

Industria y Comercio
SUPERINTENDENCIA

AS: 98.585

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-087779-00004-0000

1er. 2023 NUEOREACIONI

1er. 2023 FASE NACIONAL II

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

1

SOLICITUD DE:

☐

Corrección de Error Material.

☒

Modificación a una Solicitud.

2

SOLICITANTE

Nombre: **BRISTOL - MYERS SQUIBB
COMPANY**Dirección: P.O. Box 4000, Route 206 and Province
Line Road, Princeton, NJ 08543-4000, Estados
Unidos de América

Nacionalidad o Domicilio: Estados Unidos

Lugar de Constitución: Estados Unidos

Teléfono:

Fax:

E-mail:

IDENTIFICACION

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: JUAN PABLO CADENA SARMIENTO

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

Teléfono: 744-2200

Fax: 742-2200

E-mail:

IDENTIFICACION

C.C.

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C.E.

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Otro

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Cual _____

Número 80 410.337 TP 57492

4

Número de expediente:

05 087.779

5

Descripción de la corrección o modificación solicitada

La entrada en Fase Nacional de la presente solicitud corresponde al CAPÍTULO I del PCT

y NO al Capítulo II como se señaló inicialmente.

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Comprobante de pago No. 07-23,492

Fecha

09-05-2007

7

Anexos:

☒ Comprobante de pago de la tasa por \$99.000☐ Poderes, si fuere el caso.☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.☒ Reporte Preliminar Internacional sobre Patentabilidad Formas PCT/IB/373 y PCT/ISA/237.

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NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

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

PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference GY0111	FOR FURTHER ACTION See item 4 below	
International application No. PCT/US2004/006103	International filing date (day/month/year) 27 February 2004 (27.02.2004)	Priority date (day/month/year) 04 March 2003 (04.03.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).																									
2.	This REPORT consists of a total of 4 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																									
3.	This report contains indications relating to the following items: <table><tr><td>☒</td><td>Box No. I</td><td>Basis of the report</td></tr><tr><td>☐</td><td>Box No. II</td><td>Priority</td></tr><tr><td>☐</td><td>Box No. III</td><td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td></tr><tr><td>☐</td><td>Box No. IV</td><td>Lack of unity of invention</td></tr><tr><td>☒</td><td>Box No. V</td><td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td></tr><tr><td>☐</td><td>Box No. VI</td><td>Certain documents cited</td></tr><tr><td>☐</td><td>Box No. VII</td><td>Certain defects in the international application</td></tr><tr><td>☐</td><td>Box No. VIII</td><td>Certain observations on the international application</td></tr></table>		☒	Box No. I	Basis of the report	☐	Box No. II	Priority	☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	☐	Box No. IV	Lack of unity of invention	☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	☐	Box No. VI	Certain documents cited	☐	Box No. VII	Certain defects in the international application	☐	Box No. VIII	Certain observations on the international application
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																									

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 07 August 2006 (07.08.2006)
	Authorized officer Beate Giffo-Schmitt e-mail: pt03@wipo.int

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/06103

Box No. I Basis of this opinion

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

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

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

a. type of material

- ☒ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☒ on paper
☒ in electronic form

c. time of filing/furnishing

- ☒ contained in the international application as filed.
☒ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

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

4. Additional comments:

15A

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-87779

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **578** DE

FECHA **31 DE JULIO DEL 2007**, EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL **26 DE OCTUBRE DEL 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☐

NO ☒

DIDEOXYINOSINE BY ENZYMATIC DEAMINATION OF DIDEOXYADENOSINE

CROSS REFERENCE

This is a continuation-in-part of U.S. Ser. No. 07/074,844 filed July 17, 1987.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to an improved process to produce β -(D)-2',3'-dideoxyinosine.

2. Background — Related References

Typically, 2',3'-dideoxycytidine (ddC) is synthesized from 2'-deoxycytidine^{1,2}. This is a general method for the synthesis of 2,3'-dideoxynucleosides. The starting materials for this synthesis are, however, extremely expensive and not available in bulk. The reagents required for this deoxygenation, furthermore, are also quite costly.

U.S. Ser. No. 028,817 filed 20 Mar. 1987, owned in common by the assignee of this invention, discloses a process for producing 2',3'-dideoxynucleosides represented by the formula



wherein B is a purine or pyrimidine base and R is H or a hydroxy-protecting group by the steps of (a) converting a γ -carboxy- γ -butyrolactone to a 5-O-hydroxy-protecting group-methyl- γ -butyrolactone, (b) converting the intermediate from step (a) to the 5-O-hydroxy-protecting group-methyl-2',3'-dideoxypentofuranose, (c) converting the intermediate from step (b) to the 1-O-activating group-5-O-hydroxy-protecting group-methyl-2',3'-dideoxypentofuranose, (d) converting the intermediate from step (c) to the 1-leaving group-5-O-hydroxy-protecting group-2',3'-dideoxypentofuranose, (e) reacting the intermediate from step (d) with an activated purine or pyrimidine base, and (f) recovering the dideoxynucleoside from step (e). The resulting product comprises a mixture of β - and α -anomers which may be separated using chromatographic and crystallization techniques well-known in the field to which this invention relates.

There remains in the field a need for process improvements whereby the generally active, or more active, β -anomer of (D)-2',3'-dideoxynucleosides can be selectively obtained without the costly and time-consuming chromatographic or fractional recrystallization separation of β - and α -anomers. This is particularly important when large quantities of the desired β -anomeric form is desired.

Inosine, chemically 9- β -(D)-ribofuranosylhypoxanthine, biochemically results from enzymatic deamination of adenosine, chemically 9- β -(D)-ribofuranosyl-9H-purin-6-amino. This process, employing adenosine deaminase, acts to metabolically degrade purines to hypoxanthines for excretion in the higher animals. Inosine can be prepared from adenosine by incubation with purified adenosine deaminase obtained from biological sources, e.g. bovine intestine. In applications such as these, where natural substrates are involved, it is known that the enzyme selectively deaminates only one enantiomer of the racemic pair. Enzymatic specificity would

not be known beforehand when anomeric mixtures of structurally modified nucleosides were presented as substrates. Specificity on the basis of the known enantiomeric selection process of the enzyme, is not the basis for specificity when applied to an anomeric mixture.

SUMMARY OF THE INVENTION

In summary, this invention comprises an efficient process for selectively producing β -(D)-2',3'-dideoxyinosine represented by the formula

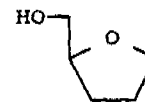


Formula A

wherein I is the purine base, inosine. The process involves producing an α , β -anomeric mixture of (D)-2',3'-dideoxyadenosine, which is then subjected to selective enzymatic deamination converting the adenosine base to inosine for only the β -(D)-isomer which is readily isolable and easily purified by simple recrystallization.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is an improved process for selectively producing β -(D)-2',3'-dideoxyinosine represented by the formula



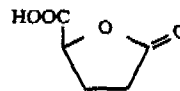
Formula A

wherein I is the purine base, inosine which comprises the steps of:

1. preparing an anomeric mixture of α - and β -(D)-2',3'-dideoxyadenosine;
2. selectively deaminating the β -(D)-2',3'-dideoxyadenosine anomer by contact of the anomeric mixture of step 1. with the enzyme, adenosine deaminase; and
3. recovering the β -(D)-2',3'-dideoxyinosine produced in step 2.

A typical process for producing the anomeric mixture used in step 1. comprises the steps of:

- (a) converting (D)- γ -carboxy- γ -butyrolactone of the formula



Formula 1

to a 5-O-hydroxy-protecting group-methyl- γ -butyrolactone of the formula



Formula 2

wherein R is a hydroxy-protecting group by reacting the Formula 1 compound with a carboxy group reduc-

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ing agent followed by protecting the resulting hydroxymethyl group;

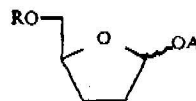
(b) converting the intermediate from step (a), Formula 2, to the 5-O-hydroxy-protecting group-methyl-2,3-dideoxy-(D)-pentofuranose of the formula



Formula 3

wherein R is a hydroxy-protecting group by reacting the Formula 2 compound with a carbonyl group reducing agent;

(c) converting the intermediate from step (b), Formula 3, to the 1-O-activating-group-5-O-hydroxy-protecting group-2,3-dideoxy-(D)-pentofuranose of the formula



Formula 4

wherein R is a hydroxy-protecting group and A is an O-activating group selected from alkylcarbonyl, arylcarbonyl, alkylthiocarbonyl, arylthiocarbonyl, alkylsulfonyl, arylsulfonyl and carbonate groups, wherein the alkyl moiety may be an unsubstituted or substituted C₁-C₃ alkyl group and the aryl moiety may be an unsubstituted or substituted phenyl group and wherein the substituent on the alkyl and aryl moieties may be selected from 1 to 3 groups selected from halo and C₁-C₃ alkoxy groups by reacting the Formula 4 compound with an acylating or sulfonating or carbonylating agents corresponding to group A above;

(d) converting the intermediate from step (c), Formula 4, by reaction with a compound having one of the formulas HX and trimethylsilyl halide to the 1-leaving-group-5-O-protecting group-2,3-dideoxy-(D)-pentofuranose of the formula



Formula 5

wherein R is a hydroxy-protecting group and X is a leaving group selected from F, Cl, Br and I;

(e) reacting the intermediate from step (d), Formula 5, with an activated derivative of adenine, wherein the base, adenine, has been activated by means of reacting the pendant amino and hydroxy groups on the adenine nucleus with an activating compound selected from silylating and acetylating and benzoylating agents, and optionally, in the presence of one of a Bronsted acid and a Lewis acid and in the presence of an inert organic solvent; and

(f) recovering the anomeric mixture of α - and β -(D)-2'3'-dideoxyadenosine after cleavage of the 5-O-hydroxyprotecting group from the intermediate product of step (e) above.

The starting material, (D)- γ -carboxy- γ -butyrolactone be conveniently obtained from L-glutamic acid by utilizing conventional techniques reported in the chemical literature³.

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A combination of chemical reactions produce a suitably blocked 2,3-dideoxypentofuranose, 3. This compound and its derivatives are known in the literature.

Thus, the conversion of the starting material, (D)- γ -carboxy- γ -butyrolactone, to a 5-O-hydroxy-protecting group-methyl- γ -butyrolactone, step (a), involves the reduction of the γ -carboxy group to a hydroxymethyl group followed by reaction with a hydroxy-protecting group reagent. For example, the reduction of the γ -carboxy group and protection of the resulting γ -hydroxymethyl group by means of the benzyl group (PhCH₂-), step (a), was achieved by the successive reaction of the starting compound of Formula 1 with BH₃.SMe₂ and PhCH₂Br.

The primary alcohol functional group may be protected as an ether, such as trialkyl or dialkyl aryl or diaryl alkyl or triaryl silyl, unsubstituted and substituted benzyl, unsubstituted and substituted alkyl, or allyl ether, or as an ester, such as a benzoyl, mesitoyl, pivaloyl, unsubstituted or substituted acetyl, or a carbonate ester. See "Protective Groups in Organic Synthesis," T. W. Greene, John Wiley, N.Y. 1981 for more detailed description of protecting groups and the chemistry relating to the same. In a more preferred embodiment, there was used as the hydroxy-protecting group for the primary alcohol group at the 5-position the benzyl group, and most preferably the benzoyl group, because of their stability and well-known preparation.

The conversion of the 5-O-hydroxy-protecting group- γ -butyrolactone, to the 5-O-hydroxy-protecting group-2,3-dideoxypentofuranose having Formula 3 in step (b) was achieved by reacting the intermediate having Formula 2 with NaH and HCO₂Et followed by HCl.

It will be understood by those skilled in the art to which this invention relates that any one of a number of reducing agents may be used to carry out either or both of steps (a) and (b) independently (i.e., in succession) or at the same time. Other useful reducing agents besides BH₃.SMe₂ used in steps (a) and (b) as described above include NaBH₄, NaBH₄ plus LiCl or AlCl₃ or BF₃, LiAlH₄, LiAlH(OMe)₃, LiAlH(O-t-Bu)₃, (Si₂)₂BH (disiamyl borane) and other dialkylboranes, and the like. Disiamyl borane is preferred as the reducing agent because of its convenient handling and reactivity.

The step (c) conversion of the intermediate having Formula 3 to the intermediate having Formula 4 bearing an "activated" hydroxy group at the C(1) position of the 2,3-dideoxypentofuranose ring system may be achieved by any reagent effective to convert this hydroxy group to a group which may be displaced readily by Cl or Br upon reaction with HCl or HBr or, preferably, TMSBr or TMSCl (+) catalytic amount of TMSI. ("TMS" represents the trimethylsilyl group). Such a group which can be so displaced readily include O-activating groups selected from alkylcarbonyl, arylcarbonyl, alkylthiocarbonyl, arylthiocarbonyl, alkylsulfonyl, arylsulfonyl and carbonate groups wherein the alkyl moiety may be an unsubstituted or substituted C₁-C₃ alkyl group and the aryl moiety may be an unsubstituted or substituted phenyl group and wherein the substituent on the alkyl and aryl moieties may be selected from 1 to 3 groups selected from halo and C₁-C₃ alkoxy groups. More preferably, this activating group is selected from corresponding (to the above) acetoxy and benzoyloxy groups and, most preferably, acetoxy. Step (c) was conveniently carried-out using acetic anhydride/pyridine reagent.

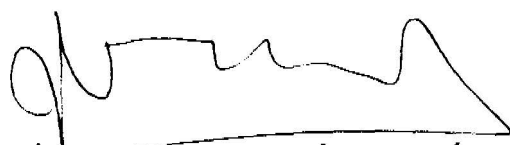
6. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US 5.011.774	1 - 21	Nivel Inventivo
D2	Dessouki y Atia	1 - 21	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



JESÚS FERNEL GARCÍA GARCÍA
Director de Nuevas Creaciones (E)

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

CONCEPTO TÉCNICO No. 4317	EXAMINADOR TÉCNICO Código No. 202089
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