BAKER &McKENzIE SUPERINTENDENCIA DE INDUSTRIA ’{ COMERCIO

DIiIIIIIIflhIIiIIIIIiIIIIIIiIIIIIIIIIIIIII
i’o. 07-134138- -00001-0000
Fec- :41 Dep, 2020 NUEGREACIONE
e J’d ASNACIONALI

Act 2PC[\fRMACiON Folios: 12

’??0
Seæora

Alix Carmenza CØspedes de Verge!
Jefe de Division de Nuevas Creaciones SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO E. S. D.

Referencia: Expediente No. 07.134.138
Solicitud de Patente de Invención titulada: "MØtodos para purificación de
tigeciclina"

Solicitante: Wyeth

MEMORIAL DE ALCANCE

ALVARO CORREA ORD614EZ, mayor de edad y vecino de Bogota D.C., identificado seguin aparece al pie de mi firma, en ml condición de apoderado de la sociedad en referencia, manifiesto lo siguiente:

El dIa 19 de diciembre de 2007, bajo el niimero de radicación 07.134.138, presentØ la solicitud de patente de invención de la referencia, para la cual adjunto Reporte Preliminar Internacional sobre patentabilidad CapItulo 1.

EZ
C.C.No.79.143.366 de Usair
T.P.20.28 I

Anexo: Reporte Preliminar Tnternacional sobre patentabilidad CapItulo 1.

BOGLMS/BOGDMS-1 03276-VI - DOC -P2007/000339

FEB-11-2088 14:48 From:FINNEGAN HENDERSON 6174521666 To:6430011420383*001400 F.3113 QD

PATENT COOPERATION 1’RLATY PCT/U82006,’020270

From ffic INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF IN1tRNATJ0NM. PRFJ IMINARY REPORT ON PATENTABILITY (Cl IAPTER 1 OF THE PATENT COOPERATION

TREATY) (PCT Rule 44b. 1(c))

To

MCOONELL, Leslie, k
FINNEGAN, HENDERSON, FARABOW
ARRET1 & DUNNER, L.L,P.
001 New York Avenue
Washington, DC 20001-4413
!TAT5-UNI5 DAMERIQUE

I ThC Jmematioiii! Buriu of WIPO Au.horzed oliiccr

I.34.chemin des CuIombcfls

1211 Oenev 20. Siitz{r1uwJ Ellen Moyse

LFucmliIe No. +4122 38 8270 -mall:p105 pet@wipnint
Form F’(771131326 Jarniry X4)
1U

Ii

FEB-11-2808 14:48 From:FINNEGAN HENDERSON 6174521666 To:6430011420383*001408 F.4113 Q’

PATENT COOPERATION TREATY z$3
PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Clmp!ef 1 of the Patent Cooperaton Treaty)

(PCT Rule 44bis)

[1

or agent’s tile reference FOR FURTHER ACTION See ilem4 below 1142,383-304
ltiternaiional:ipplicatirn No. Ititurtiuliujial filing date (Say/inon?h/yl!ar) Priority date (da)/mouth/year) PCT/U52006/020270 2S May 2(>06(25..05.2006) 7 My 00S (27.05.2005) Iniurituticiuni Patent Classification k8th edition unl"g older edition indicated)
See relevant information in Form PCT/ISA/237
Applicant
WYETH -.

L This international preliminary report on patentability (Chapter 1) is issued by the lateratitional Bureau on behalf of the
intuniutioriul ScuieWiig Authority under Rule 44 bit, 1(a).

2. This REPORT consists of a total of 10 shecta. including this covet sheet.

In the attached sheets. any reicrence to the written opinion af the International Searching Authority should he read as a reterene
to the inieniational preliminary report on patentability (Chapter 1) instead.

3. This report contains indications relating to the t,hlnwin items:

Box No. I Bats of the report

Box No. 11 Priority

Box No. 1.11 Non.etubhsl,ment of opinion With regard to iiovelty, inventive step ind industrial
applicability

Box No. IV Lack of unity of invcnhiirn

Box.No. V Reasoned statement undei Article 35(2) with regard to novelty, inventive step or industrial
applicability; citations and explanations suppuiling such statement

Box No, Vj C.CrttLiLI documents cited

Box No. VII Certain defecla in the interinitiunel application

Box No. Viii Certain obsurvulivus on the international application

4. The International Bureau will cosnmutiicCmte this report to leimitjn;mletl Offices in accurdanue with RuIcs 44bis3(c) and Q3hLr.I hut
aot. except where the applicant makes an express request under Artide 23(2). before the expiration of 30 months from the priority
date (Rule 44bis 2).

The Intcrnationul. Bureau of WJPO
34. chemin des Colomt’vtte
1211 Geneva 20. Switzerland
Facsimile No. +4122 338 82 70
Prm PCT/1B1373 (January 2004)

Date of issuance of this report
30 November 2007 30.1 1.2007)
Authorized officer

Ellen Moyse

e-mail: ptOS.pcltThwipo.int

FE9-11-2888 14:48 From:FINNEGflN HENDERSON 6174581666 To:6430011420383*801480 P.5113

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY
To:

see form PCTASA220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43b1s.1)

Date of mailing - 0007ronth4’e0 aee form PGTlSA210 (ts.cond heffi)

Applicant’s or agenls file reference FOR FURTHER ACTION
see form PCTASA,220 I See paragraph 2 below
International 3pplition No. international filing data (yAnonTh4’ear) Priority date (daynJQnU*oor) -
PCTiUS20061020270 1 25.05.2006 1 27.05.2005
Intematonat Patent CIesificatior, (]PC) or both r.ittnaI classification and IPC
INV. 0070231124 C07023726 A61K31i5 A61P31/DO

Applicant
WYETH

1. This opinion contains indications relating to the following items:
Box No, I aais of the opinion
0 Box No. II Priority
Sax No, III Non-establishment of opinion with regard to novelty, inventive step and Inductrial applicability
0 Box No, IV Lack of unity of invention
ED Box No. V Reasoned statement under Rule 43b,1(a)(i) with regard to novelty, inventive step or industrial
applicability; ctotions and explanations supporting such statement
Sox No. VI Certain documents cited

O Box No. VII Certain defects in the international application
Box No. VIII Certain observations an the international application
2. FUEITHER ACTION

It 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 notifed 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 apprraant 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 PCTiEtA20 or before the expiration of 22 months from the priority date, whichever expires later.

For Further optioric, Form PCTASA/220.
S. For Further notes to Form PCT)ISAj220.

Name and mailing address of the lSAi IDrileof completion
this opinion

20European Patent Office I see torn, D80298 Munich I PCTiISA210 -- Tel. +49 89 2399 -0 Tx: 523656
Form (PCTASAI237) (CoverSheet) (April 2005)

Auitrcri:ad Officer

FEB-11-2008 14:49 From:FINNEGnN HENDERSON 6174521666 To:6430011420383*001400 F.6113 G’ ,

S

It

WRITTEN OPINION OF THE International application No. INTERNATIONAL SEARCHING AUTHORITY PCT4J82006,020270

Box No.1 Basis otthe opinion
1. With regard to the language, this opinion has been established on the basis of;
IR the international application in the language in which it was filed
0 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:
O a sequence listing
0 table(s) related to the sequence listing
b frmt of material:
0 on paper
in electronic form
c, time of fllingiturnishlng;
U contained in the international application as flied,
filed together with the international application in electronic form.
0 furnished subsequently to this Authority for the purposes of search.

3. 0 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:

Form PCTASN237 (April 2005)

FEB-11-2O8 14:49 From:FINNEGAN HENDERSON 6174521656 To:6430011420383*0014 F.7’13 QG

WRITTEN OPINION OF THE International application No. INTERNATIONAL SEARCHING AUTHORITY PCT,1J82006,Q20270

Box No. ill Non-establishment of opinion with recjardto novelty, inventive step and industrial _apptlbiIly -
The questions whether th 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
O the entire international application
claims Nos. 41(part)-46(part) for inventive step
because:

0 the said international application, or the said claims Nos. 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. 41 (part)- 46(part) are so unclear that no meaningful opinion could be formed (specify):
see separate sheet

the claims, or said claims Nos. 41 (pa rt)-46(part) are so inadequately supported by the description mat no meaningful Opinion could be formed (specify;
see separate sheet
no international search report has been established for the whole application or for said claims Nos.

D 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.

0 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 Rating in response to an invitation under Rules l3 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 proscribed 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 avaiiabie to the International Searching Authority in a form and manner acceptable to it.
0 the tables related to the nucleotide andkr amino acid sequence listing, it 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

Form PCTASA/257 (April 2005)

FEB-11-2008 14:49 From:FINNEGN HENDERSON 617521665 To:643001120383*0D140O P.8’13

4

WRITTEN OPINION OF THE international application No. INTERNATIONAL SEARCHING AUTHORITY PCTAJ82006,020270

Box NO.V Reasoned statement under Rule 4bis.1(a)(1) with regard to novelty, Inventive step or
Industrial applicability; citations Dndplenations supporting such statement

1. Statement

Novelty (N) Yea: Claims I,2-36,41 (part)-46(part), 47-50

Inventive step (IS)

industrial applicability (IA)

2. Citations and explanations

see separate sheet

Form PCTA5N37 (April 2005)

No: Claims 37-4.0

Yes: Claims 2,15-16,22-29,49-50
No: Claims 1.3-14,17-21,30-36,41 (part)-4(part),47-48

Yes: Claims 1-50
No: Claims

FEB-11-2009 14:50 From:FINNEGAN HENDERSON 6174521666 To:643001142083*001400 P.9/13 04

WRITTEN OPINION OF THE IriterriaUonal application No. INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET) PCT/US2006/020270

Rcference is made to the following documents:

Dl: IP0582790
D2: LJ85675030

D3: Drugs of the Future, 2001, 26(9), 851-858
D4: Journal of Medicinal Chemistry, 1994, 37, 184-188

J3_item Iii
Non-establishment of opinion with regard to novelty, inventive step and Industrial applicability

Claims 41 (part)46(part) are not supported by the description as required by Article 6 POT, as their scope is broader than justified by the description. The reasons are that, according to the examples of acylation (examples 3, 3A, 5, 7, 9, 10 and 11-19), the acylation reaction as claimed in this application works in the absence of a reagent base only in water, acetonitrile or DMPU or in a mixture of these solvents. In other solvents (examples 14-19), the acylation reaction does not work or leads to an impure compound.

Re ltem,M
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application does not meet the criteria of Article 33(1) POT, because
the subject-matter of claims 37-40 is not new in the sense of Article 33(2) PCT.

1.1 The compounds disclosed in this application are already known (see Dl),
therefore the subject-matter of claim 37 Is not new in the sense of Article 33(2)
POT.

1.2 Moreover the use of the compounds disclosed in this application in a composition
is also not new in the sense of that these compounds were already known and characterized (see Dl), therefore the subject-matter of claims 38-40 is not new in the sense of Article 33(2)POT.

Form PCT/1$A/2a7 (a.p&81e Shoat) (Shoot 1) (EPO.AprI 2005)

FEB-11-2008 14:58 From:FINNEGAN HENDERSON 5174521665 To:6430011428383*881480 P. 18’13OD

WRITTEN OPINION OF THE International application No. INTERNATIONAL SEARCHING

AUTHORITY (SEPARATE SHEE)) PCT/US2006/020270

2. The present application does not meet the criteria of Article 33(1) PCT, because
the subject-matter of claims 1,3-14,17-21,30-36,47-48 does not involve an
inventive step in the sense of Article 33(3) PCT.

2.1 The document Oils regarded as being the Closest prior art to the subject-matter
of claim 1 and discloses:

The preparation of compounds of formula I of this application and more
specifically the purification of 4S-(4a,1 2a)]-4,7-Rls(dimethylamino)-9-[[(dimethylsmino)acetyi]aminoj 1,4,4a,5,5a,6,1 1,1 2a-octahydro-3, 10,12,1 2a-tetrahydroxy-i,1i -dioxo-2-naphthacenecarboxymide dihycirochloride, by dissolving this solid in 250 ml methyl alcohol, adding this solution slowly to 1600 ml of methylene chloride and collecting the precipitate (Example 5, page 13); this purification is realised at room temperature (implicit disclosure).

The difference between the disclosure of Dl and the subject-matter of claim 1 is that the combination of the compound of Formula 1 of this application with a polar aprotic solvent and a polar protic solvent is mixing for at least one period of time ranging from 15 minutes to 2 hours before the isolation.

The solution proposed in claim 1 of the present application cannot be considered
as involving an inventive step (Article 33(3) PCT) because no particular effect appears by mixing the combination described above during a specific period of
time.

22 Dependent claims 3-10,12,17,20-21,3034,36,47-48 do not contafn.any features
which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Dl claim 1 and example 5).

2.3 The choice of methyl acetate or acetone as protic apolar solvent in claims 11, 13
and 35 is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. Therefore dependent claims
11 and 13 do not involve an inventive step in the sense of Article 33(3) PCT.

Form PC7IISA/237(Separate Sheet) (Sheet 2) (EPO’A4r11 2005)

8

FEB-11-2008 14:50 Frorn:FINNEGRN HENDERSON 617452165E To:643 114 383*001400 P. 11’13’

$70

WRITTEN OPINION OF THE International application No. INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET) PCT/U$2006/020270

2.4 The solution proposed in claim 14 of the present application can also not be
considered as involving an inventive step (Article 33(3) PCT) because according
to examples 1 and 3 on pages 71-72 of this application, no particular effect
appears by combining equal volumes of the two solvents.

2.5 The solution proposed in claims 18-20 of the present application can also not be
considered as involving an inventive step (Article 33(3) POT), because in view of example 5 of Dl, the skilled person would regard it a normal design procedure to repeat again at least once the purification process to increase the purity of the compound, i.e. to combine the solid obtained after the first purification process
with methanol and rnethylerie chloride either in the ratio by volume already used
(i.e. 1:6.5 methanol:methylene chloride according to Dl) or either in a different
ratio.

3. The combination of the features of dependent claims 2,15-16,22-29,49-50 Is
neither known from, nor rendered obvious by, the available prior art. The reasons are as follows:

3.1 The document D2 is regarded as being the closest prior art of claim 2 and
discloses:

A method for selectively extracting a compound analogous of compounds of formula 1 of this application from an aqueous mixture containing a compound of formula I, its 04-epimer and its oxidative degradation by-prodcuts by adding methylene at a pH between pH 6.5-8.0; and obtaining an extract containing methylene chloride, a compound of formula I. and its C4-epimer, said epimer being present in an amount of less than 3% of the amount of the compound of formula I. By this process the purity levels of the compound of formula I are between 92-98.5% and the yields are between 26-56% (claim 1 and column 3 lines 26-36).

The problem to be solved by claim 2 may therefore be regarded as an Improved purification process to the known process disclosed in D2 to get compounds of formula I in a purer form and in a better yield.

There is no indication In Dl or D2 that compounds of formula I can be obtained

Form PCT/15N237 (Sepwi1e Sheet) <ShGOI 3) (EP(>AprIl 200)

FEB-11-208 14:51 From:FINNEGAN HENDERSON 6174516E To:5430011420383*01400 P.12/13010

- 7r7
t,I

WRITTEN OPINION OF THE International application No. INTERNATIONAL SEARCHING

AUTHORITY (SEPARATE SHEET) -- PCTIUS2006/020270

with levels of purity greater than 99%, wherein the amount of the C4-epimer is
0.4% and with a yield of 79% (cf example 4 page 72 of this application) by
performing a recrystallisation which Combine a pair of solvents and use a gradlant
of temperature instead of working at room temperature. Therefore the subject-
matter of claim 2 involves an inventive step in the sense of Article 33(3) PCT.

3.2 Claims 15-16,22-29,49-50 are dependent on claim 2 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

4. The present application does not meet the criteria of Article 33(1) POT, because the subject-matter of claims 41-46 does not involve an inventive step in the sense
of Article 33(3) PCT.

Document D4 is regarded as being the closest prior art and discloses (see Experimental Section, compounds 17 and 19, p 188):

A method for preparing compounds analogous to compounds of formula 1 of this application, comprising reacting a compound Of formula 4 of this application, with an arninoacyl compound in a mixture of acetonitrile and DMPU in the presence of sodium carbonate and purifying the compound by extraction.

The subject-matter of claims 41-43 differs from Dl in that the process is realised in a reaction medium chosen from an aqueous medium, and at least one basic solvent, in the absence of a reagent base, and that the purification is not an extraction but a crystallisation In a mixture of solvents.

The subject-matter of claims 41-43 is therefore new (Article 33(2) PCT).

The problem to be solved by these differences is to find an alternative process to the known process of 02.

According to the examples of this application (examples 3-7,9-19), the technical problem has been solved only in the case of water, acetonitrile or DMPU or in a mixture of these solvents. Thus the technical problem has not been solved for the all scope of claims 41-43. Therefore the subject-matter of claims 41-43 can not be considered as involving an inventive step (Article 33(2) PCT).

Form PCTflSN2S7 (Separate Sh1) (Sheet 4) (EPO.April 2OO)

FEB-11-2008 14:51 Fram:FINN8nN HENDERSON 6174521666 To:6430011420383*001400 P.131130140

4

IF

WRITTEN OPINION OF THE International application No. INTERNATIONAL SEARCHING

AUTHORITY (SEPARATE SHEET) 17US2006/020270

Dependent claims 44-46 do not contain any features which, in combination with
the features of claims 41-43 to which they refer, meet the requirements of the PCT
in respect of inventive step.

5. Further remarks

5.1 The term "period of timed used in claim 2 is vague and unclear and leaves the
reader in doubt as to the meaning of the technical feature to which it refers,
thereby rendering the definition of the subject-matter of said claim unclear, Article
6 PCT.

5.2 Claim 24 refers to claim 2, but it is not clear to which "period of time" the claimed
range in claim 24 is relered (period of time of step B, C or D of claim 2?), thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

5.3 Claims 6 and 34 do not meet the requirements of Article 6 PCT in that the matter
for which protection is sought is not clearly defined. The claims attempts to define
the subject-matter in terms of the result to be achieved, which merely amounts to
a statement of the underlying problem, without providing the technical features necessary for achieving this result.

5.4 Contrary to the requirements of Rule 5.1 (a)Qi) PCT, the relevant background art
disclosed in the documenat Dl and D2 is not mentioned in the description, nor are these documents identified therein.

Form POT/15N27 SvparBts Sheel) (Shout 5) (EPO-Aprfl 2O5)