

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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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/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/IB2015/055951	International filing date (day/month/year) 05.08.2015	Priority date (day/month/year) 06.08.2014
International Patent Classification (IPC) or both national classification and IPC INV. C07D401/14 C07D413/14 A61K31/506 A61P31/04		
Applicant NOVARTIS AG		

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 and 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.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Samsam Bakhtiary, M Telephone No. +49 89 2399-0
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Box No. I 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. ☐ 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 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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>1-21</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-21</u>
Industrial applicability (IA)	Yes: Claims	<u>1-21</u>
	No: Claims	

2. Citations and explanations

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

Re Item V

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

1. Reference is made to the following documents:

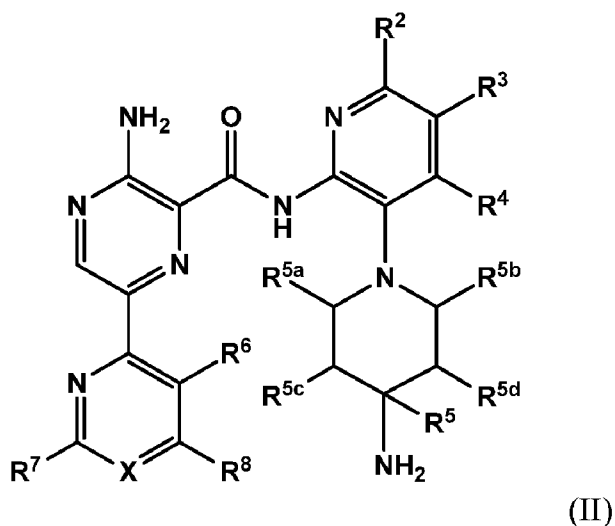
- D1 WO 2008/106692 A1 (NOVARTIS VACCINES & DIAGNOSTIC [US]; BURGER MATTHEW [US]; LINDVALL MIK) 4 September 2008 (2008-09-04)
- D2 WO 2011/068898 A1 (RIGEL PHARMACEUTICALS INC [US]; SINGH RAJINDER [US]; TSO KIN [US]; ZHA) 9 June 2011 (2011-06-09)
- D3 JI-XIA REN ET AL: "Discovery of Novel Pim-1 Kinase Inhibitors by a Hierarchical Multistage Virtual Screening Approach Based on SVM Model, Pharmacophore, and Molecular Docking", JOURNAL OF CHEMICAL INFORMATION AND MODELING, vol. 51, no. 6, 27 June 2011 (2011-06-27), pages 1364-1375, XP55028701, ISSN: 1549-9596, DOI: 10.1021/ci100464b

2. Industrial applicability

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 (see claims 10-21), but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

3. Subject matter

The present application is essentially concerned with compounds of formula II as follows:



for use to treat cancer via PKC inhibition.

4. Novelty

Documents D1-D3 disclose compounds that have the same usefulness as those of this application, namely useful for treating cancer.

Document D1 disclose pyrazinyl compounds, and the closest specific compounds structurally speaking are compounds of examples 364-368, the structural difference with the claimed compounds of this application is that the cycle linked to the pyrazinyl group (c) is different:

D1; cps 364-368: cycle (c) = phenyl

applic.; cycle (c) is a pyridine or pyrimidine

Documents D2 and D3 disclose compounds which are structurally speaking even more remote than those of D1, therefore less relevant.

The subject matter of claims 1-21 is novel.

5. Inventive step

When determining which document could be considered as the closest prior art, it has to be borne in mind that the primary aim of the application was to provide pharmaceutical compounds useful for the treatment or prevention of certain disorders, and that the pathway or mechanism by which these pharmaceuticals achieve the desired effect is of only secondary interest.

This means that in this case the treatment of cancer and not the mechanism of action such as PKc (mechanism in application) or PIM (mechanism in D1) will be relevant when choosing the closest prior art, therefore in the present case document D1 will be considered as the closest prior art.

Furthermore in D1 on paragraph 4, it is stated that PKC inhibition are well known in art when dealing with cancer diseases.

The subject-matter of claim 1 consists in the selection of a formula (II) from the compounds of formula (I) disclosed in document D1 for the same use. Such a selection can only be regarded as inventive if the compounds of formula (I) present unexpected effects or properties in relation to the rest of compounds. Since no such effects or properties are indicated and supported in the application, the subject-matter of claim 1 and pending claims 2-21 does not involve an inventive step.

Should this application be further proceeded into a European phase, then the Applicant would be invited to show any such improved or unexpected properties vis-à-vis the said prior art any comparative tests must be performed using compounds with the maximum structural similarity.

Re Item VIII

Certain observations on the international application

1. Should this application be further proceeded into a European phase we draw the attention of the Applicant to the following issue:

Claim 10 lacks of clarity, for the following reasons. The therapeutic application of the products is functionally defined by a mechanism of action (i.e. by their capability of modulating/regulating PKC), which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available (in the form of experimental tests or testable criteria, either disclosed in the patent application or known from the common general knowledge), which would allow the skilled person to recognise which additional conditions fall within the functional definition.

2. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D1 is not mentioned in the description, nor is this document identified therein.