

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-100244-00004-0000

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Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

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Referencia: Expediente No. 06.100.244

Solicitud de Patente de Invención titulada: "Síntesis regioespecífica de derivados 42-éster de rapamicina."

Solicitante: Wyeth

MEMORIAL DE ALCANCE

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad en referencia, manifiesto lo siguiente:

El día 04 de octubre de 2006, bajo el número de radicación 06.100.244, presenté la solicitud de patente de invención de la referencia, para la cual adjunto informe preliminar internacional sobre patentabilidad, capítulo I del tratado de cooperación en materia de patentes.

Atentamente,


ÁLVARO CORREA ORDÓÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281

Anexo: Informe preliminar internacional sobre patentabilidad, capítulo I

BOGLMN/BOGDMS-76371-VI-DOC

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PATENT COOPERATION TREATY

PCT/US2005/012266

From the INTERNATIONAL BUREAU

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NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)
(PCT Rule 44bis.1(c))

To:

KODROFF, Cathy, A.
Howson and Howson
321 Norristown Road, Suite 200
Spring House Corporate Center
P.O. Box 457
Spring House, PA 19477
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
26 October 2006 (26.10.2006)

Applicant's or agent's file reference
AM-100906PCT

IMPORTANT NOTICE

International application No.
PCT/US2005/012266

International filing date (day/month/year)
12 April 2005 (12.04.2005)

Priority date (day/month/year)
14 April 2004 (14.04.2004)

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)

NOV - 7 2006

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

Authorized officer

Dorothee Mülhausen

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PATENT COOPERATION TREATY

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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 AM-100808PCT	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2005/012288	International filing date (<i>day/month/year</i>) 12 April 2005 (12.04.2005)	Priority date (<i>day/month/year</i>) 14 April 2004 (14.04.2004)	
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 8 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).

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 19 October 2005 (19.10.2005)
	Authorized officer Dorothee Mülhausen e-mail: pt01@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

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REC'D 07 SEP 2005	
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From the
INTERNATIONAL SEARCHING AUTHORITY

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To:
see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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/220		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US2005/012288	International filing date (day/month/year) 12.04.2005	Priority date (day/month/year) 14.04.2004	
International Patent Classification (IPC) or both national classification and IPC C07D498/18, A61K47/48, C12P17/18			
Applicant 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"). However, 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 68.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three 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-80289 Munich Tel. +49 89 2369 - 0 Tx: 523655 spru d Fax: +49 89 2369 - 4465	Authorized Officer Scruton-Evans, I Telephone No. +49 89 2369-6272
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/012266

Box No. I 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, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 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:
☐ in written format
☐ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable 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:

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/012266

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 14,16-18

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 14,16-18
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/012266

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:
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ 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. 1-12,14,16(part),17 (part), 18(part)

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

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	14,16-18
Inventive step (IS)	Yes: Claims	
	No: Claims	1-12,14,16-18
Industrial applicability (IA)	Yes: Claims	1-12,14,16-18
	No: Claims	

2. Citations and explanations

see separate sheet

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/012266

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 14,16-18 all refer to compositions and kits containing a rapamycin derivative prepared according to the process of claims 1-12. In the absence of any distinguishing feature of these products by process claims, they are to be seen as products per se. So many of these esters are known that a meaningful search was not possible over the whole of the scope, and only a selection of the documents prejudicial to the novelty of these products is cited.

Re Item IV

Lack of unity of invention

This Authority considers that there are two inventions covered by the claims indicated as follows:

- I: Claims 1-12,14,16-18 (part) directed to a process for the preparation of a 42-ester of rapamycin using a lipase, compositions and pharmaceutical kit
- II: Claims 13,15,16-18 (part) directed to a regiospecific preparation of rapamycin 42-ester with isopropylidene ketal protected 3-hydroxy-2-(hydroxymethyl)-2-methyl propanoic acid

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

Invention 1 describes the process of preparation of rapamycin 42-ester derivatives using an acyl donor and a lipase. The problem underlying this invention was the provision of a further novel process for the preparation of known 42-ester derivatives, the solution provided being the use of a lipase.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

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Invention 2 is independent, i.e. describes only the regiospecific preparation of the ketal compound, without the use of a lipase, or, indeed any reaction conditions. It is already known from WO-A-0123395, Scheme 1, to prepare the compound B (corresponding to the compound prepared in invention 2) regioselectively.

According to Rule 13 PCT, an international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept, and their should be a technical relationship among the inventions involving one or more of the same or corresponding special technical features. Such "special technical features" shall mean those that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In the present application, it is considered that the special technical feature of invention 1 is the use of a lipase. Invention 2 is not so linked to invention 1 as to form a single general inventive concept, as the use of a lipase is not mentioned in invention 2, and thus there is a lack of unity according to Rule 13. PCT

Re item V

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

The following documents cited in the search report are referred to in this communication;

- D1: EP-A-0 464 895 (MERCK & CO. INC) 8 January 1992 (1992-01-08)
- D2: ADAMCZYK M ET AL: "Lipase mediated hydrolysis of rapamycin 42-hemisuccinate benzyl and methyl esters" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 35, no. 7, 14 February 1994 (1994-02-14), pages 1019-1022, XP002218069 ISSN: 0040-4039
- D3: WO 92/05179 A (AMERICAN HOME PRODUCTS CORPORATION) 2 April 1992 (1992-04-02)
- D4: WO 95/28406 A (AMERICAN HOME PRODUCTS CORPORATION) 26 October 1995 (1995-10-26)
- D5: WO 01/23395 A (AMERICAN HOME PRODUCTS CORPORATION) 5 April 2001 (2001-04-05)

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/012266

With regard to the requirement for novelty (Article 33(2) PCT), D1 is concerned with FK-506 derivatives, not rapamycin. D2 discloses the lipase hydrolysis of esters, but not the lipase mediated preparation of the esters per se. D3 and D4 disclose 42-esters of rapamycin which are prejudicial to the novelty of claims 14,16-18, but the process for their preparation does not involve lipases. D5 also discloses a regioselective synthesis of 42-esters, but again without lipases, although it is prejudicial to the novelty of claims 14,16-18. Article 33(2) of the PCT is thus not satisfied for claims 14,16-18.

With regard to the requirement for inventive step (Article 33(3) of the PCT), the problem underlying the present application was the provision of further novel process for the regiospecific preparation of 42-esters of rapamycin. The solution provided by the application is the use of an acyl donor in the presence of a lipase. The man skilled in the art, faced with this problem, would have been aware from D5 that the problem had been addressed by other prior arts, and would also have been aware from D1, in the related FK-506 field, that lipases and an acyl donor had been used to carry out regioselective acylation, and would have considered the use of lipases in this related field, given the teaching of D1. The present claims thus are considered to represent an obvious solution to the problem, in the light of D1, and thus lack an inventive step.