

Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y C

E. _____ S. _____

NÚMERO DE REGISTRO DE LA PATENTE: 07-135-330

NÚMERO DE REGISTRO DE LA PATENTE: 07-135-330

NÚMERO DE REGISTRO DE LA PATENTE: 07-135-330

Referencia: Expediente No. 07.135.330

Solicitud de Patente de Invención titulada: "Tigeciclina y métodos para preparar 9-nitrominociclina"

Solicitante: Wyeth

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 26
DEL 01 DE FEBRERO DE 2008, OFICIO NO. 1101 (EXAMEN DE FORMA)

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término legal:

1. El documento de cesión del derecho de patente del inventor al solicitante fue presentado junto con la solicitud el día 21 de diciembre de 2007 y obra en folios 9 a 29.
2. De igual manera, adjunto el Reporte Preliminar Internacional sobre Patentabilidad y opinión escrita.
3. Aprovecho esta oportunidad para solicitar al Examinador mayor claridad sobre las objeciones formales a las solicitudes de patente, por cuanto en el presente oficio no es claro si hace falta la firma de un inventor, o los nombres de los inventores no coinciden con los del petitorio, o la legalización es incorrecta, o definitivamente no se presentó este documento, etc... La objeción presentada por el Examinador no es clara y deja al solicitante en un estado de incertidumbre por cuanto el documento se presentó junto con la solicitud y no se sabe

PATENT COOPERATION TREATY

PCT/US2006/020540

RDB/ACT/GXP/MCM

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)

(PCT Rule 41bis.1(c))

To:

MCDONELL, Leshe, A.
Finnegan, Henderson, Farabow, Garret & Dunner, L.L.P.
901 New York Avenue
Washington, DC 20001-4413
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)

13 December 2007 (13.12.2007)

Applicant's or agent's file reference

1142.380-304

IMPORTANT NOTICE

International application No.

PCT/US2006/020540

International filing date (day/month/year)

25 May 2006 (25.05.2006)

Priority date (day/month/year)

27 May 2005 (27.05.2005)

Applicant

WYETH et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

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

Authorized official

Nora Lindner

Facsimile No. +41 22 438 82 70

e-mail: pct@wipo.int

Form PCT/IB/326 (January 2004)

Page 11 of 11

PATENT COOPERATION TREATY

PCT

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

(PCT Rule 44bis)

Applicant's or agent's file reference 1'42 380-304	FOR FURTHER ACTION		See item 3 below
International application No. PCT/US2006/020540	International filing date (day/month/year) 25 May 2006 (25.05.2006)	Priority date (day/month/year) 27 May 2005 (27.05.2005)	
International Patent Classification (8th edition unless older edition indicated): See relevant information in Form PCT/ISA/237			
Applicant WYETH			

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 10 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:

- | | |
|--|---|
| ☒ 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 |

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).

Date of issuance of this report
30 November 2007 (30.11.2007)

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

Authorized officer

Nora Lindner

Facsimile No. 441 22 338 82 70

e-mail: pct@wipo.int

Form PCT/ATN/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43b/s.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2006/020540International filing date (day/month/year)
25.05.2006Priority date (day/month/year)
27.05.2005International Patent Classification (IPC) or both national classification and IPC
INV. C07C231/02 C07C237/26 A61K31/65 A61P31/00Applicant
WYETH

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

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

2. FURTHER ACTION

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

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

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

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

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399-0 Tx: 523656 epmu d
Fax: +49 89 2399-4465

Date of completion of
this opinionsee form
PCT/ISA/210

Authorized Officer

GRENOUILLAT, N

Telephone No. +49 89 2399-6514



258
6WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US2006/020540

RTO

Box No. 1 Basis of the 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 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:

259
xWRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US2006/020540

261

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-28, 32-40

Box No. V Reasoned statement under Rule 43b/s.1(3)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-28
	No: Claims	32-40
Inventive step (IS)	Yes: Claims	1-28
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-28, 32-40
	No: Claims	

2. Citations and explanations

see separate sheet

260

5

262

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/020540

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)
and/or
2. Non-written disclosures (Rules 43bis.1 and 70.8)
see form 210

261
x
263WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2006/020540

Reference is made to the following documents:

- D1: Drugs of the Future, 2001, 26, 851-858
D2: US5675030
D3: Journal of Organic Chemistry, 2003, 68, 5838-5851
D4: Journal of Medicinal Chemistry, 1994, 37, 184-188

Re Item IV: Lack of unity of invention

1. This Authority considers that there are 2 groups of invention covered by the claims indicated as follows:
 - i: Claims 1-28, 32(part)-40(part) directed to a method for preparing at least one compound of formula 1 of the application or a pharmaceutically acceptable salt thereof, comprising a) reacting at least one nitrating agent with at least one compound of formula 2 of the application or a salt thereof, to produce a reaction mixture comprising an intermediate, and b) further reacting the intermediate to form at least one compound of formula 1 of the application, wherein the intermediate is not isolated from the reaction mixture (regarding claims 26-28 the "slurry" was considered to relate to a reaction mixture in which no compounds are isolated).
 - ii: Claims 29-31, 32(part)-40(part) directed to a method for preparing at least one compound of formula 3 of the application or a salt thereof, comprising a) reacting at least one nitrating agent with at least one compound of formula 2 of the application or a salt thereof, wherein the reacting is performed at a temperature ranging from -5 to 15 °C.
2. The document D1 is regarded as being the closest prior art and discloses (see Paragraph "Synthesis" p 851):

A process for the synthesis of tigecycline comprising the steps of:

- nitration of minocycline with KNO_3 and H_2SO_4 to form a 9-nitro derivative,

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2006/020540

- reduction of this 9-nitro derivative with H_2 over Pd/C in 2-methoxyethanol/2N H_2SO_4 to provide 9-aminominocycline,
- acylation of 9-aminominocycline either a) with 2-bromoacetyl bromide in N,N-dimethylpropyleneurea (DMPU) to form 9-(2-bromoacetamido)minocycline, followed by reaction with tert-butylamine to yield after purification the attended tigecycline, either b) with N-tert-butylglycyl chloride to form directly the attended tigecycline.

3. Therefore, the differences between the disclosure of D1 and the two inventions can be defined as follows:

Claim 1: The subject-matter of claim 1 differs from D1 in that the nitro-intermediate is not isolated from the reaction mixture but directly involved in the reductive step.

Claim 29: The subject-matter of claim 29 differs from D1 in that the first step of nitration is performed at a specific temperature ranging from 5 to 15 °C.

4. Starting from the process disclosed in D1, and according to the examples and comparative examples described in this application, it appears that claims 1 and 29 solve the same problem: how to modify the process to get the minocycline derivatives in a purer form and more specifically contaminated with a less amount of the C4-epimer.
5. The special technical feature of claim 1 is the non isolation of the nitro-intermediate from the reaction mixture.
The special technical feature of claim 29 is the specific range of temperature of the first step (nitration).
6. Since the special technical features are neither nor corresponding, there are no same or corresponding special technical features shared by independent claims 1 and 29 of the invention. Therefore the two groups of claims define two different inventions not linked by a single general inventive concept. The application, hence does not meet the requirements of unity of invention as defined in rules 13.1, 13.2 PCT.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

international application No.

PCT/US2006/020540

Re Item V.

Reasoned statement with regard to novelty, inventive step or industrial
applicability; citations and explanations supporting such statement

1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 32 to 40 is not new in the sense of Article 33(2) PCT.

The compounds disclosed in this application are already known (see D1), therefore the subject-matter of claims 32 and 34 is not new in the sense of Article 33(2) PCT.

Moreover the use of the compounds disclosed in this application in a composition is also not new in the sense of that these compounds were already known (see D1 and D2), therefore the subject-matter of claims 35-40 is not new in the sense of Article 33(2) PCT.

2. Document D1 is regarded as being the closest prior art to the subject-matter of claim 1 (see above).

The subject-matter of claim 1 differs from D1 in that the nitro-intermediate is not isolated from the reaction mixture and direct involving in the reductive step.

The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

The problem to be solved by this application is to find a process which produce the minocycline derivatives in a purer form and more specially contaminated with a less amount of the C4-epimer.

According to comparative examples 1 and 2 using the method described in D1 (see pages 44-56 of this application), the isolated aminominocycline derivative (4) is contaminated with 1.75% to 3.88% of the C4-epimer. According to example 1 using the method claimed in this application (see page 50 of this application), the isolated aminominocycline derivative (4) is contaminated with 0.9% of the C4-epimer.

264
X
266WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2006/020540

D2 discloses the purification of compounds of formula 1, contaminated with the C4-epimer and oxidative degradation by-products by performing an extraction on the crude compound. The purity of the final compounds obtained by this method is 92 to 98.5%. There is no indication in D2 to modify the process of the synthesis of compounds of formula 1 in order to get them in a purer form (column 2 line 57 to column 3 lines 35).

None of the documents cited in the search report show or suggest that the non isolation of the nitro-derivatives would allow to higher the purity of the 9-aminomincyclines. Therefore the subject matter of claim 1 appears to be novel and inventive.

Claims 2-28 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

3. Further remarks

- 3.1 Claims 1, 24 and 26 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following:

Claims 1, 24 and 26 claim the formation of an intermediate resulting of reaction of a nitrating agent with a compound of formula 2. According to the description of the complete reaction scheme described in this application, the only intermediate formed seems to be the 9-nitromincycline derivate (compound 3). Therefore the term "intermediate" using in claims 1, 24 and 26 without precisising the nature of this intermediate, renders the scope of the claims broader than justified by the description.

- 3.2 Claim 6 refers to the concentration of the nitric acid but fails to define if it is the concentration of the nitric acid solution used for the reaction or the concentration in the reaction mixture. Therefore claim 6 is not clear and does not meet the requirement of Article 6 PCT.

- 3.3 Claims 18 and 19 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/US2006/020540

the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical features necessary for achieving this result.

- 3.4 Claim 26 does not meet the requirement of Article 6 PCT in that claim 26 comprises all the features of claim 1 ("slurry" is defined as being the reaction mixture of step (a)) and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT). Claims 27 and 28 are dependent on claim 26 and also does not meet the requirements of Article 6 PCT.
- 3.5 Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 and D2 is not mentioned in the description, nor is these documents identified therein.

Re Item VI

Certain documents cited

Certain published documents

Bioorganic & Medicinal Chemistry Letters, 2006, 16, 400-403

Available online: 21 October 2005

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 268

2020
Bogotá D.C.,

Doctor(a)
CORREA ORDÓÑEZ ALVARO
Apoderado(a) y/o Representante de
WYETH

REFERENCIA	Radicación No.	7 135330
	Solicitud internacional	PCT/US2006/020540
	Fecha inicio fase nacional	27/12/2007
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	7257
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

0 5 11 2006

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpall

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-135330

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **602** DE

FECHA **31 DE MARZO DE 2009** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **02 DE JULIO DE 2009**

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 X

NO X