 g de Celite (100 por ciento en peso/peso) y se agitó. Se añadió lentamente hidróxido de amonio concentrado y se mantuvo la temperatura de la

10 suspensión entre  $0^{\circ}\text{C}$  y  $10^{\circ}\text{C}$ . Se agitó a  $0^{\circ}\text{C}$ - $5^{\circ}\text{C}$ . Se filtró la suspensión y se volvió a suspender la torta en diclorometano. Se agitó y luego se filtró. Se separó las fases y se extrajo la fase acuosa con diclorometano. Se lavó las capas orgánicas combinadas con una solución al 2 por ciento de hidróxido de amonio, con agua,

15 con solución de ácido clorhídrico al 2 por ciento, con solución de metabisulfito de sodio al 2 por ciento y con solución saturada de bicarbonato de sodio. Se secó la fase orgánica sobre sulfato de magnesio, se filtró, luego se redujo en volumen al vacío para dar un material crudo, acoplado a la base, como un sólido color crudo. Se

20 disolvió los sólidos en acetato de etilo y se dejó cristalizar. Se agitó la suspensión a  $0$ - $5^{\circ}\text{C}$  y luego se filtró. Se secó los sólidos al vacío para dar el producto puro, acoplado a la base, como un sólido color crudo pálido. Los resultados de este paso están mostrados en la tabla 4 y en la tabla 5.

25 RMN con  $^1\text{H}$  (300 MHz) ( $\text{CDCl}_3$ )  $\delta$  2.27 (s, 3H,  $\text{CH}_3$  cis), 2.29 (s, 3H,  $\text{CH}_3$  trans), 4.06 (dd,  $J = 4.5$  Hz y  $J = 10.8$  Hz, 1H, C5 cis), 4.30 (dd,  $J = 3.4$  Hz y  $J = 12.4$  Hz, 1H, C5 trans), 4.49 (dd,  $J = 3.1$  Hz y  $J = 10.8$  Hz, 1H, C5 cis), 4.72 (dd,  $J = 8.3$  Hz y  $J = 12.4$  Hz, 1H, C5 trans), 4.77 (AB,  $J = 4.5$  Hz, 2H,  $\text{CH}_2\text{OBz}$ , cis), 4.84 (AB,  $J =$

30 2.3 Hz, 2H,  $\text{CH}_2\text{OBz}$ , trans), 5.50 (dd,  $J = 3.1$  Hz y  $J = 4.5$  Hz, 1H,

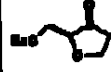
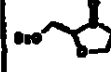
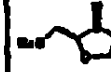
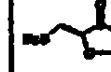
C4, cis), 5.92 (dd, J = 3.4 Hz y J = 8.3 Hz, 1H, C4, trans), 6.61 (dd, J = 2.3 Hz, trans y J = 4.5 Hz, cis, 1H, C2), 7.25 (d, J = 7.5 Hz, 1H, C5'), 7.5-8.1 (m, 10H, cis y trans aromáticos), 8.30 (d, J = 7.5 Hz, 1H, C6'), 9.50 (s, 1H, NH).

5 RMN con <sup>13</sup>C (300 MHz)(CDCl<sub>3</sub>) δ 25.9 (cis y trans), 64.3 (cis), 65.1 (trans), 65.3 (cis y trans), 76.1 (trans), 78.7 (cis), 84.7 (trans), 86.2 (cis), 97.9 (cis), 98.1 (trans), 128.6 (cis y trans), 128.7 (cis y trans), 129.2 (cis y trans), 129.4 (cis y trans), 129.8 (cis y trans), 133.5 (trans), 133.7 (cis), 145.3 (trans), 145.6 (cis), 155.2 (trans), 155.3 (cis), 162.5 (cis y trans), 162.6 (trans), 165.7 (cis), 10 171.0 (cis), 171.1 (trans).

TABLA 4

|    | Sulfóxido                                                                           | Base  | Temp.de<br>reacción<br>(°C)                                    | (-)-cis<br>(%) | (+)-cis<br>(%) | (-)-trans<br>(%) | (+)-trans<br>(%) | cis/trans<br>(%) |
|----|-------------------------------------------------------------------------------------|-------|----------------------------------------------------------------|----------------|----------------|------------------|------------------|------------------|
| 15 |  | DIPPA | -15                                                            | 48.9           | <u>27.4</u>    | 6.7              | 17               | 3.2 :1           |
|    |  | TEA   | -15                                                            | 70.4           | 5.2            | 1.6              | 22.8             | 3.1 :1           |
| 20 |  | TEA   | -15                                                            | <u>4.9</u>     | 73.6           | 20               | 1.5              | 3.6 :1           |
|    |  | DMCA  | -25                                                            | 72.4           | <u>4.5</u>     | 1.25             | 21.8             | 3.3 :1           |
| 25 |  | TEA   | -30                                                            | 1              | <u>74.4</u>    | 24.6             | 0                | 3 :1             |
| 30 |                                                                                     |       | (temp. interna), calentar a RT después de añadir base siliada. |                |                |                  |                  |                  |

**TABLA 5**

|    | Sulfóxido                                                                           | Base                        | Temperatura<br>de reacción, °C | Rendi-<br>miento | cis/trans<br>(%) |
|----|-------------------------------------------------------------------------------------|-----------------------------|--------------------------------|------------------|------------------|
| 5  |    | TEA<br>+DIPEA               | -20                            | 74               | 3.3 : 1          |
|    |    | (i-pro)<br>NMe <sub>2</sub> | -20                            | 72               | 3.7 : 1          |
| 10 |   | TEA                         | -20                            | 63               | 4 : 1            |
|    |  | (i-pro)<br>NMe <sub>2</sub> | -20                            | 72               | 3.3 : 1          |
| 15 |  | TEA                         | -20                            | 70               | 3.3 : 1          |

TEA = trietilamina

DIPEA = diisopropiletilamina

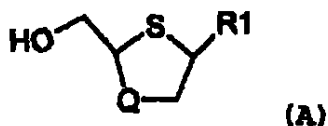
20 DMCA = dimetilciclohexilamina

(i-pro)NMe<sub>2</sub> = isopropildimetilamina

80

## REIVINDICACIONES

1.- Un proceso estereoselectivo para formar nucleósidos predominantemente cis o análogos y derivados de nucleósido de la  
5 fórmula (A):



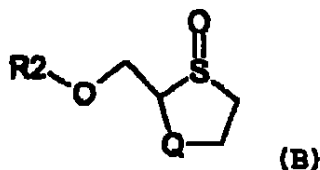
en la que:

10 R1 es una base de pirimidina o un derivado de ella, aceptable para uso farmacéutico; y

Q es carbono, oxígeno o azufre;

que consiste del paso de acoplamiento de un compuesto de la fórmula (B):

15

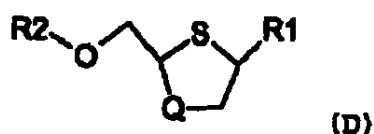


en la que:

20 R2 es aralquilo de 7 a 10 átomos de carbono, acilo de 1 a 16 átomos de carbono o Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), donde Z<sup>1</sup>, Z<sup>2</sup> y Z<sup>3</sup> están seleccionados independientemente del grupo que consiste de hidrógeno; alquilo de 1 a 20 átomos de carbono, sustituido opcionalmente con flúor, bromo, cloro, yodo, alcoxi de 1 a 6 átomos  
25 de carbono o ariloxi de 6 a 20 átomos de carbono; aralquilo de 7 a 20 átomos de carbono, opcionalmente sustituido con halógeno, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; arilo de 6 a 20 átomos de carbono sustituido con flúor, bromo, cloro, yodo, alquilo de 1 a 20 átomos de carbono o alcoxi de  
30 1 a 20 átomos de carbono; trialquilsililo; flúor; bromo; cloro y yodo;

con una base R1; donde R1 es una base de pirimidina, o un derivado de ella aceptable para uso farmacéutico;

en un solvente de acoplamiento, en presencia de una cantidad catalítica de un elemento o una combinación de elementos del grupo  
5 IB o IIB de la Tabla Periódica; una amina terciaria y un ácido de Lewis, para producir un intermediario de la fórmula (D):



10

en la que R1, R2 y Q son como fueron definidas más arriba; y

un segundo paso para desproteger el intermediario de la fórmula (D), para producir los cis-nucleósidos o análogos o derivados de nucleósido de la fórmula (A).

15 2.- Un proceso de conformidad con la reivindicación 1, caracterizado además porque el ácido de Lewis es un compuesto de la fórmula (C):



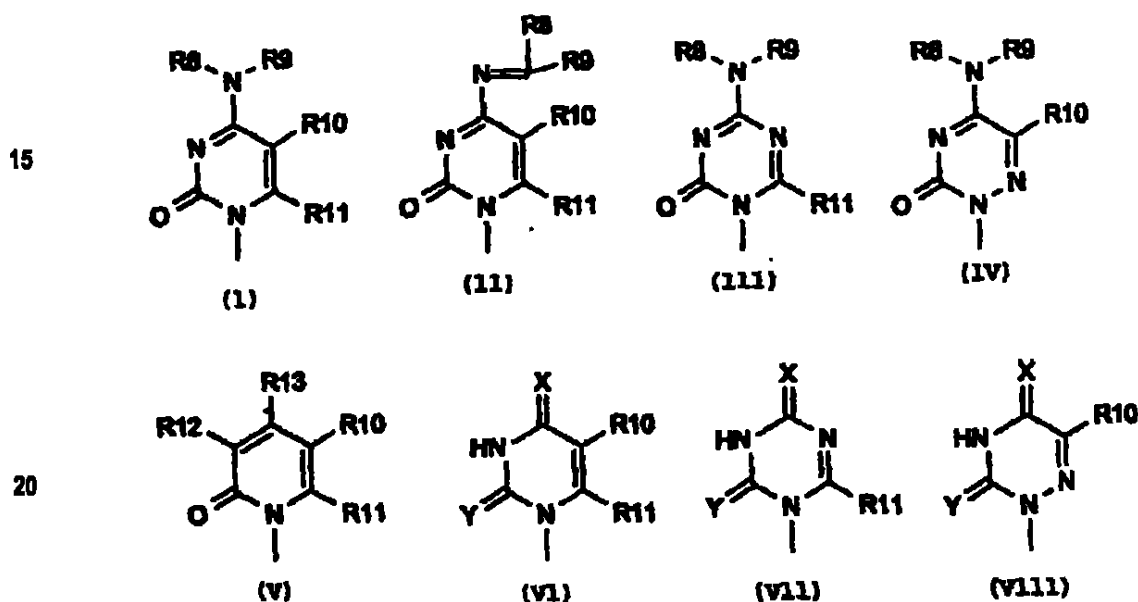
20

en la que:

R4, R5 y R6 están seleccionados independientemente del grupo que  
25 consiste de hidrógeno; alquilo de 1 a 20 átomos de carbono, sustituido opcionalmente con flúor, bromo, cloro, yodo, alcoxi de 1 a 6 átomos de carbono o arilo de 6 a 20 átomos de carbono; aralquilo de 7 a 20 átomos de carbono, sustituido opcionalmente con halógeno, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20  
30 átomos de carbono; arilo de 6 a 20 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro, yodo, alquilo de 1 a 20 átomos de carbono o alcoxi de 1 a 20 átomos de carbono; trialkilsililo; flúor; bromo; cloro y yodo; y

R7 está seleccionado del grupo que consiste de flúor; bromo; cloro; yodo; ésteres sulfonato de 1 a 20 átomos de carbono, opcionalmente sustituidos con flúor, bromo, cloro o yodo; ésteres de alquilo de 1 a 20 átomos de carbono, opcionalmente sustituidos con flúor, bromo, cloro o yodo; triyoduro; un grupo sililo de la fórmula general (R4)(R5)(R6)Si (donde R4, R5 y R6 son como se definió aquí con anterioridad); arilselenenilo de 6 a 20 átomos de carbono; arilsulfenilo de 6 a 20 átomos de carbono; alcoxialquilo de 6 a 20 átomos de carbono; y trialquilsiloxi

3.- Un proceso de conformidad con la reivindicación 1, caracterizado además porque R1 es seleccionado de:



donde:

X es oxígeno, NH o azufre;

25 Y es oxígeno, NH o azufre;

R8 y R9 son seleccionados independientemente de hidrógeno, hidroxilo, amino, alquilo de 1 a 6 átomos de carbono o alqueno de 2 a 6 átomos de carbono, alquino de 2 a 6 átomos de carbono, acilo de 1 a 10 átomos de carbono, arilo de 6 a 10 átomos de carbono, carbonilarilo de 6 a 11 átomos de carbono, carboniloxialquilo de 1 a

30

7 átomos de carbono, carboniloxiarilo de 6 a 11 átomos de carbono, carbonilaminoalquilo de 2 a 7 átomos de carbono, o aminoácidos;

R8 puede ser un anillo carbocíclico saturado o insaturado, de 3 a 8 átomos de carbono, sustituido opcionalmente con COOH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, halógeno, C(O)R14, donde R14 es un alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono y C(O)OR15, donde R15 es un alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono; y R9 es seleccionado de H, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono y alquinilo de 2 a 6 átomos de carbono;

R<sub>8</sub>R<sub>9</sub> también puede estar conectado al átomo de nitrógeno para formar un anillo heterocíclico saturado o insaturado, de 3 a 8 átomos de carbono, opcionalmente sustituido con C(O)OH, C(O)NH<sub>2</sub>, OH, SH, NH<sub>2</sub>, NO<sub>2</sub>, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, halógeno, C(O)R14, donde R14 es un alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono y C(O)OR15, donde R15 es un alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono; y

R10, R11, R12 y R13, son seleccionados, cada uno independientemente, de: hidrógeno, halógeno, hidroxilo, amino, ciano, carboxilo, carbamilo, alcóxicarbonilo de 2 a 7 átomos de carbono, hidroximetilo, trifluorometilo, ariltio de 6 a 10 átomos de carbono, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, sustituido o no sustituido con halógeno o azido, alquinilo de 2 a 6 átomos de carbono, aciloxi de 1 a 6 átomos de

carbono, tiocarboxi, tiocarbamóilo, carbamato, ureído, amidino o arilo de 6 a 10 átomos de carbono.

4.- Un proceso de conformidad con la reivindicación 1, caracterizado además porque el elemento o la combinación de  
5 elementos de los grupos IB o IIB es Cu, Ag, Au, Zn o Cd.

5.- Un proceso de conformidad con la reivindicación 1, caracterizado además porque la amina terciaria tiene la forma  $N(Z^4)(Z^5)(Z^6)$ , donde  $(Z^4)$ ,  $(Z^5)$ ,  $(Z^6)$  son seleccionados independientemente del grupo que consiste de alquilo de 1 a 6 átomos de carbono,  
10 opcionalmente sustituido con alquilo de 1 a 3 átomos de carbono, arilo de 6 a 10 átomos de carbono, o halógeno.

6.- Un proceso de conformidad con la reivindicación 1, caracterizado además porque el solvente orgánico es un cloroalquilo de 1 a 8 átomos de carbono, cloroalquenos de 1 a 8 átomos de  
15 carbono, un cloroarilo de 6 a 10 átomos de carbono, alquilonitrilo de 1 a 6 átomos de carbono, o mezclas de ellos.

7.- Un proceso de conformidad con la reivindicación 6, caracterizado además porque se selecciona el solvente orgánico del grupo que consiste de clorometanos, cloroetanos, metanonitrilos y  
20 mezclas de ellos.

8.- Un proceso de conformidad con la reivindicación 5, caracterizado además porque la amina terciaria es trietilamina, dietilciclohexilamina, dietilmetilamina, dimetiletilamina, dimetil-  
isopropilamina, dimetilbutilamina, dimetilciclohexilamina,  
25 tributilamina, dietilmetilamina, dimetilisopropilamina, diisopropil-  
etilamina o combinaciones de ellas.

9.- Un proceso de conformidad con la reivindicación 4, caracterizado además porque el elemento o la combinación de elementos de los grupos IB o IIB es Cu, Zn o sus combinaciones.

30 10.- Un proceso de conformidad con la reivindicación 1, caracterizado además porque Q es oxígeno.

11.- Un proceso de conformidad con la reivindicación 1, caracterizado además porque se efectúa el paso de acoplamiento a una temperatura igual a o menos que 30° Celsius.

12.- Un proceso de conformidad con la reivindicación 1,  
5 caracterizado además porque se lleva a cabo el paso de desprotección en presencia de un agente de desprotección y un solvente de desprotección, que favorece la cristalización de los cis-nucleósidos o los análogos o derivados de nucleósido de la fórmula (A).

10 13.- Un proceso de conformidad con la reivindicación 12, caracterizado además porque el agente de desprotección es alcalino.

14.- Un proceso de conformidad con la reivindicación 13, caracterizado además porque el agente de desprotección es hidróxido de sodio, metóxido de sodio, hidróxido de amonio,  
15 hidróxido de potasio, hidróxido de litio, amoniaco metanólico o sus combinaciones.

15.- Un proceso de conformidad con la reivindicación 12, caracterizado además porque el solvente de desprotección es agua, metanol, etanol, tolueno, éter terbutilmetílico o combinaciones de  
20 ellos.

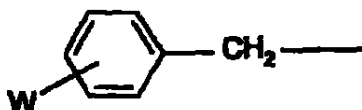
16.- Un proceso de conformidad con la reivindicación 3, caracterizado además porque se selecciona R1 de N<sup>4</sup>-alquilpirimidinas, N<sup>4</sup>-acilpirimidinas, 4-halopirimidinas, pirimidinas N<sup>4</sup>-acetilénicas, 4-amino y N<sup>4</sup>-acilpirimidinas, 4-  
25 hidroxialquilpirimidinas, 4-tioalquilpirimidinas, timina, citosina, 6-azapirimidina, 2-mercaptopirimidina, 4-mercaptopirimidina, uracilo, C<sup>5</sup>-alquilpirimidinas, C<sup>5</sup>-bencilpirimidinas, C<sup>5</sup>-halopirimidinas, C<sup>5</sup>-vinilpirimidina, pirimidina C<sup>5</sup>-acetilénica, C<sup>5</sup>-acilpirimidina, C<sup>5</sup>-amidopirimidina, C<sup>5</sup>-cianopirimidina, C<sup>5</sup>-nitropirimidina, C<sup>6</sup>-  
30 aminopirimidina, 5-azacitidinilo, 5-azauracililo, triazolopiridinilo,

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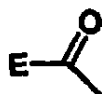
imidazolopiridinilo, pirrolopirimidinilo, pirazolopirimidinilo, o un derivado de ellos aceptable para uso farmacéutico.

17.- Un proceso de conformidad con la reivindicación 3, caracterizado además porque R2 es:

5



donde W es halógeno, alquilo de 1 a 16 átomos de carbono, alcoxialquilo de 2 a 16 átomos de carbono, arilo de 6 a 10 átomos de carbono, alcoxi de 1 a 16 átomos de carbono o nitro; o



15 donde E es arilo de 6 a 10 átomos de carbono, alcoxi de 1 a 16 átomos de carbono, alcoxialquilo de 2 a 16 átomos de carbono o alquilo de 1 a 16 átomos de carbono; o

Si(Z<sup>1</sup>)(Z<sup>2</sup>)(Z<sup>3</sup>), donde Z<sup>1</sup>, Z<sup>2</sup> y Z<sup>3</sup> son seleccionados independientemente del grupo que consiste de hidrógeno, alquilo de 1 a 20 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro, yodo; aralalquilo de 7 a 10 átomos de carbono, opcionalmente sustituido con flúor, bromo, cloro o yodo; y arilo de 6 a 10 átomos de carbono, sustituido opcionalmente con flúor, bromo, cloro o yodo.

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### **RESUMEN**

Un proceso para producir nucleósidos predominantemente cis, o análogos y derivados de nucleósido de la fórmula (A); donde

5 R1 es una base de pirimidina o un derivado de ella aceptable para uso farmacéutico, y Q es oxígeno, carbono o azufre; que comprende un paso de acoplamiento de la base de pirimidina con una molécula de la fórmula (B) descrita aquí, en un solvente de acoplamiento adecuado, en presencia de cantidades catalíticas de un elemento o

10 de una combinación de elementos de los grupos IB o IIB de la Tabla Periódica, una amina terciaria y un ácido de Lewis, para obtener un intermediario de la fórmula (D) que se desprotege en el paso subsiguiente para generar el producto de la fórmula (A).

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(12) SOLICITUD INTERNACIONAL PUBLICADA CONFORME AL TRATADO DE COOPERACIÓN SOBRE PATENTES (T C P)

(18) Organización Mundial de la Propiedad Intelectual  
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T C P

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WO 02/102798 A1

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (51) Clasificación internacional de patente:<br>C07D 409/04, 411/04                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | (81) Estados designados (nacionales): AE, AG, AL, AM, ATA, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SL, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW. |
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| (71) Solicitante: (para todos los estados designados menos US): SHIRE BIOCHEM INC. (CA/CA); 275 Amund Frappier Boulevard, Laval, Québec, H7V-4A7 (CA).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                            |
| (72) Inventor y<br>(75) Inventor/solicitante: (sólo para US): YU, Qing (CA/CA); 58 Concorde Ouest, Laval, Québec H7N 1H6 (CA)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                            |
| (74) Agentes: WHEELER, Michael E. y otros; Smart & Biggar, P. O. Box 2999, Station D, 900-55 Metcalfe Street, Ottawa, Ontario K1P 5Y6 (CA).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                            |
| CÓDIGO DE BARRAS VERTICAL<br>WO 02/102798 A1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                            |
| (54) Título: MÉTODO ESTEREOSELECTIVO PARA LA PREPARACIÓN DE ANALOGOS DE NUCLEÓSIDO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                            |
| (57) Resumen: Un proceso para producir nucleósidos predominantemente cis, o análogos y derivados de nucleósido de la fórmula (A); donde R1 es una base de pirimidina o un derivado de ella aceptable para uso farmacéutico, y Q es oxígeno, carbono o azufre; que comprende un paso de acoplamiento de la base de pirimidina con una molécula de la fórmula (B) descrita aquí, en un solvente de acoplamiento adecuado, en presencia de cantidades catalíticas de un elemento o de una combinación de elementos de los grupos IB o IIB de la Tabla Periódica, una amina terciaria y un ácido de Lewis, para obtener un intermediario de la fórmula (D) que se desprotege en el paso subsiguiente para generar el producto de la fórmula (A). |                                                                                                                                                                                                                                                                                                                                                                                                            |

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                          |                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Applicant's or agent's file reference<br><b>74872-82</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | FOR FURTHER ACTION<br>See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)                                                |                                                     |
| International application No.<br><b>PCT/CA02/00899</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | International filing date (day/month/year)<br><b>14/08/2002</b>                                                                                                          | Priority date (day/month/year)<br><b>15/08/2001</b> |
| International Patent Classification (IPC) or national classification and IPC<br><b>C07D409/04</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                          |                                                     |
| Applicant<br><b>SHIRE BIOCHEM INC. et al.</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                          |                                                     |
| <p>1. This international preliminary examination report has been prepared by this international Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>                                                                                                                                                           |                                                                                                                                                                          |                                                     |
| <p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the report</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p> |                                                                                                                                                                          |                                                     |
| Date of submission of the demand<br><b>22/11/2002</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Date of completion of this report<br><b>27.05.2003</b>                                                                                                                   |                                                     |
| Name and mailing address of the international preliminary examining authority:<br> <b>European Patent Office<br/>D-80288 Munich<br/>Tel. +49 89 2399 - 0 Tlx 523856 epmu d<br/>Fax: +49 89 2399 - 4485</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Authorized officer<br><b>Gohlke, P</b><br>Telephone No. <b>+49 89 2399 0549</b><br> |                                                     |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA02/00899

## I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, pages:

1-39 as originally filed

Claims, No.:

1-17 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/CA02/00899**

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

|                               |      |        |      |
|-------------------------------|------|--------|------|
| Novelty (N)                   | Yes: | Claims | 1-17 |
|                               | No:  | Claims |      |
| Inventive step (IS)           | Yes: | Claims | 1-17 |
|                               | No:  | Claims |      |
| Industrial applicability (IA) | Yes: | Claims | 1-17 |
|                               | No:  | Claims |      |

**2. Citations and explanations  
see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA02/00899

Reference is made to the following documents:

- D1: CAPUTO ET AL.: 'A new strategy for the asymmetric synthesis of 1,3-oxathiolane-based nucleoside analogues' EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, WILEY-VCH VERLAG, WEINHEIM, DE, 1999, pages 1455-1458, XP002210506 ISSN: 1434-193X cited in the application
- D2: BELLEAU B ET AL: 'A NOVEL CLASS OF 1,3-OXATHIOLANE NUCLEOSIDE ANALOGUES HAVING POTENT ANTI-HIV ACTIVITY' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 3, no. 8, 1993, pages 1723-1728, XP001024523 ISSN: 0960-894X cited in the application
- D3: MOON W C ET AL: 'Syntheses and antiviral activities of 1,3-dioxolanyl-, 1,3-oxathiolanyl- and 1,3-dithiolanylnucleosides with 2-hydroxymethyl substituents' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 7, no. 11, 3 June 1997 (1997-06-03), pages 1475-1480, XP004136239 ISSN: 0960-894X
- D4: WO 95 29176 A (IAF BIOCHEM INT ;MANSOUR TAREK S (CA); JIN HAOLUN (CA)) 2 November 1995 (1995-11-02) cited in the application

None of the available prior art documents discloses a stereoselective process for the asymmetric synthesis of 1,3-oxa(or thio-)thiolane-based nucleoside analogs starting from racemic sulfoxide in the presence of an element of IB or IIB group and a tertiary amine, as claimed in present claims 1-17.

All the syntheses disclosed in D1-D4 involve a last step of resolution of the diastereomeric mixture obtained therein by silica gel column chromatography or by enzymatic resolution.

The subject-matter of claims 1-17 therefore meets the requirements of articles 33(2) and (3) PCT.

Traducción

TRATADO DE COOPERACIÓN DE PATENTES  
PCT  
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL  
(Artículo 36 y Regla 70 del PCT)

|                                                                                                 |                                                                 |                                                                                       |
|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Referencia del expediente del agente o solicitante<br>74872-82                                  | PARA ACTUACIONES ADICIONALES                                    | Ver notificación de Transmisión del Reporte de Examen Preliminar (Formato PCT/PEA416) |
| Solicitud Internacional No.<br>PCT/CA02/00899                                                   | Fecha de presentación internacional (día/mes/año)<br>14/08/2002 | Fecha de prioridad (día/mes/año)<br>15/08/2001                                        |
| Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC<br><br>C07D 409/04 |                                                                 |                                                                                       |
| Solicitante<br><br>SHIRE BIOCHEM INC. et al.                                                    |                                                                 |                                                                                       |

1. Este informe de examen preliminar internacional ha sido preparado por esta Administración encargada del Examen Preliminar Internacional y se envía al solicitante en concordancia con el artículo 36.
2. Este INFORME consta de una total de 4 hojas, incluyendo la portada
- ☐ Este informe también se acompaña de ANEXOS, esto es documentos de la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base de este informe y/o documentos que contienen rectificaciones realizadas ante esta Administración (Ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas según el PCT)

Estos anexos constan de un total de \_\_\_\_\_ hojas.

3. Este Informe contiene indicaciones relativas a los siguientes aspectos:
- I ☒ Fundamentos del Informe
  - II ☐ Prioridad
  - III ☐ No se establece concepto relativo a la novedad, nivel inventivo y aplicación Industrial
  - IV ☐ Carencia de unidad de la invención
  - V ☒ Declaración razonada según el artículo 35(2), en relación con la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración
  - VI ☐ Ciertos documentos citados
  - VII ☐ Ciertos defectos de la solicitud Internacional
  - VIII ☐ Ciertas observaciones respecto a la solicitud internacional

|                                                                                                                                                                                                    |                                                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Fecha de presentación de la demanda<br><br>22/11/2002                                                                                                                                              | Fecha de terminación de este reporte<br><br>27/05/2003                      |
| Nombre y dirección de correo de la autoridad encargada del examen preliminar<br>Oficina de Patentes Europea<br>D-80296 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4485 | Fundonario Autorizado<br><br>Gohlke, P<br><br>Teléfono No. +49 89 2399 8549 |

**INFORME DE EXAMEN  
PRELIMINAR INTERNACIONAL**

Solicitud Internacional No. PCT/CA02/00899

**I. Base del Informe**

1. Respecto a los elementos de la solicitud internacional *(Las hojas de reemplazo que han sido entregadas a la Oficina receptora en respuesta a la invitación bajo el Artículo 14 se refieren en este informe como "originalmente presentadas" y no se anexan a este informe ya que ellas no contienen modificaciones (Regla 70.16 y 70.17):*

☒ La descripción, páginas:  
páginas 1 – 39, como se presentaron originalmente

☒ Las reivindicaciones, número:  
páginas 1 – 17, como se presentaron originalmente

2. Respecto al lenguaje, todos los elementos marcados anteriormente estuvieron disponibles o fueron enviados a la Administración en el lenguaje en que se presentó la solicitud internacional, a menos que se indique otra cosa en este punto.

Estos elementos estuvieron disponibles o fueron enviados a esta Administración en el siguiente lenguaje \_\_\_\_\_ el cual es:

- ☐ el lenguaje de la traducción enviada para propósitos de la búsqueda internacional (bajo Regla 23.1 (b)).  
☐ el lenguaje de la publicación de la solicitud internacional (bajo Regla 48.3(b)).  
☐ el lenguaje de la traducción entregada con propósitos del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Respecto a cualquier secuencia de nucleótido y/o amino ácidos divulgada en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:

- ☐ contenido en la solicitud internacional en forma escrita  
☐ presentado junto con la solicitud internacional en forma legible por computador  
☐ entregado posteriormente a esta Administración en forma legible por computador  
☐ La declaración de que el listado de secuencias posteriormente entregado no va más allá de lo divulgado en la solicitud internacional originalmente presentada, ha sido entregada.  
☐ La declaración de que la información grabada en la forma legible por computador es idéntica al listado de secuencias escrito que se ha entregado.

4. ☐ Las modificaciones han dado como resultado la cancelación de:

- ☐ la descripción, páginas \_\_\_\_\_  
☐ las reivindicaciones, Nos. \_\_\_\_\_  
☐ los dibujos, página \_\_\_\_\_

5. ☐ Este reporte ha sido establecido como si (parte de) las modificaciones no se hubieran realizado, ya que éstas han sido consideradas como una ampliación de lo inicialmente divulgado como se indica en la Casilla Suplementaria (Regla 70.2(c)). (Cualquier hoja de reemplazo que contenga dichas modificaciones deberá ser referida bajo el punto 1 y anexada a este informe):

6. Observaciones adicionales, si son necesarias:

V. Declaración motivada según el Artículo 35(2) en cuanto a la novedad, el nivel inventivo y la aplicación industrial; citas y explicaciones que apoyan esta declaración.

1. Declaración

|                            |                  |        |    |
|----------------------------|------------------|--------|----|
| Novedad (N)                | Reivindicaciones | 1 – 17 | SI |
|                            | Reivindicaciones |        | NO |
| Nivel inventivo (NI)       | Reivindicaciones | 1 – 17 | SI |
|                            | Reivindicaciones |        | NO |
| Aplicación industrial (AI) | Reivindicaciones | 1 – 17 | SI |
|                            | Reivindicaciones |        | NO |

2. Citas y explicaciones (Regla 70.7)

ver hoja separada

**Recuadro Suplementario**

(Para ser usado cuando el espacio en alguno de los recuadros anteriores no es suficiente)

Se hace referencia a los documentos a continuación:

**Documento D1:** CAPUTO ET AL.: 'Una nueva estrategia para la síntesis asimétrica de nucleósidos análogos con base en 1,3-oxatiolane' EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, WILEY-VCH VERLAG, WEINHEIM, DE, 1999, páginas 1455- 1458, XP002210506 ISSN: 1434-193X citado en la solicitud

**Documento D2:** BELLEAU ET AL.: 'Una novedosa de análogos de nucleósidos de 1,3-oxatiolane que tienen actividad potente de VIH' BIOORGANIC & MEDICAL CHEMISTRY LETTERS, OXFORD, GB, vol. 3, no. 8, 1993, páginas 1723 – 1728, XP001024523 ISSN: 0960-894X citado en la solicitud

**Documento D3:** MOON W C ET AL.: 'Síntesis y actividades antivirales de 1,3-dioxolanil-, 1,3-oxationlanil- y 1,3-ditolanilnucleosidos con sustituyentes de 2-hidroximetilo' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol.7, no. 11, 3 de junio de 1997 (1997-06-03), páginas 1475-1480, XP004036239 ISSN: 0960-894X

**Documento D4:** WO 95 29176 A (IAF BIOCHEM INT; MANSOUR TAREK S (CA); JIN HAOLUN (CA)) 2 de noviembre de 1995 (1995-11-02) citado en la solicitud

Ninguno de los documentos disponibles en el arte previo revela un proceso estereoselectivo para la síntesis asimétrica de nucleósidos análogos con base en 1,3-oxa (o tio-) tiolano partiendo de sulfoxido ramificado en la presencia de un elemento de un

grupo IB o IIB y una amina terciaria, como se reivindica en las presentes reivindicaciones 1 – 17.

Toda la síntesis revelada en los documentos D1-D4 envuelven un ultimo paso de resolución de la mezcla diaestereométrica obtenida en la misma por cromatografía de columna de gel de sílice o por resolución enzimática.

Por lo tanto la materia objeto de las reivindicaciones 1-17 cumple con los requerimientos de los artículos 33(2) y (3) del PCT.

SUPERINTENDENCIA COMERCIO  
Radicación : 04002061 00000000 Folios: 99  
Fecha (AMB): 2004-01-14 17:14:31  
Trámite : 011 PCI-PATENT 279 FASE NACI 411 PRESENTAC  
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 94,901  
FECHA : DICIEMBRE 29 DE 2003

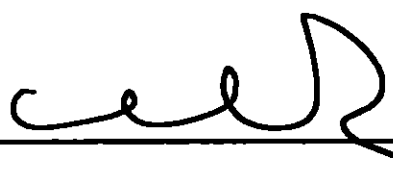
##### CONSIGNACION #####

| DEPOSITANTE       | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PGO  | Vr. PAGO      |
|-------------------|--------------|---------------|-------------|----------|------------|---------------|
| CAVELIER ABOGADOS | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 10497410 | 29/12/2003 | 15,737,000.00 |

##### CONCEPTO #####

| CANT. RENTISTICO          | CONCEPTO                            | TOTAL CONCEPTO |
|---------------------------|-------------------------------------|----------------|
| 1 50003-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 400,000.00     |
|                           | TOTAL :                             | \$ 400,000.00  |

SOM: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

Cob 14036-841-001-7

NIT : 800176089-2

Modificacion : 04002061 00000000  
Fecha (MM/AA): 2004-01-14 17:14:31  
Tramite : 011 PCI-PAIENI 475 FISC. NACIONAL  
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 891  
FECHA : ENERO 6 DE 2004

\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE       | TIPO PAGO    | BANCO         | CUENTA      | No. PAGO | FECHA PGO  | Vr. PAGO      |
|-------------------|--------------|---------------|-------------|----------|------------|---------------|
| CAVELIER ABOGADOS | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 10497411 | 06/01/2004 | 67,154,000.00 |

\*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. | RENTISTICO              | CONCEPTO                              | TOTAL CONCEPTO |
|-------|-------------------------|---------------------------------------|----------------|
| 1     | 50005-01-01 SOLICITUDES | 998 VALOR COMPLEMENTO TARIFA ABO ANTR | 22,000.00      |
|       |                         | TOTAL :                               | \$ 22,000.00   |

SON: VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

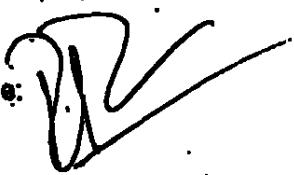
cto 14056-84(001-7)

Radicación : 04002661      Folios: 53  
Fecha (DM): 2004-01-14 17:14:31  
Tramite : 011 PCI-PATENTE 3/9-1964 NDL 411 Habiendo  
Dependencia: 2020 DIVISION DE MARCAS COLOMBIANAS

## REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

|                                                                                                              | USUARIO               | RADICADOR |
|--------------------------------------------------------------------------------------------------------------|-----------------------|-----------|
| <b>PATENTE DE INVENCION</b> ✓                                                                                | ( )                   | ( ) ✓     |
| <b>MODELO DE UTILIDAD</b>                                                                                    | ( )                   | ( ) ✓     |
| - Indicación de que se solicita la concesión de una patente.                                                 | ( )                   | ( ) ✓     |
| - Datos de identificación del solicitante o de la persona que se presenta la solicitud.                      | ( )                   | ( ) ✓     |
| - Descripción de la invención.                                                                               | ( )                   | ( ) ✓     |
| - Dibujos de ser estos pertinentes.                                                                          | ( )                   | ( ) ✓     |
| - Comprobante de Pago de las tasas establecidas.                                                             | ( )                   | ( ) ✓     |
| <b>COMPLETA</b> ( ) ✓                                                                                        | <b>INCOMPLETA</b> ( ) | ( )       |
| <b>DISEÑO INDUSTRIAL</b> ( )                                                                                 |                       |           |
| - 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                                                              | ( )                   | ( )       |
| <b>COMPLETA</b> ( )                                                                                          | <b>INCOMPLETA</b> ( ) | ( )       |
| <b>ESQUEMA DE TRAZADO</b> ( )                                                                                |                       |           |
| - Indicación de que 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 de trazado                                                              | ( )                   | ( )       |
| - Comprobante de pago de las tasas establecidas.                                                             | ( )                   | ( )       |
| <b>COMPLETA</b> ( )                                                                                          | <b>INCOMPLETA</b> ( ) | ( )       |

Firma Responsable:



Fecha:

2020  
Bogotá D C

Doctor(a)  
EMILIO FERRERO.  
Apoderado(a)

Oficio N°  
**04749**

|                |                            |               |
|----------------|----------------------------|---------------|
| <b>ASUNTO:</b> | Radicación N°              | 04-02061      |
|                | Solicitud internacional    | PCT/CA02/0899 |
|                | Fecha inicio fase nacional | 15/01/2004    |
|                | Trámite                    | 011           |
|                | Evento                     | 379           |
|                | Actuación                  | 416           |
|                | Folios                     | 001           |

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:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de 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 éste fuere una 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 Única N° 10 de 2001.

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

**07 MAYO 2004**

El anterior requerimiento fue notificado por fijación en lista de fecha, \_\_\_\_\_  
202051

1/2  
2-5-a.