

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señora

Alix Carmenza Céspedes de Vergel

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Referencia: Expediente No. 08.081.992

Solicitud de Patente de Invención titulada: "Inhibidores de 11-beta HSD1"

Solicitante: Wyeth

MEMORIAL DE ALCANCE

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

El día 6 de agosto de 2008, bajo el número de radicación 08.081.992, presenté la solicitud de patente de invención de la referencia, para la cual adjunto Reporte Preliminar Internacional sobre Patentabilidad Capítulo I.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ

C.C.No.79.143.366 de Usaquén

T.P.20.281

Anexo: Reporte Preliminar Internacional sobre Patentabilidad Capítulo I

PATENT COOPERATION TREATY

PCT/US2007/003134

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)

(PCT Rule 44bis.1(c))

To:

NABINGER, Robert, C.
Fish & Richardson P.C.
P.O. Box 1022
Minneapolis, Minnesota 55440-1022
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
21 August 2008 (21.08.2008)

Applicant's or agent's file reference
16156-048WO1

International application No.
PCT/US2007/003134

International filing date (day/month/year)
07 February 2007 (07.02.2007)

IMPORTANT NOTICE

Priority date (day/month/year)
07 February 2006 (07.02.2006)

Applicant

WYETH et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

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

Authorized officer

Athina Nickitas-Etienne

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Form PCT/IB/325 (January 2004)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 16156-048WO1	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2007/003134	International filing date (day/month/year) 07 February 2007 (07.02.2007)	Priority date (day/month/year) 07 February 2006 (07.02.2006)	
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237			
Applicant WYETH			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | |
|---|---|
| ☒ Box No. I | Basis of the report |
| ☐ Box No. II | Priority |
| ☒ Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☒ Box No. IV | Lack of unity of invention |
| ☒ Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☒ Box No. VI | Certain documents cited |
| ☐ Box No. VII | Certain defects in the international application |
| ☐ Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis.2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70 Form PCT/IB/373 (January 2004)	Date of issuance of this report 12 August 2008 (12.08.2008)
	Authorized officer Athina Nickitas-Etienne e-mail: pt04.pct@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2007/003134International filing date (day/month/year)
07.02.2007Priority date (day/month/year)
07.02.2006International Patent Classification (IPC) or both national classification and IPC
INV. C07D211/06 C07D295/22 C07D401/04 A61K31/44 A61K31/495Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinionsee form
PCT/ISA/210

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2007/003134**Box No. 1 Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ 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.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US2007/003134**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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

- ☐ the entire international application
- ☒ claims Nos. 49-92, 94-102 with respect to industrial applicability
because:
 - ☐ the said international application, or the said claims Nos. 94-102 relate to the following subject matter which does not require an international search (*specify*):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
 - ☒ no international search report has been established for the whole application or for said claims Nos. 49-92
 - ☐ 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 Searching 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 Searching 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 13 ter.1(a) or (b).
 - ☐ 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 Searching 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 Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2007/003134**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ 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
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-48, 93-102 partly

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

1. Statement

Novelty (N)	Yes: Claims	<u>9-13, 15, 16, 18-26, 30-34, 43-48, 100, 101</u>
	No: Claims	<u>1-8, 14, 17, 27-29, 35-42, 93-99, 102</u>
Inventive step (IS)	Yes: Claims	<u>11-13, 16, 18-20, 23-26, 43-48</u>
	No: Claims	<u>1-10, 14, 15, 17, 21, 22, 27-42, 93-102</u>
Industrial applicability (IA)	Yes: Claims	<u>1-48, 92</u>
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2007/003134

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)
and/or
2. Non-written disclosures (Rules 43bis.1 and 70.9)
see form 210

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

International application No.

PCT/US2007/003134**Re Item III.**

Claims 93-102 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

This Authority considers that there are 4 inventions covered by the claims indicated as follows:

1-48, 93-102 partly

Compounds wherein R1 is selected from (i) or (ii) as defined in claim 1, R2 is aryl or heteroaryl, X is S(O)_n or S(O)_nNR6, and at least one of W1, W2, Z1, Z2 is different from hydrogen and selected from (i)-(iv); compositions and methods involving such compounds;

49-74, 93-102 partly

Compounds wherein R1 is selected from (i) or (ii) as defined in claim 1, R2 is substituted aryl or heteroaryl or OR1, SR1, NR3R4, X is S(O)_n or s(O)_nNR6, and all of W1, W2, Z1, Z2 must be hydrogen; compositions and methods involving such compounds;

75-87, 93-102 partly

Compounds wherein R1 is aralkyl, cycloalkyl or alkylcycloalkyl, R2 is aryl or heteroaryl or OR1, SR1, NR3R4, X is CO, and W1, W2, Z1, Z2 are selected from (i)-(v) as defined in claim 75; compositions and methods involving such compounds;

88-92, 93-102 partly

compounds wherein R1 is aryl or heteroaryl, R2 is cycloalkyl, cycloalkenyl, heterocyclyl or heterocycloalkenyl, X is S(O)_n or s(O)_nNR6, and W1, W2, Z1, Z2 are selected from (i)-(v) as defined in claim 75; compositions and methods involving such compounds;

The reasons for which the inventions are not so linked as to form a single general inventive

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

International application No.

PCT/US2007/003134

concept, as required by Rule 13.1 PCT, are as follows:

The present application relates to compounds which are suitable as 11-beta HSD1 inhibitors. Claimed are compounds of (different) formulae (I) as defined in independent claims 1, 49, 75, and 88. The present application relates to four different inventions as defined above which are not so linked as to form a common single inventive concept.

The structural feature which is common to all the compounds of formulae (I) as defined in independent claims 1, 49, 75, and 88 is the piperidine/piperazine ring. The definitions of the further groups and substituents R1, R2, X, W1, W2, Z1, Z2 in independent claims 49, 75, and 88 are different from those of claim 1 and include other possibilities which are not found in formula (I) of claim 1.

Compounds having 11-beta HSD1 inhibitory activity and based on piperidine or piperazine derivatives are already known in the state of the art, e.g. WO2004/089416, page 210, line 4; WO2005/118538, examples E, G, H, L; WO2006/002350, example 6). Therefore neither the common activity of the claimed compounds as HSD1 inhibitors nor the structural feature common to all the claimed compounds (i.e. piperidine or piperazine ring) can be considered as a special technical feature making a contribution over the prior art and linking the individual inventions so as to form a common inventive concept.

11-beta HSD1 inhibitors wherein X is SO₂, SO₂NH, or CO, are known in the state of the art (WO2005/118538, example G; US2005/0288308, formula (I), WO2004/089416, page 210, line 4).

11-beta HSD1 inhibitors wherein the piperidine or piperazine ring is unsubstituted or substituted with alkyl are known in the state of the art (WO2005/118538, example G; US2005/0288308, example 25).

11-beta HSD1 inhibitors wherein the piperidine or piperazine ring is substituted by an aryl group corresponding to R2 are known in the state of the art (WO2004/089416, page 210, line 4).

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

International application No.

PCT/US2007/003134

The special technical features of the first invention (claim 1) which make the relevant difference over the 11-beta HSD1 inhibitors known in the prior art are the features: (a) R2 is aryl or heteroaryl; and (b) X is S(O)_n or S(O)_nNR6; and (c) one, two, three or four of W1, W2, Z1, Z2 are different from hydrogen and are selected from groups (i)-(iv) as defined in claim 1.

The further independent claims 49, 75, and 88 do not contain these special technical features (a), (b), (c) or an equivalent thereof. The inventions defined in claims 49, 75, and 88 therefore are not so linked with the first invention as to form a single common inventive concept.

Similar applies to the further inventions. The compounds defined in claims 49, 75, and 88 do not share the same or corresponding common technical features which as a whole make a contribution over the prior art in the sense of Rule 13 PCT and therefore are not so linked among each other as to form a common single inventive concept.

The search has been carried out for the invention first mentioned in the claims, i.e. claims 1-48, and claims 93-102 partly, insofar said claims 93-102 relate to compounds of formula (I) as defined in claims 1-48.

Re Item V.

1. Reference is made to the following documents:

- D1: WO 2005/115983 A (KALYPSYS INC [US]; ZHAO CUNXIANG [US]; MALECHA JAMES W [US]; NOBLE STE) 8 December 2005 (2005-12-08)
D2: MICHAEL D.B. FENSTER, BRIAN O. PATRICK, GREGORY R. DAKE:
"Construction of azaspirocyclic ketones through alpha-hydroxyiminium ion or alpha-siloxy epoxide semipinacol rearrangements" ORGANIC LETTERS, vol. 3, no. 13, 2001, pages 2109-2112, XP002444780
D3: ROBERT R. FRASER, T. BRUCE GRINDLEY, SALVATORE PASSANNANTI:

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

International application No.

PCT/US2007/003134

- CAN. J. CHEM., vol. 53, 1975, pages 2473-2480, XP009087397
- D4: YOSHINAO TAMARU, MAKOTO HOJO, SHIN-ICHI KAWAMURA, ZEN-ICHI YOSHIDA: "Synthesis of five- and six-membered nitrogen heterocycles via a palladium(II)-catalyzed cyclization of unsaturated amides" J. ORG. CHEM., vol. 51, 1986, pages 4089-4090, XP002444781
- D5: RICHARD D. GLESS, HENRY RAPOPORT: "6,7-Benzomorphans. Stereospecific synthesis of 2,9alpha- and 2,9beta dimethyl-2'-methoxy-6,7-benzomorphans" J. ORG. CHEM., vol. 44, no. 8, 1979, pages 1324-1336, XP002444782
- D6: US 2005/288308 A1 (AMRIEN KURT [CH] ET AL) 29 December 2005 (2005-12-29)
- D7: US 2006/025455 A1 (AMREIN KURT [CH] ET AL) 2 February 2006 (2006-02-02)
- D8: WO 2005/118538 A (AMGEN INC [US]; DEGRAFFENREID MICHAEL R [US]; POWERS JAY P [US]; SUN D) 15 December 2005 (2005-12-15)
- D9: WO 2004/089416 A (NOVO NORDISK AS [DK]; KAMPEN GITA CAMILLA TEJLGAARD [DK]; ANDERSEN HEN) 21 October 2004 (2004-10-21)
- D10: WO 2006/002350 A (INCYTE CORP [US]; YAO WENQING [US]; ZHANG COLIN [US]; AGRIOS KONSTANTIN) 5 January 2006 (2006-01-05)
- D11: WO 2007/070506 A (AMGEN INC [US]; POWERS JAY P [US]; SUN DAQING [US]; TU HUA [US]; YAN X) 21 June 2007 (2007-06-21)

2. Document D1 discloses numerous compounds corresponding to formula (I) of claim 1 and the use thereof for the treatment of type 2 diabetes, syndrome X, obesity, dyslipidemia, atherosclerosis, and wound healing (examples 6,7,19-21,23-25,68-73,77,78,81-83,90,94,98-114,118,149,177,192-195,197,198,200,204,206,209,213-222,224,226-229,231,232; paragraphs 174-176, claims 52,66,71,94). The subject matter of claims 1-8,17,27-29,35-42,93-99 and 102 lacks novelty in view of this disclosure.

Document D2 discloses a compound 2c which falls within the scope of claims 1,3,4,6-8,14, and 27.

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

International application No.

PCT/US2007/003134

Document D3 describes 2-methyl-4-phenyl-N-p-toluenesulfonylpiperidine and N-p-toluenesulfonyl-R-2,6-dimethyl-4-phenylpiperidine which correspond to claims 1,3-8,14, and 27.

Compound 5g of document D4 is novelty destroying for the subject matter of claims 1,3-8,14, and 27.

Compound 61 of document D5 is cited against the novelty of claims 1,3,4,6, and 27.

3. Documents D6-D8 relate to describe 11-beta HSD1 inhibitors and may be considered as the closest prior art for the subject matter of claim 1.

Documents D6 and D7 describe 11-beta HSD1 inhibitors of formula (I). The subject matter of claims 1,4,5,21,22,27-34,93-98,100,101 is considered as a selection from the compounds of D6 and D7, formula (I), for R4 is piperidyl substituted with e.g. alkyl, aryl, or certain heterocycles (cf. D6, paragraphs 1,8,9,15,28-30,69,71; D7, paragraph 13). It is not apparent from the present application that the selection made results in any unexpected or non-obvious features of the now claimed compounds over the compounds suggested in D6 and D7. The subject matter of the abovementioned claims is therefore obvious.

The subject matter of claims 1,3-10,14,15,27-34 and 93-100 is considered as a selection from the compounds and methods suggested in D8 (formula (I) with Ncyc=(b); paragraphs 31-32). Again, it is not apparent from the present application that the selection made results in any unexpected or non-obvious features of the now claimed compounds over the compounds suggested in D8. The subject matter of the abovementioned claims is therefore obvious.

Insofar the claimed compounds correspond to the general formula (I) of D1, such compounds, and compositions and methods according to claims 93-99 and 102 are obvious in view of D1 (cf. D1 claim 94).

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

International application No.

PCT/US2007/003134

4. For the assessment of the present claims 93-102 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI.

D12, published on 21 June 2007, with priority of 14. Dec. 2005, discloses compounds and methods which fall within the scope of claims 1-10, 14, 27, 35-44, 47, 48, 93-100 (examples 1-7, paragraph 1, claims 1, 28).