

No. 07-121830- -00003-0000

Fecha: 2008-04-16 15:46:44 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
Act. 444 RESPUESTAREQUE Folios: 23

**Clarke, Modet &**

**COLOMBIA**

SEÑORES  
DIVISIÓN DE NUEVAS CREACIONES  
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
E. S. D.

REF: EXPEDIENTE No. 07121830  
FECHA DE LA SOLICITUD: NOVIEMBRE 19 DE 2007  
SOLICITANTE: CADILA HEALTHCARE LIMITED  
TITULO: COMPUESTOS NOVEDOSOS COMO AGONISTAS  
GLP-1

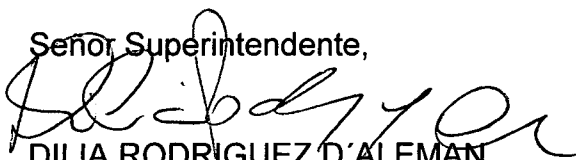
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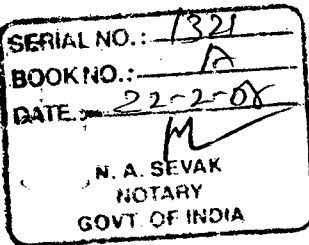
DILIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad solicitante de la patente de la referencia, en respuesta al oficio No. 315 notificado por fijación en lista el día 11 de enero de 2008, me permito presentar los siguientes documentos:

- El documento en el que consta la CESIÓN del derecho a la patente otorgado por los inventores al solicitante. debidamente legalizados.
- Su traducción oficial al Español debidamente avalada por el Ministerio de Relaciones Exteriores.
- IPER y sus anexos

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,

  
DILIA RODRIGUEZ D'ALEMAN  
C.C. 41.654.882 de Bogotá  
T.P. 20824  
ADM/srr  
P-1038 



Clarke, Modet & C<sup>o</sup>

COLOMBIA

E-MAIL: info@clarkemodet.com.co  
SANTAFÉ DE BOGOTÁ, A.A. 92397 COLOMBIA

mc-30-31 - Colombia 1038

**CESION**

**ASSIGNMENT**

El (la) abajo firmante (En adelante EL CEDENTE)

1. LOHRAY, Braj, Bhushan
2. LOHRAY, Vidya, Bhushan
3. BAHEKAR, Rajesh, H.

en su carácter de inventor /diseñador  
PCT/IN2006/000154

con domicilio en:

Cadila Healthcare Limited, Zydus Tower,  
Satellite Cross Roads, Ahmedabad 380  
015, Gujarat, India

por el presente documento declara que  
cede todos y cada uno de los derechos que  
le corresponden o puedan corresponderle  
sobre la siguiente invención , modelo de  
utilidad, diseño industrial

a:

CADILA HEALTHCARE LIMITED

con domicilio en

Zydus Tower, Satellite Cross Roads,  
Ahmedabad 380 015, Gujarat, India

En prueba de la mutua aceptación de esta  
cesión ambas partes CEDENTE y  
CESIONARIO firman el presente  
documento.

Dado y firmado en

A los                      Días de

De 2007

The undersigned (Hereinafter THE ASSIGNOR)

1. LOHRAY, Braj, Bhushan
2. LOHRAY, Vidya, Bhushan
3. BAHEKAR, Rajesh, H.

Inventor /designor of  
PCT/IN2006/000154

domiciled at

Cadila Healthcare Limited, Zydus Tower,  
Satellite Cross Roads, Ahmedabad 380  
015, Gujarat, India

do hereby declares that it assigns all and  
each of his rights and privileges on the  
following invention, industrial design,  
utility model

to

CADILA HEALTHCARE LIMITED

with domicile in

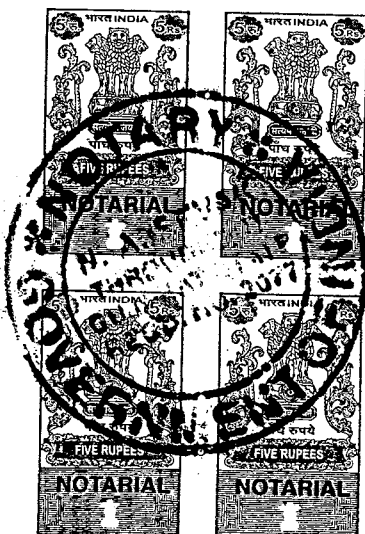
Zydus Tower, Satellite Cross Roads,  
Ahmedabad 380 015, Gujarat, India

As a proof of the mutual acceptance of this  
assignment, both parties ASSIGNOR and  
ASSIGNEE sign the present document.

Granted and signed at

on this                      day of

of 2007

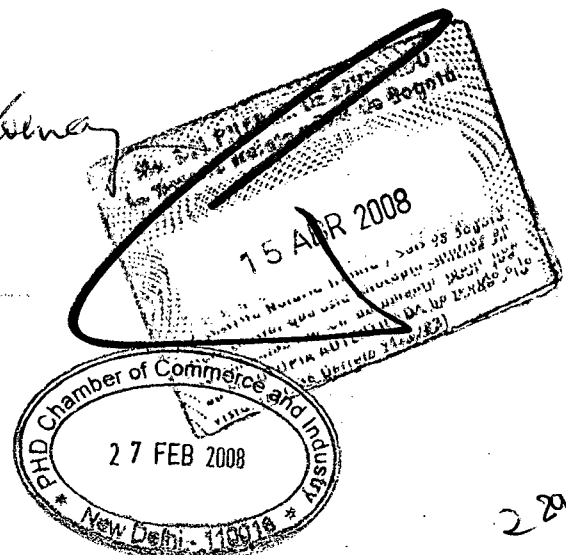


*B. B. Lohray*  
LOHRAY, Braj, Bhushan

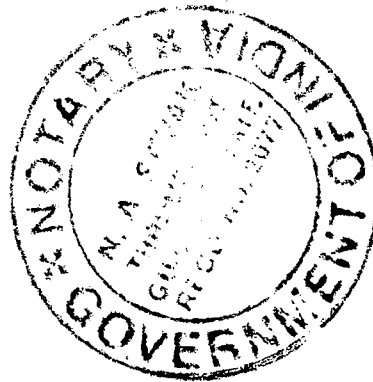
*Vidya Bhushan*  
LOHRAY, Vidya, Bhushan

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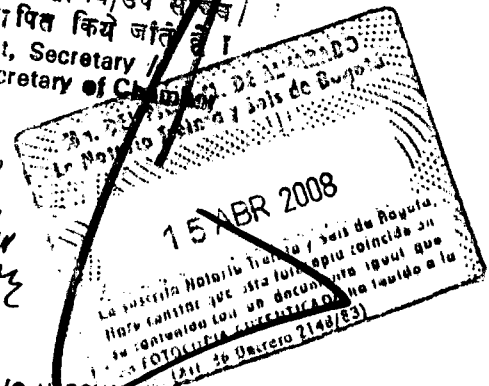
*Sarvek*  
Addl./Joint/Dy. Secy./Secretary General/Exe. Asstt.  
PHD Chamber of Commerce and Industry  
New Delhi (India)



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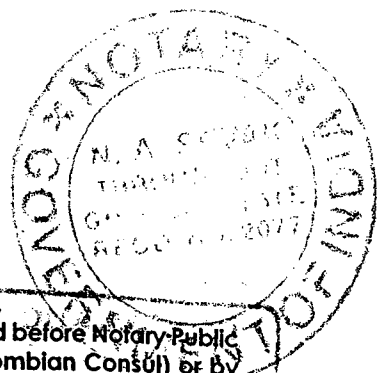
No. 36417 दिनांक 8 FEB 2008  
Date.....  
साक्षिपत्य पत्र के छायांक सचिव/उप सचिव/  
सचिव के हस्ताक्षर सत्यापित किये जाते हैं।  
The Signature of Asstt. Secretary /  
Deputy Secretary / Secretary of Chamber  
of Commerce attested.



(जी. हर्षमन/G. H. HARMAN)  
अनुभाग अधिकारी (जी.आई.)  
Section Officer (O.I.)  
सी.पी.डी. प्रभाग/CPV Division  
विदेशी मंत्रालय, नई दिल्ली  
Ministry of External Affairs, New Delhi



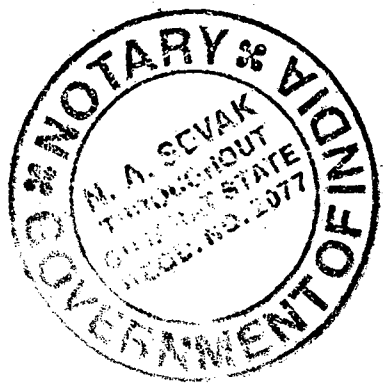
*[Signature]*  
BAHEKAR, Rajesh, H.



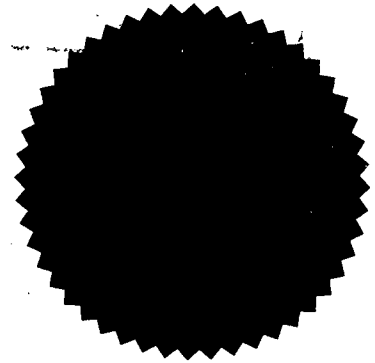
Este documento debe ser otorgado ante Notario público y legalizado por el Cónsul de Colombia) o por Apostilla

(This document must be signed before Notary Public and legalized before the colombian Consúl) or by Apostille

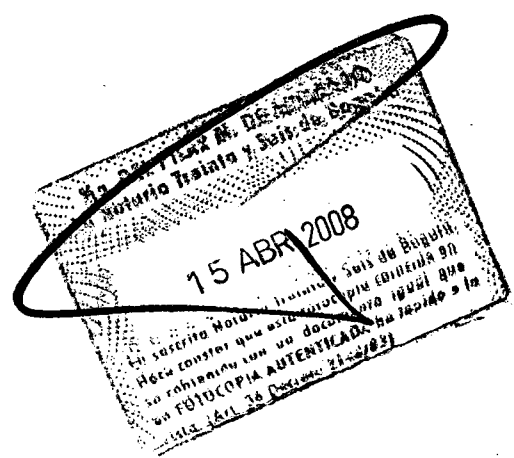
IDENTIFIED BY ME  
*[Signature]*  
ADVOCATE



SIGN BEFORE ME  
*[Signature]*  
N. A. SEVAK  
NOTARY  
GOVT. OF INDIA  
22 FEB 2008



ATTESTED  
*[Signature]*  
Addl./Joint/Dy. Secy./Secretary General/Exe. Asstt.  
PHD Chamber of Commerce and Industry  
New Delhi (India)



182

PAGADO IMPUESTO DE TIMBRE US\$ 104  
PAGADOS DERECHOS CONSULARES US\$ 54

**CONSULADO DE COLOMBIA  
NUEVA DELHI**

No. 653/08

El suscrito Cónsul de Colombia CERTIFICA  
que el señor... G. Harshappa .....  
que autoriza el presente documento, ejerce  
legitimamente en la fecha allí expresada las  
funciones de Ministro de Relaciones Exteriores .....  
y el presente documento  
aparecerá como suyo en los que usa y  
acostumbra en sus actos oficiales.

El Cónsul no asume responsabilidad alguna  
por el contenido del documento.



Lina Marcela Ibáñez  
**LINA MARCELA IBÁÑEZ**  
Consejera, E.R.C.

750068  
Lina Ibáñez  
JEFE DE LEGALIZACIÓN  
BOGOTÁ D.C.

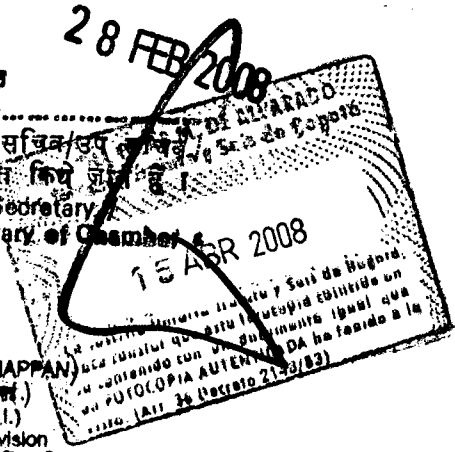
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JEFE DE LEGALIZACIÓN  
BOGOTÁ D.C.



No. 36416      Fecha 28 FEB 2008

El suscrito Asstt. Secretary of Commerce  
certifica que el Sr. G. Harshappa es el  
titular de la firma G. Harshappa & Co. y  
que el presente documento es una fotocopia  
auténtica de la original que se encuentra en  
su poder.

(Ji. Harshappa/G. HARSHAPPA)  
अनुभाग अधिकारी (जी.आई.)  
Section Officer (O.I.)  
सी.पी.डी. ब्रानच/CPV Division  
विदेश विभाग, नई दिल्ली  
Ministry of External Affairs, New Delhi



Traducción oficial de un documento que está originalmente en inglés

*El documento de Cesión adjunto lleva los siguientes sellos en inglés:*

“Cámara de Comercio e Industria de Nueva Delhi – 110016. 27 de febrero de 2008”

“Notario, Gobierno de la India. (Ilegible)”.

“Certificado (firmado) Cámara de Comercio e Industria de Nueva Delhi (India)”.

“Identificado por mí”

“Firmado ante mí, N.A. Sevak, Notario, Gobierno de la India, 22 de febrero de 2008”.

*(Reverso de las páginas):*

“No. 36417. Fecha: 28 de febrero de 2008. Se certifica la firma del funcionario de la Cámara de Comercio. (Firmado) G. Harshappan. Ministerio de Relaciones Exteriores, Nueva Delhi”.

“No. 36416. Fecha: 28 de febrero de 2008. Se certifica la firma del funcionario de la Cámara de Comercio. (Firmado) G. Harshappan. Ministerio de Relaciones Exteriores, Nueva Delhi”.

Sello redondo: “Ministerio de Relaciones Exteriores, Gobierno de India”



Traductor Oficial

JORGE E. SIERRA REYES

Licencia 376 - 1993 Minjusticia

Hay un sello del Consulado de Colombia en Nueva Delhi, con No. 653/08 fechado el 7 de marzo de 2008 y firmado por Lina Marcela Ibañez, Consejera E.E.C.

Los sellos de legalización del Ministerio de Relaciones Exteriores de Colombia están firmados y fechados el 11 de abril de 2008; su número es "750068".

*Certificación:*

*Certifico que la presente es una traducción verdadera y completa del documento adjunto:*

*Título: "Cadila H. - Sellos"*

*Fecha: 12 de abril de 2008.*

*Traductor: Jorge Enrique Sierra Reyes.*

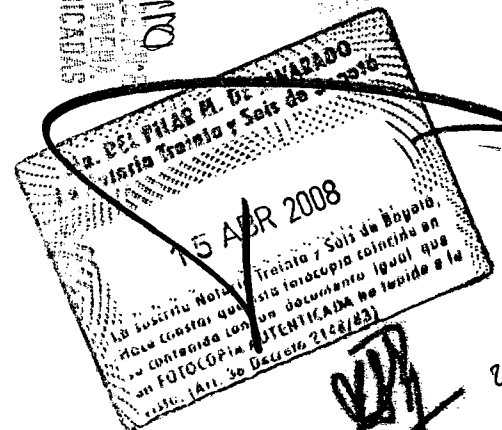
*Licencia No. 376 de 1993, del Ministerio de Justicia.*

*Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.*

*Teléfono: (57-1) 218-2308, (57-1) 623-2925.*

*E-mail: [treseser1@yahoo.com](mailto:treseser1@yahoo.com).*

*Documento No. No. 10-940*



Traductor Oficial  
JORGE E. SIERRA REYES  
Licencia 376 - 1993 Minjusticia

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |                                                                                                                                                                      |                                              |                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-----------------------|
| Applicant's or agent's file reference<br>558-645-CHL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  | <b>FOR FURTHER ACTION</b>                                                                                                                                            |                                              | See Form PCT/IPEA/416 |
| International application No.<br>PCT/IN2006/000154                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  | International filing date (day/month/year)<br>04.05.2006                                                                                                             | Priority date (day/month/year)<br>05.05.2005 |                       |
| International Patent Classification (IPC) or national classification and IPC<br>INV. C07K14/605                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |                                                                                                                                                                      |                                              |                       |
| Applicant<br>CADILA HEALTHCARE LIMITED                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |                                                                                                                                                                      |                                              |                       |
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>13</u> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of <u>2</u> sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input checked="" type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> |  |                                                                                                                                                                      |                                              |                       |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input checked="" type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input checked="" type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |                                                                                                                                                                      |                                              |                       |
| Date of submission of the demand<br><br>2006-11-30                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  | Date of completion of this report<br><br>26.11.2007                                                                                                                  |                                              |                       |
| Name and mailing address of the international preliminary examining authority:<br> European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  | Authorized officer<br><br>CERVIGNI, S<br><br>Telephone No. +49 89 2399-2835<br> |                                              |                       |

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/N2006/000154

**Box No. I Basis of the report**

1. With regard to the **language**, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
  - ☐ international search (under Rules 12.3(a) and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4(a))
  - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements\*** of the international application, this report is based on *(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):*

**Description, Pages**

1-53 as originally filed

**Sequence listings part of the description, Pages**

1-7 as originally filed

**Claims, Numbers**

1-14 as originally filed

- ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below 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)).

- ☒ the description, pages 52
- ☐ the claims, Nos.
- ☒ the drawings, sheets/figs 1/1
- ☐ the sequence listing (*specify*):
- ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "*superseded.*"

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IN2006/000154

**Box No. 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. 10-14 (IA)

because:

- ☒ the said international application, or the said claims Nos. 10-14 (IA) 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 (*specify*).
- ☐ no international search report has been established for the said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b) and 13ter.2.
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☒ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IN2006/000154

**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:
- ☐ restricted the claims.
  - ☒ paid additional fees.
  - ☐ paid additional fees under protest and, where applicable, the protest fee.
  - ☐ paid additional fees under protest but the applicable protest fee was not paid.
  - ☐ neither restricted the claims 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 separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
  - ☐ the parts relating to claims Nos. .

**Box No. 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 | <u>5-6</u>      |
|                               | No: Claims  | <u>1-4,7-14</u> |
| Inventive step (IS)           | Yes: Claims | <u>5-6</u>      |
|                               | No: Claims  | <u>1-4,7-14</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-9</u>      |
|                               | No: Claims  | <u>10-14</u>    |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IN2006/000154

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

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**Supplemental Box relating to Sequence Listing**

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**Continuation of Box I, Item 2:**

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

a. type of material:

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material:

☒ on paper

☒ in electronic form

c. time of filing/furnishing:

☒ contained in the international application as filed

☐ filed together with the international application in electronic form

☒ furnished subsequently to this Authority for the purposes of search and/or examination

☐ received by this Authority as an amendment\* on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

\* If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."

- 1 Amended page 52 and Figure 1, submitted with letter dated 16.10.2007, do not meet the requirements of Article 34(2)(b) PCT, because they clearly introduce subject-matter which extends beyond the content of the application as filed.
- 1.1 Contrary to the view of the applicant, there is no basis in the application as filed allowing to clearly and unambiguously identify which of the several hundred of peptides listed in Tables 1-9 - if any - actually corresponds to compounds I to IV of Table 10.
- 1.2 As a consequence, this international preliminary examination report is established as if such amendments had not been made.

### **SECTION III**

- 2 Claims 10-14 relate at least in part to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Therefore, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

### **SECTION IV**

- 3 This authority considers that the present application relates to multiple inventions not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT.
- 3.1 The closest prior art with respect to the present patent application can be exemplified by document D1 (WO03/011892), which discloses a number of chimeric peptides incorporating a portion of the GLP-1 sequence at their N-terminal end (cf. D1, figure 1). In the light of this prior art, the problem underlying the present application can be regarded as the provision of further GLP-1 peptide mimics. The proposed solution consists of polypeptides having the sequence of Formula (I), claim 1, comprising an N-terminal fragment ( $X_1$ ) of GLP-1, covalently coupled via optional linkers ( $S_1$ -Y- $S_2$ ) to an oligopeptide ( $X_2$ ) corresponding to the C-terminus of exendin-4, to the C-terminus of GLP-1, to oligopeptides of sequence KELEKLL or GPPS, or to a dipeptide.
- 3.2 A single general concept covering all such peptides could only be defined in that they

all are chimeric oligopeptides containing a fragment of GLP-1 at their N-terminus. However, compounds having all these structural properties are known from D1 (and also from D2 to D6) which discloses a number of these peptides and discusses their structure-function relationship. Since no further technical features can be identified which could serve as same or corresponding technical features in the sense of Rule 13.2 PCT to restore unity of invention, the search division considers that the following separate inventions are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT.

3.3 A distinction of separate subjects is made, based on structural relationship. Nine different groups of inventions have been identified as listed below.

3.3.1 *Invention 1:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.

3.3.2 *Invention 2:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is KELEKLL. Pharmaceutical compositions and use as a medicament.

3.3.3 *Invention 3:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is GPPS. Pharmaceutical compositions and use as a medicament.

3.3.4 *Invention 4:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is VKGR.

Pharmaceutical compositions and use as a medicament.

- 3.3.5 *Invention 5:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.
- 3.3.6 *Invention 6:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is KELEKLL. Pharmaceutical compositions and use as a medicament.
- 3.3.7 *Invention 7:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is GPPS. Pharmaceutical compositions and use as a medicament.
- 3.3.8 *Invention 8:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is VKGR. Pharmaceutical compositions and use as a medicament.
- 3.3.9 *Invention 9:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is a dipeptide "selected from combination of two amino acids consisting of natural or unnatural amino acids, having a side chain containing an arylalkyl or heterorylalkyl", as defined at page 55, lines 13-25. Pharmaceutical compositions and use as a medicament.

- 3.4 Since all further fees have been paid within the fixed time limit, an international search report and the present written opinion are issued covering all inventions 1 to 9.
- 3.5 In addition, several compound listed in claims 5-6 (merely as an example: those polypeptides having His-Gly, Phe-Ala, His-(CH<sub>2</sub>)<sub>n</sub> or des-amino histidine at their N-terminus; those containing a derivative of the tripeptide Bip-Pyr-Ala as group X<sub>2</sub>; those including VSSYLEGQ and fragments thereof amid their sequence) are not embraced by the scope of the independent claims on which they depend. A further objection for lack of unity under Rule 13.1 PCT accompanied by a request for further examination fees is not pursued at this stage as the general comments below are valid for the application as a whole. However, such an objection may be expected - at the latest - in the national/regional phase before the EPO.

**SECTION V**

- 4 Reference is made to the following documents:

- D1: WO 03/011892 A (US GOVERNMENT [US]; GREIG NIGEL H [US]; EGAN JOSEPHINE [US]; DOYLE MAI) 13 February 2003;
- D2: RUNGE S ET AL: "Different domains of the glucagon and glucagon-like peptide-1 receptors provide the critical determinants of ligand selectivity." BRITISH JOURNAL OF PHARMACOLOGY, vol. 138, no. 5, March 2003, pages 787-794;
- D3: HINKE SIMON A ET AL: "In depth analysis of the N-terminal bioactive domain of gastric inhibitory polypeptide" LIFE SCIENCES, vol. 75, no. 15, 27 August 2004, pages 1857-1870;
- D4: AL-SABAH SULEIMAN ET AL: "A model for receptor-peptide binding at the glucagon-like peptide-1 (GLP-1) receptor through the analysis of truncated ligands and receptors" BRITISH JOURNAL OF PHARMACOLOGY, vol. 140, no. 2, September 2003, pages 339-346;
- D5: CHAHRZAD MONTROSE-RAFIZADEH ET AL: "High Potency Antagonists of the Pancreatic Glucagon-like Peptide-1 Receptor" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 34, 22 August 1997, pages 21201-21206;
- D6: WO 2004/094461 A (SQUIBB BRISTOL MYERS CO [US]; NATARAJAN SESHIA IYER [US]; MAPELLI CLAUD) 4 November 2004.

- 4.1 Document D1 to D6 are cited as examples of documents disclosing peptides which contain a fragment of GLP-1 at their N-terminus.
- 4.2 Document D1 discloses "a series of chimeric peptides [which] incorporate fundamental features of exendin-4 and GLP-1" (cf. D1, example 1 and figure 1). Such analogues were designed to solve the same problem addressed by the present application, that is *i.a.* to provide GLP-1 agonists having an increased stability against proteolytic cleavage from DPP-IV. These analogues "include one or more amino acid residues present in GLP-1 and one or more amino acid residues present in exendin-4. The modifications also include truncations of either GLP-1 or Exendin-4 or the chimeric polypeptides". (cf. D1, page 13). "Lateral spacers", closely resembling to the definitions of  $S_1$  and  $S_2$  of the present application, are contemplated as well (cf. D1, page 14).
- 4.3 The oligopeptides described in D6 are considered to be detrimental to the novelty of invention 9 as defined above. More in detail, D6 discloses various N-terminal GLP-1 fragments exhibiting an increased stability to proteolytic cleavage and having a Bip-Bip dipeptide or its derivatives at its C-terminus (cf. D6, examples 11 and 12). For instance, compound # 3 (*i.e.*: HAEGTFTSD-Bip-Bip, cf. D6 Table I, page 56) does fall into the subject-matter of claim 1, as it can be regarded as a polypeptide of Formula (I), wherein  $A=NH_2$ ,  $X_1 = HAEGTFT$ ,  $S_1 = S_2 = \text{"a bond"}$ ,  $Y = SD$ , *i.e.*: "a short peptide containing two amino acids",  $X_2 = \text{Bip-Bip}$ ,  $B = CONH_2$ .
- 4.4 As a result, the present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-4 and 7-14 is not new in respect of prior art as defined in the regulations (Rule 64 PCT).
- 5 Concerning inventive step, the problem to be solved by the present application may be regarded in view of the prior art as the provision of further analogues of GLP-1 having an increased resistance to proteolysis.
- 5.1 The nine proposed solutions above are respectively the provision of the compounds embraced by formula (I), claim 1, wherein  $S_1$ -Y- $S_2$  represents a bond,  $X_1$  is a N-terminal fragment of GLP-1 spanning the sequence from HAEGTFTSD to

HAEGTFTSDVSSYLEGQAAKEFI of natural GLP-1 (or analogues thereof where "one or more of these amino acid may be replaced by an unnatural amino acids") and  $X_2$  is GPSSGAPPPS, the C-terminus of exendin-4 (*invention 1*), KELEKLL (*invention 2*), GPPS (*invention 3*) or VKGR (*invention 4*), the C-terminus of GLP-1. Alternatively,  $S_1$ -Y- $S_2$  does not represent a bond (and each of these three entities is defined at lines 16-22),  $X_1$  is a N-terminal fragment of GLP-1 spanning the sequence from HA to HAEGTFTSD of natural GLP-1 (or analogues thereof where "one or more of these amino acid may be replaced by an unnatural amino acids") and  $X_2$  is GPSSGAPPPS, the C-terminus of exendin-4 (*invention 5*), KELEKLL (*invention 6*), GPPS (*invention 7*), VKGR, the C-terminus of GLP-1 (*invention 8*) or a dipeptide as defined in claim 1, lines 13-25 (*invention 9*).

- 5.2 As discussed above, the subject-matter of claims 1-14 consists in the selection of a series of peptides obtainable by (specific) combinations of structural motifs.
- 5.3 This authority noted that no actual experimental data had been provided regarding any of polypeptides claimed at the date of filing. Although reference was made in the description to four "representative compounds (I to IV) [...] shown in Figure 1", which allegedly displayed an activity *in vivo* (cf. page 51 and Table 10), the chemical structure of such prophetic compounds was not disclosed and Figure 1 was not present in the application as filed.
- 5.4 In view of the late-filed experimental data, submitted by the applicant "as evidence of inventive merit" with letter of 15.09.2007, this authority has carefully reviewed its assessment of the inventive step of the application on file.
- 5.5 As pointed out by the applicant, the difference between the teaching of D1 and the subject-matter of *invention 1* as defined above is that a 9 to 23-residues long N-terminal fragment of GLP-1 - rather than the full-length GLP-1 - is coupled to a specific C-terminal fragment of exendin (GPSSGAPPPS). The applicant maintains that the design of the claimed sequences "is based upon the concept of having only the binding and activation component and deletion of middle residues of GLP-1 peptide or replacement with  $S_1$ -Y- $S_2$  spacer".

- 5.6 The authority agrees with the applicant in that, although the general concept of two-domain model was known for GLP-1 receptors, the available prior art did not disclose the specific combinations claimed in the novel claim 5. Although D1 does mention the use of truncated GLP-1 or Exendin-4 and "lateral spacers" (cf D1, pages 13-14), the chimeric GLP-1/Exendin 4 peptides prepared in D1 invariably include a full-length, 29 residues long, GLP-1(7-36) (cf. D1, Tables 2, 4 and 5). As a result, reading D1, a skilled person would have had no direct motivation to prepare the chimeric peptides of claim 5, which comprise particular N-truncated GLP-1 covalently coupled to GPSSGAPPPS.
- 5.7 The applicant provided late-filed experimental data to substantiate the statements made in the application as filed (cf. pages 3 and 53), alleging that all claimed chimeric peptides exhibited an increased stability to proteolytic cleavage and - most surprisingly - did retain an activity as GLP-1 agonists.
- 5.8 As a consequence, an inventive step shall be acknowledged for the peptides of *invention 1* as listed in claim 5.
- 5.9 The same reasoning may be followed for the subject-matter of *inventions 2-4* and *6-8*, since no pointer existed in the available prior art suggesting the skilled person to prepare chimeric peptides containing on one hand fragments of GLP-1 and on the other hand KELEKLL, GPPS or VKGR. The data provided with letter of 15.09.2007 are regarded as surprisingly confirming an increased resistance to proteases associated with a detectable bioactivity even after radical shortening of the GLP-1 portion of the chimera (e.g.: HAEGTFTFSD-(CH<sub>2</sub>)<sub>4</sub>-VKGR).
- 5.10 Such an unexpected result appears even more remarkable for the compounds of invention 9. As an example, even a tetrapeptide like HA-(CH<sub>2</sub>)<sub>3</sub>-Bip(2Me)DBip(2-Et) most surprisingly retain many of the biological properties of GLP-1 and at the same time its resistance to DPP-IV and pharmacokinetic parameters is improved.
- 5.11 In view of all the above, claims 5-6, which are directed to subject-matter that is novel over the cited prior art, are acknowledged to involve an inventive step.

- 6 The applicant will inevitably be requested in a later national/regional stage to present additional arguments and experimental data substantiating that all claimed peptides embraced by claim 1 and specifically listed in claims 5-6 do solve the objective problem underlying the application no matter how short the GLP-1 fragment is, as long as it contains at least either HAEGTFTSD (*inventions 1-4*) or HA plus S<sub>1</sub>-Y-S<sub>2</sub> (*inventions 5-9*) at its N-terminus, and independently of the actual structure of the "dipeptide selected from combination of two amino acids consisting of natural or unnatural amino acids, having a side chain containing an arylalkyl or heterorylalkyl" at their C-terminus (*invention 9*). Alternatively, the subject matter claimed should be restricted to be commensurate with the teachings of the invention.

**SECTION VI**

Certain documents cited:

| Application No | Publication date<br>(day/month/year) | Filing date<br>(day/month/year) | Priority date (valid claim)<br>(day/month/year) |
|----------------|--------------------------------------|---------------------------------|-------------------------------------------------|
| WO 2006/024275 | 09.03.2006                           | 26.08.2005                      | 03.09.2004                                      |
| WO 2005/077072 | 25.08.2005                           | 11.02.2005                      | 11.02.2004                                      |
| WO 2006/014287 | 09.02.2006                           | 30.06.2005                      | 02.07.2004<br>26.05.2005                        |

558-645-CHL

Kg/ 10 ml and blood was collected at different time intervals, via retroorbital plexus. Test compounds (peptidomimetics) were dissolved in an appropriate vehicle at a concentration in nmol/ ml equivalent to the dose that was to be administered in nmol / kg, so that each mouse would receive the same volume / weight of dosing solution.

5 Blood samples were drawn prior to Vehicle/Test compound/Glucose load (0 minute) and then at 15 min, 30 min, 60 min and 120 min. Vehicle/Test compound was administered 15 minutes prior to glucose load, via intra-peritoneal route of administration. Blood samples were centrifuged and the obtained serum was stored at - 20° C for analysis. Test compounds were examined along with a reference (positive control) and a vehicle control, with n = 6 animals per group. Glucose was determined by the GOD/POD method from serum. The mean value of duplicate results was calculated. The absolute values of glucose in serum levels were calculated using MS Excel software. The 0-minute base line corrected line graph were plotted using Graphpad prism software (ver 3.0). Area under the Curve (AUC) and Base line corrected area under the curve (BCAUC) were calculated and analyzed by performing One way ANOVA followed by Dunnett's post test using Graphpad prism software (ver 3.0).

Using above experimental protocol, in vivo glucose lowering properties of some of the selected compounds, which showed in vitro EC<sub>50</sub>, in CHO-GLP-1R cAMP assay, in the range of 1-50 nM range were determined. In Table 10, the in vivo glucose lowering potencies (ED<sub>50</sub> in IPGTT SAM model) of selected four representative compounds (Comp. I, II, III & IV) were given.

Table 10: In vivo potencies of compound I to IV (ED<sub>50</sub>), in IPGTT SAM Model

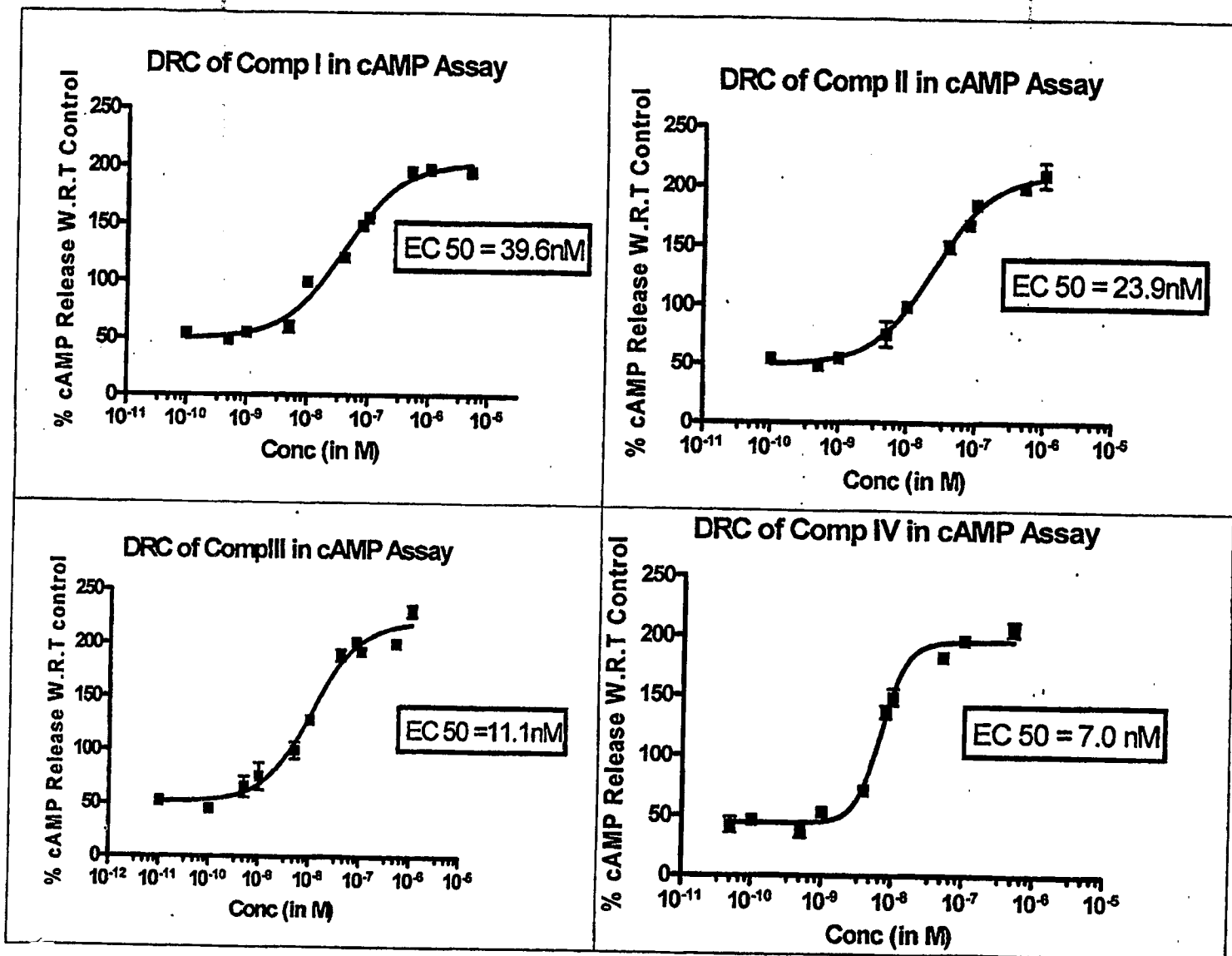
| Comp. | Sequence                                                                                                   | ED <sub>50</sub> in IPGTT SAM Model (n = 6) |
|-------|------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| I     | <u>HGEGT-(α-Me)-Phe(2-F)-TS-(CH<sub>2</sub>)<sub>5</sub>-<br/>Bip(2-Et)-Bip(2-Et)</u><br>Table 4 (94 Seq.) | 1 μmole / kg                                |
| II    | <u>HGEGTFTSDLSKOMKELEKLL</u><br>Table 3 (1 Seq.)                                                           | 500 nM / Kg                                 |
| III   | <u>HGEGTFTSDLSKOM-(CH<sub>2</sub>)<sub>3</sub>-GPSS</u><br>Table 1 (8 Seq.)                                | 250 nM / kg                                 |
| IV    | <u>HGEGTFTSD-(CH<sub>2</sub>)<sub>3</sub>-GPSSGAPPPS</u><br>Table 1 ( 1 1 Seq.)                            | 100 nM / Kg                                 |

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Figure: 1- EC<sub>50</sub> values ('S'-Curves) for some of the representative compounds (in vitro cAMP assay)



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g/kg/10 ml y se recolecta la sangre en diferentes intervalos de tiempo, por vía del plexo retro orbital. Los compuestos de ensayo (peptidomiméticos) se disuelven en un vehículo apropiado en una concentración en nmol/ml equivalente a la dosis que se administra en nmol/kg, de tal manera que cada ratón podría recibir el mismo volumen/peso de solución de dosificación.

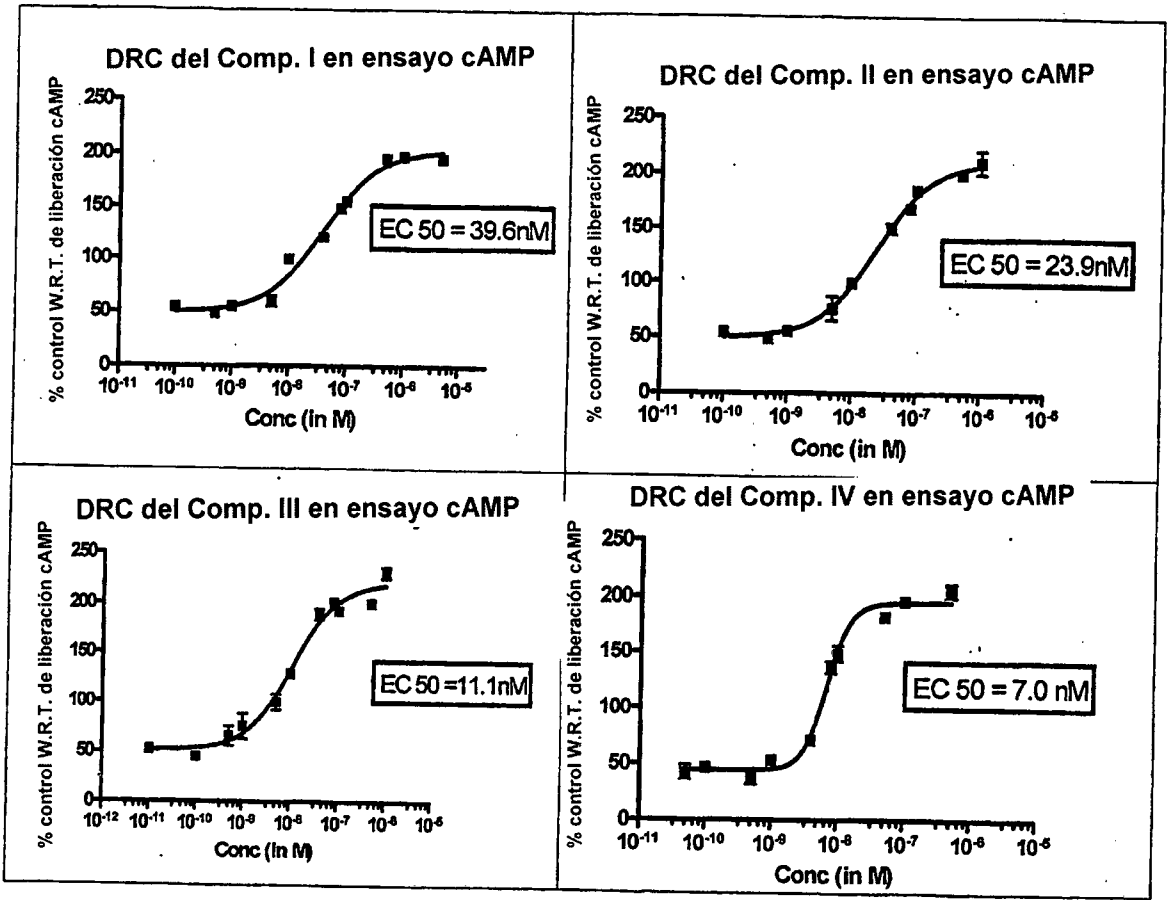
Las muestras de sangre se retiran antes para vehículo/compuesto de prueba/carga de glucosa (0 minutos) y luego en 15 min, 30 min, 60 min, y 120 min. El compuesto de vehículo/ensayo se administra 15 minutos antes para carga de glucosa, por vía de ruta intraperitoneal de administración. Se centrifugan las muestras sanguíneas y el suero obtenido se almacena a -20 °C para análisis. Los compuestos de ensayo se examinan junto con una referencia (control positivo) y un vehículo de control con n=6 animales por grupos. La glucosa se determina por el método GOD/POD de suero. El valor medio de los resultados duplicados se calcula. Los valores absolutos de la glucosa en los niveles de suero se calculan utilizando el software MS Excel. La gráfica de línea corregida de línea base de 0 minutos se grafica utilizando el software Graphpad prism (ver 3.0). El área bajo la curva (AUC) y el área de línea base corregida bajo la curva (BCAUC) se calculan y analizan al desarrollar un ANOVA de una vía seguido por el ensayo Dunnett utilizando el software Graphpad prism (ver 3.0).

Utilizando el anterior protocolo experimental, las propiedades de reducción de glucosa in vivo de algunos de los compuestos seleccionados, que muestran que EC<sub>50</sub> in Vitro, en ensayo cAMP CHO/GLP-1R, en el rango de 1-50 nM se determinan. En la tabla 10, se dan las potencias de reducción de glucosa in vivo (ED<sub>50</sub> en el modelo SAM IPGTT) de cuatro compuestos representativos seleccionados (Comp. I, II, III y IV).

**Tabla 10: Potencias in vivo de los compuestos I a IV (ED<sub>50</sub>), en modelo IPGTT SAM**

| Comp. | Secuencia                                                                                                                    | ED50 en Modelo IPGTT SAM (n=6) |
|-------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| I     | <u>HGEGT-(<math>\alpha</math>-Me)-Phe(2-F)-TS-(CH<sub>2</sub>)<sub>3</sub>-<br/>Bip(2-Et)-Bip(2-Et)</u><br>Tabla 4 (Sec. 94) | 1 $\mu$ mole / kg              |
| II    | <u>HGEGTFTSDLSKOMKELEKLL</u><br>Tabla 3 (Sec. 1)                                                                             | 500 nM / Kg                    |
| III   | <u>HGEGTFTSDLSKOM-(CH<sub>2</sub>)<sub>3</sub>-GPSS</u><br>Tabla 1 (Sec. 8)                                                  | 250 nM / kg                    |
| IV    | <u>HGEGTFTSD-(CH<sub>2</sub>)<sub>3</sub>-GPSSGAPPPS</u><br>Tabla 1 (Sec. 11)                                                | 100 nM / Kg                    |

Figura 1: valores EC50 (Curvas 'S') para algunos de los compuestos representativos (ensayo in vitro cAMP)



REPUBLICA DE COLOMBIA  
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 313

2020  
Bogotá D.C.,

Doctor(a)  
RODRIGUEZ D ALEMAN DILIA MARIA  
Apoderado(a) y/o Representante de  
CADILA HEALTHCARE LIMITED

|            |                            |                   |
|------------|----------------------------|-------------------|
| REFERENCIA | Radicación No.             | 07 121830         |
|            | Solicitud internacional    | PCT/IN2006/000154 |
|            | Fecha inicio fase nacional | 05/12/2007        |
|            | Trámite                    | 11                |
|            | Evento                     | 379               |
|            | Actuación                  | 416               |
|            | Oficio No.                 | 6855              |
|            | Folios                     | 1                 |

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

Cúmplase  
Dado en Bogotá DC,

19 OCT 2008

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

jfernand

**DIVISIÓN DE NUEVAS CREACIONES**

RADICACIÓN EXPEDIENTE No.07-121830

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**  
  
FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **599** DE  
  
FECHA **31 DE DICIEMBRE DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA  
  
LEY EXPIRA EL **30 DE MARZO DEL 2009**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI \_\_\_\_\_ NO\_\_ \_\_X\_\_ \_\_\_\_\_