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A B O G A D O S

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2788/PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

E.

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Radicacion : 05022397 00000003

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Tramite : 011 PCT-PATENT J79 FASE NACI 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. 05.022.397

Solicitud de Patente a nombre de
Janssen Pharmaceutica N.V.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 94-76, of. 305, obrando como apoderada de la sociedad Janssen Pharmaceutica N.V., domiciliada en Beerse, Belgica, solicitante de la patente de la referencia, en respuesta al oficio No. 12742 notificado por fijación en lista el día 6 de mayo de 2005, me permito presentar :

1. Copia del examen preliminar internacional junto con su traducción al español.
2. Documento (1) en que consta la cesión del derecho a la patente otorgado por los inventores a favor de mi mandante.

Sobre el particular, es importante resaltar que de conformidad con las normas legales vigentes, artículo 1 de la Resolución 210 de 2001, expedida por el Superintendente de Industria y Comercio y artículo 2 de la Convención de la Haya, el documento en inglés que se pretenda aportar como parte de los trámites de propiedad industrial ante la Superintendencia de Industria y Comercio no requieren traducción. Por otro lado, la legalización consular y/o diplomática de los documentos expedidos en el extranjero no es necesaria. Por lo tanto, el documento de cesión anexo a este memorial es válidamente presentado en idioma inglés y con la correspondiente Apostilla.

Al respecto, me permito aclarar que debido a un error involuntario el documento de cesión se otorgó por siete inventores y uno por cinco, que son los que figuran en el panfleto de publicación. En consecuencia, presento nuevo documento de cesión en el cual se incluyen los cinco inventores que coinciden con los de la publicación.

Espero con esto haber dado cabal cumplimiento a lo solicitado por ese despacho y de conformidad con lo indicado en los artículos 3º, inciso 3; 35, inciso 2 y 59, inciso 2 del CCA, al analizar este memorial, atentamente ruego se traten todas las cuestiones planteadas con motivo del mismo.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68228
Cód. 5376

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TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

INFORME EXAMEN PRELIMINAR INTERNACIONAL (PCT artículo 36 y regla 70)

Referencia del solicitante o agente PRD-26 PCT	Ver notificación de la transmisión del examen preliminar Internacional (formato PCT/IPEA/416) PARA PROSEGUIR	
No. Solicitud Internacional PCT/US 03/25782	Fecha de presentación Internacional (día/mes/año) 15/08/2003	Fecha de prioridad (día/mes/año) 16/08/2002
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C07D401/12		
Solicitante JANSSEN PHARMACEUTICA N.V.		

1. Este examen preliminar internacional ha sido preparado por esta Autoridad encargada del Examen Preliminar Internacional y es transmitida al solicitante de acuerdo con el artículo 36.

2. Este INFORME consiste de un total de 6 páginas, incluyendo esta hoja.

___ Este Informe también está acompañado por ANEXOS, esto es hojas de la descripción, reivindicaciones y/o dibujos, los cuales han sido modificados y son la base para este informe y/o hojas que contienen rectificaciones presentadas ante esta Autoridad (ver Regla 70.16 y Sección 807 de las Instrucciones Administrativas bajo el PCT).

Estos anexos consisten en un total de ___ hojas.

3. Este Informe contiene indicaciones que se relacionan con los siguientes puntos:

- I. ☒ Base del Informe
- II. ☐ Prioridad
- III. ☒ El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación Industrial
- IV. ☐ Falta de unidad de invención
- V. ☒ Declaración motivada bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración
- VI. ☐ Ciertos documentos citados
- VII. ☐ Ciertos defectos en la solicitud internacional
- VIII. ☐ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda 05/03/2004	Fecha en que se completó este informe 08/11/2004
Nombre y dirección de la autoridad encargada del examen preliminar internacional: Oficina de Patentes Europea D-80298 Munich Tel. +49 89 2399-0 Tx: 523656 epmu d Fax: +49 89 2399 -4465	Oficial autorizado Schuemacher, A Teléfono: +49 89 2399-7818

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**

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I. BASE DEL INFORME

1. En relación con los elementos de la solicitud internacional (las hojas de reemplazo que han sido suministradas a la oficina receptora como respuesta a la invitación bajo el artículo 14 serán referidas como "presentadas originalmente" y no están anexas a este informe debido a que no contienen modificaciones (Regla 70.16 y 70.17)):

CAPITULO DESCRIPTIVO, PAGINAS:

1-145 Como fueron presentadas originalmente

REIVINDICACIONES, No.:

1-89 Como fueron presentadas originalmente

2. En relación con el idioma, todos los elementos marcados anteriormente fueron suministrados a esta Autoridad en el idioma en que la solicitud internacional fue presentada, a menos que se indique lo contrario bajo este punto.

Estos elementos fueron suministrados o estaban disponibles para esta autoridad en el siguiente idioma, el cual es:

- ☐ El idioma de la traducción aportada a efectos de la búsqueda internacional (bajo la Regla 23.1(b))
☐ El idioma de publicación de la solicitud internacional (bajo la Regla 48.3(b))
☐ El idioma de la traducción suministrada para efecto del examen preliminar internacional (bajo la Regla 55.2 y/o 55.3)

3. Respecto a cualquier secuencia nucleótido y/o aminoácido revelado en la solicitud internacional, el examen preliminar internacional fue llevado a cabo con base en la lista de secuencias:

- ☐ Contenidas en la solicitud internacional de forma escrita
☐ Presentadas junto con la solicitud internacional en forma legible por computador
☐ Aportada posteriormente a esta Autoridad en forma escrita
☐ Suministrada posteriormente a esta Autoridad en forma legible por computador
☐ La declaración de que la lista de secuencias aportada posteriormente en forma escrita no va más allá que lo revelado en la solicitud internacional como fue presentada.
☐ La declaración de que la información inscrita en forma legible por computador es idéntica a la lista de secuencias en forma escrita aportada.

4. Las modificaciones han resultado en la cancelación de:

- ☐ El capítulo descriptivo páginas:
☐ Las reivindicaciones Nos.:
☐ Los dibujos hojas:

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5. ☐ Este informe ha sido establecido como si (algunas de) las modificaciones no hubieran sido efectuadas debido a que se ha considerado que van más allá de lo reivindicado mediante la solicitud internacional.

(A cualquier hoja de reemplazo que contenga dichas modificaciones debe hacerse referencia bajo el punto 1 y ser anexada a este informe)

6. Observaciones adicionales, son necesarias:

III. El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial

1. La pregunta de si la presente invención reivindicada aparenta ser novedosa, si tiene altura inventiva, o es aplicable industrialmente no ha sido examinada en relación a:

☐ toda la solicitud internacional

☒ reivindicaciones Nos. 52 y 69

Porque:

☒ dicha solicitud internacional, o dichas reivindicaciones Nos. 56 y 69 se relacionan a la siguiente materia, la cual no requiere ser objeto del examen preliminar internacional (especificar):

☐ la memoria descriptiva, las reivindicaciones, o los dibujos (indicar abajo los elementos específicos) o las reivindicaciones Nos. son tan confusas que ninguna opinión sustancial pudo ser establecida (especificar):

☐ las reivindicaciones, o dichas reivindicaciones Nos. no están soportadas adecuadamente por la memoria descriptiva, lo cual no permite que una opinión significativa sea formada.

☐ las reivindicaciones Nos. no han sido objeto de búsqueda internacional.

2. Un examen preliminar internacional significativo no pudo llevarse a cabo debido a que la lista de secuencias nucleótido y/o aminoácido no cumple con los estándares provistos por el Anexo C de las Instrucciones Administrativas:

☐ la forma escrita no ha sido suministrada o no cumple con los estándares.

☐ la forma legible por computador no ha sido suministrada o no cumple con los estándares.

V. Declaración motivada, bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación industrial; citas y explicaciones que sustentan dicha declaración

Declaración

Novedad	SI: Reivindicaciones
	NO: Reivindicaciones 1-69
Nivel inventivo	SI: Reivindicaciones
	NO: Reivindicaciones 1-69

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Aplicación Industrial SI: Reivindicaciones 1-55
 NO: Reivindicaciones

2. CITACIONES Y EXPLICACIONES

Ver hoja anexa

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**

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Re-Item III

No establecimiento de opinión con respecto a novedad, nivel inventivo y aplicabilidad Industrial.

Las reivindicaciones 56-69 relacionan la materia objeto considerada por esta Autoridad a ser cubierta por las provisiones de la Regla PCT 67.1(iv). Por lo tanto, no se formulará ninguna opinión con respecto a la aplicabilidad industrial de la materia objeto de estas reivindicaciones (Artículo 34(a)(I) PCT).

Re-Item V

Declaración razonada bajo la Regla 66.2(a)(II) con respecto a la novedad, nivel inventivo o aplicabilidad Industrial; citas y explicaciones que sustentan tal declaración.

La referencia se hace a los siguientes documentos:

D1: Bioorganic & Medicinal Chemistry Letters (1996), 6(21), 2601- 2606

D2: Journal of Medicinal Chemistry (1998), 41(14), 2492-2502

D3: WO-A-9409029

D4: Heterocycles (2001), 55(7), 1329-1345

D5: Bioorganic & Medicinal Chemistry Letters (2000), 10(4), 385-389

D6: Bioorganic & Medicinal Chemistry Letters (2001), 11(19), 2619-2622

D7: Journal of Medicinal Chemistry (1997), 40(26), 4308-4318

D8: Thrombosis and Haemostasis, Stuttgart, De (1993), 70(6), 1030-1036

D9: Current Pharmaceutical Design, (1997), 3,545-584

D10: Journal of Medicinal Chemistry (1987), 30, 999-1003

D11: J. of Chem. Soc., Perkin Transactions 1, (1994),20,2993-2999

D12: US-A-4289772

D13: US-B1-6211191

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1. Novedad, Artículo PCT 33(2):

Con respecto al arte previo divulgado en los documentos citados anteriormente la materia objeto de la presente solicitud, i.e los compuestos de piperidinil, no parecen llenar los requerimientos de novedad, cf. Artículo PCT 33(2):

Por lo tanto el solicitante define en la descripción, los términos "alquil", "alquenil" y "alquiniil" como que están opcionalmente sustituidos, los documentos D1-D5 y D10-D12 describen los siguientes compuestos comprendidos en las reivindicaciones actuales:

- en D1: compuestos 5c, 5d, 8c, y 8d
- en D2: compuestos preparados de acuerdo al esquema 1 y compuestos de la tabla 2
- en D3: compuestos III y IV en la reivindicación 6; compuestos 19,20 y 9a en el ejemplo 3
- en D4: compuestos 12 y 21
- en D5: compuestos 9a en el esquema 1
- en D10: compuesto 29 en la tabla 1
- en D11: compuestos 17 y 18 en el esquema 4
- en D12: compuestos de fórmula (IX) en la columna 6-7

La materia objeto de la presente solicitud ha sido anticipada por los documentos D1-D5 y D10-D12 y por lo tanto, se consideran que no reúnen los requerimientos del Artículo 33(2) PCT.

2. Nivel Inventivo, Artículo 33(3) PCT:

El solicitante parece tener por si mismo la tarea de hacer disponibles además inhibidores selectivos de integrina $\alpha\beta 3$ o $\alpha\beta 5$, ver p.2, 1.8-10.

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El documento D13 se considera como el más cercano del arte previo por lo tanto divulga compuestos que se enlazan selectivamente a los receptores de integrina $\alpha\beta3$ o $\alpha\beta5$.

Los compuestos reivindicados difieren de los compuestos de D13 teniendo en cuanto a la mitad obligatoria piperidin-4-il; por ejemplo, el compuesto 4-13 en la columna 50 de D13 difiere solamente en cuanto a la presencia de un tetrahidro-2-oxo-pirimidin-1-il en vez de una mitad piperidin-4-il y los compuestos 2-10 y 2-11 en la columna 43 de D13 difieren solamente por el reemplazo del piperidin-4-il por una mitad 2-oxo-piperidin-1-il.

De acuerdo con la descripción de D13 (columnas 25-27) la mitad tetrahidro-2-oxo-pirimidinil se puede reemplazar -sin pérdida de la actividad biológica- por algún nitrógeno contenido en los heterociclos entre ellos una mitad piperidin-4-il.

Por lo tanto, la presente solicitud podría ser vista como una selección de la divulgación genérica de inhibidores de integrina $\alpha\beta3$ o $\alpha\beta5$ de D13, donde la selección consistiría en escoger una mitad de piperidin-4-il entre algunas posibilidades para el grupo Z.

El problema que subraya la presente solicitud tiene, por lo tanto, tiene que ser visto con la provisión de los compuestos que tienen un efecto ventajoso no esperado de acuerdo con el arte previo D13.

En la presente solicitud p.139-143, los datos farmacológicos muestran que los compuestos reivindicados, en realidad, se unen mejor a los receptores de integrina $\alpha\beta3$ o $\alpha\beta5$ que a los $\alpha_{IIb}\beta3$, pero no hay evidencia probada que ellos posean un efecto mejorado no esperado comparado con los compuestos de D13.

Por lo tanto, no se puede reconocer un nivel inventivo como no sea el mostrado por la información apropiada que la materia objeto reivindicada incluya cualquier efecto no esperado o sorprendente.

No se pueden considerar como satisfechos los requerimientos del Artículo 33(3) PCT.

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3.

Para la evaluación de las reivindicaciones actuales 56-58 a la pregunta si ellas tienen aplicabilidad industrial, no existen criterios unificados en el PCT de Los Estados Contratantes. La patentabilidad puede ser dependiente de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como aplicable industrialmente la materia objeto de las reivindicaciones para el uso de un compuesto en un tratamiento médico, pero puede permitir, sin embargo, reivindicar un compuesto conocido para primer uso en tratamiento médico y el uso de tal compuesto para la fabricación de un medicamento para un nuevo tratamiento médico

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

RECD 8 NOV 2004

WIPO PCT

Applicant's or agent's file reference PRD-26 PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/16)	
International application No. PCT/US 03/25782	International filing date (day/month/year) 15.08.2003	Priority date (day/month/year) 18.08.2002	
International Patent Classification (IPC) or both national classification and IPC C07D401/2			
Applicant JANSSEN PHARMACEUTICA N.V.			
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 58. 2. This REPORT consists of a total of 6 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 sheets.			
3. This report contains indications relating to the following items: I ☒ Basis of the opinion 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 Rule 68.2(a)(II) 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 05.03.2004		Date of completion of this report 08.11.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-60260 Munich Tel. +49 89 2369 - 0 Fax: 825668 apru d Fax: +49 89 2369 - 4468		Authorized Officer Schuermacher, A Telephone No. +49 89 2369-7818 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US 03/25782**

1. 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

1-145 as originally filed

Claims, Numbers

1-69 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)).

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

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US 03/25782**

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

1. 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. 56-69

because:

☒ the said international application, or the said claims Nos. 56-69 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ 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 said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

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	
	No: Claims	1-69
Inventive step (IS)	Yes: Claims	
	No: Claims	1-69
Industrial applicability (IA)	Yes: Claims	1-56
	No: Claims	

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET International application No. PCT/US 03/25782

Re Item III

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

Claims 56-69 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: Bioorganic & Medicinal Chemistry Letters (1996), 6(21), 2601-2606
- D2: Journal Of Medicinal Chemistry (1998), 41(14), 2492-2502
- D3: WO-A-9409029
- D4: Heterocycles (2001), 55(7), 1329-1345
- D5: Bioorganic & Medicinal Chemistry Letters (2000), 10(4), 385-389
- D6: Bioorganic & Medicinal Chemistry Letters (2001), 11(19), 2619-2622
- D7: Journal Of Medicinal Chemistry, (1997), 40(28), 4308-4318
- D8: Thrombosis And Haemostasis, Stuttgart, De (1993), 70(6), 1030-1036
- D9: Current Pharmaceutical Design, (1997), 3, 545-584
- D10: Journal Of Medicinal Chemistry, (1987), 30, 999-1003
- D11: J. of Chem. Soc., Perkin Transactions 1, (1994), 20, 2993-2999
- D12: US-A-4289772
- D13: US-B1-6211191

1. Novelty, Article 33(2) PCT:

With regard to the prior art disclosed in the documents cited above the subject-matter of the present application, i.e. the piperidinyl compounds, does not appear to fulfil the requirements of novelty, cf. Article 33(2) PCT:

Since the Applicant defines in the description, the terms "alkyl", "alkenyl" and "alkynyl" as being optionally substituted, the documents D1-D5 and D10-D12 describe the following compounds comprised by the present claims:

-in D1: compounds 5c, 5d, 6c and 8d

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US 03/25782

- In D2: compounds prepared according to scheme 1 and compounds of table 2
- In D3: compounds III and IV in claim 6 ; compounds 19, 20 and 9a in example 3
- In D4: compounds 12 and 21
- In D5: compound 9a in scheme 1
- In D10: compound 29 in Table I
- In D11: compounds 17 and 18 in scheme 4
- In D12: compounds of formula (IX) on column 6-7

The subject-matter of the present application has been anticipated by the documents D1-D5 and D10-D12 and hence, the requirements of Article 33(2) PCT are not considered to be met.

2. Inventive step, Article 33(3) PCT:

The Applicant appears to have set himself the task of making available further selective $\alpha v\beta 3$ or $\alpha v\beta 5$ Integrin inhibitors, see p.2, 1.8-10.

Document D13 is considered as the closest prior art document since it discloses compounds that bind selectively to the $\alpha v\beta 3$ or $\alpha v\beta 5$ Integrin receptors.

The claimed compounds differ from the compounds of D13 on account of the obligatory piperidin-4-yl moiety; for example, the compound 4-13 on column 50 of D13 differs only on account of the presence of a tetrahydro-2-oxo-pyrimidin-1-yl instead of a piperidin-4-yl moiety and compounds 2-10 and 2-11 on column 43 of D13 differ only because of the replacement of the piperidin-4-yl by a 2-oxo-piperidin-1-yl moiety.

According to the description of D13 (column 25-27) the tetrahydro-2-oxo-pyrimidinyl moiety can be replaced- without loss of biological activity- by several nitrogen containing heterocycles among them a piperidin-4-yl moiety.

Consequently, the present application could be seen as a selection of the generic disclosure of $\alpha v\beta 3$ or $\alpha v\beta 5$ Integrin inhibitors of D13, wherein the selection would consist in choosing a piperidin-4-yl moiety among the several possibilities for the group Z.

The problem underlying the present application has therefore to be seen the provision of compounds having unexpected advantageous effect with regard to the prior art D13.

In the present application p.139-143, the pharmacological data show that the claimed compounds indeed bind better to the $\alpha v\beta 3$ or $\alpha v\beta 5$ than to $\alpha_{\text{L}}\beta 3$ Integrin receptor, but there is no evidence proving that they possess an unexpected improved effect compared to the compounds of D13.

Thus, an inventive step cannot be recognized as it has not been shown by appropriate information that the claimed subject-matter includes any unexpected or surprising effects.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US 03/25782

The requirements of Article 33(3) PCT cannot be considered to be satisfied.

3.

For the assessment of the present claims 56-68 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

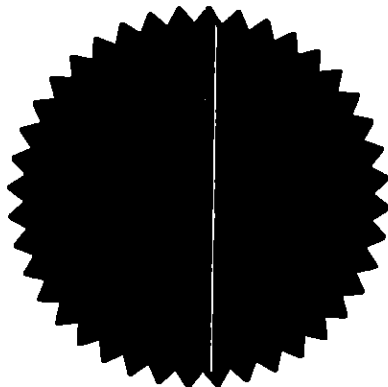
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
CHRISTINA A CLICKNER
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
CHRISTINA A CLICKNER, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 23RD DAY OF AUGUST 2005
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A236301
9. SEAL/STAMP:
10. SIGNATURE



Johnson & Johnson

**OFFICE OF
GENERAL COUNSEL**

TELE: 844-491

CABLE: AQUEDUS

NEW BRUNSWICK
NEW JERSEY
TEL: 732-524-0452

REPLY TO:

**JOHNSON & JOHNSON
INTERNATIONAL PATENT LAW DIVISION
ATTENTION: UNDERSIGNED
P.O. BOX 1222
NEW BRUNSWICK, N.J. 08903, U.S.A.**

AUGUST 22, 2005

**New Jersey Division Of Revenue
Business Services Bureau
P.O. Box 452
Trenton, New Jersey 08625-0452**

Re: PRD 26 COLOMBIA

Dear Sir/Madam:

**Would you please be kind enough to legalize the attached document(s) (VIA APOSTILLE)
and return same to THE MESSENGER.**

If you have any questions at all, please feel free to contact me.

Thank you for your cooperation in this matter.

Very truly yours,

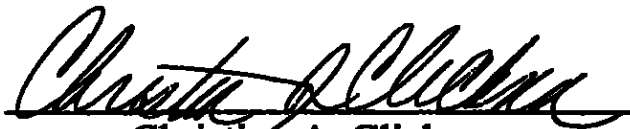
**Christina A. Clickner
Patent Specialist
(732) 524-2832**

**Encl.: (1) ASSIGNMENT
Check: \$40.00 - EXPEDITED
PLEASE RETURN TO THE MESSENGER**

PRD 26 CO

CERTIFICATION

I hereby certify that I have compared the attached document with the original, and that such said document is a true copy of the original Assignment document as filed in the U.S. Patent Office in connection with USSN 10/641,964 filed AUGUST 15, 2003.



Christina A. Clickner

(Notary Public of New Jersey)

My Commission Expires:

March 2, 2010

256
254DOCKET NO. PRD-26
Joint Inventors

A S S I G N M E N T

Serial No. 10/641,964
Filed August 15, 2003

WHEREAS, Bart De Corte, William A. Kinney, Bruce E. Maryanoff, Shyamali Ghosh, and Li Liu, residing at 1590 Winding Road, South Hampton, PA 18966; 16 Thompson Mill Road, Newtown, PA 18940; 4029 Devonshire Drive, Forest Grove, PA 18922; 906 Patriot Lane, Norristown, PA 19403; and 271 Fox Chase Lane, Doylestown, PA 18901; respectively (hereinafter called "Assignors"), have made certain new and useful inventions or discoveries relating to

PIPERIDINYL COMPOUNDS THAT SELECTIVELY BIND INTEGRINS

for which they have on the 15th day of August, 2003 filed an application for Letters Patent of the United States; and

WHEREAS, Janssen Pharmaceutica, N.V., a corporation of Belgium, (hereinafter called "Assignee"), is desirous of acquiring Assignors' entire right, title, and interest therein:

NOW, THEREFORE, BE IT KNOWN that for and in consideration of the sum of One Dollar and other valuable considerations to them moving, the receipt of which is hereby acknowledged, Assignors have sold, assigned, and transferred, and do hereby sell, assign and transfer unto said Assignee their entire right, title and interest in and to all said inventions and discoveries disclosed in said application whose identification above by serial number and filing date, when available is hereby authorized, and in and to said application, all substitutions, divisions, and continuations thereof, and in and to all Letters Patent, United States and foreign, that may be granted for said inventions and discoveries, and in and to all extensions, renewals, and reissues thereof, the same to be held and enjoyed by said Assignee, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by Assignors if this Assignment and sale had not been made;

25 20

And Assignors hereby authorize and request the Commissioner of Patents of the United States to issue said Letters Patent in accordance with this Assignment;

And for the consideration aforesaid, Assignors covenant and agree with said Assignee that he has a full and unencumbered title to the inventions and discoveries above described and hereby assigned, which title they warrant unto said Assignee, its successors and assigns;

And for the consideration aforesaid, Assignors further covenant and agree that they will, whenever requested, but without cost to them promptly communicate to said Assignee or its representatives any facts known to them relating to said inventions and discoveries, testify in any interference or legal proceedings involving said inventions and discoveries, and execute any additional papers that may be necessary to enable said Assignee or its representatives, successors, nominees, or assigns to secure full and complete protection for the said inventions and discoveries or that may be necessary to vest in said Assignee the complete title to the said inventions and discoveries and patents hereby conveyed and to enable it to record said title.

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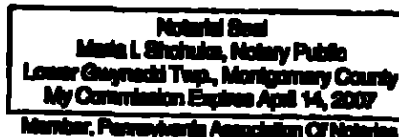
IN TESTIMONY WHEREOF, Assignors have hereunto set
their hands and seals this 17th day of November, 2003

B. De Corte (L.S.)
Bart De Corte

STATE OF *Pennsylvania*)
) ss.
COUNTY OF *Montgomery*)

BE IT REMEMBERED, That on this 17th day of
NOVEMBER, 2003, before me, a Notary Public, personally
appeared Bart De Corte, who I am satisfied is the person named
in and who executed the foregoing instrument in my presence, and
I having first made known to him/her the contents thereof,
he/she did acknowledge that he/she signed, sealed, and delivered
the same as his/her voluntary act and deed for the uses and
purposes therein expressed.

Maria I. Shchuka
Notary Public



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IN TESTIMONY WHEREOF, Assignors have hereunto set
their hands and seals this 10th day of November, 2003

William A. Kinney (L.S.)
William A. Kinney

STATE OF Pennsylvania)
) ss.
COUNTY OF Montgomery)

BE IT REMEMBERED, That on this 10th day of
NOVEMBER, 2003, before me, a Notary Public, personally
appeared William A. Kinney, who I am satisfied is the person
named in and who executed the foregoing instrument in my
presence, and I having first made known to him/her the contents
thereof, he/she did acknowledge that he/she signed, sealed, and
delivered the same as his/her voluntary act and deed for the
uses and purposes therein expressed.

Maria I. Skoluba
Notary Public

Notarial Seal
Maria I. Skoluba, Notary Public
Lower Gwynedd Twp., Montgomery County
My Commission Expires April 14, 2007
Member, Pennsylvania Association Of Notaries

253

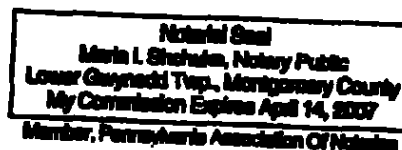
IN TESTIMONY WHEREOF, Assignors have hereunto set
their hands and seals this 11th day of Nov, 2003

Bruce E. Maryanoff (L.S.)
Bruce E. Maryanoff

STATE OF Pennsylvania)
) ss.
COUNTY OF Montgomery)

BE IT REMEMBERED, That on this 11th day of
NOVEMBER, 2003, before me, a Notary Public, personally
appeared Bruce E. Maryanoff, who I am satisfied is the person
named in and who executed the foregoing instrument in my
presence, and I having first made known to him/her the contents
thereof, he/she did acknowledge that he/she signed, sealed, and
delivered the same as his/her voluntary act and deed for the
uses and purposes therein expressed.

Maria I. Shukala
Notary Public



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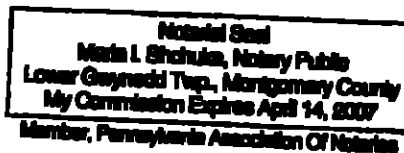
IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 10th day of 20 November 2003

Shyamali Ghosh (L.S.)
Shyamali Ghosh

STATE OF Pennsylvania)
COUNTY OF Montgomery) ss.

BE IT REMEMBERED, That on this 10th day of NOVEMBER, 2003, before me, a Notary Public, personally appeared Shyamali Ghosh, who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him/her the contents thereof, he/she did acknowledge that he/she signed, sealed, and delivered the same as his/her voluntary act and deed for the uses and purposes therein expressed.

Maria I. Shchulka
Notary Public



7/10/05
200

IN TESTIMONY WHEREOF, Assignors have hereunto set
their hands and seals this 10th day of Nov., 2003

Li Liu (L.S.)
Li Liu

STATE OF Pennsylvania)
COUNTY OF Montgomery) ss.

BE IT REMEMBERED, That on this 10th day of
NOVEMBER, 2003, before me, a Notary Public, personally
appeared Li Liu, who I am satisfied is the person named in and
who executed the foregoing instrument in my presence, and I
having first made known to him/her the contents thereof, he/she
did acknowledge that he/she signed, sealed, and delivered the
same as his/her voluntary act and deed for the uses and purposes
therein expressed.

Maria I. Shchukin
Notary Public

Notarial Seal
Maria I. Shchukin, Notary Public
Lower Gwynedd Twp., Montgomery County
My Commission Expires April 14, 2007
Member, Pennsylvania Association Of Notaries