

ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

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2746/PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref.: Expediente No. 04.120.039

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

SUPERINTENDENCIA Y COMERCIO
Radicación: 0412039 00000002 Folios: 31
Fecha (GPD): 2005-02-10 14:05:22
Trámite: 011 PCT-PATENT 379 FASE INICI 444 RESPUESTA
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

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. 11331 notificado por fijación en lista el día 10 de diciembre de 2004, me permito presentar:

1. Copia del examen preliminar internacional junto con su traducción al español.
2. Documentos (2) 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.

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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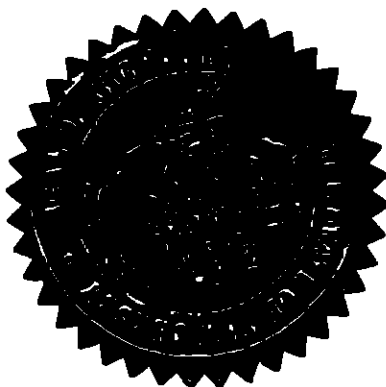
APOSTILLE

(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 22ND DAY OF NOVEMBER 2004
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A213501
9. SEAL/STAMP:
10. SIGNATURE



John E McCormac

PRD 1 COL(L)

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 10/400,006 filed MARCH 26, 2003.

A handwritten signature in cursive script, reading "Christina A. Clickner", is written over a horizontal line.

Christina A. Clickner
(Notary Public of New Jersey)
My Commission Expires:
March 2, 2005

A S S I G N M E N T

Serial No. 10/400,006
Filed March 26, 2003

WHEREAS, Henry J. Breslin, Wei He, and Robert W. Kavash, residing at 1974 Muhlenburg Drive, Lansdale, PA 19446; 2002 Kestkal Circle, Audubon, PA 19403; and 148 North Keswick Avenue, Glenside, PA 19038, respectively (hereinafter called "Assignors"), have made certain new and useful inventions or discoveries relating to

NOVEL COMPOUNDS AS OPIOID RECEPTOR MODULATORS

for which they have on the 26th day of March, 2003 filed a non-provisional application for Letters Patent of the United States; and

WHEREAS, Janssen Pharmaceutica, NV, 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;

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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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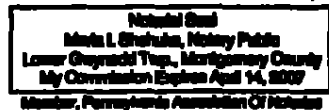
IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 22nd day of APRIL, 2003

Henry J. Breslin (L.S.)
Henry J. Breslin

STATE OF Pennsylvania
COUNTY OF Montgomery ss.

BE IT REMEMBERED, That on this 22nd day of April, 2003, before me, a Notary Public, personally appeared Henry J. Breslin, 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. Szchalek
Notary Public



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IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 22 day of APRIL, 2003


Wei He (L.S.)

STATE OF Pennsylvania,
COUNTY OF Montgomery, ss.

BE IT REMEMBERED, That on this 22nd day of April, 2003, before me, a Notary Public, personally appeared Wei He, 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.


Notary Public

Notarial Seal
Maria L. Shcherba, Notary Public
Lower Gwynedd Twp., Montgomery County
My Commission Expires April 14, 2007
Member, Pennsylvania Association of Notaries

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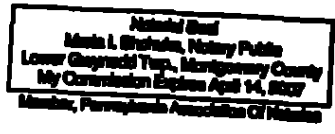
IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 22 day of April, 2003

Robert W. Kavash (L.S.)
Robert W. Kavash

STATE OF Pennsylvania
COUNTY OF Montgomery ss.

BE IT REMEMBERED, That on this 22nd day of April, 2003, before me, a Notary Public, personally appeared Robert W. Kavash, 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



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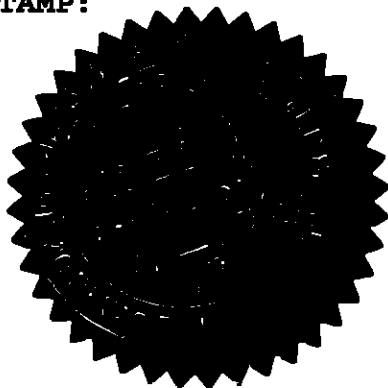
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(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

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CHRISTINA A CLICKNER, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 22ND DAY OF NOVEMBER 2004
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A213500
9. SEAL/STAMP:
10. SIGNATURE



John E McCormac

PRD 1 COL(L)

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 60/376,406 filed APRIL 29, 2002.



Christina A. Clickner
(Notary Public of New Jersey)
My Commission Expires:
March 2, 2005

A S S I G N M E N T

Serial No. 60/376,406
Filed April 29, 2002

WHEREAS, Henry J. Breslin, Wei He, and Robert W. Kavash, residing at 1974 Muhlenburg Drive, Lansdale, PA 19446; 2002 Kestkal Circle, Audubon, PA 19403; and 148 North Keswick Avenue, Glenside, PA 19038, respectively (hereinafter called "Assignors"), have made certain new and useful inventions and discoveries relating to

NOVEL COMPOUNDS AS OPIOID RECEPTOR MODULATORS

for which they have on the 29th day of April, 2002 filed a provisional application for Letters Patent of the United States; and

WHEREAS, Janssen Pharmaceutica, NV, 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;

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.

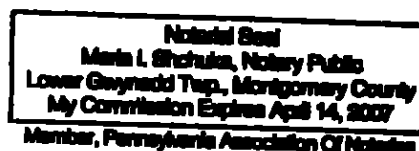
IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 22nd day of APRIL, 2003

Henry J. Breslin (L.S.)
Henry J. Breslin

STATE OF Pennsylvania
COUNTY OF Montgomery) ss.

BE IT REMEMBERED, That on this 02nd day of April, 2003, before me, a Notary Public, personally appeared Henry J. Breslin, 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



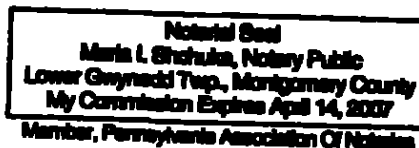
IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 22 day of APRIL, 2003

Wei He (L.S.)

STATE OF Pennsylvania)
COUNTY OF Montgomery) ss.

April BE IT REMEMBERED, That on this 22nd day of April, 2003, before me, a Notary Public, personally appeared Wei He, 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



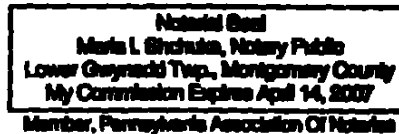
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Robert W. Kausal

STATE OF *Pennsylvania*)

BE IT REMEMBERED, That on this 22nd day of APRIL, 2003, before me, a Notary Public, personally appeared Robert W. Kavash, 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. Shchekure
Notary Public



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

REC'D 18 JUN 2004

Applicant's or agent's file reference PRD-1 PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/EP/716)	
International application No. PCT/US 03/1672	International filing date (day/month/year) 17.04.2003	Priority date (day/month/year) 28.04.2002
International Patent Classification (IPC) or both national classification and IPC A01K31/439		
Applicant BREBLIN, Henry J. et al.		

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 8 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.

EPO - DG 1

30.07.2004

3. This report contains indications relating to the following items:
 - I ☒ Basis of the opinion (107)
 - 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)(i) 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 21.11.2003	Date of completion of this report 17.08.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-69000 Munich Tel. +49 89 2369 - 0 Te. 833688 ext. 4 Fax +49 89 2369 - 4468	Authorized Officer Johnson, G Telephone No. +49 89 2369-8287 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/US 03/11672**

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. 1-13, 23, 39-42 (all part)

because:

- ☒ the said international application, or the said claims Nos. 40-42 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. 23 (part) are so unclear that no meaningful opinion could be formed (specify):

see separate sheet

- ☒ the claims, or said claims Nos. 1-13, 23, 39-42 (all part) 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.

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:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/AUS 03/1872**

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. .

V. Reasoned statement under Article 26(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting each statement

1. Statement

Novelty (N)	Yes: Claims	4,5,10-18,21,25,27-32,34,38,40-42
	No: Claims	1-3,6-9,20,22-24,26,33,35-37,39,43
Inventive step (IS)	Yes: Claims	4,5,10-18,19,21,25,27-32,34,38
	No: Claims	1-3,6-9,14,16-18,20,22-24,26,33,35-37,39-43
Industrial applicability (IA)	Yes: Claims	1-39,43
	No: Claims	

2. Citations and explanations

see separate sheet

2. Claims: 1-13 (part), 27-32, 39-42 (part)

Compounds of formula (I) wherein the R1 ring is beta to the N-atom, i.e. $n=1$, and their methods of use. Special technical feature is the position of the R1 ring.

3. Claims: 1-13 (part), 33-38, 39-42 (part)

Compounds of formula (I) wherein the R1 ring is gamma to the N-atom, i.e. $n=2$, and their methods of use. Special technical feature is the position of the R1 ring.

4. Claim : 43

Compounds of formula (II).

V. Reasoned statement

Reference is made to the following documents:

D1: Balboni et al., Peptides, 21 (2000) 1663-1671

D2: Balboni et al. J. Med. Chem. 45(3) (2002) 713-720

D3: JP 05 339240

D4: Holink et al., J. Pharm. Sci. 89(1) (2000) 108-114

D5: Salvadori et al., J. Med. Chem. 40(19) (1997) 3100-3108

D6: Obase et al., Chem. Pharm. Bull. 30(2) (1982) 474-483

D7: EP-0 506 466

D8: Krenitsky et al., Tet. Lett., 43(3) (2002) 407-410

D9: US-A-3 023 235

D10: US-A-4 563 306

D11: US-A-3 763 218

D12: Leonard et al., J. Med. Chem., 10 (1967) 476-481

D13: Masda et al., Beilstein online, accession no. 5844822

Examination of novelty and inventive step of the first invention Claims 1-13 (part), 14-26, 39-42 (part)

Novelty

The compounds of D1 and D2 falling within the scope of general formula (I) are excluded by proviso. The compounds of D5 do not possess the present R1 ring. General formula I of D3 overlaps with present formula (I), and examples 9 and 10 fall within the scope of present formula (I). Claims 1, 2, 6-9, 20, 22-24, 26 and 39 are therefore not new.

Compound D, Fig. 2 of D4 falls within the scope of general formula (I) and is

novelty-destroying for claims 1-3 and 6-8.

Claims 1-3, 6-8, 20, 22-24, 26 and 39 do not fulfil the requirements of Article 33(2) PCT.

Inventive step

In view of the lack of novelty of claims 1-3, 6-8, 20, 22-24, 26 and 39, these claims cannot be inventive.

D1, D2 and D5 describe compounds with affinity for the delta and mu opioid receptors. D3 concerns tachykinin antagonists and D4 describes degradation products of tripeptides. The technical problem underlying the present invention is the provision of further compounds with affinity for the opioid receptors. D1 and D2 may be taken as the closest prior art. Although the specific compounds of D1 and D2 are excluded from the present claims by proviso, it would be obvious to the skilled person wishing to solve the above-formulated technical problem to make minor modifications to the compounds known from D1 and D2, in the expectation that the activity would be maintained. D1 states on p. 1688, right hand column, last paragraph, that "N-alkylation of Dmt further augmented delta antagonist bioactivity by 20-fold" and refers to D5 in this respect. Thus it would be obvious for the skilled person to prepare N-alkyl derivatives of the 2 compounds known from D1 and D2. Furthermore, D2 discloses (first sentence of introduction) that both tyrosine and 2,6-dimethyltyrosine derivatives have opioid receptor affinity. Thus the skilled man receives a hint that the substituents on the 4-hydroxyphenyl ring are not important for qualitative opioid activity, and hence has an incentive to modify the phenyl ring substituents of the compounds of D1 and D2. The fact that both the uncondensed pyrrolidine derivative 9 and the isoquinoline derivative 11 both have affinity for the opioid receptors provides an incentive to the skilled man to modify 11 by removing the condensed phenyl ring to give the piperidine derivative of present claim 14.

Claims 1-3, 6-8, 14, 16-18, 20, 22-24, 26, 39-42 are considered obvious in light of D1 and D2 and therefore do not fulfil the requirements of Article 33(3) PCT.

Examination of novelty and inventive step of the second invention Claims 1-13 (part), 27-32, 39-42 (part)

Novelty

The position of the R¹ ring distinguishes the present compounds from those of D1-D4.

Inventive step

Taking D1 or D2 as the closest prior art, it would not be obvious to solve the technical problem of providing further compounds with affinity for the opioid receptors by changing the position of the R¹ group in the compounds of D1 or D2. None of the prepublished documents in the cited prior art dealing with the same technical problem suggest that the alpha-position of the R¹ group is not essential for the maintenance of the activity.

Examination of novelty and inventive step of the third invention Claims 1-13 (part), 33-36, 39-42 (part)

Novelty

Compound 8 of D6 anticipates present claims 1, 2, 6-9, 33, 35-37, 39. These claims therefore do not fulfill the requirements of Article 33(2) PCT.

Inventive step

In view of the lack of novelty of claims 1, 2, 6-9, 33, 35-37, 39, these claims cannot be inventive.

The compounds of D6 are antihypertensives. Those of D7 are peripheral opioid antagonists. D7 is taken as the closest prior art. There are 2 structural differences between those of the present compounds which were searched completely and the compounds of D7: the fact that the piperidine ring is substituted at the 4-position by the R¹ group only and the presence of a carbonyl or thiocarbonyl N-substituent. Because of these 2 differences it would not be obvious to combine D7 with D1 or D2 and to arrive at the claimed novel subject matter.

Examination of novelty and inventive step of the fourth invention Claim 43

Novelty

D6-D13 all disclose either specific compounds falling within or general formulae overlapping with present claim 43.

Claim 43 does not fulfill the requirements of Article 33(2) PCT.

Inventive step

In view of the lack of novelty of claim 43, it cannot be inventive.

Industrial applicability (of all four inventions)

Claims 1-39, 43 fulfill the requirements of Article 33(4) PCT.

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US 03/11872

No unified criteria exist in the PCT Contracting States for assessing whether present claims 40-42 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows 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.

III. Non-establishment of opinion

In view of the lack of support (Article 6 PCT) and disclosure (Article 5 PCT), the compounds of formula (I) were only completely searched insofar as X is (CR¹⁵R¹⁶)_m, the ring containing the X group is 5- or 6-membered, L is O or S, a is 0 and p is 1. For the same reasons claim 43 has only been searched insofar as k is 1. Only subject matter which has been searched will be examined (Rule 68.1(e) PCT).

Claims 40-42 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).

IV. Lack of unity

In order for a group of compounds to meet the requirements of unity (Rule 13 PCT), it is necessary that they share the same or corresponding special technical features. Special technical features are those features distinguishing the claimed compounds from the prior art.

In the present case, compounds with the same activity (an affinity for the opioid receptors) and falling within the general formula (I) are known from e.g. "Peptides", 21 (2000) 1663-1671 (examples 9 and 11). These specific compounds have been excluded from the present claims by proviso, thus rendering the present claims new over this document. However, the teaching that compounds of formula (I) have affinity for opioid receptors cannot form the special technical feature unifying all the presently claimed compounds, as this teaching is not new and thus does not distinguish the present application from the prior art. Certain of the claimed compounds differ from the compounds of the above-cited document because of the position of the R¹ group. The position of this group was therefore chosen to define potentially unitary sub-groups. The intermediates of claim 43 do not contain the essential structural element R¹ or a direct precursor thereof, and therefore are not unitary with any of the sub-groups of final products.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-13 (part), 14-26, 39-42 (part)

Compounds of formula (I) wherein the R¹ ring is alpha to the N-atom, i.e. $n=0$, and their methods of use. Special technical feature must lie in the identity of the R¹ ring or the combination of specific substituents.

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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-1 PCT	Ver notificación de la transmisión del examen preliminar Internacional (formato PCT/IPEA/416) PARA PROSEGUIR	
No. Solicitud Internacional PCT/US03/11872	Fecha de presentación Internacional (día/mes/año) 17/04/2003	Fecha de prioridad (día/mes/año) 28/04/2002
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61K31/4439		
Solicitante BRESLIN, Henry J. et al.		

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 9 páginas, incluyendo esta hoja.

X 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 1 hojas.
3. Este Informe contiene indicaciones que se relacionan con los siguientes puntos:
 - I. X Base del Informe
 - II. Prioridad
 - III. X El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial
 - IV. X Falta de unidad de invención
 - V. X 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 21/11/2003	Fecha en que se completó este informe 17.06.2004
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 Johnson, C Teléfono: +49 89 2399 7511

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III. El no-establishment 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. 1-13, 26, 39-42 (Todo)

Porque:

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

ver hoja separada

☒ la memoria descriptiva, las reivindicaciones, o los dibujos (indicar abajo los elementos específicos) o las

ver hoja separada

☒ las reivindicaciones, o dichas reivindicaciones Nos. 1-13, 26, 39-42 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.

IV. Falta de unidad de invención.

1. En respuesta a la invitación para restringir o pagar tasas adicionales, el solicitante ha:

☐ restringido las reivindicaciones

☒ ha pagado tasas adicionales

☐ ha pagado tasas bajo protesta

☐ no ha restringido ni ha pagado tasas adicionales

2. Esta autoridad encontró que el requisito de unidad de invención no es cumplido y escoge de acuerdo con la regla 68.1 no invitar al solicitante a restringir o pagar tasas adicionales.

3. Esta autoridad considera que el requisito de unidad de invención de acuerdo con la regla 13.1, 13.2 y 13.3 es

☐ cumplida

☐ no cumplida por las siguientes razones:

4. En consecuencia, las siguientes partes de la solicitud internacional fueron materia del examen preliminar internacional y se estableció un reporte de:

- ☐ todas las partes
- ☐ las partes relacionadas con las reivindicaciones Nos.

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

1. Declaración

Novedad	SI:	Reivindicaciones 4, 5, 10-19, 21, 25, 27-32, 34, 38, 40-42
	NO:	Reivindicaciones 1-3, 6-9, 20, 22-24, 26, 33, 35-37, 39, 43
Nivel inventivo	SI:	Reivindicaciones 4,5, 10-13, 15, 19, 21, 25, 27-32, 34, 38
	NO:	Reivindicaciones 1-3, 6-9, 14, 16-18,20, 22-24, 26, 33, 35-37,39-43
Aplicación industrial	SI:	Reivindicaciones 1-39, 43
	NO:	Reivindicaciones

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III. No establecimiento de Opinión

En vista de la carencia de soporte (Artículo 6 PCT) y divulgación (Artículo 5 PCT), los compuestos de fórmula (I) solamente se investigaron completamente hasta donde X es (CR15R16)m, el anillo que contiene el grupo X es de 5 o 6 miembros, L es O o S, s es 0 y p es 1. Por las mismas razones la reivindicación 43 solamente ha sido investigada hasta donde k es 1. Solamente la materia objeto que ha sido investigada será examinada (Regla 66.1(e)PCT).

Las reivindicaciones 40 – 42 se refieren a la materia objeto considerada por esta Autoridad a ser cubierta por las disposiciones de la Regla 67.1(iv) PCT. En consecuencia, no se formulará ninguna opinión con respecto a la aplicabilidad Industrial de la materia objeto de estas reivindicaciones (Artículo 34(4)(a)(i)PCT).

IV. Carencia de Unidad

Con el objeto que un grupo de compuestos reúna los requerimientos de unidad (Regla 13 PCT) es necesario que ellos compartan o que correspondan a las mismas características técnicas especiales. Las características técnicas especiales son aquellas características que distinguen los compuestos reivindicados de los del arte previo.

De PCT/Hoja Separada/409 (Hoja 1) (EPO – Abril 1997)

En el presente caso, los compuestos con la misma actividad (una afinidad por los receptores opiodes) y que caen dentro de la fórmula (I), se conocen de e.g., "Peptidos", 21 (2000) 1663 – 1671 (ejemplos 9 y 11). Estos compuestos específicos han sido excluidos de las actuales reivindicaciones por estipulación, de tal manera que se suministren nuevas reivindicaciones actuales sobre este documento. Sin embargo, la enseñanza que los compuestos de fórmula (I) tienen afinidad por receptores opiodes no puede formar la característica técnica especial que unifica todos los compuestos reivindicados actualmente, puesto que esta enseñanza no es nueva y por lo tanto no distingue la solicitud actual de la del arte previo. Ciertos compuestos reivindicados difieren de los compuestos del documento citado antes por la posición del grupo R1. Por lo tanto, la posición de este grupo se escogió para definir los subgrupos unitarios potencialmente. Los intermedios de la reivindicación 43 no contienen el elemento R1 estructural esencial o un precursor directo del mismo y por lo tanto no son unitarios con cualquiera de los subgrupos de los productos finales.

Esta Autoridad Internacional de Investigación encontró múltiples (grupos de) invenciones en esta solicitud internacional, como sigue:

1. Reivindicaciones 1-13 (parte), 14 –26, 39 – 42(parte)

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Los Compuestos de fórmula (I) en donde el anillo R1 está en alfa respecto del átomo de N, e.i., $r = 0$, y sus métodos de uso. La característica técnica especial debe apoyarse en la identidad del anillo R1 o la combinación de sustituyentes específicos.

De PCT/Hoja Separada/409 (Hoja 1) (EPO – Abril 1997)

2. Reivindicaciones: 1-13 (parte), 27 – 32, 39 – 42 (parte)

Los compuestos de fórmula (I) en donde el anillo R1 está en beta con respecto del átomo de N, i.e., $r = 1$, y sus métodos de uso. La característica técnica especial es la posición del anillo R1.

3. Reivindicaciones: 1-13 (parte), 33-38, 39-42(parte)

Los compuestos de fórmula (I) en donde el anillo R1 esta en gama con respecto del átomo de N, i.e., $r = 2$, y sus métodos de uso. La característica técnica especial es la posición del anillo R1.

4. Reivindicación 43

Los compuestos de fórmula (II).

V. Declaración argumentada.

Se hace referencia a los siguientes documentos:

D1: Balboni et al., Peptides, 21 (2000) 1663 –1671

D2 : Balboni et al., J. Med. Chem. 45(3) (2002) 713 – 720

D3 : JP 05 339240

D4: Holtink et al., J. Pharm. Sci. 89(1) (2000) 108 –114

D5 : Salvadori et al., J. Med. Chem. 40(19) (1997) 3100 – 3108

D6: Obase et al., Chem. Pharm. Bull. 30(2) (1982) 474 – 483

D7 : EP-0 506 468

De PCT/Hoja Separada/409 (Hoja 2) (EPO – Abril 1997)

D8: Krenitsky et al., Tet. Lett., 43(3) (2002) 407 - 410

D9: US-A 3 023 235

D10: US-A 4 563 308

D11: US-A 3 763 218

D12: Leonard et al., J. Med. Chem., 10 (1967) 478 – 481

D13 : Maeda et al., Beilstein en línea, no de acceso 5644822

Exámen de novedad y nivel inventivo de la primera invención.

Reivindicaciones 1- 13 (parte), 14 – 26, 39 –42(parte)

Novedad.

Los compuestos de D1 y D2 que caen dentro del alcance de la fórmula general (I) se excluyen por estipulación. Los compuestos de D5 no poseen el anillo R1 actual. La fórmula general I de D3 se sobre-lapa con la fórmula actual (I), y los ejemplos 9 y 10 caen dentro del alcance de la actual fórmula (I). Por lo tanto las reivindicaciones 1, 2, 6-9, 20, 22 - 24, 26 y 39 no son nuevas.

El compuesto D, Fig. 2 de D4 cae dentro del alcance de la fórmula general (I) y

De PCT/Hoja Separada/409 (Hoja 2) (EPO - Abril 1997)

destruye la novedad de las reivindicaciones 1-3 y 6-9.

Las reivindicaciones 1-3, 6-9, 20, 22-24, 26 y 39 no cumplen los requerimientos del Artículo 33(2)PCT.

Nivel Inventivo.

En vista de la carencia de novedad de las reivindicaciones 1-3, 6-9, 20, 22-24, 26 y 39, estas reivindicaciones no pueden ser inventivas.

D1, D2 y D5 describen compuestos con afinidad por los receptores opiodes delta, y mu. D3 concierne a antagonistas de taquikina y D4 describe los productos de degradación de tripéptidos. El problema técnico que resalta la actual invención es la provisión de otros compuestos con afinidad por los receptores opiodes. D1 Y D2 se pueden tomar como los más cercanos al arte previo. Sin embargo los compuestos específicos de D1 y D2 se excluyen de la presente invención por estipulación, será obvio para una persona versada en el arte que desee resolver el problema técnico formulado antes de hacer modificaciones menores a los compuestos conocidos de D1 y D2 con las expectativa que se mantenga la actividad. D1 establece en la página 1669, columna del lado derecho, último párrafo, que " La N-alquilación de otros Dmt aumenta la bioactividad antagonista delta en 20 veces" y se refiere a D5 al respecto. Por lo tanto, será obvio para una persona versada en el arte preparar derivados N-alquil de los 2 compuestos conocidos de D1 y D2. Además, D2 divulga (la primera frase de la introducción)

De PCT/Hoja Separada/409 (Hoja 3) (EPO - Abril 1997)

que tanto la tirosina y los derivados de la 2,6-dimetiltirosina tienen afinidad por los receptores opiodes. Así la persona versada recibe la indicación que los sustituyentes sobre el anillo 4-hidroxifenilo no son importantes para la actividad opiode cualitativa, entonces tiene un incentivo para modificar los sustituyentes del anillo fenilo de los compuestos de D1 y D2. El hecho de que ambos tanto el derivado 9 de pirrolidina no condensado y el derivado 11 de isoquinolina tengan afinidad por los receptores opiodes proporciona un incentivo a la persona versada para modificar 11 por remoción del anillo fenilo condensado para dar el derivado de piperidina de la actual reivindicación 14.

Las reivindicaciones 1-3, 6-9, 14, 16-18, 20, 22-24, 26, 39-42, se consideran obvias a la luz de D1 y D2 y por lo tanto no cumplen los requerimientos del Artículo 33(3)PCT.

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Exámen de la novedad y del nivel inventivo de la segunda invención Reivindicaciones 1-13 (parte), 27-32, 39-42(parte).

Novedad

La posición del anillo R¹ distingue los compuestos actuales de aquellos de D1 – D4

De PCT/Hoja Separada/409 (Hoja 3) (EPO – Abril 1997)

Nivel inventivo.

Tomando D1 o D2 como los mas cercanos al arte previo no será obvio resolver el problema técnico de proporcionar otros compuestos con afinidad por los receptores opiodes cambiando la posición del grupo R¹ en los compuestos de D1 o D2. Ninguno de los documentos publicados anteriormente en el arte previo citado, que trata con el mismo problema técnico sugiere que la posición alfa del grupo R¹ no es esencial para el mantenimiento de la actividad.

Exámen de la novedad y nivel inventivo de la tercera invención. Reivindicaciones 1-13 (parte), 33-38, 39-42(parte).

Novedad

El compuesto 8 de D6 anticipa las reivindicaciones actuales 1,2, 6-9, 33, 35-37,39. Por lo tanto estas reivindicaciones no cumplen los requerimientos del Artículo 33(2)PCT.

Nivel inventivo.

En vista de la carencia de novedad de las reivindicaciones 1,2, 6-9, 33, 35-37,39, estas reivindicaciones no pueden ser inventivas.

Los compuestos de D6 son anti-hipertensivos. Aquellos de D7 son antagonistas opiodes periféricos. D7 se toma como lo mas cercano al arte previo. Hay dos

De PCT/Hoja Separada/409 (Hoja 4) (EPO – Abril 1997)

diferencias estructurales entre aquellos de los compuestos actuales que fueron investigados completamente y los compuestos de D7: el hecho de que el anillo de piperidina está sustituido solamente en la posición 4 por el grupo R¹ y la presencia de un sustituyente en N carbonilo o tiocarbonilo. Por estas 2 diferencias no sería obvio combinar D7 con D1 o D2 y llegar a la materia objeto reivindicada como novedosa.

Exámen de la novedad y nivel inventivo de la cuarta invención. Reivindicación 43

Novedad.

D8 – D13 todos divulgan ya sea compuestos específicos que caen dentro o fórmulas generales que se sobrelapan con la reivindicación actual 43.

La reivindicación 43 no cumple los requerimientos del Artículo 33(2)PCT.

Nivel Inventivo

En vista de la carencia de novedad de la reivindicación 43 no puede ser inventiva.

Aplicabilidad Industrial (De todas las cuatro invenciones)

Las reivindicaciones 1-39, 43 cumplen los requerimientos del Artículo 33(4) PCT

De PCT/Hoja Separada/409 (Hoja 4) (EPO – Abril 1997)

No existen criterios unificados en los Estados Contratantes del PCT para evaluar si las reivindicaciones actuales: 40 - 42 son aplicables industrialmente. La patentabilidad puede depender de la formulación de las reivindicaciones. Por ejemplo, la EPO no considera reivindicaciones para el uso de un compuesto en un tratamiento médico que sea aplicable industrialmente, pero permite reivindicaciones para un compuesto conocido para primer uso en tratamiento médico y el uso de tal compuesto para la manufactura de un medicamento para un nuevo tratamiento médico.

2020
Bogotá D C

Doctor(a)
JIMENA ESCOBAR URIBE.
Apoderado(a)

REFERENCIA:	Radicación N°	04-120039
	Solicitud Internacional	PCT/US03/11872
	Fecha límite fase nacional	29/11/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	1548
	Folios	001

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 los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase
Dado en Bogotá D C, **06 DIC. 2005**


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones

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