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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente No. 05-015.699

Solicitud de patente titulada: "PROCEDIMIENTOS MICROBIOLÓGICOS PARA
PREPARAR 11 α -HIDROXIESTEROIDES 7 α -SUSTITUIDOS"

Solicitante: BAYER SCHERING PHARMA AKTIENGESELLSCHAFT.

N. Ref.:P2005/000189

RESPUESTA AL OFICIO No. 09242 NOTIFICADO POR FIJACION EN LISTA No. 253

DE FECHA 23 DE JULIO DE 2010.

(SEGUNDO EXAMEN DE FONDO)

J. IAN RAISBECK, 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 solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal de prórroga previsto en el artículo 45 de la Decisión 486 en los siguientes términos:

1. En primer lugar, y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado en respuesta al primer examen de fondo de fecha 25 de marzo de 2010, en donde la materia reivindicada se limita a un solo proceso microbiológico, en particular, se pide protección por aquel proceso donde la hidroxilación en posición 11-alfa y la oxidación en posición 17 se dan simultáneamente.

Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

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2. a- El Examinador establece que la patente WO9721830 (D1) afecta el nivel inventivo de la presente invención.

El Examinador establece que D1 enseña la 11 α -hidroxilación de esteroides por preparaciones de microorganismos tales como *Aspergillus ochraceus*, y señala que la única diferencia con la materia reclamada en la presente solicitud es la oxidación simultánea del esteroide (Reivindicación 1 y dependientes) o la incorporación de dos microorganismos para realizar dicho proceso en dos etapas (Reivindicación 2 y dependientes). En cuanto a la Reivindicación 3 y dependientes de la presente solicitud, el Examinador señala que la única diferencia entre el proceso de hidroxilación descrito y D1 es los microorganismos empleados para tal fin.

El Examinador concluye que la 11 α -hidroxilación del esteroide derivado de testosterona a partir de microorganismos reclamado en la presente invención carece de nivel inventivo a la luz de lo revelado por D1, ya que las diferencias en el proceso no poseen un efecto técnico inesperado, y la oxidación en la posición 17 del esteroide por parte de microorganismos es evidente para un técnico medianamente versado en la materia.

b- En primera medida, es importante resaltar que el Examinador acepta la novedad de los procesos en su último informe saliente, sin embargo, en cuando al nivel inventivo de la presente solicitud, deseo resaltar respetuosamente lo siguiente:

Las presentes reivindicaciones se refieren a un proceso microbiológico para la producción de compuestos de fórmula 4B por hidroxilación y oxidación simultánea de los compuestos de fórmula 3A usando microorganismos seleccionados entre: *Glomerella cingulata*, *Bacillus sphaericus*, *Aspergillus ochraceus* y *Gnomonia cingulata*.

El problema a ser resuelto por la invención reivindicada recae en la provisión de un método de producción de los compuestos de la fórmula 4B. Este problema se resuelve por el proceso reivindicado en la presente solicitud.

La invención reivindicada se caracteriza en que la hidroxilación y oxidación se llevan a cabo utilizando un solo microorganismo seleccionado del grupo especial definido en la reivindicación principal, de tal forma que el producto 4B se obtiene partiendo del compuesto de partida 3A.

Una persona versada en la materia para llegar a la presente invención debería definir los productos de partida, así como desarrollar el tipo de reacción (hidroxilación y oxidación) y seleccionar los

microorganismos más apropiados para lo cual se hubiera podido valer del documento D1, tal como cita el Examinador.

Sin embargo, D1 describe un método para la transformación in vitro de un esteroide en su correspondiente derivado 11-alfa-OH usando, entre otros, microorganismos del género *Aspergillus* y *Rhizopus*. La diferencia estructural sobre los compuestos revelados en la presente solicitud es que no hay sustitución en la posición 7. Además, en D1 sólo se lleva a cabo una hidroxilación 11-alfa y de ninguna manera una oxidación ya sea simultánea o subsecuente en posición 17.

Por lo tanto, dado que D1 no revela ni sugiere la hidroxilación 11-alfa y oxidación en posición 17 simultánea de un esteroide mediante el uso de los microorganismos empleados en la presente invención tal como se reivindica en la reivindicación principal, una persona versada en la materia no podría haber derivado de forma obvia el proceso microbiológico reivindicado a partir de las enseñanzas de D1.

Así, se concluye que la presente invención cumple con presentar nivel inventivo.

Asimismo, tal como fuera aclarado en respuestas previas, la presente solicitud se encuentra limitada a los microorganismos y métodos efectivamente ejemplificados con el fin de cumplir con el requisito de soporte en la descripción y, a su vez, redundar en aquellos microorganismos en donde la efectividad hacia los compuestos reivindicados se encuentra demostrada.

2. A continuación, y sólo a título ilustrativo no vinculante, deseo destacar que se halla patente equivalente concedida para la presente solicitud Colombiana, a saber: US 7,262,023 B1. Más aún, en la solicitud equivalente EP 1 523 568 se ha reconocido la novedad y altura inventiva del proceso reivindicado habiéndose citado el mismo arte previo tal como se cita en la presente solicitud colombiana (ver IPER adjunto).

Si bien es cierto que las concesiones de patentes en oficinas de otros países no son vinculantes en el sentido que obliguen a la SIC a tomar una decisión en el mismo sentido, sí considero que dichas concesiones sugieren el cumplimiento de los requisitos de patentabilidad de la materia reivindicada, ya que los criterios de evaluación y estudio aplicados para concluir la aceptación de dichas patentes resultan equivalentes a los que la SIC debe emplear. Tan cierto es lo anterior, que el Manual Andino de Patentes, al comentar el Artículo 46 de la Decisión 486, establece que una Oficina nacional competente podrá reconocer los resultados de exámenes de novedad o de

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patentabilidad efectuados respecto a la solicitud extranjera equivalente, como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad.¹

3. Finalmente, teniendo en cuenta las modificaciones realizadas, se considera que se cumple con los requerimientos solicitados por el Examinador y se cumple con los requisitos establecidos por la Decisión 486. Por lo anterior solicito respetuosamente se proceda a otorgar el privilegio de patente para las reivindicaciones pendientes. En el evento que ese Despacho considere que persisten objeciones sobre cualquier reivindicación, solicito se emita un nuevo auto de fondo para atender dicha situación.

Atentamente,



J. IAN RAISBECK
C.C. 79.376.996 de Bogotá
T.P. 135.799

Anexos:

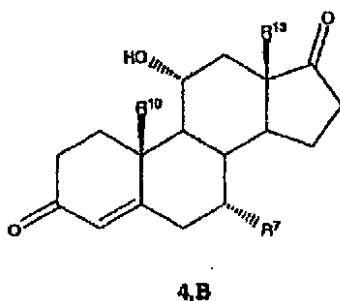
- Capítulo Reivindicatorio Modificado
- International Preliminary Examination Report (IPER) para la solicitud equivalente EP1523568.

¹ Manual Andino de Patentes. Sección 7.3.

CAPITULO REIVINDICATORIO MODIFICADO

(Segundo Examen de Fondo)

1. Procedimiento microbiológico para preparar 11 α -hidroxiesteroides 7 α -sustituídos de la fórmula general 4,B



donde

R⁷ es el grupo P-Q, donde

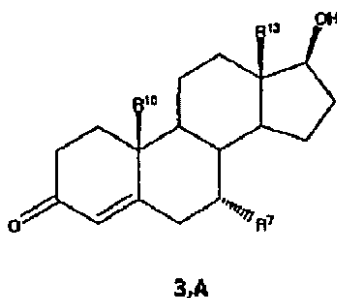
P es un alquileo-C₁-C₄ y Q es alquilo-C₁-C₄ o fluoralquilo-C₁-C₄ y el grupo

P-Q está unido a través de P con la estructura básica esteroide;

R¹⁰ puede estar en posición α o β y ser H, CH₃ o CF₃; y

R¹³ es metilo o etilo,

donde un esteroide 7 α -sustituído de la fórmula general 3,A:



donde R⁷, R¹⁰ y R¹³ tienen el mismo significado que se indicó anteriormente, se hidroxila y oxida usando un microorganismo, seleccionado del grupo que comprende *Glomerella cingulata*, *Bacillus sphaericus*, *Aspergillus ochraceus* y *Gnomonia cingulata*.

2. Procedimiento microbiológico según la Reivindicación 1, caracterizado porque, R⁷ es CH₃.
3. Procedimiento microbiológico según la Reivindicación 1, caracterizado porque, R¹⁰ es H.
4. Procedimiento microbiológico según la Reivindicación 1, caracterizado porque, R¹³ es CH₃.

Translation

PATENT COOPERATION TREATY

PCT/EP2003/008111



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 52299AWO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP2003/008111	International filing date (day/month/year) 24 July 2003 (24.07.2003)	Priority date (day/month/year) 24 July 2002 (24.07.2002)
International Patent Classification (IPC) or national classification and IPC C12P 33/10		
Applicant SCHERING AKTIENGESELLSCHAFT		

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.
2. This REPORT consists of a total of <u>12</u> sheets, including this cover sheet.
☒ 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).
These annexes consist of a total of <u>12</u> sheets.
3. This report contains indications relating to the following items:
I ☒ Basis of the report
II ☐ Priority
III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV ☒ Lack of unity of invention
V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI ☐ Certain documents cited
VII ☐ Certain defects in the international application
VIII ☐ Certain observations on the international application

Date of submission of the demand 19 February 2004 (19.02.2004)	Date of completion of this report 22 November 2004 (22.11.2004)
Name and mailing address of the IPEA/EP	Authorized officer
Facsimile No.	Telephone No.

Form PCT/IPEA/409 (cover sheet) (July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/EP2003/008111

I. Basis of the report

1. With regard to the elements of the international application:*

- ☐ the international application as originally filed
- ☒ the description:
pages 1-5, 7-10, 12-33, as originally filed
pages _____, filed with the demand
pages 6, 11, filed with the letter of 23 February 2004 (23.02.2004)
- ☒ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 1-27, filed with the letter of 22 October 2004 (22.10.2004)
- ☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

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 international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the 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/fig _____

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, as indicated in the Supplemental Box (Rule 70.2(c)).**

* 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 (Rule 70.16 and 70.17).

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

I. Basis of the report

1. This report has been drawn on the basis of *(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 the report since they do not contain amendments)*:

Continuation of: I.6

The amendments and corrections submitted with the letters of 19 February 2004 and 22 October 2004 are allowable under PCT Article 34(2)(b).

Priority

The present application is fully supported by the content of each of the priority documents DE 102 33 723.3 of 27 July 2002 and US 60/402,953 of 14 August 2002.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

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IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☒ not complied with for the following reasons:

See the Supplemental Box.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☒ all parts.
- ☐ the parts relating to claims Nos. _____

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

Lack of unity of invention

This Authority has found that the international application contains several inventions or groups of inventions which are not so linked as to form a single general inventive concept (PCT Rule 13.1), namely:

I: Claims 1, 2, 8-10 in part:

Microbiological method for the production of compounds of formula 4,B by simultaneous hydroxylation and oxidation of compounds of formula 3,A using a microorganism selected from the groups consisting of *Aspergillus sp.*, *Beauveria sp.*, *Glomerella sp.*, *Gnomonia sp.*, *Haplosporella sp.* and *Rhizopus sp.*

II: Claims 3, 5, 8-10 in part:

Microbiological method for the production of compounds of formula 4,B by hydroxylation of compounds of formula 3,A using a first microorganism selected from the groups consisting of *Aspergillus sp.*, *Beauveria sp.*, *Gibberella sp.*, *Glomerella sp.*, *Gnomonia sp.*, *Metarrhizium sp.*, *Nigrospora sp.*, *Rhizopus sp.* and *Verticillium sp.* The intermediate product of formula C so formed is oxidized to the end product 4,B in a second method step using a second microorganism, selected from the groups consisting of *Bacillus sp.*, *Mycobacterium sp.*, *Nocardia sp.* and *Pseudomonas sp.*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

III: Claims 6, 7, 8-10 in part:

Microbiological method for the production of compounds of formula 4,B by hydroxylation of compounds of formula D using a microorganism selected from the groups consisting of *Beauveria sp.*, *Curvularia sp.*, *Gibberella sp.*, *Glomerella sp.*, *Gnomonia sp.*, *Haplosporella sp.*, *Helicostylum sp.*, *Nigrospora sp.* and *Syncephalastrum sp.*

IV: Claims 11-27:

- Claims 11-20: compounds of formulae 8, 10 and 12.
- Claims 21 and 22: intermediate product of formula 6, which can be used for the production of compounds of formula 8.
- Claim 23: method for the production of compounds of formula 10, starting from compounds of formula 4,B.
- Claim 24: method for the production of compounds of formula 12, starting from compounds of formula 4,B, via compounds of formula 10.
- Claim 25: method for the production of compounds of formula 8, starting from compounds of formula 4,B, via compounds of formula 6.
- Claim 26: pharmaceutical use of compounds 8, 10 and 12.
- Claim 27: pharmaceutical preparations containing compounds 8, 10 and 12.

The reasons are as follows:

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

The present application lacks unity of invention within the meaning of PCT Rule 13. Four different inventions have been identified, each being characterized by an individual "special technical feature", and no technical relationship exists between the four inventions. PCT Rule 13.1 states that "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 a technical relationship involving common technical features must exist among those inventions. The expression "special technical features" therefore means those technical features that define a contribution which each of the claimed inventions makes over the prior art.

The problem to be solved by inventions 1 to 3 is that of providing a microbiological method for the production of (known) compounds of formula 4,B. This problem was solved in three different ways according to inventions 1, 2 and 3.

Invention 1 is characterized in that the hydroxylation and oxidation are carried out using a single microorganism selected from special groups in such a way that product 4,B is obtained from starting material 3,A.

Invention 2 is characterized in that the hydroxylation of the substance 3,A to an intermediate product C is carried out in a first step using a first selected microorganism, and the subsequent oxidation of the intermediate product C to the end product 4,B is carried out in a second step using a second selected microorganism.

Invention 3 describes the hydroxylation of a further intermediate product D to the end product 4,B using selected microorganisms.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

The groups of microorganisms mentioned in inventions 1, 2 and 3 are not identical, but overlap. A person skilled in the art must therefore develop three entirely different methods for inventions 1, 2 and 3 as regards starting products, type of reaction (hydroxylation and/or oxidation) and selection of the microorganisms.

Invention 4 relates to compounds of formulae 8, 10 and 12, the use of said compounds in pharmacy, an intermediate product 6 for the production of one of these compounds (compound 8), and specially adapted methods for the production of compounds 8, 10 and 12. The problem addressed by invention 4 is therefore that of providing compounds which are insensitive to reduction with 5-alpha-reductase. The development of the compounds claimed in invention 4 involves a totally different problem/solution concept, which is not linked with the problems of inventions 1, 2 and 3 (production of compounds 4,B by a microbial method) or their solutions, because compounds 4,B are not claimed and therefore do not appear to be novel.

The different problems addressed by the respective inventions 1, 2, 3 and 4 and/or the resulting different solutions represent four different technical approaches which are defined by different technical features and are therefore not so linked as to represent a single inventive concept. Consequently, the present inventions solve different problems in technically different ways, and therefore each invention has its own concept and each is characterized by a different special technical feature which, in itself, makes an independent contribution over the prior art.

Consequently, the above-mentioned groups of claims lack unity of invention within the meaning of PCT Rule 13.1

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

and 13.2, as regards the special technical features and the solved problems.

However, since the applicant has paid the additional examination fees, all 4 inventions have been examined.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP 03/08111

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)	Claims	1-27	YES
	Claims		NO
Inventive step (IS)	Claims	1-27	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-27	YES
	Claims		NO

2. Citations and explanations

1) . The present application:Invention I: claims 1, 2, 8-10 in part:

Microbiological method for the production of compounds of formula 4,B by simultaneous hydroxylation and oxidation of compounds of formula 3,A using a microorganism selected from the groups consisting of *Aspergillus sp.*, *Beauveria sp.*, *Glomerella sp.*, *Gnomonia sp.*, *Haplosporella sp.* and *Rhizopus sp.*

Invention II: claims 3, 5, 8-10 in part:

Microbiological method for the production of compounds of formula 4,B by hydroxylation of compounds of formula 3,A using a first microorganism selected from the groups consisting of *Aspergillus sp.*, *Beauveria sp.*, *Gibberella sp.*, *Glomerella sp.*, *Gnomonia sp.*, *Metarrhizium sp.*, *Nigrospora sp.*, *Rhizopus sp.* and *Verticillium sp.* The intermediate product of formula C so formed is oxidized to the end product 4,B in a second method step using a second microorganism, selected from the groups consisting of *Bacillus sp.*, *Mycobacterium sp.*, *Nocardia sp.* and *Pseudomonas sp.*

Invention III: claims 6, 7, 8-10 in part:

Microbiological method for the production of compounds of formula 4,B by hydroxylation of compounds of formula D using a microorganism selected from the groups consisting of *Beauveria sp.*, *Curvularia sp.*, *Gibberella sp.*, *Glomerella sp.*, *Gnomonia sp.*, *Haplosporella sp.*, *Helicostylum sp.*, *Nigrospora sp.* and *Syncephalastrum sp.*

Invention IV: claims 11-27:

Compounds which are insensitive to reduction with 5-alpha-reductase and inhibit 11-hydroxylase, and intermediate products for said compounds and the pharmaceutical use:

- Claims 11-20: compounds of formulae 8, 10 and 12.
- Claims 21 and 22: intermediate product of formula 6, which can be used for the production of compounds of formula 8.
- Claim 23: method for the production of compounds of formula 10, starting from compounds of formula 4,B.
- Claim 24: method for the production of compounds of formula 12, starting from compounds of formula 4,B, via compounds of formula 10.
- Claim 25: method for the production of compounds of formula 8, starting from compounds of formula 4,B, via compounds of formula 6.
- Claim 26: pharmaceutical use of compounds 8, 10 and 12.
- Claim 27: pharmaceutical preparations containing compounds 8, 10 and 12.

- 2.) The international search report citations are denoted by the following abbreviations:

- D1: WO-A-97/21830 (AKZO NOBEL NV; WIERSMA MARTEN (NL); MEIJDEN PIETER V D (NL)) 19 June 1997 (1997-06-19)
- D2: TAN L ET AL: "INTERACTIONS OF STEROIDS AND FUNGI. 11 ALPHA-HYDROXYLATION AND DEGRADATION OF PROGESTERONE-4-C BY A CELL-FREE PREPARATION FROM ASPERGILLUS OCHRACEUS" JOURNAL OF STEROID BIOCHEMISTRY, PERGAMON PRESS PLC, GB, Vol. 1, No. 3, 1 September 1970 (1970-09-01), pages 221-227, XP000671122 ISSN: 0022-4731
- D3: SHIBAHARA M ET AL: "MICROBIAL HYDROXYLATIONS V. 11 ALPHA-HYDROXYLATION OF PROGESTERONE BY CELL-FREE PREPARATIONS OF ASPERGILLUS OCHRACEUS" BIOCHIMICA ET BIOPHYSICA ACTA, AMSTERDAM, NL, Vol. 202, 1970, pages 172-179, XP009023368 ISSN: 0006-3002
- D4: WO-A-02/059139 (NUBBEMEYER REINHARD; BOHLMANN ROLF (DE); SCHERING AG (DE); ZOPF DIETE) 1 August 2002 (2002-08-01)
- D5: WO-A-99/13812 (POPULATION COUNCIL INC) 25 March 1999 (1999-03-25)
- D6: WO-A-2004/011008 (SCHERING AG) 5 February 2004 (2004-02-05).

D4 is a "P" document, which was published between the first priority date and the second priority date. Since the content of the earlier priority document fully supports the present application, D4 is not relevant and is therefore disregarded in the substantive examination in the international phase.

D6 is classified as a "T" document, that is, it was published after the filing date of the present application. For this reason, D6 is not used in the phase of the international preliminary examination.

3). Brief discussion of the content of the prior art documents:

D1 and D2 each describe a method for the *in vitro* transformation of a steroid into the corresponding 11-alpha-OH derivative using, *inter alia*, microorganisms of the genera *Aspergillus* and *Rhizopus*. The structural difference from the compounds disclosed in the present application is that there is no substituent on position 7. Only an 11-alpha-hydroxylation is carried out, and no simultaneous or subsequent oxidation is carried out on position 17.

D3 also describes an 11-alpha hydroxylation using *Aspergillus*, starting from progesterone and 19-nortestosterone, and therefore describes the first step of invention II. There are structural differences from the compounds described in the present application.

D5 describes the insensitivity of 7-alpha-modified androgens to 5-alpha-reductase (see page 6, lines 19 to 23 and the bottom of page 3 of the present description) and the pharmaceutical use thereof in hormone therapy in the male.

However, D5 does not describe any 11-beta-halogen substituents.

4). Novelty and inventive step for inventions I-IV (PCT Article 33(1) to (3)):

Invention I - claims 1, 2, 8-10 in part:

Simultaneous 11-alpha hydroxylation and oxidation on position 17 of a steroid with the microorganisms used in invention I is neither described nor suggested in the prior art. Novelty and inventive step can

therefore be acknowledged for claims 1, 2 and 8-10 in part.

Invention II - claims 3, 5, 8-10 in part:

This invention concerns the same reaction as in invention I, but in two steps and using 2 microorganisms. Although the first step and the use of the microorganisms *Aspergillus* and *Rhizopus* are known (see D1 to D3), there is no hint in the prior art of the second reaction step and the microorganisms used therein. Novelty and inventive step can therefore be acknowledged.

Invention III - claims 6, 7, 8-10 in part:

Invention III relates to the hydroxylation on position 11-beta of a steroid skeleton. Reactions of this kind on structurally very similar steroids are known from D1 to D3, but the microorganisms used as per the invention are neither described nor suggested in the prior art.

The subject matter claims 6, 7 and 8-10 in part is therefore novel and inventive.

Invention IV - claims 11-27:

The 11-beta-halogen steroids mentioned in these claims are not described in the prior art and therefore appear to be novel. Consequently, novelty can be acknowledged for claims 11-27.

The problem addressed by invention IV can be defined, according to the bottom of page 3 to the top of page 4 and page 21, lines 11 to 20 of the present description, as that of providing compounds which are insensitive to reduction with 5-alpha-reductase and inhibit 11-hydroxylase, and intermediate products for

said compounds and the pharmaceutical use of said compounds.

It is already known from D5 that 7-alpha-modified androgens are resistant to 5-alpha-reductase, but there is no hint in D5 of inhibition of 11-hydroxylase. The difference between D5 and the compounds as per the application consists in the substitution on position 11-beta with halogen, which thereby surprisingly results in inhibition of the 11-hydroxylase. The problem addressed by the invention was thereby solved and an inventive step can be acknowledged.

5). Industrial applicability (PCT Article 33(1) to (3)):

The subject matter of all 4 inventions, that is, of claims 1-27, is industrially applicable.