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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIRECCIÓN DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Solicitud de Patente de Invención Titulada: "PIRROLO [2,3-D]PIRIDINAS Y
USOS DE LAS MISMAS COMO INHIBIDORES DE CINASA DE
TIROSINA"

Solicitante: NOVARTIS AG

Nuestra Ref.: P2010/000115

RESPUESTA AL OFICIO No. 12036 NOTIFICADO

POR FIJACION EN LISTA No. 8322, DE FECHA 17 DE SEPTIEMBRE DE 2010

(EXAMEN DE FORMA)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, me permito dar respuesta al auto proferido por ese Despacho, dentro del término legal previsto en el artículo 39 de la Decisión 486, en los siguientes términos:

1. En respuesta a la única observación del Examinador, me permito adjuntar la traducción del reporte del examen preliminar internacional.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Copia de la traducción del reporte de examen preliminar

2

REPORTE PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD

Solicitud Internacional No.

PCT/EP2009/051281

Recuadro No. V

1. Se hace referencia a los siguientes documentos:

D1: WO 2005/107760 A (IRM LLC (US) ; HONG JIYONG (US) ; GRAY NATHANAEL S (US) ; SCHULTZ PETER (17 de noviembre de 2005)

D2: WO 2005/080393 A (IRM LLC (US) ; CHOI HA- SOON (US) ; WANG ZHICHENG (US) ; GRAY NATHANAEL SC) 1 de septiembre de 2005

D3: WO 2006/045828 A (TIBOTEC PHARM LTD (IE) ; ARTS FRANK XAVIER JOZEF HERWIG (BE) ; GUILLEMON) 4 de mayo de 2006

D4: WO 02/076985 A (SMITHKLINE BEECHAM CORP (US) ; BONDINELL WILLIAM E (US) ; HOLT DENNIS A) 3 de octubre de 2002

D5: WO 2006/096270 A (VERTEX PHARMA (US) ; LEDEBOER MARK W (US) ; PIERCE ALBERT C (US) ; BEMIS) 14 de septiembre de 2006

D6: HA- SOON CHOI, ZHICHENG WANG, WENDY RICHMOND, XIAOHUI HE, KUNYONG YANG ET AL: "Diseño y síntesis de 7H- pirrolo[2,3- d]pirimidinas como inhibidores de quinasas de adhesión focal. Parte 2" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, 2006, páginas 2689- 2692, XP002496172

2. La presente solicitud se relaciona con compuestos de fórmula I según lo ilustrado en la reivindicación 1, su preparación y uso de los mismos para la preparación de medicamentos para el tratamiento de cáncer.

3. La materia reivindicada es novedosa. Los antecedentes divulgan compuestos anticancerígenos estructuralmente relacionados (por ejemplo D1, compuestos 118, 124, 172) los cuales no caben en la reivindicación 1.

4. Los compuestos definidos en las reivindicaciones 1- 7 están dentro del alcance de los compuestos anti- tumorales sugeridos en los documentos D1 y D2 y por lo tanto se consideran como una selección de los compuestos sugeridos en D1 y D2. Es aparente a partir de la solicitud presente (tabla 3) que los compuestos del presente invento exhiben una selectividad pronunciada a favor de JAK2. Tal característica no podría derivarse a partir de los antecedentes citados. Puesto que los compuestos reivindicados exhiben tal efecto no obvio, los compuestos reivindicados y su uso y fabricación pueden considerarse no obvios.

5. Reivindicaciones 10,12: La patentabilidad puede ser dependiente de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como patentable aquellas reivindicaciones sobre el uso de un compuesto en un tratamiento médico, pero podrá permitir reivindicaciones sobre un producto, particularmente sustancias o composiciones para uso en un primer o posterior tratamiento.

Recuadro No. VIII.

3

Las reivindicaciones contienen definiciones abiertas como por ejemplo heterociclilo sustituido, aril sustituido, etcétera, las cuales abarcan prácticamente cualquier sustitución imaginable sobre tales grupos de heterociclilo, arilo, etc.

El concepto de IPEA es que es poco probable de manera inherente que prácticamente todos los compuestos que estuvieran cobijados bajo una reivindicación que comprendiera una definición abierta acerca de una característica estructural (en este caso: sustituido con cualquier sustituto) exhibiera una deseada actividad biológica en particular.

Por lo tanto, parece ser que como ciertas reivindicaciones comprenden varias definiciones estructurales abiertas, las reivindicaciones posiblemente abarcarían materia que no representaría ninguna solución al problema relevante que formula la presente solicitud. Apenas como una solución al problema de proporcionar nuevos compuestos, la materia de tales reivindicaciones parecerían obvias para aquellas persona experta en el estado de la técnica.

El alcance y los límites de los términos “menor” en conexión con las longitudes de cadena deberían aclararse tal como se encuentran en la descripción (Artículo 6 del PCT) .

Las reivindicaciones 10, 12: El alcance y límites de “Enfermedad mediada por la proteína tirosinquinasa” no están claros, y deberían aclararse tal como se encuentra en la descripción, en cuanto a cuáles enfermedades están cobijadas en tal definición (Art. 6 del PCT) .

4

- 273-

R⁵ representa de manera independiente entre sí, hidrógeno, alquilo menor, haloalquilo menor, cicloalquilo, halocicloalquilo o forma junto al carbono al cual está unido, un cicloalquilo;

R⁶ y R⁷ representan junto con el nitrógeno al cual está unidos, un heterociclo opcionalmente sustituido

ó

R⁶ representa hidrógeno o alquilo opcionalmente sustituido y

R⁷ representa alquilo opcionalmente sustituido;

R⁸ representa hidroxilo, alquilo menor, haloalquilo menor, cicloalquilo, halocicloalquilo, alquil- sulfonilo menor, haloalquil- sulfonil menor, cicloalquilo- sulfonilo, halocicloalquilo- sulfonilo, alquil- sulfinilo menor, haloalquil- sulfinil menor, cicloalquil- sulfinilo, halocicloalquil- sulfinilo;

R⁹ representa H ó alquilo menor;

R¹⁰ representa hidrógeno, alquilo menor, haloalquilo menor, cicloalquilo, halocicloalquilo;

n representa 0, 1 ó 2;

o sales de los mismos.

2. Un compuesto de fórmula I según la reivindicación 1, en donde
R¹ representa heterociclilo sustituido o no sustituido o aril sustituido o no sustituido
en donde dicho heterociclilo es seleccionado a partir de heterociclos no saturados, saturados o parcialmente saturados los cuales son monocíclicos, bicíclicos, tricíclicos, o espirocíclicos y contienen entre 4 y 16 átomos cíclicos en donde están presentes entre uno y cuatro heteroátomos;
en donde dicho arilo es seleccionado a partir de fracciones aromáticas con 6 a 14 átomos de carbono cíclicos;
en donde dichas sustituciones están seleccionadas de manera independiente a partir de una o más, preferiblemente entre una y cuatro de las siguientes fracciones: C₁₋₇- alquilo, amino- C₁₋₇- alquilo, halo- C₁₋₇- alquilo, N- C₁₋₇- alcanoilamino- C₁₋₇- alquilo, N- C₁₋₇- alcanosulfonil- amino- C₁₋₇- alquilo, pirrolidino- C₁₋₇- alquilo, oxo- pirrolidino- C₁₋₇- alquilo, piperidino- C₁₋₇- alquilo, piperazin- 1- il- C₁₋₇- alquilo, 4- (C₁₋₇- alquilo, C₁₋₇- alcoxilo- C₁₋₇- alquilo, halo- C₁₋₇- alquilo ó C₃₋₁₀- cicloalquilo) - piperazin- 1- il- C₁₋₇- alquilo, 4- (amino- C₁₋₇- alquil) - piperazin- 1- il- C₁₋₇- alquilo, 4- [N- mono- ó N,N- di- (C₁₋₇- alquilamino) - C₁₋₇- ...

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

Processed by M/D
04. März 2010
PCT

To:

NOVARTIS PHARMA AG
Patent Department
Postfach
4002 Basel
SUISSE

MÄR 04 2010

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NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

02.03.2010

Applicant's or agent's file reference
PAT052213-WO-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2009/051281

International filing date (day/month/year)
04.02.2009

Priority date (day/month/year)
06.02.2008

Applicant
Novartis AG

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Authorized Officer

Hutterer, Georg

Tel. +49 89 2399-8066



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 PAT052213-WO-PCT	FOR FURTHER ACTION See Form PCT/PEA/418	
International application No. PCT/EP2009/051281	International filing date (day/month/year) 04.02.2009	Priority date (day/month/year) 06.02.2008
International Patent Classification (IPC) or national classification and IPC INV. C07D487/04		
Applicant Novartis AG		
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. 2. This REPORT consists of a total of <u>6</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ sent to the applicant and to the International Bureau) a total of <u>1</u> sheets, as follows: ☒ 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). ☐ 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. b. ☐ (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).		
4. 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		
Date of submission of the demand 2009-12-04	Date of completion of this report 02.03.2010	
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Authorized officer Rudolf, Manfred Telephone No. +49 89 2399-8504 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2009/051281

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

1-271 as originally filed

Claims, Numbers

1(part), 2(part), 3-16 as originally filed

1(part), 2(part) received on 07.12.2009 with letter of 03.12.2009

- ☒ 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
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify):*
 - ☐ any table(s) related to sequence listing *(specify):*
5. ☐ This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).
6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2009/051281

8

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>1-16</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-16</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-9,11,13-16</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

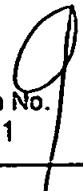
see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No. 
PCT/EP2009/051281

Supplemental Box relating to Sequence Listing

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."

Re Item V.

1 Reference is made to the following documents:

- D1 : WO 2005/107760 A (IRM LLC [US]; HONG JIYONG [US]; GRAY NATHANAEL S [US]; SCHULTZ PETER J) 17 November 2005 (2005-11-17)
- D2 : WO 2005/080393 A (IRM LLC [US]; CHOI HA-SOON [US]; WANG ZHICHENG [US]; GRAY NATHANAEL SC) 1 September 2005 (2005-09-01)
- D3: WO 2006/045828 A (TIBOTEC PHARM LTD [IE]; ARTS FRANK XAVIER JOZEF HERWIG [BE]; GUILLEMON) 4 May 2006 (2006-05-04)
- D4: WO 02/076985 A (SMITHKLINE BEECHAM CORP [US]; BONDINELL WILLIAM E [US]; HOLT DENNIS A) 3 October 2002 (2002-10-03)
- D5: WO 2006/096270 A (VERTEX PHARMA [US]; LEDEBOER MARK W [US]; PIERCE ALBERT C [US]; BEMIS) 14 September 2006 (2006-09-14)
- D6: HA-SOON CHOI, ZHICHENG WANG, WENDY RICHMOND, XIAOHUI HE, KUNYONG YANG ET AL.: "Design and synthesis of 7H-pyrrolo[2,3-d]pyrimidines as focal adhesion kinase inhibitors. Part 2" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 16, 2006, pages 2689-2692, XP002496172
2. The present application relates to compounds of formula I as depicted in claim 1, its preparation and the use thereof for preparation of medicaments for the treatment of cancer.
3. The claimed subject matter is novel. The prior art discloses structurally related anticancer compounds (e.g. D1, compounds 118, 124, 172) which do not fall within claim 1.
4. The compounds defined in claims 1-7 fall within the scope of the antitumour compounds suggested in documents D1 and D2 and therefore are considered as a selection from the compounds suggested in D1 and D2. It is apparent from the present application (table 3) that compounds of the present invention exhibit a pronounced selectivity towards JAK2. Such feature is not derivable from the cited

prior art. Insofar the claimed compounds exhibit such non-obvious effect, the claimed compounds and their use and production may be considered non-obvious.

5. Claims 10,12: The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Re Item VIII.

The claims contain open-ended definitions such as substituted heterocyclyl, substituted aryl, etc. which embrace virtually any imaginable substituents on said heterocyclyl, aryl etc. groups.

The IPEA's opinion is that it is inherently unlikely that substantially all compounds falling under a claim comprising an open-ended definition of a structural feature (here: substituted with any substituent) would exhibit a particular desired biological activity.

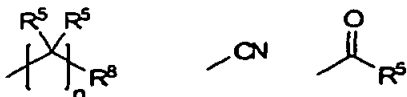
Therefore, it appears that, as certain claims comprise various open-ended structural definitions, the claims are likely to embrace subject matter which will not represent any solution to the relevant problem underlying the present application. Merely as a solution to the problem of providing new compounds, the subject matter of such claims would seem obvious to the person skilled in the art.

The scope and limits of the terms "lower" in connection with chain lengths should be clarified as found in the description (Art. 6 PCT).

Claims 10, 12: The scope and limits of "Protein tyrosine kinase mediated disease" are not clear, and it should be clarified as found in the description which diseases fall within such definition (Art. 6 PCT).

12

- 273 -



- R^5 represents independent from each other hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl or form, together with the carbon to which they are attached a cycloalkyl;
- 5 R^6 and R^7 represent together with the nitrogen to which they are attached an optionally substituted heterocycle
- or
- R^6 represents hydrogen or optionally substituted alkyl and
- R^7 represents optionally substituted alkyl;
- 10 R^8 represents hydroxy, lower alkyloxy, lower haloalkyloxy, cycloalkyloxy, halocycloalkyloxy, lower alkyl-sulfonyl, lower-haloalkyl-sulfonyl, cycloalkyl-sulfonyl, halocycloalkyl-sulfonyl, lower alkyl-sulfinyl, lower haloalkyl-sulfinyl, cycloalkyl-sulfinyl, halocycloalkyl-sulfinyl;
- R^9 represents H or lower alkyl;
- 15 R^{10} represents hydrogen, lower alkyl, lower haloalkyl, cycloalkyl, halocycloalkyl;
- n represents 0, 1 or 2;
- or salts thereof.
2. A compound of the formula I according to claim 1, wherein
- 20 R^1 represents unsubstituted or substituted heterocyclyl or unsubstituted or substituted aryl
- wherein said heterocyclyl is selected from unsaturated, saturated or partially saturated heterocycles which are monocyclic bicyclic, tricyclic or spirocyclic and have 4 to 16, ring atoms wherein one to four heteroatoms are present;
- 25 wherein said aryl is selected from aromatic moieties with 6 to 14 ring carbon atoms;
- wherein said substituents are independently selected from one or more, preferably one to four of the following moieties: C_1 - C_7 -alkyl, amino- C_1 - C_7 -alkyl, halo- C_1 - C_7 -alkyl, N- C_1 - C_7 -alkanoylamino- C_1 - C_7 -alkyl, N- C_1 - C_7 -alkanesulfonyl-
- 30 amino- C_1 - C_7 -alkyl, pyrrolidino- C_1 - C_7 -alkyl, oxo-pyrrolidino- C_1 - C_7 -alkyl, piperidino- C_1 - C_7 -alkyl, piperazin-1-yl- C_1 - C_7 -alkyl, 4-(C_1 - C_7 -alkyl, C_1 - C_7 -alkoxy- C_1 - C_7 -alkyl, halo- C_1 - C_7 -alkyl or C_3 - C_{10} -cycloalkyl)-piperazin-1-yl- C_1 - C_7 -alkyl, 4-(amino- C_1 - C_7 -alkyl)-piperazin-1-yl- C_1 - C_7 -alkyl, 4-[N-mono- or N,N-di-(C_1 - C_7 -alkylamino)- C_1 - C_7 -